CTOS 14th Annual Meeting  
November 13 — 15, 2008  

Landmark Hotel  
London, United Kingdom  

Program Chair: Ian Judson

Wednesday, November 12

17:00 - 19:00  
Registration and Poster Set-Up  
Ballroom Hall

Thursday, November 13

07:00 - 08:00  
Registration and Poster Set-Up  
Ballroom Hall

07:00 - 08:00  
Continental Breakfast  
Ballroom Hall Music Room

08:00 - 12:00  
SARC Meeting  
Ballroom

09:00 - 12:00  
Nurses and Allied Health Professionals Meeting  
Landmark 2 & 3

11  
#34981 MAGNETIC RESONANCE SIMULATION (SMR) FOR LOWER EXTREMITY SOFT TISSUE SARCOMA (LE-STS) PATIENTS TREATED WITH PRE-OPERATIVE INTENSITY MODULATED RADIATION THERAPY (IMRT)  
Colleen I Dickie-Euler, Amy L Parent; Anthony M Griffin; Anna K Kirilova; Peter W.M. Chung; Michael B Sharpe; Jay Wunder; Peter Ferguson; Charles N Catton; Brian O’Sullivan

11  
#35042 A RETROSPECTIVE STUDY COMPARING INITIAL GP DATA ON TWO WEEK WAIT REFERRALS WITH CLINICAL REVIEW AND IMAGING AT A SPECIALIST CENTRE.  
Lin Russell; Luan Suckling

11  
#35081 COLLABORATIVE MANAGEMENT OF SARCOMA PATIENTS IN 2008: INTEGRATING IMPROVEMENTS IN CARE FROM NOVEL THERAPIES TO DEVELOPMENT OF NEW RESOURCES.  
Amy S Potter; Suzanne George; George Demetri; Andrew Wagner; Jeffrey A Morgan; Melissa Hohos; Bonnie Dirr; James Butrynski; Tarsha Colon; Kathleen Polson

11  
#35090 CARE OF THE INTERNATIONAL PEDIATRIC PATIENT AND FAMILY - THE PUERTO RICO PATIENT ASSISTANCE PROGRAM  
Sara Swaim, RN; Amy Federico, PNP; Annette Werger, PNP; Holcombe Grier, MD; Mark Gebhardt, MD; Allen Goorin, MD
#35092 EXAMINING ONE SARCOMA CENTER’S EXPERIENCE WITH SUCCESSFUL RECRUITMENT TO RANDOMIZED, PLACEBO CONTROLLED CLINICAL TRIALS. Melissa Hohos; Amy S. Potter; Kathleen Polson; George Demetri; Jeffrey A. Morgan; Andrew J. Wagner; Bonnie Dirr; Tarsha Colon; James Butrynski; Serena Wong; Margaret O’Mara; Suzanne George

THE USE OF NON-INVASIVE EXTENDING ENDOPROSTHES FOLLOWING FAILED ALLOGRAFT SURGERY IN SKELETALLY MATURE PATIENTS
Chris Henry

09:00 - 12:00 Patient Advocacy Groups Meeting
12:15 - 13:00 Lunch
13:30 - 13:40 Introduction to 14th Annual Meeting
13:40 - 14:30 Molecular Pathology of Sarcomas
Session Chairs: Andrea Deyrup, Paolo dei Tos

#34879 PROGNOSTIC VALUE OF MYOGENIC DIFFERENTIATION IN ADULT SOFT TISSUE SARCOMAS. A STUDY OF 855 CASES FROM THE FRENCH SARCOMA GROUP
Nathalie Stock; Marie Christine Chateau; Francoise Collin; Louis Guillou; Agnes Leroux; Bernard Marques; Jean JacquesMichels; Dominique Ranchère; Yves Marie Robin; Philippe Terrier; Martine Trassard; Isabelle Valo; Jean Michel Coindre

#34956 GENE EXPRESSION PROFILE OF POORLY DIFFERENTIATED SYNOVIAL SARCOMA
Robert Nakayama; Tadashi Ichikawa; Tadashi Hasegawa; Akira Kawai; Akira Ogose; Teruhiko Yoshida; Hideo Morioka; Hiroo Yabe; Yoshiaki Toyama

#35080 GROWTH FACTORS AND PATHWAY ACTIVATION IN CHORDOMA
Carolyn J. Hoban; Dafydd G. Thomas; David R. Lucas; Laurence H. Baker

#35032 RECURRENT CHROMOSOMAL COPY NUMBER ALTERATIONS IN CHORDOMA
G. Petur Nielsen; Vikram Deshpande; Andrew Rosenberg; Julie Miller; John Iafrate; Francis Hornicek

14:30 - 15:30 Gynecological Sarcomas
Session Chairs: Beatrice Seddon (to give introductory talk), Martee Hensley,

#34982 STAGE SPECIFIC OUTCOMES OF PATIENTS WITH UTERINE LEIOMYOSARCOMA: A COMPARISON OF FIGO AND AJCC STAGING SYSTEMS
Oliver Zivanovic; Mario M. Leitao; Alexia Iasonos; Qin Zhou; Robert A. Soslow; Margrit M. Juretzka; Dennis S. Chi; Richard R. Barakat; Murray F. Brennan; Martee L. Hensley

#34970 PREDICTIVE VALUE OF FIGO AND AJCC STAGING SYSTEMS IN 230 PATIENTS (PTS) WITH UTERINE LEIOMYOSARCOMA (ULMS): IS IT TIME FOR A CHANGE?
Chandrajit P Raut; Marisa R Nucci; Qian Wang; Judith Manola; Michelle Ouellette; Kathleen M Polson; Amy S Potter; Monica M Bertagnolli; Michael G Muto; Elizabeth H Baldini; James E Butrynski; George D Demetri; Jeffrey A Morgan; Andrew J Wagner; Christopher D M Fletcher; Suzanne George
#34855 WILMS' TUMOR GENE 1 (WT1) IS A NEW PROGNOSTIC MARKER IN HIGH GRADE UTERINE SARCOMA
An Coosemans; Ben Van Calster; Stefaan W Van Gool; Ignace Vergote; Frédéric Amant

#34961 ADJUVANT GEMCITABINE PLUS DOCETAXEL FOR COMPLETELY RESECTED STAGE I-IV HIGH GRADE UTERINE LEIOMYOSARCOMA: RESULTS OF A PHASE II TRIAL
Martee L Hensley; Nicole Ishill; Robert Soslow; Nadeem Abu-Rustum; Paul Sabbatini; Jason Konner; William Tew; David Spriggs; Carol Aghajanian

#35073 CLINICAL FEATURES AND OUTCOME IN OVARIAN SARCOMAS: ANALYSIS OF A SINGLE-INSTITUTION EXPERIENCE.
Antonio Lopez Pousa; X. Gonzalez; M.J. Quintana; S. Bague; O. Gallego; A. Tibau; J. Perez Altoyan; N. Sala; J.M. Mazarico; V. Artigas; A. Barnadas

15:30 - 16:15 Tea and Poster Viewing
Ballroom Hall

16:15 - 16:30 Poster Discussion 1
Ballroom Hall
Session Chair: Brian O’Sullivan
34806, 34812, 34813, 34818, 34830, 34841, 34853, 34872, 34873, 34887, 34892, 34905, 34916, 34920, 34933, 34941, 34943, 34944, 34949, 34950, 34953, 34966, 34979, 34985, 34992, 34994, 34998, 34999, 35002, 35003, 35004, 35009, 35023, 35025, 35027, 35028, 35045, 35048, 35054, 35062, 35065, 35078, 35084, 35088, 35093, 35109, 35110, 35114, 35118, 35120, 35126, 35135, 35138, 35141, 35142, 35155, 35157, 35158, 35171

16:30 - 18:00 Fibromatosis: Biology & Multidisciplinary Management
Ballroom
Session Chair: Dina Lev (to give introductory talk), Andrew Hayes

#34875 ALTERNATIVE CLINICAL APPROACH IN AGGRESSIVE FIBROMATOSIS: WAIT & SEE FRONTLINE POLICY. A MULTI-INSTITUTIONAL RETROSPECTIVE REVIEW.
Marco Fiore; Annalisa Perego; Elisabetta Pennacchioli; Paola Collini; Palma Dileo; Silvia Stacchiotti; Axel Le Cesne; Paolo Giovanni Casali; Alessandro Gronchi; Sylvie Bonvalot

#35006 DESMOID TUMOURS: TO OPERATE OR NOT TO OPERATE
Rafiq H Abed; Adesegun Abudu; Simon Carter; Rob Grimer; Roger Tillman; Lee Jeys

#34885 THE DESMOID TUMOR PROTEOME; IDENTIFYING MOLECULAR MARKERS USING A CLINICALLY ANNOTATED TISSUE MICROARRAY
Shohrae Hajibashi; Wei-Lien Wang; Alexander J.F. Lazar; Daniel Tuvin; Carla L. Warneke; Dolores Lopez-Terrada; Raphael E. Pollock; Dina Lev

#35119 MESENCHYMAL PROGENITOR CELLS ARE INVOLVED IN THE FORMATION OF AGGRESSIVE FIBROMATOSIS (DESMOID TUMOR)
Colleen Wu; Benjamin A Alman

#34904 MULTIMODALITY TREATMENT OF MESENTERIC DESMOID TUMORS
Monica M Bertagnolli; Jeffrey A Morgan; Christopher DM Fletcher; Chandrajit P Raut; Palma Dileo; Ritu R Gill; George D Demetri; Suzanne George

#35057 ACTIVITY OF MEDICAL THERAPY (METOTREXATE + VINBLASTINE/VINORELBINE OR TAMOXIFEN) IN DESMOID FIBROMATOSIS (DF): RETROSPECTIVE ANALYSIS OF 79 PATIENTS FROM A SINGLE INSTITUTION.
Palma Dileo; Claudio Piovesan; Marianna Silletta; Elisa Puma; Roberta Sanfilippo; Elisabetta Pennacchioli; Marco Fiore; Alessandro Gronchi; Paolo Casali
#34852 SUCCESSFUL TREATMENT OF FIBROMATOSIS WITH HYDROXYUREA: ANALYSIS OF 20 PEDIATRIC CASES
Naomi J Balamuth; Richard B Womer

19:00 - 20:00
Welcome Reception

Friday, November 14

07:00 - 08:00
Registration and Poster Set-Up
Ballroom Hall

07:00 - 08:00
Continental Breakfast
Ballroom Hall

07:00 - 08:00
Executive Committee Meeting
Champagne Room

08:00 - 09:00
Surgery
Ballroom
Session Chair: Alessandro Gronchi, Lor Randall

#34880 MORBIDITY OF AN UNPLANNED EXCISION OF SOFT TISSUE SARCOMAS: A QUANTITATIVE ASSESSMENT
Robert M Tamurian, MD; Robert A. Zlotecki, MD PhD; Zachary B Adler, MD; Mark T Scarborough; C. Parker Gibbs, MD

#34876 MARGINAL SURGERY IN PRIMARY EXTREMITY SOFT TISSUE SARCOMA: PROGNOSTIC ROLE OF ANATOMIC BARRIER AT CLOSEST SURGICAL MARGIN.
Marco Fiore; Marzia Riccardo; Elisabetta Pennacchioli; Paola Collini; Laura Lozza; Alessandro Cadeo; Paolo Casali; Alessandro Gronchi

#34869 CLINICAL VARIABLES, PATHOLOGICAL FACTORS, AND MOLECULAR MARKERS FOR ENHANCED SOFT TISSUE SARCOMA PROGNOSTICATION
Guy Lahat; Wang Wei-lien; Daniel Tuvin; Daniel A Anaya; Caimiao Wei; Nabiyu Bekele; Kerrington D Smith; Alexander J Lazar; Peter W Pisters; Raphael E Pollock; Dina Lev

#35066 PROGNOSTIC FACTORS FOR LONG-TERM SURVIVAL AFTER PULMONARY METASTASECTOMY IN SARCOMA PATIENTS: A 16-YEAR EXPERIENCE
Simon Jordan; Peter Goldstraw; Elizabeth Belcher; Ambrus Szántó; Jeremy Whelan; Beatrice Seddon; Maria Michelagnoli; Anna Cassoni; Sandra Strauss; Michelle Scurr; Frank Saran; Ian Judson; George Ladas

09:00 - 10:00
Bone Sarcomas 1- Pediatric Oncology
Ballroom
Session Chair: Paul Meyers, Herbert Jurgens

#34849 THE MORE IT Hurts, THE BETTER IT WORKS? CHEMOTHERAPY TOXICITY AS A PREDICTOR OF OUTCOME FROM OSTEOSARCOMA: A REPORT FROM THE EUROPEAN OSTEOSARCOMA INTERGROUP
Anne McTiernan; Rachel C Morgan; Matthew R Sydes; Barbara Uscinska; Martine Van Glabbeke; Vivien Bramwell; Robert L Souhami; Ian Lewis; Antonie H Taminiav; Marianne A Nooij; Pancras C. Hogendoorn; Jeremy S Whelan
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<td>35051</td>
<td>CHANGE IN ANATOMIC DISTRIBUTION OF RELAPSES WITH ACCELERATED CHEMOTHERAPY IN EWING SARCOMA</td>
<td>Richard B Womer; Daniel C West; Mark D Krailo; Paul S Dickman; Bruce Pawel</td>
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<td>39</td>
<td>35047</td>
<td>THE VALUE OF LOCAL TREATMENT IN PATIENTS WITH EXTRAPULMONARY METASTASIZED EWING TUMORS (EPMET)</td>
<td>Uta Dirksen; Julia Häusler; Tobias Bölling; Andreas Ranft; Georg Gosheger; Volker Vieth; Heribert Jürgens</td>
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<td>35094</td>
<td>ACTIVITY OF SCH 717454 IN SUBJECTS WITH RELAPSED OSTEOSARCOMA OR EWING’S SARCOMA (STUDY P04720)</td>
<td>Peter Anderson; Keith Skubitz; Robin Miller; William Meyer; Brian Lu</td>
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<td>40</td>
<td>34973</td>
<td>ADDITION OF PAMIDRONATE TO CHEMOTHERAPY FOR TREATMENT OF OSTEOSARCOMA (OS) IS FEASIBLE.</td>
<td>Paul A. Meyers; John H. Healey; Edward Athanasian; Patrick Boland; Carol Morris; Michael P. Laquaglia; Cristina Antonescu; Leonard Wexler; Pamela Merola; Alexander Chou; Sara Abramson; Michael Kellick</td>
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10:00 - 10:30
Coffee Break & Poster Viewing
Ballroom Hall & Music Room

10:30 - 11:45
NF1: MPNST and Other Sarcomas, Diagnosis & Treatment
Ballroom

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<td>35059</td>
<td>18FDG PET/CT IN THE DIAGNOSIS OF MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS</td>
<td>Victoria S Warbey; Rosalie E Ferner; Michael J O’Doherty</td>
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<td>40</td>
<td>35152</td>
<td>GENETIC ANALYSIS OF PERIPHERAL NERVE SHEATH TUMOURS IN NF1 PATIENTS.</td>
<td>Eline Beert; Bruno Daniels; Hilde Brems; Ivo De Wever; Frank Van Calenbergh; Patrick Schöffski; Maria Debiec-Richter; Raf Sciot; Eric Legius</td>
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<td>41</td>
<td>34868</td>
<td>MALIGNANT PERIPHERAL NERVE SHEATH TUMORS (MPNST): CLINICAL, PATHOLOGIC AND MOLECULAR PREDICTORS OF SURVIVAL</td>
<td>Kerrington David Smith; Chang-ye Zou; Jun Liu; Guy Lahat; Alex JF Lazar; Raphael E Pollock; Dina Lev</td>
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<td>41</td>
<td>35055</td>
<td>MICROARRAY GENE EXPRESSION DATA UTILIZED TO IDENTIFY PUTATIVE SERUM BIOMARKERS OF NEUROFIBROMATOSIS TYPE 1 ASSOCIATED TUMORS</td>
<td>Trent Hummel; Yonatan Mahler; Shyra Miller; Walter Jessen; Bruce Aronow; Timothy Cripe; Nancy Ratner</td>
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<td>35072</td>
<td>GASTROINTESTINAL STROMAL TUMOR (GIST) IN NEUROFIBROMATOSIS 1 (NF1) PATIENTS: A CLINICOPATHOLOGIC ANALYSIS OF NINE CASES</td>
<td>Elena Fumagalli; Paola Coco; Elena Palassini; Palma Dileo; Rossella Bertulli; Paolo G. Casali</td>
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<td>41</td>
<td>34974</td>
<td>NUCLEAR TP53 EXPRESSION IN MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS IS AN INDEPENDENT MARKER OF POOR SURVIVAL</td>
<td>Helge R. Brekke; Matthias Kolberg; Rolf I. Skotheim; Kirsten Sundby Hall; Bodil Bjerkehagen; Bjorn Risberg; Henryk A. Domanski; Nils Mandahl; Sigbjørn Smeland; Håvard E. Danielsen; Fredrik Mertens; Ragnhild A. Lothe</td>
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11:45 - 12:45 Herman Suit Lecture - Professor Ivan Stamenkovic, Lausanne
Ballroom
“The Role of Mesenchymal Stem Cells in the Pathogenesis of Sarcomas”

12:45 - 14:00 Board of Directors Meeting
Champagne Room

12:45 - 14:00 Lunch
Empire, Gazebo and Harewood Rooms

14:00 - 15:00 Radiation Oncology
Ballroom
Session Chairs: Martin Robinson, Thomas DeLaney

42
#35069 ADEQUATE 3D TREATMENT VOLUME IN PREOPERATIVE RADIOTHERAPY IN EXTREMITY SOFT TISSUE SARCOMA
BoKyong Kim; Yen-Lin E Chen; David G Kirsch; Wendy K Kobayashi; Saveli I Goldberg; John A Wolfgang; Kevin A Raskin; Dempsey S Springfield; Joseph H Schwab; Sam S Yoon; Francis J Hornicek; Thomas F DeLaney

42
#35029 HYPOXIA IN RESECTABLE SOFT-TISSUE SARCOMAS ON FUNCTIONAL IMAGING WITH [18F]-FLUOROAZOMYCIN ARABINOSIDE POSITRON EMISSION TOMOGRAPHY POWERFULLY PREDICTS POOR RESPONSE TO RADIOTHERAPY AND EARLY RELAPSE
Kenneth Khamly; Peter Choong; Samuel Ngan; Rodney Hicks; Guy Toner; Jayesh Desai; Dianne Saward; David Thomas

43
#35012 CARBON ION RADIOTHERAPY FOR SACRAL CHORDOMA
Tadashi kamada; Reiko Imai; Hiroshi Tsuji; Itsuko Serizawa; Toru Okada

43
#35038 LONG-TERM FOLLOW-UP OF A PROSPECTIVE TRIAL OF PRE-OPERATIVE EXTERNAL-BEAM RADIATION AND POST-OPERATIVE BRACHYTHERAPY FOR RETROPERITONEAL SARCOMA
Lynn A. Mikula; Paul F. Ridgway; Charles N. Catton; Julia J. Jones; Brian O’Sullivan; Michael A. Ko; Carol J. Swallow

43
#34907 EFFECTIVENESS OF RADIOTHERAPY IN MYXOID SARCOMAS IS ASSOCIATED WITH A DENSE VASCULAR PATTERN
Ronald S.A. de Vreeze; Daphne de Jong; Rick L. Haas; Fiona Stewart; Frits van Coevorden

15:00 - 16:00 Biology 1 - Molecular Biology of Sarcomas
Ballroom
Session Chairs: Richard Gorlick, Jean-Michel Coindre

44
#35046 MULTIFOCAL MYXOID LIPOSARCOMA; METASTASIS OR SECOND PRIMARY? A MOLECULAR BIOLOGICAL ANALYSIS.
Ronald S.A. de Vreeze; Daphne de Jong; Petra M. Nederlof; Rick L. Haas; Frits van Coevorden

44
#35068 HUMAN MONOCLONAL ANTIBODY R1507 INHIBITS GROWTH OF OSTEOSARCOMA XENOGRAFTS AND IS EFFECTIVE IN COMBINATION WITH RAPAMYCIN
Edward Anders Kolb; Davida Kamara; Pooja Gidwani; Wengdong Ellen Zhang; Laurence H Baker; Richard G Gorlick

44
#34955 EWS/FLI REGULATES NKX2.2 VIA GLI IN A NON-SHH-DEPENDENT MANNER
Savita Sankar; Leah A. Owen; Stephen L. Lessnick
#35143 GLI2 AND P53 COOPERATE TO REGULATE IGFBP-3 MEDIATED CHONDROCYTE APOPTOSIS IN THE PROGRESSION FROM BENIGN TO MALIGNANT CARTILAGE TUMOURS
Louisa Ho; Aneta Stojanovski; Heather Whetstone; Qingxia Wei; Elaine Mau Elaine Mau; Benjamin Alman; Jay Wunder

#35037 OSTEOCHONDROMAGENESIS: SOMATIC LOSS OF HETEROZYGOSITY MODELED VIA CRE-MEDIATED INVERSION OF THE SECOND EXON OF EXT1 IN CHONDROCYTES
Kevin B. Jones; Charles Searby; Gail Kurriger; Peter Roughley; Jose A. Morcuende; Joseph A. Buckwalter; Val C. Sheffield

16:00 - 16:45
Afternoon Break & Poster Viewing
Ballroom Hall

16:45 - 17:00
Poster Discussion 2
Ballroom Hall & Music Room
Session Chair: Robert Grimer
34593, 34800, 34807, 34819, 34825, 34827, 34839, 34840, 34859, 34861, 34864, 34867, 34913, 34934, 34939, 34942, 34949, 34951, 34967, 34969, 34985, 34988, 34993, 34995, 35013, 35026, 35030, 35031, 35035, 35039, 35063, 35074, 35083, 35087, 35089, 35091, 35098, 35099, 35100, 35101, 35103, 35105, 35107, 35108, 35111, 35112, 35125, 35128, 35132, 35134, 35137, 35139, 35148, 35160

17:00 - 17:30
THE SARC CAREER DEVELOPMENT AWARD
Ballroom
Laurence H Baker; Jennifer E Keene
Young Investigator Award Lectures
Session Chair: Laurence H Baker

17:30 - 18:00
Members Business Meeting
Ballroom

19:00 - 23:00
Reception & Dinner
Ballroom

Saturday, November 15

07:00 - 08:00
Registration and Poster Set-Up
Ballroom Hall

07:00 - 08:00
Continental Breakfast
Ballroom Hall

08:00 - 09:00
Medical Oncology
Session Chairs: Shreyas Patel, Jeremy Whelan
#35064 COMBINATION THERAPY WITH TEMOZOLOMIDE AND BEVACIZUMAB (TMZ/BV) IN THE TREATMENT OF HEMANGIOPERICYTOMA/SOLITARY FIBROUS TUMOR (HPC/SFT): AN UPDATED ANALYSIS.
Min S Park; Alexander J Lazar; Jonathan C Trent; Charles A Conrad; Joseph A Ludwig; Wei-Lien Wang; Piyaporn Boonsirikamchai; Haesun Choi; Shreyaskumar R Patel; Robert S Benjamin; Dejka M Araujo

#34936 ACTIVITY OF THE VEGFR/KIT TYROSINE KINASE INHIBITOR CEDIRANIB (AZD2171) IN ALVEOLAR SOFT PART SARCOMA.
Katherine Gardner; Michael Leahy; Manuel Alvarez-Gutierrez; Ian Judson; Michelle Scurr

#35024 ADVANCED CHORDOMA FOLLOWING IMATINIB (IM) RESISTANCE
Silvia Stacchiotti; Elena Tamborini; Andrea Marrari; Emanuela Virdis; Antonella Messina; Carlo Morosi; Flavio Crippa; Alessandro Gronchi; Silvana Pilotti; Paolo Casali

#35085 RESPONSES TO THE MTOR INHIBITOR SIROLIMUS IN PATIENTS WITH MALIGNANT PECOMA: REPORT OF THREE CASES
Andrew J. Wagner; Robert Maki; Cristina R. Antonescu; Christopher D. M. Fletcher; Jeffrey A. Morgan

#35067 A PHASE II STUDY OF INTRAVENOUS REOLYSIN (WILD TYPE REOVIRUS) IN THE TREATMENT OF PATIENTS WITH BONE AND SOFT TISSUE SARCOMAS METASTATIC TO THE LUNG
Monica Mita; Kamalesh Sankhala; Alain Mita; John Sarantopoulos; Anthony Carmona; Sanjay Goel; Rashmi Chugh; Scott Okuno; Matt Coffey; George Gill; Karl Mettinger

09:00 - 09:30 Diagnostic Techniques
Ballroom
Session Chairs: J. Meirion Thomas, Haesun Choi

#34828 PERCUTANEOUS CT-GUIDED BIOPSY OF THE MUSCOLO-SKELETAL SYSTEM: RESULTS OF 1722 CASES.
Eugenio Rimondi; Pietro Ruggieri; Giuseppe Bosco; Giuseppe Ussia; Teresa Calabrò; Andrea Angelini; Giuseppe Rossi; Ugo Albisinni

#35076 CORE NEEDLE BIOPSY IS HIGHLY ACCURATE IN DIAGNOSING BONE AND SOFT-TISSUE TUMOURS
Piya Kiatisevi; Torsten Nielsen; Malcolm Hayes; Peter L Munk; Amy E LaFrance; Paul W Clarkson; Bassam A Masri

09:30 - 10:30 Bone Sarcomas 2 - Surgery and Molecular Biology
Ballroom
Session Chairs: Jay Wunder, Stephen Cannon

#34854 FREE VASCULARIZED FIBULAR GRAFTING FOR MALIGNANT BONE AND SOFT TISSUE TUMOR: RADIOLOGICAL, CLINICAL AND FUNCTIONAL OUTCOME
Mitsunori Kaya; Takuro Wada; Sataoshi Nagoya; Mikito Sasaki; Tadaki Matsumura; Toshihiko Yamashita

#34914 COMPLIANT FIXATION OF MEGA-ENDOPROSTHETICS: RESULTS OF VARIED APPLICATIONS
Judd E. Cummings; Russell A. Ward; R. Lor Randall
#35000 LENTIVIRAL SHRNA SCREEN OF HUMAN KINASES IDENTIFIES NEW REGULATORS OF OSTEOSARCOMA CELL SURVIVAL AND APOPTOSIS
Zhenfeng Duan; Diana Ji; Edward Weinstein; Cao Yang; Edwin Choy; Henry Mankin; Francis Hornicek

#35116 A NOVEL PROFILING STRATEGY IN OSTEOSARCOMA IDENTIFIES EBF2 AS A MEDIATOR OF OPG INHIBITION TO TRAIL-INDUCED APOPTOSIS
Ana Patiño-García; Marta Zalacain; Luis Sierrasésúmaga; Mikel San Julián; Cecilia Folio; Iker Antón; Diego Luis-Ravelo; Carolina Zandueta; Javier De Las Rivas; Gemma Toledo; Fernando Lecanda

#35140 NEW SURGICAL TECHNIQUE TO REDUCE DISLOCATIONS OF PROXIMAL AND TOTAL HUMERUS REPLACEMENTS AFTER TUMOR RESECTION
German Marulanda; Eric Henderson; Nazeem Virani; Dave Cheong; G. Douglas Letson

10:30 - 11:00 Coffee Break & Poster Viewing
Ballroom Hall

11:00 - 12:00 Nina Axelrad Lecture - Paul Meyers - Memorial Sloan Kettering Cancer Center
Ballroom
“Development of a New Drug: Lessons from clinical trials”

12:15 - 13:30 Lunch
Empire, Gazebo and Harewood Rooms

13:30 - 14:30 Biology 2 - New Targets - Molecular Biology & Therapy
Session Chair: Lee Helman, Ian Judson

#35145 COMBINATION PI3K/MTOR INHIBITION LIMITS CHORDOMA PROLIFERATION
Joseph H Schwab; Cristina Antonescu; John Healey; Patrick J Boland; Francis Hornicek; Zhenfeng Duan

#35008 THE PROTEOLYTIC MACHINERY AS NOVEL THERAPEUTIC TARGET IN GASTROINTESTINAL STROMAL TUMORS (GISTS)
Ying Liu; Joshua Parry; Anna Chin; Payel Chatterjee; Anette Duensing

#34962 EGR1 MEDIATES HISTONE DEACETYLASE SENSITIVITY IN SYNOVIAL SARCOMA VIA THE PTEN TUMOR SUPPRESSOR
Le Su; T. Michael Underhill; Torsten O. Nielsen

#34884 THE C-MET RECEPTOR CONTRIBUTES TO MOTILITY AND INVASION IN A BROAD RANGE OF STS HISTOLOGIES: A POTENTIAL ANTI-STS THERAPEUTIC TARGET
Sarah E Myers; Theresa G Nguyen; Quan S Zhu; Alex JF Lazar; Raphael Pollock; Dina Lev

#35041 OVERCOMING RESISTANCE TO CONVENTIONAL DRUGS IN EWING’S SARCOMA AND IDENTIFICATION OF MOLECULAR PREDICTORS OF OUTCOME.
Katia Scotlandi; Gastone Castellani; Daniel Remondini; Maria Cristina Manara; Massimo Serra; Sakari Knuutila; Piero Picci

13:30 - 14:30 Sarcoma Cooperative Trials Groups Overview
Session Chair: Jean-Yves Blay

14:30 - 15:30 Sarcoma Cooperative Trials Groups Overview
Ballroom

15:30 - 16:15 Afternoon Break and Poster Viewing
Ballroom Hall & Music Room
16:15 - 16:30  
**Poster Discussion 3**  
*Ballroom*  
*Session Chair:* Robert Maki  
34545, 34820, 34824, 34844, 34845, 34850, 34863, 34866, 34896, 34897, 34898, 34899, 34906, 34908, 34911, 34938, 34946, 34948, 34952, 34960, 34963, 34965, 34971, 34977, 34980, 34991, 35001, 35005, 35010, 35011, 35017, 35018, 35021, 35022, 35033, 35034, 35036, 35040, 35044, 35049, 35052, 35060, 35070, 35079, 35082, 35095, 35104, 35113, 35127, 35129, 35130, 35131, 35132, 35133, 35136, 35144, 35154, 35162, 35170

16:30 - 16:30  
**Meeting Adjourned**  
*Ballroom*
ORAL PRESENTATIONS
THURSDAY

Nurses and Allied Health Professionals Meeting

#34981 MAGNETIC RESONANCE SIMULATION (SMR) FOR LOWER EXTREMITY SOFT TISSUE SARCOMA (LE-STS) PATIENTS TREATED WITH PRE-OPERATIVE INTENSITY MODULATED RADIATION THERAPY (IMRT)
Colleen I Dickie-Euler1, Amy L Parent1, Anthony M Griffin2, Anna K Kirilova1, Peter W.M. Chung3, Michael B Sharpe1, Jay Wunder4, Peter Ferguson5, Charles N Catton6, Brian O’Sullivan7
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Objective: Peritumoural tissue changes, generally referred to as edema, correspond to increased T2-weighted MR signal. Their inclusion is vital for accurate Clinical Target Volume (CTV) definition in radiotherapy planning, since evidence suggests that they may harbor satellite neoplastic cells. Technological advances producing highly conformal plans require precise target contouring. However, positional differences, field-of-view limitations and temporal delays between diagnostic (dMR) and sMR scans may obscure target delineation. We reviewed all SMR datasets used for radiotherapy planning to determine if sMR should be incorporated into standard planning procedure for LE-STS patients.

Methods: We identified 60 LE-STS patients scanned on a designated oncology MR system equipped with precision lasers and a flat-tabletop overlay. This process simulates the radiotherapy set-up procedure in an MR space. All SMR datasets were compared to dMR images and the patient records to determine the average time from dMR to simulation date, patient positional differences from the diagnostic setting, and the percentage of dMR scans that failed to encompass peritumoural edema.

Results: An average of 53 days elapsed between dMR and radiotherapy simulation, 40% of patients were positioned differently, and 50% of dMR scans failed to include edema.

Conclusions: Results indicate that sMR is a valuable addition to standard planning protocols. Benefits include: heightened accuracy in target delineation, elimination of delay between sMR and CT simulation scans thereby avoiding tumour volume changes, patient set-up in treatment position preventing tumour deformation, and prioritization of edema inclusion. These elements facilitate MRI/CT dataset fusion to optimize the IMRT planning/treatment delivery process.

#35042 A RETROSPECTIVE STUDY COMPARING INITIAL GP DATA ON TWO WEEK WAIT REFERRALS WITH CLINICAL REVIEW AND IMAGING AT A SPECIALIST CENTRE.
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1ROYAL ORTHOPAEDIC HOSPITAL FOUNDATION TRUST, BIRMINGHAM, United Kingdom

Objective: Background: In 1999 all General Practitioners in the UK were sent guidelines about the criteria for urgent referral of patients with suspected sarcoma. In addition, the receiving specialist centre was given a set of targets to meet in relation to referral, diagnosis and treatment of these cancers. These targets have now been updated for 2008 in the Cancer Reform strategy.

Aim: To compare the clinical information on two week wait referrals with imaging clinical assessment within a specialist centre to confirm a malignant diagnosis. To review the sarcoma diagnosis hit-rate and to establish whether early diagnosis has been improved.

Methods: Method: All two-week wait referrals direct into our department were studied from June 2007 to June 2008 to determine whether a sarcoma was diagnosed, whether the GP criteria were met, and whether the targets were achieved.

Results: Results: Total of 166 referrals received as two week wait referrals to the specialist unit. 136 were diagnosed with benign lesions. 30 patients had a malignant diagnosis and of those 10 patients had surgery as their first definitive treatment.

Conclusions: Conclusions: Detailed analysis is still being undertaken but initial conclusions drawn seem to suggest that there are still a large number of inappropriate referrals being made under the two week wait. This is may be due to GPs not following the criteria on the referral form.

#35081 COLLABORATIVE MANAGEMENT OF SARCOMA PATIENTS IN 2008: INTEGRATING IMPROVEMENTS IN CARE FROM NOVEL THERAPIES TO DEVELOPMENT OF NEW RESOURCES.
Amy S Potter1, Suzanne George1, George Demetri1, Andrew Wagner1, Jeffrey A Morgan1, Melissa Hohos1, Bonnie Ditt1, James Butrynski1, Tarsha Colon1, Kathleen Polson1
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Objective: Discuss updates in the treatments of adult sarcoma patients. Focus on targeted therapies, survivorship, supportive therapies, young adult support, and patient involvement.

Methods: Chart reviews of patients on treatment for sarcoma in different eras were examined.

Results: The management of patients with sarcomas has changed considerably in the millennium. The advent of targeted therapies has improved patient outcomes for certain sarcoma subtypes and the plethora of new agents are changing the way patients are treated. Many resources are now available including internet support groups, improved supportive therapies, young adult support and survivorship. We examined cases of several patients treated in the past 7 years compared to the 20th century. One case study analyzes treatment of a patient with gastrointestinal stromal tumor (GIST) in the 1990s vs. treatment of a GIST patient in 2008. Multiple factors are examined in this case including patient education and increased involvement in treatment decisions as a result of participation in GIST support groups, family planning, survivorship, alterations in treatment compliance with oral therapies and participation in research studies. Another case study which highlights advances involves a patient with leiomyosarcoma treated with durable benefit on an expanded access trial of a new agent. We will examine a patient with advanced rhabdomyosarcoma treated with traditional chemotherapy followed by clinical trials, highlighting improvements in supportive care that have enabled successful aggressive treatments.

Conclusions: Novel treatments, improvements in supportive care and access to multiple innovative resources has improved the quality of life and clinical outcomes for patients living with sarcoma today.

#35090 CARE OF THE INTERNATIONAL PEDIATRIC PATIENT AND FAMILY - THE PUERTO RICO PATIENT ASSISTANCE PROGRAM
Sara Swaim, RN1, Amy Federico, PNP1, Annette Werger, PNP1, Holcombe Grier, MD1, Mark Gebhardt, MD1, Allen Goorin, MD1
1Dana Farber Cancer Institute and Childrens Hospital Boston, Boston, Massachusetts, United States

Objectives: For many families traveling from other countries, the already frightening experience of a child’s cancer diagnosis intensifies under the financial burdens resulting from treatment costs, lack of adequate health insurance coverage, and lost income. The Dana-Farber Children’s Hospital Cancer Care (DF/CHCC) program has developed the Puerto Rico Pediatric Patient Assistance Program to help serve approximately 30 young patients each year with various cancers which cannot be treated at home. They, and their families, travel to Boston for cancer treatment, sometimes resulting in a stay of up to one year. The goal of the program is to help facilitate and fund expenses related to medical needs, food, clothing, transportation, and housing for patients and families with accumulating financial burdens resulting from travel to Boston for prolonged treatment. It allows them to focus their energies on the most important task of battling the illness. During this presentation, we will describe the development and implementation of the Puerto Rico Pediatric Patient Assistance Program. In addition, we will present a case study of an 8-year-old Puerto Rican female who came to DF/CHCC program for treatment of her Ewing sarcoma. We will highlight the diagnostic findings of Ewing Sarcoma, chemotherapy treatment, surgical treatment options, and multidisciplinary care provided in the DF/CHCC program.

THE USE OF NON-INVASIVE EXTENDING ENDOPROSTHESSES FOLLOWING FAILED ALLOGRAFT SURGERY IN SKELETALLY MATURE PATIENTS
Chris Henry
Institution: Royal National Orthopaedic, Hospital London
Non-invasive extending prostheses have successfully been used in patients who previously had failed allograft surgery resulting in limb length inequality for osteosarcoma and Ewing’s sarcoma. The custom-made prosthesis contains a magnetically driven gearbox to remotely extend the implant post-operatively when placed in a mobile limb extender, consisting of a circular coil and control box. The lengthening procedure is completely painless. Three patients will be discussed, all with lower limb reconstructions, one distal femoral, one diaphyseal and one total femoral. Two patients required a partial exchange of prosthesis to gain further lengthening capacity. There was no failure of the lengthening mechanism, The mean length gained was 76mm (30 to 108) requiring a mean of 13 (8 to 19) lengthening procedures in the outpatient’s department. All patients achieved satisfactory functional results with leg length equality.

Molecular Pathology of Sarcomas

#34879 PROGNOSTIC VALUE OF MYOGENIC DIFFERENTIATION IN ADULT SOFT TISSUE SARCOMAS. A STUDY OF 855 CASES FROM THE FRENCH SARCOMA GROUP
Nathalie Stock1, Marie Christine Chateau2, Francoise Collin2, Louis Guillou2, Agnes Leroux2, Bernard Marques2, Jean Jacques Michels2, Dominique Ranchère2, Yves Marie Robin3, Philippe Terrier2, Martine Trassard2, Isabelle Valo2, Jean Michel Coindre1
1Institut Bergonie, bordeaux, France; 2Pathology subgroup French Sarcoma Group, Paris, France

Objectives: Most adult soft tissue sarcomas (STS) with specific genetic alterations are represented by leiomyosarcomas (LMS), rhabdomyosarcomas (RMS), pleomorphic liposarcomas (LPS), myxofibrosarcomas (MFS) and poorly-differentiated sarcomas or so-called malignant fibrous histiocytomas (MFH). These sarcomas are often difficult to histotype but a myogenic differentiation has been reported to be more aggressive.

Methods: 1002 cases of adult STS initially diagnosed as LMS, adult RMS, pleomorphic LPS, MFS and MFH were retrieved from the French Sarcoma Group database. They were re-classified after histological review and immunohistochemistry. The following parameters were studied: age, sex, tumour location, size, depth, grade and myogenic differentiation. We performed univariate and multivariate analyses for metastasis-free survival.

Results: After re-classification, 74 cases were ruled out and 73 cases with metastasis at time of diagnosis were excluded. The remaining 855 cases were classified as LMS (355), adult RMS (28), pleomorphic LPS (50), MFS (128) and MFH (294). Median age was 62 year (15 to 98). Tumour location was extremities (601), internal trunk (69), trunk wall (159) and head and neck (26). Median size was 8 cm and 716 cases were deeply located. Median follow-up was 102 month and 296 experienced distant metastasis. Univariate analysis indicated that internal trunk location (p=1.4x10-4), size (p=4.43x10-7), depth (p=2.74x10-9), grade (p=3.15x10-8) and myogenic differentiation (p=4.73x10-7) were significant predictors of metastasis. Multivariate analyses retained grade, tumour depth, internal trunk location and myogenic differentiation for predicting metastasis.

Conclusions: This study showed that myogenic differentiation is
an adverse prognostic factor among adult STS with no specific genetic alterations.

**#34956 GENE EXPRESSION PROFILE OF POORLY DIFFERENTIATED SYNOVIAL SARCOMA**

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1Keio University School of Medicine, Tokyo, Japan; 2National Cancer Center Research Institute, Tokyo, Japan; 3National Cancer Center Hospital, Tokyo, Japan; 4Sapporo Medical University School of Medicine, Sapporo, Japan; 5Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

**Objectives:** Poorly differentiated synovial sarcoma (SS) is a histological variant characterized by small round cell features, and accumulating clinicopathological studies have shown strong association between poorly differentiated SS and poor prognosis. However, little is known about its molecular background, and it is still difficult to clearly distinguish it from monophasic SS based on morphology alone.

**Methods:** We used an oligonucleotide microarray to analyze gene expression of 34 SYT-SSX positive SS samples.

**Results:** We found that they fell into three subgroups highly correlated with histological subtypes, namely, monophasic, biphasic and poorly differentiated SS. Differential gene expression pattern showed that poorly differentiated SS was characterized by up-regulation of genes at a specific genomic locus and down-regulation of those associated with neuronal and skeletal development.

**Conclusions:** These results suggested that the poorly differentiated SS constitutes a distinct group in terms of gene expression. This study provides novel insights into an appropriate diagnosis of SS subtypes and understanding the molecular mechanisms in the progression of SS.

**#35080 GROWTH FACTORS AND PATHWAY ACTIVATION IN CHORDOMA**

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1University of Michigan, Ann Arbor, MI, United States

**Objectives:** Chordomas occur as primary tumors in a unique microenvironment of bone and nervous system. Despite infrequent metastasis, chordomas are challenging to treat with surgery, radiation and chemotherapy regimens due to tumor location and frequent local recurrence. The goal of this study was to determine level of expression and activation of key molecules involved in bone and notochord growth factor pathways in chordoma clinical specimens.

**Methods:** A tissue microarray was constructed from a local series of chordoma clinical specimens (n=34) available as FFPE specimens represented by clival (n=23), sacral (n=8) and other (n=4) anatomic locations. Immunohistochemical detection of growth factors and notochord specific markers, including IGF1R, PDGFR a and b, Ret, brachyury, TGFB2, c-kit, HER1-4, mTOR, AKT, and MAPK pathway activation markers were measured by quantitative immunofluorescence using AQUA platform and IHC antibodies specific for total and phosphorylated/activated forms.

**Results:** Chordoma specimens obtained from both sacral and clival anatomic locations showed increased activation of signal pathways downstream of IGF1R (Table 1). mTOR, phospho-mTOR and pAKT were detected at high levels in chordoma clinical specimens. Furthermore, there was an increased amount of phosphoAKT located predominantly in the nucleus in chordoma cells.

**Conclusions:** These studies provide rationale to support participation of chordoma patients in clinical studies that examines the efficacy of combination therapy that targets both mTOR and IGF1R/ AKT pathway inhibition. Supported by Chordoma Research for All and Stephan L. Harris Fund.

<table>
<thead>
<tr>
<th>Activation Marker</th>
<th>Avge AQUA Score</th>
<th>Range</th>
<th>SEM</th>
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<tr>
<td>Phospho-mTOR</td>
<td>1254</td>
<td>15-2600</td>
<td>75</td>
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<tr>
<td>mTOR</td>
<td>779</td>
<td>30-2900</td>
<td>70</td>
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<td>Phospho-AKT</td>
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<td>38</td>
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</table>

**AQUA Analysis in Chordoma**

**#35032 RECURREN T CHROMOSOMAL COPY NUMBER ALTERATIONS IN CHORDOMA**

G. Petur Nielsen1, Vikram Deshpande1, Andrew Rosenberg1, Julie Miller1, John Iafrate1, Francis Hornicek1

1Massachusetts General Hospital, Boston, MA, United States

**Objectives:** Chordoma is an uncommon neoplasm with the majority arising in the axial skeleton. Morphologically, immunohistochemically and ultrastructurally, chordoma are identical to the normal notochord. Numerous cytogenetic studies have been performed that have demonstrated variable but inconsistent chromosomal abnormalities. We report herein another CGH study on 14 chordomas.

**Methods:** Frozen tumor was obtained from 14 chordomas. H&E slides of each tumor sample was analyzed to ensure a high proportion of tumor cells. Genomic DNA was extracted from frozen tissue using the Gentra Puregene isolation kit. We analyzed tumor genome-wide copy number alterations using array comparative genomic hybridization (array CGH). Agilent 244k oligonucleotide arrays were hybridized with tumor DNA labeled in CY5 and control normal DNA labeled in CY3. Signals were captured using an Agilent microarray scanner, and data analyzed using CGH analytics software. High-quality copy number data was produced for all tumors, with copy number gains or losses defined as log2 ratios of greater or less than 2 standard deviations.

**Results:** The tumors were all conventional chordomas by light microscopy and were located in the sacrum, skull base and mobile spine. By CGH the most common abnormality was loss of 1p that was found in all tumors. Loss of 9p (CDKN2A; p16) or chromosome 9 was identified in 12 out of 14 (85%) tumors with homozgyous deletion in three tumors. Other common changes included losses of 3p, 4, 10, 13, 14, 18, and 22. Gains were rare and included gains of chromosome 7 (3/14) and 19p (4/14). Immunohistochemical stain for p16 showed no staining in any of the tumors.

**Conclusions:** Consistent chromosomal abnormalities are present in chordomas, as well as, a variety of other infrequent changes. The loss of 1p and 9p in many chordomas suggests that tumor suppressor genes in these regions may be important in the molecular pathogenesis of this neoplasm. One such candidate gene supported by the results is p16 - a gene known to be involved in other cancers.
Gynecological Sarcomas

#34982 STAGE SPECIFIC OUTCOMES OF PATIENTS WITH UTERINE LEIOMYOSARCOMA: A COMPARISON OF FIGO AND AJCC STAGING SYSTEMS
Oliver Zivanovic1, Mario M. Leita1, Alexia Iasonos1, Qin Zhou1, Robert A. Soslow1, Margrit M. Juretzka1, Dennis S. Chi1, Richard R. Barakat1, Murray F. Brennan1, Martee L. Hensley1, 1Memorial Sloan Kettering Cancer Center, New York, New York, United States

Objectives: Uterine leiomyosarcoma (LMS) is staged by the modified International Federation of Gynecology and Obstetrics (FIGO) Staging System for uterine cancer. We aimed to determine whether the American Joint Committee on Cancer (AJCC) Soft Tissue Sarcoma (STS) Staging System is more predictive of progression-free survival (PFS) and overall survival (OS).

Methods: We analyzed all patients with uterine LMS who presented at our institution from 1982 to 2005. The patients were staged retrospectively, according to the modification of the FIGO staging system for uterine cancer and the 6th edition of the AJCC STS staging system. The predictive accuracy of the two staging systems was compared using concordance estimation.

Results: 220 patients had sufficient clinical and pathologic information for staging under both systems. 136 patients were up-staged in the AJCC staging system, whereas only 2 patients were down-staged. Stage-specific PFS and OS rates for Stage I patients differed substantially between FIGO and AJCC. In both systems there was a prognostic overlap between Stages II and III. Thus, despite the marked stage-specific differences in 5-year PFS and OS rates for Stage I, both systems had similar concordance indices.

Conclusions: Estimates of stage-specific PFS and OS for uterine LMS were altered substantially when using AJCC versus FIGO. Adjuvant treatment strategies should be tested in patients at substantial risk for progression and death. Neither FIGO nor AJCC is ideal for identifying such patients, suggesting a need for a uterine LMS-specific staging system to better target patients for trials of adjuvant therapies.

#34970 PREDICTIVE VALUE OF FIGO AND AJCC STAGING SYSTEMS IN 230 PATIENTS (PTS) WITH UTERINE LEIOMYOSARCOMA (ULMS): IS IT TIME FOR A CHANGE?
Chandrajit P Raut1, Marisa R Nucci1, Qian Wang2, Judith Manola1, Michelle Ouellette1, Kathleen M Polson2, Amy S Potter2, Monica M Bertagnolli1, Michael G Muto1, Elizabeth H Baldini1, James Wagner2, Christopher D M Fletcher1, Suzanne George2, 1Memorial Sloan Kettering Cancer Center, New York, New York, United States; 2Dana Farber Cancer Institute, Boston, MA, United States; 1Harvard Medical School, Boston, MA, United States

Objectives: Cancer staging systems identify pt groups to accurately predict outcomes based on clinically relevant prognostic factors. The FIGO system is the accepted staging system for ULMS, whereas the AJCC system is used for sarcomas of other anatomic sites. While FIGO and AJCC incorporate different variables, neither was designed specifically for ULMS. We sought to determine if either system truly discriminates pts into subsets predicting clinically distinct outcomes.

Methods: Records on 230 ULMS pts evaluated at our institution were reviewed. All were staged by FIGO and AJCC systems at time of hysterectomy. Progression-free survival (PFS) and overall survival (OS) were calculated; statistical pairwise comparisons were performed within each system.

Results: Cohort details are in the Table. The number of stage I and III pts varied drastically by system. There were few stage II pts by either system. For OS, AJCC system stratified pts into subsets distinguishing stage I pts from other stages as well as stage III from IV. In contrast, OS for all FIGO stages was more tightly clustered, distinguishing only stage I from IV. For PFS, only stage I pts by either system were discriminated from other stages.

Conclusions: Neither system distinguishes pts into 4 clinically meaningful, non-overlapping stages consistently predictive of PFS and OS. This analysis highlights the relevance of certain factors (low grade, AJCC I; serosal involvement, FIGO III) and rarity of others (cervix invasion, FIGO II). Future studies should focus on identifying relevant prognostic factors in ULMS to optimally predict clinical outcomes. We are validating both systems against a nomogram.

<table>
<thead>
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<th>Patient No.</th>
<th>Median PFS in mos (95% CI)</th>
<th>Median OS in mos (95% CI)</th>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>2 yrs (26-81 yrs)</td>
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<tr>
<td>FIGO Stage</td>
<td></td>
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<tr>
<td>I</td>
<td>110 (47.5)</td>
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</tr>
<tr>
<td>II</td>
<td>11 (4.3)</td>
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</tr>
<tr>
<td>III</td>
<td>37 (16.1)</td>
<td>13.9 (7.3-29.1)</td>
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<td>IV</td>
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<td>IV</td>
<td>55 (23.9)</td>
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Table

#34855 WILMS' TUMOR GENE 1 (WT1) IS A NEW PROGNOSTIC MARKER IN HIGH GRADE UTERINE SARCOMA
An Coosemans1, Ben Van Calster2, Stefaan W Van Gool1, Ignace Vergote4, Frédéric Amant6, 1Laboratory Of Experimental Gynaecology, Leuven, Belgium; 2Department Of Electric Engineering, Leuven, Belgium; 3Laboratory Of Experimental Immunology, Leuven, Belgium; 4Department Of Gynaecological Oncology, Leuven, Belgium

Objectives: Our group previously suggested Wilms’ tumor gene 1 (WT1) to contribute to uterine sarcoma tumor biology (Eur J Cancer, 2007). In this study, we aimed to further clarify the prognostic value of WT1.

Methods: A retrospective clinical and histopathological review of 54 women with high grade uterine sarcoma (leiomyosarcoma (LMS) (n=20), carcinosarcoma (CS) (n=27) and undifferentiated sarcoma (US) (n=7)) with a follow up of at least 12 months was performed. WT1 expression was determined by immunohistochemistry (inten-
Historical rates, and merits further study as an adjuvant strategy for HGuLMS. Achieves 2- and 3-year PFS rates that appear superior to 22%.

**Results:** 25 patients (median age 49, range 37-73) enrolled; performed at baseline, after cycle 4, and every 3 months. Progression-free scan, were treated with gemcitabine-docetaxel for four cycles. CT performed at baseline, after cycle 4, and every 3 months. Progression-free at 2 and at 3 years. Median PFS is 39 months. Among 18 patients with stage I or II HGuLMS, 59% remain progression-free at 2-3 years. No adjuvant treatment has been shown to improve survival. Gemcitabine-docetaxel achieves high response rates in metastatic HGuLMS. We sought to determine whether adjuvant gemcitabine-docetaxel would yield a 2-year progression-free survival (PFS) of at least 40% in completely resected stage I-IV HGuLMS, in order to determine its potential for further study as adjuvant therapy.

**Methods:** Women with completely resected HGuLMS, no prior gemcitabine-docetaxel or radiation, no evidence of disease on CT scan, were treated with gemcitabine-docetaxel for cycles. CT performed at baseline, after cycle 4, and every 3 months. Progression defined as evidence of new disease on CT.

**Results:** 25 patients (median age 49, range 37-73) enrolled; 23 evaluable (1 - never treated, 1 - ineligible). Toxicities grade 3: neutropenia (2/23), febrile neutropenia (2/23), anemia (2/23), thrombocytopenia (1/23), diarrhea (1/23), hyperglycemia (2/23), pulmonary (2/23); grade 4 - none. With median follow-up of 39 months, 45% remain progression-free at 2 and 3 years. Median PFS is 13 months. Median overall survival (OS) is 45 months. Among 18 patients with stage I or II HGuLMS, 59% remain progression-free at 2 and 3 years. Median PFS is 39 months. Median OS is not yet reached with median follow-up of 40 months. Sites of first recurrence were: lung -3/23 (13%); pelvis -5/23 (22%); both -5 (22%).

**Conclusions:** Post-resection gemcitabine-docetaxel for stage I-IV HGuLMS achieves 2- and 3-year PFS rates that appear superior to historical rates, and merits further study as an adjuvant strategy for HGuLMS.

**#34961 ADJUVANT GEMCITABINE PLUS DOCETAXEL FOR COMPLETELY RESECTED STAGE I-IV HIGH GRADE UTERINE LEIOMYOSARCOMA: RESULTS OF A PHASE II TRIAL**

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1Memorial Sloan Kettering Cancer Center, New York, New York, United States

**Objectives:** Approximately 30% of women with completely resected stage I-IV high-grade uterine leiomyosarcoma (HGuLMS) remain progression-free at 2 to 3 years. No adjuvant treatment has been shown to improve survival. Gemcitabine-docetaxel achieves high response rates in metastatic HGuLMS. We sought to determine whether adjuvant gemcitabine-docetaxel would yield a 2-year progression-free survival (PFS) of at least 40% in completely resected stage I-IV HGuLMS, in order to determine its potential for further study as adjuvant therapy.

**Methods:** Women with completely resected HGuLMS, no prior gemcitabine-docetaxel or radiation, no evidence of disease on CT scan, were treated with gemcitabine-docetaxel for cycles. CT performed at baseline, after cycle 4, and every 3 months. Progression defined as evidence of new disease on CT.

**Results:** 25 patients (median age 49, range 37-73) enrolled; 23 evaluable (1 - never treated, 1 - ineligible). Toxicities grade 3: neutropenia (2/23), febrile neutropenia (2/23), anemia (2/23), thrombocytopenia (1/23), diarrhea (1/23), hyperglycemia (2/23), pulmonary (2/23); grade 4 - none. With median follow-up of 39 months, 45% remain progression-free at 2 and 3 years. Median PFS is 13 months. Median overall survival (OS) is 45 months. Among 18 patients with stage I or II HGuLMS, 59% remain progression-free at 2 and 3 years. Median PFS is 39 months. Median OS is not yet reached with median follow-up of 40 months. Sites of first recurrence were: lung -3/23 (13%); pelvis -5/23 (22%); both -5 (22%).

**Conclusions:** Post-resection gemcitabine-docetaxel for stage I-IV HGuLMS achieves 2- and 3-year PFS rates that appear superior to historical rates, and merits further study as an adjuvant strategy for HGuLMS.

**#35073 CLINICAL FEATURES AND OUTCOME IN OVARIAN SARCOMAS: ANALYSIS OF A SINGLE-INSTITUTION EXPERIENCE.**

Antonio Lopez Pouss1, X. Gonzalez1, M.J. Quintanal1, S. Baguel1, O. Gallego1, A. Tibau1, J. Perez Altovano1, N. Salal1, J.M. Mazearclo1, V. Artigas1, A. Barnadass1

1Hospital Santa Creu i Sant Pau, Barcelona, Spain

**Objectives:** Gynaecologic sarcomas are bad prognosis uncommon tumours. Less than 1% of ovarian tumours are malignant sarcomas. The objective of this retrospective study was to analyze clinical and pathological prognostic factors influencing in the outcome of these patients.

**Methods:** From 1978 to 2007, 100 patients with gynaecologic sarcomas were treated at our institution. We retrospectively analyzed clinicopathological variables, treatment and outcome of 13 patients with ovarian sarcoma. A single pathologist reviewed pathologic diagnoses. Kaplan Meier method was used to evaluate outcome.

**Results:** Medium age 63 years. First-symptom was abdominal pain (46%) and metrorragia (23%). Median tumour size was 22 cms. Pathology: 1 leiomyosarcoma, 12 carcinosarcoma. Histologic grade: III (92%), II (8%). FIGO Staging: I (15%), II (23%), III (38%), IV (15%). All patients underwent total abdominal hysterectomy with bilateral salpingoophorectomy and adjuvant chemotherapy. Combination chemotherapy with Platinum + Doxorubicin (DX) or Taxanes in 6 cases, other combinations with DX in 6 cases. With a median follow-up of 46 months, 6 patients presented local relapse, 2 of them treated with successfully radical surgery - Sugarbaker-. Median time to relapse was 18(6-129) months. Overall 1, 2 and 5-year survival was 84%, 63% and 47%.

**Conclusions:** Ovarian sarcomas (like ovarian carcinomas) are usually detected in advanced stages. Most of them are high-grade carcinosarcomas and the prognosis in this small series seems to be similar to that of ovarian carcinomas. Radical treatment of relapsed disease should be always considered.

**Fibromatosis: Biology & Multidisciplinary Management**

**#34875 ALTERNATIVE CLINICAL APPROACH IN AGGRESSIVE FIBROMATOSIS: WAIT & SEE FRONTLINE POLICY. A MULTI-INSTITUTIONAL RETROSPECTIVE REVIEW.**

Marco Fiore1, Annalisa Perego1, Elisabella Pennacchioli1, Paola Collini1, Palma Dileo1, Silvia Stacchiotti1, Axel Le Cesne2, Paolo Giovanni Casali1, Alessandro Gronchi1, Sylvie Bonvalot2

1Istituto Nazionale Tumori, Milan, Italy; 2Institut Gustave Roussy, Villejuif - Paris, France

**Objectives:** Aggressive fibromatosis (AF) is a rare disease with no metastatic potential. Presently, surgery is still considered the standard approach, but local failure is expected in more than 30% of the cases. Recently, a mono-institutional series on a frontline non-surgical approach has been reported, with interesting results. Aim of this study was to extend those observations on a larger series, and focus on the natural history of those patients not undergoing any frontline treatment at all.

**Methods:** All patients affected by AF who presented to two referral institutions since 1995, selected for frontline non-surgical approach by local sarcoma board, form the population of this study. Time to progression from initial observation was analyzed.

**Results:** Overall 167 patients were identified. Fifty-eight percent were referred for primary tumor, and 42% for recurrence. F/M
ratio was 2/1, tumor site was abdominal wall 12%, trunk 13%, H&N 16%, extremity 18%, girdles 24%, and intrabdominal 17%. Overall, two-third of the patients had tumor control without surgery. A subset of these patients did not receive any medical treatment at initial presentation. They account for one-third of the entire series (76% primary and 24% recurrent tumors). In this subset, F/M ratio was 4/1, tumor site was abdominal wall 42%, trunk 12%, H&N 6%, extremity 6%, girdles 17%, and intrabdominal 17%. Thirty-six percent of female patients in this group had been pregnant within 2 years before diagnosis. Median tumor size was 4.0 cm (range 2.0-9.0). After a median follow up of 18 months, 52.9% of the patients had SD; 11.8% patients had a spontaneous minor regression in tumor size; 35.3% patients experienced tumor progression. After PD, some patients continued observation with subsequent secondary SD. Median TTP for those who progressed was 8 mos (range 6-22). Conclusions: Wait and see policy could be considered the frontline approach to aggressive fibromatosis. Two-thirds of the patients maintain the tumor under control without the need of any treatment. For those who progress, median TTP is scant and further treatments are needed. Spontaneous regression and secondary SD after initial progression were also documented. Natural history of this disease has still to be explored, with possible major changes in therapeutic standard approach.

### #35006 DESMOID TUMOURS: TO OPERATE OR NOT TO OPERATE
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Objectives: The best local treatment for desmoid tumours remains unclear. We reviewed our experience of treatment of desmoid fibromatosis and report on observation only modality in the treatment of desmoids tumours.
Methods: Retrospective review of all patients treated under a multidisciplinary team was performed. The clinical data were studied. Information regarding recurrence was obtained including timing, progression, treatment, timing of treatment and any subsequent recurrence.
Results: 160 patients were studied at mean follow up of 49 months and mean age 36 years. Male to female ratio was 1:1. 114 patients presented with primary disease and 46 presented with recurrent disease. Mean tumour size was 8.6cm (2-25). 147 patients had surgical treatment with very few having adjuvant radiotherapy. Overall recurrence rate was 41%. Recurrence for patients with primary and recurrent presentations was 30% and 66% respectively. Recurrence was more common in females. Margins of resection had no influence on recurrence. 33 patients had observation only treatment either at presentation or after recurrence. 22 patients (67%) remained in stable disease, 3 patients in active progressive disease and 8 patients had further surgery due to progression or pain.
Conclusions: Fibromatosis is a benign condition with aggressive behaviour and high recurrence rate. Our series experience is that recurrence is common after surgery even with radiotherapy. Surgical margins did not influence local recurrence. Observation alone appears to be the best policy for those with painless desmoids tumours.

### #34885 THE DESMOID TUMOR PROTEOME; IDENTIFYING MOLECULAR MARKERS USING A CLINICALLY ANNOTATED TISSUE MICROARRAY
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Objectives: To establish a clinically annotated tissue microarray (TMA) useful for correlating protein marker expression with desmoid outcomes.
Methods: A TMA that included 0.6 mm punch samples (2/case) of desmoid (n=195) and scar (n=18) was formatted into 3 standard blocks. Demographic, therapeutic, tumor, and clinical outcome data were retrieved from medical records and our soft tissue tumor database, then tabulated for correlative analyses. IHC assays were performed to identify beta-catenin, cyclin D, p53, ER-beta, c-Kit, EGFR, PDGFRs and PDGFs expression as scored by a soft tissue pathologist. Associations between possible predictors of time from primary surgery to recurrence were statistically evaluated.
Results: Nuclear beta-catenin was observed in 98% of desmoids; compared to scars, desmoids had greater percentage reactivity and intensity in nuclear and cytoplasmic compartments (p<0.0001). In primary desmoids (n=81), less intense beta-catenin nuclear staining with increased recurrence (p=0.0406). Cyclin D1 expression was observed in 34% of primary desmoids; increased nuclear cyclin D reactivity cases had higher levels of nuclear beta-catenin and lower recurrence (p<0.01). Strong nuclear p53 staining was observed in 17% of cases and associated with increased recurrence (p=0.0290). EGFR, c-KIT, ER-beta, PDGFR alpha and beta, and PDGF A and B reactivity did not correlate with desmoid outcome.
Conclusions: These studies demonstrate that higher nuclear beta-catenin intensity and increased nuclear cyclin D reactivity associate with less aggressive desmoid behaviors, whereas nuclear p53 expression associates with increased recurrence, observations warranting further investigation. Desmoid TMAs are useful for identifying novel prognostic factors that are also potentially exploitable as therapeutic targets.

### #35119 MESENCHYMAL PROGENITOR CELLS ARE EXPLOITABLE AS THERAPEUTIC TARGETS
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Objectives: Aggressive fibromatosis (AF), also called desmoid tumor is a locally invasive soft tissue lesion associated with activation of beta-catenin mediated signaling. Although the location, cellular morphology and histological profile of these tumors suggest that they may be of mesenchymal origins; the cell of origin has yet to be definitively elucidated.
Methods: Genetically engineered mice predisposed to developing AF, the Apc1638N mouse, were used in this study. The number of colony forming units fibroblastic (CFU-F, whose numbers are surrogates for mesenchymal progenitor cells) was compared with the number of AF tumors. The mice were crossed with Scal−/− mice, which are deficient in mesenchymal progenitors to determine the effect on tumor number. Bone marrow stromal cells from Apc 1638N mice or wild type littermates were injected into immuno-deficient, NOD/SCID mice to determine if they would form tumors.
Results: The number of AF tumors in individual mice positively
correlated with the numbers of CFU-F in their bone marrow, Apc 1638N mice lacking Sca-1 demonstrated substantially reduced numbers of AF tumors compared to littermate control mice expressing wild type Sca-1. Bone marrow stromal cells from Apc 1638N mice induced aberrant cellular growth when injected subcutaneously into NOD/SCID mice. In contrast, bone marrow stromal cells from wild type littersmates did not result in tumor formation.

**Conclusions:** Taken together this suggests that AF derives from mesenchymal progenitor cells. Identification of the cell of origin in this neoplasm, may allow for the development of targeted therapies that will improve the outcome for patients with AF.

### #34904 MULTIMODALITY TREATMENT OF MESENTERIC DESMOID TUMORS

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**Objectives:** Desmoid tumors are uncommon neoplasms characterized by clonal proliferation of myofibroblasts that do not metastasize, but often exhibit an infiltrative pattern and functional impairment. When desmoids arise in the intestinal mesentery, surgical resection is seldom possible without life-altering loss of intestinal function. The objective of this study was to evaluate a multidisciplinary strategy to care for patients with mesenteric desmoid tumors.

**Methods:** We undertook a retrospective review of the clinical management of 52 consecutive patients treated for desmoids of the intestinal mesentery from January, 2001 to August, 2006. A multidisciplinary treatment plan was developed based on primary disease extent, tumor behavior, and resectability. Patients with stable but unresectable disease were observed without treatment (n=4). Patients with stable, resectable disease underwent surgery (n=8). Patients with progressive, resectable disease underwent surgery (n=28), patients with unresectable progressing disease received chemotherapy (n=12), most commonly liposomal doxorubicin, followed by surgery if chemotherapy rendered the disease resectable (n=6).

**Results:** At a median follow-up of 50.0 months (range 4.6-212), 50 patients (96%) have disease control, with either no recurrence or radiographically stable disease. No patient requires total parenteral nutrition.

**Conclusions:** These data indicate the extent of disease, tumor behavior and resectability are important factors in when defining a treatment plan for mesenteric desmoid tumors. A multidisciplinary approach of surgery combined with chemotherapy is an effective and function-sparing strategy for managing this disease.

### #34852 SUCCESSFUL TREATMENT OF FIBROMATOSIS WITH HYDROXYUREA: ANALYSIS OF 20 PEDIATRIC CASES

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**Objectives:** While surgical excision is generally the initial therapy for aggressive fibromatosis, many tumors are either unresectable or recur following excision. Radiotherapy and a variety of chemotherapy regimens have been used in these patients, all with considerable toxicity. We reviewed our institutional experience in treating aggressive fibromatosis with hydroxyurea.

**Methods:** We retrospectively reviewed the charts of 16 pediatric fibromatosis patients treated with hydroxyurea. Patients were treated with an initial dose of 20 mg/kg, increasing as ANC permitted, with an intended treatment duration of one year.

**Results:** We identified 20 tumors (8 extremity, 7 torso, 4 head/neck, 1 abdominal) in 16 patients. The mean age at initiation of hydroxyurea therapy was 9.7 years. The mean administered dose was 30 mg/kg/day. Patients were grouped according to the Intergroup Rhabdomyosarcoma Study Group (IRS) system. Prior therapy (if any) included various chemotherapeutic regimens, radiation and surgery. Four out of five (80%) of IRS Group I/II patients maintained remission with hydroxyurea. Of the IRS Group III/IV patients, 4/14 (29%) had a complete or partial response, 7/14 (50%) had stable disease, and 3/14 (21%) had progressive disease. Patients experienced minimal to no symptomatic toxicity with this regimen.

**Conclusions:** Hydroxyurea seems an active single agent in the treatment of aggressive fibromatosis. Larger studies are needed to examine its efficacy further, and to test it in combination with other known active agents against this difficult disease.
Conclusions: distant recurrences. 2 pts with recurrent disease had a local recurrence, and 5 pts had of 15 months, no pt with primary disease had a local recurrence, pelvic sarcomas (RPS).

Massachusetts General Hospital, Boston, MA, United States

Sahani; Edwin Choy; *David C. Harmon; *Thomas F. DeLaney Kobayashi; Andrew E. Rosenberg; G. Petur Nielsen; Dushyant V. *Sam S. Yoon; Yen-Lin Chen; *David G. Kirsch; Wendy K. SARCOMAS

RESECTION FOR RETROPERITONEAL AND PELVIC COMBINED WITH AGGRESSIVE ANTERIOR SURGICAL AND/OR INTRA-OPERATIVE RADIATION THERAPY

34806 - PROTON BEAM, INTENSITY MODULATED, or recurrent tumors. Tumors were large (median size 9.8 cm), primarily liposarcomas and leiomyosarcomas (73%), and mostly intermediate- or high-grade (79%). PBRT was given to 10 pts, IMRT to 9, and both PBRT and IMRT to 7 to a median dose of 50 Gy. Radiation was preferably given preoperatively (81%). Surgical resection included up to 5 adjacent organs/structures, most commonly colon (n=8) and kidneys (n=7). Margins were positive (usually posteriorly) in 14 pts (54%). IORT was delivered to the posterior margin in 12 patients to a median dose of 11.8 Gy. Radiation-related complications occurred in 3 pts (ureteral stricture, delayed bleeding, and fistula). After a median follow-up of 15 months, no pt with primary disease had a local recurrence, 2 pts with recurrent disease had a local recurrence, and 5 pts had distant recurrences.

Conclusions: Aggressive resection of RPS can result in a negative anterior margin. PBRT, IMRT, and/or IORT allow delivery of adequate radiation doses to the posterior margin to control microscopic residual disease with acceptable morbidity. This strategy may reduce local recurrence, especially in patients with primary disease.

Results: 26 pts have been treated with this strategy; 18 with primary and 8 with recurrent tumors. Tumors were large (median size 9.8 cm), primarily liposarcomas and leiomyosarcomas (73%), and mostly intermediate-or high-grade (79%). PBRT was given to 10 pts, IMRT to 9, and both PBRT and IMRT to 7 to a median dose of 50 Gy. Radiation was preferably given preoperatively (81%). Surgical resection included up to 5 adjacent organs/structures, most commonly colon (n=8) and kidneys (n=7). Margins were positive (usually posteriorly) in 14 pts (54%). IORT was delivered to the posterior margin in 12 patients to a median dose of 11.8 Gy. Radiation-related complications occurred in 3 pts (ureteral stricture, delayed bleeding, and fistula). After a median follow-up of 15 months, no pt with primary disease had a local recurrence, 2 pts with recurrent disease had a local recurrence, and 5 pts had distant recurrences.

Conclusions: Aggressive resection of RPS can result in a negative anterior margin. PBRT, IMRT, and/or IORT allow delivery of adequate radiation doses to the posterior margin to control microscopic residual disease with acceptable morbidity. This strategy may reduce local recurrence, especially in patients with primary disease.
normal karyotype but unresponsive to Ewing’s type therapy with a rapidly fatal outcome. All three infantile cases had non-metastatic disease at diagnosis with EWS/FLI by karyotype t(11;22)(q24;12) or RT-PCR. All three infants are alive without disease 2 to 6 years after diagnosis with Ewing’s sarcoma therapy.

Conclusions: Both congenital cases of ESFT died of disease? one patient with t(7;22) and cutaneous metastases after prolonged clinical course whereas the case with a normal karyotype and local disease only died rapidly. The t(7;22) in congenital ESFT may account for the different clinical course of disease. In contrast, three infantile cases with ESFT and EWS/FLI all had extra-osseous ESFT with favorable outcome.

34818 - [18-F] FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY OF LARGE LIPOMA-LIKE LESIONS PREDICTS FINAL PATHOLOGY.
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Objectives: Large lipoma-like lesions identified with Magnetic Resonance (MR) imaging are usually managed with surgical excision. Identifying those lesions with dedifferentiated areas pre-operatively would facilitate easier administration of radiotherapy and wide surgical margins. We imaged these patients with PET-CT pre-operatively and correlated the results with histopathology in order to determine if PET-CT is a reliable predictor of dedifferentiation.

Methods: Prospectively collected patients diagnosed with large (>8cm), deep adipose lesions on MR imaging, who were planned for surgical excision of the tumor were consented for a pre-operative PET-CT scan. The PET-CT results were compared to the histopathology results.

Results: Twenty patients will be collected and presented. An initial analysis of 9 patients with a total of 9 tumors includes 8 in the extremities and 1 retroperitoneal tumor. The median diameter was 12.5cm (range 8-27cm). The retroperitoneal tumor demonstrated very low grade FDG uptake on PET-CT with a maximum Standardized Uptake Value (SUV) of only 1.7 however, a small (2.5cm) area of de-differentiation was identified at histopathology, therefore the PET-CT was false negative in this case. Seven cases demonstrated none or mild FDG uptake and were confirmed to be lipoma-like liposarcomas (5) or simple lipomas (2). A hibernoma showed mild/moderate inhomogeneous hypermetabolism (SUV max 3.4).

Conclusions: While PET-CT is a useful diagnostic and staging tool in many tumor sites it is not routinely used for soft tissue lesions. We aimed to establish if PET-CT could identify high grade tumor areas within lipoma-like lesions pre-operatively, however, so far this does not seem to be the case.

34830 - AN ORTHOTOPIC HUMAN UTERINE SARCOMA XENOGRAFT MODEL TO STUDY NOVEL THERAPEUTICS: A POTENTIAL ROLE FOR COMBINED VEGFR/EGFR INHIBITION
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Objectives: Uterine sarcoma is a rare tumor comprising 3% of all uterine malignancies with limited prognosis due to frequent distant metastasis and lack of effective therapies. New approaches are urgently needed. Preclinical evaluation of relevant therapies requires currently unavailable reproducible human uterine sarcoma xenograft models. Our goal was to (1) establish an orthotopic uterine sarcoma mouse model and (2) test its utility in assessing a novel VEGFR/EGFR inhibitor (vandetanib; AstraZeneca) as potential therapy for this devastating malignancy.

Methods: Luciferase-expressing MES-SA human uterine sarcoma cells were implanted into uterine muscles (bioluminescence tumor growth assessment) or injected subcutaneously; tumor take and growth rates were compared. The orthotopic model so established was utilized in a four-armed therapeutic experiment: 1) control (vehicles only); 2) doxorubicin (1.2 mg/kg/biweekly, i.p.); 3) vandetanib (50mg/kg/d, gavage); and 4) doxorubicin+ vandetanib. Tumor growth was followed by BLI. Harvested tumors were analyzed using IHC.

Results: Direct injection of MES-SA into nude mouse uterine muscles resulted in high tumor take (88%) and enhanced growth, whereas subcutaneous injection resulted in minimal growth, suggesting microenvironmental tumor growth modulation. Vandetanib with/without chemotherapy significantly inhibited uterine sarcoma growth, induced apoptosis, abrogated tumor cell proliferation, and decreased angiogenesis.

Conclusions: Using a reproducible orthotopic uterine sarcoma xenograft model, we demonstrated possible microenvironment tumor growth modulation and efficacy of novel combined VEGFR/EGFR inhibition. Per this model, given the pressing need for better uterine sarcoma treatments, clinical evaluation of VEGFR/EGFR inhibition, with or without low dose chemotherapy, appears quite promising.

34841 - OSTEOSARCOMA OF THE PROXIMAL RADIUS IN MAZABRAUD’S SYNDROME
Eileen A. Crawford; John J. Brooks; Rachel L. Slotcavage; *Christian M. Ogilvie
University of Pennsylvania, Philadelphia, Pennsylvania, United States

Objectives: Mazabraud’s syndrome (MS) is a rare syndrome characterized by polyostotic fibrous dysplasia and intramuscular myxomas. Although MS is thought to have a higher incidence of malignant transformation than monostotic fibrous dysplasia, its rarity gives us only four reported cases of sarcomatous degeneration. Here we report a 5th case.

Methods: A 63 year-old man presented with a dull ache in his right forearm of 2 months duration. Initial imaging showed a benign-appearing, mixed lytic-sclerotic lesion spanning the length of the radius with cortical expansion and soft tissue extension. Biopsy revealed fibrous dysplasia containing a high grade osteoblastic osteosarcoma. Imaging of other sites demonstrated polyostotic fibrous dysplasia. Treatment involved resection of the proximal radius and involved soft tissues, reconstruction with an allograft-prosthetic composite (APC), and pre- and post-operative chemotherapy. Post-operatively, the patient regained hand strength and full elbow motion. Nine months after surgery, he reported ipsilateral shoulder pain. MRI of the site showed multiple, well-defined intramuscular masses with a characteristic myxoma appearance. Without known endocrine abnormalities, he was diagnosed with Mazabraud’s syndrome.

Results: The patient is currently without recurrence at 33 months post-operatively. There is evidence of graft resorption proximally, but with good radial head and hardware position.

Conclusions: This case represents the 5th reported incidence
of malignant degeneration of fibrous dysplasia in Mazabraud’s syndrome. The highly unusual location of the osteosarcoma in the proximal radius led us to use an APC for reconstruction, which is providing an excellent functional outcome. Continued monitoring for osteolysis will be necessary to ensure a good long-term outcome.

34853 - CONCURRENT OSTEOCHONDROMA AND OSTEOSBLASTOMA OF THE PROXIMAL HUMERAL SHAFT
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Objectives: We present what we believe is the first reported case of synchronous osteochondroma and osteoblastoma, occurring in the proximal humerus of a young man.

Methods: A 15 year-old male presented to orthopaedic oncology clinic with a painful left arm mass for 3 months. A firm mass was palpable in the proximal medial arm, and he had mild arm weakness secondary to pain. Imaging showed an eccentric lesion involving the proximal 1/3 of the humerus, with central lysis, surrounding sclerosis and edema, endosteal scalloping, and cortical thinning and expansion. The proximal medial diaphysis showed a bony growth with corticomedullary continuity, consistent with an osteochondroma. The cartilage cap was <5mm thick. Within the proximal portion of the osteochondroma was a 2cm rim-enhancing cystic lesion with edema, concerning for a secondary process such as malignant transformation. On open biopsy, the mass grossly appeared to be a sessile osteochondroma, which was removed with a rongeur. The cystic lesion was curedtted out of the bone.

Results: Pathology confirmed that the raised lesion was an osteochondroma. The cystic lesion contained osteoblasts in a matrix of osteoid and immature bone, characteristic of an osteoblastoma. The multidisciplinary team agreed that this was an osteoblastoma within an exostosis. At follow-up, his pain had fully resolved and radiographs showed good early healing.

Conclusions: We present this case to document the extraordinary, simultaneous existence of an osteochondroma and adjacent osteoblastoma in the proximal humerus of a young patient. Although similar in presentation, the tumors consist of cells of different origins making the pathogenesis unclear.

34872 - CORRELATION OF KARYOTYPE WITH FISH AND RT-PCR FOR DIAGNOSIS OF EWINGS SARCOMA (EWS) *Lynn Million; Phillip Barnette; *Lor Randall; *Cheryl Coffin; *Stephen L. Lessnick
Primary Childrens Medical Center and Huntsman Cancer Institute, Salt Lake City, UT, United States
Objectives: Molecular testing for EWS may be more reliable than standard tumor karyotyping. RT-PCR and FISH are sensitive and specific methods but each has limitations. Our objective is to compare these techniques as a diagnostic adjunct in EWS.

Methods: Molecular analysis of EWS was performed on 53 samples in 51 patients using an RT-PCR assay specific for EWS. Of these samples, 34 were also tested using FISH. 29 of these samples had karyotyping.

Results: RT-PCR showed 43/53 samples positive including 39 EWS-FLI, 3 EWS-ERG and 1 EWS-ETV1. FISH showed 26/34 samples positive for EWSR1 rearrangement. 34 samples had both RT-PCR and FISH testing; 23 both tests were positive, 4 both were negative, 3 only FISH positive and 4 only RT-PCR positive. Of 29 Karyotypes, 17 were normal but 15 tested positive for FISH and/or RT-PCR; 12 were abnormal, all tested positive for FISH and/or RT-PCR including 2 karyotypes with structural abnormalities but no translocation.

Conclusions: Karyotype may be least reliable genetic method to confirm EWS as over 85% of cases with a normal karyotype were positive for either FISH or RT-PCR. All translocations detected by cytogenetics were confirmed by either FISH or RT-PCR or both. Complex structural rearrangements without characteristic translocation on karyotype can be further classified by FISH or RT-PCR. These results emphasize the diagnostic utility of both FISH and RT-PCR in evaluation of potential EWS. We also recognize that only karyotypic analysis will identify chromosomal abnormalities that are not recognized by molecular tests, and should be strongly considered.

34873 - NEWLY DESCRIBED TRANSLOCATION IN ABDOMINAL WALL SOFT TISSUE TUMOR RESEMBLING EWING SARCOMA/PERIPHERAL NEUROECTODERMAL TUMOR
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Objectives: In Ewing sarcoma, the most common translocation partner is FLI1 located at 11q24, but rearrangements with other loci have also been reported. We describe a soft tissue sarcoma morphologically and immunohistochemically similar to Ewing sarcoma but with a novel translocation of t(18;19)(q23;q13.3).

Methods: A 15 year-old male presented with an abdominal wall soft tissue mass. Abdominal computerized tomography (CT) detected a non-specific, superficial, heterogeneous 2.5-3.0 cm mass. Complete staging failed to show any evidence of metastatic disease. The tumor was eventually widely resected. Complete histology, immunohistochemistry, FISH, and karyotyping were performed.

Results: Immunohistochemical studies were positive for CD99, vimentin and NB84a. No immunoreactivity was seen with synaptophysin, chromogranin, desmin, smooth muscle actin, Myo-D1, myogenin, CD3, CD20, CD45, CD30, CD31, CD34, TdT, ALK, S-100, pancytokeratin or EMA. FISH analysis showed that the tumor was negative for the EWSR1 break-apart rearrangement. Karyotype analysis identified a translocation between the long arms of chromosomes 18 and 19, t(18;19)(q23;q13.3).

Conclusions: This tumor is unique in that, to our knowledge, the translocation has not previously been reported and by the fact that the tumor itself morphologically and immunohistochemically resembled EWS/PNET but did not express the EWSR1 rearrangement. The findings of this case further suggest the presence of a tumor suppressor gene at either 18q23 or 19q13.3, or both.

34887 - WIDE RESECTION WITH RADIATION THERAPY OF EXTRA-ABDOMINAL DESMOID TUMORS
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Objectives: The approach to treatment of extra-abdominal desmoid tumors with surgical resection alone has resulted in control rates from 50-70%. The use of radiation therapy has shown a local control rate in some series up to 85%. The purpose of this study is to describe the effectiveness of resection-radiotherapy for extra-
abdominal desmoid tumors.

**Methods:** We performed a retrospective chart review of 25 consecutive patients who presented with a total of 28 extra-abdominal desmoid tumors. Patients were included if the following criteria was met: 1) histologically proven diagnosis of extra-abdominal desmoid tumor, 2) the lesion was resected with a wide margin allowing limb salvage, and 3) no contraindication to radiotherapy. Functional analysis of the limb was assessed using the Musculoskeletal Tumor Society (MSTS) scoring system.

**Results:** 17 patients with 19 tumors met the above criteria. Mean age at diagnosis was 23.6 years in 10:9 M:F ratio with a mean follow up of 3 years. Patients were followed with serial clinical exams & MRI of tumor sites. 6, 10, and 3 patients were treated with brachytherapy post-operatively, EBRT, or both respectively. Of the 16 patients with negative margins of resection, 2 suffered local recurrence and one of which had an extensive chronic history of intra- and extra-abdominal desmoids tumors. No other complications were noted in this series for a local control rate of 89.5%. The average MSTS score was 29/30 (96.7%).

**Conclusions:** The role of surgery, radiotherapy, chemotherapy, hormonal therapy, and other treatments for extra-abdominal desmoid tumors is not well defined. When a wide margin and radiotherapy can be performed with limb preservation surgery, our local control and complication rate compares favorably to most other methods.

**34892 - THE MEGAVOLTAGE RADIOTHERAPY IN TREATMENT OF 77 PATIENTS WITH ADVANCED/ DIFFICULT GIANT CELL TUMORS OF BONE (GCTB) - ONE-CENTER STUDY**

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**Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland**

**Objectives:** Radiotherapy can be used in treatment of GCTB patients who cannot be operated for medical reasons, technical difficulties, unacceptably disfiguring, locally resected because of tumor location or in recurrent cases. The aim of study was assessment of outcomes of radiotherapy in advanced/difficult GCTBs.

**Methods:** In group of 122 consecutive patients with histologically confirmed GCTB (years: 1985-2007), 77 cases, not feasible for conservative surgery, underwent megavoltage radiotherapy for tumor local control (median follow-up - 57months; 6-391). Clinical/pathological/radiological data retrospective analysis was performed for progression-free survival (PFS) and treatment morbidity.

**Results:** In irradiated group there were 35male and 42female, median age-28 years (16-69). Maximal tumors (femur-27, tibia-19, radial/ulnar bone-12, sacrum-9, pelvic bones-5, others-6) size ranged 5-18cm (median 8.5). 56 patients (73%) had not previous operation, 21(27%) were referred for local recurrence after >=1 operation. Median radiation dose was 56Gy (26-89Gy), administered at 1.8-2.0Gy/fraction (average treatment duration: 5-7weeks). 8 patients(10%) received total dose <50Gy. All patients tolerated treatment well without severe/chronic complications. 75/77 patients are alive at time of last follow-up. Local control was achieved in 64 patients(84%) [bone recalciﬁcation, joint functions restitution]. 13 patients showed local progression signs (within irradiated field), 9 treated successfully with salvage surgery. 5-year and 10-year local-PFS was 83% and 73%, respectively. Three patients developed lungs metastases(2-isolated, 1-simultaneously with local progression); 2-malignant transformation.

**Conclusions:** GCTBs can be safely and effectively treated with radiotherapy, 5-year local control rate >80%, similar to reports on smaller series. GCTB radiotherapy offers alternative to difficult, mutilating/complex surgery or option of choice in inoperable patients treatment.

**34905 - EVALUATION OF LONG TERM SURVIVAL IN HIGH GRADE OSTEOSARCOMA TREATED AT A SINGLE INSTITUTION**

*Piero Picci; Mario Mercuri; Stefano Ferrari; Antonio Briccoli; Marco Alberghini; Cristina Ferrari; Elettra Pignotti; Gaetano Bacci

*Istituto Ortopedico Rizzoli, Bologna, Italy**

**Objectives:** Analyze improvements in overall survival over 21 years (1982-2002), with a 5-year minimum follow-up, in the largest series from a single center ever reported, including all high grade osteosarcomas, despite histology varieties, age, site and stage. Data are also analyzed in subgroups to define patients who benefitted most.

**Methods:** 1656 new diagnoses were made. 198 cases were excluded (41 consultation only, 129 low-grade varieties and 28 lost). Within 1456 included patients, 1032 had characteristics to be enrolled in conventional clinical trials (classic histology, age < 41, localized and extremity disease).

**Results:** With a median follow-up of 12 years (5-25), 754 patients (51.7%) are alive, 613 continuously disease-free. Survival at 5, 10, and 15 years is 57%, 52%, and 51% respectively. Under age 41, with localized and extremity tumors have survival at 68%, 64%, and 61% respectively. In the other patients, survival is 30%, 25%, and 24% respectively. Trend (jointpoint statistical analysis at real 5-year follow-up) shows a yearly statistically significant improvement of 1.3%, from 51% for patients treated in 1982 to 68% for those treated in 2002. Patients who statistically benefitted were those who relapsed, or presented with metastatic disease at diagnosis, or had axial tumors. Surgery was also analyzed: with statistical significant improvement in percentage of limb salvages, local recurrences remained unvaried.

**Conclusions:** Despite the lack of new drugs for osteosarcoma, survival has statistically improved, especially for those patients with the worst outcome. Aggressive treatments are recommended for all patients including those with poor prognosis.

**34916 - EXHAUSTIVE AND PROSPECTIVE EVALUATION OF CONCORDANCE BETWEEN FIRST DIAGNOSIS AND SYSTEMATIC REVIEW BY EXPERT FOR SARCOMAS IN RHÔNE-ALPES REGION**

Antoine Lurkin1; Françoise Ducimetière1; Jean-Yves Blay7; Dominique Ranchère-vince1; Anne-Valérie Decouvelaere1; Dominic Cellier2; François Gilly3; Mathieu Laramas4; Pierre Biron2; Guy Delaroche2; *Isabelle Ray-Coquard1

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**Objectives:** Sarcomas are rare malignant tumors and accurate initial histological diagnosis is essential for adequate management. An exhaustive prospective study of the medical management of these patients was initiated to identify determinants of medical practices...
and realize a systematic comparison of initial histological diagnosis and a second opinion (SO) from regional and national experts of the disease.

**Methods:** Histological data of all diagnosed patients with sarcoma in the Rhône-Alpes region from March 2005 to Feb 2006 were collected. Primary diagnoses were systematically compared with SO performed by experts.

**Results:** Of 448 patients screened in this concordance study, 363 patients who complied with inclusion criteria were evaluated. Among patients included, 199 (54.8%) had total concordance (TC) to the SO with the primary diagnosis, 97 (26.7%) had partial concordance (PC) and 67 (18.5%) had total discordance (TD). The major reason of non conformity was the histological grading of these tumors (n=68, 19%), different histotypes (n=39, 11%), subtype (n=17, 5%) and grade + subtype or grade + histotype (n=40, 11%).

**Conclusions:** Sarcomas are well known by pathologists to be very difficult lesions to diagnose since more than 35% of first diagnoses were modified by the SO. Rapid and efficient help is necessary for primary pathologists in this rare disease, and a systematic second expert opinion seems essential.

Financial support: Merck Serono, Ain and Rhône region Cancer Ligues, CONTICANET network.

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**34920 - CT/ MRI FUSION AND INTENSITY MODULATED RADIOTHERAPY (IMRT) FOR MARGINALLY RESECTED PARASPINAL SOFT TISSUE SARCOMAS WITH METAL IMPLANTS**

Emma J Wells; Vibeke Nordmark Hansen; Chris P South; Christine WY Kong; *Frank H Saran

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**Objectives:** Infiltrative high risk paraspinal soft tissue sarcomas (hrPS_STS) treated with marginal resection and metal implants pose a challenge for radiotherapy. Image signal artefacts inhibit target volume and organ at risk (OAR) definition on conventional CT scans and curative radiation doses exceed the spinal cord tolerance.

**Methods:** Registered CT-MRI images were used for volume definition of patients with hrPS_STS treated with marginal excision and metal implants. The treatment aim is to deliver a curative dose while sparing the spinal cord, preventing long term damage. The tumour bed and relevant OAR were identified on MRI images which were registered with planning CT scans over a limited volume of interest, chosen to avoid misalignment effects caused by internal organ motion. All patients were treated with IMRT, enabling a reduction in received spinal cord dose to less than 50Gy.

**Results:** Four patients have been treated at the Royal Marsden Hospital with 50Gy in 25# to the extended tumour area. Three patients received simultaneous integrated boosts of 13Gy to the primary tumour volume; one received an 8Gy boost, limited by a previous single fraction of TBI. The patients were treated with 7-9 beams, three with Varian dynamic delivery and one with Elekta step and shot delivery.

**Conclusions:** Radical adjuvant radiotherapy is feasible in patients with hrPS_STS and metal implants when using CT/MRI registered images and IMRT. Acute toxicity was minimal and no late spinal cord morbidity has been recorded to date. This technique could offer long term local control in patients previously not considered conventionally treatable.

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**34933 - ADVANTAGE OF FISH ANALYSIS USING FKHR PROBES FOR AN ADJUNCT TO DIAGNOSIS OF RhabdomyosarcomaS**

Tadaki Matsumura1; Tadashi Hasegawa1; Takehiko Yamaguchi1; Kunihiko Seki1;

*Takuro Wada1; Toshihiko Yamashita1

1Sapporo Medical University School, Sapporo, Japan; 2Kanto Medical Center NTT EC, Tokyo, Japan; 3National Cancer Center Hospital, Tokyo, Japan

**Objectives:** Translocations can be detected using fluorescence in situ hybridization (FISH) in formalin-fixed paraffin-embedded (FFPE) tissues. Recently, a commercially available FKHR (13q14) dual colour, break-apart rearrangement probe has been developed. However, the advantages of using this probe have not been reported. This study demonstrated the usefulness of this probe for the clinical diagnosis of rhabdomyosarcomas (RMS).

**Methods:** We studied 33 RMS (19 embryonal rhabdomyosarcomas [ERMS], including three sclerosing-type RMS, and 14 alveolar rhabdomyosarcomas [ARMS]). We performed the FISH assay after confirming the most histologically typical areas using H&E stained sections. Fifty to sixty nuclei exhibiting both green and orange signals were counted using fluorescence images and IMRT. Acute toxicity was minimal and no late spinal cord morbidity has been recorded to date.

**Results:** Fluorescence signals were detected for 18 of the 19 (94.7%) ERMS and 13 of the 14 (92.8%) ARMS. A split-signal pattern was detected in 12 of 13 (92.3%) ARMS but was not detected in any of the ERMS, including the three sclerosing-type RMS.

**Conclusions:** We analyzed 33 RMS specimens using FISH and a commercial FKHR break-apart rearrangement probe. Our FISH study highlighted the excellent performance of the commercial break-apart probe for detecting rearrangements of the FKHR gene in RMS specimens. Amplification and polyploidy were detected in both ERMS and ARMS specimens, so care should be taken when...
counting the nuclear signals. No rearrangements of the FKHR gene were found in all three of the sclerosing-type RMS specimens when examined using the FISH assay, supporting the inclusion of sclerosing RMS in the ERMS category.

34941 - PRIMARY ANGIOSARCOMA OF BONE: REPORT OF TWO CASES INCLUDING A NOVEL TRANSLOCATION
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Objectives: Primary bone angiosarcomas are extremely rare, accounting for less than 1% of primary malignancies in bone. We present clinicopathologic analysis of two cases of primary bone angiosarcoma, one of which demonstrates a novel chromosomal translocation. In both cases other primary sites were ruled out by extensive radiographic workup.

Methods: Routinely processed hematoxylin and eosin sections were analyzed. Immunohistochemical studies were performed, using standard protocols to identify the cellular line of differentiation. Both cases were submitted for routine cytogenetic analysis.

Results: Angiosarcoma was diagnosed by open biopsy of a large infiltrative tibial lesion in a 79 year old woman. The vascular nature of the tumor was confirmed by positive endothelial immunostains (CD31, and CD34). Cytogenetic analysis showed a novel translocation: t(1;14)(p21;q24). The patient underwent tumor resection with oncologic prosthesis. With 9 months of follow-up, her tumor has not recurred. Angiosarcoma, epithelioid type was diagnosed by open biopsy of a S1-S5 sacral mass, in a 56 year old man. A cytogenetic abnormality was not demonstrated. The patient underwent four cycles of chemotherapy with doxorubicin and ifosfamide followed by radiation therapy for a total dose of 6600cGy in 33 fractions. Following chemotherapy, MRI showed marked decrease in tumor size and clinical improvement in pain. There has been no evidence of progression after 7 months.

Conclusions: We describe two primary bone angiosarcomas, one treated with surgical resection and the other with chemotherapy and radiation. To the best of our knowledge, we also report the first described cytogenetic abnormality in a primary bone angiosarcoma: t(1;14)(p21;q24).

34944 - FIBROMATOSIS IN A CHILD WITH TUBEROUS SCLEROSIS: TREATMENT RESPONSE TO SIROLIMUS.
*Joseph G Pressey; Rebecca Cook; Judy Pugh
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Objectives: A 7 year-old male with tuberous sclerosis (TS) was found to have a large recurrent thoracic wall mass and bilateral multifocal epithelial angiomylipomas. In an attempt to control tumor growth, the patient was treated with the mammalian target of rapamycin (mTOR) inhibitor sirolimus.

Methods: The patient was treated with twice daily oral doses of sirolimus, with levels generally maintained between 9 and 12 ng/ml. His response was measured radiographically by computed tomography (CT) and magnetic resonance imaging (MRI).

Results: Biopsy of the chest wall mass revealed a lesion characterized by a proliferation of spindle cells with bland oval to spindled, mildly to moderately pleomorphic nuclei and wavy, indented nuclei. Numerous thin fibrous fronds and whorls were noted. The lesion stained positive for CD31 and CD34. Following 3 months of therapy, the patient tolerated the therapy with minimal adverse effects.

Conclusions: An invasive chest wall fibromatosi tumor was detected in a child with tuberous sclerosis. His tumor regressed with sirolimus therapy. Our findings suggest a possible link between activation of mTOR and the development of fibromatosis. There may be a potential role for mTOR inhibitor therapy in sporadic fibromatosi.

34949 - DEFINITIVE RADIOTHERAPY FOR INOPERABLE, INTERMEDIATE AND HIGH GRADE RETROPERITONEAL SOFT TISSUE SARCOMA (RSTS)
Jose Luiz Fuser; Joseph Meirion Thomas; Andrew Hayes; Sue Ashley; Frank Saran
The Royal Marsden NHS Foundation Trust, London, London, United Kingdom

Objectives: To access toxicity and outcome for patients with inoperable high risk retroperitoneal sarcoma treated with definitive radical radiotherapy.

Methods: A retrospective audit of patients treated at the Royal Marsden Hospital between 1996 and 2008 was performed. All patient characteristics and treatment details were recorded. Progression free survival (PFS) and overall survival (OS) were calculated with last follow-up or death used to calculate overall survival.

Results: 20 patients (11 male, 9 female) with a median age of 59.5 years (22-84) were identified. All patients had a histopathologically proven inoperable intermediate to high grade rSTS. Patients received radical radiotherapy with a median dose of 54...
Gy (50-60 Gy) with a fractional size of 1.67 - 2 Gy. 17 patients were treated using 3D conformal CT planning. Mean gross tumour volume was 991.15 cm³ (123 cm³ - 2917 cm³), mean planning target volume was 2363.4 cm³ (719.87 - 5061.92 cm³). Acute toxicity greater than CTC grade 3 was recorded in 1 patient (Grade 4 skin ulceration).

Follow-up ranged from 1 to 54 months (median 12 months). The median overall survival for patients was 25 months (95% CI: 22-27). The median DFS for patients was 19 months and median DFS at any site 14 months (95% CI: 4-25).

Conclusions: These data suggest that patients with large, inoperable rSTS, not suitable for chemoradiation, derive a substantial clinical benefit from radically planned high dose radiotherapy. Treatment is well tolerated and should be considered for this patient group as a viable option.

34950 - AGGRESSIVE FIBROMATOSIS IN CHILDREN AND ADOLESCENTS
Cristina Meazza1; Gianni Bisogno2; Alessandro Gonchi1; Marco Fiore3; Michela Casanova1; Francesca F avi1; Giovanni Ceccheto2; Modesto Carli2; Andrea Ferrari1
1Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; 2Clinica Universitaria, Padova, Italy

Objectives: We retrospectively analysed 94 patients (age 1 month-21 years, median 10 years; tumor site was: 38 extremities, 31 head-neck, 18 trunk, 7 intra-abdominal) treated for aggressive fibromatosis (AF), focusing on the role of systemic treatment.

Methods: Twenty-three patients underwent complete surgery (group I); 42 patients received incomplete surgery with macroscopic residual tumor (group II) and 5 subsequently had radiotherapy; 29 patients underwent biopsy or incomplete surgery with macroscopic residual tumor (group III) and, among them, 15 received systemic treatment, 9 delayed surgery and 1 radiotherapy.

Results: Disease-free survival and overall survival at 5-year were 44% and 99%, respectively. Local relapse occurred in 22% group I patients, 76% group II and 76% group III. Two out of 7 patients with abdominal disease died of tumor progression, while all patients with extra-abdominal AF were alive. Systemic treatment was given to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relapse. Response rate (complete + partial remission) was 40% in front-line and 50% to 15 group III patients as front-line, 34 at relase.

Conclusions: Local relapse did not change either the possibility to respond to systemic therapy or survival. Since disease control after marginal resection was similar to that observed in case of intralesional surgery/biopsy, primary surgical attempt would be indicated when complete (and non-mutilating) excision is considered feasible. Interesting responses to chemotherapy were reported.

34953 - ASSOCIATION OF A MISSENSE SINGLE NUCLEOTIDE POLYMORPHISM, CYST367ARG OF THE WRN GENE, WITH THE RISK OF BONE AND SOFT TISSUE SARCOMAS IN JAPAN
Robert Nakayama1; Akira Kawai2; Fumihiko Nakatani3; Hirokazu Chuman2; Yasuo Beppu3; Hiroo Yabe1; Teruhiko Yoshida3; Yoshiaki Toyama1; Hideo Morioka1
1Keio University School of Medicine, Tokyo, Japan; 2National Cancer Center Research Institute, Tokyo, Japan; 3National Cancer Center Hospital, Tokyo, Japan

Objectives: Although bone and soft tissue sarcomas (BSTSs) frequently occur in some hereditary cancer syndromes with germline mutations of DNA repair genes, genetic factors responsible for sporadic cases have not been determined. In the present study we undertook a case-control study and analyzed possible associations between the susceptibility to BSTS and the single nucleotide polymorphisms (SNPs) in DNA repair genes.

Methods: Genomic DNAs extracted from case and control peripheral blood leukocytes were genotyped by pyrosequencing. For candidate polymorphisms, we chose 50 non-synonymous missense SNPs, which we have previously been identified by resequencing 36 DNA repair genes among the Japanese population.

Results: In the first screening, we analyzed 240 cases and 685 controls and selected six SNPs at the significance level of P < 0.1 (Fisher’s exact test). The six SNPs were further analyzed in the second genotyping on an additional set of 304 cases and 834 controls. In the joint analysis (the first and second genotyping combined) of 544 cases and 1378 controls, Cys367Arg of the WRN gene was found to be a protective factor of BSTS (odds ratio = 0.66, 95% confidence interval = 0.49-0.88, P = 0.005).

Conclusions: Our findings on the WRN SNP on BSTS may add another example of the possible sharing, at least in part, of the oncogenesis pathway between the monogenic and polygenic forms of the same type of cancer and a continuity of the genotype-phenotype spectrum.

34966 - THE ROLE OF ADJUVANT PELVIC RADIOThERAPY IN RESECTED NON-METASTATIC UTERINE LEIOMYSARCOMA: A SINGLE CENTRE EXPERIENCE
Julia Hall; *Beatrice Seddon
University College Hospital, London, United Kingdom

Objectives: We assessed the value of adjuvant pelvic radiotherapy in patients with resected non-metastatic uterine leiomyosarcoma (ULMS). A recently published EORTC study has reported no benefit for radiotherapy for stage I-II disease. Our unit policy is to routinely treat only stage III/IVA disease.

Methods: Women with resected FIGO stage I-IVA ULMS treated on a Sarcoma Unit were included. Time to progression (TTP) and overall survival (OS) were calculated and the effect of adjuvant radiation assessed.

Results: Twenty six patients with stage I-IVA ULMS were seen over five years. Median age at presentation was 54 (37-68) years. Eighteen (69.2%) had stage I disease, 3 (11.5%) stage II, 4 (15.4%) stage III and 1 (3.8%) stage IVA. Eighteen patients (69%) had grade 3 tumours. Seven (26.9%) received adjuvant pelvic radiotherapy: external beam radiotherapy with vault brachytherapy (6) and brachytherapy alone (1). Five stage I/II patients had radiotherapy for high risk disease; 3 stage III patients received no radiotherapy (previous pelvic radiotherapy, or rapid relapse after surgery). Median follow up was 19 (4-79) months. Local recurrence occurred in 0/5 and 1/2 patients with stage I/II disease and III/IVA disease treated with radiotherapy, and 6/16 and 3/3 patients with stage I/II and III/IVA disease without radiotherapy. Median OS (61 months) and TTP (16 months) were not significantly affected by radiotherapy (Table 1).

Conclusions: In this single centre series of patients with resected stage I-III/IVA ULMS, adjuvant radiotherapy appeared to be associated with fewer local recurrences, although it did not affect OS or TTP.
Table 1

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Disease Site</th>
<th>Treatment</th>
<th>Follow-Up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral</td>
<td>Sarcoma</td>
<td>Brachytherapy</td>
<td>25 months</td>
<td>Improvement in referral time</td>
</tr>
<tr>
<td>No referral</td>
<td>Sarcoma</td>
<td>Brachytherapy</td>
<td>25 months</td>
<td>No improvement in referral time</td>
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</table>

Results: Brachytherapy with a high isodosis induced less fibrosis in group 1. macroscopically a more normal aspect of the muscle in group 1 compared to group 2. Microscopically quantification of extra cellular matrix was lower, and there was a smaller area of fibrosis and quantity of collagen in the group treated with the peptide. The immunohistochemistry showed a lesser rate of P-smad 2/3, CTGF and alpha-SMA in the treatment group. No side effects of the peptide were seen.

Conclusions: P144 reduces the radiation-induced fibrosis. This peptide opens a new way of treatment to reduce complications in cancer patients. Furthermore, the effect of this peptide in other difficult diseases such as fibromatosis should be explored.
**Objectives:** HLA class I displays endogenously processed peptides to CD8+ T lymphocytes and has a key role for host immune surveillance and anti-tumor immunotherapy. Therefore, we analyzed HLA class I expression and T cell infiltration in Ewing’s sarcoma family of tumors (ESFT).

**Methods:** Biopsy specimens from 32 ESFT patients were stained by immunohistochemical (IHC) study with the anti-HLA class I monoclonal antibody (EMR8-5). We classified 32 cases into three groups, negative (positive cells <5%), low (positive cells 5-50%), and high (positive cells >50%). The grade of infiltration of CD8+ T cells was also evaluated semiquantitatively by IHC study using anti-CD8 monoclonal antibody. Next, we analyzed correlations between HLA class I expression, clinicopathologic factors, and infiltration of CD8+T cells.

**Results:** Expression of HLA class I was negative in 4 tumors, low in 15 tumors, and high in 13 tumors. ESFT patients with low or negative expression of HLA class I showed significantly poorer survival than those with high expression of HLA class I. Intratumoral infiltration of CD8+ T cells were detected in 29 of 32 (90.6%) cases to various extents. There was a statistically significant relationship between the extent of infiltrating CD8+ T cells and the degree of HLA class I expression.

**Conclusions:** These results suggested that CD8+ T cell-mediated immune response restricted by HLA class I might play an important role in immune surveillance of patients with ESFT.

**34998 - PROSPECTIVE INCIDENCE OF SARCOMA AFTER SYSTEMATIC REVIEW OF PATHOLOGICAL DIAGNOSIS: NEW FINDINGS.**

Françoise Ducimetiere1; Antoine Lurkin1; Dominique Ranchere-Vince1; Anne-Valerie Decouvelaere1; Luc Istier2; Christine Muller3; Marie-Georges Roux-Gilly4; Sylvie Isaac5; Catherine Herve-Nicoll6; Catherine Claret-Tournier6; Laurent Alberti1; Pierre-Paul Ciapa1; Thierry Cruel6; Ariane Economides-Jarsaillon1; Pierre Terdjman7; *Jean-Yves Blay8; *Isabelle Ray-Coquard9

1Centre Leon Berard, Lyon, France; 2University Jean Moulin, Lyon, France; 3Institut de Cancerologie de la Loire, Saint Priest en Jarez, France; 4ARCERRA Children Cancer Registry, Saint-Etienne, France; 5Private Pathology Laboratory, Grenoble, France; 6Private Pathology Laboratory, Pringy, France; 7Private Pathology Laboratory, Pringy, France; 8Private Pathology Laboratory, Lyon, France; 9University Hospital, Lyon, France

**Objectives:** It has been shown that cancer distribution varies from one country or one region to another and is widely dependent on the environment. Sarcomas are rare cancers with a broad range of subtypes, and their etiology remains unknown. This study aimed to describe the spatial distribution of sarcomas and identify risk areas within a French region of 6 million inhabitants.

**Methods:** A prospective and exhaustive collection of new sarcoma cases was performed within the pathologists’ network of the Rhône-Alpes region. All patients from the region diagnosed with sarcoma between March 2005 and February 2006 were included. The geographical distribution of the patients was mapped by health geographers, using the INSEE codes of the patients’ home town at the time of diagnosis.

**Results:** 376 patients meeting the inclusion criteria were included. A general map of all sarcomas taken together seemed to show a higher density of cases in urban areas and in the north of the region. Spatial discrepancies appeared when considering subtypes separately. GIST (gastrointestinal stromal tumor) distribution specifically superposed with urban areas, while leiomyosarcomas were more homogeneously distributed over the whole area.

**Conclusions:** Urban areas seem to be particularly associated with sarcoma, thus raising the question of risk factors inherent in the urban environment. Variations of medical practices could be an explanation for the over incidence of urban cases. Additional data and further comparison with other regions are required.

Supported by Merck Serono, CONTICANET project, Ligues Ain Rhône.
35002 - MEASURING INTERFRACTION AND INTRA-FRACTION MOTION WITH CONE BEAM COMPUTED TOMOGRAPHY (CBCT) AND AN OPTICAL LOCALIZATION SYSTEM (OLS) FOR LOWER EXTREMITY SOFT TISSUE SARCOMA PATIENTS TREATED WITH PREOPERATIVE INTENSITY MODULATED RADIATION THERAPY (IMRT)

Colleen I Dickie-Euler 1; Amy Parent 1; Anthony Griffin 2; Jay Wunder 1; Peter Ferguson 1; Peter Chung 1; Charles Catton 1; Brian O'Sullivan 1
1The University Health Network Princess Margaret Hospital, Toronto, Ontario, Canada; 2Mount Sinai Hospital University Musculoskeletal Oncology Unit, Toronto, Ontario, Canada

Objectives: To evaluate residual positional and out of plane rotational errors for lower extremity soft tissue sarcoma patients using Image-Guided IMRT.

Methods: 29 patients receiving IMRT were scanned with a pre-treatment CBCT. Any deviation >3mm from the planned isocenter was recorded. Mean residual set-up uncertainties and out of plane rotations were calculated in the left-right (LR), supero-inferior (SI), and postero-anterior (AP) dimensions. Intrafraction motion was assessed using the OLS system combined with pre and post fraction CBCT scans performed for 14 of the 29 patients once per week. The OLS system consists of an infrared emitting camera, reflective markers placed on the patient, and software designed to interpret the reflected signal and record the marker position at a speed of 30 Hertz. The displacement was calculated for the OLS markers and the pre and post fraction CBCT scans. The overall error was calculated for PTV margin calculation.

Results: The mean SD of the residual random error (RE) and the systematic error (SE) SD, the average out of plane rotation, the mean displacement of the OLS markers, and the max positional displacement for pre and post fraction CBCT scans support a 4mm LR, 5mm SI and 4mm AP PTV margin using the formula derived by van Herk. Refer to Table.

Conclusions: The largest RE, SE and rotation was seen in the SI direction, which may have implications for the quantification of non-uniform PTV margins. Due to their small magnitude, intrafraction motion and out of plane rotations were not a significant concern in margin design.

Results for Positional Error

<table>
<thead>
<tr>
<th></th>
<th>Left-Right</th>
<th>Supero-Inferior</th>
<th>Postero-Anterior</th>
</tr>
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<tbody>
<tr>
<td>Residual Positioning Error (SD)</td>
<td>1.9 mm</td>
<td>2.1 mm</td>
<td>1.8 mm</td>
</tr>
<tr>
<td>Systematic Positioning Error (SD)</td>
<td>0.8 mm</td>
<td>1.3 mm</td>
<td>0.9 mm</td>
</tr>
<tr>
<td>Out of Plane Rotation (degrees)</td>
<td>1.1 degrees</td>
<td>2.1 degrees</td>
<td>0.8 degrees</td>
</tr>
<tr>
<td>Max Displacement OLS Markers</td>
<td>0.9 mm</td>
<td>1.3 mm</td>
<td>1.3 mm</td>
</tr>
<tr>
<td>Max Displacement for pre and post CBCT scans</td>
<td>1.0 mm</td>
<td>0.2 mm</td>
<td>0.1 mm</td>
</tr>
<tr>
<td>PTV Margin</td>
<td>4 mm</td>
<td>5 mm</td>
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35003 - OSTEOSARCOMA, HYPOCALCEMIA AND 22Q11.2 DELETION SYNDROME

Francis J Mussai 1; Constantine A Stratakis 1; Robert M Henshaw 2; 1Lee J Helman 1; Diane C Arthur 1; Su Young Kim 1
1National Institutes of Health, Bethesda, MD, United States

Objectives: Hypocalcemia is a rare complication of osteosarcoma, having been described in only four case reports. We present the case of a patient with metastatic osteosarcoma, severe hypocalcemia and 22q11.2 deletion syndrome. Hemizygous microdeletion of 22q11.2 has been associated with a heterogeneous group of disorders that includes DiGeorge syndrome, velocardiofacial syndrome and others, many of which may be associated with hypocalcemia.

Methods: A 16-year-old male who presented with metastatic osteosarcoma and a massive lesion of the right humerus underwent palliative forequarter amputation followed by adjuvant chemotherapy. Pre-operatively, he was noted to have persistent refractory hypocalcemia, despite supplementation with 29 grams of calcium daily. This finding, in addition to the presence of a ventricular septal defect and short stature, led us to explore other etiologies for his hypocalcemia. Cytogenetic analysis of peripheral blood revealed a 22q11.2 microdeletion.

Results: The patient’s calcium level improved following amputation of the tumor-bearing extremity, but continued to remain low. This finding suggested that the etiology of his hypocalcemia was osteoblastic utilization of calcium by the primary tumor, exacerbated by 22q11.2 deletion syndrome. The presence of the CHEK2 gene in this chromosomal location is very interesting.

Conclusions: Activated CHEK2 is a checkpoint gene that stabilizes p53. CHEK2 is mutated in 4 of 57 (7%) sporadic osteosarcoma samples. The possibility that deletion of the 22q11.2 chromosomal region resulted in loss of heterozygosity of CHEK2 and subsequent development of osteosarcoma is an intriguing possibility. Further molecular analysis of our patient’s tumor sample may lead to a better understanding of the pathogenesis of osteosarcoma.

35004 - RADIOFREQUENCY ABLATION (RFA) OF PULMONARY METASTASES IS WELL-TOLERATED AND FEASIBLE IN PATIENTS WITH RELAPSED BONE AND SOFT TISSUE SARCOMA

Sandra J. Strauss 1; Alice Gilliams 1; Beatrice M. Seddon 1; Simon Jordan 1; George Ladas 1; William Lees 1; Jeremy S. Whelan 1
1University College Hospital, London, United Kingdom; 2Royal Brompton Hospital, London, United Kingdom

Objectives: Standard curative treatment of pulmonary metastases in patients with sarcomas is surgical resection but this is associated with morbidity and recurrence is common. Repeat metastasectomy is not routinely performed in specialist units, but other methods of tumour ablation are required for patients unsuitable for surgery.

Methods: Retrospective analysis of patients with relapsed sarcoma referred for RFA at a single centre.

Results: Eight patients aged 17-90 years (median 45), 4 with primary bone tumours and 4 with soft tissue sarcomas underwent RFA a median of 3.7 years (1.8-12) from diagnosis, after a median of 3 (1-5) recurrences and 1 (1-5) thoracotomies. Thirteen lesions 0.4-5.3 cm (median 1.6) were percutaneously ablated under CT fluoroscopic-guidance. Procedural complications included 2 asymptomatic pneumothoraces and 1 haemopneumothorax requiring drainage. One patient developed a temporary brachial plexus injury, and a 90 year old developed urinary retention. At the first outcome assessment at approximately 3 months, 10/12 (83%) evaluable lesions demonstrated no active tumour at site of ablation. Two patients had lesions with residual active tumour, and had progressive disease (PD) in the contralateral lung. One patient had PD outside the lung. With a median CT follow-up of 4 months (1-7), 1 further
A 57 year-old woman with biopsy-proven leiomyosarcoma of the inferior vena cava (IVC). CT and MRI of the abdomen revealed an IVC intravascular mass 5.5 x 4.4 cm in the transverse plane, and 7.7 cm in the craniocaudal dimension. The lesion started from the entrance of the renal veins and ended below the level of the hepatic veins. Preoperative radiotherapy with a total dose of 50.4 Gy was delivered using 4D CT, 5-field IMRT with combined full body stereotactic alignment and ultrasound-guided verification. 

**Methods:** A 57 year-old woman with biopsy-proven leiomyosarcoma of the inferior vena cava (IVC). CT and MRI of the abdomen revealed an IVC intravascular mass 5.5 x 4.4 cm in the transverse plane, and 7.7 cm in the craniocaudal dimension. The lesion started from the entrance of the renal veins and ended below the level of the hepatic veins. Preoperative radiotherapy with a total dose of 50.4 Gy was delivered using 4D CT, 5-field IMRT with combined full body stereotactic alignment and ultrasound-guided verification.

**Results:** The intra IVC mass was directly visible by US image guidance, thus allowing for an independent validation of the precision of the full body stereotactic target alignment via US imaging and, offering an opportunity to perform stereotactic US image guided shifts to tune the precision of delivery. The US image guided shifts for the 28 fraction treatment saw mean shifts of less than 3 mm in all three principle directions, indicating excellent precision for the daily full body stereotactic alignment. This technique proved consistently accurate for this particular patient, due to fortuitous limited interfraction motion for this particular patient/tumor combination, and it would be imprudent to assume such limited motion without imaging confirmation.

**Conclusions:** The unique combination of full body stereotactic alignment and stereotactic US image guidance for this case proved highly accurate, thus indicating the potential for future application in similar situations.

**35009 - COMBINED 4D IMAGING, FULL BODY STEREOTACTIC ALIGNMENT AND ULTRASOUND-GUIDED VERIFICATION FOR PRE-OPERATIVE RADIOTHERAPY OF LEIOMYSARCOMA OF THE INFERIOR VENA CAV A** 

*Ying Hitchcock; Robert Andtbacka; Bill Salter
Huntsman Cancer Hospital University of Utah, Salt Lake City, UT, United States

**Objectives:** 4D CT, Stereotactic Ultrasound Image Guidance represents a viable and effective image guidance tool for lesions of the upper abdomen.

**Methods:** A 57 year-old woman with biopsy-proven leiomyosarcoma of the inferior vena cava (IVC). CT and MRI of the abdomen revealed an IVC intravascular mass 5.5 x 4.4 cm in the transverse plane, and 7.7 cm in the craniocaudal dimension. The lesion started from the entrance of the renal veins and ended below the level of the hepatic veins. Preoperative radiotherapy with a total dose of 50.4 Gy was delivered using 4D CT, 5-field IMRT with combined full body stereotactic alignment and ultrasound-guided verification.

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**Conclusions:** The unique combination of full body stereotactic alignment and stereotactic US image guidance for this case proved highly accurate, thus indicating the potential for future application in similar situations.

**35023 - THE ROLE OF RADIOTHERAPY IN METASTATIC GASTROINTESTINAL STROMAL TUMOUR (GIST)**

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Royal Marsden Hospital, London, United Kingdom

**Objectives:** GISTs are rare malignancies characterised by KIT oncogene mutation. Surgery is the standard treatment for localised GIST. Imatinib has radically changed outcomes for patients with metastatic or unresectable tumours, but resistance does develop, and the benefit of second line treatment is limited. Radiotherapy is generally not considered a therapeutic option for symptomatic GIST. We aim to assess the role of palliative radiotherapy for locally progressive and / or symptomatic metastatic GIST.

**Methods:** A retrospective review was performed of 12 patients with recurrent or metastatic GIST who had received palliative radiotherapy at our institution between 2001 and 2008. A descriptive study of the indications, radiotherapy doses and clinical outcomes is presented.

**Results:** The primary tumour sites were: 4 small bowel, 3 gastric, 3 pelvic, 1 peri-anal and 1 unknown. Four patients received radiotherapy for bone metastases, 7 for intra-abdominal/pelvic disease, and 1 to the abdominal wall. Eleven of the 12 patients experienced clinically relevant symptomatic improvement. For intra-abdominal disease, the most commonly used regimen was 30Gy in 10 fractions. Treatment was generally well-tolerated, with most toxicities being grade 1-2.

**Conclusions:** It is traditionally perceived that GISTs are “radio-resistant”. Our experience suggests that radiotherapy can be useful for the palliation of symptomatic and progressive soft tissue disease, especially in the pelvis. It can be delivered with minimal toxicity and should be considered as a therapeutic option for selected patients.

**35025 - ACTIVATION OF PDGFRA, PDGFRB AND EGFR PATHWAYS IN SYNDROMIC AND SPORADIC MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS**

Federica Perrone; Alessandro Gronchi; Luca Da Riva; Marta Orsenigo; Marco Losa; Genny Jocolle; Clara Millefanti; Elisa Pastore; Marco alessandro Pierotti; Silvana Pilotti
 Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

**Objectives:** To investigate PDGFRA, PDGFRB and EGFR activation pathways in malignant peripheral nerve sheath tumours (MPNSTs).

**Methods:** PDGFRA, PDGFRB and EGFR were immunohistochemically, biochemically, cytogenetically and mutationally analysed in 16 neurofibromatosis type 1 (NF1)-related and 11 sporadic MPNSTs. The activation of the receptor pathways was also studied by means of RAS, BRAF, PI3KCA and PTEN mutational analysis, PI3KCA and PTEN fluorescent in situ hybridisation, and PTEN, AKT, ERK and mTOR activation / expression.

**Results:** PDGFRA, PDGFRB and EGFR were expressed/activated, with higher levels of EGFR expression/phosphorylation paralleling increasing EGFR gene copy numbers in the NF1-related cases (71%). Autocrine loop activation of these receptors was suggested by the expression of the related cognate ligands in the absence of receptor mutations. No BRAF, PI3KCA or PTEN mutations were found in either group of MPNSTs, but 18% of the sporadic MPNSTs showed RAS mutations. PTEN monosomy segregated with the NF1-related cases (50%, p=0.018), but PTEN protein was expressed in all but two cases. Both MPNST groups showed AKT, ERK and mTOR expression/phosphorylation.

**Conclusions:** PDGFRA, PDGFRB and EGFR seem to be promising molecular targets for tailored treatments in MPNST. EGFR activation, the low occurrence of RAS mutations in the absence of BRAF, PI3KCA and PTEN mutations/loss, strongly support anti-EGFR treatment for sporadic MPNSTs, whereas neurofibromin loss-mediated RAS activation in the presence of high levels of the EGFR expression/activation and PTEN monosomy in NF1-related cases may provide a rationale for anti-MAPK or -AKT treatment, in addition to the use of anti-EGFR inhibitors.
Conclusions: Adjuvant radiotherapy to a dose of 60-66Gy is considered part of the standard management in high risk STS with local control rates in the range of 75-85%. Radiotherapy is not routinely offered to STS in retroperitoneal sites due to the limited radiation tolerance of surrounding organ at risks (OAR) resulting in local control rates in the range of 10-30% following surgery alone. The aim of this study was to assess the feasibility to deliver radical radiotherapy to a dose of 60Gy using intensity modulated radiotherapy (IMRT).

Methods: Five patients were planned using conventional conformal simultaneous boost radiotherapy and IMRT. A 3D margin of 2 cm was added to the primary tumour bed, to achieve PTV1 and a 0.7 cm margin was added to achieve PTV2. Kidney, spinal cord, bowel and liver were outlined to compare the OAR doses between the two plans. Dose prescriptions were 45Gy/25# to PTV1 and 57Gy/ 25# to PTV2 (biologically equivalent to 60Gy/30#).

Results: The IMRT plans demonstrated a superior conformity while significantly reducing the dose to OAR especially bowel, when compared to conventionally 3D conformal plans. Specifically, all Grade 2 bowel dose constraints that were not met by simultaneous boost were met by IMRT plans for all 5 patients (see Figure1). The mean volume of bowel receiving a dose of 50Gy or more was reduced by 65% in IMRT plans when compared to conventionally planned conformal boost plans.

Conclusions: Adjuvant radical radiotherapy to a dose of 60Gy can be considered in patients with high risk rSTS using IMRT while staying within OAR dose volume constraints. This technique may even allow further dose escalation and should improve local control and thus potentially survival.

Figure1

35028 - PARAVERTEBRAL METASTASES IN MYXOID LIPOSARCOMA OF LOWER EXTREMITIES
Sebastian Fehlberg; Dimosthenis Andreou; Carmen Tiedke; Carmen Tiedke; Mathias Werner; Daniel Pink; Peter Reichardt; Per-Ulf Tunn
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Objectives: Soft tissue sarcomas in general tend to metastasize to the lungs. Myxoid liposarcoma, the second most common subtype of liposarcoma, occurs predominantly in the extremities of young adults and has a disproportionately high tendency to metastasize to unusual sites in bone and soft tissue. We chose to investigate this in our patient population, in particular the incidence of paravertebral metastases.

Methods: In a retrospective study we investigated the incidence of paravertebral metastases and correlated this endpoint with clinicopathological findings.

Results: From 1993 to 2008, 82 patients; 45 men (54.9%) and 37 women (45.1%) with a median age of 48.5 years (range, 18-79 years) were diagnosed with a myxoid liposarcoma. At the time of diagnosis 37 tumors (45.1%) were classified as pure myxoid liposarcoma, while in 45 tumors a round cell morphology was detected. In 26 patients (31.7%) primary and secondary metastases were detected with a median interval of 19 months (range, 1-350 month). Thirteen patients (15.4%) developed paravertebral metastases, comprising 50% of all metastatic events. In these patients the primary tumor was diagnosed as a low-grade myxoid liposarcoma in three patients (23.1%) and as a high-grade myxoid liposarcoma with round cell morphology in ten patients (76.9%).

Conclusions: These findings suggest that myxoid liposarcoma has an uncommonly high incidence of paravertebral metastasis. Screening and follow-up of myxoid liposarcoma patients should include images of the spine and paraspinal tissue to identify metastatic disease at this site.
**Objectives:** Although desmoid tumours, also called aggressive fibromatosis, are histologically benign, they exhibit a locally malignant behaviour and are notorious for a high incidence of local recurrence. The experience of a single institute is reviewed to determine the risk factors for local disease recurrence and progression.

**Methods:** Retrospectively, 147 patients were identified to have been treated for recurrent or residual desmoid tumours in our institute during the last 35 years. Potential prognostic factors for local tumour control failure, including gender, age (with various cut off points), size (with various cut off points), presentation (primary or recurrent), site (extremities, head and neck, abdominal wall, other trunk or intra-abdominal), treatment (surgery only, radiotherapy only, surgery plus radiotherapy or other) and margins (positive or negative), were analyzed for their significance using the log-rank test for Kaplan-Meier time to local tumour control curves.

**Results:** After a median follow-up period of 86 months (mean 102, 1-327) the overall 5- and 10-years local tumour control rate were 87% and 85%, respectively. Gender, age, presentation and treatment were not of prognostic significance. Positive margins (p=0.015) as well as extremity and intra-abdominal localizations (p=0.043) were associated with increased probability of tumour recurrence or progression. There was a trend for tumours larger than 6 cm (p=0.091) to be associated with worse local tumour control.

**Conclusions:** Various local treatment modalities provide local disease control in the majority of cases (87% at 5 years). Positive margins and extremity or intra-abdominal localizations were associated with the highest probability of tumour control failure.

**35054 - POTENTIAL UTILITY OF CD5 IMMUNOHISTOCHEMICAL STAIN IN THE DIAGNOSIS OF MUSCULAR TUMORS**

Patricia Moody Mcnab, MD; Nicole M DeMers, MD; Scott M Schlauer, MD; *Marilyn M Bui, MD, PhD

**University of South Florida, Tampa, Florida, United States**

**Objectives:** CD5 is a glycoprotein receptor that presents on a variety of lymphocytes and is routinely used for the diagnosis of lymphoid malignancies. This pilot study evaluated the CD5 expression pattern by immunohistochemical study in the formalin fixed and paraffin embedded tissue of benign and malignant muscular tumors in comparison with normal muscular tissue counterparts to explore the potential utility of CD5.

**Methods:** A retrospective computer assisted query of a tertiary care cancer center identified the following cases: leiomyoma (10), rhabdomyoma (3), leiomyosarcoma (33), and rhabdomyosarcoma (9). Additionally, non-neoplastic smooth muscle tissue (10) and skeletal muscle tissue (6) are identified within the tissue. Immunohistochemical analysis was performed on unstained slides of formalin fixed paraffin embedded tissue blocks using a CD5 monoclonal antibody (Clone 4C7, Cell Marque, Hot Springs, AR) with appropriate controls following the manufacture’s recommendation. Positive immunoreactivity to CD5 is determined as 2+ (moderate) to 3+ (strong) cytoplasmic staining.

**Results:** CD5 is strongly and diffusely positive in non-neoplastic skeletal (6/6) and smooth (10/10) muscle. CD5 is negative in rhabdomyoma (3/3), rhabdomyosarcoma (6/6) and high-grade leiomyosarcoma (27 cases). Leiomyomas (10/10) are CD5 positive but exhibit variable intensity within the same tumor. Low-grade leiomyosarcoma (6/6) has variable CD5 expression pattern.

**Conclusions:** CD5 proven to be a useful stain with minimal background interference and high specificity in muscular tissue and may be used to differentiate benign muscular tissue from malignancy. Albeit a limited case series, this study demonstrates the potential utility of CD5 in the diagnosis of muscle tumors.
233) and GST (41-1940, 1134+/– 501). Unsupervised hierarchical clustering separated the tumors into 4 distinct groups, which were compared to survival. One of these groups appeared to have a worse prognosis when compared to the other three groups. The main discriminators were CYP3A and GST.

Conclusions: Our results demonstrate a robust quantitative immunofluorescence method for measuring the relative concentrations of proteins in tumor cells. Although, this study is small, our results suggest that CYP3A and GST may represent prognostic factors. Further studies with a larger cohort are therefore suggested.

35078 - IMMUNE MEDIATED MECHANISMS IN EWINGS SARCOMA (ESFT)
*Carolyn R. Hoban; Michael Smith; *Dafydd G. Thomas; *David R. Lucas; Kenneth Pienta; *Laurence H. Baker
University of Michigan, Ann Arbor, MI, United States

Objectives: Primary or metastatic tumor sarcoma may arise in distinct microenvironments (bone or soft tissue). In sarcomas and other tumor types involving stromal reactions, angiogenic factors and immune networks provide a rich environment for tumor growth. Recent work by VandeRijn [CCR14(5):1423(2008)] showed a significant association between macrophage infiltration in non-gynecologic leiomyosarcomas and worse clinical outcome. In this study, we evaluated immune cell involvement in chemotherapy-naive ESFT patients and ESFT cell lines.

Methods: Tissue microarrays were probed by IHC for chemokine ligands, receptors and macrophage specific markers. ESFT cell lines were assayed for proliferation and apoptosis.

Results: Macrophage and monocyte infiltration was evident by IHC detection in tissue microarrays of ESFT. Intensely (IHC score 3+) stained, CD68 positive cells were predominantly located at the border between tumor cells and stromal tissue. Gene expression and analysis of proteins secreted into conditioned media show that ESFT cell lines express chemokine receptors and secrete chemokines. Direct chemokine stimulation of ESFT sarcoma cell lines in vitro resulted in proliferation. Treatment with antibodies to human macrophage chemoattractant protein (MCP1) blocked proliferation by 40-60% in several ESFT cell lines examined in vitro.

Conclusions: Immune cells (macrophage/monocytes) were detectable in Ewings sarcoma tumors. ESFT cell lines displayed a proliferative response to chemokines in vitro and secreted chemokines. These data suggest that ESFT tumors may recruit monocytes. Combination therapies aimed at both chemokine networks and tumor cell growth will be further explored. Supported by SARC Developmental Therapeutic grant program.

35084 - RESPONSE OF IMATINIB-RESISTANT EXTRA-ABDOMINAL AGGRESSIVE FIBROMATOSIS TO SUNITINIB
*Keith M. Skubitz; Jerry W. Froelich
University of Minnesota, Minneapolis, MN, United States

Objectives: Aggressive fibromatosis (AF) is usually a slowly growing locally invasive tumor, but may exhibit a much more aggressive phenotype. The role of chemotherapy in AF is not well defined, but can be useful in some cases.

Methods: We report a case of an aggressive extra-abdominal AF that was responsive to sunitinib but resistant to imatinib.

Results: A 23 year old woman developed painful multifocal AF of both legs and gluteal muscles that progressed on treatment with methotrexate/vinblastine, and pegylated-liposomal doxorubicin. She received 6 cycles of ifosfamide/etoposide (IMV), and obtained a good response with elimination of pain. Five months later she developed progression and again received 6 cycles of IMV, with elimination of symptoms. Thirteen months later, tumors recurred. Although the AF was symptomatic and progressing, she was hesitant to receive chemotherapy, and she began sunitinib 50 mg/d for 28 days of a 42-day cycle. At 4 months she could walk on her heels without pain. After 13 months of sunitinib, therapy was changed to imatinib 400 mg per day; after 7 days she noticed increasing pain in the AF lesions and decreased knee flexibility. Imatinib was continued, but at 2 months of imatinib, she could only walk a few steps due to pain. Sunitinib was begun at 50 mg/day, and symptoms improved within 1.5 weeks, with a marked reduction of symptoms at 1 month. Twenty-two months after initially beginning sunitinib she was doing well with a normal activity level.

Conclusions: We conclude sunitinib may be useful in some cases of AF.

35088 - DOES PRIOR CONTAMINATED RESECTION INCREASE LOCAL RECURRENCE FOR DESMOID FIBROMATOSES?
*Ernest U. Conrad; *Jason Weisstein
University of Washington, Seattle, WA, United States

Objectives: Desmoid fibromatoses are considered to be benign tumors, but are locally aggressive and have high local recurrence rates. Treatment approaches, which include surgery plus radiation therapy are controversial for the reduction of local recurrence and morbidity.

Methods: We have retrospectively reviewed our results with patients (N = 75) diagnosed with desmoid fibromatoses tumors from June 2001 to June 2008.

Results: These patients account for 4% of all the soft tissue tumors seen by our multidisciplinary sarcoma service. Of the patients who received all their treatment at our institution (N = 44), 70% were female (N = 31) with a median age of 36.5 (18-82) years at diagnosis. The majority presented in the extremity (N = 24, 32%), followed by the abdominal wall, retroperitoneum, and thorax (N = 12 each, 16%), the pelvis (N = 8, 11%), and lastly the spine (N = 7, 9%). Almost 91% (N = 40) were treated with surgical excision and of those 50% (N = 20) had positive surgical margins. Sixty-eight percent (N = 30) of the total treated group (N = 44) received adjuvant radiation therapy and of those treated 47% (N = 14) did not have a local recurrence, 16% had a local recurrence (N = 5) and the remaining 11 patients (37%) were lost to follow-up. In the group that did not receive radiation therapy, 42% (N = 5) did not have a local recurrence, one patient (8%) had a local recurrence and the remaining 6 (50%) were lost to follow-up.

Conclusions: A combination of radiation and surgery may improve local control, while prior contaminated resection does not seem to have an effect on local control based on this preliminary dataset.

35093 - DESMOIDS TUMORS: USING PET IMAGING TO DISTINGUISH RISK OF RECURRENCE
*Ernest U. Conrad; *Jason Weisstein; *Janet F Eary
University of Washington, Seattle, WA, United States

Objectives: Desmoid tumors have variable aggressive behavior with respect to local recurrence. [F-18] - FDG PET imaging may provide another means of evaluating tumor behavior preoperatively.

Methods: We have retrospectively reviewed our results with
Using Deformation Image Registration in Two Pathological Subtypes of Sarcomas.

**Results:** The mean age and local recurrence was similar between two study groups separated by time, Cohort 1: 1982-1998 and Cohort 2: 2001-2007. Local recurrence was similar between both cohorts, 27% vs. 22%. However, when divided by three treatment groups local recurrence with surgical resection only was 47% (cohort 1) and 30% (cohort 2) vs. surgical resection + radiation therapy was 19% (cohort 1) and 25% (cohort 2). In Cohort 1 patients were treated with radiation therapy 64.6% of the time and in Cohort 2, 61.4% of the time. Anatomic location and patient ages had similar distribution in both groups. A subset in Cohort 2 were imaged using [F-18] FDG (N=12) with correlation to local recurrence.

**Conclusions:** Patients with higher SUVmax had a trend toward a higher risk of local recurrence and a shorter interval in time to recurrence. PET imaging may be useful in evaluating the risk of recurrence for desmoids tumors.

This work is supported by NIH/NCI CA R01 65537.

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**35109 - RETROSPECTIVE STUDY OF VOLUME CHANGES IN TWO PATHOLOGICAL SUBTYPES OF SARCOMAS USING DEFORMATION IMAGE REGISTRATION**

Kara Magierowski1; Joanne Moseley1; Gina Lockwood1; Amy Parent1; Colleen Euler1; Michael Sharpe1; Anthony Griffin1; Kristy Brock1; *Charles Catton1; *Brian O’Sullivan1

1Princess Margaret Hospital, Toronto, Ontario, Canada; 2Mount Sinai Hospital, Toronto, Ontario, Canada

**Objectives:** Radiotherapy (RT) and limb salvage surgery are important in the management of extremity soft tissue sarcomas (STS). Clinical evidence suggests varied radiation responses for different pathologic subtypes of sarcomas. Quantitative analysis of data is necessary to support these findings. The study objective is to perform deformation image registration to quantify tumour volume changes in Myxoid Liposarcomas (MLS) and Malignant Fibrous Histiocytomas (MFH) for patients receiving pre-operative radiotherapy.

**Methods:** Twenty patients enrolled in an ongoing IMRT (pre-op 50 Gy) trial with lower extremity MLS (n=10) and MFH (n=10) STS were selected for this study. The gross tumour volume (GTV) and bone were contoured on pre and post RT computed tomography (CT) or magnetic resonance image (MRI) datasets using a 3D Pinnacle planning system. A radiation oncologist reviewed all GTV contours. Tumour volumes pre and post RT were calculated in Pinnacle based on contours. MORFEUS, a finite element model-based multi-organ deformable registration platform resolved the geometric discrepancies between pre and post contours and subsequently measured tumour response in the left/right (LR), anterior/posterior (AP) and superior/inferior (SI) directions.

**Results:** See table below.

**Conclusions:** Deformation image registration was valuable in assessing sarcoma GTV changes. The greatest change occurred in the SI direction for both MLS and MFH patients. Overall, MLS had a 51% median reduction and MFH had an 11% median growth post radiotherapy. These changes were not statistically significant due to the small sample size. Further investigation is required to examine the dosimetric implications of GRTV response during the course of treatment.

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>Median Volumes Pre-RT</th>
<th>Median Volumes Post-RT</th>
<th>Change in Plane LR</th>
<th>Change in Plane AP</th>
<th>Change in Plane SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLS</td>
<td>98 cm³ [62 to 146]</td>
<td>62 cm³ [23 to 90]</td>
<td>-0.40 cm [-0.81 to 0.25]</td>
<td>0.09 cm [-0.44 to 0.23]</td>
<td>0.35 cm [-0.90 to 0.66]</td>
</tr>
<tr>
<td>MFH</td>
<td>338 cm³ [140 to 580]</td>
<td>378 cm³ [152 to 886]</td>
<td>0.11 cm [-0.21 to 0.31]</td>
<td>0.25 cm [0.04 to 0.45]</td>
<td>1.10 cm [-0.02 to 1.63]</td>
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**35110 - ENDOMETRIAL STROMAL SARCOMA WITH 6P21 (BUT NOT 7P15) REARRANGEMENT MAY CHARACTERIZE A MORPHOLOGICALLY DISTINCT SUBGROUP**

*Paola Dal Cin; Bradley J. Quade; Marisa R. Nucci

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**Objectives:** Low grade endometrial stromal sarcoma (LGESS) typically resembles normal endometrial stroma; however, it may exhibit smooth muscle, sex-cord like, and fibrous differentiation. The most common cytogenetic abnormality is the t(7;17)(p15;q21) resulting in JAZF1-JJAZ1 fusion. Rearrangements of PHF1 at 6p21, however, have been reported. We sought to determine whether LGESS with 6p21 aberrations were associated with a different morphologic phenotype.

**Methods:** LGESSs identified intraoperatively were submitted for cytogenetic analysis, and FISH analysis for rearrangements of JAZF1 at 7p15 and PHF1 at 6p21 were performed if the t(7;17)(p15;q21) was not identified.

**Results:** 5 cases with 6p21 rearrangement were identified. FISH analysis with JAZF1 and PHF1 probes demonstrated that 3/5 cases exhibit a variant t(6;7)(p15;q21) consistent with involvement of JAZF1 and PHF1; these have a classic histologic appearance. The 2 tumors negative for JAZF1 involvement by FISH had an unusual histologic appearance. One had limited infiltration of the myometrium and lacked the typical permissive growth pattern, whereas the other was widely metastatic to the peritoneum, had the typical growth pattern, but a striking histologic phenotype with epithelioid and smooth muscle differentiation.

**Conclusions:** In those tumors with involvement of PHF1 and JAZF1, the histologic appearance is similar to the classic morphology associated with JAZF1/JJAZ1 fusion. Interestingly, 2 cases with involvement of 6p21 but not 7p15 had an unusual appearance suggesting that the partner gene(s) of 6p21 not yet identified may be influencing their morphology, and potentially, behavior (viz limited infiltration vs metastasis).

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**35114 - DEGENERATION OF BENIGN CARTILAGE TUMORS: DIAGNOSIS AND PROGNOSIS**

Gerard Delepine; Salwa Alkhallaf; Helene Cornille; Nicole Delepine

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**Objectives:** In our records on bone tumours, secondary chondrosarcomas account for less than 15% of chondrosarcomas (23/150). We reviewed our experience to evaluate diagnosis, frequency, and prognosis.

**Methods:** From 1981, we treated 23 chondrosarcomas developed on pre-existing lesions: solitary exostoses (13), solitary chondroma (1), multiple exostosis (7), multiple enchondromatosis (2). Localisations: pelvis (11), femur (3), humerus (2), tibia (3), spine (2), scapula (1)
fibula (1). Histological classification: grade I (9), grade II (10), grade III (1), dedifferentiated sarcoma (3). Surgery was performed in all.

**Results:** At last FU (mean 13 years 9 months), six patients died after local recurrence (4) or metastatic dissemination (2). The other 17 were living (mean FU 182 months). The main prognostic factor was histological grade. All patients with grade I (7) survived versus only two-thirds of those with grade II and half (2/4) of those with grade III or dedifferentiated chondrosarcoma. The second prognostic factor was initial management. Inadequate care initially led to misdiagnosis or delayed diagnosis (4), local recurrence (3) loss of chance of survival (3). Grade I was occasionally taken for benign exostosis.

**Conclusions:** Because of the severity of secondary dedifferentiated chondrosarcoma, resection should be performed in adults presenting exostosis with a large residual cartilage cuff, particularly in high-risk locations (pelvis). Because of difficulty in recognising histological features of grade I chondrosarcoma, diagnosis of degeneration should be retained in adults if cartilage cuff exceeds 1 cm. Lesions are suspicious if the cartilage cuff exceeds 5 mm.

35118 - PET/CT FOR RADIOTherapy TREATMENT PLANNING IN PATIENTS WITH SOFT Tissue SARCOMAS

Irene Karam; Slobodan Devic; Marc Hickeger; David Roberge; Robert E Turcotte; Carolyn R Freeman

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**Objectives:** To study the possibility of incorporating positron emission tomography/computed tomography (PET/CT) information into radiotherapy treatment planning in patients with high-grade soft tissue sarcomas.

**Methods:** We studied seventeen patients treated with pre-operative radiotherapy at our institution from 2005 to 2007. All patients had a high-grade soft tissue sarcoma and had had a staging PET/CT scan. For each patient, an MRI-based gross tumor volume was outlined on a T1-gadolinium enhanced axial MRI (GTVMRI) and a set of gross tumor volumes were outlined using different threshold values on PET images (GTVPET). PET-based target volumes were compared to the MRI-based gross tumor volume, considered to be the contemporary standard for radiotherapy treatment planning. Threshold values for target contouring were determined as a multiple (from 2 to 10 times) of the background soft tissue uptake values (B) sampled over healthy tissue.

**Results:** PET-based GTVs contoured using a threshold value of 2 or 2.5 most closely resembled the GTVMRI volumes. We observed relatively large standard deviations between the average volumes of GTVPET and GTVMRI ratios for all thresholds, ranging from 36% for the 2 x B up to 93% for the 10 x B segmentation methods.

**Conclusions:** It is unlikely that PET/CT will make a significant contribution in GTV definition for radiotherapy treatment planning in patients with STS using threshold methods on PET images. Future studies will focus on molecular imaging and tumor physiology.

35126 - CASTLEMAN DISEASE PRESENTING AS A FOREARM MASS

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**Duke University Medical Center, Durham, NC, United States**

**Objectives:** Raise awareness of Castleman’s disease, a rare lymphoproliferative disorder typically presenting as a mediastinal mass, as a possible cause of extremity soft-tissue tumor.

**Methods:** A 76 yo woman was referred with a several month history of a 6.5 cm mass in her left volar forearm which was mildly painful. X-rays show a soft-tissue mass with scattered calcifications. MRI showed an heterogenous high T1 signal lesion which was hypointense to normal muscle on T2 weighted imaging. An 18F-FDG PET CT showed uptake in the forearm mass with no other areas of increased signal intensity. Two biopsies at outside institutions were interpreted as an atypical lymphoid neoplasm, and soft tissue with nonspecific changes insufficient for diagnosis of lymphoproliferative disorder. A generous incisional biopsy was then performed.

**Results:** Lymphoid follicles of variable size and shape with an extensive network of vascular channels indicative of hyaline vascular type Castleman disease (HVCD) were identified within the specimen. Immunohistochemical analysis showed CD20-staining B cells within the follicular units surrounded by T cells staining positive for CD3, CD5, and CD45. PCR analysis identified a clonal T-cell population. B-cell PCR analysis was negative. The patient was treated with definitive resection with no adjuvant therapy. She has had no evidence of recurrence with 12 months of follow-up.

**Conclusions:** Castleman’s disease, a rare lymphoproliferative disorder, has been associated with a variety of neoplasms. It typically presents as a mediastinal mass. This report describes presentation of an isolated focus of disease in the extremity treated with definitive resection.
**35135 - A GENE EXPRESSION SIGNATURE OF MALIGNANT FIBROUS HISTIOCYTOMA IDENTIFIED THROUGH CROSS-SPECIES GENOMIC ANALYSIS**

Jeffery Mito; Rebecca Dodd; Lars Strangenberg; Francis J. Hornicek; Sam S. Yoon; Sayan Mukherjee; David G Kirsch

Duke University, Durham, NC, United States; Massachusetts General Hospital, Boston, MA, United States

**Objectives:** The classification of soft-tissue sarcomas (STS) is complex and sometimes controversial. Recent gene expression studies have classified different types of human STS. Although malignant fibrous histiocytoma (MFH) was once a relatively frequent diagnosis, this diagnosis has recently fallen out of favor and questions have been raised over whether MFH is a diagnostic entity. To gain insight into human STS, we have performed genomic analysis on a mouse model of STS.

**Methods:** Primary STSs were generated in mice with conditional mutations in oncogenic K-ras and p53. Tumors (n=14) or normal skeletal muscle (n=4) were collected and RNA extracted. Gene expression data was normalized using RMA. The 100 genes that most correlate with sarcomas compared to normal muscle were used to generate a mouse sarcoma signature using a signal-to-noise metric. This signature was compared with published gene expression data sets of human STS.

**Results:** As shown in Table 1, geneset enrichment analysis of human STSs demonstrates MFH samples are highly enriched in the mouse STS signature (p<.0001, FDR 0.022) compared to six other human STSs. Human STS data are from Nakayama R, et al. Mod. Path 2007.

**Conclusions:** Cross-species gene-expression analysis has identified a signature for MFH. Because this signature is conserved across vertebrate species and is not present in other sub-types of sarcomas, it suggests that MFH may in fact be a separate clinical entity. Further cross-species genomic-analysis with the mouse model may identify molecular features that are clinically useful for the treatment of patients with STS.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>p-value</th>
<th>FDR</th>
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</thead>
<tbody>
<tr>
<td>MFH</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td>Myxofibrosarcoma</td>
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<td>0.559</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>0.177</td>
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</tr>
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</tr>
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<tr>
<td>Dedifferentiated Liposarcoma</td>
<td>DNE</td>
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</tr>
</tbody>
</table>

**Geneset Enrichment Analysis of Human STSs**

**35138 - NOVEL USE OF INTENSITY MODULATED RADIOTHERAPY**

Nicole Larrier; Brian Brigman

Duke University Medical Center, Durham, NC, United States

**Objectives:** One of the major complications of preoperative radiotherapy for sarcomas is an increased risk of wound complications. Our goal was to use intensity modulated radiotherapy (IMRT) to create a treatment plan that spared the tissues most at risk for wound complications.

**Methods:** The case is a 31 yo man who presented with a retroperitoneal osteosarcoma. He received neoadjuvant chemotherapy. Preoperative radiotherapy was recommended due to the extensive nature of the tumor including extension into the neural foramena. Surgery was expected to include vertebral resection and the use of orthopedic hardware.

In conjunction with the orthopedic surgeon, an avoidance structure was created during the IMRT planning process. Primarily, this area consisted of soft tissue in the midline soft tissues of the back. A dose constraint of less than 20Gy was applied to this region. The tumor volume received 45 Gy. Other restrictions were given to the kidneys, and bowel.

**Results:** Nine axial beams were utilized in creating the plan. The IMRT plan provided adequate sparing of the soft tissue at risk. The contralateral kidney did receive more radiation when compared to a traditional 3D conformal plan. However, the dose to each kidney was acceptable.

The patient tolerated radiotherapy well with mild nausea which was controlled with medication. His pain decreased significantly.

**Conclusions:** IMRT may be used to create avoidance structures in sarcoma treatment. Further patients are needed to see if this can affect the overall risk of wound healing complications associated with preoperative radiotherapy.

**35141 - PROTON RADIOTHERAPY AS ADJUVANT OR DEFINITIVE LOCAL TREATMENT FOR CARDIAC AND PULMONARY VESSEL SARCOMAS**

Yen-Lin Chen; David Kirsch; John Wolfgang; Hsiao-Ming Lu; Judith Adams; David Harmon; Dempsey Springfield; Shawn Gregory; Suhny Abbara; George T Chen; Thomas T DeLaney

Massachusetts General Hospital, Boston, MA, United States

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The patient tolerated radiotherapy well with mild nausea which was controlled with medication. His pain decreased significantly.

**Conclusions:** IMRT may be used to create avoidance structures in sarcoma treatment. Further patients are needed to see if this can affect the overall risk of wound healing complications associated with preoperative radiotherapy.
Objectives: Cardiac and pulmonary vessel sarcomas are rare tumors and challenging for both local and distant control. We report our single institution experience with proton radiotherapy for these tumors.

Methods: We analyzed 9 patients with cardiac or pulmonary artery sarcoma with proton radiotherapy from 2005-8 for tumor characteristics, treatment modalities, planning techniques, and early outcomes.

Results: There were 5 men and 4 women, mean age 49.7 years (22-75). Tumor involved pulmonary artery(3), right atrium(2), left atrium(3), or interventricular septum(1) with histology consisting of doxil +/- gemcitabine or MAID. Radiation planning took into account cardiac and respiratory motion using echocardiogram and cardiac MRI. In 4 cases, ITV’s of tumor position throughout the full cardiac cycle were created using high resolution ECG-gated cardiac CT and treated with gating at end-expiration. Median dose was 66.0 GyE (proton equivalent of 1Gy; relative RBE=1.1), ranging from 34.2GyE (after 17.5 Gy intraoperative electrons) to 68.4GyE.

Conclusions: Proton radiotherapy appears to be a feasible local modality for cardiac and pulmonary vessel sarcomas. ECG-gated cardiac imaging allows better visualization of target and cardiac motion for proton planning. Distant metastasis, however, remains the main challenge for these tumors.

35155 - PREOPERATIVE HIGH-DOSE (54 GY) HELICOIDAL TOMOTHERAPY (HTT) PLUS SURGERY IN RETROPERITONEAL LIPOSARCOMA (RPLS): A FEASIBILITY STUDY

*Eberhard Stoeckle; Guy Kantor; Catherine Dejean; Antoine Italiano; Nathalie Stock; Michele Kind; Jean-Michel Coindre; *Eberhard Stoeckle; Guy Kantor; Catherine Dejean; Antoine Italiano; Nathalie Stock; Michele Kind; Jean-Michel Coindre; *Eberhard Stoeckle; Guy Kantor; Catherine Dejean; Antoine Italiano; Nathalie Stock; Michele Kind; Jean-Michel Coindre; *Eberhard Stoeckle; Guy Kantor; Catherine Dejean; Antoine Italiano; Nathalie Stock; Michele Kind; Jean-Michel Coindre; *Eberhard Stoeckle; Guy Kantor; Catherine Dejean; Antoine Italiano; Nathalie Stock; Michele Kind; Jean-Michel Coindre

Institut Bergonie, Bordeaux, France

Objectives: The potential benefit of radiotherapy in RPLS is not established because of dose limiting toxicity. Preoperative HTT could circumvent these difficulties by sparing radiosensitive normal tissues. This is a feasibility study of the association of pre-op HTT and surgery in RPLS.

Methods: From 08/07 to 06/08, 5 female and 5 male patients (pts.), median age 63 years with 9 primary and 1 recurrent RPLS, 2 well differentiated and 8 dedifferentiated, median size 24 cm, were enrolled. The treatment volume was jointly delineated by the radiotherapist and the surgeon. Positioning with a daily CT-scan achieved margins of 7 - 10 mm from CTV to PTV. 54 Gy in 30 fractions of 1.8 Gy were prescribed at the median of PTV. IMRT maximal dose constraints were: total (D2%) = 55 Gy, controlateral kidney < 12 Gy (median < 6 Gy), bowel = 54 Gy with % of volume receiving < 45 Gy (V45 Gy) = 33% and V20 Gy = 50%. Surgery was planned four weeks after radiotherapy.

Results: One patient is still under treatment. HTT in the 9 treated pts. was completed to 54 Gy without interruption. Dositometric constraints were respected. CTCaeV3 Grade 1 and 2 weight loss and nausea occurred. Resections in 7 operated pts. were 4 R0, 2 R1, 1 R2. One patient required blood transfusion. Postoperative outcome was uneventful with a median hospital stay of 8 days.

Conclusions: This treatment association appears feasible. Treatment
results will be updated. A multicentric prospective phase II study is planned.

**35157 - IMAGING THE PATIENT WITH TUMOR PROSTHESIS: TIPS AND TRICKS FOR METAL ARTIFACT REDUCTION**

M. LLUISA PICO-FUSTER; LORENZO MUNTANER-GIMBERNA; OSCAR TENDERO-GOMEZ; EVA-REGINA AMADOR; JAVIER MARTIN-BROTO; JAVIER PUEYO-MUR

SON DURETA UNIVERSITY HOSPITAL Comite de Tumores Musculosqueleticos COTMES, Palma de Mallorca, Balearic Islands, Spain

**Objectives:** Orthopaedic hardware are often used for musculoskeletal tumor reconstructive procedures. The usefulness of MR imaging to answer clinical questions about tumor recurrence may be limited by metal induced artifacts which remains a significant problem in patient follow-up. This educational exhibit reviews the state-of-the-art use of artifact reduction MRI techniques in evaluating patients with orthopaedic hardware after limb salvage surgery.

**Methods:** We reviewed our experience in performing 14 MRI follow-up examinations High field 1.5 T in 8 patients with orthopaedic hardware reconstruction in limb salvage surgery for musculoskeletal tumors.

**Results:** The recent experience of other publications advocating the use newer reduction artifact techniques by using optimal sequences and parameters for image acquisition and reconstruction and by positioning the patient for optimal orientation along the main magnetic field are discussed and presented in a pictorial fashion. In the focused limb salvage MRI study, pitfalls generated by the use of certain sequences and parameters need to be avoided in order to reduce misregistration artifacts arising from metal hardware. Rationale and discrepancies between techniques are presented.

**Conclusions:** The objective of this pictorial essay is to familiarize with metal artifact-reducing MRI techniques which are used in patients with limb salvage surgery follow-up. Appropriate knowledge of these technical strategies and its tips and tricks assure an accurate follow-up diagnosis and avoid pitfalls in postoperative MRI interpretation.

**35158 - MELOXICAM, A COX-2 INHIBITOR, AS A NON-SURGICAL THERAPY FOR DESMOID TUMORS**

Yoshihiro Nishida; Satoshi Tsukushi; Yoji Shido; Kozo Hosono; Naoki Ishiguro

Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan

**Objectives:** A prospective, non-randomized consecutive analysis of therapeutic outcomes of meloxicam for the patients of desmoid tumors, compared with retrospective control patients with surgical treatment.

**Methods:** Fifteen patients with histologically diagnosed as desmoid tumors were treated with meloxicam (10mg/day). The mean age of the patients was 51 years old (20-86) with 5 males and 10 females. An average follow up was 31 months. Size of the tumors was determined with MR imaging every 6 months, and efficacy of meloxicam was evaluated as CR, PR, SD, and PD. Treatment was discontinued for patients with severe complications or with evaluation of PD. Twenty patients with surgical treatment were retrospectively reviewed with an average 4.9 year follow-up (2.2-11). The mean age was 36 years old (7-62) with 8 males and 12 females.

**Results:** There were 2 abdominal desmoid and 13 extra-abdominal desmoid tumors in meloxicam group. COX-2 over-expression was observed with immunohistochemical methods. Patients outcome was evaluated as PR in 6, SD in 6, PD in 3. Although gastritis occurred in 2 patients, there were no severe complications. Reduction of ADL was not observed in 3 patients with PD evaluation. In surgical treatment group, 11 patients (55%) recurred at mean follow-up of 15 months.

**Conclusions:** Meloxicam might be able to regulate the aggressiveness of desmoid tumors.

**35171 - THE PROGNOSTIC VALUE AND CONSISTENCY OF DNA CONTENT IN PATIENTS WITH EWING’S SARCOMA DURING DISEASE PROGRESSION: MIND THE HETEROGENEITY**

Addy Van de Luitjgaarden; *Winette van der Graaf; Irene Otte-Holler; Bart Schreuder; Rene Veth; Peter Hoogerbrugge; Piet Slootweg

Radboud University Nijmegen Medical Center, Nijmegen, Netherlands

**Objectives:** Cells with an abnormal DNA content may represent clones expressing multiple mutations. This possible prognostic indicator has only sparsely been studied before. In this era of fast development of targeted therapies, in Ewing’s sarcoma currently focusing on the Insulin-Like Growth Factor type 1 receptor (IGF1R), it is also of interest to determine uniformity between different tumor manifestations in a single patient.

**Methods:** We performed DNA image cytometry (IC) on 41 adequately preserved samples of consecutive Ewing’s sarcoma patients and evaluated the prognostic value of DNA content for recurrence of disease, occurrence of metastases and mortality. We also evaluated if ploidy status remained constant over time and between different lesions in each patient.

**Results:** Our data showed a remarkable higher frequency of recurrences, metastases and mortality in patients with non-diploid lesions though, probably due to the relative small number of patients, statistical significance was not reached. It was shown that ploidies vary in time and that different ploidies coexist at a single time point in a single patient.

**Conclusions:** Patients with non-diploid Ewing’s sarcoma lesions seem to have an adverse outcome as compared to those with diploid lesions. However, larger studies are necessary to confirm these data. The change in ploidy during progression and the heterogeneity in ploidy we encountered has not been described before. This may have major implications for clinical management when selecting candidates for targeted therapies. Data of IGF1R immunohistochemistry results in this tumor material and correlation of these results with ploidies will be demonstrated during the meeting.

**ORAL PRESENTATIONS FRIDAY**

**Surgery**

**#34880 MORBIDITY OF AN UNPLANNED EXCISION OF SOFT TISSUE SARCOMAS: A QUANTITATIVE ASSESSMENT**

Robert M Tamurian, MD1, Robert A. Zlotecki, MD PhD1, Zachary B Adler, MD1, Mark T Scarborough1, C. Parker Gibbs, MD1


**Objectives**: Unplanned excision of a soft tissue sarcoma results in a contaminated tumor bed in approximately 50% of cases. In the absence of clinically detectable disease, there are no reliable methods to identify which patients will have microscopic residual disease. Therefore, tumor bed re-excision has been the standard treatment for this group of patients. The impact of this procedure on local morbidity has not yet been evaluated.

**Methods**: A retrospective review of the orthopaedic oncology database identified 55 patients who were referred following an unplanned excision of an extremity soft tissue sarcoma. We established an experimental model to determine what the primary multidisciplinary management would have been, had no prior intervention been performed. We then compared this optimal scenario to that which was actually performed.

**Results**: The volume of tissue that needed to be removed during tumor bed resection was increased by 266%, p = 0.007. The incidence of skin grafts and flaps was increased from 12% to 56% and 7% to 26% respectively. Radiation dose was increased by 15% and the field size increased by 122%, p < 0.001. The incidence of residual tumor present in the tumor bed was 44.2% and patients with residual tumor were more likely to develop local recurrence, p < 0.0001, non extremity primary site (p=0.0016); high histologic grade (p=0.001), non extremity primary site (p<0.0001), male gender (p=0.01), non extremity primary site (p<0.0001), high histologic grade (p=0.001), and margin positivity (p<0.0001) were identified as independent predictors of local recurrence. MMP2 (p=0.003), 

**Conclusions**: Irrespective from any anatomic barrier, in marginal surgery a minimal (1-2 cm) additional margin should be obtained to achieve similar local control rates as obtained in the non contaminated primary tumor bed resection group.

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**Figure 1**

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**#34869 CLINICAL VARIABLES, PATHOLOGICAL FACTORS, AND MOLECULAR MARKERS FOR ENHANCED SOFT TISSUE SARCOMA PROGNOSTICATION**

Gyu Lahat1, Wang Wei-lien1, Daniel Tuvin1, Daniel A Anaya1, Caimiao Wei1, Nabiyu Bekele1, Kerrington D Smith1, Alexander J Lazar1, Peter W Pisters2, Raphael E Pollock1, Dina Lev1

1University of Texas MD Anderson Cancer Center, Houston, United States

**Objectives**: To identify and validate clinical, pathological, and molecular factors as descriptors of STS clinical behavior.

**Methods**: Prospectively accrued data were analyzed for 1,091 AJCC Stage I-III primary STS patients who had complete macroscopic resection at our institution (1996 to 2007); a tissue microarray was created from 210 formalin-fixed paraffin-embedded STS blocks. Criteria were evaluated using univariable and multivariable analyses to identify independent prognostic factors for local recurrence and overall survival (OS).

**Results**: Three distinct size cohorts (p<0.0001) were identified: T1 (<5cm; 5 year OS 85%), T2 (5-15cm; OS 68%), and T3 (>15cm; OS 52%). A multivariable Cox proportional hazards model identified tumor size (5-15cm vs. ?5cm, p=0.03; or >15cm vs. ?5cm; p<0.0001), non extremity primary site (p=0.0016); high histologic grade (p=0.001), specific histology (p=0.001), and margin positivity (p<0.0001) as significant adverse independent prognostic factors. Local recurrence during follow-up also significantly affected STS-specific mortality (p<0.0001); older age (p<0.0001), male gender (p=0.01), non extremity primary site (p<0.0001), high histologic grade (p=0.001), and margin positivity (p<0.0001), were identified as independent predictors of local recurrence. MMP2 (p=0.003),
MMP9 (p=0.05), and ki67 (p=0.002) added additional predictive value for disease free and OS when included in the multivariable Cox proportional hazards model.

Conclusions: A T3 size category, primary site, histologic subtype and margin status should be included in STS staging systems. Moreover, inclusion of MMP2, MMP9, and ki67 expression in STS staging may enable more precise prognostic estimates, which in turn could facilitate more specifically individualized STS therapeutic strategies.

#35066 PROGNOSTIC FACTORS FOR LONG-TERM SURVIVAL AFTER PULMONARY METASTASECTOMY IN SARCOMA PATIENTS: A 16-YEAR EXPERIENCE
Simon Jordan1, Peter Goldstraw1, Elizabeth Belcher1, Ambrus Szántó1, Jeremy Whelan2, Beatrice Seddon2, Maria Michelagnoli3, Anna Cassoni2, Sandra Strauss2, Michelle Scurr1, Frank Saran3, Ian Judson1, George Ladas1
1Royal Brompton Hospital, London, United Kingdom; 2University College Hospital, London, United Kingdom; 3Royal Marsden Hospital, London, United Kingdom

Objectives: Pulmonary metastasectomy is an established treatment modality for selected patients with sarcoma. However, the prognostic factors that influence survival and the selection criteria remain unclear.

Methods: Demographic, clinical, operative and survival details of all patients undergoing pulmonary metastasectomy at our institution have been entered into a specifically designed database. We examined the impact of age, gender, sarcoma type, disease-free interval (DFI), number and distribution of metastases, completeness of resection and prior metastasectomy on survival. Actuarial survival was estimated using Kaplan-Meier methods and comparisons by Cox regression.

Results: 222 consecutive patients underwent 380 pulmonary metastasectomy procedures over a 16 year period. 101 patients had unilateral metastatic disease and 121 patients had bilateral involvement. The mean age was 41 years (range 7 to 83). 58% of patients were female. 61 patients had redo operations. The mean number of nodules excised per operation was 5.2 (median of 3 and range 1 - 39). 83% of the excised nodules were disease-related on histological examination. Survival analysis for sarcoma types, disease-free intervals and number of metastases to be presented. The peri-operative mortality was 0.26% (1 patient developed a pulmonary embolus on post-operative day 8).

Conclusions: Resection of sarcomatous pulmonary metastases in selected patients confers good long-term survival, with low operative mortality.

#34849 THE MORE IT HURTS, THE BETTER IT WORKS? CHEMOTHERAPY TOXICITY AS A PREDICTOR OF OUTCOME FROM OSTEOSARCOMA: A REPORT FROM THE EUROPEAN OSTEOSARCOMA INTERGROUP
Anne McTiernan1, Rachel C Morgan2, Matthew R Sydes2, Barbara Uschinska2, Martine Van Glabbeke1, Vivien Bramwell4, Robert L Souhami5, Ian Lewis1, Tamiaiou H Antonie5, Nooj A Mariann6, Hogendoorn C Pancras6, Jeremy S Whelan1
1University College Hospital, London, United Kingdom; 2MRC Clinical Trials Unit, London, United Kingdom; 3EORTC Data Centre, Brussels, Belgium; 4Tom Baker Cancer Centre, Calgary, Canada; 5St James Hospital, Leeds, United Kingdom; 6Leiden University Medical Center, Leiden, Netherlands

Objectives: To determine the influence of chemotherapy-related toxicity on outcomes in patients with localised extremity osteosarcoma.

Methods: A retrospective analysis of patients treated with doxorubicin and cisplatin chemotherapy within 3 consecutive randomised trials of the European Osteosarcoma Intergroup. Between 1982 and 2002, 533 patients were randomised to 6 cycles of doxorubicin 75mg/m² and cisplatin 100mg/m²: the common regimen across all trials. Surgery was scheduled after 2 (n=288) or 3 (n=245) cycles of chemotherapy. Toxicity was graded according to the WHO toxicity criteria.

Results: 5- and 10-year overall survival (OS) was 57% (95% confidence interval (CI) 52-61%) and 53% (49-58%) respectively. Grade 3-4 oral mucositis (hazard ratio (HR) 0.50, 95% CI 0.28-0.90), grade 1-2 nausea and vomiting (HR, 0.38, 95% CI, 0.16-0.88), and grade 1-2 thrombocytopenia (HR 0.48, 95% CI, 0.27-0.86) were statistically significant for OS in multivariate analysis, together with good histological response (HR: 0.42, 95% CI, 0.27-0.65), distal tumour site (HR: 0.45, 95% CI, 0.28-0.71), and female gender (HR 0.67, 95% CI, 0.45-0.99). The only factors that were independently associated with histological response in multivariate analysis were age > 26 years (odds ratio (OR): 0.20, 95% CI: 0.05-0.80) and chondroblastic tumour (OR: 0.26, 95% CI: 0.9-0.73), which were both associated with a significantly lower chance of reporting a good histological response.

Conclusions: Chemotherapy-induced toxicity was associated with improved survival, but not increased rates of good histological

Bone Sarcomas 1- Pediatric Oncology

#34860 ROLE OF SENTINEL LYMPH NODE BIOPSY IN THE STAGING OF SYNOVIAL, EPITHELIOID, AND CLEAR CELL SARCOMAS
Ugwuji Maduekw1, Francis J. Hornicek1, Mark J. Ott1, Dempsey S. Springfield1, Kevin A. Raskin1, Edwin Choy1, David C. Harmon1, Andrew E. Rosenberg1, G. Petur Nielsen2, Thomas F. DeLaney1, Sam S. Yoon1
1Massachusetts General Hospital, Boston, MA, United States

Objectives: Soft tissue sarcomas (STS) in general have a

Methods: Twenty-nine patients with non-metastatic synovial, epithelioid, or clear cell sarcoma who underwent SLNB were examined.

Results: Median age was 35 years old (range 11-73), and 69% were male. Tumors were located in the lower extremity in 17 patients (59%) and the upper extremity in 12 (41%). The histological subtypes were synovial sarcoma in 16 patients (55%), epithelioid sarcoma in 10 (35%), and clear cell sarcoma in 3 (10%). All patients had a staging chest CT scan, of which 19 were negative and 10 were indeterminate. 20 patients had staging PET scans (16 negative, 3 indeterminate, and 1 suspicious). Median number of sentinel nodes identified was 2 (range 1-4), and only 1 patient (3.4%) had a positive sentinel node. All patients had resection of their primary tumor, 17 (59%) received adjuvant radiation therapy, and 8 (28%) received adjuvant chemotherapy. Five patients later developed distant metastases, and one patient developed a lymph node metastasis after a negative SLNB. Median time to recurrence was only eight months.

Conclusions: For patients with these sarcoma subtypes without radiological evidence of nodal or distant metastases, the incidence of occult lymph node metastasis is low. Thus SLNB is of limited value in the staging of these patients.
response, in patients with localised extremity osteosarcoma. Research should be directed towards identifying pharmacogenomic markers which may be associated with host and tumour chemoresponsiveness.

#35051 CHANGE IN ANATOMIC DISTRIBUTION OF RELAPSES WITH ACCELERATED CHEMOTHERAPY IN EWING SARCOMA

Richard B Womer1, Daniel C West1, Mark D Krailo1, Paul S Dickman1, Bruce Pawel1
1Childrens Oncology Group, Arcadia, CA, United States

Objectives: The INT-0091 study of Ewing sarcoma showed that the addition of ifosfamide-etoposide to vincristine-doxorubicin-cyclophosphamide improves survival by decreasing the risk of local recurrence. The Children’s Oncology Group study AEWS0031 found that every-two-week chemotherapy is more effective than every-three-week chemotherapy for localized Ewing sarcoma. We analyzed patterns of recurrence in AEWS0031 to find differences between the regimens.

Methods: We reviewed submitted data on patients suffering relapse on AEWS0031, classifying relapses as local only, distant only, or combined. The distant and combined relapses were analyzed for the sites of distant relapse, and classified as lung, bone, other, or multiple. We then evaluated the on-study characteristics of patients in each category.

Results: 568 eligible patients were randomized in the study, 284 to each regimen. As of November 2006, there were 124 relapses, 73 in the standard arm and 51 in the intensive arm. The relapses were local only in 18 standard and 16 intensive regimen patients, distant only in 40 standard and 27 intensive regimen patients, and combined in 15 standard and 8 intensive regimen patients. The sites of distant relapse were lung in 20 standard and 11 intensive regimen patients, bone in 17 standard and 15 intensive regimen patients, other in 11 standard and 6 intensive regimen patients, and multiple in 7 standard and 3 intensive regimen patients.

Conclusions: Accelerated (every-two-week) chemotherapy improves prognosis in localized Ewing sarcoma by decreasing the frequency of lung and “other” relapses. It has no apparent effect on local and bone relapse.

#35047 THE VALUE OF LOCAL TREATMENT IN PATIENTS WITH EXTRAPULMONARY METASTASISED EWING TUMORS (EPMET)

Uta Dirksen1, Julia Häusler1, Tobias Bölling1, Andreas Ranft1, Georg Goshser1, Volker Vieth1, Heribert Jürgens1
1University of Muenster Children Hospital Pediatric Hematology and Oncology, Münster, Germany; 2University of Muenster Department of Radiotherapy and Radiooncology, Münster, Germany; 3University of Muenster Department of Orthopedics, Münster, Germany; 4University of Muenster Department of Clinical Radiology, Münster, Germany

Objectives: In contrast to patients diagnosed for localized Ewing tumours and/or pulmonary metastases, those with extrapulmonary disseminated Ewing sarcoma (EPMES) have an unfavourable prognosis. The value of local treatment in patients with EPMET was investigated.

Methods: We analyzed 120 German patients (pts) with EPMES registered from 1998-2006 onto the EURO E.W.I.N.G. 99 trial. Median age was 16.2 years. Median follow up was 1.5 years. 26 of 120 pts received surgery (OP), 21 pts OP and radiotherapy (RT), and 40 pts RT of the primary tumour (PT). Viewing local treatment of metastases, 8 of 122 pts received OP, 7 pts OP and RT, and 37 pts definite RT. 6 pts received whole lung RT. 49 pts (41%) received local treatment to the PT and EPMES, and 90 pts (75%) to the PT or EPMES.

Results: Event-free survival (EFS) in the whole group was 0.24 [95% CI 0.16-0.33] at 3 years. Univariate analyses on the value of local treatment modalities showed favourable outcome for local therapy of the PT (3-years EFS): OP 0.25, OP&RT 0.47, and RT 0.23 vs. no local therapy 0.13 (p<.001) and of the metastases: OP 0.25, OP&RT 0.86 (N=7), and RT 0.27 vs. no local therapy of metastases 0.17 (p=.002). Multivariate analysis in patients with bone metastases (n=94), that more than one bony lesion (>1 EPMES; N=83) is a major risk factor (Hazard Ratio [HR]= 2.9, p=.05; 3y-EFS=0.18). Multivariate analyses of the value of local treatment in pts with bone metastases were performed. OP (with or without RT) of the PT was no longer a significant favourable factor (HR=0.92; p=.756), but OP (with or without RT) of EPMES was (HR=0.37; p=0.39).

Conclusions: In patients with EPMES, local therapy is essential. Multidisciplinary planning of radiotherapy and surgery both of the PT and metastases must complement systemic treatment whenever possible.

#35094 ACTIVITY OF SCH 717454 IN SUBJECTS WITH RELAPSED OSTEOSARCOMA OR EWING’S SARCOMA (STUDY P04720)

Peter Anderson1, Keith Skubitz1, Robin Miller1, William Meyer2, Brian Lu3
1Schering Plough Research Institute, Kenilworth, NJ, United States; 2MD Anderson Cancer Center, Houston, Texas, United States; 3University of Minnesota, Minneapolis, MN, United States; 4University of Oklahoma, Oklahoma City, Oklahoma, United States; 5Alfred I duPont Hospital for Children, Wilmington, DE, United States

Objectives: SCH 717454 (19D12) is a high-affinity fully human monoclonal IgG1 antibody that binds to the human IGF1R. SCH 717454 can induce anti-tumor effects through multiple mechanisms including 1) inhibition of insulin-like growth factor (IGF) binding, 2) down-regulation of the IGF-1R, and 3) antibody-dependent cell-mediated cytotoxicity (ADCC). IGF-1R signaling may be of particular importance in Ewing’s sarcoma and osteosarcoma, and SCH 717454 is active against these tumor xenografts in preclinical studies.

Objective(s) Evaluate activity and potential clinical benefit of SCH 717454 in subjects with relapse/refractory osteosarcoma and Ewing’s sarcoma.

Methods: Subjects with relapsed or refractory Ewing’s sarcoma, and osteosarcoma were eligible for the study. Subjects with resectable osteosarcoma received a dose of SCH 717454 prior to surgery, and continued to receive treatment every two weeks for one year or until disease progression. Subjects with unresectable osteosarcoma or Ewing’s sarcoma received SCH 717454 once every two weeks until disease progression.

Results: Over 30 subjects have been enrolled in the study as of June, 2008 (including 8 subjects with Ewing’s sarcoma). Dosing has so far been well-tolerated, without initial evidence of significant hyperglycemia or thrombocytopenia. Enrollment is continuing on the study. Two partial responses have been observed in subjects with
Ewing’s sarcoma. Additional updated preliminary data on safety, tolerability and activity will be presented.

Conclusions: SCH 717454 administered IV every 2 weeks is generally well-tolerated and demonstrates preliminary evidence of antitumor activity in subjects with Ewing’s sarcoma.

#34973 ADDITION OF PAMIDRONATE TO CHEMOTHERAPY FOR TREATMENT OF OSTEOSARCOMA (OS) IS FEASIBLE.

Paul A. Meyers1, John H. Healey1, Edward Athanasian1, Patrick Boland1, Carol Morris1, Michael P. Laquaglia1, Cristina Antonescu1, Leonard Wexler1, Pamela Merola1, Alexander Chou1, Sara Abramson1, Michael Kellick1
1 Memorial Sloan Kettering Cancer Center, New York, NY, United States

Objectives: Bisphosphonates have anti-proliferative activity against OS and inhibit metastasis. They could stabilize reconstruction following resection of OS. We investigated the safety of the addition of pamidronate to chemotherapy for treatment of OS.

Methods: Chemotherapy: cisplatin (C, 120 mg/m²), doxorubicin (A, 37.5 mg/m²/d x 2) and high-dose methotrexate (M, 12 g/m²). We gave dexamethasone 375 mg/m² 15 minutes prior to each dose of A. We gave 10 weeks of induction, resected primary and metastatic sites, 20 weeks of maintenance. We gave pamidronate 2 mg/kg, max 90 mg, monthly for one year. We separated pamidronate from C or M by at least 48 hours.

Results: We treated 29 patients with localized OS and 11 with metastatic OS. None developed renal failure or jaw necrosis. Hypocalcemia was rare, transient, and asymptomatic. We inserted 21 endoprostheses. 13 of 14 uncemented implants osteointegrated, success better than our historical norm. We inserted 12 allografts. Results included 2 failures, 4 delayed unions (11, 14, 17, 22 months), and 6 successful grafts that healed after a median of 18 months. 5 of 33 reconstructions failed. There were no stress fractures or growth disturbances related to the bisphosphonates. Event-free (EFS) and overall survival was comparable to previous experience with the same chemotherapy regimen.

Conclusions: The addition of pamidronate to MAP chemotherapy for the treatment of OS is safe and well tolerated. Dexamethasone did not impair the efficacy of the regimen. Reconstructive results appeared better for endoprostheses, and equivalent for allografts, compared with our published historical experience. Evaluation of benefit will require a larger prospective trial.

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<th>EFS</th>
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<td>Metastatic</td>
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Outcome at 4 years

NF1: MPNST and Other Sarcomas, Diagnosis & Treatment

#35059 18FDG PET/CT IN THE DIAGNOSIS OF MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS

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Objectives: PET only scans have been shown to identify malignant change in peripheral nerve sheath tumours. We have evaluated whether the use of early and delayed imaging with 18FDG PET/CT is as effective in this role.

Methods: Patients with symptomatic neurofibromas referred for 18FDG PET/CT were identified from the PET/CT reports archive. 18FDG PET/CT was performed in all patients with the maximum standard uptake value (SUVmax) measured on early (90 minutes) and delayed imaging (4 hours). Neurofibromas which demonstrated a SUVmax of greater than 3.5 and whose SUVmax rose on delayed imaging were classified as malignant.

Results: 83 studies were performed between August 2004 and September 2007. Analysis is ongoing. To date, 73 studies in 59 patients (31 males, 28 females) performed over a 35-month period from August 2004 to June 2007 have been analysed. 48 studies were eligible for inclusion, with a total of 66 plexiform neurofibromas analysed. On the basis of the PET/CT findings, 33 neurofibromas were classified as malignant. Histological correlation in 17 lesions confirmed malignancy in 14 cases, with 3 false positives (although in 1 case the initial biopsy demonstrated atypia). Of the 33 benign lesions, none have progressed on clinical follow-up. Complete analysis will be available soon.

Conclusions: 18FDG PET/CT with delayed imaging appears to distinguish between benign and malignant lesions and enhances lesion localisation compared to PET alone. PET/CT should be routinely performed in the evaluation of NF1 patients with symptomatic neurofibromas.

#35152 GENETIC ANALYSIS OF PERIPHERAL NERVE SHEATH TUMOURS IN NF1 PATIENTS.

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Objectives: Some individuals with neurofibromatosis type 1 have atypical neurofibromas. Clinically, these lesions are symptomatic (pain and growth) and they usually show an increased glucose uptake by FDG-PET scan. Atypical neurofibromas are clinically difficult to differentiate from MPNSTs. Pathologically atypical neurofibromas show regions of hypercellularity and atypical (hyperchromatic) nuclei, which is not seen in benign neurofibromas. At this moment it is not clear what the importance of these tumours is.

Methods: We performed genetic analyses on frozen material of 8 benign neurofibromas, 10 atypical neurofibromas and 25 MPNSTs (3 low, 1 intermediate and 21 high grade) from 28 NF1 patients. We searched for genome wide copy number variations using the 244K microarrays (Agilent Technologies) and we screened the samples for mutations in TP53 and CDKN2A.

Results: Atypical neurofibromas already underwent some genomic changes towards malignancy. These genomic aberrations were not found in benign neurofibromas, and were comparable to those observed in MPNSTs. In intermediate and high grade MPNSTs more and larger genomic abnormalities were seen than in atypical and low grade MPNST. CDKN2A and TP53 mutations were only found in MPNSTs.

Conclusions: By genetic analysis we were not able to differentiate atypical neurofibromas from low grade MPNSTs. These data suggest that the atypical neurofibroma is a stage between benign neurofibroma and MPNST, and that we propose that they should be treated accordingly.
MALIGNANT PERIPHERAL NERVE SHEATH TUMORS (MPNST): CLINICAL, PATHOLOGIC AND MOLECULAR PREDICTORS OF SURVIVAL

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Objectives: To identify clinical, pathologic and molecular predictors of outcome in patients with/without NF-1-associated MPNST.

Methods: MPNST patients treated from 1985 to 2006 (n=140) were identified; 72 had NF-1 syndrome and 68 did not. 139 formalin-fixed paraffin-embedded neurofibroma or MPNST blocks were assembled in a tissue microarray; expression of proliferation and angiogenesis factors prognostic of disease specific survival (dss).

Results: After median follow up of 91 months, dss at 10 years was 31.6% for 87 primary disease patients, 25.9% for 26 recurrent patients, and 7.5% for 27 metastatic patients. The 10-year dss for localized resectable tumor patients was 23.6% for NF-1 syndrome patients and 44.0% for sporadic patients. Tumor size >10 cm at time of diagnosis, negative S-100 staining, partial surgical resection, and metastasis development were significant negative predictors of dss. TMA p53, ki67, VEGF, pAKT and pMEK expression differentiated benign neurofibromas from MPNST, whereas only pAKT expression differentiated metastatic MPNST from primary or recurrent tumors. The potential correlation between protein expressions and outcomes are currently being analyzed.

Conclusions: MPNST is a markedly metastatic tumor, especially in NF-1 patients who have a higher risk of developing metastases despite aggressive multimodality therapy. Compared to primary MPNST, metastatic lesions exhibit higher pAKT expression; the AKT signaling pathway should therefore be evaluated for possible specific therapeutic targetability.

GASTROINTESTINAL STROMAL TUMOR (GIST) IN NEUROFIBROMATOSIS 1 (NF1) PATIENTS: A CLINICOPATHOLOGIC ANALYSIS OF NINE CASES

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Objectives: NF1 is generally associated with high incidence of neoplasms, possibly related to overexpression of p21-ras, playing a cardinal role in mitogenic intracellular pathways. GIST is the most common NF1 associated gastrointestinal tumor and generally lacks KIT/PDGFRα mutations.

Methods: In our institution, we analyzed 9 patients who had GIST and NF1. All pts had clinical presentation suggestive of NF1, 4 pts had histological diagnosis of neurofibroma.

Results: 5/7 pts were females; median age 51 years (36-59 yrs). Most tumors occurred in ileum or duodenum, multiple tumors occurring in 5 cases. In one pt gastric and duodenal GIST were found with different morphologic features. In one case, GIST was associated with pheochromocytoma, and in another with pheochromocytoma and ampullary neuroendocrine tumor. Mostly, tumors were small and mitotically inactive; only 2 had >10/50 HPF, and 4 were >5 cm. 8/9 tumors didn’t have KIT exon 9, 11, 13 or 17 and PDGFRA exon 12, 14 or 18 mutations, as typically seen in sporadic GISTs. Pt with gastric and duodenal GIST had PDGFRA exon 18 (D842V) mutation in gastric GIST and none KIT/PDGFRA alteration in duodenal GIST. One pt died of metastatic disease, having a tumor >5 cm and mitotic rate >10/50 HPF. The presence of multiple small tumors was not associated with progressive disease and these pts are on a long-term follow-up.

Conclusions: GISTs in NF1 pts have different clinicopathologic and mutational profile in comparison to sporadic GISTs. In this analysis, one GIST showed a PDGFRA alteration (D842V). Molecular analyses for NF1 confirmation are ongoing, as feasible.

NUCLEAR TP53 EXPRESSION IN MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS IS AN INDEPENDENT MARKER OF POOR SURVIVAL

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1Department of Cancer Prevention Institute for Cancer Research Norwegian Radium Hospital Rikshospitalet University Hospital, Oslo, Norway; 2The Cancer Clinic Department of Oncology Norwegian Radium Hospital Rikshospitalet University Hospital, Oslo, Norway; 3Division of Pathology Norwegian Radium Hospital Rikshospitalet University Hospital, Oslo, Norway; 4Institute of Clinical Genetics Lund University Hospital, Lund, Sweden; 4Institute
for Medical Informatics Norwegian Radium Hospital Rikshospitalet University Hospital, Oslo, Norway

**Objectives:** We wanted to identify prognostic markers in malignant peripheral nerve sheath tumour (MPNST), a cancer type for which no consensus therapy exists besides excisional surgery. Potential differences between patients diagnosed with neurofibromatosis type 1 (NF1) and sporadic patients were also explored.

**Methods:** We have used a tissue microarray (TMA) containing 96 tumour tissue cores and developed a new software application to facilitate flexible visual evaluation and logistics of TMA images. The in situ protein expression of 14 key cell cycle regulating proteins has been studied by immunohistochemistry in 64 MPNST patients with long follow-up. Of these, 28 were diagnosed with neurofibromatosis type 1 (NF1).

**Results:** We found a clear association between the nuclear expression level of TP53 and poor survival (P = 0.008), in particular for the NF1-associated MPNSTs (P = 0.004). Nuclear expression of cyclin D1 was correlated with prolonged survival for the sporadic MPNST patients (P = 0.011). Cytoplasmic and nuclear expression of p27Kip1 and cytoplasmic expression of MDM2 were more frequently observed in sporadic MPNSTs (P = 0.03, P = 0.05, and P = 0.05, respectively).

**Conclusions:** For both groups of MPNST combined, we found that nuclear expression of TP53, together with the clinical parameters complete remission and tumour size, were the strongest predictors of disease-specific survival. Patients without remission, tumour size larger than 8 cm, and positive TP53 expression had 60 times higher risk of disease-related death within the first 5 years as compared to the remaining patients (P = 0.000002).

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**Surgical extent** | **No. of patients** | **Resection margin** | **No. of patients** | **No. of patients with LR** | **Cumulative** |
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The status of surgical margin and local recurrence

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**Objective:** We analyzed the 56 stage 1-3 extremity STS patients who underwent CT-planned XRT between 7/26/2000 and 12/14/2006 to determine the local control (LC) and the location of LF. CTV included the T1 post-Gd defined GTV with 1-1.5 cm radial and 3.5 cm longitudinal margins. PTV expansion was 5 mm and > 95% of dose was delivered to the PTV. Preoperative CTV dose was 44-50.4 Gy (median: 50). Postoperative boost of 10-20 Gy was given to 12 patients (6 with positive margin, 6 with multiple close margins).

**Results:** Range of follow-up was 15- 70 months (median: 36.5). 5 year LC, distant metastasis-free, disease-free and overall survival rates are 87.5%, 79.8%, 73.5% and 82.2%. 3 patients (all with positive margin) experienced LF as first relapse (2 isolated, 1 with distant failure) and 2 additional patients (all with margin < 1 mm) had late LF following initial distant metastasis. Preliminary analysis of the site of LF showed 4 failure occurred within the edge of GTV and within CTV while 1 failure occurred within but extending beyond CTV, as well.

**Conclusions:** These margin definitions appear appropriate for the majority of patients. Patients with positive or < 1 mm margin are at highest risk for local recurrence and should be treated more aggressively.

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**Objectives:** There is little information on the most appropriate clinical target volume (CTV) for patients undergoing preoperative irradiation (XRT) for extremity soft tissue sarcomas (STS). We retrospectively analyzed the pattern of local failure (LF) in those patients to evaluate optimal field design.

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**Objectives:** Tumor hypoxia has been related to poor prognosis and resistance to radiotherapy. Angiogenesis inhibitors may offer therapeutic opportunities to normalise tumor vasculature, and enhance radiosensitivity of resectable soft-tissue sarcomas (STS). The novel hypoxic positron emission tomography (PET) tracer, [18F]-fluorothymidine (FAZA) was used to identify the frequency of hypoxia in STS, and whether hypoxia predicts poor response to neoadjuvant radiotherapy (RT).
Methods: Patients with histologically confirmed STS undergoing RT and surgery were prospectively enrolled. PET-FAZA scans were performed at baseline. Biospecimens were collected for treatment response, assessment of vascular markers, and plasma vascular endothelial growth factor before and during RT.

Results: Twenty-two patients are currently enrolled (14 Female, 8 Male; ages 35-81 years; high-grade pleomorphic sarcoma 45%, liposarcoma 32%, other 23%) with 16 having undergone PET-FAZA scans thus far. Hypoxia on PET-FAZA was seen in 44% of patients and was strongly associated with outcomes. Of patients with hypoxia, 83% progressed during RT or relapsed within 6 months of completing treatment compared to 22% in patients without hypoxia (p<0.02). No patient with hypoxic STS demonstrated a good histological response (>90% necrosis) to radiotherapy at resection. Updated results will be presented at the meeting including molecular markers.

Conclusions: PET-FAZA is a promising tool for imaging hypoxia in STS, which is strongly correlated with resistance to radiotherapy and early relapse. We are currently evaluating the impact of angiogenesis inhibitors in modifying hypoxia during radiotherapy for STS.

#35012 CARBON ION RADIOThERAPY FOR SACRAL CHORDOMA
Tadashi kamada¹, Reiko Imai¹, Hiroshi Tsuji¹, Itsuko Serizawa¹, Toru Okada¹
¹National institute of radiological sciences, Chiba, Chiba, Japan

Objectives: To evaluate the effectiveness and safety of carbon ion radiotherapy in patients with sacral chordoma and to compare the results of carbon ion radiotherapy with those of surgical series in literature.

Methods: Between 1996 and 2007, 95 patients with sacral chordoma were included in the phase I/II and phase II study of carbon ion radiotherapy for unresectable bone and soft tissue sarcomas. There were sixty-eight males and 27 females. Median age was 66 years (30 - 85). Eighty-four patients was presented with primary disease and 11 patients with post operative recurrent tumor. Total dose of 52.8 to 73.6 GyE was given in 16 fractions over 4 weeks(4 days a week).

Results: All patients completed the planned carbon ion radiotherapy. Median survival time was 42 months (13-112). Overall survival rate at 5 years (86%) in patients treated by carbon ion radiotherapy is similar to reported data on patients treated by surgical resection with/without adjuvant radiotherapy. Local control rate at 5 years (88%) in patients with sacral chordoma treated by carbon ion radiotherapy is better than those in reported data. Median time to local failure was 35 months(13-60). Four patients treated with a total dose of 73.6 GyE experienced Grade 3/4 skin/soft tissue complications. No other treatment-related surgical interventions including colostomy or urinary diversion were carried out in this series. Fifteen patients required persistent medication for peripheral neuropathy.

Conclusions: Carbon ion therapy is suggested to be an effective and safe treatment for sacral chordomas, but further experience and longer follow-up are still needed.

#34907 EFFECTIVENESS OF RADIOThERAPY IN MYXOID SARCOMAS IS ASSOCIATED WITH A DENSE VASCULAR PATTERN
Ronald S.A. de Vreeze¹, Daphne de Jong¹, Rick L. Haas¹, Fiona Stewart¹, Frits van Coevorden¹
¹The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Objectives: Surgery and adjuvant radiotherapy (RT) have long been the standard treatment for most deep-seated sarcomas; however, since the randomized trial from the National Cancer Institute of Canada, which described similar local control for pre- vs. postoperative RT, both modalities are now widely accepted. As a group, sarcomas are classified as radiation resistant. The subgroup of myxoid liposarcoma (MLS), a sarcoma with a typical vascular crow’s feet pattern, is highly radiosensitive, but a mechanism for this phenomenon is unknown. Here we describe our results with preoperative RT and propose a mechanism explaining the high sensitivity based on the distinctive vascularization pattern of MLS.

Methods: Between 2002 and 2006, 31 sarcoma patients, including 10 with MLS, underwent preoperative RT at our institute. Resected specimens were histologically evaluated, focusing on classification, grade, and vascularization patterns.

Results: Twenty sarcomas showed more than 80% pathologic response after preoperative RT. A pathologic complete response was found in all 'pure' MLS specimens after preoperative RT (n = 8). There were no pathologic complete responses in the remaining sarcoma patients (n = 23), although 12 showed 80% to 90% pathologic response. In contrast to the remaining RT-resistant sarcomas,
the highly responding specimens contained branching vasculature, partial thrombus formation and inflammation of medium sized arterioles, similar to the vascular changes in MLS.

**Conclusions:** Both MLS and sarcomas with MLS-like vasculature are highly radiosensitive. Radiation sensitivity may be explained by changes in medium-sized arterioles, obstructing the specific crow’s feet vascularization and inducing hypoxia with secondary tumor cell death.

**Biology 1 - Molecular Biology of Sarcomas**

**#35046 MULTIFOCAL MYXOID LIPOSARCOMA; METASTASIS OR SECOND PRIMARY? A MOLECULAR BIOLOGICAL ANALYSIS.**
Ronald S.A. de Vreeze1, Daphne de Jong1, Petra M. Nederlof2, Rick L. Haas1, Frits van Coevorden1

1The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

**Objectives:** Multifocal sarcoma, defined as the presence of sarcoma at least two separate sites before manifestation in the lungs, is a rare and controversial entity. Differentiation between metastasis and second primary tumor is important because a second primary sarcoma deserves a local curative approach, whereas metastatic disease would justify palliative treatment.

Most multifocal sarcomas are myxoid-roundcell liposarcomas (MRLS). Characteristic genetic alteration for MRLS include the t(12;16)(q13;p11) or t(12;22)(q13;q12), of which several genomic breakpoints with different incidence exist. We analyzed a potential clonal relationship between the tumors at different sites.

**Methods:** The different incidence of the several known breakpoints of MRLS, detected by RT-PCR, was used to estimate the chance of clonality. Additionally, loss of heterozygosity analysis was used.

**Results:** In all patients the tumor sites showed identical genomic breakpoints, demonstrated by RNA-fusion transcripts. In patient 1-6 a rare fusion transcript was found. Patients 7-15 had the more common 5-FUS/2-CHOP fusion transcript. In six of these patients (7-12) harboring the common breakpoint, adequate frozen tumor is available which allows the detection of the exact genomic breakpoint to prove clonal relation. For patients 13-15, loss of heterozygosity analysis was informative in one patient. In this patient several markers showed similar losses. No decision could be established regarding patients 14-15.

**Conclusions:** This study suggests that multifocal MRLS is in fact metastasized (clonal) disease. Clinically, this implicates that these patients should be treated with systemic therapy and/or limited/palliative surgical resection. Extensive initial screening should be considered in case of MRLS.

**#35068 HUMAN MONOCLONAL ANTIBODY R1507 INHIBITS GROWTH OF OSTEOSARCOMA XENOGRAFTS AND IS EFFECTIVE IN COMBINATION WITH RAPAMYCIN.**
Edward Anders Kolb2, Davida Kamara2, Pooja Gidwani1, Wengdong Ellen Zhang1, Laurence H Baker2, Richard G Gorlick1

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**Objectives:** R1507 is a humanized monoclonal antibody that specifically inhibits signaling through the IGF-1R. Rapamycin is a specific inhibitor of mTOR and may induce apoptosis in human sarcoma cells under growth factor deficient conditions. In the current study we evaluate the combination of rapamycin and R1507 in osteosarcoma in vitro and in vivo.

**Methods:** Three osteosarcoma cell lines (HOS, SAOS and 143B) are evaluated for growth inhibition after treatment with rapamycin, R1507, and the combination of the 2 compounds. R1507 is further evaluated in vivo in 6 xenograft models of osteosarcoma, both as a single agent and in combination with rapamycin. Phosphorylation of Akt and S6 ribosomal protein are evaluated by immunoblotting.

**Results:** In vitro, R1507 inhibits growth of the 3 osteosarcoma lines at a concentration of 0.5 μg/ml. Within 24 hours there is a marked decrease in the p-Akt and IGF-1R in treated cells. In a panel of 6 osteosarcoma tumor lines, R1507 induces statistically significant improvements in event-free survival in 4 lines, including one complete response. In 2 lines where rapamycin and R1507 as single agents result in progressive disease, the combination yields a partial response suggesting more than additive activity. Pharmacodynamic analysis of the combination studies both in vitro and in vivo are ongoing, but these results suggest a biologic rationale for the combination.

**Conclusions:** R1507 and rapamycin inhibit growth of osteosarcoma xenografts.

This work has been supported in part by a Developmental Therapeutics Grant from SARC.

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**#34955 EWS/FLI REGULATES NKX2.2 VIA GLI IN A NON-SHH-DEPENDENT MANNER.**
Savita Sankar1, Leah A. Owen1, Stephen L. Lessnick1

1Huntsman Cancer Institute, Salt Lake City, UT, United States; 2University of Utah, Salt Lake City, Ut, United States

**Objectives:** The Ewing sarcoma-specific EWS/FLI fusion protein is an aberrant transcription factor that dysregulates genes required for oncogenesis. The EWS/FLI-regulated gene NKX2.2 is regulated by sonic hedgehog (SHH) signaling. We sought to understand how NKX2.2 is regulated by EWS/FLI in Ewing sarcoma.

**Methods:** Knock-down studies, luciferase reporter assays, drug-inhibition studies, and chromatin immunoprecipitation experiments were used to study the regulation of NKX2.2 by EWS/FLI.

**Results:** Chromatin immunoprecipitation on microarray (ChIP-chip) studies of EWS/FLI in Ewing sarcoma cells suggested that EWS/FLI did not directly bind the NKX2.2 promoter. Luciferase assays also did not show direct EWS/FLI regulation of the NKX2.2 promoter. Furthermore, treatment of Ewing sarcoma cells with cyclopamine, an inhibitor of SHH signaling, did not result in changes in NKX2.2 expression. However, ChIP-chip studies demonstrated that GLI, a downstream mediator of SHH signaling, may be a direct EWS/FLI target. Importantly, knockdown of GLI with RNAi demonstrated a
Objectives: Our data are consistent with a model in which EWS/FLI directly regulates GLI to drive Ewing sarcoma cells, which in turn directly regulates NXX2.2. This occurs in a SHH-independent manner. These data suggest that approaches targeting GLI directly could be effective for Ewing sarcoma. These data also demonstrate a unique mechanism of target gene dysregulation by a transcription factor oncprotein that bypasses a canonical signaling pathway, thus rendering the cells insensitive to inhibitors of that pathway.

GLI2 AND P53 COOPERATE TO REGULATE IGFBP-3 MEDIATED CHONDROCYTE APOPTOSIS IN THE PROGRESSION FROM BENIGN TO MALIGNANT CARTILAGE TUMOURS

Louisa Ho2, Aneta Stojanovski2, Heather Whetstone2, Qingxia Wei1, Elaine Mau Elaine Mau2, Benjamin Alman2, Jay Wunder1
1Samuel Lunenfeld Research Institute at Mount Sinai Hospital, Toronto, Ontario, Canada; 2Hospital for Sick Children, Toronto, Ontario, Canada

Objectives: While clinical evidence suggests that benign cartilage lesions can progress to malignant chondrosarcoma, the molecular events involved in this progression are unknown.

Methods: Since constitutive hedgehog signaling activation is common in benign and malignant cartilage tumors, we investigated tumor progression in transgenic mice that develop benign cartilage lesions due to overexpression of the hedgehog activated transcription factor Gli2. Gli2 overexpressing mice were crossed with p53 deficient mice. Tumors and fetal limbs were examined for differentiation by measuring type X collagen, proliferation using Ki67 or Phospho-histone H3, apoptosis by Caspase-3 and TUNEL staining. Microarray identified genes regulated by Gli2 overexpression. ChIP analysis examined Gli2 binding to the IGFBP3 promoter.

Results: Gli2 overexpressing mice developed lesions similar to low grade chondrosarcomas when also deficient in the p53 tumor suppressor gene. Fetal limbs were examined to determine how p53 and Gli2 might interact to regulate chondrocyte cell behavior. Gli2 overexpression and p53 deficiency had opposing effects on expression of type X collagen, a marker of chondrocyte differentiation, but had additive effects negatively regulating apoptosis. Gli2 negatively and p53 positively regulated the expression of Igfbp3 in chondrocytes. Human cartilage tumors had low levels of IGFBP3 expression compared to normal chondrocytes, with chondrosarcomas having lower levels than benign lesions. Treatment of human chondrosarcomas or fetal mouse limbs explants with IGFBP3 resulted in a substantial increase in apoptosis.

Conclusions: This data demonstrates that chondrosarcomas can derive from benign cartilage lesions, and identifies IGFBP3 as an important regulator of chondrocyte apoptosis and a potential therapeutic agent for patients with chondrosarcoma.

OSTEOCHONDROMAGENESIS: SOMATIC LOSS OF HETEROZYGOSITY MODELED VIA CRE-MEDIATED INVERSION OF THE SECOND EXON OF EXT1 IN CHONDROCYTES

Kevin B. Jones1, Charles Searby1, Gail Kurriger1, Peter Roughley2, Jose A. Morcuende1, Joseph A. Backwalter1, Val C. Sheffield1
1University of Iowa Hospitals and Clinics, Iowa City, Iowa, United States; 2Shriners Hospitals for Children, Montreal, Montreal, Quebec, Canada

Objectives: Hereditary multiple exostoses (HME) is caused by heterozygosity for mutations in EXT1 or EXT2. Osteochondroma pathogenesis in this disorder remains elusive. Mice homozygous null for homologous Ext1 or Ext2 die prenatally; only rarely will a heterozygote form a rib osteochondroma.

Methods: Gene-targeting generated a unique conditional allele of Ext1 with trans-orientation loxP sites flanking exon 2. Mice bearing trans-floxed Ext1 were crossed with mice bearing transgenic Cre-recombinase driven by a doxycycline-inducible collagen IIa1 promoter. Doxycycline was administered during week 2 of life. Mice were sacrificed for analysis at 4, 6, and 10 weeks.

Results: PCR from cartilage containing tissues demonstrated both forward- and reverse-orientation exon 2 of Ext1 in mice bearing the trans-floxed Ext1 and doxy-ColIIa1-Cre after receiving doxycycline. Homozygotes lacking Cre and heterozygotes with Cre had no demonstrable phenotype. Homozygotes with induced Cre consistently developed numerous osteochondromas as well as hypertrophic articular chondrocytes and early osteoarthritis.

Conclusions: Reversible Cre-mediated inversion of a trans-floxed genomic fragment results in a 50:50 distribution of forward and reverse orientation. Typical Cre efficiency thus yields 40% reverse-orientation by allele and 20% bi-allelic reverse-orientation among homozygous cells. This genetic recapitulation of loss of heterozygosity, applied to Ext1 in physeal chondrocytes generated numerous osteochondromas, when heterozygosity for a null-allele failed to. This argues that loss of heterozygosity is critical to the phenotypic expression of HME. Rare physeal chondrocytes without functional Ext1 may directly become the cartilaginous cap of an osteochondroma or may dysregulate physeal signals sufficiently to generate osteochondromas containing a mix of chondrocytes with and without functional Ext1.

SARC Award

THE SARC CAREER DEVELOPMENT AWARD

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1SARC, Ann Arbor, Michigan, United States; 2SARC, Ann Arbor, Michigan, United States

Objectives: To announce the SARC Career Development Award (CDA) to support clinician-scientists as they begin careers working towards becoming independent clinical researchers. To describe and compare other career development award programs.

Methods: A systematic review of existing career development awards (ASH, ASCO, NIH) was conducted. Eligibility requirements, institutional commitment and review process was compared and contrasted (See Table). Interviews were conducted with program leaders. We also developed a focus group of newly awarded NIH K08 grantees.

These criteria were reviewed by a committee of international experts in sarcoma research who will also select the candidates.

Results: Candidates must be a physician, 0-5 years post subspecialty training. The award is available to physicians in the United States, Canada or Europe who have a full-time faculty level position and spend 50-75% effort dedicated to research. Institutional commitment to the candidate and the research project is important in selection. Candidates with outstanding scientific merit and a thoughtful proposed research plan will be invited to complete a full grant proposal. There will be 2 SARC CDA’s made annually. Awardees will receive $100,000 per year for a total of 3 years as well as travel support to attend a SARC/CTOS meeting. Thus far, $2.5 million are available for this award program.
Conclusions: The SARC Career Development Award will significantly promote clinician-scientists to make the transition from training to independent clinical research investigators and help develop a new generation of sarcoma scholarship. SARC CDA’s will begin in 2009.

Eligibility criteria

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Review of Career Development Awards

Young Investigator Award Lectures

#35020 SOFT TISSUE SARCOMA (STS) OF THE EXTREMITY - COMPARISON OF CONFORMAL POST-OPERATIVE RADIOTHERAPY (CRT) AND INTENSITY MODULATED RADIOTHERAPY (IMRT)
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Objectives: Post-operative radical radiotherapy doses using conventionally planned STS potentially exceed tolerance doses of surrounding organs at risk (OAR). The aims were to define reproducible prospective planning dose volume constraints and to assess the ability of IMRT plans to minimise the dose to surrounding OAR.

Methods: A 5cm margin was added superiorly and inferiorly and 3cm circumferentially to the primary tumour bed to define PTV1 and a 2cm isotropic margin to create PTV2. OAR were defined as whole femur, neurovascular bundle, skin corridor and normal tissue. CRT, 2/3 and 4/5 field IMRT plans were created for 10 patients designated for postoperative radiotherapy of primary sarcomas. Dose prescriptions were 50Gy/25# to PTV1 and 16Gy/8# to PTV2. The primary planning objective was to minimise the dose to femur. Volumetric analysis, conformity and heterogeneity indices were used to compare plans.

Results: 4/5 field IMRT plans showed best conformity and least dose heterogeneity compared to the other plans (table1). The use of 2/3 (p=0.01) and 4/5 field IMRT resulted in significantly lower femur V45 compared to CRT. 4/5 field IMRT resulted in a significantly lower normal tissue V55 (p=0.004) and Dmax (p=0.04) than CRT.

Conclusions: For the first time a prospective and reproducible set of planning guidelines and dose volume constraints for CRT and IMRT planning for adjuvant radiotherapy of STS of the extremity was devised. The 4/5 field IMRT approach resulted in a significantly decreased dose to OAR compared to CRT. The achieved reduction is potentially clinically significant and could lead to a reduction in late toxicity.

#34891 PFETIN AS A PROGNOSTIC BIOMARKER OF GASTROINTESTINAL STROMAL TUMORS REVEALED BY PROTEOMICS
Yoshiyuki Suehara1, Kazutaka Kikuta1, Kunihiko Seki2, Tadashi Hasegawa2, Kiyonaga Fujii1, Tadakazu Shimoda1, Akira Kawai1, Setsuo Hirohashi1, Tadashi Kondo1
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Objectives: We aimed to develop prognostic biomarkers for gastrointestinal stromal tumors (GISTs) employing a proteomic approach.

Methods: We examined the proteomic profile of GISTs using two-dimensional difference gel electrophoresis (2D-DIGE). The prognostic performance of biomarker candidates was examined using a large-scale sample set and specific antibodies.

Results: We identified 43 protein spots whose intensity was statistically different between GISTs with good and poor prognosis. Mass spectrometric protein identification demonstrated that the 43 spots corresponded to 25 distinct gene products. Eight of the 43 spots derived from pfetin, a potassium channel protein, and four of the eight pfetin spots had a high discriminative power between the two groups. Western blotting and real-time PCR showed that pfetin expression and tumor metastasis were inversely related. The prognostic performance of pfetin was also examined by immunohistochemistry on 210 GIST cases. The 5-year metastasis-free survival rate was 93.9% and 36.2% for patients with pfetin positive and negative tumors respectively (p<0.0001). Uni- and multivariate analyses revealed that pfetin expression was a powerful prognostic marker among the clinicopathological parameters examined, including risk classification and c-kit or PDGFRA mutation status.

Conclusions: These results establish pfetin as a powerful prognostic marker for GISTs, and may provide novel therapeutic strategies to prevent metastasis of GIST.
ARIAD Pharmaceuticals, Inc. is pleased to announce SUCCEED – a multinational, randomized, Phase 3, double-blind, placebo-controlled trial to determine the efficacy and safety of oral deforolimus when administered as maintenance therapy to patients with metastatic soft-tissue or bone sarcomas who have had a favorable outcome to chemotherapy.

To learn more about the SUCCEED trial, or to find a trial site nearby, please call the international number **1-617-621-2302** or visit [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) (NCT00538239).
OBJECTIVE: To assess the pulmonary effects of aerosol gemcitabine as a potential therapy for lung metastases from osteosarcoma. Dogs with resected osteosarcoma (appendicular, n=13; mandibular, n=1; soft tissue, n=2), which did (n=12) or did not (n=4) receive prior intravenous chemotherapy with (n=12) or without (n=4) gross evidence of pulmonary metastasis were enrolled in this trial. Dogs were desensitized to wearing a custom fitted polyethylene hood and were then treated (n=280; range 2-98; median=10) with 25 mg gemcitabine via aerosol over 45-60 minutes on a M/Th or T/F schedule. Complete blood counts, serum biochemistry and arterial blood gases were assessed every 2 weeks. Thoracic radiographs were monitored every 8-12 weeks. When quality of life decreased dogs were euthanatized and then underwent complete necropsy and histological evaluation.

RESULTS: Clinically, aerosol gemcitabine was well tolerated. No hematomal, serum biochemical, or arterial blood gas parameter changes were noted in any patient during the treatment which could be ascribed solely to aerosol gemcitabine. Histological assessment showed no airway pathology associated with aerosol gemcitabine. Histopathology demonstrated increased necrosis of osteosarcoma metastases without increased lung inflammation.

CONCLUSIONS: Aerosol gemcitabine resulted in increased necrosis of osteosarcoma metastases as compared to historical controls. Thus, inhalational gemcitabine has potential to become a safe and effective outpatient therapy to treat or prevent osteosarcoma lung metastases. This demonstration of clinical activity with low toxicity in dogs provides sufficient data to proceed with studies against osteosarcoma in humans.

34807 - BODY MASS INDEX (BMI) AT DIAGNOSIS IS ASSOCIATED WITH SURGICAL WOUND COMPLICATIONS IN PATIENTS WITH LOCALIZED OSTEOSARCOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

Malnutrition is a common symptom at diagnosis and during treatment for sarcoma patients. Poor nutritional status has been associated with increased risk of complications, particularly infections. We investigated the role of body mass index (BMI) on the incidence of surgical wound complications in children and young adults with localized osteosarcoma treated on the Children's Oncology Group (COG) legacy trial, INT-0133.

METHODS: Eligible patients were enrolled on INT-0133, had localized disease, remained on protocol to have definitive surgery 6-16 weeks after study entry, and had adequate height, weight, and surgical complication data for analysis. By protocol design, de-thrombosis was rare (1.2% of patients) and more common in high BMI (OR=2.0, p=0.04) and high BMI (OR=1.7, p=0.25) patients. Post-operative complications occurred in 15.3% of patients. Wound infection or slough were more common in low BMI (OR=2.0, p=0.04) and high BMI (OR=1.7, p=0.25) patients. Thrombosis was rare (1.2% of patients) and more common in high BMI patients (OR=9.4, p=0.03).

CONCLUSIONS: Low BMI at the start of treatment for localized
osteosarcoma was associated with an increased risk of wound infection or slough after definitive surgery. Future studies should evaluate whether correction of malnutrition reduces the risk of surgical complications.

**34819 - Zoledronate Treatment of Benign Bone Tumors**

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**Objectives:** Benign aggressive bone tumors arising in complex anatomic sites such as the pelvis prove challenging to the orthopaedic oncologist. Prior alternatives to surgery include radiation therapy, cryotherapy, and angiographic embolization. Zoledronate has been shown to effectively treat patients with hypercalcemia of malignancy as well as multiple myeloma and bone metastases from other solid tumors such as breast and renal cell carcinoma.

**Methods:** We present a series of six cases of symptomatic benign inoperable bone tumors treated with zoledronate. All six patients were treated with a 6–24 month course of zoledronate and followed both clinically and radiographically over an average period of thirty months. Favorable outcomes were measured by resolution of symptoms as well as radiographic demonstration of tumor consolidation and bony reconstitution.

**Results:** Five patients demonstrated resolution of symptoms over the course of zoledronate treatment as well as radiographic signs of bony reconstitution and mineralization. One patient underwent scapulectomy due to pain from pre-existing glenoid fracture. No patient had significant complications or side effects.

**Conclusions:** We are not aware of any formal investigation on zoledronate as primary treatment for benign bone tumors in areas that are not amendable to surgical resection without significant morbidity. In our study, nearly all patients had favorable outcomes by resolution of symptoms as well as radiographic demonstration of tumor consolidation and bony reconstitution over the course of zoledronate treatment. Although a larger prospective study needs to be undertaken, it appears that zoledronate is a safe and effective treatment for benign bone tumors in the short-term.

**Giant Cell Tumor: Initial, 6 mo, 30 mo**

**34825 - Do Radiation Associated Sarcomas Have the Same Prognosis as Sporadic Sarcomas?**

*Rebecca A. Gladdy2; Li-Xuan Qin2; Mark A. Edgar2; Cristina R. Antonescu2; Kaled Alekitar2; Murray F. Brennan1; *Samuel Singer1
1Mount Sinai Hospital, Toronto, Ontario, Canada; 2Memorial Sloan Kettering Cancer Center, New York, NY, United States

**Objectives:** To determine if radiation associated sarcomas (RAS) are associated with an inferior prognosis compared to case-matched sporadic soft tissue sarcoma (STS) patients.

**Methods:** Prospective data on 199 primary RAS was identified from 7,649 STS patients in a single institution from 1982 to 2007. A multivariate analysis of clinicopathologic factors for disease-specific survival (DSS) and a case-matched analysis stratified by histologic subtype were performed using known prognostic variables.

**Results:** Of the 199 RAS identified, most were high grade (86%) of deep (87%) truncal (56%) lesions and an R0 resection was achieved in 55% of patients. The median interval between RT and RAS development was 10 (1-74) years, which varied significantly by histologic type (P = 0.001). The 5-year DSS was 49% and independent predictors of DSS were high grade, size 5 to 10 cm, size >10 cm, positive microscopic margin, grossly positive margin, and histologic type. In the case-match analysis, RAS MFH the most common histologic type, had a poorer prognosis (P = 0.005), when compared to case matched MFH controls even when adjusted for MFH subtype (myxofibrosarcoma vs. pleomorphic). Angiosarcoma and leiomyosarcoma had the same prognosis as controls. Finally, limited numbers of MPNST cases precluded matching, however DSS was significantly worse in cases compared to unmatched controls (P = 0.008).

**Conclusions:** RAS are associated with an inferior outcome in MFH and likely MPNST histologic types compared to their sporadic counterparts. This may aid in the counseling and selection of patients for clinical trials and neoadjuvant treatment strategies.

**34827 - Surgery of Giant Cell Tumor of the Sacrum: An Analysis of 26 Cases**

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University of Bologna Istituto Rizzoli, Bologna, Italy

**Objectives:** were to review a series of patients surgically treated for giant cell tumor of the sacrum in a single Institution.

**Methods:** Twentysix cases of sacral GCT were treated between 1987 and 2005. Histologic diagnoses and imaging studies were reviewed. Patients included 20 females and 6 males, ranging in age from 14 to 68 years. Mean follow-up was 9.6 years (min. 2-max. 21). In 21 cases S1 was involved, in 5 cases lesion was distal to S2.

Surgical treatment was intraleisional excision in 25 patients with local adjuvants in 15 (phenol or liquid nitrogen) and 1 marginal resection. In 19 cases preoperative selective arterial embolization was performed in order to reduce bleeding.

Seventeen patients received radiotherapy. Surgical approach was posterior in 12, anterior and posterior in 14 patients.

**Results:** Twentytwo patients were NED at a mean follow up of 9.6 years, 2 patients NED1 after treatment of local recurrence (1 local recurrence at 16 months postoperatively treated with further curettage and NED1 8 years post second surgery; 1 local recurrence at 2 months treated with two consecutive radiofrequency ablations and NED1 at 3 years post second treatment), 2 patients died of disease (one with postoperative massive pulmonary embolism, one 6 years with local recurrence and subsequent radioinduced malignant transformation).

**Conclusions:** One case (6%) of radioinduced malignancy was observed. Local recurrence rated 12%.

Of 9 patients who had surgery only (excluding the postoperative death), 7/8 were NED (87.5%) and 1/8 was NED1 (12.5%). Therefore radiotherapy should be avoided if possible.

**34839 - Intralesional Curettage for Benign Bone Lesions in Young Athletes**

*Christian M. Ogilvie; Eileen A. Crawford; Rachel L. Slotcavage; *Richard D. Lackman
University of Pennsylvania, Philadelphia, Pennsylvania, United States
34840 - RETROPERITONEAL LIPOSARCOMAS
Ser Yee Lee1; MH Chew1; Brian KP Goh1; London LPJ Ooi1; WK Wong2; KC Soo2
1Singapore General Hospital, Singapore, Singapore, Singapore; 2National Cancer Centre Singapore, Singapore, Singapore, Singapore

Objectives: To evaluate the clinical results of resection for retroperitoneal liposarcomas in a single institution and determine the prognostic factors for disease recurrence and patient survival.

Methods: A retrospective review of departmental records was used to identify all the patients with primary retroperitoneal liposarcoma treated between July 1990 and June 2005. Histology at primary presentation was reviewed and subtyped into 5 distinct groups according to WHO classification. The influence of clinicopathological factors on recurrence and overall survival was analyzed.

Results: Twenty-one patients with primary retroperitoneal liposarcoma had surgery for curative intent (12 Males, 9 Females; mean age: 52.4 years, range: 29-71) were evaluated. Of these, 13 (61.9%) presented with well differentiated, 3 (14.3%) with dedifferentiated, 3 (14.3%) with myxoid, 1(4.8%) with pleomorphic and 1 (4.8%) with round cell morphology. The median tumor burden was 36 cm (9-83). Median follow-up time was 69 months. There was no peri-operative mortality and morbidity occurred in 6(28.6%) patients. Surgical margins were involved in 9(42.9%) patients. Resection of contiguous organs was required in 17(81%) to achieve gross surgical margins. Eleven out of the 21(52%) of the patients had tumor recurrence. Median disease-free survival was 19 months and overall 3- and 5-year survival rate was 95% and 81% respectively.

Conclusions: An aggressive surgical approach in primary RPS is associated with long-term survival. Local control continues to be a significant problem in the management of RPS, requiring contiguous organ resection resulting in considerable morbidity. However as new surgical options for these problems are limited, further outcome improvement requires novel adjuvant therapies.

34859 - INJECTION OF MESTHYPREDNISOLONE ACETATE IN TREATMENT OF EOSINOPHILIC GRANULOMA OF BONE
Giuseppe Bosco1; Alessio Bosco1; Giuseppina Paone2; Elisa Pala1; Teresa Calabrò1; *Pietro Ruggieri1
1University of Bologna Istituto Ortopedico Rizzoli, Bologna, Italy; 2Department of Pediatrics Oncology University of Bologna, Bologna, Italy

Objectives: Eosinophilic granuloma (EG) is Langerhans cell histiocytosis localized in the skeleton, either mono-ostotic or polyostotic. Aim of this study was to evaluate results and define indications of injection of steroids in the treatment of localized EG.

Methods: this was a retrospective analysis of a single institution experience. From January 1994 to December 2004, 50 patients with EG were treated in our Institution, including 31 males and 19 females, ranging in age from 2 to 60 years. All patients had a bone scan to exclude multiple bone involvement. In monostotic EG site was lower limb in 17, upper limb in 12, pelvis in 11 , spine in 4. Six patients had multiple localizations: 2 primarily had local treatment with steroid injection since at presentation only one site was involved and subsequently they showed other sites involvement, 4 had primarily a systemic skeletal disease and received treatment according to Vinblastine and Prednison. Every patient was followed periodically with plain X rays every three months and periodical clinical evaluation. If X-rays showed response at three months and clinical improvement no further injection was done.

Results: most of the patients (40) with a single bone lesion had only one local injection of prednison. Mean time to healing (radiographic regression of disease) was 9 months.

Conclusions: This study confirm the efficacy of steroid injection in the treatment of eosinophilic granuloma of bone, while systemic treatment is required when multiple sites are affected. Bone scan should be repeated every year for 2 years.
therapy 13/16 indicated open thoracotomy as the initial therapeutic approach. Manual exploration during thoracotomy was uniformly considered as standard. Exploration of the contralateral side in seemingly unilateral pulmonary disease was refuted by one third, who considered unilateral exploration as sufficient. The approach towards metastases seemingly disappearing during induction chemotherapy was most heterogeneous, with half preferring surgical exploration and the others supporting a wait and watch strategy.

**Conclusions:** The survey highlights consensus in some areas and strikingly diverse practices in others, even amongst experts in the field. Heterogeneous approaches reflect the current lack of evidence regarding practical aspects of management in a rare disease and call for longitudinal research into the clinical efficacy of diagnostic and therapeutic procedures.

**34864 - ARE ALL ANGIOSARCOMAS CREATED EQUALLY?**

*James M. Lewis*; Mark I. Gimbel; Jonathan S. Zager; Mecker Moller; Hideko Yamauchi; Marilyn M. Bui; David Cheong; Charles Cox; Jane Messina; *G. Douglas Letson*; *Vernon K. Sondak* 1

1H Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, United States; 2University of South Florida, Tampa, Florida, United States

**Objectives:** Angiosarcoma (AS) is divided into subcategories based predominantly on anatomy. We sought to identify if any angiosarcoma subtypes were associated with improved outcomes.

**Methods:** All patients with a diagnosis of AS from 1991 to 2008 were reviewed. Patients with deep/visceral AS were excluded, as were living breast and cutaneous patients with less than 2 year follow-up.

**Results:** We identified 44 patients with breast (BA) or cutaneous (CA) angiosarcoma. Fifteen patients (34%) had BA, and 29 patients (66%) had CA. Median age for the BA and CA cohorts was 64 (34-73 years) and 70 (24-87 years), respectively. Median follow-up was 39 (30-66) months for BA patients and 31(25-57) months for CA patients. The CA cohort was comprised of 21 head and neck, 6 extremity, and 2 truncal tumors. Five BA patients (33%) had primary tumors and 11 (67%) had radiation induced tumors. Thirteen patients (87%) with BA had R0 resections compared to 21 (72%) CA patients. There was a trend toward overall survival in BA patients compared to CA patients (67% vs. 34%, p=0.09). Recurrence rates for BA and CA were 53% and 72%, respectively (p=0.3). Recurrence was associated with poor outcome for both subtypes. Sixty-three percent of BA patients and 76% of CA patients who recurred died. There was no significant difference between non-surgical treatment modalities between the two cohorts.

**Conclusions:** Patients with BA may have a better prognosis than patients with CA. Clinigenomic factors rather than location may contribute to these differences. Further molecular investigation into angiosarcoma sub-types warranted.

**34867 - LIMB-SPARING SURGERY FOR RECURRENT POPLITEAL MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MPNST) WITH GOOD CHEMOTHERAPEUTIC RESPONSE**

Eisuke Kobayashi; *Akira Kawai; Yasuo Beppu; Hirokazu Chuman

1Department of Orthopaedic Surgery National Cancer Center Hospital, Tokyo, Japan; 2Keio University, Tokyo, Japan

**Objectives:** MPNST frequently occurs in patients with neurofibromatosis. It is an aggressive tumor with high rates of local recurrence and metastasis. Wide surgical resection is the only established method of treatment, and limb salvage is often difficult because the primary tumor is located adjacent to neurovascular structures. In addition to these difficulties, no effective chemotherapy has yet been established. Here we present two cases of recurrent popliteal MPNST that were successfully treated by limb-sparing surgery after a good response to chemotherapy with ifosfamide and etoposide.

**Methods:** The two patients, a 28-year-old woman and a 33-year-old man, were treated at our institution. Both had a history of neurofibromatosis type 1. Their primary tumors were initially excised with an intralesional margin, and local recurrences were observed after 4 and 6 months, respectively.

**Results:** We performed 4 and 5 cycles of chemotherapy using a combination of ifosfamide 9 g/m2 and etoposide 500 mg/m2 for 5 days. Both tumors demonstrated significant shrinkage after chemotherapy, allowing us to perform limb-sparing surgery with preservation of neurovascular structures. After surgery, the patients received 3 and 2 cycles of the same chemotherapy regimen, respectively, and currently, 5 years later, neither of them has recurrence or metastasis.

**Conclusions:** Although chemotherapy is usually considered to be of little benefit for MPNST, and surgery is generally challenging, treatment was successful in these two cases. Further studies therefore seem warranted to establish the optimal therapeutic strategy for MPNST.

**34913 - DOES STRINGENT PATIENT SELECTION IMPROVE ALLOGRAFT OUTCOMES?**

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**Objectives:** We hypothesized that stringent patient selection in the use of large bulk structural allografts for limb preservation would positively affect outcomes and decrease complication rates compared to historical controls.

**Methods:** We reviewed our experience from September 1998 through March 2007. Selection criteria included patients less than 50 years old, non-smokers, non-obese (BMI< 40), who did not receive radiation therapy perioperatively, and who underwent intercalary allograft reconstruction except in the upper extremity where osteoarticular allografts were permitted. Compensation rates were compared to historical controls. Outcomes were assessed utilizing the MSTS and TESS scoring systems.

**Results:** We found 23 patients fulfilling our cohort inclusion criteria. Twenty patients had greater than 2 year follow-up and all patients had at least 1 year follow-up. Fourteen patients were male and 9 were female. The mean patient age was 21 years (range, 7-49). The overall survival rate for the 23 allografts was 91% (21/23). 22 of 23 (96%) patients, including those who had graft removal, retained the limb.
**Objectives:** To evaluate local control, survival and complication rate after treatment of bone sarcomas (BS) with limb-sparing surgery and reconstruction of bone defects with vascularised fibula grafts.

**Methods:** Eight consecutive patients (mean age at operation 13 (range 4-24) years, female/male= 6/2) with BS (osseous/chondrosarcoma/Ewing’s sarcoma/chondrosarcoma= 4/3/1) had during the year’s 2000 - 2006 limb-sparing surgery and reconstruction of bone defects with vascularised fibula grafts. Seven of the patients also underwent treatment with chemotherapy. The bone defects after surgery, that was reconstructed with insertion of one (n=6) or two (n=2) vascularised fibular grafts, were: femoral diaphysis including the proximal epiphysis (n=2), humeral diaphysis (n=2), humeral diaphysis including the proximal epiphysis (n=1), femoral diaphysis (n=1), ulnar diaphysis (n=1), and tibial diaphysis (n=1).

**Results:** One patient suffering from Ewing’s sarcoma had an early hip disarticulation (because of poor effect of chemotherapy and only marginal tumour resection), and died 9 months after the operation. The remaining patients (n=7) were all alive 3.8 (range 1.7-7.5) years after surgery. With the exception of one patient, who had a lung metastasis removed surgically, all patients were without any signs of local recurrence or distant metastases. During the follow-up the following major complications were seen: 1-3 fractures (n=5), pseudarthrosis (n=1), and hip disarticulation (n=1).

**Conclusions:** Limb-sparing surgery with reconstruction of bone defects using vascularised fibular grafts in BS cases unsuitable for reconstruction with insertion of a tumour prosthesis was feasible with good results with respect to survival, but complications, especially fractures, should be expected in most patients.

**34934 - VASCULARISED FIBULA GRAFTS FOR RECONSTRUCTION OF BONE DEFECTS AFTER TUMOUR RESECTIONS BECAUSE OF BONE SARCOMAS**

Dorrit Hovgaard; Michael M. Petersen; Jens J. Elberg; Catherine Rechnitzer; Søren Daugaard; Aida Muhic

*Righospitalet, Copenhagen, Denmark*

**Objectives:** To evaluate local control, survival and complication rate after treatment of bone sarcomas (BS) with limb-sparing surgery and reconstruction of bone defects with vascularised fibula grafts.

**Methods:** Eight consecutive patients (mean age at operation 13 (range 4-24) years, female/male= 6/2) with BS (osseous/chondrosarcoma/Ewing’s sarcoma/chondrosarcoma= 4/3/1) had during the year’s 2000 - 2006 limb-sparing surgery and reconstruction of bone defects with vascularised fibula grafts. Seven of the patients also underwent treatment with chemotherapy. The bone defects after surgery, that was reconstructed with insertion of one (n=6) or two (n=2) vascularised fibular grafts, were: femoral diaphysis including the proximal epiphysis (n=2), humeral diaphysis (n=2), humeral diaphysis including the proximal epiphysis (n=1), femoral diaphysis (n=1), ulnar diaphysis (n=1), and tibial diaphysis (n=1).

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**Conclusions:** Limb-sparing surgery with reconstruction of bone defects using vascularised fibular grafts in BS cases unsuitable for reconstruction with insertion of a tumour prosthesis was feasible with good results with respect to survival, but complications, especially fractures, should be expected in most patients.

**34939 - PROTEOMIC ANALYSIS OF A CELL CULTURE MODEL OF PAX3-FKHR MEDIATED TRANSFORMATION**

*Joseph G Pressey; Richie Herring; Gloria Robinson; Landon Wilson; Christine S Pressey*

*University of Alabama at Birmingham, Birmingham, AL, United States*

**Objectives:** To investigate the consequences of PAX3-FKHR (P3F) expression in RMS tumorigenesis, we have undertaken a comprehensive proteomic analysis of a robust in vitro model of A-RMS tumorigenesis.

**Methods:** P3F and/or SV40 Large-T antigen (LT) were transduced into murine C3H10T1/2 embryonic fibroblasts. Whole cell protein lysates were obtained from stably transduced cells. To generate conditioned media (CM), confluent cells were cultured in serum free media. The proteome of cells transformed by P3F + LT were compared with cells transduced by LT alone. Protein samples from whole cell lysates or CM were labeled with cy-dyes, mixed, and analyzed by two dimensional differential in-gel electrophoresis (2D-DIGE). Protein spots with significant differential expression were analyzed by matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) or tandem mass spectrometry (MS).

**Results:** The co-expression of P3F + LT led to the transformation of fibroblasts as evidenced by focus formation, anchorage-independent growth, and allograft tumor formation. 2D-DIGE analysis comparing whole cell lysates derived from cells expressing P3F + LT versus cells expressing LT alone identified 83 differentially expressed protein spots. MS analysis identified proteins with potentially critical roles in RMS tumorigenesis including valosin containing protein (VCP), ANXA3, and heat shock proteins including HSP90. Abundant type I collagen was detected in conditioned media of cells expressing P3F + LT, suggestive of increased collagenase activity. Follow-up qRT-PCR studies demonstrated that P3F + LT sharply upregulated matrix metalloproteinase 13 (MMP-13) expression.

**Conclusions:** Proteomic analysis of cell culture models of A-RMS provides a powerful means of identifying P3F related biomarkers and effector proteins.

**34942 - ADDITION OF MURAMYL TRIPEPTIDE TO CHEMOTHERAPY FOR PATIENTS WITH NEWLY DIAGNOSED METASTATIC OSTEOSARCOMA: A REPORT FROM THE CHILDREN’S ONCOLOGY GROUP**

*Alexander J. Chou; *Eugenie Kleimerman; Mark D. Kralio; Donna Betcher; *John H. Healey; *Ernest Conrad; Helen Nadel; Michael Nieder; Judith Sato; Michael A. Weiner; Robert J. Wells; *Richard B. Womer; *Paul A. Meyers*

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**Objectives:** With longer followup, the addition of muramyl tripeptide (MTP) to chemotherapy has been shown to improve overall survival in patients with non-metastatic osteosarcoma (OS). We report the results of MTP addition to chemotherapy for patients with metastatic OS.

**Methods:** Intergroup-0133 was a prospective randomized trial for the treatment of newly diagnosed patients with OS. We compared three drug chemotherapy with cisplatin, doxorubicin, and high-dose methotrexate (Regimen A) to the same three drugs with the addition of ifosfamide (Regimen B). We evaluated the addition of MTP to chemotherapy. We report herein the first analysis of 91 patients with metastatic OS at presentation. Outcome measures included event free survival (EFS) and overall survival.

**Results:** Five-year EFS for patients who received MTP (n=46) was 42% versus 26% for those who did not (n=45), p=0.38. The 5-year overall survival for patients who received MTP versus no MTP was 53% and 40% respectively (p=0.36). The comparison of Regimen A
with regimen B did not suggest a difference for EFS (35% v. 34% respectively, p=0.75) or overall survival (52% v. 43% respectively, p=0.95). While the small numbers of patients in the metastatic cohort preclude statistical significance, the pattern of outcome for the metastatic cohort was the same as the pattern of outcome for the non-metastatic cohort.

Conclusions: When the metastatic cohort was considered in isolation, the addition of MTP to chemotherapy did not achieve a statistically significant improvement in outcome. The pattern of outcome is similar to the pattern in non-metastatic patients.

34951 - COMPRESSION OSSEOTRANSMACTIVE OF PROXIMAL FEMORAL ENDOPROSTHESIS FOR LARGE ONCOLOGIC RECONSTRUCTION

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Objectives: Compressive osseointegration technology has been developed in order to avoid endoprosthetic failure through the attainment of immediate, durable compliant fixation. This study was undertaken to determine the effectiveness of the Compress® device for anchorage of massive proximal femoral endoprostheses.

Methods: A retrospective review of all proximal femoral Compress® reconstructions performed at the time of primary oncologic resection by a single surgeon at a single institution over a 7.5 year period was performed. Medical records, radiographs, and clinical examinations were reviewed in order to assess surgical, functional, oncologic, and prosthetic outcomes.

Results: Nine consecutive patients operated upon between October, 2000 and March, 2008 were identified. There were 7 males and 2 females with an average age of 45 years (range 6-86). Follow-up averaged 2.3 years (range 0.7-4.5). Diagnoses included chondrosarcoma (4) osteosarcoma (2), Ewing sarcoma (2), leiomyosarcoma, 1 chondrosarcoma). The types of excision included internal hemipelvectomy in 4 cases, extended hemipelvectomy in 1, and wide excision of soft tissue sarcoma in 5. The reconstructive procedures were rectus abdominus flaps in 4 cases, free latissimus dorsi flaps in 5, and thigh fillet flap in 1. The mean duration of the procedure was 10.8 hours and mean blood loss was 1,650 mL. Complications included partial flap necrosis in 1 and infection in 1. Three patients suffered local recurrence.

Conclusions: To reduce the risk of complications associated with resection of pelvic malignancies, aggressive use of soft tissue reconstruction with well-vascularized tissue is advisable. A pedicled rectus abdominus flap or a free latissimus dorsi flap provides adequate tissue mass to eliminate dead space and cover the exposed bone or implants.

34969 - RESULTS OF A PHASE IIB/IIA STUDY OF SLIT (SUSTAINED RELEASE LIPID INHALATION TARGETING) CISPLATIN BY INHALATION IN THE TREATMENT OF PATIENTS WITH RELAPSED/PROGRESSIVE OSTEOSARCOMA METASTATIC TO THE LUNG

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Objectives: Encapsulating cisplatin within liposomes, SLIT (Sustained release Lipid Inhalation Targeting) Cisplatin is designed to target lung metastases with minimal systemic exposure. An open-label, phase IIb/IIa study was performed to characterize the safety and efficacy of SLIT Cisplatin in OS patients who only had pulmonary metastases.

Methods: SLIT Cisplatin was administered via nebulizer once every 2 weeks. Response was evaluated radiographically according to the WHO criteria every 2 cycles. When possible, metastectomy was undertaken in patients on study after 2 cycles. Patients with stable disease or better response continued drug after resection until disease progression or one year.

Results: Nineteen patients were treated. No patients experienced hematologic toxicity, nephrotoxicity or peripheral neuropathy. Nausea/vomiting (> or = grade 3) was attributed to study drug in 1 patient. Respiratory symptoms were observed in 13/19 patients with only 1 patient experiencing a > or = grade 3 respiratory symptom (not related to study drug). Eleven patients had bulky disease, and progressed prior to cycle 7. Eight patients had all lesions < 2 cm. Two of these had stable disease after 2 cycles, underwent resection of metastases, and remained pulmonary disease free one year after initiation of therapy. One additional patient had sustained PR.
Systemic cisplatin exposure was minimal.

**Conclusions:** SLIT Cisplatin is well tolerated in heavily treated OS patients. Three of 8 patients with less bulky disease had sustained benefit. This study suggests there may be activity in those patients with limited pulmonary disease, and further study is warranted in this subgroup of patients.

34986 - ACCURACY OF TRUCUT AND INCISION BIOPSY IN THE DIAGNOSIS OF SOFT TISSUE MASSES

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**Objectives:** The Aim of this study was to compare the accuracy of Trucut biopsy and open Incision Biopsy in our centre.

**Methods:** This was a retrospective review of clinical and pathology records. Between January 2006 and June 2007, 34 Trucut biopsies without imaging guidance in an outpatient setting and 57 inpatient incision biopsies were performed on patients referred with a soft tissue mass. In each case the accuracy of biopsy in providing a diagnostic sample, in determining the tumour type and the histological grade were calculated. For each biopsy method we compared the diagnosis after biopsy with the final diagnosis after excision. The proportion of diagnostic biopsies was calculated, as were the sensitivity and specificity of each technique in providing a diagnosis. Fisher’s exact test was used to test for differences in the techniques.

**Results:** In this series there were 41 soft tissue sarcomas, 8 metastatic adenocarcinoma soft tissue deposits, 7 lymphomas, 1 non soft tissue sarcoma, 32 benign soft tissue tumours and 1 infection. 33/34 Trucut biopsies and 55/57 open biopsies provided the final histological diagnosis. There was no statistical difference between the techniques in the accuracy of identifying the type and grade of soft tissue sarcoma

**Conclusions:** Trucut biopsy is equivalent to incision biopsy in its accuracy of diagnosing soft tissue tumours. Biopsy in an outpatient setting for appropriate tumours is cost effective and likely shortens the time to diagnosis. Our results are comparable to published data from other centres.

34988 - DISTAL FEMUR DEFECTS RECONSTRUCTED WITH PMMA AND INTERNAL FIXATION DEVICES: A BIOMECHANICAL STUDY

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**Objectives:** Benign aggressive distal femur tumors are treated with curettage, adjuvant phenol or argon, and PMMA packing. For large defects, internal fixation device is added to reduce the fracture risk. The purpose of this study is to compare the strength of locking plates to other fixation devices for stabilization of these defects.

**Methods:** Lateral condyle defects in young, fresh frozen femurs were packed with PMMA and augmented by internal fixation. Three groups of 4 matched pairs of femurs were organized for the following comparisons: 1) stacked Steinmann pins vs crossed screws; 2) stacked pins vs locking plates; and 3) crossed screws vs locking plates. Specimens were subjected to axial load-to-failure testing on an MTS machine.

**Results:** There was no difference in load-to-failure strength (p=0.177) using Steinmann pins (14916 + 2959 N) or crossed screws (11651 + 3074 N). Locking plate constructs (24245 + 8228 N) were stronger (p=0.028) than Steinmann pin constructs (11728 + 2724 N). Locking plate constructs (22188 + 3622 N) were also stronger (p<0.001) than crossed-screw constructs (9880 + 1130 N). Steinmann pin constructs failed with severe intra-articular fractures; crossed screw constructs failed with bulging of the defects, articular impaction, and minimal fracture propagation. Locking plate constructs failed with extra-articular spiral shaft fractures.

**Conclusions:** For lateral femoral condyle defects packed with PMMA, locking plate fixation provides greater strength in axial load-to-failure testing compared to stacked Steinmann pins or crossed screws. The mode of failure for locking plates is through an extra-articular fracture of the shaft that preserves the articular surface.

34993 - INNOVATIVE CONCAVE-CONVEX ALLOGRAFT JUNCTIONS IN FEMORAL ALLOGRAFTS: A BIOMECHANICAL STUDY

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**Objectives:** Intercalary allografts are the preferred method of reconstruction following femoral diaphyseal tumor resection. We believe a novel approach to allograft junctions using concave-convex reamers improve the rate of healing by increasing contact surface area (s.a) and stability of these junctions. The purpose of this study was to compare these novel junctions to straight osteotomy junctions in regard to these parameters.

**Methods:** 30 large femoral artificial poly-resin femurs were randomly separated into 3 groups to compare: 1) perfectly matched transverse-cut, 2) random non-matched transverse-cut, and 3) paired concave-convex reamed allograft junctions. Prior to fixation with a locking plate, a piece of contact pressure film was placed between each junction. The contact surface area was analyzed by digital software and compared to the total potential contact area for each junction site.

**Results:** Perfectly matched transverse-cut allograft-host junctions fixed with flat or pre-bent locking plates had a mean s.a. of 136.04 mm2 and 215.66 mm2 respectively; mean % s.a. of 19.9% and 31.6% respectively. Non-matched, transverse-cut allograft junctions fixed with flat plates or pre-bent locking plates had a mean s.a. of 123.18 mm2 and 155.84 mm2 respectively; mean % s.a. of 18.29% and 21.8% respectively. While concave-convex allograft junctions fixed with a flat plate or pre-bent plates had a mean s.a. of 335.84 mm2 and 343.28 mm2 respectively, and a % contact s.a. of 39.8% and 43.5% respectively.

**Conclusions:** Concave-convex allograft-host junctions produce a greater contact s.a. compared to current standard transverse osteotomies used in intercalary allograft procedures (p-values <0.01). Increasing the s.a., while maintaining stability may promote better healing and minimize nonunions. The novel concave-convex reamers likely make intra-operative junction site preparation easier to match.

34995 - LONG TERM RESULTS OF 77 SOFT TISSUE SARCOMA UNSOLVED BY THE FIRST SURGEON

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**Objectives:** To stress the importance of adequate primary
management in adult STS of the extremities

Methods: Retrospective comparison of a series of 77 consecutive patients referred to our centre after a whoops procedure (Group A: 32 patients) or after being diagnosed of locally recurrent disease (Group B: 45 patients).

Results: Group A: All patients had a re-excision (tumoral cells were found in 40%). Median follow-up was 59 months (12-216). Three had local recurrence, one of them needing an amputation. Disease free survival is 87.5%.

Group B: Surgical treatment of the recurrence was carried out in 38 patients. The mean follow-up (from diagnosis) was 72 (12-242) months. Twenty two patients developed metastases after the recurrence procedure. 43% died. Twenty two had any complication, mainly in the re-irradiated patients subset. Disease free survival is 26.7%.

Conclusions: After a whoops procedure, long term disease free survival can be achieved in patients properly managed by multidisciplinary teams in experienced centres. Local relapse should be minimized with proper primary management in specialised centres because the probability of long term success after locally recurrent disease is low.

35013 - AROMATASE EXPRESSION IN JUVENILE ANGIOFIBROMAS
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Objectives: The pathophysiology behind Juvenile Angiofibromas (JAF) has not been fully elucidated but the influence of steroid hormones in their growth has been suggested. This neoplasm has a predilection for adolescent males. However, only a minority of the neoplastic cells express androgen receptors. The estrogen receptor beta was recently demonstrated in a majority of the cases.

Methods: Five cases of sinonasal juvenile angiofibromas archived at Tampa General Hospital were retrieved by computer assisted search. Hematoxylin and Eosin stained slides of the selected cases were reviewed by a single soft tissue pathologist (MMB) who confirmed the diagnosis.

Results: All of the evaluated cases (5/5) expressed aromatase. This enzyme appeared to be preferentially expressed within the intrallesional fibroblasts (3+). The perivascular cells were also diffusely positive (2-3+). The overlying mucosal epithelium was focally positive (2+).

Conclusions: We examined the expression of the p450 aromatase enzyme in five cases of JNA’s. All five of our cases showed positive staining for aromatase. Moreover, we demonstrated aromatase enzyme positivity in tumor cells in a similar fashion to estrogen receptor beta expression reported by Montag et al. Based on these results, we propose that one mechanism for the hormone-induced growth theory of these tumors may be the presence of the aromatase enzyme, which facilitates proliferation by converting androgens into estrogens. To our knowledge, no prior study has explored this relationship between aromatase and JNA’s. However, this may suggest the need for further studies to investigate the use of antagonists of aromatase or estrogen receptors for treatment of JNA’s.

35030 - MARGINAL EXCISION WITH ADJUVANT RADIOTHERAPY VERSUS WIDE SURGICAL EXCISION WITH OR WITHOUT ADJUVANT RADIOTHERAPY OF MALIGNANT SOFT TISSUE SARCOMAS - RATES OF PROGRESSION AND LOCAL RECURRENCE: THE NOTTINGHAM EXPERIENCE
Ben Jamnadas-Khoda; Sáidy Hasham; James Risley; Kishan Ubayasiri; Abigail Ash; *Mike Sokal; Tom McCulloch; Julia Fairbairn; Cheika Kennedy; Graeme Perks; Anna Raurell
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Objectives: Surgical margin for soft tissue sarcoma (STS) is an important prognostic factor though it is unclear whether a positive margin alone has an effect on local recurrence. The use of adjuvant radiotherapy has allowed for less radical surgery and is currently employed in our unit for marginal excisions and positive margins. The purpose of this study is to compare our local recurrence rate and to look at the effect of adjuvant radiotherapy and its impact on local control and disease free interval in patients with marginal excision.

Methods: Retrospectively collected data from 344 patients who underwent surgical excision for STS over a 10-year period (Jan 1997 - Dec 2007) were analysed. Two main groups were identified: Patients that had wide excision, strictly speaking no margins involved (>1mm), and patients who had marginal excision (involvement of pseudo-capsule) with adjuvant radiotherapy were evaluated and a number of variables (e.g., local recurrence rate) were compared for each group.

Results: The local recurrence rate was 16% for wide excision with or without radiotherapy and 37% for marginal excisions with
radiotherapy. Mean disease free interval was 49.4 months and 40.5 months respectively. Mortality rate was 26% and 29% respectively for each of the groups (Table 1).

**Conclusions:** Based on this study, our local recurrence rate is comparable to published data for patients undergoing wide excision; adjuvant radiotherapy appears to provide similar disease free intervals to wide excision although other factors such as tumour grade/type and anatomical site need to be considered.

### Table 1 showing results of the different variables

<table>
<thead>
<tr>
<th></th>
<th>WIDE EXCISION WITH OR WITHOUT RXT</th>
<th>MARGINAL EXCISION WITH RXT</th>
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<tbody>
<tr>
<td>NUMBER</td>
<td>303</td>
<td>41</td>
</tr>
<tr>
<td>RECURRENCE</td>
<td>49 (16%)</td>
<td>15 (37%)</td>
</tr>
<tr>
<td>MORTALITY</td>
<td>80 (26.5%)</td>
<td>12 (29%)</td>
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<tr>
<td>DISEASE FREE INTERVAL</td>
<td>49.4MTHS</td>
<td>40.5MTHS</td>
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**35031 - FACTORS ASSOCIATED WITH OUTCOME IN RE-EXCISION AFTER UNPLANNED EXCISIONS FOR SOFT TISSUE SARCOMA**

Han-Soo Kim; Ilkyu Han; Hwan Seong Cho
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**Objectives:** Unplanned excision of a soft tissue sarcoma (STS) without preoperative diagnosis necessitates re-excision to obtain an adequate margin. This study aimed to identify the prognostic factors for disease-free survival (DFS) and local recurrence (LR) in unplanned excision of STS.

**Methods:** Retrospective review of 74 patients who had been operated after an unplanned excision of STS was performed. The average age was 42 years (range, 5-70) and average follow-up was 4.5 years (range, 0.3-14.8). Most common diagnoses were MFH (n=26) and synovial sarcoma (19). Locations of the tumors were; lower extremity (40), upper extremity (26) and trunk (8). Mean interval to definitive surgery was 54 days (range, 8-630). Residual tumor was found in 53% (39) at definitive surgery. Postoperative radiation was administered in 59% (43). 5-year DFS was 78% and 5-year cumulative incidence of LR was 25%.

**Results:** In univariate analyses, significant prognostic factors were; for DFS (high histological grade, large tumor size at unplanned excision and positive margin at definitive surgery) and for LR (longer interval to definitive surgery, large tumor size at unplanned excision and positive margin at definitive surgery). Large tumor size and positive margin remained significant after Cox multivariate analyses for both DFS and LR. Presence of residual disease at definitive surgery or postoperative radiation was not associated with DFS or LR.

**Conclusions:** Tumor size at unplanned excision and surgical margin at definitive surgery seems to be associated with outcome in unplanned excision of STS.

**35035 - THE FUNCTIONAL CONSEQUENCE OF FEMORAL NERVE RESECTION IN THE THIGH**

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**Objectives:** The functional consequences of femoral nerve resection during soft tissue sarcoma management are not well described. Sciatic nerve resection with a sarcoma, once considered an indication for amputation, is now commonly performed during limb salvage. We compared the functional outcomes of femoral and sciatic nerve resections in patients undergoing wide resection of soft-tissue sarcomas.

**Methods:** The prospectively collected database from a tertiary referral center for sarcomas was retrospectively reviewed to identify patients with resection of the femoral or sciatic nerve performed during wide excision of a soft tissue sarcoma. Patient demographics, treatment, complications and functional outcomes were collected.

**Results:** Ten patients with femoral nerve resections were identified, all women, aged 47 to 78, with large soft tissue sarcomas of varied subtypes. All patients received adjuvant radiotherapy, most pre-operatively. Six patients developed fractures with long-term follow-up, only two of which were in the prior radiation field. Musculoskeletal Tumor Society (MSTS) 1987 scores demonstrated one excellent, 4 good, and 5 fair results. MSTS 1993 scores averaged 71.4 ± 17.2 percent and Toronto Extremity Salvage Scores (TESS) averaged 61.7 ± 21.8. There were no significant differences between the functional scores for patients with femoral or sciatic nerve resections (P=1.0).

**Conclusions:** Femoral nerve resection appears more morbid than anticipated. The falls to which patients are prone, even years after surgery, subject them to ongoing long-term risks for fractures and other injuries. Nerve-specific functional outcomes should be considered when counseling patients prior to possible resection of the femoral nerve for involvement by a soft tissue sarcoma.

**35039 - SYSTEMIC ADMINISTRATION OF REOLYSIN INHIBITS GROWTH OF HUMAN SARCOMAXENOGRAFTS ALONE AND IN COMBINATION WITH CISPLATIN AND RADIATION**

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**Objectives:** Reolysin® is an unmodified oncolytic reovirus which replicates selectively in ras transformed cells causing cell lysis. Activating mutations in ras or mutations in oncogenes signaling through the ras pathway may occur as many as 80% of human tumors. In the current study we evaluate systemic administration of reovirus in xenograft models of human sarcomas as a single agent and in combination with cisplatin and radiation therapy.

**Methods:** Mice engrafted with the RH30 rhabdomyoscaroma line, the SKE51 Ewing’s sarcoma line, the HSSY-II Synovial Sarcoma line, and the OS2 and O33 osteosarcoma lines are treated with reovirus 5 x 10e9 pfu daily for 3 days per week for 3 doses every 21 days. Combination studies with cisplatin and external beam radiation are also reported. Relative tumor volume (RTV) is recorded weekly.

**Results:** In all tumor lines evaluated, the reovirus exhibits significant antitumor activity, including a complete response in a rhabdomyoscaroma line. The combination of reovirus and RT caused significant tumor regression in both RH30 and SKE5 xenografts. (P value for mean RTV at day 22 was 0.007 in both RH30 and SKE5 xenografts). The EFS was also significantly increased in the combination group as compared to the other 3 groups in both xenografts (P value 0.001.
for RH30 and 0.002 for SKES). On histological analysis, increased degree of apoptosis was seen in each of the treatment groups but was markedly increased in the combination group.

**Conclusions:** Reolysin® demonstrates excellent anti-tumor activity in childhood sarcoma xenografts.

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**35063 - WHAT HAPPENS TO CARBONATED APATITE CEMENT USED IN THE TREATMENT OF BENIGN AND LOW-GRADE MALIGNANT TUMOURS OF BONE? DOES IT EVER REABSORB?**

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**Objectives:** The intralesional curettage of low-grade malignant or benign bone tumours leaves a defect in the bone which may be larger than the original tumour. Surgeons may elect to fill the resulting defect with a number of substances. This study reviews the use of carbonated apatite cement.

**Methods:** We present a review of 17 patients treated for contained bone defects after resection of benign or low-grade malignant tumours between June 2001 and November 2003. The diagnosis was giant cell tumour (GCT) in 9, fibrous dysplasia in 2, low-grade chondrosarcoma in 2 patients, and one case each of enchondroma, chondromyxoid fibroma, osteo-fibrous dysplasia and chondroblastoma.

**Results:** Average follow up was 54 months. There was 1 case of early fracture in a GCT, 1 case of late fracture in a case of fibrous dysplasia, 2 cases of periostitis and 3 cases of GCT recurrence. The cement incorporated well into the bone at the bone cement interface, but showed little resorption, even at a follow up of 78 months. However, in cases of GCT recurrence, growth was aggravated, and the carbonated apatite cement was rapidly reabsorbed over a period of a few weeks.

**Conclusions:** Carbonated apatite cement represents a realistic, effective alternative in the treatment of contained defects following excision of benign and low-grade malignant tumours of bone. However, caution is advised in its use in cases where contact between the material and the soft-tissues is unavoidable as periostitis may occur, and in the treatment of giant cell tumours where growth is aggravated in cases of recurrence.

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**35074 - FINDINGS FROM THE INAUGURAL NIH PEDIATRIC GIST CLINIC**

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**Objectives:** Gastrointestinal stromal tumor (GIST) is a rare disorder and only a small fraction of patients with GIST are children. The rarity of patients, combined with an apparent biological difference between children and adults with GIST, has made it difficult to determine what is the best treatment for pediatric patients. In an effort to help answer this question, we announce the NIH Pediatric GIST clinic. This clinic is a collaborative effort between basic science and clinical researchers, national and international GIST support groups, and children and young adults with GIST, to bring together patients and medical specialists.

**Methods:** Announcement of the clinic was posted on the websites of two GIST support groups, LifeRaft Group and GIST Support International. The first clinic will take place on June 19th 2008.

**Results:** Twenty-one patients registered on-line, of which we selected the first 14 for participation in the inaugural clinic. Our patients included 10 females and 4 males. The average age of the patients was 21.5 (range 11-35), age at the time of first symptoms was 15.1 (range 9-21) and the age at diagnosis was 16.4 (range 9-22). Histological subtype was available for 12 patients (2 epithelioid, 4 spindled, 6 mixed epithelioid and spindled). Ten patients had sequencing of their tumor samples and all ten had wildtype KIT.

**Conclusions:** These patients represent the largest cohort of children and young adults with GIST. We will present the results of what we have learned from this clinic. This includes histological, molecular, radiographic results and response to different treatment regimens.

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**35083 - THE EFFICACY OF CHEMICAL ADJUVANTS ON GIANT CELL TUMOR OF BONE: AN IN VITRO STUDY**

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**Objectives:** Irrigation of contained bone defects in the treatment of GCT with solutions such as Phenol and Ethanol is widely accepted. Little is known about the comparative efficacy of the different chemical treatments. This study evaluates the effect of different chemical adjuvant treatments on giant cell tumor (GCT) of bone in vitro.

**Methods:** Cells isolated from fresh GCT samples were placed in monolayer culture. After overnight culture the cells were trypsinized and the mononuclear cell component was seeded at a density of 3*10^5 cells/cm2. After 24 hours cells were washed three times (1 minute each) with sterile water, 5% Phenol, 95% Ethanol, 3% H2O2 and 50% ZnCl2. Metabolic activity, DNA content, viability and histology were evaluated at various times (24, 48 and 120 hrs).

**Results:** All adjuvants, except sterile water, were equally efficient at killing the cells as demonstrated by the live-dead assay. The metabolic activity of these cells was less than 5% of that of untreated cells as determined by the MTT assay. Sterile water treatment resulted in an initial decline of 90% in MTT activity at 24 hrs but it increased to 30 % of control by 120 hrs. H2O2 treatment appeared to affect mononuclear cells preferentially.

**Conclusions:** Phenol (5%), ethanol (95%), H2O2 (3%), and ZnCl2 (50%) had similar cytotoxic effect on GCT cells in vitro. Sterile water appeared to be less effective as the cells that survived treatment were able to proliferate. Further study is required to determine whether cells in the intact tumor will respond similarly.

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**35087 - SOFT-TISSUE RECONSTRUCTION OF INTERNAL HEMIPELVECTOMY DEFECTS FOLLOWING PELVIC TUMOUR EXCISION**

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**Objectives:** Internal hemipelvectomy involves the excision of a pelvic tumour while salvaging the lower limb. This can result in large soft-tissue deficiencies not able to be addressed with primary closure. Soft-tissue reconstruction involving complex plastic surgical techniques is often employed in our institution. The objective was to review our experience with using an aggressive approach involving the liberal use of flap closure, in terms of wound complications and re-operation.

**Methods:** So far we have reviewed 11 cases of internal
hemipelvectomy with primary flap closure collected in our prospective database between 2001 and 2007. The type of closure flap and associated complications were noted.

**Results:** Patients (7 male, 4 female) had a mean age of 49.7 years (24-71yrs). There were six reconstructions with a vertical rectus abdominis myocutaneous (VRAM) flap; one latissimus dorsi free tissue flap; one fasciocutaneous flap; one anterior thigh flap; one tensor fascia lata flap; and one V-Y advancement flap. Two early complications (18% of cases) of flap necrosis were noted, one of which required debridement and reclosure while the other was managed medically. Late complications developed in two cases (18%). Due to infection, the tensor fascia lata flap was replaced with a VRAM flap. Due to necrosis, one of the original VRAM flaps was replaced with a contralateral VRAM flap. The original flaps successfully healed in nine patients (82%) while the two failed flaps were successfully revised.

**Conclusions:** This study demonstrates that even with aggressive plastic surgical techniques it is difficult to achieve durable wound closure in these patients.

**References**

Conclusions: There were no significant differences in functional outcome between the different resection and reconstruction methods commonly used to treat primary bone tumors around the shoulder. Lack of shoulder stability appears to have no negative impact on patient perceived function.

MSTS classification

35099 - NEUROVASCULAR INVASION IN BONE SARCOMA. LIMITING FACTOR TO LIMB SALVAGE? (520 CASES) EVALUATION OF ACTUAL INCIDENCE, PROGNOSTIC AND SURGICAL IMPLICATIONS
Gerard Delepine; Salwa Alkhallaf; Helene Cornille; Nicole Delepine
Raymond Poincare Hospital, Garches, France

Objectives: Neurovascular invasion remains the main limiting factor of limb salvage. What is the impact on limb salvage?

Methods: 520 bone sarcoma of limbs, scapula or innominate bone (265 osteosarcomas, 135 chondrosarcomas, 130 Ewing ), followed up from 1981 to 2003, 503 treated by limb salvage. Preoperative screening included standard X rays, CT of bone and technetium in all, MRI (350), vascular imaging (45). Diagnosis of neurovascular invasion was suggested on preoperative screening, confirmed by surgery and histology, and analysis of records of patients who suffered from regional relapse after surgery. Median FU is 15 years (minimal 5).

Results: 25 neurovascular invasions (5%) were observed. Nerves were involved in tumour in 16, veins 6, arteries 3. 19/25 neurovascular invasions were observed in patients with osteosarcoma (7% /265). Most involved radial or fibular nerves; Veins were invaded by tumoral thrombi in 6 and arteries in 2. Out of 135 chondrosarcomas, 6 suffered from neurovascular invasion. Out of 130 Ewing, none had neurovascular invasion. Prognostic value of neurovascular invasion was directly correlated with nature of invasion and efficacy of chemotherapy. In patients with vein thrombosis, when chemotherapy is suboptimal the prognosis is dismal. Nerve invasion is not a prognostic factor.

Conclusions: Neurovascular invasion is rare in osteosarcoma (7%) and chondrosarcoma (5 %). Prognostic value of vein thrombi is protocol dependant. With effective preoperative screening including veinography and optimal chemotherapy, the vein thrombi are no longer adverse prognostic factor. Neurovascular invasion does not represent significant limiting factor of limb salvage.

35100 - SURVEY OF HEDGEHOG SIGNALING IN PEDIATRIC MUSCULOSKELETAL SARCOMA
Jason A. Horton; *Timothy A. Damron
Upstate Medical University, Syracuse, NY, United States

Objectives: Hedgehog signaling is an important regulator of embryonic pattern formation and emerging evidence suggests that this pathway may be an important etiologic factor in a number of malignancies. The purpose of this study was to survey seven pediatric musculoskeletal sarcoma cell lines including osteosarcoma (Saos-2,LM2,LM7), rhabdomyosarcoma (RC-13,RD), and Ewing sarcoma (TC-71,RD-ES) for expression of the basal elements of this pathway, and determine whether pharmacologic inhibition of this pathway would inhibit tumor cell proliferation.

Methods: These cell lines were probed for mRNA and protein expression of the hedgehog ligands Indian(Ihh), Sonic(Shh) and Desert(Dhh), the transmembrane receptors Patched(PTC) and Smoothened(Smo), and/or Gli-family transcription factors (Gli1,Gli2,Gli3) involved in hedgehog transduction.

Results: We observed that 6/7 cell lines studied expressed the basal gene products necessary to transduce signals along this pathway. The hedgehog ligand Ihh was detected at both the transcript and protein level in the RD-ES Ewing sarcoma cell line only, however transcripts for Shh and Dhh transcripts were not detected in any cell lines tested. MTT assay of cells exposed to graded doses of the Smo inhibitor cyclopamine produced significant reductions in 2/3 osteosarcoma, 0/2 Rhabdomyosarcoma, and 2/2 Ewing sarcoma lines. Exposure to the adenylyl cyclase agonist Forskolin reduced proliferation of 1/3 osteosarcoma, 1/2 rhabdomyosarcoma and 2/2 Ewing Sarcoma lines, presumably acting through non-specific PKA-mediated phosphorylative inhibition of the Gli-family factors.

Conclusions: Taken together, these early results suggest that pharmacological agents inhibiting the hedgehog signal transduction pathway show promise as novel targeted therapies in the treatment of pediatric musculoskeletal sarcoma, and prompt further investigation.

Table 1

35101 - The Oncologie and Functional Outcome for Radiation-induced Soft-Tissue Sarcoma in Adults
Soha Riad; Anthony Griffin; *Ginger Holt; Cindy Wong; Joel Werier; *Robert Tircotte; *Brian O’Sullivan; *Peter Ferguson; *Benjamin Deheshi; *Jay Wunder
Mount Sinai Hospital, Toronto, On, Canada

Objectives: Soft tissue sarcomas arising in a previously irradiated field are relatively rare but are associated with poor prognosis. To compare the clinical and functional outcome of patients with radiation-induced soft tissue sarcomas (RI-STS) to those with primary extremity soft-tissue sarcoma.

Methods: Databases of four orthopaedic oncology centres were searched for RI-STS cases treated from 1989-2004. Primary cancer, current histology, original radiation dose, latency period between the two tumors, overall and disease-free survival and functional
outcome were determined.

**Results:** 33 patients had a median age of 54.5 years. Median period from irradiation of primary cancer to RI-STS diagnosis was 18 years (3-56 years). Main primary diagnoses were Hodgkin’s lymphoma and breast cancer (33%). Mean radiation dose for the primary tumor was 46 Gy (20 patients, 28-74 Gy). Most common STS histologic subtypes were MFH (33.3%) and angiosarcoma (15.2%). 32/33 were high grade. 23 were upper extremity (69.7%). 31 patients (94%) had surgery; 4 with positive margins. Eleven had adjuvant radiation, 9 adjuvant chemotherapy, 8/31 (26%) had local recurrences, compared to 10% for general STS group. 5-year overall survival for disease-free survival were 34% and 22% respectively, compared to 85% and 62% for general STS group. 14 patients had functional assessment with TESS, MSTS87: mean 83 (61-100), 27 (17-33) respectively, compared to 86 (13-100), 30 (14-35) for the general STS group.

**Conclusions:** Patients with RI-STS have a poor prognosis due to high local and systemic recurrence rates. Although these patients can achieve good functional results, novel systemic treatments are necessary to help improve their oncologic outcomes.

**35103 - PEDIATRIC FUNCTION AFTER OSTEOSARCOMA/ EWING’S TREATMENT**

*Melissa Sheiko; *Ernest U. Conrad

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**Objectives:** This study describes physical function and ambulatory levels of children following chemotherapy treatment (PT) for Ewing’s sarcoma (EWS) and Osteosarcoma (OGS) compared to typically developing youth (TDY).

**Methods:** Twenty children (PT) previously treated for either EWS/OGS were evaluated by both step counter (Step Watch) technology and functional questionnaires (ASKp and CHQ). Study patients were matched by age and gender to a control group of TDY (N=20). Mean age for both groups was 15.8 years with 12 females and 8 males in each group. Patient follow-up was 4.3 years.

**Results:** PT children walked an average of 5,460 steps/day compared to 7,438 steps/day for TDY (p=0.005). PT children showed low, intermediate, high activity of 28.4%, 13.1%, 3.1%, while TDY children showed 28.0%, 15.4%, 6.1% respectively. Difference in high activity level was significant. BMI for PT vs. TDY was 21.9 vs. 21.1 respectively. ASKp scores were 88.3 for PT children vs. 97.7 for TDY (p<0.001). The Spearman Rho correlation between ASKp scores and the total number of steps was 0.41 (p<0.01).

**Conclusions:** The PT children took significantly fewer steps than the TDY, but had similar performance with low and intermediate activity levels. PT children had an apparent decreased activity with high activity via step counter (3.1% for PT and 6.1% for TDY, p<0.001). The ASKp questionnaire showed a positive correlation with the step counter data, demonstrating higher activity in TDY vs. PT children (97.7 vs. 88.3, p=0.001). All pediatric limb salvage assessment should include step counters and functional assessment tools.

**35105 - BONE ALLOGRAFT FAILURES FOLLOWING OSSEOUS RESECTION**

Ted C Sousa; *Ernest U. Conrad

**University of Washington, Seattle, WA, United States**

**Objectives:** The Human Leukocyte Antigen (HLA) molecule is a highly polymorphic gene involved in both acute and chronic rejection of large organ transplants and is thought to be involved with nonunion and rejection of bone allografts. The purpose of this study was to determine if foreign HLA sensitization to a bone allograft results in graft complications.

**Methods:** We retrospectively reviewed 300 patients who received bone allografts by a single surgeon. Of those 86 were included in this study. Flow cytometry was used to detect anti-HLA Class I and II IgG antibodies in their serum. Major complications were defined as the removal of the allograft or complications which showed graft non union.

**Results:** Of the 86 patients who underwent allograft limb salvage procedures 37% (n=32) had a major complication. Graft survival was 91% at two years, 73% at 5 yrs as well as at 10 years with a mean survival of 47.4 months. In those patients with a positive immune response, 39% of patients (18/46) had a major complication, while 61% (28/46) did not have a major complication (p=0.02). Patients with a deep infection requiring irrigation and debridement had an increased rate of major allograft complications compared to those without a deep infection (60% vs. 40%, p=0.01).

**Conclusions:** Non-union of bone is the largest cause of allograft complications. It has yet been determined if HLA immune response contributes to this non-union.
35111 - RISK ASSESSMENT OF INTRAMEDULLARY ROD FIXATION FOR PATHOLOGIC FRACTURES IN PRIMARY BONE TUMORS
*Jennifer W Lisle; *Ernest U Conrad; *Jason S Weisstein
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Objectives: Patients presenting with a pathological fracture through a primary bone tumor represent a treatment challenge. This study’s purpose was to retrospectively review the outcome of a group of patients treated with an intramedullary rod (IM rod) prior to referral to a sarcoma surgical specialist.

Methods: A retrospective review of our sarcoma registry found 195 primary osseous sarcomas from January 2003 - June 2008 with 10 patients presenting after an outside biopsy and rodding procedure of a primary bone tumor that had a pathological or impending fracture.

Results: Ten patients were treated prior to referral with an IM rod placed through their primary bone tumor, which included osteosarcomas and Ewing’s sarcoma. Seven of ten (70%) were managed surgically with amputation. Biopsy at time of rodding was carried out in 9 of 10 patients and biopsy results were not documented at the time of surgery in 3 of the 9 patients. Overall disease-free survival was 89% at 6 months after initial rodding, 89% at 12 months, 44% at 18 months, and 22% at 24 months. Kaplan-Meier survival curve based on this group of patients found that 44% of patients had an amputation at 3 months after initial treatment, 56% at 6 months, 70% at 12 months, and 85% at 18 months.

Conclusions: Osseous tumors treated with IM fixation are associated with adequate local control following amputation. Based on this data set after 18 months, 15% of patients with this procedure will still retain their limb and their overall survival may or may not be comprised.

35125 - MODULAR ENDOPROSTHETIC REPLACEMENT FOR METASTATIC TUMOURS OF THE PROXIMAL FEMUR
Coonoor Chandrasekar; Robert Grimer; Simon Carter; Roger Tillman; Adesegun Abudu
Royal Orthopaedic Hospital, Birmingham, United Kingdom

Objectives: The aim of this study was to assess the clinical and functional outcomes following METS modular tumour prosthetic reconstruction of the proximal femur in 100 consecutive patients with metastatic tumours.

Methods: 100 consecutive patients who underwent modular tumour prosthetic reconstruction of the proximal femur for metastases using the METS system from 2001 to 2007 were studied. The patient, tumour and treatment factors in relation to overall survival, local control, implant survival and complications were analysed.

Results: There were 45 male and 55 female patients. The mean age was 60 years. 75 patients presented with pathological fracture or with failed fixation. The mean follow up was 15.9 months (range0-77). 69 patients have died and 31 are alive. Of the 69 patients who were dead 68 did not need revision surgery. Three patients had revision surgery. There were three dislocations. Six patients had deep infections. The estimated 5 year implant survival was 83.1% with revision as end point.

Conclusions: We conclude that METS modular tumour prosthetics provides versatility; low complication rate and lasts the lifetime of the patients with metastatic tumours of the proximal femur.

35128 - OUTCOME OF TREATMENT FOR MALIGNANT TUMOURS OF THE SCAPULA
Coonoor Chandrasekar; *Robert Grimer; *Simon Carter; Roger Tillman; Adesegun Abudu
Royal Orthopaedic Hospital, Birmingham, United Kingdom

Objectives: The aim of this study was to document the outcomes of treatment of one of the largest series of patients with the malignant tumours of the scapula
Methods: The study was a retrospective review of the demographic details, diagnosis, treatment and outcomes 157 patients with a malignant tumour of the scapula.

Results: Malignant tumours of the scapula was common in the seventh decade (31 patients, 20%). The mean age was 50.9 years. The commonest diagnosis was primary tumours (76 patients, 48%) followed by metastatic disease (58 patients, 37%) and haematological and lymphoreticular malignancy (23 patients, 15%). The tumours most likely to metastasise to the scapula were bronchogenic carcinoma (40%), renal carcinoma (19%) and unspecified adenocarcinoma 15%. Chondrosarcoma (31 patients, 41%) was the commonest primary malignant bone tumour followed by Ewing’s sarcoma 20% and Osteosarcoma 16%. Radiotherapy and chemotherapy either alone or in combination was the mainstay of treatment for the 87 patients (55%) with secondary tumours and lymphoproliferative disorders. 40 patients (25%) had partial or subtotal scapulectomy, 15 patients (10%) had total scapulectomy and 15 patients (10%) had other procedures. The overall 5 year survival was 33.2%, with chondrosarcoma having the best survival (5 year survival of 54.2%). Patients who had partial or subtotal scapulectomy had better prognosis (66% 5 year survival)

Conclusions: Malignant tumours of the scapula are rare occurring more often in the seventh decade. Chondrosarcoma, metastatic bronchogenic carcinoma and non Hodgkin’s lymphoma are the common diagnoses. Chondrosarcoma has better prognosis. Partial or subtotal scapulectomy had the best prognosis.

35134 - THE EFFECT OF CONTAMINATED RESECTION IN THE TREATMENT OF SARCOMA: A “WHOOPS” PROCEDURE
Amy Cizik; *Ernest U. Conrad
University of Washington, Seattle, WA, United States

Objectives: Sarcoma excision by a non-sarcoma surgeon frequently results in a contaminated resection, and has been referred to as a “whoops” procedure.1 Approximately 42% (240/570) of all adult soft tissue sarcomas presenting to our regional sarcoma center have had a ?contaminated? resection or excisional biopsy in their local community prior to their referral.2

Results: A contaminated resection represents a lower (10-15%) risk of recurrent tumor for low-grade sarcoma patients than for higher grade sarcoma patients where that risk appears higher (20-50%).3 The addition of chemotherapy and/or radiation therapy may improve local control in both low and high-grade patients. Contaminated excision of soft tissue sarcomas occur in 50-60% of all soft tissue sarcoma patients as described by multiple authors (Table 1). Recent studies have not shown any improvement in recognizing sarcomas or the lowering of contaminated excisions prior to referral to a sarcoma center of excellence.

Conclusions: In the final analysis, “whoops” surgery adds the need for additional surgical procedures by an experienced sarcoma surgeon and carries an increased risk of local and metastatic recurrence. Contaminated resection is not advised for sarcoma patients and involves a greater risk for patients with high-grade tumors, with regards to controlling tumors at its site of origin (primary site). Patients deserve careful re-excision when suffering a contaminated resection. Re-excision with uncontaminated margins is not possible in a few patients because of anatomic issues (tumor adjacent to major nerve or vessel) and can lead to an amputation.

35137 - NOVEL TECHNIQUE FOR RESECTION OF LARGE MUSCULOSKELETAL SARCOMAS WITH THE USE OF A CUTTING STAPLER AND A BIPOLAR SEALER DEVICE
German Marulanda; Trevor Born; Dave Johnson; David Cheong; *G. Douglas Letson
Moffitt Cancer Center and Research Institute, Tampa, Florida, United States

Objectives: A bipolar sealer device coupled with saline has shown benefit in common orthopedic applications. A cutting stapler (extrapolated from general surgery) has been used to obtain clean linear margins in oncologic surgery. The purpose of this study is to describe the use of these two novel devices as part of a surgical protocol for the resection of large musculoskeletal sarcomas.

Methods: From the year 2004, the authors have utilized a surgical protocol that includes a bipolar sealer and a cutting stapler to excise 39 large extremity sarcomas. The tumors included in this study were unevenly distributed in the lower (87%) and upper (13%) extremities. Variables such as intraoperative blood loss, pre and post operative hemoglobin levels, number of transfusions administered, length of the procedure, and hospital stay were stratified.

Results: A statistically significant reduction in intraoperative blood loss and requirement of transfusions (p<0.05) was found. A clean, healthy appearing surgical bed with no charred tissue was seen in 98% of the cases. The controlled tissue temperature eliminated the presence of smoke in all cases. The use of a cutting stapler allowed rapid identification of surgical specimens. Reattachment of structures was facilitated by strong staple lines that contributed to hemostasis.

Conclusions: The authors believe that these devices favorably affected hemostasis in patients with large musculoskeletal sarcomas. Additional findings such as the absence of intraoperative smoke and non-charring of tissue were also noted. The use of these surgical devices should be evaluated in multicenter randomized trials to further validate our findings.

35139 - USING PRIMARY OSTEOSARCOMA SAMPLES TO IDENTIFY NOVEL MARKERS OF AGGRESSIVENESS AND CHARACTERIZE TUMOR-INITIATING CELLS
Thomas Johnson; Alex Boiko; David Mohler; Neyssa Marina; Stephen Dubois; Douglas Hawkins; Irving Weissman; Alejandro Sweet-Cordero
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Objectives: 1)To establish the feasibility of obtaining xenografts directly from osteosarcoma patients. 2)To identify novel gene expression predictors of chemotherapy response and long-term prognosis 3)To identify potential subpopulations of cells in osteosarcoma biopsies that are enriched for tumor-initiating capabilities.

Methods: We established a multi-institutional collaboration to acquire fresh tumor samples from patients undergoing either a diagnostic biopsy or post-chemotherapy resection of an osteosarcoma. We have employed a xenograft approach where fragments of tumor are implanted underneath the renal capsule of immunocompromised mice. FACs was used to compare the cell surface markers of biopsy samples and compare them to those of surgical resection specimens.

Results: We have established xenografts from multiple patient samples in mice. We have confirmed the ability to passage these tumors in vivo to generate secondary xenografts, validating our transplantation methods. Preliminary studies involving flow cytometric analysis of these samples for a range of cell surface
markers has identified subpopulations that are altered during the course of chemotherapy treatment. Grafting of specific subpopulations of tumor cells is being used as a strategy to identify potential markers of tumor-initiating cells. Our data suggest that the recently described marker of skeletal progenitors CD146 is also a marker of osteosarcoma tumor cells.

Conclusions: A protocol for establishment of osteosarcoma xenografts has been established. Preliminary data suggest that this will be a fruitful approach for the identification of novel markers of osteosarcoma aggressiveness and characterization of tumor-initiating cells.

35148 - THE INTERACTION BETWEEN TOPOISOMERASE II ALPHA AND P-GLYCOPROTEIN EXPRESSION AS AN IMPORTANT FACTOR PREDICTING EARLY METASTASIS IN CHILDREN AND YOUNG ADULTS WITH OSTEOSARCOMA

* I. Lugowska; *W. Wozniak; *K. Szamotulska; *T. Klepacka; *E. Michalak; M. Rychlowska-Prusynska
Institute of Mother and Child, Warsaw, Poland

Objectives: To investigate the immunohistochemical expression of topoisomerase II alpha (TOP2A) in patients with osteosarcoma, and to assess the interaction between the TOP2A and P-gp expression in relation to clinical outcomes.

Methods: The tumour biopsy specimens of 93 osteosarcoma patients (aged 4-20) were studied. Inclusion criteria: primary, non-metastatic osteosarcoma, extremities localisation, no oncological treatment in anamnesis, follow-up for a minimum 5 years. The expression of TOP2A and P-gp was investigated using immunohistochemistry. Cut-off points for the TOP2A expression was established as 25% of positive tumor cells, and for the P-gp as 50%.

Results: A significant correlation was observed between TOP2A expression more than 25% and reduced overall survival (43% vs. 79%; p=0.002) and DFS (33% vs. 74%; p=0.000). The TOP2A expression showed a statistically significant correlation with the expression of P-gp (p=0.001). Early distant metastasis were observed in 13/18 patients (72.2%) with TOP2A+/P-gp+ expression, in 10/32 (31.3%) with TOP2A+/P-gp-; in 1/3 (33.3%) with TOP2A+/P-gp+ and in 13/40 patients (32.5%) with TOP2A+/P-gp+ (p=0.020). The interaction between TOP2A and P-gp expression remained statistically significant after adjustment for covariates in logistic regression model (p=0.040), and was independently related to the occurrence of early metastasis. The risk of early metastasis significantly increased in patients with high expression of both TOP2A and P-gp compared to patients with low expression of both proteins (OR 5.54; 95% CI (1.45-20.57)).

Conclusions: The interaction between P-glycoprotein and TOP2A expression at diagnosis is an important prognostic factor of early metastasis in osteosarcoma patients.

35160 - COMPLICATIONS OF ENDOPROSTHETIC RECONSTRUCTION AFTER SEGMENTAL BONE RESECTION FOR BONE TUMORS: 242 PATIENTS OVER 22 YEARS OF INSTITUTIONAL EXPERIENCE

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Objectives: Long-term experience with endoprostheses implanted after resections led to a better understanding of the natural history of endoprosthetic reconstruction. In order to evaluate patterns of complications after endoprosthetic reconstruction for bone tumors, the authors reviewed all procedures performed over a 22-year period at a single institution.

Methods: Between 1980 and 2002, 332 patients underwent endoprosthetic reconstruction after segmental bone resection for neoplastic disease. Ninety patients were excluded. A total of 242 patients with 242 endoprostheses were available for review. From 1980 to 1988, our institute used a custom-made endoprosthesis manufactured by Howmedica (Rutherford, NJ); after 1988, the Modular Reconstruction System (MRS) by the same manufacturer was used for all patients.

Results: Complications: mechanical (13.2%), soft tissues (13%), infection (12%), extensor mechanism failure and pseudomemunic formation (8%), and dislocation (1%). Sixty percent of patients (144/242) underwent only one surgery. The remaining 98 patients underwent an average of 3.0 procedures. Of patients undergoing repeat surgery, 53 (54%) retained their prostheses. Failure rate was 46% (23/50) for custom prostheses and 13% (22/173) for modular prostheses, and the total failure rate was 19% (45/242). Infection and mechanical complications are the only types of complications that led to prosthesis failure. Infection contributed to 56% of failures and mechanical complications to 44%.

Conclusions: Endoprosthetic reconstruction is a good method of skeletal reconstruction and MRS endoprostheses have greatly improved the long term results of the reconstruction. Infection remains the leading cause of endoprosthetic failure despite the introduction of new technology in endoprosthetic design and new techniques in soft tissue reconstruction.

ORAL PRESENTATIONS SATURDAY

Medical Oncology

#35064 COMBINATION THERAPY WITH TEMOZOLOMIDE AND BEVACIZUMAB (TMZ/BV) IN THE TREATMENT OF HEMANGIOPERICYTOMA/SOLITARY FIBROUS TUMOR (HPC/SFT): AN UPDATED ANALYSIS.
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Objectives: Patients with advanced HPC/SFT have limited therapeutic options. Combination therapy with TMZ/BV has demonstrated activity in glioblastoma, and recent phase II studies with VEGFR inhibitors sorafenib and sunitinib have suggested potential activity in HPC/SFT.

Methods: We analyzed 14 HPC/SFT patients treated at our institution from 05/2005 to 06/2007. All were treated with TMZ 150 mg/m2 orally D1-7, D15-21 and BV 5 mg/kg intravenously D8, 22 every 28 days. We used CT assessment of tumor size and radiodensity (Choi criteria) to determine best response. Patients with available tumor specimens were analyzed for the presence of VEGF, PDGF-alpha, PDGF-beta, PDGFR-alpha, and PDGFR-beta using immunohistochemical analysis.

Results: We identified 14 patients with HPC/SFT (M:F=9:5; mean age 59.5 yrs (44-75)). The most common primary tumor sites were dura (n=6) and lung/pleura (n=3). Seven patients had metastatic
disease at initiation. Twelve patients had received prior treatment: 10 had surgery, 7 had radiation, and 5 had chemotherapy. The median number of cycles of TMZ/BV administered was 7.5 (2.5-20.5), with 1 patient still undergoing therapy. Grade 3/4 adverse events included neutropenia (n=1) and thrombocytopenia (n=3). Choi criteria revealed 11/14 (79%) partial responses (PRs), 2/14 (14%) stable disease (SD), and 1/14 (7%) with disease progression (PD). The median progression-free survival was 8.2 (3.6-28.2) months. VEGF expression did not correlate with response to TMZ/BV.

**Conclusions:** TMZ/BV is a well-tolerated and clinically beneficial regimen for HPC/SFT whose efficacy should be further investigated prospectively. The exact therapeutic mechanism of TMZ/BV on HPC/SFT and their relationship with the VEGF pathway remain to be better studied.

#34936 ACTIVITY OF THE VEGFR/KIT TYROSINE KINASE INHIBITOR CEDIRANIB (AZD2171) IN ALVEOLAR SOFT PART SARCOMA.

Katherine Gardner\(^1\), Leahy Michael\(^1\), Manuel Alvarez-Gutierrez\(^1\), Ian Judson\(^1\), Scrr Michelle\(^1\)

\(^1\)Royal Marsden Hospital, London, United Kingdom; \(^2\)Astra Zeneca, Macclesfield, United Kingdom; \(^3\)The Christie Hospital, Manchester, United Kingdom

**Objectives:** Alveolar soft part sarcoma (ASPS) is a rare entity making up <1% of soft tissue sarcomas (STS). It is typically indolent but with a high incidence of metastatic disease, usually to the lungs, but also to unusual sites, such as brain. Response to conventional systemic treatment is poor. This is a preliminary report of the activity and safety of chronic administration of cediranib in this disease

**Methods:** Efficacy and tolerability data was collected for 7 patients (pts) with ASPS; 1 treated in a randomised trial of two cediranib doses +/- prophylactic antihypertensive therapy and 6 in a phase II study in pts with imatinib refractory GIST or other STS. Cediranib was administered once daily PO at an initial dose of 45mg. Response was assessed using RECIST

**Results:** Median age at diagnosis was 30 years (range:23-70). 4 were male and 3 female. All pts had pulmonary metastases and 2 had additional sites of disease (brain, bone, intraabdominal) at study entry. Tolerability: Treatment was well tolerated; the most common side effects being fatigue, hoarse voice, hypertension, diarrhoea and sore mouth - generally grade 1-2 and manageable. 1 patient died following surgery for brain metastases. Objective responses: 5 pts had a confirmed partial response and 2 pts stable disease. 6 pts remain on treatment with a median duration to date of 34 weeks (range 15-97)

**Conclusions:** There is no effective systemic treatment for pts with advanced ASPS. These data demonstrate the exciting preliminary activity and safety of chronic administration of cediranib in this disease. Further investigation is warranted.

#35024 ADVANCED CHORDOMA FOLLOWING IMATINIB (IM) RESISTANCE

Silvia Stacchiotti\(^1\), Elena Tamborini\(^1\), Andrea Marrari\(^1\), Emanuela Virdis\(^1\), Antonella Messina\(^1\), Carlo Morosi\(^1\), Flavio Crippa\(^1\), Alessandro Gronchi\(^1\), Silvana Pilotti\(^1\), Paolo Giovanni Casali\(^1\)

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**Objectives:** Chordomas are insensitive to chemotherapy. Imatinib (IM) has antitumor activity, but primary and secondary resistance may occur.

**Methods:** Since 2004 we have been treating patients (pts) with progressive IM-resistant advanced chordoma with high-dose ifosfamide (3 pts), nilotinib (5 pts), trabectedin (2 pts), IM plus low-dose cisplatin (11), sirolimus alone (2 pts) and in combination with IM (9 pts), on an individual patient basis. At the same time, 21 primary chordomas were analyzed for RTK expression and downstream signaling.

**Results:** No responses were observed to ifosfamide, trabectedin or sirolimus alone. One patient had a short lasting RECIST PR to nilotinib, while 2 were stable for 3 mos. Among 8 evaluable pts treated with IM and cisplatin, 5 showed signs of response (RECIST: 0 PR, 6 SD, 2 PD; Choi’s criteria: 4 PR; PET responses/evaluable pts: 5/7). In the group of 6 evaluable pts treated with IM + sirolimus, all showed signs of response (RECIST: 1 PR, 5 SD, 0 PD; Choi’s criteria: 5 PR, 0 PD; PET responses/evaluable pts: 5/5). RTK expression analysis on primary tumor revealed that, in addition to PDGFRB, other receptors of the same family were activated: Fli3 and MCSFR, plus EGFR and Her2/neu. Among the downstream effectors, MAPK proved highly expressed and phosphorylated.

**Conclusions:** Even if preliminary, these data suggest that the combination of IM plus cisplatin or IM plus sirolimus may be active in IM-resistant chordomas. Furthermore, biochemical analyses revealed that EGFR family inhibitors are worth testing in chordoma.

#35085 RESPONSES TO THE MTOR INHIBITOR SIROLIMUS IN PATIENTS WITH MALIGNANT PEComA: REPORT OF THREE CASES

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**Objectives:** Malignant PEComa (perivascular epithelioid cell tumor) is a recently recognized sarcoma of uncertain lineage. No effective therapy for metastatic disease has been described. Because it may share activation of the mTOR pathway with the related diseases lymphangiioleiomyomatosis and angiomyolipoma, we investigated the activity of sirolimus in patients with PEComa.

**Methods:** Three patients with metastatic PEComa were treated with sirolimus. Routine clinical imaging was obtained. Patients provided informed consent for retrospective review of medical records according to IRB-approved protocols.

**Results:** Objective responses were observed in three consecutive patients treated with sirolimus. Patient 1 is a 64-year-old man with recurrent retroperitoneal PEComa. Disease progressed after 8 weeks on an investigational Met inhibitor. Sirolimus (8 mg/d) was initiated in January 2008 and was well tolerated. Restaging at 6 weeks demonstrated a PR that was confirmed at 3 months.

Patient 2 is a 69-year-old man with recurrent renal PEComa. Disease progressed after 6 weeks on sunitinib. Sirolimus (4 mg/d) was initiated in April 2008 and reduced to 1 mg/d because of diarrhea and fatigue. Restaging at 6 weeks demonstrated a PR.

Patient 3 is a 61-year-old woman with uterine PEComa. Disease progressed after 8 weeks on an investigational Met inhibitor. Sirolimus (8 mg/d) was initiated in May 2008 and reduced to 4 mg/d because of stomatitis. Restaging at 4 weeks demonstrated significant reduction in size and central cavitation of pulmonary nodules.

**Conclusions:** Significant radiologic responses were observed in 3 patients with PEComa treated with sirolimus. Molecular genetic analysis of tumors is ongoing. Clinical trials of mTOR inhibitors in PEComa are warranted.
A PHASE II STUDY OF INTRAVENOUS REOLYSIN (WILD TYPE REOVIRUS) IN THE TREATMENT OF PATIENTS WITH BONE AND SOFT TISSUE SARCOMAS METASTATIC TO THE LUNG

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Objectives: Reolysin is a Dearing strain, naturally occurring, revealed signifi

cantly in in vitro and in vivo studies with Reolysin in sarcoma cell lines transformed cells possessing an activated Ras pathway producing RNA-activated protein kinase (PKR) and replicates ubiquitously in human reovirus. The virus inhibits the double-stranded RNA-activated protein kinase (PKR) and replicates specifically in transformed cells possessing an activated Ras pathway producing lysis. In vitro and in vivo studies with Reolysin in sarcoma cell lines revealed significant antitumor activity.

Methods: This phase II open-label, single agent study was designed to characterize the efficacy and safety of Reolysin given IV every 28 days in patients with bone or soft tissue sarcoma with lung metastasis using a Simon two-stage design.

Results: Since July 2007, 22 pts (pts) age 28-70 (median 51) were enrolled (13 females and 9 males) and received a total of 54 cycles (range 1-11). All pts had performance status 1 (11 pts) or 0 (11 pts). 19 pts received prior chemotherapy, radiotherapy, biological agents or combinations for their metastatic disease, eight patients more than 3 chemotherapy regimens. Side effects were mild to moderate (grade 1-2) and included constitutional symptoms fever, chills, fatigue. Two pts experienced respiratory side effects (cough and SOB) and 2 pts had diarrhea. Hematological side effects included grade 2-3 neutropenia (5 pts) and grade 2 thrombocytopenia (2 pts). One patient experienced grade 2 AST elevation. 16 patients are evaluable for response to date: 11 patients had SD (10+, 5+ and 2+ months). Five patients had PD. The study proceeded to the second stage of enrolment.

Conclusions: Reolysin is well tolerated and shows promise for the treatment of metastatic sarcoma. Accrual is ongoing.

Diagnostic Techniques

PERCUTANEOUS CT-GUIDED BIOPSY OF THE MUSCULO-SKELETAL SYSTEM: RESULTS OF 1722 CASES

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Objectives: this was a retrospective analysis of a single institution experience with percutaneous CT-guided biopsy of muscolo-skeletal lesions, to evaluate results and define indications

Methods: From January 1990 to May 2008 1722 core needle CT-biopsy were performed. All histologic diagnoses and imaging studies were reviewed. Site of procedure included spine in 648, thoracic cage in 67, upper limb in 125, pelvis in 433 and lower limb in 449 patients.

Results: At histology 1030 lesions were tumors or pseudotumoral lesions: 384 malignant bone tumors, 321 benign, 40 pseudotumors, 285 metastases. In 170 patients an acute or chronic inflammatory disease was found, 117 had other diagnoses (stress fractures, metabolic diseases, chronic degenerative arthropathies, etc.). In 405 CT-guided biopsies the procedure was not diagnostic: 45 patients had incisional biopsies and 360 a second CT-biopsy, diagnostic in 316 patients. This gives an overall rate of non-diagnostic exams of 5%. Major difficulties in obtaining a diagnostic sample were related to site, histotype (small cells, myelomas, lymphomas are more difficult for adequate sampling), insufficient pre-biopsy evaluation, insufficient cooperation from the patient.

Conclusions: CT-guided biopsy is a useful technique that should be recommended for most bony lesions, namely deeply located and spinal lesions. Ultrasound-guided biopsy with tru-cut is usually preferable for soft tissues. Failures of this procedure can be reduced in experienced hands with a careful previous evaluation of the case and a team approach from the radiologist, orthopedic surgeon and the pathologist.

CORE NEEDLE BIOPSY IS HIGHLY ACCURATE IN DIAGNOSING BONE AND SOFT-TISSUE TUMOURS

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Objectives: Core needle biopsy is increasingly accepted for the diagnosis of bone and soft-tissue tumours. Advantages over open biopsy include reduced morbidity, time and cost; however diagnostic accuracy remains a concern. Our objective was to assess and compare the diagnostic accuracy of core needle, open, and fine needle biopsies.

Methods: We reviewed 286 cases collected in a prospective database between 2004 and 2007. Of these, 229 had core needle, 32 open, and 25 fine needle biopsies. 230 had soft-tissue lesions, 56 had bone lesions. The results of these biopsies were compared to the final resection diagnosis for accuracy and, where inaccurate, any effects on management.

Results: Ninety-two percent of the core needle, 100% of the open and 72% of the fine needle biopsies had adequate tissue to make a diagnosis. Of the adequate specimens, the accuracy of core/open/fine needle biopsy was 96%, 97% and 94% for determining malignant versus benign; of the correctly identified malignant lesions 97%, 100% and 80% were accurate for histological grade; and 79%, 84%, 59% for histological subtype.

Conclusions: Core needle biopsy yields diagnostic results comparable to open biopsy for determining malignancy and grade in bone and soft-tissue tumours. Fine needle biopsy has a high inadequate sampling rate and should not be used for diagnosing bone and soft-tissue tumours. Given the reduced cost and morbidity associated with core needle biopsies we believe they should be used routinely for diagnosis where possible, and open biopsy reserved for situations where an inadequate specimen is obtained or core biopsy is not feasible.
Bone Sarcomas 2 - Surgery and Molecular Biology

#35016 PRELIMINARY EXPERIENCE USING PET-CT IN SUSPECTED PEDIATRIC BONE AND SOFT TISSUE SARCOMAS
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¹BC Children's Hospital University of British Columbia, Vancouver, Canada

Objectives: To review preliminary experience using PET-CT in the staging and surveillance of children with suspected bone and soft tissue sarcomas and to determine the optimum scan timing.

Methods: 55 children with presumed diagnosis of bone or soft tissue sarcomas were imaged with low dose FDG-PET-CT (90 scans) and compared to other standard imaging to detect malignancy at diagnosis, evaluate tumor response and detect relapse. To assess impact, 90 scans were retrospectively grouped into the following clinical time intervals: T1: pre biopsy, T2: pre local therapy; T3: end of therapy; T 4: surveillance.

Results: Unsuspected metastases or disease progression was detected in 23/90 scans. At T1, 24 scans were done and 21 scans were of pathologically confirmed sarcomas. At T2, a positive response to neo-adjuvant therapy was identified in 12/21 scans. In 7/21 surgery was altered on the basis of scan findings. At T3, 19 scans were done. Recurrence or progression of disease was seen in 5/19 scans which impacted management. At T4, 26 scans were completed. 10 scans were performed in patients without clinical signs or relapse detected on other radiologic studies and were classified as non indicated. 10/10 non indicated scans had no impact. The other 16 scans were indicated and management was impacted in 15/16 scans.

Conclusions: FDG PET-CT shows promise in the management of pediatric bone and soft tissue tumors. The chosen four scan time intervals appear most useful. Surveillance scans are indicated only when there are clinical symptoms or management decisions required.

#34914 COMPLIANT FIXATION OF MEGA-ENDOPROSTHETICS: RESULTS OF VARIED APPLICATIONS
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Objectives: Durable fixation of mega-endoprosthetics is a surgical challenge as stress shielding remains a major concern. While multiple device designs have attempted to minimize this phenomenon, none are reproducibly reliable. We describe our single institutional experience with a compliant fixation device with which we have no financial interest.

Methods: We retrospectively reviewed our prospective database of the first 24 index implants of a compliant fixation device for mega-endoprosthetics. In addition to demographics, we critically assessed complications. Outcomes were measured employing MSTS and TESS scores.

Results: Twenty-three patients were identified with 24 index implants (14 male, 9 female). Average patient age was 24.2 years (range 7–62). Average follow-up was 23 months (range 6-66 months). Histologic diagnoses included osteosarcoma (16), Ewing’s sarcoma (2), chondrosarcoma (2), lymphoma, MFH of bone, and malignant giant cell tumor (1 each). The distal femur was the most common site of reconstruction (15), followed by the proximal femur (5), proximal tibia, proximal humerus, and pelvis (1 each). 7 of 24 (29%) index implants required revision/explantation, 4 (17%) of which were implant related. 1 revision was due to infection. 2 patients underwent subsequent amputation due to local recurrence or severe flexion contracture. 20 of 24 implants (83%) were fully osteointegrated.

Conclusions: Compliant fixation represents a dynamic manner by which a mega-endoprosthetic can harness bone biology for osteointegration. Our single institution experience supports early oligo-institutional data reflecting successful biopurchase of bone by long lever arm endoprosthetics foreshadowing long term, reproducible durability. Failure of the device appears related to surgeon experience.

#34854 FREE VASCULARIZED FIBULAR GRAFTING FOR MALIGNANT BONE AND SOFT TISSUE TUMOR: RADIOLOGICAL, CLINICAL AND FUNCTIONAL OUTCOME
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Objectives: The purpose of this study was to analyze 30 patients with malignant bone and soft tissue tumor treated with wide resection and free vascularized fibular graft (FVFG) reconstruction.

Methods: We retrospectively reviewed 30 patients with malignant bone and soft tissue tumor in the proximal humerus, the pelvis and around the knee, in which wide tumor resections were performed and reconstructed with FVFG. Reconstruction methods performed were sling procedures for 8 patients with tumor of proximal humerus, resection arthrodesis for 15 patients with tumor around the knee, and pelvic reconstruction for 7 patients with tumor of pelvis. Patients were followed for a mean 88 months (minimum 60 months) and functionally evaluated according to the MSTS scoring system.

Results: At final-follow up, 26 patients were continuously disease free. No patient presented a local recurrence. Four patients died of pulmonary metastasis. Twenty-one patients suffered complications that included 7 stress fractures of fibular, 5 peroneal nerve palsies, 5 absorptions of fibular head, 3 nonunions, and 1 deep infection. Amputation was performed for the patient who suffered deep infection and limb preservation was obtained remaining 29 patients. The average functional score of the 29 available patients by the MSTS scoring system was 80% at final follow-up.

Conclusions: Despite the high rate of complications, satisfactory results were obtained using this technique. We conclude that this is a reasonably effective technique of limb salvage after resection of bone and soft tissue tumors.

#35000 LENTIVIRAL SHRNA SCREEN OF HUMAN KINASES IDENTIFIES NEW REGULATORS OF OSTEOSARCOMA CELL SURVIVAL AND APOPTOSIS
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¹Massachusetts General Hospital, Boston, MA, United States; ²Sigma Aldrich Corporation, St. Louis, United States

Objectives: Induction of RNA interference (RNAi) in cancer cells has enabled high-throughput genome-wide loss-of-function studies via reverse genetic screens. Kinases play an essential role in cancer cell growth and survival, and these enzymes are actively targeted by the pharmaceutical industry to create molecular therapies. Our
goal was to identify kinases whose function is vital to the survival of osteosarcoma cells.

Methods: We describe an optimized systematic screen of known kinases using osteosarcoma cell lines (KHOS and U-2OS) and a lentiviral-based short hairpin RNA (shRNA) human kinase library. We used the CellTiter 96® AQueous One Solution Cell Proliferation Assay as a marker for cell growth and survival.

Results: We identified two kinase genes when knocked down inhibit cell growth and induce apoptosis in osteosarcoma cells: ROCK1 and PLK1. Thus, we introduce previously unrecognized roles for these kinases in osteosarcoma cells. Western blot analysis confirmed that these kinases are highly expressed and activated in different osteosarcoma cell lines as well as in resected tumor samples. In addition, small molecule inhibitor to ROCK1 and PLK1 significantly inhibit osteosarcoma cell growth and induces apoptosis as well.

Conclusions: These results demonstrate the feasibility of high-throughput screening with a large collection of lentiviral kinases to identify drug targets. The development of more potent inhibitors that target these kinases may lead to potential new anti-cancer strategies.

#35116 A NOVEL PROFILING STRATEGY IN OSTEOSARCOMA IDENTIFIES EBF2 AS A MEDIATOR OF OPG INHIBITION TO TRAIL-INDUCED APOPTOSIS

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Objectives: Osteosarcoma (OS) is the most frequent sarcoma among children and adolescents. To date, the mechanisms of initiation, maintenance and metastasis are poorly understood. The goal of this study was to identify novel molecular targets and to study their relevance in the pathogenesis of osteosarcoma.

Methods: We isolated and characterized the phenotype of tumor-derived chemo naïve osteoblastic populations and paired control normal osteoblasts. We performed cDNA array (Affymetrix) coupled to a stringent bioinformatics analysis.

Results: We identified a robust gene clustering that was further validated by real-time qPCR. We identified TRAIL/FAS as the main altered pathway. Transcription factor EBF2, a functional regulator of bone homeostasis, was significantly overexpressed in OS samples as compared to control cells. Interestingly, elevated levels of EBF2 were correlated with high levels of its downstream target, the antiosteoclastogenic cytokine osteoprotegerin (OPG), a negative regulator of TRAIL-induced apoptosis. Moreover, high levels of EBF2 were validated in an independent set of OS, by real-time PCR and Western blot analysis. Knock-down of EBF2 (shEBF2) using lentiviral shRNA transduction led to significant decrease in EBF2 levels that were associated with marked abrogation of OPG expression. More importantly, shEBF2 increased the sensitivity to TRAIL-induced apoptosis.

Conclusions: Our study identified EBF2 as a novel OS marker which partially mediated OPG overexpression. Thus, targeting EBF2 may be beneficial in lowering OPG levels and increasing sensitivity to TRAIL-induced apoptosis. These findings reveal novel mechanistic insights in the pathogenesis of the OS which may have clinical implications.
Solution Cell Proliferation Assay.

Results: Western blot analysis of 13 samples obtained from surgically resected human chordomas were positive for key components of the PIP3/mTOR pathway including PDK, AKT, mTOR and S6. Activation of AKT and mTOR was inhibited in the UCH-1 cell line by the addition of PI-103 at the concentration as low as 0.01 μM. In addition PI-103 inhibited proliferation in the UCH-1 cell line.

Conclusions: The PIP3/AKT/mTOR pathway is active within human chordomas based on western blot analysis of 13 surgical specimens. PI-103 effectively limited proliferation and decreased activation of AKT and mTOR in the human derived chordoma cell line UCH-1 at nanomolar concentrations. Dual inhibition of PIP3 and mTOR in human chordomas deserves further study.

#35008 THE PROTEOLYTIC MACHINERY AS NOVEL THERAPEUTIC TARGET IN GASTROINTESTINAL STROMAL TUMORS (GISTS)

Ying Liu¹, Joshua Parry¹, Anna Chin¹, Payel Chatterjee¹, Anette Duensing¹, Ying Liu¹, Joshua Parry¹, Anna Chin¹, Payel Chatterjee¹, Anette Duensing¹

University of British Columbia, Vancouver, BC, Canada

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#34962 EGR1 MEDIATES HISTONE DEACETYLASE SENSITIVITY IN SYNOVIAL SARCOMA VIA THE PTEN TUMOR SUPPRESSOR

Le Su¹, T. Michael Underhill¹, Torsten O. Nielsen¹

University of British Columbia, Vancouver, BC, Canada

Conclusions: Taken together, our results underscore that an active ubiquitin-proteasome system is crucial for GIST cell survival and proliferation and that it can be exploited to develop novel therapeutic approaches.

#35008 THE PROTEOLYTIC MACHINERY AS NOVEL THERAPEUTIC TARGET IN GASTROINTESTINAL STROMAL TUMORS (GISTS)

Ying Liu¹, Joshua Parry¹, Anna Chin¹, Payel Chatterjee¹, Anette Duensing¹

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Objectives: GISTs are caused by activating mutations of KIT or PDGFRA. Most GIST patients benefit from treatment with imatinib mesylate (Gleevec®), but complete remissions are rare and a substantial proportion of patients develop resistance. Our goal is to better understand the mode of action of imatinib in order to develop novel treatment options.

Methods: The human GIST cell line GIST882 was used as model system. A variety of in vitro methods including immunoblotting, immunofluorescence, subcellular fractionation, inhibitor treatment, overexpression and siRNA were performed.

Results: We found that imatinib leads to a dramatic increase of soluble histone H2AX in GIST cells. This upregulation of H2AX was causatively involved in the induction of apoptosis. Our results suggest that untreated GIST cells keep H2AX at low levels in a pathway that involves oncogenic KIT and the ubiquitin-proteasome machinery. In addition, we found that imatinib modulates the activity of the APC/CDH1 and SCF/SKP2 ubiquitin ligases to induce tumor cell quiescence. Based on these results, we tested the proteasome inhibitor bortezomib (Velcade®), for its antitumor activity in GIST. Bortezomib was able to induce apoptosis in a dose- and time-dependent manner. Effective concentrations were similar to those used in multiple myeloma. Similar to imatinib-treated cells, histone H2AX was upregulated and mislocalized from chromatin after bortezomib treatment. Importantly, bortezomib also efficiently induced apoptosis in short-term cultures of an imatinib-resistant GIST.

Conclusions: Taken together, our results underscore that an active ubiquitin-proteasome system is crucial for GIST cell survival and proliferation and that it can be exploited to develop novel therapeutic approaches.

#34962 EGR1 MEDIATES HISTONE DEACETYLASE SENSITIVITY IN SYNOVIAL SARCOMA VIA THE PTEN TUMOR SUPPRESSOR

Le Su¹, T. Michael Underhill¹, Torsten O. Nielsen¹

University of British Columbia, Vancouver, BC, Canada

Objectives: EGR1 is a transcription factor whose targets include the PTEN tumor suppressor, a key regulator of the Akt-mTOR antiproliferative pathway. The EGR1 promoter is bound by the SS18-SSX oncogene, and is suppressed in synovial sarcoma through Polycomb recruitment and epigenetic histone modifications. We recently showed that histone deacetylase inhibitor drugs reverse the epigenetic silencing of EGR1, and lead to apoptosis of synovial sarcoma cells. We sought to determine if the mechanism of synovial sarcoma cell death requires EGR1 reactivation and/or PTEN induction.

Methods: SYO-1 and Fuji synovial sarcoma cell lines and HEK cells with and without forced expression of SS18-SSX were used as experimental models. Cells were treated with vehicle or varying doses of the histone deacetylase inhibitor romedipsin (FK228), and with siRNA directed against EGR1 or PTEN (with scrambled control). Cell death was monitored using a Cellomics analyzer. EGR1 and PTEN levels were measured by Taqman quantitative real time PCR and by Western blot.

Results: In synovial sarcoma models, EGR1 expression is induced within 1h of treatment with even low doses of romedipsin; PTEN follows after 9h. Cotreatment with siRNA directed against EGR1 abrogates both EGR1 and PTEN activation. In addition, HDAC inhibitor-induced killing of synovial sarcoma cells is dramatically reduced in the presence of EGR1 siRNA knockdown.

Conclusions: EGR1 is a direct target of SS18-SSX. Restoration of its expression is required for histone deacetylase inhibitor induced cell killing and PTEN activation in synovial sarcoma.

#34884 THE C-MET RECEPTOR CONTRIBUTES TO MOTILITY AND INVASION IN A BROAD RANGE OF STS HISTOLOGIES; A POTENTIAL ANTI-STS THERAPEUTIC TARGET

Sarah E Myers², Theresa G Nguyen¹, Quan S Zhu¹, Alex JF Lazar¹, Raph Pollock¹, Dina Lev¹

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Objectives: STS metastasis involves cell migration and invasion, processes potentially involving the c-Met tyrosine kinase receptor. STS c-Met dysregulation occurs; however, its functional significance is unknown. Consequently, c-Met expression was evaluated in a cohort of human STS specimens and cell lines, determining the impact of c-Met expression and its downstream signaling on STS migration and invasion.

Methods: c-Met, HGF, and phospho-c-Met expression were IHC evaluated in > 400 diverse histology STS specimen TMA. WB analysis was used to evaluate c-Met, activated c-Met, activated c-Met downstream signaling AKT and ERK in human STS cell lines. Migration and invasion assays were utilized to assess the effect of c-Met activation; the c-Met tyrosine kinase inhibitor, PHA665752, the PI-3K inhibitor (LY-290042), and the AKT inhibitor (A674563), were evaluated for their effect on STS migration and invasion.

Results: Activated c-Met, total c-Met, and HGF were expressed at varying levels in human STS specimens. STS cell lines highly expressed c-Met, which was undetectable in normal human fibroblasts. HGF stimulation induced c-Met phosphorylation and downstream ERK and AKT1 and AKT3 signaling. c-Met activation resulted in significantly increased STS motility and invasion. c-Met blockade abrogated the HGF-induced downstream signaling and STS migration/invasion. AKT inhibition blocked HGF-induced migration and invasion.

Conclusions: Human STS tumors and cell lines express the c-Met receptor which, upon activation, results in increased STS migration and invasion, at least partially via activation of AKT signaling. Inhibition of c-Met-mediated signaling could impair STS metastatic
Results: used to evaluate EWS in vitro sensitivity to NBDEX performed by Real-Time PCR in 42 EWS patients. MTT test was which are unresponsive to conventional chemotherapy. NBDHEX is proposed as a therapeutic possibility for EWS patients, inhibits GST enzymes. Six cell lines were found sensitive to this associated with doxorubicin chemosensitivity. This prompted us to GSTP-1 was found to clearly predict EWS prognosis. MGST1 was the membrane-bound microsomal glutathione transferase, and of clinical outcome. The prognostic relevance of glutathione expression, collagenase, invasion assays were used for the study.

Methods: Affimetrrix platform was used for profiling. Patients were classified according to event-free survival. Validation was performed by Real-Time PCR in 42 EWS patients. MTT test was used to evaluate EWS in vitro sensitivity to NBDEX

Results: We identified a molecular signature that reflects tumor resistance to chemotherapy. Functional annotation analysis was applied to reveal the biological functions that critically influenced clinical outcome. The prognostic relevance of glutathione metabolism pathway was validated. The expression of MGST1, the membrane-bound microsomal glutathione transferase, and of GSTP-1 was found to clearly predict EWS prognosis. MGST1 was associated with doxorubicin chemosensitivity. This prompted us to assess the in vitro effectiveness of 6-(7-nitro-2,1,3-benzoxadiazol-4-ythio)hexanol (NBDHEX), a new anticancer agent that efficiently inhibits GST enzymes. Six cell lines were found sensitive to this new drug.

Conclusions: Glutathione metabolism pathway emerged as one of the most significantly altered prognosis-associated pathway. NBDHEX is proposed as a therapeutic possibility for EWS patients, which are unresponsive to conventional chemotherapy.

**POSTER DISCUSSION 3  SATURDAY**

**34545 - MOLECULAR MECHANISM OF TENASCIN C ACTION ON MATRIX METALLOPROTEINASE-1 INVASIVE POTENTIAL**
*Karina A Galoian; Nandor Garamszegi; Susanna P Garamszegi; Sean P Scully University of Miami Health System Miller School of Medicine Department of Orthopedics, Miami, Florida, United States

Objectives: The aim of the current study was to confirm that tenascin-C large splice variant (TNC320) stimulates matrix metalloproteinase-1 (MMP-1) expression and to elucidate molecular mechanisms underlying this activation.

Methods: Transient transfection of Human Chondrosarcoma JJ012 cells, reporter gene assay RT-PCR, analysis of MMP-1 gene expression, collagenase, invasion assays were used for the study.

Results: The analysis of gene expression in cultured JJ012 cells grown under different conditions indicated significant increases of MMP-1 mRNA steady-state levels in the cells treated with TNC320 (200%) compared with TNC220 and bovine serum albumin. RT-PCR results demonstrated significantly higher levels of MMP-1 gene expression in TNC320 cultured cells than in all other treatment groups. The result was confirmed by examining the level of MMP-1 promoter transactivation by different extracellular proteins. Data demonstrated 30-fold activation of MMP-1 promoter by TNC320 treatment in comparison with other treatments.

Both invasion and collagenase activity assays demonstrated a 3-fold difference in the cells treated with TNC320 in comparison with the control. Experiments with constitutively active expression kinases indicated that MMP-1 expression induced by TNC320 was associated with mitogen-activated protein kinase (MAPK) cascade activation. Culture with TNC320 resulted in more than 2-fold activation of MMP1-luciferase in the presence of mitogen-activated protein kinase kinase kinase 1 and also 2-fold down-regulation in the presence of mitogen-activated protein kinase kinase 1.

Conclusions: We hypothesize that Tenascin-C (large splice variant), secreted by host stromal cells stimulates tumor growth and metastatic spread in vivo via upregulation of MMP-1 activity involving activation of MAPK pathway.
Conclusions: including frequent phosphorylation of Rb (Group 2). Furthermore, cluster analysis showed two different groups of LMS, was also prevalent in all the tumors but not in the normal tissue. Loss of FAK Y397 phosphorylation distinguished leiomyosarcoma tumors as compared to normal muscle used as a control. Alterations which could drive the selection of targeted treatments. Thus, a better understanding of the LMS biology needs to be elucidated in order to develop new therapeutic agents. The aim was to identify the molecular mechanisms of signal transduction of LMS through a large screening of phosphorylated protein kinases.

Methods: A screen of 652 signaling protein was performed on a set of 13 Leiomyosarcoma tumors using the Kinex antibody microarray.

Results: Higher levels of PKC theta, Tyro3 and MSH2 strongly distinguished leiomyosarcoma tumors as compared to normal muscle used as a control. Loss of FAK Y397 phosphorylation was also prevalent in all the tumors but not in the normal tissue. Furthermore, cluster analysis showed two different groups of LMS, one with an expression protein profile close to that of the normal tissue (Group 1: with high levels of activation of several tyrosine kinase levels), the other with a distinct set of expression profile, including frequent phosphorylation of Rb (Group 2).

Conclusions: Specific kinases and proteins were found activated in leiomyosarcomas with distinct groups of diseases. These will be matched with CGH arrays and miRNA profiles. A better understanding of the leiomyosarcoma biology may enable to identify potential therapeutic targets.

Objectives: Leiomyosarcoma is a rare mesenchymal tumor, but one of the most frequent sarcoma subtypes. Response to cytotoxic chemotherapy is limited and there are not yet clear molecular alterations which could drive the selection of targeted treatments. Thus, a better understanding of the LMS biology needs to be elucidated in order to develop new therapeutic agents. The aim was to identify the molecular mechanisms of signal transduction of LMS through a large screening of phosphorylated protein kinases.

Methods: A screen of 652 signaling protein was performed on a set of 13 Leiomyosarcoma tumors using the Kinex antibody microarray.

Results: Higher levels of PKC theta, Tyro3 and MSH2 strongly distinguished leiomyosarcoma tumors as compared to normal muscle used as a control. Loss of FAK Y397 phosphorylation was also prevalent in all the tumors but not in the normal tissue. Furthermore, cluster analysis showed two different groups of LMS, one with an expression protein profile close to that of the normal tissue (Group 1: with high levels of activation of several tyrosine kinase levels), the other with a distinct set of expression profile, including frequent phosphorylation of Rb (Group 2).

Conclusions: Specific kinases and proteins were found activated in leiomyosarcomas with distinct groups of diseases. These will be matched with CGH arrays and miRNA profiles. A better understanding of the leiomyosarcoma biology may enable to identify potential therapeutic targets.

34844 - VOLUME CHANGE FOLLOWING NEOADJUVANT CHEMOTHERAPY AS A PREDICTOR OF OVERALL SURVIVAL IN SOFT TISSUE SARCOMAS

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Objectives: Histologic tumor necrosis following neoadjuvant chemotherapy is an established prognostic factor for bone sarcomas, but its predictive value for soft tissue sarcomas (STS) remains uncertain. This study investigates change in tumor volume post-chemotherapy to determine its prognostic value.

Methods: Our STS database was searched for patients treated with neoadjuvant chemotherapy and surgery. Inclusion criteria were 3-dimensional tumor measurements reported by the radiologist (pre- and post-chemotherapy, pre-radiation therapy) and minimum 12-month follow-up. Tumor growth ≥10% was defined as progression. Shrinkage of ≥10% was defined as response. Change of <10% was defined as stability. Kaplan-Meier and Cox Regression analyses were performed.

Results: Forty-one of 92 patients met inclusion criteria. Mean follow-up was 36 months (range 12-113). Response was seen in 22 patients, progression in 15, and stability in 4. Mean volume change was +134 cm³ (-2217 to +4255 cm³). Mean percent volume change was +20% (-97% to +931%). One patient developed local recurrence 2 months post-operatively. Seven patients developed metastasis at a mean of 12.8 months. Seven patients died. Patients with progression were more likely to have a shorter overall survival than those with response or stability (p=0.005 [Kaplan-Meier], p=0.02 [Cox Regression]). However, disease-free survival was similar for these groups (p=0.448, p=0.496). Neither overall survival nor disease-free survival was significantly different based on histologic necrosis (<90% vs. >=90%)(p=0.239 and p=0.469, respectively [Kaplan-Meier], p=0.202 and p=0.518, respectively [Cox Regression]).

Conclusions: Percent volume change measured on MRI may be a more useful predictor of overall survival than histologic necrosis for STS. Neither measure reliably predicted disease-free survival.

34845 - A PHASE 1B OPEN-LABEL STUDY OF AMG 655 IN COMBINATION WITH DOXORUBICIN FOR THE FIRST-LINE TREATMENT OF PATIENTS WITH LOCALLY ADVANCED OR METASTATIC, UNRESECTABLE SOFT TISSUE SARCOMA

*Jean Yves Blay; Sant Chawla; George D Demetri; Robert Maki; Mandy Parson; Natalie Hyland; Kerry Dillingham; Matt Hsu; Ada Braun; Thomas Brodowitz
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Objectives: AMG 655 is a fully human IgG1 monoclonal agonist antibody that binds human death receptor 5, activates caspases, and induces apoptosis in sensitive tumor cells. Study objective: to assess the safety, tolerability, and clinical benefit of AMG 655 in combination with doxorubicin.

Methods: Eligibility: >/=18-years old, locally advanced or metastatic, unresectable soft tissue sarcoma, ECOG 0 or 1. Doxorubicin (75mg/m²) and AMG 655 (15mg/kg) were administered on day 1 of each 21-day cycle for up to 6 cycles, followed by AMG 655 monotherapy. Endpoints: incidence of dose-limiting toxicities (DLT), adverse events (AE), pharmacokinetics (PK), objective tumor response rate (by modified RECIST).

Results: Six patients received >/=1 dose of AMG 655 plus doxorubicin. Four were women; 3 were ECOG 1; median (range) age was 68.5 (46-86) years; histologies included 1 undifferentiated high-grade pleomorphic sarcoma, 1 fibrosarcoma, 1 leiomyosarcoma, 3 liposarcoma. Median (range) time on treatment: 16.9 (5.3-22.1+) weeks; 4 patients remain on treatment. There were no DLT or deaths; see table for AE. Patients with toxicities grade >/=3: 3 neutropenia, 1 leukopenia, 1 anemia, 1 thrombocytopenia, 1 staphylococcal sepsis, 1 general physical health deterioration. There was no apparent effect of doxorubicin on PK of AMG 655 or effect of AMG 655 on PK of doxorubicin after one dose. Tumor-response data were available for 5 patients: 2 confirmed partial response, 2 stable disease, and 1 progressive disease.

Conclusions: The combination of AMG 655 with doxorubicin appears to be well tolerated and shows encouraging activity in this patient population. A randomized phase 2 trial is ongoing.
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<th>Preferred Term (a)</th>
<th>All Patients (N = 6)</th>
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<td>Number of patients reporting any adverse event - n (%)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Number of patients reporting any serious adverse event - n (%) (b)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Number of patients reporting any AMG 655-related adverse event - n (%) (c)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Pyrexia (grade 1)</td>
<td>2</td>
</tr>
<tr>
<td>Asthenia (grade 2)</td>
<td>1</td>
</tr>
<tr>
<td>Chills (grade 1) (d)</td>
<td>1</td>
</tr>
<tr>
<td>Headache (grade 1)</td>
<td>1</td>
</tr>
<tr>
<td>Increased lipase (grade 1)</td>
<td>1</td>
</tr>
<tr>
<td>Flu-like symptoms (grade 1)</td>
<td>1</td>
</tr>
<tr>
<td>(a) Graded using CTCAE</td>
<td></td>
</tr>
<tr>
<td>(b) One patient with general physical health deterioration; 1 with staphylococcal sepsis.</td>
<td></td>
</tr>
<tr>
<td>(c) There were no AMG 655-related serious AEs.</td>
<td></td>
</tr>
<tr>
<td>(d) Infusion reaction attributed to AMG 655.</td>
<td></td>
</tr>
</tbody>
</table>

**Objectives:** Plexiform neurofibromas are benign nerve sheath tumors that grow along the length of nerves and their branches in patients with Neurofibromatosis Type 1 (NF1). They are typically large, have a complex shape, exhibit an unpredictable growth pattern, and are a major source of morbidity. Complete surgical resection is the only standard treatment for plexiform neurofibromas, although their size, infiltrative growth pattern, and location often make surgery a nonviable option. We describe a case of a patient with NF1 with a large plexiform neurofibroma that responded to high dose carboplatin therapy.

**Methods:** A 20-year-old male with a history of NF1 and spastic paraplegia presented to the oncology service with a right thigh mass. On the initial MRI, there was a large mass centered in the adductor muscles. Biopsy revealed many enlarged nerves with low cellularity consistent with a plexiform neurofibroma. While evaluating the right thigh mass, he was found to have a malignant Stage 1 seminoma of the left testis. He underwent two cycles (8 weeks total) of high dose carboplatin (AUC of 7) for the malignant seminoma.

**Results:** MRI performed 1 month after the final dose of carboplatin showed that the plexiform neurofibroma had decreased in volume by approximately 74% on the T1 weighted post-contrast images (Image 1) compared to pre-therapy.

**Conclusions:** To our knowledge, there are no other reports of high dose carboplatin inducing a response in plexiform neurofibromas. While further studies are warranted, we believe high dose carboplatin should be considered as a treatment option for large plexiform neurofibromas.

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34863 - HISTONE DEACETYLASE (HDAC) INHIBITION BY PCI-24781 SENSITIZES SOFT TISSUE SARCOMA (STS) CELLS TO CHEMOTHERAPY IN VITRO AND IN VIVO: A POSSIBLE ROLE FOR RAD51 TRANSCRIPTIONAL REPRESSION

Gonzalo Lopez; Juehui Liu; Wenhong Ren; Guy Lahat; Suizhao Wang; Quan-Sheng Zhu; *Alexander J. F. Lazar; *Raphael E. Pollock; *Dina C. Lev

**Objectives:** STS chemotherapy remains suboptimal due to toxicity, expense, and chemoresistance. HDAC inhibitors may be relevant as...
anti-cancer therapeutics, exhibiting significant synergy with ionizing radiation and DNA damaging agents. We investigated potential anti-STS effects of PCI-24781, an HDAC inhibitor, seeking to elucidate its potential STS-related mechanisms of action.

Methods: STS cell proliferation and chemosensitivity were examined in MTS and clonogenic assays. In vivo studies assessed local tumor growth and STS lung metastasis. PCI-24781 effects on gene expression were examined in high-throughput cDNA oligoarrays, with results validated by PCR and western blot (WB). Reporter and ChIP assays were used to evaluate PCI-24781 effects on RAD51 transcription.

Results: PCI-24781 exhibited significant anti-proliferative activity in vitro, an effect that was enhanced by combining PCI-24781 with chemotherapy. This combination also demonstrated marked synergistic anti-STS effects in vivo, inhibiting both local tumor growth and metastasis. Oligoarrays identified a panel of 44 genes that were deregulated in all four STS cell lines tested, including a significant PCI-24781 induced reduction in RAD51 expression. PCR and WB confirmed these oligoarray results, demonstrating time-dependent reductions of RAD51 mRNA and protein, respectively. Reporter assays showed PCI-24781 induced reduction in RAD51 promoter activity, and ChIP assays revealed reduced polymerase II binding to the RAD51 transcription initiation site.

Conclusions: HDAC inhibitors such as PCI-24781 may be useful for treating STS, and combination with standard chemotherapy results in superior anti-STS effects than either agent alone. Moreover, the mechanism underlying these enhanced chemosensitivity effects may involve PCI-24781 induced transcriptional repression of RAD51.

34866 - DOSE-INTENSE CHEMOTHERAPY AND PREOPERATIVE HYPOFRACTIONATED RADIATION FOR HIGH-RISK SOFT TISSUE SARCOMAS: A MULTISTitutionAL UPDATED ANALYSIS

Kelly S Perlewitz; Arthur Y Hung; Caroline W Koudelka; James B Hayden; Anthony G. Montag; Atiya Mansoor; Janet R. Hosenpud; Brian Samuels; Samir Undevia; Christopher W Ryan

Objective: We previously reported a phase II study of dose-intense chemotherapy with preoperative hypofractionated radiation in patients with high-risk STS (Ryan CW, et al. Cancer 2008). We present further follow-up including additional data from patients treated off-study at our institution.

Methods: Patients with localized STS of the extremity or body wall measuring >5cm and of intermediate or high-grade were treated with epirubicin 30mg/m2/day Days 1-4 and ifosfamide 2.5g/m2/day Days 1-4 every 21 days for 3 preoperative and 3 postoperative cycles. During cycle 2 of preoperative therapy, epirubicin was omitted, and ifosfamide 30mg/m2/day Days 1-4 and ifosfamide 2.5g/m2/day Days 1-4 were added. 25 patients were treated on the phase II study, and an additional 12 patients were identified from a retrospective chart review.

Results: N=37; Median age : 53 years; Median tumor size: 10cm; Histology: pleomorphic/MFH (41%), synovial (16%), liposarcoma (14%), other (30%); Primary site: lower extremity (65%), upper extremity (24%), body wall (11%). 32% of tumors (95% CI 17%, 48%) had > or = 95% histologic necrosis at time of surgical resection. Estimated 3-year rates of freedom from local recurrence, distant disease-free survival, and overall survival were 78%, 61%, and 79%, respectively. Log-rank analysis did not detect an association between > or = 95% histologic necrosis and any measure of outcome.

Conclusions: With continued follow-up, this aggressive neoadjuvant chemoradiotherapy regimen demonstrates clinical outcome rates similar to those reported in other studies of neoadjuvant chemoradiotherapy. No association between > or = 95% histologic necrosis and outcome was detected.

34896 - SPECIFIC TYROSINE KINASE INHIBITORS REDUCE MOTILITY, COLONY FORMATION, AND INVASIVENESS BY OSTEOSARCOMA CELLS

Patrick J Messerschmitt; Ashley N Rettew; Robert E Brookover; Ryan M Garcia; Patrick J Getty; Edward M Greenfield

University Hospitals Case Medical Center and Case Western Reserve University, Cleveland, Ohio, United States

Objective: Tyrosine kinases (TKs) regulate cellular proliferation, migration, angiogenesis, and apoptosis. This study determined whether activation of specific TKs contributes to cell culture correlates of metastasis by osteosarcoma (OS) cells.

Methods: Two families of genetically-related human OS cell lines were used: non-tumorigenic/non-metastatic parental cell lines (TE85 and SAOS-2), a tumorigenic but non-metastatic cell line (MNNNG), and highly tumorigenic/metastatic cell lines (143B and LM7). Motility assays measured migration in a scrape created in confluent cultures. Colony formation assays quantified formation of non-adherent colonies in collagen gels. Invasion assays quantified invasiveness of OS cells through a basement membrane matrix.

Results: The EGF-R inhibitor slowed motility of all five cell lines by 50-75% (p<0.001)(Fig. 1). The inhibitor specific for IGF-1R preferentially slowed motility of the metastatic LM7 cell line by 42% (p<0.001)(Fig. 1) and an inhibitor specific for met/HGF-R preferentially slowed motility of the MNNNG cell line by 80% (p<0.001)(Fig. 1). Colony formation was reduced 95-100% by inhibitors specific for EGF-R, IGF-1R, and met/HGF-R in all tested cell lines (p<0.001). Additionally, pre-formed 143B colonies rapidly became disrupted following the application of inhibitors specific for EGF-R and IGF-R, which may mimic treatment of metastatic lesions. Invasiveness of the metastatic 143B cell line was reduced 62% by the EGF-R inhibitor. Inhibitors specific for HER-2, PDGF-R, and NGF-R had little or no effect on motility, colony formation, or invasiveness.

Conclusions: Inhibition of specific TKs decreases motility, colony formation, and invasiveness, all critical components of metastasis. TK inhibition therefore provides a promising avenue in the evolving treatment of osteosarcoma.
34897 - 3,4-METHYLENEDIOXY-ß-NITROSTYRENE (MNS) REDUCES THE MOTILITY AND COLONY FORMATION OF OSTEOSARCOMA CELLS

Patrick J Messerschmitt; Ashley N Rettew; Robert E Broookover; Avanti P Jakatdar; Patrick J Getty; Edward M Greenfield

University Hospitals Case Medical Center and Case Western Reserve University, Cleveland, OH, United States

Objectives: 3,4-Methylenedioxy-ß-nitrostyrene (MNS), a recently described inhibitor of platelet activation, inhibits src and syk. Since these tyrosine kinases regulate tumorigenesis and metastasis of other cancers, we determined the effect of MNS on in vitro correlates of metastasis by human osteosarcoma (OS) cell lines.

Methods: Two families of genetically-related human OS cell lines were used. The families include non-tumorigenic/non-metastatic parental cell lines (TE85 and SAOS-2), a tumorigenic but non-metastatic cell line (MNN), and highly tumorigenic/metastatic cell lines (143B and LM7). Motility assays measured migration in a scrape created in confluent cultures. Colony formation assays quantified formation of non-adherent colonies in collagen gels.

Results: MNS preferentially reduced motility of the SAOS-2, LM7, and 143B cell lines by 80%, 61%, and 53% (p<0.001) (Fig. 1) and reduced colony formation of all tested cell lines by 95-100% (p<0.001). In contrast, motility and colony formation was not affected by a specific inhibitor of src or by different inhibitors of syk (Syk Inhibitor I, II, or IV). Combinations of the src and syk inhibitors also did not affect motility of any of the tested cell lines. However, the src inhibitor reduced colony formation by 50% in the 143B and MNN cell lines (p<0.002). Addition of MNS 72 hours following the src inhibitor reduced colony formation by 50% in the 143B and SAOS-2, which could help drive cancer development. However, the presence of IFNG in the MDM2 amplicon suggests its involvement, in its turn, in the lack of aggressiveness of parosteal sarcoma. In vitro analyses of MDM2, CDK4 expression and IFNG overexpression results suggest this gene may be involved in cell survival against cytotoxic challenges.

Conclusions: In OSA and parosteal sarcoma the amplified 12q13-15 region consists of two units centered on MDM2 and CDK4. Amplification translates in overexpression of MDM2 and CDK4, which could help drive cancer development. However, the presence of IFNG in the MDM2 amplicon suggests its involvement, in its turn, in the lack of aggressiveness of parosteal sarcoma. In vitro analyses of MDM2, CDK4 expression and IFNG overexpression are currently underway to help elucidate their specific roles in cancer progression.

34898 - CHARACTERIZATION OF THE 12Q13-15 AMPLIFIED REGION IN OSTEOSARCOMA AND PAROSTEAL SARCOMA

Salvador Mejia-Guerrero1; *Jay S Wunder1; *Nalan Gokgoz2; Michael Quejada1; Mona Gill1; *Irene L Andrulis1

1Samuel Lunenfeld Research Institute at Mount Sinai Hospital, Toronto, Ontario, Canada; 2University of Toronto, Toronto, Ontario, Canada

Objectives: The chromosome region 12q13-15 is amplified in 12% cases of osteosarcoma (a high grade bone cancer, OSA), but in 67% of parosteal sarcomas, a low grade tumor. This suggests 12q13-15 could be involved in slower cancer development. We decided to define the boundaries of the 12q13-15 amplicon and to determine if MDM2 is, as suggested, its main amplification target.

Results: Real-time PCR of specimens amplified for MDM2 showed that it is frequently coamplified with CDK4 in OSA (11 out of 14 cases, 79%), and in all 9 parosteal sarcomas analyzed. Further analysis of genes in 12q13-15 showed that it harbors two amplicons: a ~3.3 Mb one, centered on MDM2, that includes close to 20 genes (IFNG among them), and a ~1.9 Mb one, centered on CDK4, with approximately 15 genes. Not a single case of a continuous amplicon was detected. Expression analysis showed that MDM2 and CDK4 expression is higher in amplified specimens than in non-amplified ones (p<0.05). Preliminary MDM2 overexpression results suggest this gene may be involved in cell survival against cytotoxic challenges.

Conclusions: In OSA and parosteal sarcoma the amplified 12q13-15 region consists of two units centered on MDM2 and CDK4. Amplification translates in overexpression of MDM2 and CDK4, which could help drive cancer development. However, the presence of IFNG in the MDM2 amplicon suggests its involvement, in its turn, in the lack of aggressiveness of parosteal sarcoma. In vitro analyses of MDM2, CDK4 and IFNG overexpression are currently underway to help elucidate their specific roles in cancer progression.

34899 - THE THIRD VACCINATION TRIAL OF SYT-SSX JUNCTION PEPTIDE IN PATIENTS WITH DISSEMINATED SYNOVIAL SARCOMA

Takuro Wada1; Satoshi Kawaguchi1; Tomohide Tsukahara2; Kazunori Ida3; Satoshi Nagoya4; Mitsunori Kaya1; Toshihiko Yamashita1; Toshihiko Torigoe2; Noriyuki Sato2

1Department of Orthopaedic Surgery Sapporo Medical University, Sapporo, Japan; 2Department of Pathology Sapporo Medical University, Sapporo, Japan

Objectives: We previously reported our first and second vaccination trials of SYT-SSX gene-derived peptide and its modified peptide for 9 patients with synovial sarcoma. Subsequently we started the third phase I study using a combination of the original SYT-SSX junction peptide and interferon-alpha.

Methods: A 9-mer peptide (SYT-SSX B) spanning the SYT-SSX fusion region with HLA-A*2402 anchor motif was synthesized. Patients who are HLA-A*2402 positive and have disseminated synovial sarcoma (SYT-SSX positive) are considered eligible. A mixture of SYT-SSX B (1.0mg) and an immune adjuvant (Montanide ISA-51) was given in combination with interferon-alpha (3x106U) to 4 patients at 14-day intervals. The patients were monitored for adverse events, DTH skin test, tumor size, tetramer staining, and peptide-specific CTL induction. One patient underwent resection of lung metastatic lesions after vaccination. Immunohistochemical study was performed to identify CD8 positive T-cells and expression of HLA-Class I of the tumor cells.

Results: All of 4 patients completed six-time vaccinations and showed skin inflammation at vaccination sites and grade 2 fever following vaccination. None of them showed DTH reactions, increases in CTL precursors or successful CTL induction. Tumor status was stable disease (SD) in 3 of 4 patients. Immunohistochemical study showed that invasion of CD8 positive T cell in the tumor tissue was scanty and expression of HLA-Class I of the tumor cells was weak.

Conclusions: Thre vaccination protocol using a combination of SYT-SSX junction peptide, Montanide ISA-51 and interferon-alpha found to be effective. For more efficacy, up-regulation of the HLA-
Class I molecule of the tumor cells would be needed.

34906 - GLOBAL ANALYSIS OF COPY NUMBER VARIATIONS IN OSTEOSARCOMA
Nalan Gokgoz; *Jay S Wunder; *Irene L Andrulis
Samuel Lunenfeld Research Institute Mount Sinai Hospital, Toronto, Ontario, Canada

Objectives: In osteosarcomas (OS), a number of genetic alterations have been identified through cytogenetic techniques providing insight into the underlying genetic abnormalities. However, OS karyotypes are usually very complex with extensive numerical and structural alterations, particularly in high-grade tumors. Detection of genomic regions containing these changes is extremely important for identifying novel cancer related genes. In this study we performed Whole Genome Genotyping (WGG) using high-density SNP arrays. A major advantage of this technology is the simultaneous detection of both allelic ratios and Copy Number Variations (CNV).

Methods: We performed WGG on 750 nanograms of DNA from flash-frozen OS specimens using Illumina 1M BeadChips and the Infinium II WGG assay protocol on arrays from the Centre of Applied Genomics (http://www.tcg.ca). After assay the BeadChips were scanned with a two-colour BeadArray reader and the data were analysed using Bead Studio software.

Results: We used WGG to investigate 12 high-grade OS tumors for CNVs. Preliminary analysis showed high levels of recurrent amplification of 12q13-15, 17p11.2 and 1p36 regions in addition to other alterations. A common region of loss was detected on 10q23. Some tumors exhibited whole chromosome arm deletions and/or duplications.

Conclusions: From these studies we hope to identify genes that are important in the development and progression of osteosarcoma. In addition, comparisons of SNPs and CNVs in tumor and germline DNAs may help to identify genes related to chemotherapeutic response.

34908 - CHARACTERIZATION OF HEDGEHOG PATHWAY DYSREGULATION IN OSTEOSARCOMA
Winnie Wan-Hsin Lo1; Jay Wunder2; Nalan Gokgoz2; Irene Andrulis3
1University of Toronto, Toronto, Ontario, Canada; 2Samuel Lunenfeld Research Institute Mount Sinai Hospital, Toronto, Ontario, Canada

Objectives: We previously observed a strong positive association between IHH, GLI1, and PTCH1 of the Indian Hedgehog Pathway in 43 osteosarcoma samples. Moreover, these genes were overexpressed in a subset of tumors when compared to normal osteoblasts. To characterize the dysregulation of the IHH pathway in osteosarcoma we have conducted genetic and in-vitro functional analyses.

Methods: DNA from 54 osteosarcoma specimens were investigated for PTCH1 mutations by SSCP. Osteosarcoma cell-lines were used to characterize the mechanism of Hedgehog activation. GLI1 was knocked-down by siRNA in U2-OS and Saos-2 cells.

Results: SSCP was performed on five hot-spot regions of PTCH1 in 54 specimens. Four shifts identified were within the introns. Treatment with purmorphamine, a Hedgehog signaling agonist, induced GLI1 in MG-63, KHS, and MNNG/HOS but not U2-OS, Saos-2, and HOS cells. 48-hour post-transfection of GLI1 siRNA resulted in 80-90% GLI1 knockdown in Saos-2, and 65-70% knockdown in U2-OS. However, GLI1 knockdown did not result in decreased cell proliferation.

Conclusions: IHH Pathway genes are overexpressed in human osteosarcomas. This does not appear to be due to ligand-independent activation of the Hedgehog pathway through PTCH1 as mutations were not detected in osteosarcoma samples. In cells that normally have low endogenous level of GLI1, Hedgehog signaling can be activated by inducing GLI1 levels. However, purmorphamine was not able to activate Hedgehog signaling in cells that have constitutively high levels of GLI1. GLI1 knockdown did not result in decreased proliferation. This result may be explained by the redundant functions of GLI1 and GLI2 transcriptional activators and requires further study.

34911 - IDENTIFICATION BY FISH OF CHROMOSOMES 13 AND 16 DELETIONS AS A DIAGNOSIS CRITERIA IN PLEOMORPHIC AND SPINDLE CELL LIPOSOMAS
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Objectives: Pleomorphic and spindle cell lipomas classically occur as subcutaneous masses in the upper trunk/neck of older men and are composed of mature fat, CD34-positive spindle and pleomorphic cells. These tumors posed diagnostic difficulties because differential diagnosis with malignant variant, mainly liposarcomas and solitary fibrous tumor, is sometime histologically difficult. Even if the spindle cell lipomas genetics is still largely unknown, it appears that they are characterized by a chromosome 13 and/or a chromosome 16 deletion. The aim of this work is therefore to delineate precisely these deletions in order to establish a FISH diagnostic probe set.

Methods: Using a TMA (tissue micro array) composed of 31 well characterized spindle cell lipomas we studied by FISH the chromosome 13 and 16 deletions. In order to identify a common region of deletion, we hybridized 30 BACs along the chromosome 13 and 10 BACs in the 16q13-q24 region.

Results: Twenty six cases (83%) were interpretable for most of the probes and we identified a common region of deletion on both chromosomes. On chromosome 13, this region is 11 Mb long and contains 14 BACs deleted in all interpretable cases. On an the other hand, the common chromosome 16 deletion is only one BAC deleted in 80% (12/15) of the interpretable cases.

Conclusions: Finally we identified two common regions of deletion which can be identified by FISH using a probe set composed of the most frequently deleted BAC of each region and be used as diagnosis criteria of spindle cell lipomas.

34938 - NOVEL GENE EXPRESSION IN METASTATIC EWING’S SARCOMA
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Objectives: Ewing’s sarcoma (ES) most often affects children and young adults between 5 and 30 years of age. It is the second most common bone tumor in children. Despite surgical resection, chemotherapy and radiotherapy, survival for this group of patients remains dismal at 20-40% and has not improved over the last 15 years. Of patients with metastatic disease, 80-90% will succumb to their disease. Our objective was to identify novel genes differentially expressed in metastatic ES patients.

Methods: Human Ewing’s sarcoma cells (TC-71) were injected
int into nude mice
The mice either developed pulmonary metastasis or localized chest wall tumors and no metastasis. RNA was extracted from these explanted tumors and gene expression differences in local tumors and metastatic tumors were compared using microarray. Validation was completed using RT-PCR. Immunohistochemistry on xenograft and human ES tumors was then evaluated.

Results: Only 9 genes of over 30,000 were found to be significantly over or underexpressed. A novel gene, TOX-4, was found to be overexpressed in pulmonary metastasis tumors from our orthotopic xenograft model of ES.(p=0.00023) On validation by RT-PCR, TOX-4 was found to be expressed in osteosarcoma and Ewing’s sarcoma cells but not normal cells. Using IHC, we demonstrate increased staining of TOX-4 in pulmonary metastasis and in human ES specimens TOX-4 is highly expressed.

Conclusions: TOX-4 is a novel gene that is overexpressed in Ewing’s sarcoma and lung metastasis. There are no previously published reports on TOX-4 in tumor or non-tumor literature. TOX-4 may be an important gene target in ES.

34946 - CLINICAL OUTCOMES OF SYSTEMIC THERAPY FOR PATIENTS WITH DESMOID TUMORS
Veridiana F. Camargo; *Mary Louise Keohan; *David R. D’Adamo; *Cristina R. Antonescu; Mark A. Edgar; *Samuel Singer; Murray F. Brennan; *Robert G. Maki
Memorial Sloan Kettering Cancer Center, New York, NY, United States

Objectives: We examined outcomes of patients with desmoid tumors receiving systemic therapy at a single institution, to provide a basis for examination of newer agents.

Methods: Retrospective chart review of 682 patients with desmoid tumors (1982-2006) from a prospectively collected sarcoma database. The activity of NSAIDs was not addressed. Patients without measurable disease, those receiving therapy we could not document, and those receiving prophylactic therapy were excluded.

Results: A total of 69 patients received 163 lines of well-documented systemic therapy starting before 1/1/2007. Nine patients died, 7 of progressive disease/surgical complications, and two with Gardner syndrome-related malignancies. Demographics: 45 females (65%), median age 30 (range 15-75), 21 with Gardner syndrome (30%), median follow-up 68 months, and median of 2 lines of therapy (1-7).

Conclusions: Our findings suggest that ILK expression may serve as a marker for disease progression and that ILK correlates with angiogenesis, apoptosis and invasion in osteosarcoma.

34952 - THE PUTATIVE ANTI NEOPLASTIC AGENT TAUROLIDINE PROMOTES OSTEOSARCOMA LUNG AND LIVER METASTASIS AND CAUSES HEPATIC DEFORMATION IN MICE
Matthias Arlt; Ingo Banke; Denise Walters; Patrick Steinnmann; Walter Born; *Bruno Fuchs
University Hospital Balgrist, Zurich, Switzerland

Objectives: Taurolidine is a well-known broad spectrum antibiotic. It has antineoplastic properties against a variety of human cancers.

Recently, we could show pro-apoptotic and growth-inhibitory activity of taurolidine against 10 osteosarcoma cell lines in vitro. Since metastasis is the leading cause of death in Osteosarcoma (OS) patients, we here investigated the antimetastatic potential of taurolidine in two established murine OS models in vivo.

Methods: For experimental metastasis, 5x10^5 K7M2-LacZ or 1x10^6 LM8-LacZ OS cells were injected intravenously into BALB/c and C3H mice, respectively. For primary tumor growth and spontaneous metastasis, 1x10^7 LM8-LacZ OS cells were inoculated subcutaneously into C3H mice. Taurolidine or vehicle control were given intraperitoneally in different treatment regimens. At the end of each experiment mice were sacrificed and lungs and livers removed. LacZ-tagged, indigo-blue OS metastases on the organ surfaces were counted after X-Gal staining.

Results: Treatment with taurolidine significantly enhanced experimental K7M2 lung and liver metastasis. Also in the LM8 model, experimental metastasis was dramatically elevated upon taurolidine therapy. Furthermore, taurolidine significantly increased spontaneous LM8 lung and liver metastasis, whereas no effect on
primary tumor growth was detectable. Interestingly, dose dependent hepatic deformations could be observed in tumor-bearing as well as healthy mice upon treatment with taurolidine.

**Conclusions:** This study reveals for the first time an unexpected, lung and liver metastasis promoting activity of taurolidine, accompanied with severe liver deformations.

### 34960 - PHASE II STUDY OF PATHOTOXIC NANOPARTICLES BEARING A CYTOCIDAL CYCLIN G1 CONSTRUCT (REXIN-G) REVEALS SIGNIFICANT ANTI-TUMOR ACTIVITY WITH NO TOXICITY IN CHEMO-RESISTANT METASTATIC OSTEOSARCOMA

*Sant P Chawla1; Victoria S Chua1; Arun Kalra1; Doris Quon1; Karlo Beltran1; Andreh Saralou1; Kenneth Y Kita1; Frederick L Hall2; Erlinda M Gordon2

1Sarcoma Oncology Center, Santa Monica, California, United States; 2Epeius Biotechnologies Corporation, San Marino, California, United States

**Objectives:** Rexin-G is the first and so far only targeted gene therapy vector that has been tested in the clinic (Nature Reviews/Genetics 2007). The objective of the study is to evaluate the clinical efficacy and over-all safety of Rexin-G in patients with chemo-resistant metastatic osteosarcoma.

**Methods:** Patients were treated with 1-2 x 10e11 cfu Rexin-G i.v. 3 times a week for 4 weeks. Patients with Grade 1 or less toxicity were given additional treatment cycles in escalating doses.

**Results:** Safety Analysis: There were no adverse events attributed to the study drug. No vector antibodies were detected in serum, and no vector DNA integration or replication competent retrovirus was detected in peripheral blood lymphocytes of treated patients. Efficacy Analysis: The table shows the tumor responses, progression-free survival and over-all survival data of 15 evaluable patients. Histopathological analysis revealed extensive necrosis and calcification of resected tumors in one patient, indicating a positive tumor response.

**Conclusions:** Taken together, the clinical data suggest that (i) repeated infusions of Rexin-G are safe and well-tolerated, and (ii) Rexin-G stabilizes tumor growth, induces necrosis and calcification of tumors, and may prolong progression-free survival and over-all survival in patients with chemo-resistant metastatic osteosarcoma.

**Response By RECIST** | **Response By PET** | **Median PFS By RECIST and PET (months)** | **Median OS (months)**
---|---|---|---
10 SD, 5 PD | 5 PR, 6 SD, 4 PD | > 3 | > 5.5

*Recent Enrollees (n=6) | > 1.5* | > 3.5*

### 34965 - GEMCITABINE WITH WEEKLY DOXETAXEL IS A LESS TOXIC ALTERNATIVE TO GEMCITABINE WITH HIGHER DOSE THREE-WEEKLY DOXETAXEL FOR TREATMENT OF METASTATIC SARCOMA

*David R D’Adamo
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**Objectives:** Gemcitabine (G) and three-weekly docetaxel (D) is an established regimen for treatment of metastatic soft-tissue sarcoma. The standard regimen includes gemcitabine 900 mg/m2 over 90 minutes on days 1 and 8, and docetaxel 100 mg/m2 on day 8, with filgrastim or pegfilgrastim. Response rate, time to progression and overall survival were superior in one randomized study compared to gemcitabine alone. However, the toxicity of this regimen is substantial. In lung and breast cancers, taxanes weekly are as effective as three-weekly, with less toxicity.

**Methods:** We reviewed charts of 46 advanced sarcoma patients treated with gemcitabine and docetaxel in one of 3 schedules: (1) patients receiving docetaxel every 3 weeks; (2) patients receiving G (800 mg/m2 in 30 min) and D (35 mg/m2) on a two week on, one off schedule; (3) patients switched from three-weekly to weekly docetaxel after development of toxicity.

**Results:** Gemcitabine with weekly docetaxel was better tolerated, with fewer grade 3/4 events including hematologic and non-
hematologic toxicity. There were less asthenia, alopecia, and use of hematopoietic growth factors with weekly dosing. Responses were seen in all subgroups of patients.

**Conclusions:** Split (weekly) dosing of docetaxel is a less toxic alternative to three-weekly docetaxel. 85% of the dose intensity of the standard regimen is maintained, with decreased use of growth factors. This regimen permits the treatment of older patients or those with a poorer performance status, and also allows for longer treatment of responding patients. A formal comparison of the efficacy of these two schedules requires a randomized trial.

**34971 - COMBINED COPY NUMBER CHANGES OF 7P, 9P AND 17Q IN MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS IS A STRONG MARKER FOR DISEASE-SPECIFIC SURVIVAL**

Helge R. Brekke1; Francilim R. Ribeiro2; Guro E. Lind3; Mette Eknæs4; Kirsten Sundby Hall5; Bodil Bjerkehagen6; Eva van den Berg7; Sigbjorn Smeland8; Manuel Teixeira9; Nils Mandahl6; Rolf I. Skotheim10; Fredrik Mertens11; Ragnhild A. Lothe12

1Department of Cancer Prevention Institute for Cancer Research The Norwegian Radium Hospital Rikshospitalet University Hospital, Oslo, Norway; 2Portuguese Oncology Institute, Porto, Portugal; 3The Cancer Clinic Department of Oncology The Norwegian Radium Hospital Rikshospitalet University Hospital, Oslo, Norway; 4Division of Pathology The Norwegian Radium Hospital Rikshospitalet University Hospital, Oslo, Norway; 5Clinical Genetics University Hospital of Groningen, Groningen, Netherlands; 6Department of Clinical Genetics Lund University Hospital, Lund, Sweden

**Objectives:** The goal was to provide a detailed overview of the complex genomic changes in malignant peripheral nerve sheath tumours (MPNST), which so far have not been well characterized. Furthermore, by linking chromosomal profiles with gene expression data, we aimed to identify specific genes that may contribute to the clinical aggressiveness of these tumours.

**Methods:** Chromosomal comparative genomic hybridisation (CGH) was performed for 48 MPNSTs and 10 neurofibromas, and array-based CGH was performed for 20 MPNSTs. Of the 48 patients with MPNST, 20 had been diagnosed with neurofibromatosis type 1 (NF1). Gene expression array data were collected for 30 MPNSTs and 1 neurofibroma. Gene expression was verified with TaqMan Low Density Array cards.

**Results:** Most tumours presented complex chromosomal profiles with a median of 16 aberrations per sample. No significant differences were found in the genomic profiles of sporadic versus NF1-related MPNSTs. Gains at 17q (69%), 8q (65%) and 7p (56%), and losses at 9p (46%), 11q (46%) and 17p (42%) were the most common. Regions of high-level amplification or homozygous deletion are presented along with expression levels for the most interesting genes in these regions.

**Conclusions:** Gain of 7p and 17q and loss of 9p were each associated with poor survival, and were even stronger in combination. Integrated DNA and RNA analyses identified TWIST1 (7p), BIRC5 (17q) and CDKN2A (9p) as candidate targets at these chromosome arms.

**34972 - EXPRESSION AND PROGNOSTIC RELEVANCE OF TELOMERE MAINTENANCE MECHANISMS IN MALIGNANT SCHWANNOMA**

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Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

**Objectives:** Human tumours maintain their telomeres by telomerase activity (TA) or by alternative lengthening of telomere (ALT). No information is currently available concerning the presence of telomere maintenance mechanisms in malignant schwannoma. Taking advantage of a relatively large mono-institutional series of malignant schwannoma patients with a long follow-up, in this study we proposed to investigate the prevalence and the prognostic role of the two known telomere maintenance mechanisms, TA and ALT, in this malignancy.

**Methods:** In 45 malignant schwannoma specimens obtained from 37 patients, TA was determined using the telomeric repeat amplification protocol and ALT was detected by assaying ALT-associated promyelocytic leukaemia nuclear bodies. The prognostic significance of telomere maintenance mechanisms was analysed by Cox regression in the overall series of patients.

**Results:** Telomere maintenance mechanisms were detectable in 66.7% of malignant schwannomas: ALT or TA alone was found in 28.9% or 26.7% of lesions, respectively, whereas 5 samples (11.1%) were ALT+/TA+. TA was found to be more frequently expressed in samples from patients with neurofibromatosis type 1 (57.1 vs 29.0%, P = 0.067). TA was prognostic for 5-year disease-specific survival (TA+ vs TA−, 25% vs 58%; hazard ratio, 2.73; 95% CI, 1.14-6.56; P = 0.025), whereas ALT failed to significantly affect clinical outcome (ALT+ vs ALT−, 35% vs 50%; hazard ratio, 1.03; 95% CI, 0.43-2.46; P = 0.94).

**Conclusions:** Our results indicate that both known telomere maintenance mechanisms, TA and ALT, are present in malignant schwannoma, and differentially affect patient prognosis.

**34980 - DETAILED ANALYSIS OF SURVIVAL AND SAFETY WITH SUNITINIB IN A WORLDWIDE TREATMENT-USE TRIAL OF PATIENTS WITH ADVANCED IMATINIB-RESISTANT/INTOLERANT GIST**

Beatrice Seddon1; Peter Reichardt2; Yoon-Koo Kang3; Wlodzimierz Ruka4; Alejandra Nieto5; Aurora Breanza5; Thomas Lechner6; George D. Demetri7

1University College Hospital NHS Trust, London, United Kingdom; 2HELIOS Klinikum Bad Saarow, Bad Saarow, Germany; 3Asan Medical Center, Seoul, Korea (South); 4Maria Skłodowska Curie Memorial Cancer Center, Warsaw, Poland; 5Pfizer Inc, New York, New York, United States; 6Ludwig Center at Dana Farber Harvard Cancer Center, Boston, Massachusetts, United States

**Objectives:** Sunitinib is an oral multitargeted tyrosine kinase inhibitor approved multidimensionally for treatment of advanced imatinib-resistant/intolerant GIST. The objectives of this study were to provide sunitinib to GIST patients who were otherwise ineligible for sunitinib clinical trials and to evaluate efficacy and safety in a broad GIST population.

**Methods:** This was an open-label study assessing safety, antitumor response, TTP, and OS in patients with advanced imatinib-resistant/intolerant GIST receiving sunitinib 50 mg/day in 6-week cycles (4 weeks on treatment, 2 weeks off).

**Results:** As of December 2007, 1,126 patients had been enrolled and 1,117 comprised the ITT population. Median estimated TTP was 41 weeks (95% CI, 36-47), and OS was 75 weeks (95% CI, 68-84), with 50% of patients alive in the overall population. OS estimates based on age, ECOG PS, and prior imatinib treatment history are presented in the table below. The most common non-hematologic treatment-related grade 3/4 AEs were fatigue, hand-foot syndrome, hypertension, and diarrhea (all <8%). Treatment-related grade 3/4 hematologic AEs included neutropenia, thrombocytopenia,
and anemia (all <u>&lt;/u>&gt;8%). Treatment-related hypothyroidism (all grades) was reported in 10% of patients. Treatment-related AEs related to cardiac function included heart failure, congestive heart failure, myocardial infarction, reduced ejection fraction, and pulmonary edema (all <u>&lt;/u>&gt;0.6%). The total incidence of treatment-related hypertension was 22% (5% grade 3/4).

**Conclusions:** Sunitinib showed efficacy and acceptable tolerability in patients with advanced imatinib-resistant/intolerant GIST who are ineligible for other sunitinib trials, with a safety profile consistent with that observed with sunitinib in other GIST trials.

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<th>Group</th>
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<th>Alive n (%)</th>
<th>Median OS (95% CI), weeks</th>
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<td>ECOG PS</td>
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<td>0/1</td>
<td>935</td>
<td>519 (56)</td>
<td>88 (77-97)</td>
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<td>2</td>
<td>134</td>
<td>34 (25)</td>
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<td>Prior maximum imatinib dose (mg)</td>
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<td>Intolerance</td>
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<tr>
<td>PD &lt;6 months</td>
<td>150</td>
<td>71 (47)</td>
<td>60 (53-75)</td>
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<tr>
<td>PD &gt;6 months</td>
<td>862</td>
<td>430 (50)</td>
<td>75 (68-84)</td>
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<td>NC = not yet calculable</td>
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**34991 - INITIATION OF SUNITINIB TREATMENT 24 HOURS FOLLOWING A FINAL DOSE OF IMATINIB IN PATIENTS WITH ADVANCED GIST: SAFETY AND TOLERABILITY**

**Objectives:** The objective of this sub-study is to evaluate the safety/tolerability associated with initiating treatment with sunitinib 37.5 mg/day 24 hours after a final dose of imatinib 400 mg/day, prior to a phase IIIb trial that will evaluate the efficacy/safety of sunitinib 37.5 mg/day vs. imatinib 800 mg/day following PD on imatinib 400 mg/day.

**Methods:** Endpoints in this sub-study are treatment-related AEs in the first week of sunitinib treatment, changes in QTc interval, and elevations in total drug plasma concentrations. If treatment-related AEs of grade &lt;u&gt;3 are observed in &lt;u&gt;1/6 patients during the first 7 days of treatment, 6 additional patients could be enrolled in the sub-study and the main study will commence.

**Results:** No treatment-related grade &lt;u&gt;&lt;u&gt;3 AEs were observed in the first cohort of 6 patients during the first 7 and 14 days of treatment (5 patients remain on study; 1 discontinued due to PD at 15 weeks). A total of 6 treatment-related grade 1/2 AEs occurred in 4 patients, with grade 2 AEs occurring in 2 patients (asthenia, diarrhea, and mucosal inflammation). Recruitment of the second cohort was initiated and 1 additional patient has been enrolled. By 3/2008, 4 treatment-related grade 3 AEs had occurred. No grade 4 events were recorded. All QTc values were within normal ranges, and all plasma drug concentrations were within the expected range.

**Conclusions:** Sunitinib administration 24 hours after the last dose of imatinib appeared to be safe and well tolerated. The criteria for enrolling the second patient cohort and initiating the main trial were met.

**35001 - HOW SHOULD ADULTS WITH PLEOMORPHIC RHABDOMYOSARCOMA (RMS) BE TREATED?**

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University College London Hospital, London, United Kingdom

**Objectives:** To identify consensus between experts on treatment of a patient with RMS in adults and to identify supporting evidence for guidance.

**Methods:** Sarcoma specialists (10 from the UK, 13 from mainland Europe and the US) were sent an e-mail requesting advice about further management of a 37 year old woman after resection from the thigh of a 7 cm pleomorphic RMS. She had a normal chest CT. Comments were invited about further staging and indications for chemotherapy and for radiotherapy. Responses were categorised and literature was searched for publications relevant to the categories.

**Results:** Seventeen responses were received (8 from the UK, 9 from elsewhere). Nine (52%) recommended staging in addition to chest CT, including molecular characterisation, CT abdomen and pelvis, bone marrow biopsy and PET scanning. Thirteen (76%) recommended adjuvant chemotherapy but with no consistency in regimen. Radiotherapy was advised by 11 (64%). There appeared to be variation between the UK and other oncologists, particularly in the use of chemotherapy.

**Conclusions:** We conclude that (i) RMS occurring in adults may be managed in widely different ways, (ii) the importance of PET-CT and identification of translocations should be further evaluated (iii) more evidence is required to develop treatment strategies for adult RMS, (iv) consensus guidance on treatment of RMS occurring in adults may be valuable.

**35005 - ANALYSIS OF AN OBSERVATIONAL REGISTRY OF GASTROINTESTINAL STROMAL TUMOR (GIST) PATIENTS (PTS) IN THE USA: REGISTRY**

Charles D Blanke2; *Peter W.T. Pisters3; Jonathan C Trent3; *Margaret von Mehren4; Joel Picus5; Erica Stealey1; Karen McDougall1

1Novartis Pharmaceuticals, East Hanover, NJ, United States; 2University of British Columbia, Vancouver, British Columbia, Canada; 3University of Texas MD Anderson Cancer Center, Houston, TX, United States; 4Fox Chase Cancer Center, Philadelphia, PA, United States; 5Washington University, St Louis, MO, United States

**Objectives:** This observational reGISTry, initiated 11/04, characterizes evolving community- and academic-based patterns of care for GIST.

**Methods:** Data from consented pts (e.g. demographics, clinical characteristics, therapy, outcomes) are entered onto an internet-based database. Analyses are performed every 6 months, with data from unique sites being compared to the aggregate.

**Results:** 753 pts were enrolled from 116 centers with 56% from community practices. 81% were diagnosed with localized tumor. 94% had KIT immunohistochemistry, and 4% had genotyping...
performed at any time. Drug efficacy was assessed by CT tumor size (74%) or size and density (31%), or by PET (10%). 79% of pts receiving imatinib at any time (436 pts total) started at 400mg, and best response was 33% PR, 43% SD, 12% PD and 12% unknown. 77% of pts receiving sunitinib (75 pts total) started at 50mg, and best response was 16% PR, 29% SD, 38% PD and 16% unknown. 136 pts received adjuvant imatinib. The median therapy durations were 167/366 days for those continuing (58 pts) and discontinuing (78 pts) therapy. In 2007, 14% of all pts received adjuvant imatinib versus 18% in 2008.

Conclusions: reGISTry is a useful tool for determining evolving management patterns in GIST. It can be used to illustrate treatment variations from official guidelines. Genotyping and PET scanning are still infrequently performed, though the use is increasing over time. The starting dose of imatinib and sunitinib remains 400mg and 50mg respectively for most pts. The percentage of reGISTry patients receiving adjuvant imatinib is increasing.

35010 - INITIAL RESULTS OF A PHASE II STUDY OF THE SAFETY AND EFFICACY OF THE APOMAB DR5 AGONIST ANTIBODY IN ADVANCED CHONDROSARCOMA AND SYNOVIAL SARCOMA PATIENTS
* Sant Chawla1; * Demetri George2; * Desai Jayesh1; Pao Mary1; * Skettino Sandra1; Novotny William1; Durbin Blythe1; Treddinick Alexandria1; Wagner Andrew4 1 Genentech Inc, South San Francisco, CA, United States; 2 Sarcoma Oncology Center, Santa Monica, CA, United States; 3 Ludwig Center at Dana Farber, Harvard Cancer Center, Boston, MA, United States; 4 Peter MacCallum Cancer Centre, Melbourne, Australia

Objectives: Preclinical data suggest TNF-receptor apoptosis inducing ligand (Apo2L/TRAIL) induces cell death in sarcoma cells through the pro-apoptotic receptors DR4 and DR5. Apomab is a fully human, affinity-matured IgG1 DR5 agonist monoclonal antibody. The primary objectives of this study were to determine objective response rate, safety and tolerability of Apomab in advanced chondrosarcoma or previously treated, advanced synovial sarcoma patients.

Methods: Patients received a loading dose of Apomab 15mg/kg, followed by 10mg/kg doses in 21 day cycles.

Results: 14 chondrosarcoma and one synovial sarcoma patient received treatment. There were no RECIST-defined objective responses in the chondrosarcoma cohort. However, 8 of 14 patients had stable disease by investigator assessment at cycle 3. Resection specimens from 2 patients showed 50 and 60% tumor necrosis following treatment. After one dose of Apomab, the synovial sarcoma patient with known extensive pulmonary involvement developed respiratory dysfunction and was treated with anticoagulation therapy for pulmonary embolus. She developed massive hemoptysis and died. Autopsy showed gross necrosis of lung metastases.

Conclusions: No responses per RECIST were seen in chondrosarcoma patients following Apomab, although stable disease and tumor necrosis are of interest. Potential signs of Apomab activity against synovial sarcoma warrant further investigation in this disease.

35017 - AGGRESSIVE PATTERN OF RECURRENCE IN KAPOSI SARCOMA (KS) TREATED WITH BEVACIZUMAB (B).
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Objectives: Bevacizumab (B), a humanized monoclonal antibody against vascular endothelial growth factor, has activity against soft tissue sarcomas (SAR) either as single agent or in combination. Several reports documented aggressive infiltrating breakthrough disease when used to treat malignant gliomas. Such pattern of recurrence was not reported in SAR the reason we reviewed our data base.

Methods: We retrospectively reviewed our experience with SAR patients who received B between 2004 and 2008.

Results: We identified 20 patients with SAR treated with B alone or in combination. A 79 yo man with multiple classic KS lesions of the feet fit such a pattern of recurrence. Patient was intially treated with B-Doxil Q2weeks, with early rapid response after the first cycle and maximum blanching and flattening after 3rd cycle. Treatment was stopped due to mild mucositis and moderate Hand-Foot-Syndrome. After 7 month break, his disease progressed slowly over both feet with a single lesion in the stomach. Patient was restarted on B-Doxil with quick response over the feet and resolution of gastric mass.
Methods: For s.c. PT growth and spontaneous metastasis, 1x10^7 Dunn- or LM8-lacZ OS cells were injected into the flank of syngeneic C3H mice. For i.t. PT growth and spontaneous metastasis, 5x10^5 Dunn- or LM8-lacZ cells were inoculated into the tibia of C3H mice. For experimental metastasis, 1x10^6 Dunn- or LM8-lacZ cells were injected into the tail vein of C3H mice.

Results: PT growth in the i.t. model was significantly enhanced with LM8 cells compared to Dunn cells. The opposite was found upon s.c. inoculation. Spontaneous LM8-metastasis in the s.c. model was mainly to the lung, while liver and ovaries represented the predominant target organs of metastasis in the i.t. and i.v. models. Life-threatening morbidity in the s.c. model seemed to be mainly caused by massive PT growth, whereas in the i.t. and i.v. model metastatic load of livers appeared to be the crucial determinant.

Conclusions: This study demonstrates a potential impact of the tumor cell injection site on PT growth capacity, extent and localisation of metastasis and cause of death in OS.

35022 - DUNN-/LM8 OSTEOSARCOMA MOUSE MODEL: LACZ-TAGGING OF TUMOR CELLS PROVIDES NOVEL PERSPECTIVES AS PRECLINICAL TOOL FOR CANCER RESEARCH

Matthias Arlt; Ingo Banke; Denise Walters; Gabor Puskas; Patrick Steinmann; Roman Muff; Walter Born; *Bruno Fuchs

University Hospital Balgrist, Zurich, Switzerland

Objectives: Osteosarcoma (OS) is the most common primary bone cancer and metastasis the leading cause of death. Animal models of OS metastasis are important preclinical tools. The murine Dunn/LM8 model is the most favoured syngeneic OS model. However, its primary tumor growth and metastatic pattern is contradictorily described. Therefore, a concise and comparative evaluation of the Dunn/LM8 OS model was performed in the present study, introducing lacZ-tagging of OS cells for optimized tumor cell detection.

Methods: Dunn and LM8 OS cells were retrovirally tagged with the lacZ-gene, enabling selective indigo-blue staining of the tumor cells. Tagged and untagged cells were compared in vitro regarding proliferation, migration and invasion. In vivo, subcutaneous primary tumor growth and pattern of spontaneous metastasis of lacZ-tagged and untagged Dunn and LM8 cells were evaluated in syngeneic C3H-mice.

Results: LacZ-tagging had no influence on OS cell behaviour in vitro and OS primary tumor growth in vivo. In vitro, LM8 cells showed increased proliferation, migration and invasion compared to Dunn cells. In vivo, subcutaneous injection of Dunn cells resulted in significantly increased primary tumor growth compared to LM8 cells. On the metastatic level, lacZ-tagging of OS cells improved detection of macro- and micrometastatic foci, even at the level of single cells.

Conclusions: This study provides a concise and comparative evaluation of the Dunn/LM8 OS model. LacZ-tagging of the OS cells enabled highly efficient detection of metastases, leading to novel insights into this frequently used mouse model.

35033 - SOFT TISSUE SARCOMAS OF THE TRUNK WALL (STS-TW): A STUDY OF 343 PATIENTS FROM THE FRENCH SARCOMA GROUP (FSG) DATABASE

Sebastien Salas1; Binh Bui1; Stoeckle Eberhard1; Philippe Terrier2; Dominique Ranchere-Vince3; Louis Guillou3; Francoise Collin3; Agnes Leroux3; Jean Jacques Michels3; Martine Trassard3; Isabelle
Valo²; Yves Marie Robin²; Bernard Marques³; Marie Christine Chateau²; Veronique Brouste²; Jean Michel Coindre²
¹Institut Bergonie, Bordeaux, France; ²Pathology subgroup French Sarcoma Group, Paris, France

Objectives: STS-TW are usually studied together with soft tissue sarcomas (STS) of other locations. We report a study on STS developed in the trunk wall and entered in the FSG database.

Methods: 343 adults with a STS-WT and no metastasis at diagnosis were included and the following parameters were studied: age, sex, tumor location, size, depth, histotype, grade, previous history of radiotherapy (PHR) and surgical margins. We performed univariate and multivariate analysis for overall survival (OS), metastasis-free survival (MFS) and local-recurrence-free survival (LRFS).

Results: The median age was 55.5 years. 57% of patients were female. Tumor locations were as follows: thoracic wall, 82.5%; abdominal wall, 12.3%; and pelvic wall 5.2%. Median tumor size was 6.0 cm. The most frequent tumor types were undifferentiated sarcoma (27.7%) and rhabdomyosarcoma and leiomysarcoma (19.2%). Dermatofibrosarcoma protuberas and angiosarcoma comprised 11.1% and 7.9%, respectively. 19% of cases were grade 1; 34.2% grade 2 and 44.6% grade 3. 21.9% of patients had a PHR. 79.3% of patients had a macroscopically complete surgical resection. Median follow-up was 7.6 years. The 5-years OS, MFS and LRFS rates were 60.4%, 68.9% and 58.4%, respectively.

Multivariate analysis retained age, previous PHR, size, depth and grade for predicting OS, and PHR, size and grade for MFS. The factors influencing LRFS were PHR, depth and surgical margins.

Conclusions: Our results suggest a similar outcome and classical prognostic factors as compared to extemity sarcomas. However, the PHR had an impact on OS, MFS and LRFS.

35034 - BONE TURNOVER MARKERS CHANGES IN OSTEOSARCOMA PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY
Emanuela Palmerini¹; Laura Pratelli¹; Stefano Ferrari¹
¹Istituto Ortopedico Rizzoli, Bologna, BO, Italy; ²Istituto Ortopedico Rizzoli, Bologna, BO, Italy

Objectives: To assess bone turnover markers changes in osteosarcoma patients undergoing neoadjuvant chemotherapy

Methods: Serum levels of 2 bone formation markers, bone-specific alkaline phosphatase (BALP) and osteocalcin (OC) and of the bone resorption marker carboxy-terminal telopeptide of type I collagen (ICTP) were prospectively collected prior and at the completion of neo-adjuvant chemotherapy. Immunometric essay measurements were expressed as ng/mL (ICTP and BALP) or μg/L (OC). 46 patients (median age 17; 7-42) with osteosarcoma of the extremity (6 with lung metastases at presentation) entered the study. All patients became tumor free. With a median follow up of 26 months, 15/46 patients relapsed.

Results: Formation markers significantly decreased: BALP baseline was 48.1 ±38 to 16 ±9 (p:0.0001) and OC baseline: 38.2 ±22 to 21 ±9.7 (p:0.0001). The resorption marker ICTP increased (1.05 ±0.5 to 1.4 ±0.5; 0.0002).

Patients with a good histologic response (GR) to primary chemotherapy showed higher baseline BALP serum level compared to those with a poor response (40 ±42 vs 28 ±17, p=0.008). No differences were found in the post primary chemotherapy samples according to the histologic response.

Patients who relapsed had higher baseline level of BALP (69 vs 39, p= 0.008), OC ( 47.6 vs 34.1, p=0.06), and ICTP (1.26 vs 0.9, p=0.09).

Conclusions: The present study showed a significant reduction of bone formation and increase of bone resorption after neo-adjuvant chemotherapy. Higher baseline BALP was predictive for GR. A higher bone remodelling activity at presentation in relapsed patients was shown. This finding suggests a relation between tumor aggressiveness and bone turnover.

35036 - HIGH DOSE IFOSFAMIDE CHEMOTHERAPY FOR ADVANCED/RECURRENT EWING’S SARCOMA
Stefano Ferrari¹; Emanuela Palmerini¹; Adalberto Brach del Prever²; Eric L. Staals³; Marilena Cserzi¹; Massimo E. Abate³; Alessandra Longhi¹; Antonio Briccoli¹; Franca Fagiolì²; Daniel Vanel³
¹Istituto Ortopedico Rizzoli, Bologna, BO, Italy; ²Ospedale Regina Margherita, Torino, TO, Italy; ³OIRM S Anna, Torino, TO, Italy

Objectives: To determine activity and toxicity of high dose ifosfamide(HDIFO) in Ewing’s sarcoma family of tumors(EFST).

Methods: ESFT patients with advanced/recurrent disease were eligible. All patients who received at least 2 courses of 15 g/m² ifosfamide over a 5-day IV continuous infusion were evaluable for response. Primary endpoint was response rate (RR); complete response(CR) + partial response(PR), according to RECIST criteria. Radiographic response was determined after 6 weeks.

Results: 37 patients were enrolled from 2001 to 2007. Median age: 17 years(6-45). Median time to progression was 15.8 months(9-152). All patients had previously received standard dose ifosfamide; high dose busulphan and melphalan was delivered in 12 of them. 17 patients presented with lung metastases only (monolateral in 1), 20 had multiple metastatic sites. Transient grade 4 neutropenia and thrombocytopenia were recorded in 97% and 54% of HDIFO courses, respectively. Severe CNS toxicity was recorded in 1 patient. One patient had clinical progression after the first cycle, one was not assessable by RECIST, one had a severe CNS toxicity after the first cycle. Thirty-four patients were evaluable for response. The overall RR was 35%(1 CR + 11 PR); 32.5%(11/34) of patients achieved stable disease; 32.5%(11/34) progressed. 11(32.5%) patients subsequently received busulphan and melphalan with autologous PBSC cells rescue. 10 patients were alive, 5 of them disease-free, with a median post HDIFO survival time of 10.5 months(1-47 months). The 3-year post HDIFO overall survival was 23%(0% at 1 year for patients with PD).

Conclusions: HDIFO is active in advanced/recurrent ESFT patients, previously treated with standard dose Ifosfamide.

35040 - SARCOMAS OF THE HEART AND GREAT VESELS, A RETROSPECTIVE ANALYSIS OF 9 CASES: ONE CENTER EXPERIENCE.
Marcin Zdzieńicki; Sławomir Falkowski; Anna Nowak-Dement; Tomasz Switaj; *Piotr Rutkowski; *Włodzimierz Ruśka
Soft Tissue and Bone Sarcomas Department of Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland

Objectives: To evaluate the results of treatment of patients with heart and large vessels sarcomas.

Methods: Retrospective analysis of institutional database revealed 9 cases of the heart and great vessels soft tissue sarcomas admitted between January 2003 and May 2008 for systemic chemotherapy. There were 4 males and 5 females in the group. Median age at diagnosis was 35 years (range:27-55). 7 tumors were localized in the heart, 2 in the pulmonary trunk. The histopathological types comprised of:angiosarcoma (2 cases), leiomyosarcoma (2 cases),
undifferentiated sarcoma (2 cases), fibrosarcoma (1 case) malignant fibrous histiocytoma (1 case) and desmoplastic small round cell tumor-DSRCT (1 case).

Results: 7 patients primarily underwent surgical treatment: 1 heart transplantation, 6 local resection of the tumor. All patients received systemic chemotherapy consisting in the first line of doxorubicin and dacarbazine. 6 patients died due to disease progression, 3 are still alive with active disease. Median time of survival was 33 weeks (9-140 weeks). Overall survival was 57% after one year from diagnosis and 27% after 2 years. Observed patterns of relapse: in 6 patients-local recurrence, and in 7 patients systemic dissemination.

Conclusions: The prognosis in heart and great vessels sarcomas in adults is poor. Primary surgical treatment usually fails in those patients. More aggressive approach (as heart transplantation) is not reasonable, because of high rate of metastatic disease. In most cases palliative chemotherapy is the only treatment option.

35044 - INSULIN-LIKE GROWTH FACTORS AND INSULIN-LIKE GROWTH FACTOR-BINDING PROTEINS IN RELATION TO DISEASE STATUS AND INCIDENCE OF HYPOGLYCAEMIA IN PATIENTS WITH A GASTROINTESTINAL STROMAL TUMOUR

Bart Rikhorst; Jaap van Doorn; Albert J.H. Suurmeijer; Maaike W. Rautenberg; Piet L. Jager; Steven de Jong; Jourik A. Gietema

Objectives: Patients with a gastrointestinal stromal tumour (GIST) suffering from non-islet cell tumour induced hypoglycaemia (NICTH) have been reported occasionally. NICTH is associated with increased plasma levels of pro-insulin-like growth factor (IGF)-IIE[68-88] and concordant changes in IGF-I and IGF-binding proteins (IGFBPs). We studied the clinical relevance of determining these proteins in patients with a GIST.

Methods: Twenty-four patients were included. Plasma samples were collected prior to, 1 week, and median 5 months after start of treatment with imatinib, and levels of IGF-I, total IGF-II, pro-IGF-IIE[68-88], IGFBP-2, -3 and -6 were determined. GIST-specimens from 17 patients were analysed for IGF-II mRNA, IIE[68-88] containing peptides and IGFBP-2, and tumour cyst fluid from two patients for pro-IGF-IIE[68-88] and IGFBP-2

Results: Before treatment and/or during follow-up, 3/24 (13%) patients showed increased (i.e. standard deviation score (SDS) >2.0) plasma levels of pro-IGF-IIE[68-88]. All three developed NICTH. Overall, patients with either metastatic disease, elevated serum LDH activity, or total tumour size >12 cm had the highest pro-IGF-IIE[68-88] levels. Most patients had plasma IGFBP-2 levels exceeding 2.0 SDS and these levels were significantly higher in patients with progressive disease. IGFBP-2 was expressed in 6%, IGF-II in 82% of GISTs. Additionally, a high molar ratio of pro-IGF-IIE[68-88] between cyst fluid and plasma was found suggesting that pro-IGF-IIE[68-88] is secreted by the tumour.

Conclusions: We identified IGFBP-2 and pro-IGF-IIE[68-88] as markers that may potentially be used in the surveillance of patients with a GIST. NICTH appears to be a common phenomenon in GIST and may be predicted by increased pro-IGF-IIE[68-88] levels.

35049 - LONG-TERM SURVIVAL IN A PHASE III TRIAL OF SUNITINIB IN IMATINIB-RESISTANT/INTOLERANT GASTROINTESTINAL STROMAL TUMOR (GIST) WITH NOVEL STATISTICAL ANALYSIS TO ACCOUNT FOR CROSSOVER

Christopher R. Garrett; Xin Huang; Paolo G. Casali; Patrick Schöffski; Martin E. Blackstein; Manisha Shah; Jaap Verweij; Vanessa Tassell; Charles M. Baum; George D. Demetris

Objectives: Sunitinib is an oral multitargeted tyrosine kinase inhibitor approved for treatment of imatinib-resistant/intolerant GIST. Interim analysis of this double-blind, placebo-controlled phase III trial with crossover revealed a significant difference in OS between patients randomized to sunitinib vs. placebo favoring sunitinib. However conventional statistical methods gave rise to biased estimates of treatment effect for mature OS data due to the crossover design. The main objective of this analysis was to evaluate mature survival results using a novel statistical method to account for the effect of crossover on survival.

Methods: In addition to the log-rank test, Cox model, and Kaplan-Meier method, OS was analyzed using the rank-preserving structural failure time (RPSFT) method.

Results: A total of 243 patients were randomized to sunitinib and 118 to placebo (99 of whom crossed over to sunitinib). Conventional analysis showed that median OS converged in the two groups (sunitinib: 73.3 weeks, 95% CI, 61.3-85.7; placebo: 64.9 weeks, 95% CI, 45.7-96.0; HR, 0.834, P=0.161) as expected, given the crossover design. However, median OS for placebo estimated by RPSFT analysis was 35.7 weeks (95% CI, 25.7-49.8), demonstrating a significant sunitinib treatment effect (HR, 0.47; P<0.001). Throughout the entire study the most common treatment-related AEs on sunitinib were fatigue (47%), diarrhea (43%), and nausea (36%). The incidence of cardiac AEs was low across the study with sunitinib (6%; all grades).

Conclusions: The long-term OS benefit provided by sunitinib vs. placebo in this phase III study was confirmed using RPSFT analysis. Sunitinib demonstrated acceptable and predictable safety with long-term treatment.

35052 - COMMON GENETIC CHANGES IN LEIOMYOSARCOMA AND GIST - IMPLICATION FOR ATM INVOLVEMENT

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Objectives: It is well established that majority of GISTs overexpress KIT and have characteristic mutations within the gene. These mutations are the targets of drug treatment with tyrosine kinase inhibitors. Leiomyosarcoma to date, however, lack a tumour specific genetic alteration. Genetic aberrations including gene amplifications and deletions play an important role in tumour development and progression. The aim of the study was to investigate genetic changes in both leiomyosarcoma and GIST.
Methods: DNA was extracted from a series of formalin fixed, paraffin embedded cases of leiomyosarcoma and GIST, and screened for genomic imbalances. Specific areas of imbalances were confirmed using fluorescence in situ hybridisation (FISH). Protein expression of candidate genes within the regions identified was investigated with immunohistochemistry.

Results: Genomic imbalance was found to be widespread. We have shown a specific loss/deletion in the distal region of chromosome arm 11q (ATM locus), confirmed with FISH, in both tumours. Investigation of the protein expression revealed a negative/decreased ATM expression in correlation with the ATM locus deletion.

Conclusions: As one of the major regulators of the cell cycle following DNA damage, loss of wild-type ATM function may have an important role in leiomyosarcoma and GIST, and a contributory factor to the high genomic imbalance observed.

35060 - MATURE RESULTS OF 1,067 PATIENTS TREATED IN THREE EUROPANE OSTEOSARCOMA INTERGROUP (EOI) RANDOMISED STUDIES

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Objectives: The EOI has conducted three consecutive randomised trials for localised extremity osteosarcoma. All 3 trials shared a standard arm, doxorubicin 75mg/m² and cisplatin 100mg/m² for 6 cycles. This was compared with a 3-drug schedule including methotrexate (MRC BO02; EORTC 80831), a T10-like schedule (BO03/80861) and a dose-compressed schedule (BO06/80931). Results from the three trials were analysed together to identify prognostic factors, temporal and other influences on outcome.

Methods: Standard survival analysis methods were used, including Cox regression, to assess selected factors.

Results: 1,067 patients were randomised in the 3 trials including 533 to the standard arm. Median follow up is over 9 years. Age range of participants was 3-40 yrs (median 15 yrs); 62% were male. No statistically significant differences in survival were evident between trials, treatment arms or country of treatment. Survival at 5 and 10 years after starting chemotherapy was 56% (95% CI 53%-59%) and 52% (48%-55%), respectively. Limb salvage was achieved in 69%. Distal primary site, female gender, and good histological response to preoperative chemotherapy were associated with improved survival.

Conclusions: Prolonged survival was achieved in more than half of all patients with localised osteosarcoma. Relapses after 5 years were uncommon. Tumour- and host-related factors can be identified which may influence the outcome of patients with different prognoses.

35079 - REMARKABLE TUMOR RESPONSE TO EVEROLIMUS IN A PATIENT WITH ADVANCED RETROPERITONEAL LYMPHANGIOLEIOMYOMATOSIS (LAM).

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Objectives: LAM is a rare progressive disease characterized by proliferation of aberrant smooth muscle cells and it mainly involves lungs. Extrapulmonary LAM is rare and typically affects premenopausal women. Recently, somatic or genetic mutations of tumour suppressor genes tuberous sclerosis 1 (TSC1) and 2 (TSC2) have been reported in LAM. The TSC1/TSC2 protein complex seems to function as a negative regulator of the mammalian target of rapamycin (mTOR)/p70 S6 kinase (S6K1) signalling pathway, which induces abnormal cell proliferation. The rapamycin analogue everolimus, a novel mTOR inhibitor, might be active in LAM.

Methods: A 42 year-old woman was diagnosed in September 2002 with sporadic advanced retroperitoneal LAM, without evidence of pulmonary involvement. She was initially treated with triptorelin, experiencing disease stabilization for two years. After progression while on hormone therapy was administered. Two months later, there was an important disease worsening, and antiestrogenic therapy was started in association with interferon-alfa, obtaining tumor control. After 3 years, she developed a slow disease progression, and at this stage she was treated with everolimus.

Results: Everolimus was started at the dose of 1.5 mg/day, quickly increased to 3 mg/day during the first month of treatment, with plasma concentrations between 6.96 and 18 ng/mL. An MRI after one month of treatment demonstrated a partial response (>30% decrease in maximal diameter), a subsequent follow-up at three months showed an overall response > 80%. Response is maintained after nine months. The treatment is ongoing without toxicity.

Conclusions: Treatment of extrapulmonary LAM is still not well...
modified RECIST.  

**Results:** 147 pts (85 sarcomas) were enrolled. Median age: 56 (23-84) years; 44% male; median of 2 prior cytotoxic therapies (range 0-7). DLT (all regimens) was transient aphthous-ulcer-like mouth sores that were reversible by dose reduction or symptomatic therapy. A weekly dose holiday increased the maximum tolerated dose (MTD). Clinical benefit (CB; i.e., stable disease or better ≥ 4 cycles) was achieved by 36 pts (23 sarcomas). 24 pts received 40 mg QDX5/wk: 3/13 (23%) sarcomas had CB and 2 (15.4%) achieved PR. For sarcomas, the 6-month progression-free survival (PFS) rates and median PFS times were 30%, 17 weeks (all regimens) and 23%, 16 weeks (40mg QDX5/wk).

Cmax occurred at 2-3 hours; median terminal half life was 35-70h. Predicted AUCs (0-28 days) were highest for QDX5/wk (34.6 μg*h/mL) and QDX6/wk (36.3 μg*h/mL). P-4E-BP1 levels in PBMCs decreased by 83%-93% within 24h. For 40 mg QDX5/wk pts, mTOR inhibition was >90% within 24h and >75% throughout the cycle.

**Conclusions:** The 40 mg QDX5/wk regimen is active, is safe, inhibits the target, and has been selected for a global phase 3 trial in metastatic sarcoma in the maintenance setting (SUCCEED trial).

**35104 - A PHASE 2 STUDY OF THE KIT INHIBITOR XL820 IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMORS (GIST) RESISTANT TO OR INTOLERANT OF THE TYROSINE KINASE INHIBITORS (TKI) IMATINIB AND/OR SUNITINIB**

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**Objectives:** XL820 is an orally bioavailable, small molecule inhibitor of KIT, VEGFR2, and PDGFR. Because XL820 potently targets wild-type KIT as well as some mutant forms of KIT that are resistant to inhibition by imatinib and sunitinib, we studied the effects of XL820 in patients with TKI-resistant GIST.

**Methods:** This was a randomized Phase 2 Simon two-stage study. Patients (pts) with metastatic GIST are randomized to receive XL820 at 800 mg once daily or 300 mg twice daily. Tumor response is assessed by RECIST and by 18FDG-PET imaging. Biological samples (tissue and/or plasma) are collected for pharmacokinetic and pharmacodynamic analyses.

**Results:** Fourteen pts have enrolled to date (age 21-91 years, ECOG 0-1). Seven pts had FDG-PET at 4 wks: 4 pts had >20% reduction in SUVmax (-38%, -38%, -27%, -20%) and 3 pts had increased SUVmax (+73%, +8%, +8%). Tumor response was assessed using RECIST criteria at 4 wks (9 pts evaluable: 6 SD, 3 PD), at 8 wks (5 pts evaluable: 4 SD, 1 PD) and at 16 weeks (2 pts evaluable: 1 SD, 1 PD). One pt died at 2 wks from bowel perforation (possibly related to treatment and underlying disease). Most frequent possibly related grade 2 adverse events were fatigue (6), diarrhea (4), nausea (4), and neutropenia (3); grade 3 toxicities possibly related to treatment included fatigue (1), leucopenia (1), and urticaria (1).

**Conclusions:** XL820 is generally well tolerated in pts with advanced GIST. Decreased FDG uptake and SD for 16+ weeks have been observed. Pt enrollment and follow-up continue.
35113 - HEDGEHOG SIGNALING REGULATES GROWTH PLATE CHONDROCYTE PROLIFERATION AND GROWTH FACTOR EXPRESSION

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Objectives: Growth plate chondrocyte proliferation and differentiation are governed by a feedback loop involving Indian hedgehog (Ihh) and parathyroid hormone-related peptide (PTHRP). The purpose of this study was to evaluate alterations of proliferative activity and gene/protein expression in growth plate chondrocytes induced by treatment with the hedgehog pathway agonist Purmorphamine(PUR) or the antagonist Cyclopamine(CYC).

Methods: Rat costal chondrocytes were exposed in vitro to 10 uM PUR or CYC, and relative changes in proliferative activity were determined by MTT assay and FACSc-based cell cycle analysis. A Gli-luciferase reporter was used to demonstrate transcriptional activation by the hedgehog pathway. Expression of Ihh, PTHrP, IGF2, their respective receptors, and key cell cycle regulators were assayed by RT-PCR, immunoblotting and/or immunocytochemistry.

Results: Chondrocyte proliferation increased 26.3% following 72-hour exposure to PUR and cell number was reduced to 20.1% by CYC treatment. Both agents appear to affect progression through the S-to-G2/M transition. Reporter activity was increased 3-fold by PUR exposure. Concomitantly, PUR up-regulated PTHrP and IGF-2 at the protein and mRNA level, while CYC down-regulated these factors. Neither agent affected the expression or localization of PTH1R and IGF1R, Smo or Ihh.

Conclusions: Taken together, our results demonstrate that hedgehog signaling regulates growth plate chondrocyte proliferation as well as expression of several pro-mitotic gene products. These preliminary results suggest that this pathway may be targeted to stimulate functional recovery of the growth plate following collateral radiation injury incurred during the course of pediatric musculoskeletal sarcoma treatment.

35127 - TREATING RESISTANT EWING SARCOMA USING ONCOLYTIC VIRUS THERAPY: FROM THE BEDSIDE TO THE BENCH AND BACK

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Objectives: Ewing sarcoma (ES) is the second most common form of adolescent primary malignant bone tumors. Despite current adjuvant and neo-adjuvant therapies, the 5 year disease free survival of ES patients is 50%. Oncolytic virus therapy (OVT) is an innovative alternative to conventional therapies against ES. It is based on the concept of selecting or engineering viruses to preferentially replicate in and kill tumor cells by exploiting their unique genetic defects, such as impaired antiviral immunity. OVT have demonstrated preclinical specificity and efficacy in treating numerous aggressive in vivo carcinoma models. To date, no testing has been performed on Ewing sarcoma.

Our objective is to determine whether ES refractory to current treatment regimens can be susceptible to OVT.

Methods: A novel ES cell line was established from a biopsy sample of a patient who failed chemotherapy. Immunohistochemical markers and cytogenetic analysis were used to confirm the homogeneity of the established cell line. An animal tumor model bearing either lung or subcutaneous ES tumors was established to evaluate the safety and efficacy of systemically delivered OVT. Vesicular stomatitis virus is the oncolytic agent used in this study.

Results: A sustainable Ewings Sarcoma animal model was developed. Animals treated with OVT (vesicular stomatis virus) showed regression of tumor and enhanced survival.

Conclusions: OVT selectively targets ES cells for infection after systemic administration, and significantly enhanced survival of mice bearing aggressive ES tumors. OVT provides a promising alternative for treating ES refractory to current adjuvant treatments.

35129 - PHASE I-II STUDY OF A NEW FORMULATION OF NON-PEGYLATED LIPOSOMAL DOXORUBICIN (DOXO GP-PHARM) AS FIRST-LINE TREATMENT OF OLDER PATIENTS WITH ADVANCED SOFT-TISSUE SARCOMAS (STS): A GEIS STUDY

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Objectives: Dose-intensity of Doxorubicin is limited by bone marrow and cardiac toxicity. A first-line phase II randomised trial with Caelyx ® (pegylated-liposomal formulation) showed lower toxicity in comparison to DX and similar activity. No clinical studies have been performed in STS with non-pegylated formulations of DX. This formulation would improve the therapeutic index and reduction of cardiac toxicity (particular impact upon elderly patients). Doxo GP-Pharm is non-pegylated liposomal DX (active DX placed in the membrane).

Methods: First-line Phase I/II multicenter prospective trial in STS pts aged 65 and over. Maximum tolerated dose (MTD) when 2 or more of at least 3 pts experience dose-limiting toxicity (DLT). Dose level below MTD was recommended.

Results: Dec’06 to mar’08: 12 pts included. Medium age 74 y. No DLT in the first 3 pts treated at 70 mg/m2. Subsequent 3+3 pts received 80 mg/m2: 1/6 grade IV neutropenia (7 days) and 1/6 grade IV dispnea (DLT). The 3 pts treated at 90 mg/m2 presented grade IV neutropenia and 2/3 DLT: 1/3 neutropenia >7 days, 1/3 febrile neutropenia (MTD). All DLT were hematologic, reversible grade IV neutropenia, grade III thrombocytopenia and occasional anemia. Non-hematological toxicities: grade II stomatitis and alopecia. 42 cycles administered, median 3 (1-6); no cumulative or cardiac toxicity was observed. CR, PR and SD were observed in 1 (10%), 1 (10%) and 2 (20%) pts.

Conclusions: Doxo GP-Pharm shows acceptable safety at 80 mg/m2 in older pts with STS. Preliminary data suggest evidence of antitumor activity. A phase II trial is ongoing in STS.

35130 - THERAPEUTIC FACTORS AND OUTCOME IN EWING’S SARCOMA (EWS) AT PEDIATRIC (PI) VS. ADULT INSTITUTION (AI)

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Objectives: To determine the impact of therapeutic differences at a pediatric (PI) vs. adult institution (AI) on the outcome in EWS.

Methods: 84 EWS patients [1990-2005] were reviewed at PI (n=41) and AI (n=43) in Toronto.
Results: Mean age was 13.3 yrs at PI and 30.2 yrs at AI. Pelvic tumors comprised 9.8% and 44% of patients at PI and AI. Metastatic disease was present in 30% of PI patients and 44% of AI patients. The median number of cycles of chemotherapy was greater for PI (n=15) than AI (n=10). Median cumulative dose of ifosfamide at PI=69388mg/m², AI=44815mg/m². Time from start of chemotherapy to local control was shorter at PI=3.5m, AI=7.6m. 5 yr EFS localized disease at PI and AI: 70%(SE:8.9) and 43%(SE:13.4), p=0.1. 5 yr EFS [loc+met] at PI was 59%(SE:7.9) and AI 39%(SE:7.9), p=0.02. 5 yr OS [loc+met] at PI and AI was 67%(SE:7.9) and 31%(SE:9.2), p=0.002. In univariate analysis, adult hospital (p=0.026), pelvic disease (p=0.024), longer time to local control (p=0.047), lower dose of alkylating agent (p=0.001), but not dose intensity of doxorubicin, were associated with a decreased EFS. In a CPH multiple regression analysis, only pelvic disease (p=0.03) and total dose of alkylating agent (p=0.003) was significantly associated with an inferior outcome, adjusting for hospital.

Conclusions: Patients at PI have superior outcome compared to AI. Less alkylating agent is associated with inferior outcome, independent of hospital. Time-to-local-control may be an important factor. In order to improve survival, adults with Ewing’s sarcoma need to be accrued onto pediatric clinical trials.

35131 - A RANDOMIZED, PHASE II STUDY OF PREOPERATIVE PLUS POSTOPERATIVE IMATINIB IN GIST: EVIDENCE OF RAPID RADIOGRAPHIC RESPONSE AND TEMPORAL INDUCTION OF TUMOR CELL APOPTOSIS
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Objectives: Gastrointestinal stromal tumor (GIST) is the most common sarcoma arising in the GI tract. Imatinib mesylate (imatinib) is efficacious in treating advanced and metastatic GIST. Patients undergoing resection of high-risk GIST have high recurrence rates. Thus, we conducted a randomized, phase II study to assess the safety and efficacy of preoperative and postoperative imatinib for the treatment of GIST.

Methods: GIST patients undergoing surgical resection were randomized to receive 3, 5, or 7 days of preoperative imatinib (600 mg daily). Patients received postoperative imatinib for 2 years. Perioperative adverse events were compared to those in an imatinib-naïve historical control. The efficacy of imatinib was assessed by positron emission tomography (18FDG-PET), dynamic-computed tomography (dCT), TUNEL assay, and DFS.

Results: Imatinib did not affect surgical morbidity as compared to an imatinib-naïve cohort (p = 0.1). Most patients responded to preoperative imatinib by 18FDG-PET and dCT (69% and 71%, respectively). Tumor cell apoptosis increased by an average of 12% (range, 0%-33%) and correlated with the duration of preoperative imatinib (p = .04). Median DFS of patients treated with surgery and imatinib was 46 months (range, 10-46 months). Tumor size was a predictor of recurrence after postoperative imatinib (p = .02).

Conclusions: Imatinib is safe and may be considered in patients undergoing surgical resection of their GIST. Radiographic response and tumor cell apoptosis occur within the first week of imatinib therapy.

35132 - S100A4 IS REGULATED BY WNT SIGNALING TO MEDIATE METASTASIS OF OSTEOSARCOMA
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Objectives: Lung metastasis is the major cause of death of osteosarcoma (OS) patients. Novel preventive and therapeutic strategy need to be developed. S100A4 is a member of the multi-gene S100 family. Increased expression of S100A4 has been associated with cancer metastasis. In this study, the role of S100A4 and its regulation by Wnt signaling in OS was examined.

Methods: To examine potential Wnt target gene, Genechip microarray was performed using an OS cell line transfected with dominant negative LRPI5 (DNLRP5). S100A4 mRNA level was examined by real time PCR. The expression of S100A4 in Saos-LM7 cells was stably knocked down by shRNA. Wnt antagonists DKK3 and Fzrb were stably transfected into OS cells. S100A4 protein expression in these cells was confirmed by western blot. A nude mouse model was used to assay the effect of S100A4 shRNA on lung metastasis.

Results: By real time PCR and western blot assay, the expression of S100A4 was up-regulated in 5 out of 8 OS cell lines. Genechip microarray showed that S100A4 is a potential Wnt target gene and significantly down-regulated by DNLRP5. ShRNA-mediated knockdown of S100A4 in Saos-LM7 cells significantly inhibited lung metastasis in a mouse model. The expression of S100A4 in OS cells was inhibited by blocking Wnt signaling with several Wnt inhibitors.

Conclusions: Our study suggests that S100A4 is a potential Wnt target gene in OS and plays an important role in mediating metastasis. Blocking S100A4 at various points in its regulatory pathway may represent a novel strategy to reduce lung metastasis in OS patients.

35133 - CHEMOKINE RECEPTOR-4 AS A THERAPEUTIC TARGET IN RHABDOMYOSARCOMA AND EWING’S SARCOMA
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Objectives: The chemokine CXCL12(SDF-1) and its receptor CXCR4(chemokine receptor-4) play an important role in invasion and metastases in a number of epithelial tumors but have not been extensively investigated in sarcoma. Ewing’s sarcoma (EWS) and rhabdomyosarcoma (RMS) are invasive and metastatic sarcomas, thus we examined the functional role of CXCR4 and its inhibition in OS and RMS in vitro.

Methods: Expression of CXCR4 on tumor cells was determined by flow cytometry and immunoblot of cell lines, and immunohistochemistry of a 106 sample RMS tissue microarray. Cell viability, cell cycle, apoptosis, migration, and invasion assays were utilized to assess the effects of a small peptide inhibitor of CXCR4, CTCE-9908(Chemokine Therapeutics) on cultured cells. Immunoblotting techniques were used to evaluate effects of this inhibitor on CXCR4 activation and downstream signaling.

Results: CXCR4 was expressed and activated in our EWS and RMS cell lines, and phosphorylation was shown to be enhanced by CXCL12. Stimulation also caused activation of Akt, p42/44 MAPK, JAK2 and PLC-gamma-1. CTCE-9908 was able to inhibit downstream signaling of Akt, p42/44 MAPK and JAK2 but not
PLC?1 in a cell specific manner. Decrease in cell viability (20-30%, p < .05), increase in cell apoptosis (20-40 %, p < .05) and cell cycle arrest was also observed with CTC-9908. CTCE-9908 significantly inhibited migration and invasion (68-93 %, p < .05) in these cell lines.

Conclusions: CXCR4-CXCL12 axis appears to be important for EWS and RMS invasion, migration and survival. Inhibition of this axis warrants additional investigation as a potential therapeutic approach.

35136 - INDIVIDUALIZING THERAPIES FOR SOFT TISSUE SARCOMA: A FOCUS ON GENOMIC STRATEGIES

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Objectives: Novel therapeutics strategies are needed in the treatment of patients with soft tissue sarcoma. Genomic approaches hold enormous promise for identifying biologically important pathways that may serve as potential therapeutic targets.

Methods: Two publicly-available gene expression datasets (GSE6481, GSE2719) were obtained from Gene Expression Omnibus (GEO) representing a total of 140 samples among 12 histological subtypes. Datasets were combined, adjusted and standardized using ComBat to limit batch effect. Differentially expressed genes and pathways were identified using GeneCluster and Gene Set Enrichment Analysis. Signatures of oncogenic pathway deregulation were applied to assess the probability of pathway activation for Beta-catenin, E2F, MYC, PI3K, RAS, and SRC among individual sarcoma samples and histological subtypes.

Results: Unsupervised hierarchical clustering identified well-defined clusters for synovial sarcoma, GIST, and myxoid/round cell liposarcoma with less organized clustering for the remaining subtypes. Supervised analysis identified a number of differentially expressed genes and pathways among individual subtypes. Signatures of oncogenic pathway deregulation revealed marked heterogeneity within individual subtypes with no consistent evidence of subtype-specific pathway deregulation, with the exception of SRC deregulation in myxoid/round cell liposarcoma.

Conclusions: Genomic strategies hold great promise for individualizing the future therapy of patients with soft tissue sarcoma. These preliminary results highlight the marked heterogeneity of soft tissue sarcomas and the need for individualizing therapies to improve patient outcomes.

35144 - METADHERIN CONTRIBUTES TO INVASIVENESS IN OSTEOSARCOMA

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Objectives: To evaluate the expression, function and therapeutic potential of metadherin (MTDH, AEG-1 or LYRIC) in osteosarcoma using preclinical tissue culture models.

Background: Metadherin is involved in tumorigenesis and metastasis in breast cancer, prostate cancer and glioma. In breast cancer, metadherin has been found to provide a lung-homing domain, mediating pulmonary metastasis. Metadherin bears structural relationship to other adhesion molecules, but has no normal expression in non-malignant adult tissues.

Methods: cDNA microarray (Agilent) evaluation of 7 osteosarcoma cell lines with known invasive properties identified metadherin as a gene potentially associated with metastasis. Expression of metadherin in a panel of 12 cell lines was assessed using western blot. Using matrigel invasion as an in vitro surrogate for invasive/metastatic potential, we assessed the importance of metadherin on this process by blocking metadherin with specific monoclonal antibodies, and by downregulating expression with shRNA. Proliferation was assessed using ViCell.

Results: Metadherin was observed by western in all lines assessed. Antibody blockade caused profound reduction in matrigel invasion, but little effect on cell proliferation or survival. Reduction of metadherin expression using shRNA reduced both invasion and proliferation in some osteosarcoma lines.

Conclusions: Metadherin appears to play an important role in osteosarcoma invasion, perhaps by mediating binding to components of the extracellular matrix. In addition, it may promote mitogenic signals in some osteosarcoma lines. Since control of metastasis is essential for survival in osteosarcoma, therapies targeting metadherin may have clinical benefit and should be further evaluated.

35154 - RAI A NEW DIAGNOSTIC MARKER OF MALIGNANT PERIPHERAL NERVE SHEATH TUMORS (MPNST)

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Objectives: Malignant peripheral nerve sheath tumor (MPNST) is a rare variety of soft tissue sarcoma. Although a combination of histo-pathological and immunohistochemical studies are actually used for diagnosis, still these tumors may be misinterpreted with other sarcomas.

Rai (Shc C), a member of the Shc adaptor family, is expressed in brain, neurons but not in glial cells. Recently Rai expression has been detected in cell types other than neurons, including glial cells in the gastrointestinal tract. In order to find a useful marker for differential diagnosis of MPNSTs we studied Rai expression by immunohistochemical analysis with a specific Rai antibody.

Methods: We selected 23 MPNSTs and 60 benign schwannoma. Ten synovial sarcomas (SS), 17 leymiosarcomas (LMS), 11 fibrosarcomas (FS), 3 localized neurofibroma (NF), and 10 desmoid tumors (DT) were also immunostained for comparison.

Results: All benign schwannomas (100%) showed in most of the cells Rai nuclear and cytoplasmic immunoreactivity. More than half MPNSTs (56,5%) exhibited Rai immunoreactivity, diffusely in 10 cases, and focally in the remaining 3. Rai expression correlated with low as compared to high grade tumors (p = 0,0457). The other mesenchimal non-schwannian tumors showed only weak cytoplasmatic Rai expression in peripheral areas of 3/17 LMS (17,6%). All SSs, FSs, DTs and NFs resulted Rai immunonegative.

Overall, the sensibility and specificity of Rai expression in the detection the MPNST group were 56,5% and 92,1%, respectively.

Conclusions: Immunohistochemical analysis of Rai expression improves the ability to distinguish MPNSTs from other spindle cell sarcomas. We propose Rai as a new diagnostic marker of MPNSTs.
**35162 - SUNITINIB RESPONSE IN AN IMATINIB REFRACTORY IRRESECTABLE CHORDOMA**

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**Objectives:** Chordoma is a rare low to intermediate grade malignant tumor of the axial spine that recapitulates notochord. Despite surgery and radiotherapy, many patients eventually experience an irresectable recurrence, often leading to pain and/or neurological deficits. Chordomas are not sensitive to chemotherapy. However, imatinib treatment was reported to achieve clinical benefit in some patients (Casali et al, Cancer 2004).

**Methods:** This is a case report of a 61 year old female with a chordoma of the first lumbar spine that was resected in September 2004 and, because of a local recurrence, again in December 2005, followed by radiotherapy 60 Gy. In May 2007 she underwent palliative surgery for a second local recurrence. From August-December 2007 she was treated with imatinib for residual tumor mass. However, there was progressive disease at first evaluation after 4 months in December 2007. She directly started treatment with the VEGFR/PDGFR/KIT-inhibitor sunitinib 50mg daily in a 4 weeks on-2 weeks off schedule (= 1 cycle), based on known PDGFRB expression in chordoma.

**Results:** MRI evaluation after cycle 1 showed progression arrest and she had improvement of symptoms. After 3 cycles a partial response on MRI was observed. As of June 2008, the patient is now in her 5th cycle and experiences further improvement of symptoms.

**Conclusions:** To our knowledge this is the first report of a partial response to systemic therapy in a chordoma patient. It also shows that in chordoma, in parallel to GIST, treatment with sunitinib after imatinib progression can achieve responses.

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**35170 - SORAFENIB ACTIVITY IN IMATINIB, SUNITINIB, AND NILOTINIB RESISTANT GASTROINTESTINAL STROMAL TUMOURS (GIST)**

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**Objectives:** Currently, no standard third- and fourth-line therapeutic options exist in imatinib, sunitinib and nilotinib resistant GIST. Similar targets of the tyrosine-kinase inhibitors (TKI) are VEGFR, PDGFR and KIT, while sorafenib also inhibits RAF-kinases. Sorafenib activity in imatinib and sunitinib resistant GIST has been shown preclinically and clinically (Guo, Clin Cancer Res, 2007; Maki, ASCO 2008, abstract 10502) and might be related to primary and secondary KIT and PDGFR mutations.

**Methods:** A retrospective analysis of 6 metastatic GIST patients treated with compassionate-use sorafenib 400 mg orally bi-daily was done. Patient characteristics, mutation analysis, toxicity and objective response using RECIST based on CT-scans Q2 28-day cycles were reviewed.

**Results:** All patients were imatinib, sunitinib and nilotinib-resistant. One patient also had received doxorubicin. Patient characteristics: male: 4, female: 2, median age 74 (range 54-82), performance status 0/1/2: 0/5/1. Mutation analysis was done in 4 patients and revealed a KIT exon-11 mutation in all. An exon-14 T670A mutation was found in a patient with stable disease (exon-14 T670I mutation has been associated with in vitro sorafenib sensitivity) and one of the patients with progressive disease had a secondary exon-13 mutation. No exon-9 or PDGFR exon-12 or exon-18 mutations were found. Toxicity was manageable being all grade 1-2 and one grade 3 diarrhoea. Disease control (minor response and stable disease) was obtained in 4 out of 6 patients. Median progression-free survival was 4 months (range 2 - 5.5).

**Conclusions:** These data show that sorafenib has activity as fourth line TKI in metastatic GIST. Additional mutational analysis is ongoing.