Imatinib failure-free survival (IFS) in patients with localized gastrointestinal stromal tumors (GIST) treated with adjuvant imatinib (IM): The EORTC/AGITG/FSG/GEIS/ISG randomized controlled phase III trial.

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Background: In 2004 we launched an open-label randomized trial with adjuvant IM for 2 yrs in localized, surgically resected, high/intermediate-risk GIST. Methods: Pts were randomized between 2 yrs of IM, 400 mg daily, and no further therapy after surgery. The primary end-point was OS, while RFS, RFI and toxicity were secondary end-points. Main eligibility criteria were: age >18 yrs, PS 0-2, localized CD117-positive GIST, intermediate or high risk according to the 2002 Consensus classification, R0 or R1 surgical margins, no previous medical therapy. Pts were stratified by risk, tumor site and margins. An accrual of 400 pts was planned, then escalated to 900. Given the prognostic improvement of advanced GIST pts, in 2009 the study IDMC authorized to change the primary end-point into IFS, whose failure was defined as the time when a different tyrosine kinase inhibitor (TKI) is started. We report on a planned interim analysis carried out after 115 events according to the new primary end-point, with a significance level of 1.5%. Hazard ratios (HR) and p-values were adjusted for stratification factors. Results: 908 pts were randomized between 2005 and 2008, 454 to IM and 454 to observation arm; 835 pts were eligible. 17% of pts treated with IM stopped early due to toxicity or refusal. With a median follow-up of 4.7 yrs, 5-yr IFS was 87% in the IM-arm vs 84% in the control arm (HR=0.80, 98.5% CI [0.51; 1.26], p=0.23); RFS was 84% vs 66% at 3 yrs, and 69% vs 63% at 5 yrs (p=0.001); 5-yr OS was 100% vs 99%. Among 528 pts with high-risk GIST by local pathology, 5-yr IFS was 79% vs 73% (p=0.11), and 77% vs 73% (p=0.44) amongst 336 high-risk GIST pts by centrally reviewed pathology. Conclusions: This study confirms that adjuvant IM has an overt impact on short-term freedom from relapse. In the high-risk subgroup, a non-statistically significant trend in favor of the adjuvant arm was observed in terms of IFS. This new end-point for the adjuvant setting, i.e. survival free from any failure of the first employed TKI, was designed to incorporate secondary resistance, i.e. the currently main factor adversely affecting prognosis of advanced GIST pts. Clinical trial information: NCT00103168.
Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Phase III trial of nilotinib versus imatinib as first-line targeted therapy of advanced gastrointestinal stromal tumors (GIST).

Jean-Yves Blay, Lin Shen, Yoon-Koo Kang, Piotr Rutkowski, Shukai Qin, Steven C. Novick, Lilia Taningco, Shuyuan Mo, Peter Reichardt, George D. Demetri; University Claude Bernard Lyon I, Centre Léon Bérard, Lyon, France; Department of Gastrointestinal Oncology, Key laboratory of Carcinogenesis & Translational Research under Ministry of Education, Peking University Cancer Hospital, Beijing, China; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; No. 81 Hospital of PLA, Nanjing, China; Blokhin Oncology Research Center, Moscow, Russia; Novartis Pharmaceuticals Corp, East Hanover, NJ; Novartis Pharmaceuticals, Oncology, Florham Park, NJ; HELIOS Klinikum Bad Saarow, Bad Saarow, Germany; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA

Background: Nilotinib (N) is a Bcr-Abl, KIT, and PDGFR tyrosine kinase inhibitor. This Phase III trial compared N and imatinib (I) as first-line therapy of advanced GIST. Accrual was stopped when a futility boundary was crossed at interim analysis (IA). This final analysis of the core study examined the effect of mutation on outcomes. Methods: Patients (pts) with unresectable and/or metastatic GIST who had no prior antineoplastic therapy or had recurrence ≥6 months (mos) after adjuvant I were randomized 1:1 to open-label N 400 mg bid or I 400 mg qd (400 mg bid for KIT exon 9 mutants). The primary endpoint was progression-free survival (PFS) per adjudicated central review. Enrollment targeted 736 pts to observe 375 events, yielding 90% power to detect a hazard ratio (HR) of 0.71 (median, 28 [N] and 20 [I] mos) with two-sided 5% type I error. Prior to IA, crossover was allowed only for pts with progressive disease (PD); after IA, pts on N with or without PD were offered I. Results: At IA, the PFS HR for N vs I of >1.111 suggested a low probability of N superiority to I. Final analysis was performed in 644 pts; both PFS and OS favored I. In subgroup analysis of 401 pts who had mutational data, there was a large PFS difference favoring I in KIT exon 9 mutants, but similar PFS in KIT exon 11 mutants (Table). Based on immature data, OS favored I in all mutants. Conclusions: The IA showed N could not be superior to I for PFS in the overall population as first-line targeted therapy for pts with advanced GIST. PFS of N and I differed according to molecular subtypes, with PFSfavoring I in KIT exon 9 mutants but roughly similar in exon 11 mutants. Clinical trial information: NCT00785785.

<table>
<thead>
<tr>
<th></th>
<th>Nilotinib (n=324)</th>
<th>Imatinib (n=320)</th>
<th>HR (95% confidence interval [CI])</th>
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<tr>
<td>Median PFS, mos (95% CI)</td>
<td>25.9 (19.1–NE)</td>
<td>29.7 (26.6–NE)</td>
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<tr>
<td>KIT mutant</td>
<td></td>
<td></td>
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<tr>
<td>Exon 11</td>
<td>NE</td>
<td>32.3 (29.7–NE)</td>
<td>1.120 (0.683–1.836)</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>24 mos PFS, % (95% CI)</td>
<td>51.6 (43.0–59.5)</td>
<td>59.2 (50.9–66.5)</td>
<td>1.466 (1.104–1.945)</td>
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<tr>
<td>KIT mutant</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Exon 11</td>
<td>6/24</td>
<td>6/24</td>
<td></td>
</tr>
<tr>
<td>Exon 9</td>
<td>NE</td>
<td>67.5 (55.9–76.7)</td>
<td>1.120 (0.683–1.836)</td>
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<tr>
<td>24 mos OS, % (95% CI)</td>
<td>81.8 (76.6–86.0)</td>
<td>90.0 (85.9–93.0)</td>
<td>1.850 (1.198–2.857)</td>
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</table>

NE, nonestimable. *All exon 9 mutants on N had a PFS event or censoring within 6 mos.
Randomized phase III trial of imatinib (IM) rechallenge versus placebo in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) after failure of at least both IM and sunitinib (SU): Right study.

Yoon-Koo Kang, Min-Hee Ryu, Baek-Yeol Ryoo, Hyun Jin Kim, Jong Jin Lee, Changhoon Yoo, Byung-Ho Nam, Nikhil Ramaiya, Jyothi Priya Jagannathan, George D. Demetri; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; National Cancer Center, Goyang, South Korea; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA

The full, final text of this abstract will be available at abstract.asco.org at 7:30 AM (EDT) on Monday, June 3, 2013, and in the Annual Meeting Proceedings online supplement to the June 20, 2013, issue of Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Monday edition of ASCO Daily News.
Mutational analysis of plasma DNA from patients (pts) in the phase III GRID study of regorafenib (REG) versus placebo (PL) in tyrosine kinase inhibitor (TKI)-refractory GIST: Correlating genotype with clinical outcomes.

George D. Demetri, Michael Jeffers, Peter Reichardt, Yoon-Koo Kang, Jean-Yves Blay, Piotr Rutkowski, Hans Gelderblom, Peter Hohenberger, Michael Gordon Leahy, Margaret von Mehren, Heikki Joensuu, Giuseppe Badalamenti, Martin E. Blackstein, Axel Le Cesne, Patrick Schoffski, Robert G. Maki, Jian-Ming Xu, Toshirou Nishida, Iris Kuss, Paolo Giovanni Casali; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; Bayer HealthCare Pharmaceuticals, Montville, NJ; HELIOS Klinikum Berlin-Buch, Berlin, Germany; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Centre Léon Bérard, Lyon, France; Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; Department of Clinical Oncology, Leiden University Medical Center, Leiden, Netherlands; Department of Surgery, Mannheim University Medical Center, Mannheim, Germany; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Fox Chase Cancer Center, Philadelphia, PA; Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland; Department of Surgical and Oncological Sciences, University of Palermo, Palermo, Italy; Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada; Institut Gustave Roussy, Villejuif, France; Laboratory of Experimental Oncology and Department of General Medical Oncology, KU Leuven and University Hospitals, Leuven, Belgium; Mount Sinai School of Medicine, New York, NY; Cancer Center, 307 Hospital, Academy of Military Medical Science, Beijing, China; Department of Surgery, Osaka Police Hospital, Osaka, Japan; Bayer HealthCare Pharmaceuticals, Berlin, Germany; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: The phase III GRID study showed that REG provides a significant improvement in progression-free survival (PFS) compared with PL in pts with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib (IM) and sunitinib (SU; HR 0.27, p<0.0001). Determining GIST genotype in TKI-refractory disease has proven challenging due to inter-tumoral heterogeneity and pt preference to avoid serial biopsies. To overcome this, we analysed circulating DNA in plasma as a source of tumor DNA and studied the correlation between mutational status and clinical outcome. Methods: DNA was isolated from both archival tumor tissue (n=102) and plasma at baseline (n=163) and analyzed for mutations via Sanger sequencing (tissue) or BEAMing (plasma). Results: Mutational frequencies for tumor tissue samples were: KIT, 66%; PDGFRA, 3%; KRAS, 1%; BRAF, 0%. For plasma, frequencies were: KIT, 58%; PDGFRA, 1%; KRAS, 1 out of 2 samples, BRAF, 0%. Detection of primary KIT mutations showed 84% concordance between tissue and plasma. Secondary KIT mutations were more commonly detected in plasma (47%) than in tissue (12%). Subgroup analysis based on mutational status showed an improved PFS in REG-treated pts vs PL in all subgroups by both central and local review of imaging studies. The presence of a secondary KIT mutation in plasma was associated with shorter PFS in pts receiving PL (HR 1.82, p=0.05). Pts with a KIT-exon 9 mutation received IM for a shorter period of time, and SU for a longer period of time, relative to other GIST genotypes. Pts with a PDGFRA mutation showed variable clinical responses, while 1/1 KRAS-mutant GIST did not respond well to IM, SU, or REG. Conclusions: KIT mutational status correlated to IM and SU treatment duration. While consistent with prior reports using tissue sampling, this validates the utility of plasma-based circulating DNA analysis of target oncogenes. Secondary KIT mutations appear to have a negative prognostic impact in GIST, while the clinical benefit of REG vs PL was not influenced by KIT mutational status. Clinical trial information: NCT01271712.
MAP plus maintenance pegylated interferon α-2b (MAP-IFN) versus MAP alone in patients (pts) with resectable high-grade osteosarcoma and good histologic response to preoperative MAP: First results of the EURAMOS-1 good response randomization.

Stefan S. Bielack, Sigbjorn Smeland, Jeremy Whelan, Neyssa Marina, Jane Hook, Gordana Jovic, Mark D. Krailo, Trude Butterfass-Bahloul, Thomas Kühne, Mikael Eriksson, Lisa A. Teot, Hans Gelderblom, Leo Kager, Kirsten Sundby Hall, Richard Greg Gorlick, R. Lor Randall, Pancras C. W. Hogendoorn, Gabriele Calaminus, Matthew Robert Sydes, Mark L. Bernstein; Klinikum Stuttgart, Olgahospital, Cooperative Osteosarcoma Study Group (COSS), Stuttgart, Germany; Oslo University Hospital, The Norwegian Radium Hospital, Scandinavian Sarcoma Group, Oslo, Norway; University College London Hospitals NHS Foundation Trust, London, United Kingdom; Stanford University, School of Medicine, Palo Alto, CA; MRC Clinical Trials Unit, London, United Kingdom; Children’s Oncology Group, Arcadia, CA; Center for Clinical Trials, University of Muenster, Muenster, Germany; University Children’s Hospital Basel, Basel, Switzerland; Skane University Hospital and Lund University, Lund, Sweden; Children’s Hospital Boston, Boston, MA; Department of Clinical Oncology, Leiden University Medical Center, Leiden, Netherlands; St Anna’s Children’s Hospital, Vienna, Austria; The Children’s Hospital, Bronx, NY; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Department of Pathology, Leiden University Medical Center, Leiden, Netherlands; University Hospital of Muenster, Muenster, Germany; IWK Health Center, Dalhousie University, Halifax, NS, Canada

The full, final text of this abstract will be available at abstract.asco.org at 7:30 AM (EDT) on Monday, June 3, 2013, and in the Annual Meeting Proceedings online supplement to the June 20, 2013, issue of Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Monday edition of ASCO Daily News.
LMS-02: A phase II single-arm multicenter study of doxorubicin in combination with trabectedin as a first-line treatment of advanced uterine leiomyosarcoma (u-LMS) and soft tissue LMS (ST-LMS): First results in patients with u-LMS.

Patricia Pautier, Anne Floquet, Didier Cupissol, Benjamin Lacas, Emmanuelle Bompas, Christine Chevreau, Frédéric Selle, Beatrice E. Weber, Cécile Guillemet, Nicolas Penel, Florence Duffaud; Institut Gustave Roussy, Villejuif, France; Institut Bergonié, Bordeaux, France; Centre Val d’Aurelle, Montpellier, France; Centre René Gauducheau, Nantes St Herblain, France; Institut Claudius Regaud, Toulouse, France; Universite Pierre et Marie Curie, Oncology, GHU-Est Tenon, Paris, France; Centre Alexis Vautrin, Vandoeuvre-lès-Nancy, France; Centre Henri Becquerel, Rouen, France; Centre Oscar Lambret, Lille, France; La Timone University Hospital, Marseille, France

Background: U-LMS and ST-LMS are rare tumours with poor prognosis when metastatic or locally advanced, presenting moderate chemosensitivity mainly to doxorubicine (doxo), ifosfamide (ifo), cisplatin, gemcitabine (gem) and trabectidine (trab). Response rates (RR) in combination therapies (1st line) does not exceed 50% for U-LMS and 35% for ST-LMS. The most active ones are doxo combinations (most of the time with ifo or dacarbazine) and gem + docetaxel (in particular in U-LMS) with a mean response durations of 3 to 6 months. Trab was demonstrated a definite activity on pre-treated LMS (RR of approximately 20% in LMS overall [U-LMS in particular]). In view of these encouraging results on LMS, a study combining trab with doxo as first line therapy for LMS is of interest.

Methods: Patients (pts) received every 3 weeks, 6 cycles of doxo 60 mg/m² followed by trab 1.1 mg/m²3-h at day 1, and pegfilgrastim 6 mg on Day 2. Study primary objective: to determine the disease control rate (DCR) (ORR+SD). Secondary objectives: PFS 12 wks, RR by RECIST and duration, OS and toxicities. Patients were stratified into U-LMS (n=45) and ST-LMS (n=62) group. Herein, we report the first results in pts with U-LMS; mature data will be shown in ASCO Meeting. Results: 45 pts with U-LMS have been enrolled until November 2012. Median age is 58 years, 38 where of with data collected for at least 1 cycle, 85% had metastatic disease (mostly lung 30/33, liver and bone), and 26 pts have received 6 cycles. For 33 pts with at least 1 disease assessment (every 2 cycles), the ORR was 55% (18 PR) and 13 SD (39%) had SD disease for a DCR of 94% at that time. Presently, the median PFS at 12 weeks is 94,3% [95%IC:86-100]. Main grade 3-4 toxicities in 187 cycles were neutopenia (51%), febrile neutropenia (7%), thrombopenia (14%), anemia (7%), fatigue (5%), vomiting (6%) and transiet transaminase increase (22%). Conclusions: The combination of trab plus doxo seems to be an effective first-line treatment for pts with U-LMS, with meaningful clinical benefits and an acceptable and manageable safety profile. Clinical trial information: 2009-012430-70.
A randomized, double-blind, placebo (Pbo)-controlled phase III study of ombrabulin plus cisplatin in patients (pts) with advanced-stage soft-tissue sarcoma after failure of anthracycline and ifosfamide chemotherapies.

Zsuzsanna Papai, Anthony W. Tolcher, Antoine Italiano, Didier Cupissol, Antonio Lopez-Pousa, Sant P. Chawla, Emmanuelle Bompad, Nicolas Penel, Nicolas Isambert, Arthur P. Staddon, Antoine Thyss, Armando Santoro, Fabio A. Franke, Patrick Cohen, Solenn Le-Guennec, George D. Demetri, Jean-Yves Blay; Állami Egészségügyi Központ, Budapest, Hungary; South Texas Accelerated Research Therapeutics (START), San Antonio, TX; Institut Bergonié, Bordeaux, France; Centre Val d’Aurelle, Montpellier, France; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; St. John’s Hospital, Santa Monica, CA; Centre René Gauducheau, Nantes, France; Centre Oscar Lambret, Lille, France; Centre Georges François Leclerc, Dijon, France; Pennsylvania Oncology Hematology Associates, Philadelphia, PA; Centre Antoine Lacassagne, Nice, France; Istituto Clinico Humanitas IRCCS, Milano, Italy; CACON-Hospital de Caridade de Ijui, Ijui, Brazil; Sanofi, Vitry-sur-Seine, France; Ludwig Center at Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Centre Léon Bérard, Lyon, France

**Background:** Ombrabulin (AVE8062) is a vascular disrupting agent that damages established tumor vasculature and has demonstrated synergistic antitumor activity with cisplatin in vivo. In a phase I study, ombrabulin 25 mg/m² plus cisplatin 75 mg/m² was identified as the recommended dose in pts with solid tumors (AACR 2008; Abs 08-AB-4925). This phase III study evaluated the efficacy and safety of ombrabulin plus cisplatin in pts with advanced soft-tissue sarcoma (NCT00699517).

**Methods:** Pts (aged ≥18 yrs, ECOG PS ≤2) with metastatic soft-tissue sarcoma who had received prior anthracycline and ifosfamide, with ≤2 prior chemotherapies for advanced disease, were randomized (1:1) to receive either ombrabulin 25 mg/m² or Pbo plus cisplatin 75 mg/m² every 3 weeks. The primary objective was to compare progression-free survival (PFS) between arms; secondary objectives included overall survival (OS) and safety.

**Results:** Overall, 355 pts (median age 52 yrs; 51.5% male) were randomized (176 ombrabulin, 179 Pbo) in 44 centers worldwide. Median duration of follow-up was 27.9 and 30.5 months in Pbo and ombrabulin arms, respectively. PFS analysis showed a statistically significant improvement with ombrabulin (median 1.54 vs 1.41 months Pbo; HR=0.76, 95% CI 0.59–0.98; p=0.0302), with 3- and 6-month rates in favor of ombrabulin vs Pbo: 35.4% vs 24.9% and 19.3% vs 10.6%, respectively. A trend for an improvement with ombrabulin was observed in 3 of the 4 prespecified histology strata: liposarcoma, leiomyosarcoma, and “other”, but not for pleomorphic. Analysis of OS did not show statistically significant improvement with ombrabulin (median 11.43 vs 9.33 months Pbo, HR=0.85, 95% CI 0.67–1.09). OS rates at 1 year were in favor of ombrabulin (48.6% vs 42.4% Pbo). Grade 3/4 TEAEs more frequently seen with ombrabulin included neutropenia (19.2% vs 7.9% Pbo) and thrombocytopenia (8.5% vs 3.4% Pbo).

**Conclusions:** Although this trial met its primary efficacy endpoint, the combination of ombrabulin and cisplatin did not demonstrate sufficient clinical benefit in pts with advanced soft-tissue sarcoma to warrant further study. Clinical trial information: NCT00699517.
Detection of mutant-free circulating tumor DNA in the plasma of patients with gastrointestinal stromal tumor (GIST) harboring activating mutations of C-Kit or PDGFRA.

Nikolas von Bubnoff, Irina Kerle, Katja Specht, Melanie Bruegel, Claudia Wickenhauser, Philipp Jost, Dietger Niederwieser, Christian Peschel, Justus Duyster, Thoralf Lange, Jacqueline Maier; Universitätsklinikum Freiburg, Freiburg, Germany; Technische Universität München, München, Germany; Institute of Pathology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; Universitätsklinikum Leipzig, Leipzig, Germany; University of Leipzig, Leipzig, Germany

Background: In gastrointestinal stromal tumor (GIST), there is no biomarker available that indicates success or failure of therapy. We hypothesized that tumor specific CKIT or PDGFRA mutant DNA fragments can be detected and quantified in plasma samples of GIST patients. Methods: We prospectively collected 291 plasma samples from 38 subjects with GIST harbouring activating mutations of CKIT or PDGFRA detected in tumor tissue, irrespective of current disease status or treatment. We used allele-specific Ligation PCR to detect mutant free circulating (fc)DNA. Results: We were able to detect fcDNA harbouring the tumor mutation in 15 out of 38 patients. Patients with active disease displayed significantly higher amounts of mutant fcDNA compared to patients in CR. The amount of mutant fcDNA correlated with disease course. We observed repeated positive test results or an increase of mutant fcDNA in five patients with progressive disease or relapse. A decline of tumor fcDNA or conversion from positive to negative was seen in five patients responding to treatment. A negative to positive conversion was seen in two patients with relapse and one patient with progression. In two cases, we aimed to identify additional mutations, and found four additional exchanges, including mutations not known from sequentially performed tumor biopsies. Conclusions: Our results indicate that free circulating DNA harbouring tumor specific mutations in the plasma of patients with GIST can be used as tumor-specific biomarker. The detection of resistance mutations in plasma samples might allow earlier treatment changes and obviates the need for repeated tumor biopsies. Clinical trial information: NCT01462994.
Use of ponatinib to inhibit kinase mutations associated with drug-resistant gastrointestinal stromal tumors (GIST).

Michael C. Heinrich, Jonathan A. Fletcher, Rana Anjum, Cesar Serrano-Garcia, Sadanand Vodala, Sebastian Bauer, Ajia Town, Meijun Zhu, Yaoyu Ning, Grant Eilers, Diana Griffith, Janice Patterson, Arin McKinley, Frank Y Wang, Andrew P Garner, Victor M. Rivera; Portland VA Medical Center and Oregon Health and Science University Knight Cancer Institute, Portland, OR; Brigham and Women’s Hospital/Harvard Medical School, Boston, MA; ARIAD Pharmaceuticals, Inc., Cambridge, MA; Department of Medical Oncology, West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany

**Background:** Ponatinib (PO) is a multi-targeted tyrosine kinase inhibitor with potent pan-BCR-ABL activity that has recently been approved for treatment of CML and Ph+ ALL. PO also inhibits the kinase activity of KIT. Approximately 80% of gastrointestinal stromal tumors (GIST) contain primary activating KIT mutations, the majority of which cluster in exon 11. Imatinib (IM) is approved for the 1st line treatment of GIST; however, patients frequently relapse due to the acquisition of secondary resistance mutations located in either the KIT ATP-binding pocket or the activation (A) loop. Sunitinib (SU) is approved for 2nd line treatment of GIST but does not effectively inhibit A-loop mutants. Here we explored the activity of PO against major primary and secondary KIT mutants found in GIST. **Methods:** The drug sensitivity of KIT mutants was determined using engineered Ba/F3 cells harboring mutant forms of KIT exon 11 with or without ATP binding pocket or A-loop mutations. The abilities of PO, IM, SU, and regorafenib (RE) to inhibit viability and/or KIT kinase activity were compared using this system as well as an isogenic CHO cell system. We also profiled these same drugs using a panel of GIST cell lines, including cell lines with IM-resistant secondary KIT mutations. **Results:** In all in vitro systems, PO potently inhibited KIT exon 11 mutant kinases, with an IC50 of < 30 nM. PO also potently inhibited a range of secondary KIT mutants, including multiple A-loop mutant kinases. PO induced substantial tumor regression in Ba/F3 tumor models expressing a KIT exon 11 mutant with or without an A-loop mutation (D816H). Using GIST cell lines, PO inhibited the viability of those harboring primary KIT exon 11 and secondary resistance mutations more effectively than IM, SU, and RE. Importantly, in patients dosed once daily with 45 mg ponatinib, plasma concentrations achieved are predicted to lead to inhibition of all KIT mutants tested with the possible exception of V654A. **Conclusions:** PO potently inhibits the majority of clinically relevant KIT mutant kinases and has a broader spectrum of activity compared to IM, SU, or RE. Based on these data, a phase 2 study of PO in drug-resistant GIST is being initiated.
In vitro and in vivo activity of regorafenib (REGO) in drug-resistant gastrointestinal stromal tumors (GIST).

Cesar Serrano-Garcia, Michael C. Heinrich, Meijun Zhu, Chandrajit P. Raut, Grant Eilers, Gloria Ravegnini, George D. Demetri, Sebastian Bauer, Jonathan A. Fletcher, Suzanne George; Brigham and Women’s Hospital/Harvard Medical School, Boston, MA; Portland VA Medical Center and Oregon Health and Science University Knight Cancer Institute, Portland, OR; Division of Surgical Oncology, Brigham and Women’s Hospital, Boston, MA; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; Department of Medical Oncology, West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany; Dana-Farber Cancer Institute, Boston, MA

Background: KIT and PDGFRA mutations (mut) are the crucial transforming events in most GISTs, and tyrosine kinase inhibitors (TKIs) with activity against KIT and PDGFRA, such as imatinib (IM) (front-line therapy) and sunitinib (SU) (second-line therapy), are effective treatments in GIST patients (pts). Resistance to IM and SU is commonly associated with evolution of secondary kinase mut. REGO is a multi-targeted TKI that inhibits KIT, PDGFR, and other oncologic targets and has recently shown benefit in pts with metastatic GIST after progression on standard treatments. We evaluated the in vitro and in vivo activity of REGO compared with IM, SU, and sorafenib (SOR) (a multi-TKI structurally related to REGO). Methods: REGO, IM, SU, and SOR inhibition of viability and KIT phosphorylation was assessed in human GIST cell lines and in Ba/F3 cells transformed by KIT oncproteins with IM-resistant ATP binding pocket or activation-loop mut. KIT/PDGFRA genotyping was performed in GISTs responding or progressing on REGO in the academic phase II clinical trial. Results: In GISTs with KIT exon 11 mutant oncproteins, REGO potently inhibited viability, KIT phosphorylation, and downstream effector phosphorylation (AKT, MAPK, S6). IM-resistant activation loop mut were more potently inhibited by REGO than SU, whereas the gatekeeper IM-resistant mut T670I was inhibited by both REGO and SU, and the common ATP-binding pocket mutant V654A was more potently inhibited by SU than REGO. Two GIST metastases progressing in one pt after initial response to REGO contained KIT V654A mut. SOR and REGO demonstrated comparable in vitro overall activity. Representative GIST cell line viability IC50s are shown in the Table (values in bold indicate expected clinical relevance). Conclusions: In vitro studies confirm REGO is a potent inhibitor of KIT exon 11 mut in GIST and appears to have stronger activity than SU against the most common KIT activation-loop mut observed in GIST. Ongoing clinical correlative analyses from REGO-treated study patients will be presented.

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Prolonged survival and disease control in the academic phase II trial of regorafenib in GIST: Response based on genotype.

Suzanne George, Yang Feng, Margaret von Mehren, Edwin Choy, Christopher L. Corless, Jason L. Hornick, James E. Butrynski, Andrew J. Wagner, Sarah Solomon, Jeffrey A. Morgan, Michael C. Heinrich, George D. Demetri; Dana-Farber Cancer Institute, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; Massachusetts General Hospital, Boston, MA; Knight Diagnostic Laboratories, Oregon Health & Science University, Portland, OR; Brigham and Women's Hospital/Harvard Medical School, Boston, MA; Portland VA Medical Center and Oregon Health and Science University Knight Cancer Institute, Portland, OR; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA

Background: Regorafenib (REGO) is a broad-spectrum tyrosine kinase inhibitor with activity against KIT, PDGFR, VEGFR, and FGFR. Phase II and III trials demonstrated significant activity in patients (pts) with advanced GIST following failure of at least imatinib and sunitinib. Pts have continued on the Phase II trial, and we now report longer-term follow-up as related to primary and secondary tumor genotype (KIT, PDGFRA) and SDH expression. Methods: This multicenter Phase II study of RE in GIST enrolled 33 pts with metastatic GIST. REGO was started at a dose of 160mg per day, d1-21 of each 28d cycle. Anatomic restaging was performed every 2 cycles. Clinical benefit rate (CBR) was defined as CR, PR or prolonged SD (>16 wks) per RECIST 1.1. KIT genotype was determined for tumors with adequate tissue available. SDHB staining was performed on a subset of patients whose tumors lacked activating mutations in KIT or PDGFRA. Response, progression-free survival (PFS), and overall survival (OS) were determined for the entire cohort and for subsets based on KIT genotype and SDHB immunohistochemical status. Results: Median followup as of 20Jan2013 was 20 mos. Four pts remain on REGO without progression. CBR for the entire cohort was 81%, with 9% PR (n=3). Median PFS for the entire cohort was 13 mos (95%CI 9-18). Median OS was 27 mos (95%CI 16-NR). Tumor primary KIT mutations and associated median PFS are as follows: exon 11(n=19), 13 mos (95%CI 10-21); exon 9(n=3), 6 mos (95%CI 2-NR) (log-rank p-value=0.93). 6 pts had SDH-deficient GIST, 2 of whom experienced PR. Median PFS of pts with SDH-deficient GIST was 12 mos (95%CI 7-NR). Secondary KIT mutations in a GIST lesion were identified prior to enrollment in 9 pts: exon 17 (n=7), one each in exon 13 and exon 18. Median PFS for pts with a documented exon 17 mutation was 18 mos (95%CI 6-NR). Conclusions: REGO is an active agent in advanced GIST. Prolonged disease control and OS is demonstrated in heavily pre-treated pts with KIT exon 11-mutant GIST; although with small sample size, there is no statistical significance in outcomes between genotypes. Objective responses were seen in 2 of 6 of pts with SDHB-deficient GIST. Other biomarkers of response and benefit are under active investigation. Clinical trial information: NCT01068769.
Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified liposarcoma.

Mark Andrew Dickson, William D. Tap, Mary Louise Keohan, Sandra P. D’Angelo, Mrinal M. Gounder, Ping Chi, Cristina R. Antonescu, Jonathan Landa, Li-Xuan Qin, Dustin D. Rathbone, Yelena Ustoyev, Aimee Marie Crago, Samuel Singer, Gary K. Schwartz, Mercedes M. Condy; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Biostatistics and Epidemiology, Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Approximately 90% of well-differentiated / de-differentiated liposarcomas (WD/DDLS) have CDK4 amplification. The selective CDK4/CDK6 inhibitor PD0332991 inhibits growth and induces senescence in liposarcoma cell lines and xenografts. Our prior phase II study demonstrated that treatment with PD0332991 (200mg daily x 14d every 21d) results in clinical benefit in WD/DDLS but moderate hematologic toxicity (48% Grade 3/4 neutropenia; dose reduction in 24%). Aiming to reduce toxicity, we conducted a phase II study to assess progression-free survival (PFS) and toxicity with PD0332991 at a new dose and schedule, 125mg daily x 21d every 28d. Methods: Participants were patients with advanced WD/DDLS. Eligibility criteria were age ≥ 18 years, measurable WD/DDLS (RECIST 1.1), documented progression on at least one systemic therapy directly before enrollment, CDK4 amplification by fluorescence in situ hybridization and retinoblastoma protein expression by immunohistochemistry (≥1+). Pts received oral PD0332991 at 125mg daily for 21 days in 28-day cycles. The primary endpoint was PFS at 12 weeks. Based on historical data, a promising result was defined as a 12-week PFS of ≥40% and not promising as ≤20%. The sample size was up to 28 evaluable patients. If 9 patients were progression free at 12 weeks, then PD0332991 would be considered to have activity in WD/DDLS. Results: 29 pts were enrolled and 25 were evaluable for the primary endpoint. Median age was 62 (range 42-85); 55% were male; median ECOG score was 0 (range 0-1). PFS at 12 weeks was 56% (14/25 patients; 90% CI 41-100%), and thus the study significantly exceeded its primary endpoint. Median PFS was 23.6 weeks (95% CI: 11.6 to Not Reached). There was 1 confirmed partial response lasting >1 year. Grade 3 and 4 adverse events included anemia (grade 3, 21%), thrombocytopenia (grade 3, 7%; grade 4, 3%), and neutropenia (grade 3, 34%). Dose reduction was required in only 1 patient. Conclusions: In patients with WD/DDLS with CDK4 amplification, PD0332991 treatment was associated with a favorable PFS and objective tumor response. This dose and schedule appears active and may have less toxicity than 200mg x 14d. The 125mg x 21d schedule warrants evaluation in a phase 3 study. Clinical trial information: NCT01209598.
Potentially actionable kinase fusions in inflammatory myofibroblastic tumors.

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Background: Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal neoplasm that harbors anaplastic lymphoma kinase (ALK) gene rearrangements in approximately 50% of cases. ALK inhibitors have been validated as an effective therapeutic approach in this subset of IMTs. The goal of this study was to characterize a series of IMTs using both immunohistochemistry (IHC) and next generation sequencing (NGS). Methods: 30 formalin-fixed, paraffin-embedded IMT specimens from 28 patients were evaluated by IHC for ALK expression using standard techniques. DNA was extracted and sequenced using a targeted capture-based NGS assay for 3769 exons of 236 cancer-related genes and 47 introns of 19 commonly rearranged genes, including 8 tyrosine kinases in a CLIA laboratory (Foundation Medicine). Selected specimens were also evaluated for ALK fusions by fluorescence in situ hybridization (FISH). Results: 20 samples were ALK positive and 10 samples were ALK negative by IHC. Targeted NGS was successfully performed in 16/20 ALK positive and 10/10 ALK negative cases. Among the 16 ALK positive cases analyzed by NGS, 12 harbored ALK fusions with various 5’ gene fusion partners, including LMNA, TPM3, TPM4, SEC31A, TFG, RANBP2, and CLTC. The remaining 4 were also negative by FISH suggesting a different mechanism of ALK overexpression. Among the 10 ALK negative cases, 2 harbored ALK fusions (EML4-ALK, TPM3-ALK). In the other 8 ALK negative samples, 2 contained distinct ROS1 fusions (YWHAE-ROS1, TFG-ROS1) and 1 contained a PDGFRβ fusion (NAB2-PDGFRβ), none of which have been described in IMT samples to date. Overall, kinase gene fusions were identified in 18/26 (69%) evaluable samples. Conclusions: This study represents the most comprehensive NGS analysis of IMTs. 12/12(100%) ALK IHC and FISH positive cases contained ALK fusions, while 5/8 (63%) of distinct ALK IHC negative cases harbored kinase fusions, involving ALK, ROS1, or PDGFRβ. Since these fusions are all targetable with existing kinase inhibitors (i.e. crizotinib, dasatinib), this study suggests that IMTs should be routinely profiled for kinase fusions and not just by ALK IHC. Efforts are ongoing to identify “driver mutations” in the fusion-negative specimens.
Phase Ib study of RG7112 with doxorubicin (D) in advanced soft tissue sarcoma (ASTS).

Sant P. Chawla, Jean-Yves Blay, Antoine Italiano, Martin Gutierrez, Axel Le Cesne, Carlos Alberto Gomez-Roca, Laurence G. Gouw, Margaret von Mehren, Andrew Wagner, Robert G. Maki, Brian Higgins, Steven Middleton, Gwen L. Nichols, David Geho, Steven Blotner, Jianguo Zhi, Lin Chi Chen; Sarcoma Oncology Center, Santa Monica, CA; University Claude Bernard Lyon I, Centre Léon Bérard, Lyon, France; Institut Bergonié, Bordeaux, France; Hackensack University Medical Center, Hackensack, NJ; Institut Gustave Roussy, Villejuif, France; Institut Claudius Regaud, Toulouse, France; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Fox Chase Cancer Center, Philadelphia, PA; Dana-Farber Cancer Institute, Boston, MA; Mount Sinai School of Medicine, New York, NY; Hoffmann-La Roche Inc., Translational Clinical Research Center, Nutley, NJ; Hoffmann-La Roche Inc., Translational Clinical Research Center, Nutley, NJ

Background: Preclinical data demonstrate p53-dependent MIC-1 activation by both D and the MDM2 inhibitor RG7112. This study evaluated the tolerability of combining D with RG7112 in ASTS patients (pts) and pharmacokinetic (PK) and pharmacodynamic (PD) parameters of the combination. Methods: A phase 1b 3+3 dose escalation study was designed. Pts with ASTS in whom D was considered appropriate were eligible. D was administered IV at either 50 mg/m² or 60 mg/m² on day 1 with RG7112 administered orally 500 or 1000 mg QD for 3 or 5 days (d1-3 or d1-5) in 28-d treatment cycles. Safety, PK and PD, including serum MIC-1 (an indicator of p53 activation), were assessed. Results: As of January 15, 2013, enrollment was complete with 23 pts with ASTS accrued; safety data for cycle 1 was available for preliminary review in 20 pts. Growth factor support was mandated following the first dosing group (D 60 mg/m² and RG7112 500 mg x 5d) due to febrile neutropenia or grade 4 neutropenia. Of the 20 pts for which cycle 1 safety data is available, 13 pts reported neutropenia (12 grade 3/4); 5 reported grade 3/4 febrile neutropenia (3 following mandatory GCSF prophylaxis); 12 pts developed thrombocytopenia (9 grade 3/4). PK parameters of the combination therapy are similar to single agent values and did not demonstrate evidence of drug-drug interactions. Serum MIC-1 rapidly increased to levels greater than for either agent alone. Best response to date is stable disease in 8/16 pts who have had interim evaluations. Conclusions: Combination therapy with D and RG7112 resulted in a high rate of grade 3/4 neutropenia (60%) or thrombocytopenia (45%). PK analysis does not suggest this is due to changes in the metabolism of either drug. This combination demonstrates apparent potentiation of p53 activation demonstrated by increased MIC-1 levels greater than additive effects of the single agents. Biomarker analyses, safety, PK, and MIC-1 data will be presented. Clinical trial information: NCT01605526.

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NA: data not yet available.

Reversing the oncogenic roles of misdirected chromatin remodeling: Mechanistic insights into the SS18-SSX fusion protein in synovial sarcoma.

Cigall Kadoch, Gerald R. Crabtree; Stanford University, School of Medicine, Stanford, CA; Stanford University, School of Medicine, Howard Hughes Medical Institute, Stanford, CA

Background: Synovial sarcoma (SS) accounts for ~10% of soft-tissue malignancies and is generally resistant to chemotherapy-based approaches, underscoring the need for a mechanistic understanding of its pathogenesis and the development of disease-specific biologic agents. The hallmark molecular feature is a precise and uniform translocation, t(X;18), which results in the fusion of exactly 78 amino acids of SSX to the SS18 C-terminus. Because the SS18-SSX genetic lesion is observed in 100% of cases, it is likely the driving oncogenic event in these tumors; however, the molecular basis for its role in oncogenesis is undefined. Methods: We performed an affinity purification-/mass spectrometry-based analysis of endogenous mSWI/SNF (BAF) chromatin remodeling complexes in several primary cell types. Using these data in combination with protein biochemical methods, we discovered that SS18 is a dedicated, non-exchangeable subunit of these complexes with a binding affinity comparable to that of ribosomal subunits. Subsequent biochemical and functional investigations were performed to assess the oncogenic consequences of addition of 78aa of SSX to the SS18 subunit in SS. Results: We demonstrate that the SS18-SSX fusion incorporates into BAF complexes, evicting both wild-type (WT) SS18 and the tumor suppressor subunit, hSNF5 (BAF47), known to be biallelically inactivated in pediatric malignant rhabdoid tumors (MRTs). The altered complex binds the Sox2 locus, reversing polycomb-mediated repression and activating Sox2. Sox2, a pro-pluripotency transcription factor, is uniformly expressed in SS tumors and is essential for proliferation. Remarkably, increasing the concentration of WT SS18 leads to reassembly of WT complexes, retargeting of BAF complexes, returned polycomb-mediated repression at the Sox2 locus and cessation of SS cell proliferation. This mechanism of transformation depends on a region of only two amino acids of SSX, and hence provides a strong foundation for therapeutic intervention. Conclusions: These studies provide a novel oncogenic mechanism for SS tumors and inform strategies for therapeutic development in this intractable cancer.
An open-label international multicentric phase II study of nilotinib in progressive pigmented villo-nodular synovitis (PVNS) not amenable to a conservative surgical treatment.

Hans Gelderblom, David Pérol, Christine Chevreau, Martin HN Tattersall, Silvia Stacchiotti, Paolo Giovanni Casali, Claire Crozet, Sophie Piperno-Neumann, Axel Le Cesne, Antoine Italiano, Virginia Ferrari, Florence Duffaud, Nicolas Penel, Palma Dileo, François Bertucci, Andrew Bassim Hassan, Judith R. Kroep, Severine Denizot-Guillemaut, Jean-Yves Blay; Department of Clinical Oncology, Leiden University Medical Center, Leiden, Netherlands; Centre Léon Bérard, Lyon, France; Institut Claudius Regaud, Toulouse, France; University of Sydney, Sydney, Australia; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Centre Léon Bérard, Unité de Biostatistique et d’Évaluation des Thérapeutiques, Lyon, France; Institut Curie, Paris, France; Institut Gustave Roussy, Villejuif, France; Institut Bergonié, Bordeaux, France; Regina Elena National Cancer Institute, Rome, Italy; La Timone University Hospital, Marseille, France; Centre Oscar Lambret, Lille, France; University College London Hospitals NHS Foundation Trust, London, United Kingdom; Institut Paoli Calmettes, Marseille, France; University of Oxford, Oxford, United Kingdom; Leiden University Medical Center, Leiden, Netherlands; Unité de Biostatistique et d’Évaluation des Thérapeutiques, Lyon, France; University Claude Bernard Lyon I, Centre Léon Bérard, Lyon, France

Background: PVNS, also known as tenosynovial giant cell tumor (TGCT), is a rare pathological entity affecting the synovium in young adults. This neoplastic disease is driven by a t(1;2) translocation resulting in the fusion of COL6A3 and M-CSF genes. Nilotinib has inhibitory properties on M-CSF receptor pathway which could be of therapeutic interest in patient (pts) with non resectable PVNS. Methods: In this open-label international, multicentric, non-randomized, phase II study the primary objective is to evaluate the efficacy of nilotinib treatment (800 mg/day) in pts with progressive or relapsing PVNS not amenable to surgery or in whom surgery would be mutilating, as measured by the 12-week progression-free rate (12-w PFR). Results: From December 2010 to September 2012, 56 pts with progressive disease were enrolled by 17 institutions from Europe and Australia. Successive previous IA led to positive results in favour of the study continuation. 47 pts (median age 37 y (range: 18-74), 51% of males) were evaluable at the time of the last IA, with a median follow-up of 11.2 months (range: 0.6-12.7). Median time since diagnosis was 2.5 years (range: 0.02-26). Primary tumour was mainly located on knee (25 pts, 53%), hip (6 pts, 13%), ankle (6 pts, 13%). 4 pts had already received imatinib, 76% of pts had undergone a previous surgery. The 12-w PFR was 93.6% (95%CI, 82.5%-98.7%), without any OR. PR were observed later (2 at w-24 and 1 at w-48). Nilotinib was well tolerated, with only 4 pts experiencing grade 3 adverse events (anorexia: 1 pt; prurit: 1 pt; diarrhea: 1 pt; hepatic failure: 1 pt). 8 pts (17%) had a dose reduction and/or temporary discontinuation of nilotinib due to toxicity. Final results will be further presented. Conclusions: Nilotinib treatment induces disease stabilisation in a large proportion of PVNS patients with non resectable disease or in whom resection would be mutilating. Clinical trial information: NCT01261429.
Results of the randomized phase III trial of trabectedin (T) versus doxorubicin-based chemotherapy (DXCT) as first-line therapy in patients (pts) with translocation-related sarcoma (TRS).

Andrew Eugene Hendifar, Sant P. Chawla, Michael Gordon Leahy, Antoine Italiano, Shreyaskumar Patel, Armando Santoro, Arthur P. Staddon, Nicolas Penel, Sophie Piperno-Neumann, George D. Demetri, Larry Hayward, Jeff White, Launce G. Gouw, Bernardo De Miguel, Arturo Soto, Antonio Nieto, Jean-Yves Blay; Sarcoma Oncology Center, Santa Monica, CA; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Institut Bergonié, Bordeaux, France; The University of Texas MD Anderson Cancer Center, Houston, TX; Humanitas Cancer Center, Rozzano, Italy; Pennsylvania Hospital, Philadelphia, PA; Centre Oscar Lambret, Lille, France; Institut Curie, Paris, France; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; Edinburgh Cancer Research UK Center, Western General Hospital, Edinburgh, United Kingdom; The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; PharmaMar, Madrid, Spain; University Claude Bernard Lyon I, Centre Léon Bérard, Lyon, France

Background: T is the first of a new class of anticancer agents with a transcription-targeted mechanism of action. In vitro, T interferes with the aberrant transcription factors binding to DNA promoters in TRS.

Methods: Pts with advanced TRS of the subtypes: myxoid liposarcoma (ML), alveolar soft part sarcoma, angiomatoid fibrous histiocytoma, clear cell sarcoma, desmoplastic small round cell tumor, low grade endometrial stromal sarcoma, low grade fibromyxoid sarcoma, myxoid chondrosarcoma and synovial sarcoma, stratified by performance status (0 vs 1-2) and subtype (ML vs other TRS) were randomized (1:1 ratio) to T (1.5 mg/m² in 24h iv infusion q3wk) or doxorubicin, either single agent 75 mg/m² q3wk, or 60 mg/m² combined with ifosfamide (6-9 g/m² q3wk) as 1st line treatment. Primary endpoint: efficacy of T vs DXCT by comparing progression-free survival (PFS). Secondary: PFS at 6 months (PFS6), response rate (RR), PFS/RR by subtype (ML vs other TRS); overall survival (OS), safety.

Results: 121 pts enrolled from 22 centers. 88 were confirmed by central pathology review and evaluable for the primary efficacy endpoint by independent review assessment (IR), and all 121 pts randomized were evaluable by investigators’ assessment (IA). The main limitation of the study analyses in both arms was high censoring rate (70% IR; 61% IA) mostly due to surgery (~30%) or chemotherapy/ radiotherapy (~30%). PFS results are shown in the Table. PFS6 was not different between arms (IR: 66.4% vs 80.8% p=0.18/IA: 60.7% vs 62.4% p=0.88). Current median OS: not reached (NR) for T (24.1-NR) and 21.7 mo. for DXCT (21.2-NR). Safety: Most frequent AEs in both arms were nausea (70% vs 65%), vomiting (44% vs 26%) and fatigue (64% vs 63%). ALT increase G4 occurred in 10% pts treated with T and neutropenia G4 in 25% of pts in the T arm vs 52% in the DXCT arm.

Conclusions: Although with a high censoring rate, this prospective study suggests that PFS/OS with trabectedin are not significantly different from DXCT in first-line treatment. Clinical trial information: NCT00796120.

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P value: 0.79 0.47 0.67

NR: not reached.

Nathalie Gaspar, Bernadette Brennan, Lee Jeys, Uta Dirksen, Stephanie Foulon, Anna Cassoni, Beatrice M. Seddon, Line Claude, Perrine Marec-Berard, Anne Streitbuerger, Jeremy Whelan, Michael Paulussen, Robert Grimer, Marie-Cécile Le Deley, Heribert Jurgens; Institute Gustave Roussy, Villejuif, France; Royal Manchester Children’s Hospital, Manchester, United Kingdom; The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, United Kingdom; Department of Pediatric Hematology and Oncology, University Hospital, Muenster, Germany; Institut Gustave Roussy, Villejuif, France; University College Hospital London, London, United Kingdom; University College London Hospitals NHS Foundation Trust, London, United Kingdom; Department of Radiation Oncology, Centre Léon Bérard, Lyon, France; Institut d’Hématologie et d’Oncologie Pédiatrie, Lyon, France; Universitätsklinikum Münster, Münster, Germany; Universität Basel, Basel, Switzerland; Royal Orthopaedic Hospital, Birmingham, United Kingdom; Institut Gustave Roussey, Paris, France; University of Muenster, Muenster, Germany

Background: Uncertainty exists on the most appropriate use of surgery, radiotherapy (RT) or both for treatment of primary Ewing sarcoma (ES). The objective of this study was to assess the impact of postoperative RT on local control in pts with localized ES and good (<10% residual cells) histologic response to chemotherapy (CT).

Methods: We analyzed data of all pts included in the EE99-R1 trial (comparing 2 consolidation CT regimens) undergoing surgery after induction CT. Local recurrence (LR) cumulative incidence (CI) was estimated using a competing risk approach. As local therapy was not randomized but tailored to the individual patient and tumor characteristics, impact of RT was assessed in multivariable models, adjusted for possible confounders: country, age, tumor type, site and volume, quality of resection and histologic response. We also evaluated the heterogeneity of RT effect by patient and tumor characteristics (interaction).

Results: Among the 599 pts included from 1999 to 2009, 142 (24%) had received postoperative RT. With median follow-up of 6.2 yrs, disease failure was reported in 156 pts, including a LR in 67 (with concomitant metastases in 28), leading to an 8-yr LR-CI = 12% (se 1.4%). Overall survival = 21% (se 5%) 3 yrs after LR (31% in isolated LR). Controlling for possible confounders, the risk of LR was halved in pts treated by surgery + RT (HR=0.43, 95%CI, 0.21-0.88, p=0.02) compared to surgery alone. Postoperative RT had a rather homogeneous positive effect in all studied subgroups. The benefit of RT was very significant in pts with a tumor volume of >200mL at diagnosis and 100% necrosis. Although not significant, we observed a trend for benefit associated with RT in terms of disease-free, event-free and overall survival.

Conclusions: LR contributes significantly to disease failures in this standard risk group who experience few systemic failures. Outcome after LR is very poor. Postoperative RT appears to improve local control for all pts. Good histologic response and complete resection of residual mass may not be sufficient criteria to omit RT. Further study of RT in ES is required to assess the balance between benefit and risk (secondary malignancies, functional sequelae). Clinical trial information: NCT00020566.

Preoperative chemoradiation therapy for localized retroperitoneal sarcoma (RPS): Final results of a phase II study from the Italian Sarcoma Group.

Alessandro Gronchi, Antonino De Paoli, Carla Dani, Domenico Franco Merlo, Vittorio Quagliuolo, Giovanni Grignani, Giulio Bertola, Piera Navarria, Claudia Sangalli, Angelo Paolo Dei Tos, Marco Fiore, Paolo Giovanni Casali; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Centro di Riferimento Oncologico, Pordenone, Italy; Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy; Humanitas Cancer Center, Rozzano, Italy; Medical Oncology, Institute for Cancer Research and Treatment, Candiolo, Italy; Humanitas Institute, Rozzano, Italy; Istituto Nazionale dei Tumori, Milano, Italy; Azienda ULSS 9 Treviso, Treviso, Italy

Background: To study the feasibility, safety and activity of the combination of high dose long-infusion Ifosfamide (HLI) and radiation therapy (RT) as preoperative treatment for resectable localized RPS.

Methods: Patients received 3 cycles of HLI (14 g/m²). RT was started in combination with the onset of the 2nd cycle and administered up to a total dose of 50.4 Gy. Surgery was scheduled 4-6 weeks after the end of RT. Primary end-point was 3-yr relapse free survival (RFS). The expected 3-yr RFS in the study population treated with surgery alone was 40%. The experimental treatment was aimed at achieving a relative reduction in relapses of at least 1/3, corresponding to a 3-yrs RFS of 55%. With 60 enrolled patients, the study would have had a 90% power to discriminate between the hypotheses of 3-yrs RFS of 40% (H0) and 55% (H1), using a 1-sided 10% level of significance. Results: Between December 2003 and 2010, 86 patients were recruited. 3 patients were ineligible after central pathological review. 63 were affected by primary tumor and 20 by local recurrence. The 3 main histological subtypes were well differentiated liposarcoma (19/83, 23%), dedifferentiated liposarcoma (26/83, 31%) and leiomyosarcoma (14/83, 17%). Median tumor size was 120 mm (IQ range 82-160). The overall preoperative treatment was completed in 60 patients. CT was completed in 65 patients, while RT in 73. Five patients had progression before surgery (3 distant and 2 local) and were not operated. 78 patients underwent surgery. At a median follow-up of 4.8 years (IQ range 3-6.1), 23 and 15 patients developed local recurrence (LR) and distant metastases (DM) respectively; 30 patients died of disease. 3-yr and 5-yr RFS and overall survival were 56% and 44%, and 74% and 59%, respectively. Crude cumulative incidence of LR and DM at 5 yrs were 37% and 26%, respectively. Conclusions: The combination of preoperative HLI and RT was feasible in two thirds of patients, while pre-operative RT could be completed in most (73/83). The primary endpoint of the study was met. Although a systemic coverage can be added to RT when this is felt to be appropriate, the ongoing international Phase III trial is exploring the role of RT alone. Clinical trial information: ITASARC_*II_2004_003.
Association of perioperative radiation therapy with outcome in 204 patients with primary retroperitoneal sarcoma: A two-institution study.

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Background: Radiation therapy (RT) for retroperitoneal and pelvic sarcomas (RPS) is controversial. We examined the association of perioperative, advanced modality RT on outcomes in primary RPS. Methods: Prospectively maintained databases were reviewed to compare primary RPS patients (pts) treated at two institutions between 2003 and 2011. Clinicopathologic variables were analyzed with endpoints of local recurrence-free survival (LRFS) and disease-specific survival (DSS). Results: At one institution 172 pts were treated with surgery alone while at the other 32 pts were treated with surgery and perioperative proton beam or intensity-modulated RT intraoperative RT. The groups were similar in age, gender, tumor grade, tumor size, and margin status (p = NS). The RT group had a lower percentage of retroperitoneal versus pelvic tumors and leiomyo/liposarcoma versus other histologies (p < 0.05). Median follow-up was 38.7 months (36.9 for RT group, 38.8 for surgery alone). Five-year predicted LRFS was 91% (95% CI, 79-100%) in the RT group and 65% (57-74%) in the surgery only group (p = 0.06). RT was marginally significant in univariate analysis of LRFS. Upon adjusting for univariate predictors, RT was significantly associated with better LRFS (p = 0.046; Table). Five-year predicted DSS was 93% (95% CI, 82-100%) in the RT group and 84% (78-91%) in the surgery-only group (p = 0.25). The only independent predictor of DSS was age. Morbidity was higher in the RT group (41% vs 17%; p = 0.004). Conclusions: In this retrospective study, the addition of advanced modality RT to surgery for primary RPS was associated with a reduced risk of local recurrence, although this did not translate into a statistically significant improvement in DSS. This treatment strategy warrants further investigation in a randomized trial.

### Multivariate analysis.

<table>
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<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>HR (95% CI)</th>
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<tr>
<td>Perioperative RT (Y vs N)</td>
<td>0.35 (0.13-0.98)</td>
<td>0.046</td>
<td>0.5 (0.23-2.23)</td>
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<td>Grade (high vs low)</td>
<td>4.1 (2.01-8.16)</td>
<td>0.001</td>
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<tr>
<td>Histology (leiomyo vs others)</td>
<td>0.19 (0.06-0.56)</td>
<td>0.003</td>
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<td>Margin (pos vs neg)</td>
<td>1.8 (0.03-14.88)</td>
<td>0.076</td>
<td>2.2 (0.97-4.93)</td>
<td>0.058</td>
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<tr>
<td>Size (&gt;18 cm vs ≤18 cm)</td>
<td>1.8 (0.94-3.39)</td>
<td>–</td>
<td>1.03 (1.01-1.06)</td>
<td>0.006</td>
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<tr>
<td>Age</td>
<td>–</td>
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A model for multi-institutional, multidisciplinary sarcoma videoconferencing.

Steven Attia, Robert G. Maki, Jonathan C. Trent, Scott H. Okuno, Daniel J. Indelicato, Nicolas P Webber, Kelly Kevelin Curtis, Kevin Robert Kozak; Mayo Clinic, Jacksonville, FL; Mount Sinai School of Medicine, New York, NY; Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; Mayo Clinic, Rochester, MN; University of Florida Proton Therapy Institute, Jacksonville, FL; Aurora Healthcare, Milwaukee, WI; Mayo Clinic, Scottsdale, AZ; University of Wisconsin School of Medicine and Public Health, Madison, WI

Background: Sarcomas are rare cancers, with > 50 subtypes, and require multi-disciplinary care. Their management benefits from multi-institutional input due to the paucity of concentrated experience with each subtype. However, sarcoma tumor boards, wherein a patient-specific, consensus treatment approach is determined, are predominantly conducted in isolation at individual centers. Methods: Since March 2010, we have conducted a weekly multi-institutional, multi-disciplinary sarcoma tumor board to combine knowledge and experience in the management of our most challenging patients. The Mayo Clinic bridge links sites by interactive videofeed. Each site may contribute cases. De-identified history, radiology and pathology are reviewed. A didactic series reviews a rotation of seminal papers, newly published research, or our own data. An “Expert Guest” series allows outside experts to connect to one conference. A yearly participant survey assesses quality. Conference is free to sites and is CME accredited. Results: Currently, 8 sarcoma programs connect Mondays from 8-9am ET. Median attendance is 20 (range: 8-27). In 2012, 342 cases were reviewed over 43 conferences (median: 8 cases/conference; range: 4-12 cases/conference). The 2012 survey revealed 96% (25/26) agreed HIPAA rules are followed; 93% (25/27) agreed conference is educational; 93% (25/27) agreed recommendations are evidenced-based or reasonable; 100% (27/27) agreed participants are respectful; and 86% (18/21) agreed input from other sites has changed their management. Staff attendance (quantity) rated as meets/exceeds needs was 100% (25/25) for medical oncology; 96% (26/27) for pathology; 93% (25/27) for orthopedic oncology; 92% (23/25) for radiation oncology, surgical oncology and radiology; and 61% (17/23) for thoracic oncology. Conclusions: To our knowledge, this is the only weekly multi-institutional sarcoma tumor board in existence. It permits consistent oncology care across a wide geographic area, and is a model for providing consensus recommendations regardless of the remoteness of the patient and care team. Future plans for this group include prospective collection of outcomes data.
SARC006: Phase II trial of chemotherapy in sporadic and neurofibromatosis type 1 (NF1)-associated high-grade malignant peripheral nerve sheath tumors (MPNSTs).

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Background: MPNSTs occur in 10% of the NF1 population, and retrospective, pooled analyses have reported worse chemotherapy response for NF1 (9-18%) compared to sporadic MPNSTs (39-55%).

Methods: We prospectively evaluated the objective response (OR) rate, [complete responses (CR) and partial responses (PR) WHO criteria] of children and adults with high-grade, unresectable or metastatic chemotherapy naive NF1 associated versus sporadic MPNST after 2 cycles of ifosfamide and doxorubicin (IA) followed by 2 cycles of ifosfamide and etoposide (IE) as primary endpoint. This was followed by surgery and/or radiation for local control and up to 2 more cycles of IA and IE each. Pathology was centrally confirmed. A Simon optimal two-stage design was used with a target response rate of 40% and 17 patients per stratum in the first stage. With 4/17 ORs, enrollment was to be expanded to 37 patients per stratum, and 11+37 ORs would be potentially consistent with a 40% OR rate. Results: Both initial stages met criteria for enrollment expansion with 4/17 PRs in NF1 and 4/12 PRs in sporadic MPNSTs, but only 1 additional PR was observed in the expanded NF1 stratum. Of the 9 PRs, 5 were first observed after 2 cycles IA, and additional 4 after 2 cycles IE. Enrollment was slower than expected and the trial was closed before full accrual.

Conclusions: While the primary trial objective was not reached due to slow enrollment, with only 5/29 ORs in the NF1 stratum the desired OR rate of 11+37 would have unlikely been met even if accrual had been completed. We observed a lower OR rate in NF1 compared to sporadic MPNSTs similar to retrospective literature reports. However, our trial was not powered to detect a difference in response rates between the two strata. In addition to PRs after both IA and IE, disease stabilization was achieved in most patients. Novel strategies including the evaluation of targeted agents in combination with chemotherapy should be considered. Clinical trial information: NCT00304083.
Phase II trial of ifosfamide in combination with sorafenib in patients with advanced soft tissue sarcoma: A Spanish Group for Research on Sarcomas (GEIS) study.

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Background: Recent studies suggest that VEGFR inhibition could play a role in the treatment of soft tissue sarcoma (STS). Prior studies by our group showed that the combination of ifosfamide with sorafenib resulted in preclinical additive activity and that was feasible and safe in the phase I trial. Methods: Patients (pts) with advanced STS, previously treated with doxorubicin, no prior ifosfamide, ECOG PS 0-2, and adequate hematological, renal and hepatic function, were enrolled in this multicenter phase II study, receiving sorafenib 400 mg bid po continuously and ifosfamide 2 g/m2 iv for 3 days together with mesna 400 mg/m2 every 3 weeks. The primary endpoint was progression-free rate (PFR) at 3 months. A one-sample binomial design was used (PFR P0=40%, P1=60%, α=0.10, β=0.20), requiring at least 19 of 35 pts free of progression at 3 months to be considered positive. Results: From September 09 to March 12, 35 pts were enrolled at 11 centers. Median age was 55 (18-73). PS: 0-1, 1-2; 2-4 pts. Histologic types were: LMS 12, Lipo 6, SS 5, MPNST 2, other 10 pts. The median number of cycles administered per patient was 4. PFR at 3 months was 67%, with 23 pts being free of progression at 3 months. Median progression-free survival was 4.8 months (95% CI, 1.9-6.3) and median overall survival was 16.2 months. PR was achieved in 17% pts. Most common grade 3-4 toxicities were asthenia (25%), hand-foot syndrome (11%) and neutropenia (20%) resulting in 3 episodes of neutropenic fever. Other common toxicities (G1-4) included emesis (34%), rash (22%), diarrhea (34%), hypertension (11%) and mucositis (9%). Conclusions: The combination of ifosfamide and sorafenib is active and has acceptable toxicity in pts with doxorubicin pretreated STS. The PFR at 3 months might exceed the expected with ifosfamide alone warranting further investigation. Clinical trial information: ÉudraCT: 2007-002176-34.
Neo/adjuvant doxorubicin (A) and ifosfamide (I) versus gemcitabine (G) and docetaxel (T) in patients (PTS) with localized, high risk soft tissue sarcoma (STS): A randomized phase II comparative effectiveness trial.

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**Background:** Approximately 50% of pts with localized, >5 cm, high grade STS develop metastatic disease. Although controversial, adjuvant chemotherapy has demonstrated improved disease-free (DFS) and overall survival (OS). AI can cause significant toxicities that often lead to hospitalization. GT is active in metastatic STS pts and as compared to AI has a favorable schedule and toxicity profile. **Methods:** In a single-institution phase II study, pts with localized, resectable, high grade STS >5 cm were randomized to receive AI or GT. Pts were stratified by neo- or adjuvant treatment and extremity or non-extremity tumor. Pts received A (75 mg/m\(^2\) over 48 hrs) and I (2.5 g/m\(^2\)/d on D1-3) or G (900 mg/m\(^2\) over 90 min on D1,8) and T (100 mg/m\(^2\) on D8), both arms with GCSF, for 4 cycles unless progression. Radiation was given after chemotherapy. The primary endpoint of the trial was hospitalization rate during chemotherapy and was compared using a chi square test and multiple logistic regression adjusting for other variables. The trial was powered to detect a reduction in hospitalization rate from 35% to 10% using GT. Survival functions were estimated using Kaplan-Meier method. **Results:** 84 pts were enrolled from 11/04-8/12 with 80 pts evaluable. The median age is 56 yrs (19-76) and tumor size is 7.8 cm (3.2-25). 55 pts received neoadjuvant therapy and 48 had extremity STS. In the AI arm, 13/37 (35%) pts were hospitalized vs. 11/43 (26%) in the GT arm (p=0.25). The most frequent reason for hospitalization in AI arm was febrile neutropenia (7 events) and in GT arm was hypersensitivity reaction (4 events). The median DFS of pts treated with AI vs GT is 24 months vs not reached, respectively; median follow up is 30 (1-87) months. The 2-year DFS rate is 53% (SD 9%) in the AI arm vs. 71% (SD 7%) in the GT arm and remains marginally significant after adjusting for age, gender, neoadjuvant therapy, tumor site and size (p=0.054). OS rates are not significantly different between arms. **Conclusions:** Hospitalization rate was not significantly lower with GT compared to AI, although toxicity profile was different. DFS but not OS is marginally improved with GT. Clinical trial information: NCT00189137.
Association of circulating VEGF-A levels with outcome in patients with vascular sarcomas receiving sorafenib (Sor): Exploratory analysis from AngioNext study.

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Background: We have carried out a stratified phase II study of Sor in pts with advanced angiosarcoma (AA, n=32), malignant solitary tumour (SFT, n=4) & epithelioid hemangioendothelioma (EE, n=13). We report here the correlative analysis of predictive value of circulating pro/anti-angiogenetic biomarkers. Methods: Using ELISA method (R&D SYSTEMS) Circulating biomarkers (VEGF-A [pg/mL], Thrombospondin-1 (TSP1) [μg/mL], Stem Cell Factor (SCF) [pg/mL], Placental growth factor (PlGF) [pg/mL], VEGF-C [pg/mL] & E-selectin [ng/mL]) have been measured before Sor treatment & after 7 days. We analyze the correlation with histological subtypes, presence of metastases, best response and occurrence of hemorrhage and Gr3-4 arterial hypertension. Results: VEGF-A (mean value 475 vs 541 pg/mL, p=0.002), TSP1 (16 vs 24 μg/mL, p=0.0002), PlGF (20.9 vs 40.7 pg/mL, p=0.0001) significantly increased during the treatment. Sor treatment did not affect the levels of SCF, VEGF-C & E-selectin. The distributions of all biomarkers were similar across the histological subtypes, whatever the presence of metastasis, the occurrence of hemorrhage or arterial hypertension. 2 biomarkers were associated with better outcome: VEGF-A & PlGF. Best objective response and non-progression at 180 days were associated with low level of VEGF-A at baseline (p=0.04 and p= 0.03 respectively). There was a correlation between circulating level of VEGF-A & time to progression (TTP) (r=-0.47, p=0.001). Best objective response and non-progression at 180 days were not associated with baseline level of PI GF (p=0.34 and 0.07), but there was a correlation between circulating level of PI GF at baseline and TTP (-0.31, p=0.02). Conclusions: In pts with vascular sarcomas receiving Sor, we have observed a significant decrease in circulating level of VEGF-A. Low level of VEGF-A at baseline (<500 pg/mL) was significantly associated with better outcome, especially best objective response rate, non-progression at 180 days and time to progression. Clinical trial information: 2007-004651-10.
Using pegylated arginine deiminase (ADI-PEG20) for the treatment of sarcomas that lack argininosuccinate synthase 1 expression.

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Background: To better understand the metabolism of sarcomas, we explored the role of argininosuccinate synthase 1 (ASS1), the rate-limiting enzyme in the conversion of citrulline to arginine in the urea cycle. When ASS1 is not expressed the amino acid arginine becomes an essential amino acid that must be delivered from the diet. The potential for therapeutic manipulation of this pathway with pegylated arginine deiminase (ADI-PEG20) was explored using metabolomic mass spectroscopy. Methods: Immunohistochemistry (IHC) of ASS1 expression on 701 patient specimens representing 45 subtypes of sarcoma was performed. Proliferation and cell death were analyzed in a panel of cell lines. Clonogenic assays were performed using ADI-PEG20 and chloroquine. Autophagy induction and inhibition was assessed. Xenograft models were tested. Metabolomic mass spectroscopy was performed in the presence and absence of ADI-PEG20. Results: IHC analysis demonstrated that ASS1 is not expressed in over 85% of sarcomas (619 of 701 patient samples). Treatment of a panel of LMS, synovial, ASPS, GIST, MPNST, chondrosarcoma, osteosarcoma, and Ewings sarcoma cell lines with ADI-PEG20 resulted in cell cycle arrest but not apoptosis when ASS1 expression was low (13/15 lines). Xenografts of the ASS1 low MNNG/HOS cells and SKLMS1 cells into nude mice followed by treatment with ADI-PEG20 +/- chloroquine demonstrated significantly slower tumor growth as compared to PBS or chloroquine treated controls. Treatment of sarcomas that lack ASS1 with ADI-PEG20 induced autophagy. Global analysis of metabolomic mass spectroscopy demonstrated alterations in PKM2, glutamine dependence, the Warburg effect, the TCA cycle and glutathione biology. Conclusions: This suggests that sarcomas may be sensitive to the arginine depletion therapy using ADI-PEG20. Autophagy induction has global metabolic consequences for sarcoma. Successful control of tumor burden by using arginine deprivation therapy and autophagy inhibition in our preclinical studies will help to orient clinical trials for this innovative treatment in patients with sarcoma that lack ASS1 expression.
Outcome and prognostic factors in localized primitive neuroectodermal tumors with uniform chemotherapy protocol: A single center experience of 224 cases.

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Background: Data on localized PNET with uniform protocol is minimal. Methods: This is single institutional patient review treated between June 2003-Nov 2011, and evaluated on intent-to-treat analysis. All patients received uniform chemotherapy (VAC/IE) as follows: neo-adjuvant chemotherapy (NACT), surgery and/or radiotherapy as local treatment followed by ACT. Results: 224/374 (60%) PNET patients were localized with median age 15 years (range: 0.1–55), tumor diameter 8 cm (range: 1.6-25) and symptom duration 4 months (range: 0.5-30). Regions were extremities 40%, thorax 25% and head & neck 14%. Post-NACT, CR was 32(14%); PR 152(68%) with ORR 82%. Ninety-nine patients underwent surgery (50/99 received adjuvant radiotherapy); 80 received radical radiotherapy as local therapy. There were no adverse tumor characteristics or poor NACT response in radical radiotherapy group versus surgery group. At median follow-up of 31.1 months (range: 1.3–113.4), 5-year EFS, OS and local control rate (LCR) were 34±3.5%, 52.5±4.7% and 59.5±4.8%, respectively. Multivariate analysis of prognostic factors is shown in the Table. Conclusions: This is largest data of localized PNET from Asia which identified unique prognostic factors. Localized PNET constituted 60% of entire cohort with delayed presentation. High WBC may be a marker of micrometastatic disease or an adverse paraneoplastic response. Skeletal primary and tumor diameter >8 cm predicted inferior OS and LCR; additionally radical radiotherapy predicted inferior LCR. All efforts should be made to resect primary tumor post-NACT as radical radiotherapy alone despite good NACT response results in inferior LCR.

<table>
<thead>
<tr>
<th>Multivariate analysis</th>
<th>EFS</th>
<th>OS</th>
<th>LCR</th>
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<td>Radical RT</td>
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Discordance of oncologic surgical classifications in COG studies.

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Background: “Wide resection” (a cuff of normal tissue) versus “radical resection” (the entire compartment) indicate very distinct oncologic surgical procedures and hence potential margin status. Distinguishing between these two oncologic classifications is important for understanding oncologic outcomes. Methods: We examined the available data for COG AOST0331: A Randomized Trial of the European and American Osteosarcoma Study Group to Optimize Treatment Strategies for Resectable Osteosarcoma Based on Histological Response to Pre-Operative Chemotherapy. We reviewed the surgical and pathology reports of patients considered to have received a wide or radical resection according to the investigator at the patient’s institution. Results: In 956 patients, the overall discordance rate was 43%. Of those patients reported to have had a wide excision by the reporting institution, only 5% of patients were reclassified to radical resection. However, of those patients reported to have undergone radical resection, 75% were reclassified to wide. In the absence of this re-review of the data, 56% of the patients would have been reported to have had a radical resection when in fact only 17% met the criteria for true radical resection. The greater number of patient reclassified to wide from radical is likely indicative of the influence and limits of the CPT coding system currently used for billing by surgeons; only CPT codes for radical resection currently exist. Conclusions: These discrepancies complicate subsequent data analysis, particularly assessing predictors of local recurrence. While this reporting problem is not unique to COG studies, we aim to use this example to raise awareness among our colleagues about the importance of accurate data reporting. Providing better training to those individuals responsible for submitting data may decrease the incidence of erroneous data entry and is essential to the successful completion of study objectives.
Prognostic significance of Wnt signaling pathway molecules in nongastric GIST patients: A tissue microarray-based (TMA) analysis.

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Background: Pathogenesis in GIST could be related to cancer stem cell hypothesis (highly chemo resistant, very uncommon complete responses, kit is stem cell marker) even though no stem cell component in GIST has been yet demonstrated. Wnt signaling regulates proliferation in some normal and cancer stem cells as it occurs with intestinal epithelium. We have explored the prognostic significance of several Wnt signaling pathway and related molecules. To investigate the prognostic significance of β-Catenin, CDC25A, ROR2, p53, CUL4A, AKT-p and VEGFR-3 by immunohistochemical (IHC) analysis in TMA specimens of 101 non-gastric GIST. Methods: Data of diagnostic, therapeutic and follow-up procedures stem from the GIST Registry of GEIS. Cytoplasmic and/or membrane staining was deemed positive for ROR-2, VEGFR-3 and p-AKT antibodies whereas nuclear staining was positive for β-Catenin, CDC25A, CUL4A and p53 antibodies. IHC positive cases were considered if they displayed staining in at least 10% of cells. Statistical analyses for correlation of protein expression with known prognostic variables (mitoses, size) were performed with Mann-Whitney U test. Results: A subset of 101 non-gastric localized GIST patients was selected (90 intestinal, 15 others: mainly rectum and omentum). The median age was 62 y with gender distribution of 59M/42F and the median of follow-up was 36 months. The positivity for each protein was distributed as follows: ROR-2 63%, p-AKT 55%, β-Catenin 53%, VEGFR-3 22%, CDC25A 20%, p53 8% and CUL4A 7%. A statistically significant correlation was found between mitoses and β-Catenin (median 5 if negative/ 10 if positive, p=0.028); VEGFR-3 (median 5 if negative/21 if positive, p=0.002); CUL4A (median 6 if negative/60 if positive, p= 0.027). Additionally, tumor size was statistically correlated with VEGFR-3 (median 7 if negative/11 if positive, p=0.007). Conclusions: VEGFR-3, β-Catenin and CUL4A are correlated with the highest proliferative non-gastric GIST. These findings deserve further analysis and lead to potential new molecular therapeutic targets in GIST. This study was partially granted by Buesa Grant of GEIS.
Switching chemotherapy in adult osteosarcoma patients with poor necrosis rates post neoadjuvant methotrexate, cisplatin, and doxorubicin (MAP).

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Background: Chemotherapy in the treatment of osteosarcoma has improved 5 year overall survival (OS) from 20% with surgery alone to 60-70%. However, poor tumor necrosis following neoadjuvant chemotherapy (NAC) is associated with decreased survival, therefore strategies to improve outcomes are required for these patients. Methods: Records from all adult patients diagnosed with osteosarcoma between 1986 and 2012 were retrospectively reviewed. Patients were stratified according to age at diagnosis (<40yrs and >40yrs), stage (localised or metastatic) and tumor necrosis post NAC (<90% and >90%). All patients received 2 cycles of methotrexate alternating with cisplatin/doxorubicin (MAP) preoperatively. Following surgery, patients with >90% tumor necrosis continued MAP whilst those with <90% necrosis switched to 4 cycles of ifosfamide and etoposide (IE). Results: 105 patients were identified and 98 who received systemic chemotherapy were included. Median age was 23yrs (Range 15-75yrs); 68% of patients were male. Limb sparing surgery was performed in 76% of applicable patients. Of the patients with localised disease (N=85), 5 year OS, with a median follow up of 8 years (1-26 yrs) was 68% (p=0.002). Patients <40 yrs with localised disease had a 5yr OS of 71% (N=73) compared to 40% in those >40 yrs (N=12) (p=0.05). 2/13 patients with metastatic disease at diagnosis are disease free >10 years post diagnosis. 65 of 73 patients with localised disease < 40 yrs had histology reviewed post neoadjuvant MAP. 34/65 (52%) had >90% tumor necrosis and continued on MAP, 5 yr OS 79%. 31 patients (48%) had <90% necrosis and received adjuvant IE, 5 yr OS 68% (P=0.10). Conclusions: Age and stage are important prognostic factors in patients with osteosarcoma treated with chemotherapy and surgery. Historically, patients with <90% tumor necrosis post NAC are considered to have a poorer prognosis. Switching from MAP to IE is an appropriate salvage regimen in such patients and appears to improve long term survival.
Background: Osteosarcoma (OS) is a clinically challenging primary malignant bone tumor that has a high rate of local recurrence and metastasis. Disease-free survival has been reported to be as low as 19% despite contemporary chemotherapy regimens and surgery. Wnt signaling is known to play a role in osteogenesis and cancer pathogenesis, therefore is a promising target for therapeutic intervention in OS. Secreted Frizzled Related Proteins (sFRPs), Dickkopf-1 (DKK1), and Sclerostin (SOST) are secreted Wnt inhibitor proteins that regulate Wnt signaling in bone. This study investigates the activity of sFRP3, DKK1, and SOST in serum from OS patients with the goal of developing therapeutic Wnt inhibitors and clinically useful biomarkers. Methods: Enzyme linked immunosorbent assays were used to quantify sFRP3, DKK1 and SOST levels in human serum (n=40 pairs; 20 OS patients, 20 aged matched non-diseased controls). Patients were stratified into 2 age groups: >35 (n=26 pairs) and <30 (n=14 pairs) years of age. Clinical data from the medical records was correlated with experimental results. Using a Wilcoxon signed rank test, a p-value <0.05 was significant. Results: sFRP3 levels were significantly decreased in 55% (22/40) of diseased samples compared to 20% (8/40) of the non-diseased controls (p=0.007). DKK1 levels were elevated in 40% (16/40) of OS samples compared to 30% (12/40) of the non-diseased controls (p=0.08). SOST levels were increased in 42.5% (17/40) of diseased samples compared to 32.5% (13/40) of the non-diseased controls (p=0.38). When stratified by age, the younger patients showed a statistically significant decrease in sFRP3 expression (p<0.001). Serum levels of sFRP3, DKK1, and SOST were not statistically significant between metastatic and non-metastatic OS. Conclusions: Serum sFRP3 levels were significantly decreased in OS patients, a difference that was even more pronounced in the pediatric strata. Since sFRP3 is differentially expressed in patient serum it has potential as a clinical biomarker for initial tumor diagnosis and early detection of recurrence. Decreased sFRP3 expression may be responsible for the up regulation of Wnt signaling in OS. Wnt inhibitors such as sFRP3 have potential as therapeutic agents in OS warranting further investigation.
MicroRNA profiling analysis in a series of high-risk intestinal GISTs.

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Background: Resected localized GISTs exhibit a wide range of biological behavior from low to high risk of recurrence. Risk categories (low, intermediate and high) are built from mitotic count, size and location. However, the molecular mechanism related to GIST relapse has not yet been fully clarified. The purpose of this study is to characterize miRNA expression profile in high risk GIST patients for both, recurred and not recurred, and detect those differentially expressed in these two subsets.

Methods: Twelve cases of high risk intestinal GIST, 6 with relapse and 6 without relapse, were selected for this analysis. Sections were obtained for RNA extraction using the miRNeasy FFPE kit (Qiagen) and miRNA was hybridized to the GeneChip miRNA 3.0 Array (Affymetrix) including more than 1800 human miRNA. Normalization and statistical analysis were performed with Partek Genomic Suite 6.6 software by means of ANOVA test. Fold-change (FC) and p-values were applied to generate miRNA differentially expressed lists.

Results: A subset of 85 miRNA were significantly deregulated (p<0.05; FC>1.5) when comparing both groups. Among them, the highest p-values and associated FC were: mir-4776 (FC = 1.95, p = 0.011), mir-1973 (FC = 1.59, p = 0.014) mir-4649 (FC = 1.74, p = 0.028) and mir-3605 (GC = 1.58, p = 0.045). All of these were up-regulated in recurred patients. Interestingly, the two samples that correspond to the biggest tumors with relapse showed a significantly different expression profile that separated them from the rest of the samples. We have identified 44 miRNAs that discriminate these two samples from the rest and show a very high statistical significance. The most significantly up regulated miRNAs were miR-100 (FC = 90.87, p<0.0001), miR-30a (FC = 156.086, p<0.0001) and down regulated miR-1184 (FC = -24.94, p<0.0001) and miR-4529 (FC = -16.61, p<0.0001). These miRNAs are involved in cell cycle and cell proliferation. Conclusions: This is the first wide characterization of miRNA profile in high risk GIST. The highest differences in expression are related to not previously described miRNAs in GIST tumors. All of them are involved in cell cycle and cell proliferation, thus expecting to regulate many GISTs associated genes, related to the relapse event.
MAPK7 gene: A target for multimodal therapies.

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**Background:** Osteosarcoma (OS) is a class of cancer originating from the bone, affecting mainly children and young adults. In a previous work we observed that the overexpression of MAPK7 gene was significantly associated to tumor progression, a poor response to treatment, and worse overall survival, suggesting that MAPK7 could play an important role in osteosarcoma tumorigenesis. This present study investigated if any genomic structural alteration could be related to MAPK7 overexpression in OS samples. **Methods:** The MAPK7 gene was fully sequenced in 33 OS samples (15 prechemotherapy, 15 post-chemotherapy and 3 OS cell lines) using the 3500 Genetic Analyser (Applied Biosystem) and 15 custom primers pairs that amplified overlapping genomic fragments. **Results:** From the 30 patient samples analyzed, 16 could not be completely sequenced. Samples containing these deleted regions were significantly correlated to clinical and pathologic features of patients with OS. No deletions were observed in patients with the favorable outcome (non-metastatic at diagnosis, >90% degree of necrosis in the surgical specimen and with complete remission at end of treatment). There was no correlation found between deletions and overexpression in pre-chemotherapy, even in patients that after chemotherapy still overexpressed MAPK7. **Conclusions:** Progress related to improved survival of patients with OS is at a plateau, and the intensification of therapy or incorporation of new therapeutic agents has not been successful, especially in patients metastatic at diagnosis. To our knowledge, no molecular marker for OS that could be related to its development, evolution or progression has been described yet. Based on our findings, we observed that patients who have no genomic deletion of MAPK7 gene respond better to treatment and have a favorable outcome. Studies available to date suggest that a single targeted therapy may not provide clinically significant anti-tumor effects, therefore we believe that specific inhibitors of the MAPK/ERK pathway are emerging as a relevant addition to multimodal therapies.
Gene expression of the MAPK pathway in osteosarcoma.

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Background: Osteosarcoma (OS) is the most common malignant bone tumor in adolescents. A feature of the OS is its high risk of lung metastasis. Unlike other sarcomas, OS does not have genetic markers. We suggest that abnormalities in the expression levels of genes involved in important cell signaling pathways, as MAPKs pathway, may contribute to OS progression and aggressiveness. In a recent study, we found an overexpression of MAPK7 gene in prechemotherapy specimens when compared to postchemotherapy specimens and when compared with normal bone. This previous study suggests that MAPK7 overexpression may be contributing to the worse response to treatment and therefore a poor overall survival. To understand the relationship between the OS genesis process and the MAPK pathway, we investigated the expression of genes involved in the regulation of MAPK pathway (MAP2K5, MAP2K6, MAP3K1, MAP3K3, MAP4K3 and DUSP1).

Methods: Total RNA was extracted from 68 tumor samples obtained from 28 patients (28 prechemotherapy specimens, 28 postchemotherapy specimens and 12 metastasis specimens) and five normal bone tissues. cDNA was synthesized and expression of the six genes were determined by quantitative real-time PCR. Clinical variables were correlated with gene expression. Results: MAP2K6 and MAP4K3 had a similar gene expression profile. Both genes were overexpressed in postchemotherapy specimens and were strongly associated with important clinical parameters as presence of metastasis (P = 0.0159 and P = 0.0014, respectively), shorter overall survival (P = 0.0040 and P = 0.0040, respectively) and disease progression (P = 0.0142 and P = 0.0109, respectively). DUSP1 overexpression in postchemotherapy specimens was related with metastasis at diagnosis (P = 0.0004), worse response to treatment (P = 0.0009) and disease recurrence (P = 0.0039). MAP2K5, MAP3K1 e MAP3K3 showed no significant correlations in the present study. Conclusions: The overexpression of MAP2K6, MAP4K3 and DUSP1 in postchemotherapy specimens presented a significant association with poor prognosis. The current study suggests that these genes could play an important role in OS tumorigenesis and may be in the future new therapeutic targets in OS treatment.
Role of glutathione S-transferase and cytochrome P-450 polymorphisms in the clinical outcome of osteosarcoma patients.

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**Background:** Osteosarcoma (OS) is the most common malignant bone tumor in children and adolescents. Glutathione S-transferase (GST) and Cytochrome P-450 (CYP) family genes are involved in almost all anticancer drugs metabolism. The polymorphisms in these genes are associated with anticancer drugs resistance and toxicity events. This study aims to investigate the genotype frequencies of GSTM1, GSTT1, GSTM3, CYP1A2, CYP2C9 and CYP3A5 genes in OS patients and the influence of these polymorphisms in their clinical outcome. **Methods:** We investigated the peripheral blood DNA of 70 OS patients (25 metastatic and 45 nonmetastatic at diagnosis), following the GLATO - Latin American Group of Osteosarcoma Treatment - 2006. GSTM1 and GSTT1 deletion polymorphisms were examined through a multiplex-PCR and the GSTM3 polymorphism of three base pair-deletion using PCR-RFLP method. CYP1A2, CYP2C9 and CYP3A5 single nucleotide polymorphisms (SNPs) were investigated through real time PCR using TaqMan probe. **Results:** We found that GSTM1 null genotype was correlated with relapse occurrence (p=0.031) in patients that received high doses of chemotherapy. The CYP1A2*F allele was associated with lung metastasis (p=0.032), lung relapse (p=0.018) and high grade of ototoxicity (p=0.039). The CYP3A5*3 allele was associated with high grade of hepatotoxicity (p=0.010). The presence of at least one GSTM3*B allele was associated with better overall survival (p=0.045). The presence of CYP3A5*3 homozygous genotype was associated with better overall survival (p=0.043) in metastatic patients at diagnosis. The genotype GSTM3*B/GSTM1 present, GSTM3*B/GSTT1 present and GSTM3*B/CYP3A5*3 in metastatic patients at diagnosis were associated with better survival (p=0.048; p=0.004; p=0.012, respectively). **Conclusions:** The findings of this study suggest that GST and CYP polymorphisms may have a role in treatment response and may be an important marker in the future to personalized therapy in OS. Furthermore, CYP1A2*F allele is correlated with risk of lung metastasis and GSTM3*B homozygous genotype in combination with GSTM1 present, GSTT1 present and CYP3A5*3 were associated with better survival.
Does a diagnosis of GIST predict a second primary cancer?

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**Background:** There have been reports of a high frequency of metachronous cancers in patients diagnosed with GIST. The purpose of this study was to identify and describe patients with GIST who develop second primary cancers, and to calculate standardized incidence ratios (SIRs) to quantify the risk of additional malignancy. **Methods:** This was a retrospective, population-based cohort study using SEER data. Individuals diagnosed with GIST from 2001-2009 were identified as having a malignant primary tumor in the digestive tract, and included the following sites: C15.0-C26.9; C48.0-48.8; C49.4-49.5; C80.9 and a recorded histology code of 8935 and 8936. This restricted timeframe was imposed to account for changes in the recording of GIST incidence. Individuals with a previous cancer diagnosis or diagnosed post mortem only were excluded. Multiple primary SIRs and 95% confidence intervals (CI) were calculated using SEER*Stat software (V.7.1.0) and compared to general population rates. The SIR was interpreted as an estimate of relative risk (RR). Comparison of characteristics between single and multiple cancer GIST patients was performed using chi-square tests, p-values of <0.05 were considered significant. **Results:** We identified n=1397 cases of GIST, of which 1291 analyzed. We observed a statistically significant increased incidence of second tumours in patients with a primary GIST (n=78, RR 1.36, 95% CI:1.1-1.7). Older age (p<0.001) and tumor grade (p=0.014) were associated with second primaries, with grade being the only significant variable remaining after logistic regression. In both sexes we observed a significantly increased incidence of kidney cancer (RR 4.3, 95% CI: 1.7-8.9). In females there was a 3 fold higher incidence of colon cancer (RR 2.96 95% CI: 1.2-6.1). **Conclusions:** Patients with a diagnosis of GIST have a higher incidence of second cancers when compared with standardized incidence in the general population. High grade GISTs were associated with an additional malignancy. Both sexes were observed to have increased incidence of kidney cancer, with females at an increased risk of developing colon cancer. As part of GIST surveillance, screening for colon cancer in females and kidney cancer in both sexes may be considered.
Demonstration of gender-specific variability in a pharmacokinetic (PK) analysis of the PERSIST-5 trial of adjuvant imatinib (IM) for patients with primary gastrointestinal stromal tumor (GIST) at significant risk of recurrence.

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**Background:** The PERSIST-5 phase II trial is evaluating 5 years of adjuvant IM therapy in patients with resected GIST at significant risk of recurrence. This analysis studied the effect of chronic therapy on steady-state trough levels in patients who received IM for up to 24 months to evaluate potential PK variations. **Methods:** Eligible patients were adults with KIT+/H11001 primary GIST who were considered to be at significant risk for recurrence (primary tumor any site ≥2 cm and mitotic rate ≥5/50 high-power fields, or non-gastric primary GIST ≥5 cm) without metastases. R0 resection of primary GIST was performed ≤12 weeks prior to the first IM dose. Patients are to receive oral IM 400 mg/day for up to 5 years or until progression, relapse, or intolerance. Plasma samples for PK analysis were collected at 1, 4, 12, and 24 months. IM plasma concentrations were measured using a validated liquid chromatography-tandem mass spectrometry assay. **Results:** In-study assay performance (%CV) was ≤9.6% and bias was -1.3% to 5.2%. IM concentrations ranged from below quantifiable limits to 4798 ng/mL. After daily IM doses for up to 12 months (or 24 months in 3 patients), IM trough levels remained constant over time. The range of IM trough levels (mean ± SD) was 957 ± 750 ng/mL to 1219 ± 822 ng/mL at month 1, and 727 ± 430 ng/mL to 996 ± 405 ng/mL at month 12. Inter-patient variability was 40.7-78.4%. There was no significant difference in IM trough levels between months 1 and 4, 1 and 12, or 4 and 12. Trough levels did not significantly differ by location of GIST. Most notably, mean IM trough concentrations were on average ~33% higher in females vs males. **Conclusions:** In this study, IM trough levels remained relatively unaltered in patients with high-risk GIST who received adjuvant IM for 1 year. The 33% higher mean trough levels in females warrants further study for clinical decision making. Clinical trial information: NCT00867113.

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Gastrointestinal stromal tumor associated with neurofibromatosis type I.

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Background: Most gastrointestinal stromal tumors (GIST) have either KIT or PDGFRA mutations. Neurofibromatosis type 1 pts caused by mutations in the NF1 gene have increased risk of GIST development, which may have no mutation in both genes. In this study, we analyzed clinical and pathological features of NF-1 associated GISTs. Methods: Study 1: We have screened 95 adults NF1 pts (age 31-66, 35 male and 60 female) by enhanced MDCT between 2003 and 2012. Study 2: We collected 1,184 sporadic GISTs from community hospitals in Japan between 2001 and 2010 retrospectively, and found 24 primary NF1-GISTs (1.7% of sporadic) and 2 recurrent NF1-GISTs, of whom clinicopathological features were analyzed. Results: Study 1: By MDCT screening, we have found histologically confirmed 6 GISTs (4 males and 2 female; 6/1,000 NF1-persons/year) in the small intestine. Median age of NF1-GIST was 45, and five pts had multiple tumors, ICC hyperplasia in the normal intestine and no mutation in the KIT and PDGFRA genes. Study 2: Median age of 26 NF1-GIST (12 male and 14 female) was 58. 25 GISTs were located in the small bowel and one in the stomach. 17 pts had multiple GISTs and 9 pts single lesion. Pathologically, KIT was positive for all NF1-GISTs. 24 pts had spindle cell tumors and 2 had mixed or epithelioid. No mutation was found in the KIT and PDGFRA genes of 11 pts examined. Median values of mitosis (0/50HPF) and Ki67 (0.5%) were lower than those of sporadic GIST (3/50HPF and 2.5%). With media follow-up of 3.6 years, 8 pts had recurrences and 4 pts died of the disease. By western blotting, KIT was faintly phosphorylated but its downstream kinases including MEK, p44/22, AKT, mTOR, p38 and STAT3, were activated. Six pts received imatinib and had no response and, subsequently, 5 pts received sunitinib with 4 PD and 1 short-term SD. Conclusions: NF1-associated GIST is a rare entity of GIST and has distinctive features from conventional sporadic GISTs. KIT-targeted TKI appeared to be ineffective to recurrent and advanced NF1-GISTs.
Background: Mutations of the receptors KIT and PDGFRA in GIST are the oncogenic events of disease as well as the targets of molecular therapies. Within the PDGFRA mutations, the D842V mutation in exon 18 confers in vitro and in vivo resistance to imatinib. Next generation sequencing techniques may completely dissect all the possible somatic mutations and genomic rearrangements in order to identify novel therapeutic targets in this patients population. Methods: Five patients with gastric GIST were analysed (3 M, 2 F; mean age 65.5 years, range 51-77). The tumor dimension ranged between 3 and 15 cm, MI < 2 and 8 /50 HPF. No metastases were present in all cases. The KIT and PDGFRA analysis showed a D842V mutation in exon 18 of PDGFRA in all cases. Whole transcriptome sequencing was performed with Illumina HiScanSQ platform with a paired-end strategy (75x2). After performing quality controls, the short reads were mapped with Tophat-Bronte pipeline against the human reference genome (HG19). The variations, such as Single nucleotide variants (SNVs) and InDels, were called by SNVMix2 (a software suited for SNVs discovery in tumor samples) implementing an accurate filtering procedures developed in our laboratory. Two predictors of mutations effect at protein level (SNPs&GO and Provean) were employed in order to prioritize the emerging variation. Results: An average of 206 coding non-synonymous variants were highlighted in the five GIST samples, of which ~ 30% were predicted as deleterious with at least one predictor. In addition to PDGFRA D842V mutation, in all five patients were found mutations on different receptor tyrosine kinases, such as FGFR4 and DDR2. Moreover three out of five patients harboured mutations on members of the MDR/TAP subfamily that are involved in multidrug resistance, in particular on ABCB1, ABCB4 and on ABCB6 genes. Other mutations were found on the hedgehog and MAPK signaling pathway and on SNF/SWI chromatin remodeling complex. Conclusions: New molecular events have been identified in PDGFRA D842V mutant GIST. These data should be validated in larger series and the role of these mutations as therapeutic targets should be further investigated.
Ten-year prospective experience of gastrointestinal stromal tumors (GISTS) from the Cambridge GIST Study Group, United Kingdom.

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Background: Cambridge GIST study group was formed in 2003. GIST specialist multidisciplinary team (MDT) and GIST clinic were established with central review of histology/pathology and management plans. We present our 10 year experience of a prospective database which formed the template for the United Kingdom national GIST registry. Methods: All patients (pts) who have been referred to the GIST MDT were included in the study. The following data was prospectively collected: patient demographics, presenting symptoms, site, size, histology including mutational data (where available) risk stratification of the GISTS, surgical interventions, systemic therapies, other tumours occurring in GIST pts.

Results: 260 patients (pts) were reviewed in the GIST MDT. 29 pts had endoscopic/imaging diagnosis of a GIST and were not included in the final analysis. 41 pts had other tumours diagnosed when GIST was initially suspected. Histologically confirmed GISTS N=190. Male: Female 52%:48%. Median age 64 years (range 14-94), 4% <40 years. 84% had surgical intervention (primary or metastatectomy), 9% had resections on imatinib/sunitinib. Tumour characteristics: Site: Stomach-73%, small bowel-16%, EGIST-4%, colorectal-3%, duodenum-3% and oesophagus-1%. Size 0.1-40 cm. Histology subtype: Spindle cell 84%, mixed 12% and epitheloid=4%. Miettinen risk stratification groups: High risk 27%, intermediate risk 16% and very low risk/low risk 57%. Mutational status results in 36 pts: exon 11 = 64%, PDGFRA = 14%, wild type = 11%, exon 9 = 5.5%, exon 13 = 5.5%. 14% of GIST pts had other tumour either prior to diagnosis or during treatment/follow up of GISTS. Conclusions: This is the first prospective regional GIST registry data from UK. Our results mirror other large prospective series. GISTS should be managed by an experienced multidisciplinary specialist team to provide a high quality patient centred service.
Relationship of the topography of KIT exon 11 alterations and predictive value for PFS in patients with advanced GIST: Results of the BFR14 prospective French Sarcoma Group randomized phase III trial.

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Background: The mutations of KIT exon 11 are those most frequently observed in GIST, but there is a substantial level of heterogeneity in their nature and topography. We investigated the impact of the type of KIT exon 11 mutations on clinical presentation and outcome under imatinib in advanced GIST patients (pts) included in the BFR14 study. Methods: Among the 434 pts included, 167 were identified as having GIST with KIT exon 11 mutation (85% of all KIT mutations and 73% of all mutations available in the entire cohort). We analyzed the topography of the mutations and identified 3 groups (G) of mutations according to the first codon involved in the genetic alteration in which the precise topography was available (from codon 549 to 579). The distribution of these G in the different clinical presentations was investigated, as well as their predictive value for progression-free (PFS) and overall survival (OS). Results: Three G with distinct sites of altered codons were distinguished: G1 whose 1st mutated codon was <556 (n=41, 24.5%), G2 whose 1st mutated codon was 557 and 558 (n=74, 44.3%), including those with the deletion 557-558 (n=37, 22.1%), and G3 whose 1st mutated codon was 559 and beyond (n=52, 31.1%). All investigated parameters at inclusion, gender, tumor site and size, site of metastases, age, PS, CD34 expression, biological characteristics were well balanced between the three G of patients. Pts of G2 reached a statistically difference in terms of complete response under imatinib (p=0.028). In contrast, this G have the poorer PFS compared to the other two groups: the median PFS were 30.6 months (CI95%: 21.5;39.4), 49.4 months (CI95%: 33.5; 109.9) and 63.3 months (CI95%: 27.6; 84.7) for the G 2, 1 and 3 respectively (p=0.0176). OS was not significantly different in the 3 G of pts. Conclusions: Despite a favorable sensitivity to imatinib, GIST pts harbouring a genetic alteration initially involving the 557 and 558 codons develop statistically more secondary resistance than the others. These results deserve confirmation in other prospective series in advanced GIST and may be worth exploring in adjuvant series.
Imatinib plasma concentrations during long-term effective treatment of metastatic gastrointestinal stromal tumor.

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Background: Imatinib concentrations at one month after the start of imatinib have shown an association with clinical benefit in pts with gastrointestinal stromal tumors (GISTs) and a significant decrease of 30% within twelve months. This retrospective study investigated imatinib plasma concentrations in pts with metastatic GISTs in a long-term (≥2 years) effective treatment. Methods: 31 metastatic GIST pts, who had been treated with imatinib for two or more years in our hospital, were enrolled in this study. 11 pts were excluded because of adjuvant setting (n=5) and rejection to concentration testing (n=6). 20 pts were included in this study. GISTs were immunohistochemically diagnosed, and radiologically assessed as effective GIST by Choi’s criteria without relapse. Results: 10 pts were male, median age was 63 years (range, 31-84), and median imatinib exposure time was 3.5 year (range, 2-12). The median plasma concentration was 1093 ng/ml (range, 417-2091) and minimal level after at least five years was 789 ng/ml. Imatinib concentration has no significant correlation with age, gender, gastrectomy, leukocyte count, platelet count, serum albumin, serum creatinine, cholesterol, and duration of imatinib exposure. Body surface area (BSA) isn’t directly associated with imatinib dose; median BSA of pts taking 300mg imatinib was 1.560 m² and that of 400mg 1.595 m², but minimal BSA of 400mg imatinib was 1.560 m², which is higher than the minimum of 300mg. Conclusions: Plasma concentrations of long-term (≥2 years) response pts was scattered, but one of longer-term (≥5 years) response pts were more than 789 ng/ml. Effective imatinib plasma level might be more than 789 ng/ml and 400mg imatinib may be recommended for a pt with BSA(≥1.56 m²).
Frequent mutations in MLH1, MET, KIT, PDGFRA, and PIK3CA genes in human gastrointestinal stromal tumors.

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Background: Identifying mutations in individual tumor is critical to improve the efficacy of cancer therapy by matching targeted drugs to specific mutations. Gastrointestinal stromal tumor (GIST) is a stromal or mesenchymal subepithelial neoplasm affecting the gastrointestinal tract and it frequently contains an activating mutation in either the KIT or platelet-derived growth factor A (PDGFRA) gene. Although GIST is highly responsive to several selective tyrosine kinase inhibitors, combined use of inhibitors targeting other mutations is needed to further prolong survival. Methods: In this study, we aim to screen and identify genetic mutations in GIST for targeted therapy using the new Ion Torrent next-generation sequencing platform. Results: By utilizing the Ion Ampliseq Cancer Panel, we sequenced 737 loci from 45 cancer-related genes from DNA extracted from formalin-fixed and paraffin-embedded (FFPE) samples of 125 human gastrointestinal stromal tumors, set up stringent parameters for reliable variant calling by filtering out potential raw base calling errors, and identified frequent mutations in PDGFRA, KIT, APC, MLH1, MET, RET, and PIK3CA. Moreover, frequent missense mutations were detected in MLH1 (12%), MET (16.8%), KIT (51.2%), and PIK3CA (41.6%) genes. The mutations in MLH1 gene were frequently detected in the exon 14, while MET gene was frequently mutated in the exon 2. In addition, we identified missense mutations in other genes, including FLT3, KRAS, PDGFRA, and STK11, at lower frequencies. Conclusions: This study demonstrates the utility of using Ion Torrent sequencing to efficiently identify human cancer mutations. With the finding of the frequent mutations in MLH1 and MET genes, in addition to KIT, PDGFRA and PIK3CA, in GISTs, this study provides a molecular basis for clinically developing new drugs targeting these gene mutations for GIST therapy.
Predictors of complete response following disease recurrence in gastrointestinal stromal tumor (GIST) patient: A retrospective patient chart review analysis.

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Background: Adjuvant imatinib (IM) treatment reduces the risk of GIST recurrence and improves survival particularly when IM is used for a longer duration among moderate to high risk patients. However, among patients who recur, little is known about the factors impacting the probability of achieving complete treatment response (CR). This study identifies factors associated with the probability of achieving CR among patients who had a recurrence following cessation of initial adjuvant IM treatment for a KIT + GIST.

Methods: An online tool was used to retrieve clinical data on 410 patients who were treated with adjuvant IM for ≥6 months for primary resectable KIT+GIST, discontinued, had a recurrence after discontinuation, and then restarted IM or initiated sunitinib. Tumor and treatment characteristics were collected at primary diagnosis and disease recurrence. Patient response status was assessed by physicians based on different measures (e.g., RECIST, Choi, other subjective measures). Predictors of CR were identified using logistic regression models. Results: Among the 410 (IM = 314, sunitinib = 96) patients treated for GIST recurrence, 22.4% achieved CR (25.2% of pts on IM and 13.5% of patients on sunitinib). On average, CR was achieved after 11 weeks of treatment and only 2% of patients had a subsequent disease progression/recurrence. RECIST criteria were most widely used for CR evaluation in 68% of patients followed by subjective measures (29%) and Choi criteria (17%), respectively. Patients with a unifocal tumor (Odds Ratio[OR]=2.61; p<.001 ), small tumor size (<2 cm) (OR=2.16; p=.023), lower mitotic rate ≤5/50 HPF (OR=1.87; p=.017) at recurrence, or tumor recurrence inside gastrointestinal system (OR=2.27; p=.036) were more likely to achieve CR. Conclusions: Among study patients, 22.4% achieved CR following disease recurrence. The main predictors of CR were tumor focality, size, location, and the mitotic rate at recurrence. This suggests that detecting recurrence at an early stage and managing disease with re-initiation of KIT inhibitor therapy may improve the probability of achieving CR following recurrence.
Clinical experience with sunitinib (SU) in patients over age 65 with metastatic gastrointestinal stromal tumors (GIST): A retrospective study from the French Sarcoma Group (FSG).

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Background: Elderly GIST patients (pts) represent a consistent portion of all GIST pts, but are under-represented in clinical trials. Data on benefits, tolerance of SU in elderly GIST pts and their specific outcome are very limited. Methods: Charts of elderly pts (≥ 65 yrs) treated with SU in routine clinical practice from 11 Centres of the FSG were reviewed to evaluate the efficacy and safety of SU. Results: 71 elderly GIST pts were reviewed, with a median age of 74, [distributed as 65-74, n=36; 75-84, n=30; > 85, n=5], 41 (57%) men, with median ECOG-PS = 1 (0-2), and median active comorbidities of 1 (0-4). SU was administered after progression on first-line Imatinib (400 mg/d for 21 pts, 400 then 800 mg/d for 45 pts) or masitinib (5 pts). SU was started at 50 mg/d 4-wks-on/2 wks-off in 37 pts (52%), at 37.5 mg daily in 32 pts (45%), and at 25 mg daily in 2 pts. All but 2 pts experienced at least one adverse event (AE). Drug related AE were mainly of grade 1 or 2 (298/388, 76%), and medically manageable. Most frequent AE were fatigue (20%), diarrhea (11%), mucositis (7%), abdominal pain (7%), hand-foot syndrome (6%), neutropenia (6%), and hypertension (5%). Permanent dose reduction was reported in 33 pts (46%). In 17 pts (24%) SU was permanently stopped due to grade 3 or 4 AE.; this occurred within 3 months after starting SU in 10 pts. At a median 36 months follow-up, 53 pts progressed, and 28 pts were alive. The median PFS and OS were 10.2 (0.2-54) and 21 (0.5-77) months, respectively. Univariate analysis showed that age (≥ 80), PS (<1), WBC (≥ 4 Giga/l), Hb and Albumin have a positive impact on OS (all p < 0.04) and PFS (all p < 0.05). In multivariate analysis, Albumin and Hb had an impact on OS and PFS, PS had an impact only on OS, and WBC only on PFS. A correlation was found between comorbidities and Grade 3/4 toxicities, but no correlation between any toxicities and outcome. Conclusions: Compared to data from clinical trials, SU yields similar rates of GIST control and OS in elderly pts despite frequent dose reductions or interruptions. Since comorbidities may increase the risks of AEs, careful follow-up to assess tolerance is particularly indicated in elderly GIST pts.
The influence of gastrointestinal resection on sunitinib exposure in GIST patients.

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Background: GIST patients often have an altered anatomy of the GI tract due to either primary resection of the tumor or palliative surgery. It is unknown whether such GI resections affect the exposure to sunitinib and its active metabolite SU12662. Previous studies showed that the exposure to imatinib and nilotinib was decreased in GIST patients with prior major gastrectomy. Therefore, we postulated that GI resections might similarly affect sunitinib exposure. Methods: A retrospective analysis was performed to assess the effect of GI resections on sunitinib exposure. Pharmacokinetic data from 305 GIST patients included in 4 phase I-II trials were analyzed. Patients were subdivided into 6 groups according to prior GI surgery: 1) Major gastrectomy; 2) Partial gastrectomy; 3) Small bowel resection; 4) Combination of gastrectomy and small bowel resection; 5) Colon resection and 6) Controls with no prior GI surgery. Patients with uncertain GI resections were excluded. Dose normalized exposure (AUC<sub>0-24hr</sub>) of sunitinib and SU12662 was estimated with a population PK approach using NONMEM. Analysis of covariance was performed to test for significant differences in AUC between each of the subgroups and controls. Results: The geometric mean of total exposure to sunitinib and SU12662 was decreased by 21% and 28% in subgroup 4, (n=8; sunitinib: 931 ng*hr/mL (95%CI;676-1283) and SU12662: 354 ng*hr/mL (95%CI;174-720)) compared to controls (n=63; sunitinib: 1177 ng*hr/mL (95%CI;1097-1263) and SU12662: 491 ng*hr/mL (95%CI;435-553)), with the differences being significant (p<0.05) on the log scale. However, no significant differences in total exposures were observed between each of the other subgroups and control. Conclusions: In patients with a combined gastrectomy and small bowel resection, sunitinib and SU12662 exposure is significantly decreased as compared to subjects with no prior GI surgery. Contrary to previous results for imatinib, gastrectomy alone does not appear to influence sunitinib exposure. This should be taken into consideration for the treatment of GIST patients who had a gastrectomy. In theory, such patients might have better outcomes if treated with sunitinib, given the risk of subtherapeutic exposure to imatinib.
Impact of mutational status and other prognostic factors on survival in patients with advanced GIST treated with standard-dose imatinib (IM): Results from the BFR14 phase III trial of the French Sarcoma Group.

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Background: Factors predicting progression free survival (PFS) and overall survival (OS) of patients (pts) with advanced GIST treated with 400 mg daily dose IM were investigated. As mutational status was a secondary objective of the BFR14 study, we wanted to evaluate the added value of these genomic profiles to conventional clinical prognostic factors. Methods: 434 pts were included in this prospective multicenter trial from June 2002 to July 2009. Prognostic factors for survival were investigated in the cohort where the mutational status was available. A multivariate Cox model including baseline characteristics statistically significant in univariate were included in a backward procedure to identify independent prognostic factors for PFS then OS. Results: Mutational analysis were available in 322 pts. Material was insufficient in 55 cases (12.5%), incomplete results were obtained in 39 pts (9%). There were 196 KIT genetic alterations (exon 11: 173 pts, exon 9: 22 pts, exon 17: 1 pt), 6 GIST with a PDGFRA mutations and 26 GIST WT. The analysis of prognostic factors was performed in all mutated and non-mutated GIST (221 pts) except for pts with a KIT exon 17 and PDGFRα mutation. As of January 2013, median follow-up was 73 months (m) (CI95%:63; 86), 147 progressions (67%) were notified and 84 deaths (38%) occurred. The median PFS and OS were 12.3 m (CI95%: 2.1;32.7) and 54.9 m (CI95%:16.5;83.8) for WT GIST, 12.6m (CI95%: 6.1;30.8) and 55m (CI95%:33.5;83.0) for KIT exon 9 and 39.4m (CI95%: 31.4;54.4) and not reached for KIT exon 11, respectively. An initial low tumour volume, gender (female), and CD34 positivity were the three independent prognostic factors of a higher PFS. A higher OS was independently predicted by PS, low neutrophil counts, KIT exon 11 alterations, normal lymphocyte count, lower tumor size and female’s gender. Conclusions: GIST pts harboring a KIT exon 11 mutations have the better outcome but the mutational status is not the only prognostic factor influencing the outcome of pts. The clinical (gender, PS, tumor size) and biological characteristics (lymphocytes and neutrophil counts) remain critical for OS.
Background: GIST are rare tumors and before 2000 patients had a dismal prognosis when metastasized. Since the introduction of imatinib and other tyrosine kinase inhibitors overall survival has increased from less than 1 year before 2001 to more than 5 years now. Research on psychosocial consequences for this particular cancer type is scarce. This study focuses on quality of life and fear of disease progression in GIST patients. Methods: Eighty patients with locally advanced or metastatic GIST, being treated with imatinib or sunitinib, from the Radboud University Nijmegen Medical Centre in the Netherlands were asked to participate. Patients completed self-report questionnaires including the EORTC-QLQ-C30, the Cancer Worry Scale, and the Fear of Cancer Recurrence Inventory. Results: Fifty two patients (median age 64.2; range 22-84 years) completed the questionnaires. Two subgroups were identified: patients with locally advanced (n = 27) and metastatic GIST (n = 25). Overall, GIST patients demonstrate a good overall quality of life (EORTC-QLQ-C30 mean global health 76.1). However, 50% of them (n = 26) experienced high levels of fear of cancer progression (CWS cut-off point ≥ 14). High levels of fear were not associated with age, gender or between patients with locally advanced or metastatic GIST. Subgroup analyses revealed that patients with high levels of fear of disease progression showed significantly higher levels of psychological distress related to fear of cancer progression and more functional impairments including domains that can be disturbed by fear of cancer progression (e.g. work, daily and social activities, the ability to make future plans or set life goals). Conclusions: Despite a good overall quality of life, a substantial percentage of GIST patients experience high levels of fear of cancer progression, experiencing more psychological distress and more functional impairments compared to patients with low levels of fear. No relation was found with demographic variables nor with stage of disease. This research demonstrates that it is necessary to focus on more specific rather than general quality of life of GIST patients.
The role of surgical resection following imatinib treatment in patients with metastatic or recurrent GIST.

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Background: Several retrospective studies have suggested that surgical resection of residual lesions could be beneficial if resection was done after disease control (partial response or stable disease) with imatinib in patients with metastatic or recurrent GIST. However, the benefit of surgical resection has not been proven yet compared to imatinib alone. Therefore, we compared the outcomes of surgical resection of residual lesions after imatinib (SI group) with those of imatinib alone (IM group) in patients with metastatic or recurrent GIST controlled with imatinib treatment. Methods: A total of 134 patients with metastatic or recurrent GIST who showed at least 6 months of disease stabilization or response to imatinib were included in this retrospective analysis. Patients were categorized into SI (n=42) or IM (n=92) group. To reduce the selection bias, propensity scores and inverse-probability-weighting (IPTW) adjustment were used in the outcome analysis. Results: Patient and tumor characteristics were statistically similar between SI and IM groups, except median age (51 in SI, 58 in IM, p=0.002), and metastases to peritoneum (12 in SI, 56 in IM, p=0.001). The patients in SI group underwent surgery of residual disease after a median 19.1 months of imatinib treatment (range, 7.2-87.0). With a median follow-up of 58.9 months (range, 15.4-129.1), progression-free survival (PFS) and overall survival (OS) were significantly longer in SI group than in IM group (PFS, 87.7 vs 42.8 months, p<0.001; OS, not reached vs 88.8 months, p<0.001). Multivariate analysis revealed SI group as well as female sex, KIT exon 11 mutation, and low initial tumor burden were associated with longer PFS, and SI group and low initial tumor burden were associated with longer OS. Even after applying IPTW adjustment, SI group showed significantly better outcome in terms of PFS (hazard ratio [HR], 2.326; 95% CI, 1.034-5.236; p=0.0412) and OS (HR, 5.464; 95% CI, 1.460-20.408; p=0.0117). Conclusions: This study strongly suggests that surgical resection of the residual lesions after disease control with imatinib may be beneficial in patients with metastatic or recurrent GIST.
Results from a phase III trial (GRID) evaluating regorafenib (REG) in metastatic gastrointestinal stromal tumour (GIST): Subgroup analysis of outcomes based on pretreatment characteristics.

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Background: REG, an oral receptor kinase inhibitor with activity against KIT, PDGFR, VEGFR, FGFRs, and other oncologic targets, demonstrated significant improvement in progression-free survival (PFS) over placebo (PL) in a phase III study (GRID) of patients (pts) with advanced GIST following failure of at least imatinib (IM) and sunitinib (SU). To understand the impact of pts’ baseline characteristics on outcome, we performed an exploratory analysis of REG effects across pt subgroups based on sex, age, and mitotic index of primary GIST tissue, as well as duration and number of lines of previous therapies. Methods: Adult pts with metastatic GIST (n=199) progressing after at least IM and SU were randomized 2:1 to receive oral REG 160 mg or PL once daily for the first 3 weeks of each 4-week cycle. Subgroup analysis of centrally assessed PFS was performed, based on sex, age (<65, ≥65 years), mitotic index of primary GIST (<5, ≥5 to <10, ≥10 mits/50 hpf), duration of IM and SU treatment (<6, ≥6 to <18, ≥18 months), and number of prior anticancer treatment lines (2 or ≥3). Mitotic index data on primaries were available for 119 patients.

Results: REG demonstrated improvement in PFS vs PL in all subgroups, as summarized in the Table. Conclusions: REG had substantial efficacy in all patient subgroups included in this analysis. Clinical trial information: NCT01271712.

| Subgroup analysis of PFS from patients in the GRID study. |
|--------------------------------|-----------------|-----------------|
| Subgroup | Hazard ratio for REG vs PL (95% confidence interval) |
| Sex | Male | 0.31 (0.20, 0.48) |
| | Female | 0.18 (0.09, 0.34) |
| Age | <65 | 0.15 (0.09, 0.26) |
| | ≥65 | 0.30 (0.19, 0.46) |
| Duration of prior IM for metastatic GIST | <6 | 0.55 (0.31, 1.0) |
| | ≥6 to <18 | 0.37 (0.18, 0.77) |
| | ≥18 | 0.39 (0.24, 0.63) |
| Duration of prior SU for metastatic GIST | <6 | 0.21 (0.13, 0.35) |
| | ≥6 to <18 | 0.25 (0.19, 0.35) |
| | ≥18 | 0.20 (0.13, 0.30) |
A risk-based individualized follow-up after complete surgery as an effective procedure to reduce the relapse (R) impact in GIST patients (pts).

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Background: FU care poses a burden on both pts and health system. FU aims to precociously identify recurrences, metastases or treatment-related adverse events so to undertake the appropriate therapy as soon as possible. Guidelines (NCCN, ESMO) admit lack of knowledge on optimal surveillance, but suggest FU based on experts’ opinion and risk stratification. Moreover, tumor burden (TB) is a well known negative prognostic factor (Van Glabbeke 2005). Therefore, low-TB at R might affect final outcome. To identify the impact, if any, of regular FU, we examined our prospectively collected database looking for Rs in which the early detection affected both clinical management and, likely, the outcome.

Methods: 140 pts were stratified (AFIP classification). High risk (HR) pts had complete history + physical examination (H&P) and CT every 3 mos for 2 years, 4 mos in 3rd year, 6 mos in the 4th and 5th yrs, yearly thereafter; intermediate (IR), low (LR) and very low risk (VLR) pts had H&P + CT every 4 mos for 2 years, every 6 mos up to the 5th year, then yearly. Rs were divided in: low-TB + completely resectable R (Group 1) and high-TB + disseminated R (Group 2). The number of CT needed to detect (NND) one R and the incidence of early (<6 mos) R was calculated. Overall survival (OS) was estimated by Kaplan-Meier method.

Results: In 73 male and 67 female, median age 63 (23-82), risk stratification was: HR 73, IR 31, LR 28, VLR 8. After a median FU of 63 mos we observed 58 Rs: 25 (43%) and 33 (57%) in group 2 and 1, respectively. Relapsed pts genotype was KIT Ex11 72%; Ex9 10%; Ex13 3%; wild-type 15%. Median time to R was 16 mos (1-120). 21 pts underwent surgical resection of their R. 16 pts remained free from progression for a median of 90 mos. We detected 15 (26%) early Rs. NND was 17 and 32 CT for HR and non-HR pts, respectively. Group 1 and 2 median estimated OS was 112 and 87 mos (p=.05), respectively.

Conclusions: Though retrospective, this series shows that FU may detect low-TB Rs. In principle, this might affect pts final outcome and, therefore, justify this costly effort. Since it is difficult to foresee a prospective randomized trial, a confirmation of these data in a different series might increase their reliability.

Long-term responders and survivors on pazopanib for soft tissue sarcomas (STS): Subanalysis of two European Organisation for Research and Treatment of Cancer (EORTC) clinical trials 62043 and 62072.

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Background: Pazopanib has recently received approval in US, EU & Japan for use in certain STS subtypes. We conducted a retrospective analysis on pooled data from two EORTC clinical trials on pazopanib in STS in order to characterize long term responders and survivors. Methods: Patients selected for analysis were treated with pazopanib in phase II study 62043 (n = 142) and phase III study 62072 (PALETTE) (n = 246). Combined median progression-free survival (PFS) was 4.0 months; median overall survival (OS) was 11.3 months. 34 % of patients had a PFS ≥ 6 months (n = 133) and were defined as long term responders; 33 % of patients survived ≥ 18 months (n = 128), defined as long term survivors. Following patient characteristics were studied: gender, age, performance status, tumor localization, histology, grading, treatment exposure and dose modifications, severity of adverse events and post protocol therapy. Results: Clinical cut-off dates for this analysis resulted in a pooled database with a median follow-up of 2.3 years. Patient characteristics were compared between four subgroups based on short / long term PFS and OS, respectively. 79 patients were both long term responders and long term survivors. The descriptive analysis confirmed the importance of known prognostic factors such as age, performance status and grading, but did not add additional characteristics translating into long term response or survival. We identified 12 patients remaining on pazopanib for more than two years: 9 aged younger than 55 years, 9 females, four with smooth muscle tumors and nine with low or intermediate grade tumors at initial diagnosis. Only two of those patients achieved a partial response; the remaining 10 experienced stable disease as best overall response. Median time on pazopanib in these patients was 2.4 years with the longest duration of 3.7 years. Four patients were still on pazopanib at the end of the studies with a median PFS of 2.3 years and a median OS of 2.8 years. Conclusions: 34 % and 33 % of STS patients given pazopanib in these studies have a long PFS and / or OS respectively. 3.1 % of patients demonstrate a clinical benefit even beyond 2 years.
Patterns of toxicities and outcome in children versus adolescents/young adults (AYA) with metastatic rhabdomyosarcoma (RMS): A report from the Children’s Oncology Group (COG) Soft Tissue Sarcoma Committee.

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**Background:** Age at diagnosis is a prognostic factor in patients with RMS. We sought to determine whether AYA with metastatic alveolar (ARMS) or embryonal (ERMS) RMS had a different failure-free survival (FFS) compared to younger patients, and to identify treatment related factors that may be associated with outcome. **Methods:** COG ARST0431 patients were reviewed. The incidence of toxicities (AE, grade3/4 using CTCAEv3) by age was determined in 4 reporting periods (RP: wks 1-6; RP2:7-19; RP3: 20-34; RP4: 35-54). The AEs in younger patients (<13 years) were compared with those in AYA. Fisher’s exact test was used to compare differences between the groups. **Results:** Of 109 patients, 60 (55%) were AYA. In RP1, they were more likely to have nausea/vomiting (4.1 vs. 16.9%, p=0.06), pain (6.1 vs. 20.3%, p=0.05), and metabolic disturbances (4.1 vs. 20.3%, p=0.02) compared to younger patients. In RP4, older patients trended to have less infection (15.8 vs. 30.1, p=0.07). All other toxicities were similar between the two age cohorts in the other RPs. AYA were less likely to complete therapy (52 vs. 73%, p=0.03) and more likely (in RP 4) to have unplanned dose modifications (outside of protocol guidelines) (23 vs. 2.7%). Of patients that completed therapy, there was no age-related difference in the time to completion. As shown in the table, younger patients had better 3-yr FFS, driven by a lower FFS for AYA with ARMS. **Conclusions:** This evaluation suggests that AYA with RMS were less likely to complete therapy and experienced a higher prevalence of pain and nausea compared to younger patients; the role of reporting bias and reasons for treatment discontinuation need further study. Children were more likely than AYA to have infection. Inferior FFS was only seen in AYA with ARMS suggesting a clear need for novel therapies for these patients. This study may be underpowered to demonstrate significant differences in other toxicities or in FFS among ERMS patients.

<table>
<thead>
<tr>
<th></th>
<th>Age ≤ 13 years</th>
<th>Age &gt; 13 years</th>
<th>P</th>
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<tbody>
<tr>
<td>ERMS</td>
<td>57% (34%, 75%), n=27</td>
<td>64% (34%, 83%), n=22</td>
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<tr>
<td>ARMS</td>
<td>37% (14%, 59%), n=22</td>
<td>13% (5%, 26%), n=42</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>51% (35%, 65%), n=49</td>
<td>28% (17%, 40%), n=60</td>
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</tbody>
</table>

Correlation of PTEN loss and PI3K/AKT/mTOR pathway upregulation with malignant peripheral nerve sheath tumor (MPNST) development and outcome.

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**Background:** MPNST is an aggressive soft tissue sarcoma often arising from preexisting neurofibromas (NF). Our previous study using murine models demonstrated that PTEN loss and PI3K/AKT/mTOR pathway upregulation is a potential mechanism of malignant transformation. The goal of this study is to determine whether a similar mechanism also drives human MPNST development. **Methods:** A tissue microarray was created from 144 surgical specimens (MPNST n=58, NF n=51, schwannoma n=11, and normal nerve n=24). Cores were stained in triplicate for PTEN and PI3K pathway-associated markers (PTEN, P-AKT, P-S6, GLUT1, SKP-2), other previously identified alterations (p53, p16, P-ERK and c-Myc) as well as tumor grade biomarkers Ki-67 and cleaved caspase 3. Density, intensity and subcellular localization of each marker were quantified and compared using linear regression and survival analysis was performed using Cox proportional hazards modeling. **Results:** Consistent with our mouse model study, P-S6, GLUT1 and SKP-2, downstream surrogate markers for PI3K pathway, are upregulated in MPNST compared to benign NF (p=0.002, p=0.000, p=0.016, respectively). Upregulated GLUT1 is notable as we have shown that FDG imaging can be used to stratify MPNST lesions from benign. In the 34 primary MPNST patients, PTEN protein expression correlated with improved disease specific survival (DSS) and disease free survival (DFS) (p=0.066 and p=0.014, respectively). In this cohort, large size (p=0.085), low PTEN (p=0.066), and low c-MYC (p=0.001) were associated with poor DSS. Large size (p=0.074), low PTEN (p=0.023), skp2 (p=0.097), p-AKT (p=0.086), and c-MYC (p=0.001) all correlated with poor DFS. NF-1 patients and spontaneous patients had different expression patterns associated with survival. NF-1 patients had improved DSS with high p53 (p=0.044) and smaller size (p=0.013), whereas spontaneous patients showed improved DSS only with increased c-MYC (p=0.008). **Conclusions:** PTEN loss and PI3K/AKT/mTOR pathway activation are important in MPNST development/prognosis and serves as a potential therapeutic target.
Clinicopathologic predictors (CP) of survival in patients with endometrial stromal sarcomas (ESS) treated with multi-modality therapy.

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Background: ESS is a rare uterine neoplasm in which there is minimal data about CP prognostic markers. Our study aims to determine the association of CP variables on overall survival (OS). Methods: Patients at Moffitt Cancer Center between January 1, 1990 and April 30, 2012 with the diagnosis of ESS were identified using our institutional database. Vital status, demographics, and therapeutic information were recorded. Survival time was estimated using the Kaplan-Meier method, and Cox proportional hazard model was used to identify potential risk factors for the time to event data. A p value < 0.05 was significant.

Results: 64 patients were identified. 11 were excluded for incomplete records or inaccurate pathology, and 53 patients were analyzed. Median OS was 214 months (95% Confidence Interval (CI) 60-338). Median follow up was 133 months (95% CI 84-182). Mean age was 53±14 years, 45 (85%) underwent oophorectomy at or prior to diagnosis, 12 (23%) were diagnosed with metastatic disease, 37 (70%) were low grade, 19 (36%) were FIGO stage III-IV. Mean BMI was 29±8 kg/m². 23 (43%) received adjuvant therapy (adjT) of any type (hormonal, chemotherapy, or radiation) and 16 (30%) received hormonal therapy at any time (HRT). 27 (51%) patients had ER or PR testing and 19 (70%) were ER(+) , 20 (74%) were PR (+). The sample size was too small for multi-variable analysis. The Table shows the results of select univariable analysis and OS. Conclusions: Age, initial tumor size, ER and PR status had the greatest impact on survival while BMI, FIGO stage, AdjT or HRT did not. The association between survival and ER or PR status was seen independent of if a patient received HRT. Multicenter collaborative efforts are needed in order to further study the effects of ER and PR status on survival in ESS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT</td>
<td>0.76</td>
<td>0.31-1.90</td>
<td>0.56</td>
</tr>
<tr>
<td>AdjT</td>
<td>0.78</td>
<td>0.34-1.80</td>
<td>0.56</td>
</tr>
<tr>
<td>ER (+)*</td>
<td>0.20</td>
<td>0.06-0.68</td>
<td>0.01</td>
</tr>
<tr>
<td>PR (+)*</td>
<td>0.25</td>
<td>0.08-0.75</td>
<td>0.01</td>
</tr>
<tr>
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<td>0.99-1.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Age (1 year increase)</td>
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<td>1.01-1.08</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Oophorectomy</td>
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<td>0.29-17.1</td>
<td>0.43</td>
</tr>
<tr>
<td>Initial tumor size (1 cm increase)</td>
<td>1.15</td>
<td>1.04-1.28</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FIGO stage (1 stage increase)</td>
<td>1.25</td>
<td>0.90-1.74</td>
<td>0.18</td>
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</table>

*Independent of HRT.
Recombinant adenoviral human p53 gene combined with radiotherapy in treatment-advanced sarcoma.

Jianhao Geng, Shaowen Xiao, Shenwen Zhang; Peking University Cancer Hospital, Beijing, China

Background: Advanced soft tissue sarcoma generally are resistant both chemo- and radiotherapy. P53 gene has multiple anti-tumor functions including sensitizing tumor cells to chemo- or radiotherapy. Methods: Thirty-six patients with advanced, unresectable soft tissue sarcoma, with an age of 48.3±19.1 years old, 19 males and 17 females, were treated with combination of p53 gene and radiotherapy. Recombinant adenoviral human p53 gene (rAd-p53) was given through intratumoral injection at a dose of $2 \times 10^{12}$ rAd-p53 viral particles (VP) once per week for 4-9 times. If tumors spread to the peritoneal cavity with or without malignant peritoneal effusions, $2 \times 10^{12}$ VP diluted into 500 ml of physiological saline was infused into abdominal cavity, once a week for 4 times. Intensity modulated radiation therapy were given at a total dose of 20 – 70 Gy in 2-7 weeks. Results: The overall response rate at 3 months after treatment was 44.4% (16/36, 2/36 in CR and 14/36 in PR). Twenty patients (55.5%) were stable. The tumor in two patients was successfully resected after the combined therapy. Medium overall survival and progress free survival time were 17.8 and 13.5 months, respectively. The survival rates of one year, two years three years, and 5 years were 58.3%, 25.0%, 13.9%, and 8.3%, respectively. Mild or medium fever was observed in all patients after application of rAd-p53. No serious adverse events or complications observed. Conclusions: Combination of local p53 gene and radio-therapy is effective and safe treatment regimen for advanced soft tissue sarcoma.
A phase Ib/II study of imatinib and everolimus in patients with PDGFRA+ synovial sarcoma.

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Background: Our group previously reported that PDGFRA is the most highly overexpressed kinase gene in synovial sarcoma. Our preclinical studies also demonstrated synergistic anti-tumor activity by inhibiting both PDGFRA and mTOR signaling with imatinib and rapamycin respectively in PDGFRA + synovial sarcoma cell lines. Based on these data, a phase Ib/II study to evaluate the toxicity and efficacy of imatinib and everolimus was undertaken. Methods: The primary endpoint of the phase 1b portion of the study was to determine the maximum tolerated dose (MTD) of everolimus administered with imatinib. Starting dose of everolimus and imatinib was 5 mg/day and 400 mg/day respectively. Response rate (RR) by RECIST was the primary end-point of the Phase II study. The phase II study used a Simon two stage design. 9 patients (pts) were to be accrual initially. If there were no responses, further accrual would be stopped and treatment declared ineffective. If there was at least 1 response, an additional 15 pts would be accrued for a total of 24. Key eligibility: metastatic disease, any number of priors. Pre and post treatment tumor biopsies were mandated. Results: 12 pts were treated.5 M and 7 F, median age 44 (range: 22-71), median priors 4 (range: 0 - 6). Two DLTs were observed at dose level 2 (10 mg everolimus /400 mg imatinib) with grade 3 transaminases and hypophosphatemia. Everolimus 5 mg/ imatinib 400 mg was the MTD in the phase II study. 10 pts evaluable for response, included 4 pts treated at the MTD in the Phase 1b study. There were no RECIST responses. Stable disease was observed in 3 pts (7, 7, 19 mos.). Western blot and IHC analysis of matched pair tumor biopsies indicate inhibition of p-AKT, p-S6 and decreases in Ki 67. Conclusions: Imatinib and everolimus failed to achieve its primary response endpoint. However, prolonged stable disease in 3 pts in association with inhibition of PDGFRA and mTOR suggest clinical benefit and biological effect for this drug combination. Clinical trial information: CTEP 8603.
Assessment of multimodality therapy use for extremity sarcoma in the United States.

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Background: National guidelines for extremity sarcoma recommend multidisciplinary consultation, but treatment approaches are not standardized. Our objectives were to (1) examine trends in the multimodality treatment of extremity sarcoma in the US, (2) examine adjuvant therapy practice patterns, and (3) identify factors associated with the use and sequencing of adjuvant treatment. Methods: Using the National Cancer Data Base (2000-2009), use of multimodality treatment for non-metastatic extremity sarcoma was examined. Regression models were developed to identify factors associated with adjuvant therapy receipt and treatment sequence. Results: A total of 22,051 patients underwent resection (Stage I: 45%, stage II: 28%, Stage III: 27%). Trend analysis demonstrated relatively constant rates of radiation therapy (RT) (58% to 65%), chemotherapy (21% to 23%), and any adjuvant therapy (65% to 72%), however the proportion receiving neoadjuvant therapy increased (RT: 14% to 28%; chemotherapy: 9% to 13%; any: 18% to 27%; all p <0.001). Stage-specific treatment use is shown in the table below. Though RT rates were similar for all histologies, chemotherapy rates for synovial sarcoma were higher for all stages (I: 24.3%; II: 24.9%; III: 53.2%, p < 0.001). After adjusting for differences in tumor factors, patients were more likely to receive neoadjuvant therapy (chemotherapy and/or RT) if treated at high-volume academic center (p<0.001). After adjusting for histology, patients were more likely to receive adjuvant radiation therapy if younger, healthier, privately insured, or tumor size >5cm. Patients were more likely to receive adjuvant chemotherapy if were younger, healthier (fewer comorbidities), underinsured, treated at a high-volume academic center, or tumor size >5cm. Conclusions: Use of a multimodality approach for extremity sarcoma management has increased over time, particularly for neoadjuvant therapy. However, practice patterns are related to hospital type and socioeconomic factors. There may remain opportunities to increase multidisciplinary care and multimodality treatment for extremity sarcoma in the United States.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Surgery alone</th>
<th>Adjuvant RT</th>
<th>Adjuvant chemotherapy</th>
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<tbody>
<tr>
<td>I</td>
<td>61%</td>
<td>37%</td>
<td>5%</td>
</tr>
<tr>
<td>II</td>
<td>37%</td>
<td>58%</td>
<td>14%</td>
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<tr>
<td>III</td>
<td>25%</td>
<td>66%</td>
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Relationship of FAP-alpha, ADAM12, WISP1, and SOX11 expression to tumor activity in aggressive fibromatosis: Demonstration of heterogeneity within and between cases.

Benjamin Misemer, Amy Skubitz, Carlos Manivel, Stephen Schmechel, Edward Cheng, Jonathan Henriksen, Joseph Koopmeiners, Keith M. Skubitz; University of Minnesota, Minneapolis, MN

Background: Aggressive fibromatosis (AF) represents a group of tumors with an unpredictable clinical course and is characterized by a monoclonal proliferation of myofibroblasts. The optimal treatment for AF is unclear. In earlier gene expression studies we identified four genes, ADAM12, WISP1, SOX11, and FAP-alpha, that were uniquely overexpressed in AF compared with 16 different normal tissues. This study was designed to examine the expression of these four proteins in AF. Methods: Immunohistochemistry (IHC) was performed in 29 cases of AF, and analyzed by a pathologist with expertise in the field. Automated imaging analysis was performed to independently quantify IHC staining, nuclear size, and nuclear chromatin density. Nuclear size was determined on control slides. Slides were scanned using ScanScope XT (Aperio) and images were divided into tiled regions of interest (ROIs) for measurements. A nuclear chromatin density ratio (CDR), defined as the measure of nuclear area with light staining divided by nuclear area with dark staining, was quantified as a surrogate for nuclear activity. To compare the image analysis with pathologic examination, an operational definition of “morphologic tumor activity” (MTA) was determined by a pathologist using a scale of 1 (inactive), 2 (probably inactive), 3 (probably active), and 4 (active) on a random set of 322 ROIs. The MTA score was then correlated with the CDR. We also assessed the relationship of CDR to IHC staining intensity for each of the four proteins in ~26,000 ROIs derived from all 29 AF samples. Results: Different areas of AF cases had different degrees of MTA. The expression of the four proteins generally correlated with the areas of tumor that were pathologically more “active.” Staining was more intense in areas with larger more open nuclei suggesting “more active” regions. There was a significant correlation between MTA and log [CDR] (0.46, p<0.001). Conclusions: The results confirm, on the protein expression level, our earlier gene expression results, and demonstrate the regional variation of tumor activity within and among AF cases.
Prediction of metastatic behavior in high-grade pleomorphic soft tissue sarcomas by gene expression.

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Background: The biologic heterogeneity of soft tissue sarcomas (STS) complicates treatment. Metastatic propensity may be determined by gene expression patterns that do not correlate well with morphology. In earlier studies, gene expression patterns were identified that distinguish 2 subsets of clear cell renal carcinoma (RCC), serous ovarian carcinoma (OVCA), and aggressive fibromatosis (AF). We reported the use of a gene set derived from these three studies to separate 73 high grade STS into groups with different probabilities of developing metastatic disease (PrMet). We wished to confirm our findings using an independent data set. Methods: We utilized these gene sets, hierarchical clustering (HC), Kaplan-Meier, and log-rank analyses to examine the Affymetrix HU_133 expression profiles of 309 STS. Results: HC using a pooled gene set derived from the AF-, RCC-, and OVCA-gene sets identified subsets of the STS samples. Kaplan-Meier analysis revealed differences in PrMet between the clusters defined by the first branch point of the clustering dendrogram (p=0.048), and also among the 4 different clusters defined by the second branch points (p<0.0001). Analysis also revealed differences in PrMet between the leiomyosarcomas (LMS), dedifferentiated liposarcomas (LipoD), and undifferentiated pleomorphic sarcomas (UDS) (p=0.0004). HC of the LipoD and UDS samples with the pooled probe set divided the samples into 2 groups with different PrMet (p=0.013, and 0.0002, respectively). HC of the UDS samples also showed 4 groups with different PrMet (p=0.0007). In contrast, HC found no subgroups of the LMS samples. Each individual gene set (AF-, RCC-, and OVCA-) separated the UDS samples into subsets of different metastatic outcome, but only the AF- gene set separated the LipoD samples, and no gene set identified LMS subsets. Conclusions: These data confirm our earlier studies and suggest that this approach may allow the identification of more than 2 subsets of high grade STS, each with distinct clinical behavior, and may be useful to stratify STS in clinical trials and in patient management.
Expression of neurotrophins and their receptors in adult sarcomas.

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Background: Neurotrophins (NT) influence proliferation, survival, death, and differentiation by binding Tropomyosin-related kinase (Trk) receptors and p75NTR(CD271). While the three Trk-receptors TrkA, TrkB, and TrkC display specific binding to their ligands, i.e. TrkA to NGF (nerve growth factor), TrkB to BDNF (brain-derived neurotrophic factor), NT4/5 (neurotrophin 4/5) and TrkC to NT3 (neurotrophin 3), CD271 shows low affinity to all neurotrophins. Notably, CD271 has been suggested as marker for the prospective isolation of bone marrow mesenchymal stromal cells (MSC), and rhabdomyosarcomas have previously been found to express neurotrophins and NT receptors. Methods: RNA was isolated from sarcoma cell lines and freshly obtained sarcoma (src) cells from patients after surgical resection. RNA was reverse transcribed and cDNA products underwent PCR analysis with specific primers. Furthermore, cell lines from the same primary tissues were established and treated with doxorubicin. Effects of K252a (Trk receptor inhibitor), Pep5 (CD271-Inhibitor), and neurotrophins on sarcoma cell proliferation and survival were analyzed. Results: An array of freshly obtained clinical src samples (n=10 each subtype) was screened for expression of NT3, NT4/5, BDNF, NGF as well as TrkA, TrkB, TrkC, and CD271. Interestingly, src subtype-specific expression patterns were observed. In the established cell lines, K252a increased doxorubicin-induced tumor cell death, while CD271-Inhibitor Pep5 enhanced proliferation in doxorubicin treated cells, especially under serum free conditions and when combined with BDNF and NGF. Conclusions: NT and NT receptors are expressed on all adult src samples screened in this study. Chemotherapy resistant liposrc as well as myxofibrosrc samples displayed the strongest expression of NT3 as well as TrkB, TrkC, and CD271. The concomitant expression of NT and their receptors suggests autocrine self-stimulation, which may propagate survival, proliferation, and treatment resistance. NT receptor tyrosine kinases may represent an interesting therapeutic target in adult src.
A large retrospective analysis of trabectedin in 885 patients with advanced soft tissue sarcoma.

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**Background:** Trabectedin (Yondelis) is the first marine-derived antineoplastic drug approved in Europe for the treatment of patients with recurrent ASTS or for patients unsuited to receive anthracyclines and ifosfamide. We retrospectively analyzed the RetrospectYon database with patients’ data treated with trabectedin between Jan 2008 - Dec 2011. **Methods:** Trabectedin was given at the approved dose of 1.5 mg/m² as a 24-h infusion every 3 weeks. Patients who achieved partial response (PR) or stable disease (SD) after 6 cycles could receive maintaining trabectedin treatment. Uni- and multivariate analyses of prognostic factors were performed. **Results:** 885 patients (486 women) from 26 centers in France with ASTS with a median age of 54 years (range 12-84) were included. Most had leiomyosarcoma (36%), liposarcoma (18%) or synovial STS (11%). At baseline, performance status (PS) was 0 in 26%, 1 in 47% and >1 in 27% of patients. A median of 4 trabectedin cycles (range 1-28) was given as a 2nd (41%), 3rd (39%) or ≥4th (20% of patients) treatment line. Toxic death and unscheduled re-hospitalization occurred in 0.5% and 8% of patients, respectively. The objective response rate was 15% (6 complete and 127 PR), and SD rate was 45.5% (n=403). After a median follow-up of 22.6 months (range 0.03-51.2), the patients who received trabectedin as 2nd, 3rd or ≥4th line had the median PFS of 4.3, 4.2 and 3.4 months, respectively, and the median OS of 12.9, 12.3 and 9.5 months. Multivariate analysis identified liposarcoma, leiomyosarcoma, angiosarcoma, undifferentiated pleomorphic sarcoma (UPS) and trabectedin line as independent prognostic factors for PFS, and UPS, angiosarcoma, rhabdomyosarcoma, gender, PS and trabectedin line for OS. After 6 cycles, 205 of the 273 patients with non-progressive disease received trabectedin as maintenance treatment and obtained a superior PFS (median 11 vs. 7.2 months, p=0.0001) and OS (median 25.1 vs. 16.9 months, p<0.0001) that those who stopped trabectedin after 6 cycles. **Conclusions:** Patients with ASTS treated with trabectedin had PFS and OS comparable or better to those observed in phase II/III trials. Trabectedin maintenance beyond 6 cycles is associated with improved OS and warrants further exploration.
Efficacy and safety of hypofractionated preoperative radiotherapy in treatment of localized extremity/trunk wall soft tissue sarcoma (STS): Final results of the study.

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**Background:** The primary treatment of STS is surgical resection combined with pre- or postoperative radiotherapy. Conventional fractionation in neoadjuvant radiotherapy is 50Gy (fractions: 2Gy/day). Radiobiological studies shown that alpha/beta ratios of some sarcoma cells are below 10Gy, what is rationale for hypofractionation. Aim of the study was to assess the efficacy and safety of hypofractionated radiotherapy in preoperative setting in patients with STS treated in one institution. **Methods:** 220 patients (median age 54 years) participated in this prospective study (2006-2010). Median follow up is 34 months. 140 patients (64%) had high grade (G3) tumors, median size -9 cm (45% ≥ 10 cm), 68% on lower limb. 137 patients (62.2%) had primary tumors. Preoperative radiotherapy 5x5 Gy per 5 consecutive days was applied, with immediate tumor resection. **Results:** R0 resection was possible in 79%. 61 patients died (3-year overall survival OS 72%), 91 (41%) had disease relapse. Local recurrence (LR) was found in 20% of the patients (3-year LR-free survival 80%). Negative prognostic factors for LR were: tumor size ≥ 10 cm (p=0.037), grade 3 (p=0.0041) and primary vs. recurrent tumor with borderline significance. LRs had significant impact on OS (p=0.0001). 101 patients (46%) had any kind of complications, majority on lower limb (early: 17.2% prolonged healing of the wound > 1 month, 12.7% - wound dehiscence, 4% - prolonged punctures of lymph fluid, 2.7% - acute skin toxicity; late: 0.9% - severe fibrosis with contracture, 11% - prolonged edema, 2.7% - bone fracture), but only 6.3% required additional surgery. **Conclusions:** In this non-selected group of advanced STS use of hypofractionated preoperative radiotherapy was associated with similar local control (80%) when compared to previously published studies. The early toxicity is tolerable, with small rate of late complications. Presented results warrants evaluation in randomized trial.
Sirolimus in advanced hemangioendothelioma.

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**Background:** Haemangioendothelioma (HE) is a very rare vascular tumor. The epithelioid variant is characterized by a specific t(1;3)(p36.3;q25) translocation, resulting in the WWTR1-CAMTA1 fusion product. We retrospectively reviewed patients with HE treated with sirolimus, an mTOR inhibitor, at our institution. **Methods:** We identified 12 patients (M/F: 4/8 – mean age: 46 years – epithelioid HE/ retiform HE: 10/2 – locally advanced/multifocal: 1/11 – pretreated: 6) with advanced HE who were treated with sirolimus, as a single agent, 5 mg/day, from 2005 on. They had evidence of progression in the 3 months before starting treatment. The daily dose of sirolimus was adjusted according to drug blood levels (range 10-20 ng/dl). Response was evaluated with CT/MRI/PET scans after 4-6 weeks of treatment, then every 3 months, by RECIST and Choi criteria. WWTR1 gene rearrangement was evaluated by FISH, and the histochemical expression of mTOR effectors, S6 and 4BP1, is ongoing. **Results:** 10 patients are evaluable for response (2 pts are too early). Sirolimus daily dose ranged from 3 to 6 mg/day. Best response by RECIST was PR = 1, SD = 6 (all >6 months, range 6-48+), PD = 3 cases. In 3 cases, a Choi response could be detected. PET response was observed in 6/6 evaluated case. Median PFS (range) was 24 (3-48) months. Two patients with evidence of tumor stabilization while under sirolimus stopped their treatment after 12 and 24 months of therapy, respectively, with evidence of interval progression in both. A new disease stabilization was obtained after restoring sirolimus. **Conclusions:** HE is known for its potentially long-lasting course, even in typical cases with multicentric/multifocal disease. Progressive HE may require a medical therapy, but is insensitive to cytotoxic chemotherapy, while mainly anecdotal responses were reported to interferon, bevacizumab and thalidomide. In this retrospective series, sirolimus resulted in a high proportion of mainly non-dimensional, possibly long-lasting, tumor responses.
Desmoid tumor (DT): Clinical and treatment characteristics and quality of life (QoL) in a large cohort from a referral center.

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Background: Due to its low incidence, evidence regarding DT is scarce, and consensus on recommended treatment is difficult to achieve. This study systematically assesses clinical presentation, treatment characteristics and QoL in a large cohort of DT patients (pts). Methods: Demographic and clinical variables were retrieved from a database of 224 pts with histologically confirmed DT presenting to our referral center from 10/04-7/12. For a subset of 46 pts, QoL was assessed with the SF-12 questionnaire. The distribution of variables in the entire pt population and clinically relevant subgroups was calculated and compared with appropriate statistics (t-test, nonparametric tests). Denominators varied due to non-availability of variables for some pts. Results: 153 (68.3%) pts were female. Mean age at first diagnosis was 36.9 (3-73) yrs. Primary tumor site was limb/intraabdominal/rectus abdominis/trunk in 40/43/66 (21/22/22/35%) of 192 pts. 65/108 (60%) pts recalled a trauma or medical intervention at the DT site. 38/43 (88%) pts with rectus abdominis DT were female, and 31/38 (82%) had previous pregnancies, median time to DT diagnosis after end of pregnancy was 17 months. Primary therapy was resection/imatinib/tamoxifen/watchful waiting in 136/9/8/7 (83/6/5/4%) of 192 pts. 65/108 (60%) pts recalled a trauma or medical intervention at the DT site. 38/43 (88%) pts with rectus abdominis DT were female, and 31/38 (82%) had previous pregnancies, median time to DT diagnosis after end of pregnancy was 17 months. Primary therapy was resection/imatinib/tamoxifen/watchful waiting in 136/9/8/7 (83/6/5/4%) of 192 pts. Resection was R0/R1/R2 in 47/66/22 (35/49/16%) pts. After R0/R1 resection, DT recurred in 46% and 62% resp. after a median of 356/334 days. Physical/mental SF-12 summary scores were 39.2/40.8, 41.5/45.4, and 48.0/44.5 in pts with limb, intraabdominal, and trunk DT and 38.6/42.6 and 43.3/42.5 in pts with and without recurrence (reference population score 50; all p>0.05 for subgroup comparisons). Five women delivered a healthy child in parallel to clinically existent DT. 56% of our patients are alive with disease, whereas 44% have no evidence of disease. Conclusions: In 83% of DT pts, resection is the first treatment step and is R0 only in one third. 60% of the pts recall trauma/medical intervention at the DT site. Rectus abdominis DT occur after a median of 1.5 yrs after pregnancy. Despite the fact that 56% of our pts live with disease, their QoL is only slightly decreased, with lowest values for physical QoL in pts with recurrence.
Hypoxia, angiogenic markers, and response to neoadjuvant radiotherapy in soft-tissue sarcomas.

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Background: Hypoxia is common in soft-tissue sarcomas (STS) and may correlate with radiotherapy (RT) resistance and worse outcomes. We aimed to quantify intratumoral hypoxia with 18-fluoroazamycin arabinoside (FAZA)-PET in resectable STS and correlate this to 18-fluorodeoxyglucose (FDG)-PET, tumour response, angiogenesis biomarkers and patient (pt) outcomes. Methods: This phase II prospective study enrolled pts with resectable STS prior to neoadjuvant RT. Pts underwent FDG-PET and FAZA-PET prior to RT. Circulating and immunohistochemical (IHC) markers of hypoxia and vessel architecture were measured weekly. Response to RT was measured by surgically resected pathologic necrosis (PN), radiological response and relapse-free survival. Results: 23 pts were recruited. 47% (8/17) demonstrated hypoxia on FAZA-PET with a possible association between hypoxia and enhanced metabolic activity on FDG-PET (FDG SUVmax = 15.33 with hypoxia; SUVmax = 5.86 without hypoxia p = .08). FDG-PET response to RT correlated with PN (good/equivocal FDG-PET response: 59% PN; poor FDG-PET response: 19% PN p = .008). All relapses were distant (n = 10) at average follow up of 5 years. Relapse was associated with higher FAZA-PET SUV (1.94 vs 1.28 p = .02), FDG-PET SUVmax (14.4 vs 6.2 p = .05), and poorer response to RT (PN 36% vs 66%, p = .04). Baseline VEGF-C (531±82pg/ml, mean±SEM) were higher than VEGF-A (35±8pg/ml) and VEGF-D (131±17pg/ml), and correlated with protein expression on IHC staining. Hypoxia on FAZA-PET correlated with lower baseline VEGF-A/C (VEGF-C: 292pg/ml vs 688pg/ml p = .016) and VEGF–A (14pg/ml vs 46pg/ml p = .013). Low VEGF-C correlated with resistance to RT assessed by FDG-PET. In hypoxic tumors after 1 week of RT, VEGF-A and C levels were significantly increased (VEGF-A 80pg/ml vs 14pg/ml; VEGF-C 541ng/ml vs 292ng/ml). Response to RT correlated with less induction of VEGF-A/C. Relapse was associated with lower baseline VEGF and higher IHC levels of other hypoxic markers (GLUT-1, CA 9). Conclusions: In STS, hypoxia is common, measurable, predicts poorer response to RT and is associated with adverse outcomes. Circulating levels of VEGF-C, the dominant isoform, inversely correlated with hypoxia and is induced by RT.
Two doses of NGR-hTNF (N) given alone or in combination with doxorubicin (D) in soft tissue sarcomas (STS).

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Background: N, a tumor-targeted antivascular agent, displays a biphasic dose response curve with activity shown at low dose (LD) or high dose (HD). Vascular effects involve at LD an early vessel stabilization that enhances intratumor D uptake followed by late vessel damage and at HD a rapid vessel disruption.

Methods: STS patients (pts), stratified by prior D dose (> vs ≤ 300 mg/m²), were randomized to N alone given at LD (0.8 μg/m²) in arm A and at HD (45 μg/m²/d1/q1w) in B, or combined with D (60 mg/m²/d1/q3w/6 cycles) at LD in arm C and at HD in D. Primary aim of this 4-arm phase II trial was progression free survival (PFS) with CT scans performed q6w until progressive disease (PD). Using 2-stage design, each regimen was rejected if ≤ 2/14 and ≤ 7/24 pts were PD free at 3 months after 1st and 2nd stage, respectively (β=20%, α=10%, n=96). Secondary aims: adverse events (AEs), response rate by RECIST criteria and early metabolic response (MR), as quantified by fractional change in SUV using FDG-PET according to EORTC criteria

Results: 66 pts have been enrolled and 55 were included in 1st study stage analysis: median age: 57 yrs; male: 30; PS ≤ 1: 26; leiomyosarcomas: 12; median prior lines: 3 (range, 0-7). In all, 488 weekly cycles were given (mean, 9; range, 1-45). Main grade 3/4 AEs were: neutropenia 18%, chills 7%. After first study stage, primary endpoint was met only in arm C (LD N + D), with 7/14 pts PD free at 3 months. Median PFS was 1.3 months (95% CI, 1.1-1.5) for arm A, 1.5 (1.1-1.8) for B, 4.5 (3.6-5.4) for C and 1.3 (1.1-1.5) for D (p=.01 for trend). By RECIST, there were no objective responses and 20/48 (42%) evaluable pts had stable disease (SD), including 1/12 in arm A, 6/12 in B, 9/12 in C and 4/12 in D. Median SD duration in arm C was 5.5 months (95% CI, 3.7-7.3). By FDG-PET imaging done after 3 weeks, 7/30 (23%) assessable pts had partial MR (4 SD/3 PD per RECIST), with mean change in SUV of -34% (SD, ± 12), while 18 pts (60%) had stable MR (7 SD/11 PD per RECIST), with mean change in SUV of 2% (± 11). Median PFS was 4.2 months in pts who achieved partial MR and 1.5 months in pts who did not (HR=0.67). Complete follow-up for arm C and central histology/radiology review are under way.

Conclusions: LD NGR-hTNF plus D is safe, with promising activity as measured by FDG-PET. Clinical trial information: NCT00484341.
Epithelioid haemangioendothelioma.

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Background: Epithelioid haemangioendothelioma (EHE) is a rare vascular tumour which can arise in any site. There is little published data about the clinical behaviour and management of these tumours. Methods: A retrospective review of the management of patients with histologically proven EHE presenting to the Royal Marsden Hospital from January 1999 to January 2012. Demographics, site, treatment and survival outcomes were collected. Results: 28 patients (21 females) were identified with a mean (SD) age of 44 (17). 20 patients presented with diffuse disease involving one or more organs at presentation. The predominant site of disease was identified as liver n=8, mediastinum n=6, lung n=2, limb n=1, pancreas n=1, spleen n=1, back n=1, abdominal wall n=1, oesophagus n=1, neck n=1, pelvis n=1, not known n=2. Median overall survival (Interquartile range) [OS (IQR)] in months was the longest in 10 patients who had localised operable disease at presentation, 116 (71). Amongst those with inoperable disease (n=16), patients with liver disease had the longest OS (IQR), 18 (43) months and those with lung and mediastinal disease had the shortest OS (IQR), 10 (2.5) and 11 (17) months respectively. A variety of treatment modalities were used for patients with inoperable disease and these are summarised in the Table. Conclusions: The clinical behaviour of EHE can vary depending on the site of disease. Surgery, if feasible, has the best outcome. In those with inoperable disease a period of observation to assess the clinical behaviour of the tumour is recommended. Non-steroidal anti-inflammatory drugs are a reasonable, relatively non-toxic first line treatment option. The use of anti-angiogenic drugs merits further exploration.

Management of patients with inoperable epithelioid haemangioendothelioma.

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Number</th>
<th>Median PFS (IQR) in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>3 (on going)</td>
<td>2,635 (1601)</td>
</tr>
<tr>
<td>Cytotoxic chemotherapy</td>
<td>13</td>
<td>119 (92)</td>
</tr>
<tr>
<td>Immunomodulatory drugs</td>
<td>5</td>
<td>128 (51)</td>
</tr>
<tr>
<td>Immunomodulatory drugs and cytotoxic chemotherapy</td>
<td>3</td>
<td>109 (195)</td>
</tr>
<tr>
<td>NSAID</td>
<td>4 (on going in 3 patients)</td>
<td>110 (126)</td>
</tr>
<tr>
<td>NSAID plus other</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor</td>
<td>1</td>
<td>1095</td>
</tr>
<tr>
<td>Cytotoxic chemotherapy and angiogenic</td>
<td>1</td>
<td>147</td>
</tr>
<tr>
<td>Angiogenic</td>
<td>5</td>
<td>127 (225)</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory.
Guidelines for the definitions of time-to-event endpoints in randomized clinical trials: Results of the DATECAN Project for Sarcomas and GISTs.

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Background: With the necessity of reducing randomized clinical trial (RCT) duration, cost and number of patients, surrogate endpoints of overall survival (OS) are increasingly being used as replacement for OS in cancer RCTs. However, most of these endpoints currently lack of standardized definition enabling a comparison of RCT results. Some recommendations have been proposed for specific cancer sites but they do not rely on a formal consensus methodology. The objective of the Definition for the Assessment of Time-to-event Endpoints in Cancer trials (DATECAN) project is to provide guidelines to standardize definitions of time-to-event endpoints in RCTs for different cancer sites. We present results for sarcomas and GISTs. Methods: We relied on the modified Delphi consensus method, a validated formalized consensus process for the development of practice guidelines. International experts with various backgrounds and expertise were involved. First, the coordinating committee, a group of statisticians and epidemiologists involved in the design and conduct of RCTs, led a comprehensive literature review to identify time-to-event endpoints and events of interest. The steering committee, which included additional medical experts, validated the list and prepared the questionnaire sent for rating to an independent expert committee. Results: The consensus process is finalized. It involved 2 rounds of scoring (28 experts) and 1 in-person meeting (in parallel to ASCO’12). Each expert had to rate on a 1-9 scale if s/he agreed or not for including events (e.g. death related to primitive cancer) in the definition of time-to-event endpoints (e.g. progression-free survival). 16 events were rated for inclusion or not in the definitions of 14 time-to-event endpoints. Consensus was reached for 73% of the events after the 2 rounds of scoring. Consensus was finalized at the in-person meeting for the remaining events. Conclusions: The DATECAN guidelines should help standardizing definitions of commonly used endpoints. This process should (i) facilitate the comparison of RCTs and (ii) improve the quality of future RCTs by providing better estimation of sample size and treatment effect.
Synovial sarcoma: Is chemotaxis important to tumor progression?

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Background: Synovial sarcoma (SS) is a rare and aggressive soft tissue tumor. In a first study (Palmerini E, Cancer 2009) we analyzed clinical prognostic factors in a retrospective series of 250 patients (pts) who were treated at Rizzoli Institute between 1976 and 2006. Stage, age, size, histology and use of radiotherapy influenced survival, whereas the role of chemotherapy was unproven. In the present study on the same patient population, in order to identify new prognostic factors and potential therapeutic targets, a panel of markers involved in chemotaxis and tumor growth were assessed.

Methods: The expression of the chemokine receptor CXCR4 (a marker for chemotaxis which plays a critical role in cancer progression) and the insulin-like growth factor receptor-1 (IGFR1) (a marker of growth activation) were evaluated by IHC staining.

Results: Tissue samples were available for the analysis in 88 patients (45 female and 43 male); median age was 37 years (range 11-63); size of the lesion was > 5 cm in 60 patients (71%); histology was biphasic in 30 (34%) of patients. All pts underwent surgery, 56% of pts underwent adjuvant radiotherapy (RT) and 68% adjuvant chemotherapy. With a median follow-up of 6 years (1-30 years), the 5-year overall survival (OS) was 70% (60-81). A positive stain for IGFR1 was detected in 55 pts (62.5%), with expression in the nucleus in 21 pts. CXCR4 was expressed in 74 pts (84%), nuclear pattern in 31 pts. No relation between IGFR1 and CXCR4 expression and clinical variables was found. The 5-year OS was 63% (95%CI 41-85%) for pts with positive IGFR1/nuclear expression and 73% (95%CI 61-85%) p = 0.05, in pts with negative IGFR1/nuclear staining. Similarly, the 5-year OS was 47% (95%CI 27-66%) in patients with positive CXCR4/nuclear expression and 86% (95%CI 76-96%), p = 0.003, in negative cases. In a multivariate analysis including age, histology, size and use of RT, nuclear expression of IGFR1 and CXCR4 were confirmed statistically significant independent factor for OS.

Conclusions: The nuclear expression of CXCR4 or IGFR1 negatively influences the survival in patients with SS. Further studies addressing the role of CXCR4 as a potential target in this high risk subgroup of SS patients are needed.
Metronomic continuous oral cyclophosphamide as second and further line in soft-tissue sarcomas (STS) of the adult.

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Background: In STS third line treatment is poorly defined. However many patients (pts), after aggressive therapy as first and second line progress in their disease ask to be treated. Oral cyclophosphamide (CPM) was already used in breast cancer, prostate cancer and in elderly pts with STS with favourable results. Aim of our study was to define the feasibility, tolerability and activity of oral CPM as third line and further line chemotherapy. Methods: 45 pts (19 M; 26 F) with advanced or metastatic STS heavily pretreated were included. Oral CPM was given daily at total dose of 50 mg/day without interruption excepted for toxicity or progressive disease. Results: Median age was 60 (32-81), histological subtypes were: leiomyosarcoma 12, liposarcoma 10, condrosarcoma 5, sinovialsarcoma 4, sarcoma NOS 4, other 10. Primary sites were: extremities 21, retroperitoneum 19, trunk 5. 41 pts were metastatic, 4 locally advanced. 41 pts were pretreated with chemotherapy (15 were in II line, 17 in III line, 7 in IV line, 2 in V line). Median PS (ECOG) was 2. Median duration of therapy was 4 months (1-38). Progression free survival (PFS) ranged from 0 to 42+ months (median 4 months). Treatment was well tolerated, we registred only one episode of leucopenia G2 and one of asthenia G2. No complete responses were seen. Only 3 minimal responses and 18 stable disease were seen. Conclusions: Oral CPM showed a mild activity and good tolerability in advanced soft tissue and metastatic STS. It could be an appropriate solution as second line and further therapy and in unfit or elderly pts.
Identification of potential molecular biomarkers for response of soft tissue sarcoma to eribulin: Translational results of EORTC trial 62052.

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Background: The phase II study EORTC 62052 demonstrated potential antitumor activity of eribulin, a tubulin-interacting cytotoxic agent, which is a synthetic analogue of the natural compound halichondrin B, in patients with various subtypes of metastatic soft tissue sarcoma (STS) including leiomyo- (LMS) and adipocytic (ADI) sarcomas, but not synovial sarcomas (SYN) and other sarcoma histotypes (OTH) (Schöffski P et al. Lancet Oncol. 2011;12:1045). In addition to histotypes, we aimed to identify potential biomarkers responsible for eribulin sensitivity or resistance to eribulin using gene expression and miRNA profiling. Methods: From 68 consenting patients archived tumor tissue was collected, including 22 LMS, 15 ADI, 10 SYN and 21 OTH sarcoma histotypes. Total RNA was isolated from 65 samples and analyzed using GeneChip Human Exon ST Array (for mRNA expression) and Taqman Low Density Array (for miRNA). Progression free survival (PFS) at week 12 (RECIST 1.0) was the primary endpoint of the clinical trial and used for correlative studies. Eighteen out of 56 (32.1%) evaluable patients in this analyzed subset had non progressive disease at week 12 (“responders”). Results: Overall expression of 62 transcripts including ALS2CR11 (uncorrected p<0.001) and 26 miRNAs (p<0.05) differed significantly between non-responders and responders. Additional transcripts and miRNAs were identified when considering the different histological groups (Table). Conclusions: The level of (mi)RNA expression in soft tissue sarcoma samples may predict response of soft tissue sarcoma to eribulin. Further validation studies are required.

<table>
<thead>
<tr>
<th>Number of differentially expressed transcripts</th>
<th>Number of differentially expressed miRNAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downregulated*</td>
<td>Upregulated*</td>
</tr>
<tr>
<td>All STS</td>
<td>20</td>
</tr>
<tr>
<td>Subtypes**</td>
<td></td>
</tr>
<tr>
<td>ADI</td>
<td>58</td>
</tr>
<tr>
<td>LMS</td>
<td>11</td>
</tr>
<tr>
<td>OTH</td>
<td>66</td>
</tr>
</tbody>
</table>

*In responders. ** SYN subgroup not taken into account as only one patient reached PFS at 12 weeks.
Incidence and predictive factors of late relapse in patients with soft tissue sarcomas: Implications for prolonged follow-up.

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Background: There is no consensus on how to follow soft-tissue sarcoma (STS) patients after their initial management. In particular, the incidence of late relapse which would justify prolonged surveillance is unknown. Methods: Follow-up data were reviewed from 719 patients with localized STS, included in the French Sarcoma Group database from January 1990 to June 2005, and who achieved complete remission maintained for at least five years after their initial management. The outcomes of interest were the cumulative probabilities of late (>5 years) local and metastatic relapse with death as a competing event. Estimations and 95% confidence intervals (CIs) were computed with the cumulative incidence function. Patients who did not experience the event of interest or death over the course of the study were censored at their last follow-up. Results: 67 (9.3%) and 42 (5.8%) patients had late local and metastatic relapse respectively. On univariate analysis, internal trunk location, liposarcoma histological subtype, tumor size >10 cm, R1 margins, no adjuvant radiotherapy were significantly associated with increased risk of late local relapse. On multivariate analysis, internal trunk location (HR = 3.9, 95% CI 2.2-6.7, p<0.001) and tumor size >10 cm (HR = 2.1, 95% CI 1.1-4, p=0.03) were the two factors independently associated with local relapse. On univariate analysis, leiomyosarcoma histological subtype, and grade >1 were significantly associated with increased risk of late metastatic relapse. On multivariate analysis, grade >1 (HR = 4.7, 95% CI 1.1-21, p=0.04) was the sole factor independently associated with the risk of late metastatic relapse. Conclusions: Late relapse of STS (>5 years after initial management) is relatively uncommon. However, its existence and our results emphasize the critical role of long-term follow-up to detect late local recurrence in patients with retroperitoneal or very large STS and late metastatic recurrence in patients with high grade disease.
Impact of adjuvant treatments on local and metastatic relapse of soft-tissue sarcoma patients in the setting of competing risks.

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**Background:** Competing risk is the risk of an event that interferes with the probability of experiencing the disease-specific outcome of interest. Indeed, the occurrence of a competing risk (for instance death by local relapse or another cause) may preclude the onset of the event of interest (for instance metastatic relapse) or at least modify its probability. Competing risk is ignored by Kaplan Meier method and standard Cox survival model. **Methods:** 3369 adult patients with localized STS were included prospectively in the French Sarcoma Group (GSF) database from January 1990 to December 2009. The outcomes of interest were the cumulative probabilities of local (LR) and of metastatic (MR) relapse with death as a competing event. Estimations and 95% confidence intervals (CIs) were computed with the cumulative incidence function. **Results:** Median follow-up was 4.5 years. 1-year and 5-year cumulative incidence of LR were 6.4% (95% CI 5.6-7.3) and 25.9% (95% CI 24.2-27.6), respectively. Age, histological subtype, anatomic site and grade were independently associated with the cumulative probability of LR. After adjustment to these prognostic factors, adjuvant radiotherapy was associated with a significant impact on LR (HR = 0.5 95% CI 0.4; 0.6, p <0.001). The magnitude of this effect was similar whatever the grade or the anatomic site. Because of the competing effect of death, adjuvant chemotherapy had no significant impact on the cumulative probability of LR. 1-year and 5-year cumulative incidence of MR were 7.4% (95% CI 6.5-8.3) and 26.9% (95% CI 25.2-28.7), respectively. Tumor depth, histological subtype, tumor size and grade were independently associated with the cumulative incidence of MR. After adjustment to these prognostic factors, adjuvant chemotherapy was associated with a significant impact on MR (HR = 0.5 95% CI 0.4-0.7, p < 0.001) in grade 3 but not in grade 2 patients (HR = 1.3 95% CI 0.9-1.9, p = 0.1). **Conclusions:** Adjuvant radiotherapy was associated with improved LR outcome even in patients with high risk of competing death from metastatic disease or other causes. Adjuvant chemotherapy was associated with improved MR outcome in patients with grade 3 but not grade 2 disease.
Background: T is a marine-derived cytotoxic alkaloid approved in the European Union for further-line chemotherapy of advanced STS. Most common side effects are fatigue, neutropenia and transient transaminitis. Overall the drug is well tolerated with no cumulative toxicity. Studies in elderly pts are lacking. Methods: We retrospectively reviewed all pts 65 year-old, with pre-treated advanced STS, who received T at our Institution from January 2002 to January 2013, focusing on tolerability. All patients received premedication with dexamethasone 4 mg p.o. bid 24 hours prior to T administration. Treatment toxicity was graded according to CTCAE (v 4.0). Results: Fourty-two pts were identified (males = 22, females = 20; median age = 69 years, range 65-82; ECOG PS 0 = 1 pt, 1 = 38 pts and 2-3 = 3 pts; main histotypes = 22 liposarcoma: 12 myxoid-round cell liposarcoma, 10 well/dedifferentiated liposarcoma, 17 leiomyosarcoma, 2 synovial sarcoma, 4 others; disease extent = 34 metastatic and 8 locally advanced; median line of administration of T= 3rd, range 1st-5th; median T dose = 2.2 mg, range = 2.7-1.7 mg). A total of 319 cycles were administered (median 6, range = 1-23). Starting dose was 1.3 mg/mq in 37 pts and 1.1 mg in 5 pts. The most common side effects were: fatigue (all grades: 19% of cycles), reversible myelosuppression, mainly neutropenia (grade 3-4: 50%), transient transaminitis (grade 3-4: 21%). Eighteen pts needed a dose reduction: inter-cycle transient transaminitis (3 pts), neutropenia ( 13 pts), asthenia (2 pts). In 7 patients, cycles needed to be delayed as well. Three pts interrupted T due to toxicity: grade 3 thrombocytopenia in 1 pt and grade 4 neutropenia in 2 pts. Conclusions: This retrospective analysis confirms that T is well tolerated in elderly pts. No major differences were found in the safety profile compared to historical controls, except a higher incidence of myelosuppression, which however was not influential on subsequent T administration.
Targeted next generation sequencing of sarcomas for identification of therapeutic targets.

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Background: Sarcomas are a diverse group of mesenchymal tumors with significant heterogeneity. Evolving personalized cancer care strategies require identification of recurrent genomic alterations that can be targeted therapeutically. Due to the rarity of these tumors and lack of fresh or frozen tissue in routine clinical practice, DNA sequencing has been a challenge. Objective: To demonstrate the feasibility of a next-generation sequencing (NGS) platform that utilizes archival formalin-fixed paraffin-embedded (FFPE) tissue to evaluate the spectrum of DNA alterations seen in sarcomas. Methods: Study population included 35 consecutive patients with advanced sarcoma presenting to the sarcoma center at MD Anderson Cancer Center beginning August 2012 with archival FFPE tissue available for NGS. DNA was extracted from FFPE samples and used for hybridization capture and NGS on the Illumina HiSeq 2000 platform. A total of 182 cancer-associated genes and 37 introns of 14 commonly rearranged genes were evaluated for genomic alterations. In the absence of an individual–matched normal control, germline variations were removed using dbSNP and the remaining variants were classified on the basis of current knowledge of specific variants from cancer databases such as COSMIC. Results: 35 patients (10 Angiosarcomas, 9 Leiomyosarcomas, 3 synovial sarcomas, 13 other subtypes) underwent DNA extraction with a median yield of 3376 ng tumor DNA. The average sequencing depth was >900X. 43% of patients had point mutations/indels previously described in COSMIC and/or in known mutation hotspots. 54% of patients showed structural variants such as amplifications, deletions or rearrangements. 68% of genomic alterations are in genes that are actionable. We identified an apparently novel variant in KDR T771R in 2/10 patients with angiosarcoma. KDR amplifications were identified in 20% of patients with angiosarcoma. Outcomes of matched targeted therapy of patients with actionable targets will be presented with more mature follow-up. Conclusions: Targeted NGS of DNA from archival FFPE tissue is feasible with the potential for identifying actionable targets and discovery of novel mutations.
Prognostic significance of radiologic and histologic response to neoadjuvant chemotherapy in localized synovial sarcoma.

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Background: The role of neoadjuvant and adjuvant chemotherapy in localized synovial sarcoma (SS) is still controversial. Histologic response to neoadjuvant chemotherapy is an independent prognostic variable in bone sarcomas. Data regarding the prognostic value of response to neoadjuvant chemotherapy in STS are limited.

Methods: 68 patients with localized STS, treated with neoadjuvant anthracycline/ifosfamide-based chemotherapy and assessable for response to chemotherapy were included prospectively in the French Sarcoma Group (GSF) database from 1985 to 2011. All the cases were reviewed by the pathology subcommittee of the GSF. Radiological response to chemotherapy was assessed according to RECIST criteria. Good response was defined as partial response or stable disease according to RECIST and ≤10% recognizable tumor cells in the surgical specimen. Poor response was defined as stable or progressive disease according to RECIST and ≥ 50% recognizable tumors cells in the surgical specimen. All the other cases were defined as intermediate response.

Results: Median age was 38 years. Median tumor size was 8 cm (range 2-20). 56% of tumors were located in the limbs and 52% were grade 3. Response to chemotherapy was considered as good in 9 cases (13%), intermediate in 20 cases (29.5%) and poor in 39 cases (57.5%). Median metastasis-free (MFS) and overall (OS) survivals were 45 (95% CI 11-79) and 84 months (95%CI 88-120), respectively. On univariate analysis, grade, tumor size and response to chemotherapy were significantly associated with metastasis-free survival (MFS). Radiological response according to RECIST has no prognostic value. On multivariate analysis, grade was the sole variable independently associated with MFS (HR=3.4, 95% CI 1.5-7.5, p=0.003). On univariate analysis, grade, and response to chemotherapy were significantly associated with overall survival (OS). On multivariate analysis, grade was the sole factor independently associated with OS (HR=2.5, 95% CI 1.2-5.7, p=0.03).

Conclusions: Response to neoadjuvant chemotherapy may not have prognostic value in patients with SS. Grade represents the most significant predictive factor of outcome in this setting.
Isolated limb perfusion for soft-tissue sarcoma and regional melanoma.

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**Background:** Isolated limb perfusion (ILP) represents a treatment option for locally advanced melanoma and sarcoma confined to a limb. The advantage of this approach is to deliver high-dose regional chemotherapy without serious systemic effects. However, the ILP technique involves a complex and invasive operative procedure, requiring accurate monitoring to avoid major local toxicity. **Methods:** From November 2004 to December 2011, 58 patients underwent IPL for unresectable soft tissue sarcoma (STS=34) and advanced in-transit melanoma (n=24). IPLs were performed at mild hyperthermic conditions with 1-2 mg of TNF and 40-80 mg of melphalan (M) for arm and leg perfusions, respectively. The response rate, disease free intervals, overall survival, toxicity and limb salvage rate were evaluated. **Results:** Median age was 68 years (range: 29-91 years), with 58% of women. For sarcoma patients, median tumor size was 60 mm, 16 patients (47%) had a high grade STS. Twenty-one patients (61%) received IPL before definitive surgery. Eight patients finally underwent amputation, giving a long-term limb salvage of 77%. The overall response rate was 73.5% (Complete response rate 14.7%, partial response rate 58.8%). For melanoma patients, 9 (38%) had an AJCC stage III disease, the median thickness of the primary tumor was 3.5 mm. A complete response was obtained in 21% of patients while 54% exhibited a partial response. The local and metastatic recurrence rates were similar between sarcoma and melanoma patients (41% and 33% respectively). All but one of the patients with non-operated sarcoma presented a local or metastatic relapse. There was no mortality and no systemic toxicity. Regional toxicity (Wieberdink scale) was: grade I (no reaction) 53 %, II (erythema, oedema) 34%, III (blistering) 8% and IV 3%. The median local relapse-free survival was 40 months in sarcoma group (26.6 months for non operated patients) and 10 months in melanoma one. The overall 3-years survival rate was 44% for sarcoma and 25% for melanoma patients. **Conclusions:** ILP induces a high tumour response rate, leads to a high limb salvage rate but is associated with an important recurrence rate. It provides a limb salvage alternative to amputation when local control is necessary.
Poor prognostic features in angiosarcoma: A single institution retrospective study of 324 patients.

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Background: Angiosarcoma (AS) is a rare, malignant endothelial cell tumor of vascular origin with a five year overall survival (OS) of approximately 35%. It is a heterogeneous disease whose natural history is poorly defined. We sought to identify clinical and treatment outcomes to better define this disease. Methods: In a retrospective study using an institutional sarcoma database, we identified all patients(pts) with AS treated at Memorial Sloan-Kettering Cancer Center between 1992-2011 and collected their correlative clinical information. Kaplan-Meier method and Cox’s proportional-hazard models were used to determine OS and prognostic factors. Hazard ratios (HR) are listed with their 95%confidence intervals (CI). Results: We identified 324 pts, median age was 63 (range 15-94), 127(39%) were men. At presentation, 188 (58%), 19 (6%) and 117(36%) had localized disease (L), local recurrences (LR) or distant metastases (M), respectively. L sites included: RT breast 43 (23%), head&neck 33 (18%), scalp 30 (16%), breast 26 (14%), extremity 23 (12%), abdomen/pelvis 14 (7%), thorax 10 (5%) and trunk 9 (5%). The median OS is 3.3 years (2.44-4.33) for pts w L disease and 0.89 years (0.74-1.11) for pts with M disease. Among pts that presented with L disease, 29% had a LR and the median local relapse free survival (RFS) time was not reached (8.71-NA); 31% had distant recurrences with a median distant RFS of 12.8 yrs (4.13-NA.) Among L disease patients, older age (HR 1.04, 1.03-1.06, p <0.0001) and site were independent predictors of decreased OS. Visceral tumors arising in the abdominal/pelvis (AP) (HR 2.89, 1.27-6.61, p = 0.012) had worse OS compared to those arising the breast. Conclusions: AS remains an aggressive, heterogeneous malignancy with poor OS and high rates of local and distant recurrences. Patients with M disease do poorly. Adverse prognostic factors include AP visceral tumors and older age. These factors could be helpful for stratification in future clinical trials. The identification of genomic differences is necessary to define therapeutic targets in AS.
Serum protein acidic and rich in cysteine (SPARC) as a prognostic marker in soft tissue sarcoma.

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**Background:** SPARC is a matricellular secreted glycoprotein that performs several functions, including modulating cellular adhesion and proliferation. It has been implicated in tumorigenesis and identified as an adverse prognostic factor in a number of cancers. The specific mechanisms involved have yet to be identified. Agents targeting SPARC-expressing tumors, such as nanoparticle albumin-bound-paclitaxel (NAB-P), have been developed. Soft tissue sarcomas (STS) represent a heterogeneous group of tumors with inadequate systemic therapies. Our objective was to explore the pattern of SPARC expression and its prognostic significance in STS. **Methods:** Formalin-fixed paraffin-embedded tissue sections were stained by immunohistochemistry using a mouse monoclonal antibody for SPARC (Abnova). Staining intensity was scored blindly. Patient survival was determined from patients’ medical records. Kaplan-Meier and log-rank analyses were used to compare survival by SPARC expression level. **Results:** 27 tissue specimens of various STS subtypes were investigated (Table). Elevated SPARC expression was observed in 56% of specimens, but did not correlate with underlying histology. Overall survival segregated into 2 groups based on SPARC levels. Patients who expressed low-to-moderate levels of SPARC exhibited median survival of 22.1 months, while the median survival of patients with moderate-to-high expression levels was 4.4 months (log rank; \( p = 0.0016 \)). **Conclusions:** A significant proportion of STS specimens exhibit elevated SPARC expression. Elevated SPARC does not correlate with underlying histology, although analysis of a greater number of specimens might reveal subtypes with more frequently elevated expression. Overall survival segregates strongly by degree of SPARC expression, with elevated expression being adverse. Our results suggest that analysis in STS of agents targeting SPARC, such as NAB-P, should be stratified by extent of SPARC expression.

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<th>Subtype or STS subtypes</th>
<th>Median survival (months)</th>
<th>Survival range (months)</th>
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<td>Low SPARC</td>
<td>22.1</td>
<td>4 – 32</td>
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<tr>
<td>High SPARC</td>
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Adjuvant radiotherapy (adj RT) for extremity and trunk wall atypical lipomatous tumor/well-differentiated LPS (ALT/WD-LPS): A French Sarcoma Group (GSF-GETO) study.

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Background: The role of adj RT in the management of ALT/WD-LPS remains controversial. Methods: 284 patients (pts) with operable ALT/WD-LPS, no history of previous cancer, CT or RT, treated between 1984 and 2011 and registered in the Conticabase database were included and described. Overall (OS) and local relapse free (LRF) survival were evaluated from the time of first treatment (trt). Their distributions were estimated by Kaplan-Meier method and compared between RT groups using Log-Rank test. Independent prognostic factors and adj RT, were explored with Cox model. Results: Among the 20 centers, 3 enrolled 58% of the pts. Median age at diagnosis was 61 (range 25-94), 146 pts (51%) were males, 223 (79%) pts had distal tumors while 35 (12%) and 26 (9%) had tumors involving the girdle and the trunk wall. The median size of primary tumors was 17 cm (range 2-48), 272 (96%) lesions were deep seated, 24 (9%) were multifocal within the same anatomical area. Surgery quality was unknown for 42 pts. Among the remaining pts, 102 (43%) were R0, 130 (54%) R1 and 8 (3%) R2. Adj RT was given to 129 pts (45%). Pts who received adj RT had larger tumors (p=0.034), involving more often the distal limbs (p<0.001) and were more often multifocal in the same anatomical area (p=0.009). The use of adj RT varied across centers and along the study period. Other characteristics, including margin resection, were balanced between RT groups. Median follow-up for the whole population was 38.6 months (mo) (CI 95% [34.0-47.6]): 51.9 mo [43.0-62.3] for the RT group and 30.7 mo [23.3-37.8] for the surveillance group (Surv). None of the pts developed metastasis during follow-up. With 23 LR, 4 in the RT group and 19 in the Surv group, 3-years LRF rates were 98.8% [91.8-99.8] vs 90.4% [82.3-95.0] with and without adj RT (p<0.001). Once stratified on time period (before/after 2003), adj RT, age and margin resection (R0 vs other) were independently associated with LRF. No OS difference was observed (p=0.151). Conclusions: In this study, adj RT following resection of ALT/WD-LPS was associated with a reduction of local recurrence risk. More prolonged and homogeneous follow-up is required to confirm these results.
Preoperative Tru-Cut biopsy (POB) for the diagnosis of retroperitoneal soft tissue sarcomas (RPS) and risk of local recurrence (LR) compared to primary surgery of the tumor.

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Background: Regardless optimal surgery LR is still a major challenge in RPS affecting 60% of the patients (pts). To improve these results pre-operative radiotherapy +/- chemotherapy are under investigation. This strategy requires to perform a POB. The surgical removal of the whole needle track is mandatory for limb sarcomas, but it can hardly ever be achieved in RPS. We explored whether POB did increase the risk of LR in terms of tumor cell seeding (along the needle track) or in the tumor mass area. Methods: We scanned our prospectively (01/2000 to 12/2010) collected RPS database including 176 pts. Complete information (records, CT scans, biopsy-track, follow up data) were available and retrospectively examined in 100 pts. Pts were divided into: group A (POB), group B (direct surgery). The 7 year probability of disease free survival (DFS) was estimated for each pt (ASCO 2012 abs 10000). T student test and Fisher’s exact test were used to compare the estimated DFS and the incidence of LR in the 2 groups, respectively. Kaplan-Meier method was used to estimate DFS and overall survival (OS). Results: In 51 male, 49 female, median age 58 years (22-81) RPS histotype distribution was: lipo 43, leio 28, pleomorphic 9 and other 20. RPS grades were: G1 29%, G2 32%, G3 39%. POB was performed in 25 pts (25%) without major complications. The baseline probability of 7 year DFS was 0.43 and 0.51 (p = .24) for group A and B, respectively. After a median follow up of 71 mos, LR was 8% and 23% (p > .05) for group A and B, respectively. No relapse along the needle track was detected. As expected, liposarcoma was associated with a higher rate of LR (Odds Ratio 5.6 CI 95% 2-13). Median DFS, local DFS and OS were 24, 88 and 71 months, respectively. Conclusions: With the limit of the retrospective nature of our data, we didn’t find any increased risk of LR for POB in RPS. Although surgery is still the standard therapy in RPS, knowledge of histotype and differential diagnosis might encourage to consider inclusion of pts into pre-operative clinical trials and to avoid surgery for other retroperitoneal tumors (e.g. lymphomas, germinal cell tumors, IgG4-related sclerosing disease).
Incidence of brain metastases and overall survival in patients with primary cardiac sarcoma: A retrospective case series.

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Background: Primary cardiac sarcoma (PCS) is the most common primary cardiac malignancy, but is a rare primary site of sarcoma. We present 21 cases from a tertiary care center to better understand this uncommon malignancy. Methods: A cancer center-based registry and pathology database were searched to identify pts diagnosed with PCS from 1992-2013 at University of Michigan. Kaplan-meier method was used to estimate survival. Cox proportional hazard model was used to associate variables to occurrence of metastases (mets) or death. Results: A total of 21 pts (12F, 9M) with PCS were identified, median age 36 (range 11-74). The most common presenting symptoms included dyspnea (16) and chest pain (6; 5 with associated pericardial effusion). Histologies included: angiosarcoma (9), leiomyosarcoma (4), undifferentiated pleomorphic (3), spindle cell (2), fibrosarcoma (1), rhabdomyosarcoma (1) and synovial (1). Sites of origin were R atrium (7), R ventricle (2), L atrium (10) and pericardium (2). Ten pts presented with mets; most common sites were lung (8), liver (2), brain (2), pancreas (2) and bone (2). Surgery was attempted in 12 pts, achieving 1 R0 resection. Pts received a median of 1 (0-7) systemic therapies. Median overall (OS) was 12.6 mos (range 3-79) from diagnosis. Pts without prior surgery were more likely to have mets or death (p=0.038). Brain mets were common, occurring in 7 of 21 pts after a median of 7 mos (range 1-75) from diagnosis. Median OS after diagnosis of brain mets was 8 mos. Of the 7 pts who developed brain metastasis, 5 had PCS originating in the left heart. Of the 2 pts with PCS in the right heart, one was evaluated for and had a right to left shunt. The likelihood of developing brain mets did not correlate with age, chemotherapy, or surgery. Conclusions: PCS portends an extremely poor prognosis, marked by inability to achieve complete resection and a high incidence of disseminated disease at diagnosis. Metastatic disease to the brain was much more common in PCS (33%) as compared to STS of any origin (approximately 1-8%), particularly in pts with PCS originating in the left heart. Clinicians should have a low threshold for brain imaging evaluation of PCS pts.
Targeted radiofrequency ablation of metastatic posterior vertebral body lesions in patients with soft tissue sarcomas.

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Background: Metastatic spinal lesions can be debilitating with significant impact on patients quality of life. Concern for damage to adjacent neural elements during treatment exist due to high radiation doses required to treat certain radioresistant spinal lesions such as soft tissue sarcoma. Radiofrequency ablation (RFA) of metastatic lesions has been shown to be effective in bone. Spine anatomy presents challenges for minimally invasive (MI) treatment of posterior vertebral body lesions. Targeted RFA (t-RFA) using a novel tumor ablation system, designed for spinal anatomy is evaluated in patients with symptomatic posterior vertebral wall spinal lesions. Methods: Five patients with metastatic leiomyosarcoma or liposarcoma and posterior vertebral body spine lesions, treated by prior radiation with continued progression of lesion size and pain received t-RFA, using a novel spinal tumor ablation system (STAR, DFINE), which contains an articulating bipolar, extensible electrode for navigation. Device thermocouples (TC) permit real time monitoring of the ablation zones to determine size. Sequential post-procedural pain scores, PET and contrast enhanced magnetic resonance imaging, and histopathology of treated area was performed. Results: No complications or thermal injury occurred. Intra-procedural imaging demonstrated the articulated, bipolar instrument was able to navigate to posterior lesions. Post-ablation MRI demonstrated lesion necrosis within a discrete ablation zone. No evidence of malignancy by PET or histopathology was noted through 10 months. All patients reported post procedural pain relief. Systemic therapy was not interrupted. Conclusions: Navigational t-RFA proved a safe and effective, non-ionizing palliative therapy alternative for radioresistant lesions. Post-ablation imaging and histology confirmed metastatic lesions were necrotic and included in ablation zone with tumor control 10 mos post treatment. Ablation zone was very consistent with real time temperature readings. t-RFA permitted MI targeted treatment of lesions within close proximity of spinal cord, not controlled by systemic therapy. Prospective clinical trial is under preparation.
Nuclear SMAD4 as a predictor of survival in patientes with extremity soft tissue sarcomas submitted to neoadjuvant chemotherapy.

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Background: Neoadjuvant chemotherapy for locally advanced soft tissue sarcomas, although not standard, represents a promising option for resectable tumours. The discovery of biological predictors of chemotherapy response highlights the possibility to develop individualised therapeutic approaches in selected group of patients or predict survival also. The SMAD4 protein, a member of TGFβ superfamily has a role in progression and tumor metastasis and may be involved sarcomas recurrence. Methods: 30 patients with soft tissue sarcomas (STS) of high-grade located in extremities treated with neoadjuvant doxorubicin and ifosfamide chemotherapy were observed prospectively since January 2005 to June 2011. All patients were submitted to radiation therapy adjuvant. Surgical specimens after neoadjuvant treatment were evaluated of SMAD4 nuclear expression by immuno-histochemistry and percentage of viable cells

Results: The median follow-up time was 42 months. The overall survival (OS) was 91.7% in patients with low expression SMAD4 nuclear protein associated with ≤10% of viable cells (n=12) in the surgical specimen and 68.9% in the remaining patients. Likewise, the disease free survival (DFS) was 91.7% versus 38.6% (p 0.01) respectively. Conclusions: The combination of nuclear SMAD4 low expression and 10% or less of viable cells in the surgical specimen was statistically significant in better DFS in patients with locally advanced extremity STS treated with neoajuvant chemotherapy with benefit in OS.
A phase II trial of novel anthracycline amrubicin in advanced soft tissue sarcoma.

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Background: Amrubicin is a 9-aminoanthracycline with significantly less cardiotoxicity than doxorubicin, a current standard against soft tissue sarcoma, and may represent an appealing alternative first line therapy. We report findings in a phase II study investigating tolerability and efficacy of amrubicin in patients with advanced STS. Methods: We enrolled adult patients in a single-arm open label study with locally advanced or metastatic soft tissue sarcoma, no prior systemic treatment, measurable disease, an ECOG PS ≤2, and adequate organ function. We administered amrubicin (40 mg/m² IV over 10’) on D#1-3 of a 21D cycle with GCSF support. Six cycles were planned with continuation at clinician discretion. We used RECIST 1.1 to radiologically assess response to therapy. Toxicities were assessed using CTCAE 4.0. The primary objective was overall response rate (CR+PR), and clinical benefit (CR+PR+SD). We employed a 2-stage design, with 15 patients treated in the first stage. Error rates were α=5% for accepting a poor regimen and β=10% for rejecting a promising regimen, with planned enrollment of 30 patients through the second stage if activity was observed. Results: 15 of 15 planned patients enrolled in the first stage of this phase II clinical trial; 10 males and 5 females, with median age 59 (range 30-73). Of the 13 evaluable patients, at 6 cycles 3 patients achieved a PR, with best response of 78% reduction of target lesions; 4 patients demonstrated minor response/stable disease (SD), ranging from 11-28% reduction of target lesions, and 4 patients had minor progression/SD (less than 20% progression). Two patients progressed >20%. Clinical benefit is currently 85.7% (12/14). Amrubicin has been well tolerated, with primarily grade I and II AEs. A single dose adjustment has occurred but no treatment delays. No cardiac complications, ECG or significant echocardiogram changes have been noted. Conclusions: Amrubicin is a novel anthracycline with encouraging activity against STS and an extremely well tolerated side effect profile. Further study of amrubicin in STS is warranted. With minor treatment-related morbidity, amrubicin would also be a good candidate for combination therapy with other standard or experimental therapeutics. Clinical trial information: NCT01259375.
Background: Kaposi sarcoma (KS) is a multifocal angioproliferative disorder. VEGFR2-3, PDGFR and c-kit are implicated in KS pathogenesis and inhibited by sorafenib (So). KS is commonly HIV-associated. The antiretroviral drug ritonavir (R) inhibits CYP3A4, and may affect So metabolism and tolerability.

Methods: We performed a phase I study of So in KS. HIV+ patients (pts) were eligible if on combination antiretroviral therapy (cART) for >3 months with progressive KS or >4 months with no KS regression. Dose level 1 for pts on R-containing cART (R1) was So 200 mg daily, for pts not receiving R (NR1) So 200 mg every 12 hours. Treatment cycles were 21 days. So pharmacokinetic assessment performed cycle 1 day 8. Adverse event (AE) grade (Gr) by CTCAE v3.0 (2006-10) and v4.0 (2011-12). KS response graded by modified ACTG criteria.

Results: 10 pts, R1 (8), NR1 (2). Baseline characteristics: median (med) (range) age 49 (35-72), CD4 in HIV 500 cells/uL (35, 747), time on cART 9 months (3.5, 27), previous KS therapies 2 (0-5). 9 HIV-infected, 8/9 HIV viral load <50 copies/mL. 6 had KS-associated edema. Med number cycles 4 (1, 13). Common AE at least possibly attributable to So: anemia, AST/ALT elevation, lipase elevation, hypertension, proteinuria, fatigue, infection, voice alteration. Dose-limiting toxicities (DLT): R1- Gr3 asymptomatic elevated lipase (1), Gr4 thrombocytopenia (1, likely due to multicentric Castleman disease); NR1- Gr3 hand-foot syndrome not resolved by week 6 (1). Other Gr 3-4 AE: R1-hand-foot syndrome (1), Gr3 thrombocytopenia (1), Gr3 transient cerebral ischemia (1), Gr3 hypertension (1); NR1- Gr3 hypertension (2). Best response: partial response (PR) (2), stable disease (SD)(5), progressive disease (1), not evaluable (2). Med duration SD 12 weeks (5, 33). 5/6 with KS-associated edema had objective decrease in edema. R was not associated with clear difference in So C_{Max} or AUC at steady state.

Conclusions: Preliminary estimate of PR or better is 20%. Even in some cases where KS did not respond, KS-associated edema improved. However, So was relatively poorly tolerated, with DLT observed at R1 and NR1, and these doses did not yield better responses than established therapies. Additional studies evaluating R’s effect on So metabolites are warranted. Clinical trial information: NCT00287495.
A prospective multicenter phase II study of sunitinib in patients with advanced aggressive fibromatosis.

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**Background:** There have been reports on responses and prolonged disease stabilizations with imatinib which may be associated with PDGFR-β pathway and KIT mutation in the treatment of aggressive fibromatosis (AF). Sunitinib has not only PDGFRs, KIT, and FLT3 inhibiting activity, but also VEGFRs blockade as antiangiogenesis. The aim of this study is to evaluate the efficacy and safety of sunitinib for patients with advanced AF. **Methods:** Nineteen patients with pathologically proven AF were accrued between Jun 2008 and Mar 2012. Sunitinib was administered with 37.5 mg/day for 4 weeks without break, comprising one cycle. Primary endpoint was response rate. **Results:** Ten (53%) patients were female and the median age was 30 years (range, 22-67). Most of the primary sites were intra-abdominal (12, 63.2%), and AF associated with familial adenomatous polyposis was observed in 10 (52.6%). With a median 6 cycles per patients (range, 1-47 cycles), 5 (26.3%) achieved a partial response and 8 (42.1%) had stable disease; the overall response rate was 26.3% (95% CI, 6.3-45.7) in intention-to-treat analysis. With median follow-up time of 20.3 months (range, 1.8-50.7), the 2-year progression-free survival and overall survival were 74.7% and 94.4%, respectively. Grade 3 or 4 adverse events of sunitinib with frequency > 5% of patients included neutropenia (33.3%), diarrhea (5.3%), and hand-foot syndrome (5.3%). In 3 patients out of 12 patients with mesenteric AF, mesenteric mass bleeding (n=1), bowel perforation (n=1), and bowel fistula (n=1) with tumor mass necrosis, were observed during an early period of sunitinib. **Conclusions:** Sunitinib showed potential antitumor activity and was relatively tolerated in patients with AF, especially non-mesenteric AF. Further investigation of sunitinib treatment is necessary in patients with AF.
Evaluating surgery and first-line imatinib (ima) treatment patterns for patients with gastrointestinal stromal tumors (GIST).

Michael Eaddy, Brian S. Seal, Mark R. Green, Dana Staffey-Mailey; Xcenda, Palm Harbor, FL; Bayer HealthCare Pharmaceuticals, Wayne, NJ

Background: In 2002, ima was FDA approved for advanced metastatic GIST, followed in 2008 with an indication for adjuvant therapy. Real-world data on changing patterns of ima therapy, including adjuvant management, is sparse. This study evaluated changes in treatment patterns, resection rates, and corresponding costs of care among patients receiving first-line (1LT) ima for GIST over an 8-yr period, with a breakpoint around time of initial reporting of phase III adjuvant therapy data showing survival benefit.

Methods: The study was conducted Jan 1, 2003–Dec 31, 2010 utilizing pharmacy/medical claims data from a large health plan. Patients with a GIST-related ICD9 code who also received ima were eligible, and excluded if they received any chemotherapy prior to date of first diagnosis or ima. All were designated into 1 of 3 cohorts: metastatic disease at first recognition (MP), non-metastatic non-surgical (NS) patients, and non-metastatic patients undergoing a GIST-related surgical procedure before ima (SP). Patients were followed from diagnosis to end of study period or loss of continuous eligibility. Results: Patient assignment across the disease extent and surgery/no surgery cohorts by the phase III reporting event is shown in the Table. A change in distribution of primary disease presentation and/or management across two time intervals is suggested by marked decrease in percentage of MP (54.9% → 36.1%) and greater than doubling of SP patients presumably receiving adjuvant therapy following initial resection attempt. In the study population, 18.8% of patients who initiated 1LT with ima went on to 2LT (73.7% sunitinib); 5.9% receive 3LT (44.4% nilotinib and 38.9% sorafenib); <1% receive 4LT (66.7% sorafenib). In general, 1LT was more costly than subsequent therapies. Across all lines of care, oral TKI drug acquisition cost was the dominant determinant of total cost of care. Conclusions: A change in distribution of primary disease presentation and/or management across the two time intervals is suggested. In each cohort, overall cost of care was largely a function of TKI acquisition cost.

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A randomized, double-blinded, placebo-controlled, multi-institutional, cross-over, phase II.5 study of saracatinib (AZD0530), a selective Src kinase inhibitor, in patients with recurrent osteosarcoma localized to the lung.

Kristin Baird, Denise K. Reinke, Joseph Gerald Pressey, Noah Federman, Neyssa Marina, Sant P. Chawla, Joanne Pigues Lagnay, John M. Goldberg, Mohammed M. Milhem, David Mark Loeb, James E. Butynski, Katherine A. Janeway, Brian Turpin, Arthur P. Staddon, Sheri L. Spunt, Eve T. Rodler, Scott Schuetze, Scott H. Okuno, Lee J. Helman; National Cancer Institute, Bethesda, MD; Sarcoma Alliance for Research through Collaboration, Ann Arbor, MI; University of Alabama at Birmingham, Birmingham, AL; Children’s Hospital Los Angeles, Los Angeles, CA; Department of Pediatrics, University of California, Los Angeles, Los Angeles, CA; Stanford University, School of Medicine, Palo Alto, CA; Sarcoma Oncology Center, Santa Monica, CA; Nationwide Children’s Hospital, Gainesville, FL; University of Miami, Miller School of Medicine, Miami, FL; University of Iowa Hospital and Clinics, Iowa City, IA; The Johns Hopkins University, Baltimore, MD; Dana-Farber Cancer Institute, Boston, MA; Cincinnati Children’s Hosp Med Ctr, Cincinnati, OH; University of Pennsylvania, Philadelphia, PA; St. Jude Children’s Research Hospital, Memphis, TN; Seattle Cancer Care Alliance, Seattle, WA; University of Michigan, Ann Arbor, MI; Mayo Clinic, Rochester, MN; Center for Cancer Research, National Cancer Institute, Bethesda, MD

Background: Osteosarcoma is a rare cancer and 33% of patients who have completed primary treatment will recur. The Src pathway has been implicated in the metastatic behavior of several tumors including osteosarcoma where 95% of samples express Src or have evidence of downstream activation of this pathway. Saracatinib (AZD0530) is a potent and selective Src kinase inhibitor. The recommended phase II dose in adults was found to be 175mg daily. The primary goal of this study is to determine if treatment with Saracatinib can increase progression free survival (PFS) for patients who have undergone complete resection of metastatic osteosarcoma nodules in the lung. Secondary goals are evaluation of overall survival, time to treatment failure, and evaluation of several biological correlatives. Methods: This is a multi-institutional, phase II.5, placebo-controlled study with an accrual goals of 88 randomized patients. Patients between 15 and 75 years, with histological confirmation of recurrent osteosarcoma, localized to the lung, who have potential for complete surgical resection, are eligible for enrollment. After complete resection, patients are randomized to treatment with saracatinib or placebo, of a daily oral dose of 175 mg, continuously for up to 1 year or until progression. Patients who recur in the lung while on-study and who are amenable to complete surgical resection will be un-blinded. Those patients who received placebo may have the option to undergo surgical resection. If fully resected, they will be offered therapy with saracatinib under the same treatment guidelines as above. As of January 2013, 38 patients have enrolled and 32 patients met the criteria to be randomized and began oral therapy with either saracatinib or placebo. An interim analysis is planned after 40 patients have been randomized. Clinical trial information: NCT00752206.
Alliance A091103: Multicenter phase II study of the angiopoietin-1 and -2 peptibody trebananib for the treatment of angiosarcoma.

Sandra P. D’Angelo, Michelle R. Mahoney, Brian Andrew Van Tine, Douglas Adkins, Maria T. Grosse Perdekamp, Mercedes M. Condy, Eliza Hartley, Cristina R. Antonescu, Gary K. Schwartz, William D. Tap, Alliance Clinical Trials in Oncology Group; Memorial Sloan-Kettering Cancer Center, New York, NY; Mayo Clinic, Rochester, MN; Washington University in St. Louis, St. Louis, MO; Washington University School of Medicine in St. Louis, St. Louis, MO; Cancer Care Specialists of Central Illinois, Chicago, IL; Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Angiosarcomas (ASs) are rare, aggressive, malignant endothelial cell tumors that constitute 1% to 2% of all soft tissue sarcomas with 5-year survival of 35%. Cytotoxic agents have demonstrated response rates of about 15%. Gene-array data from MSKCC has revealed up-regulation of endothelial associated genes, including active members of the angiopoietin system e.g., Tie2 and Angiopoietin 2 (Ang2). Trebananib (AMG386) is a novel agent that targets Ang1 and Ang2. We hypothesize that inhibition of angiopoietin 2 with trebananib will be an effective therapy in patients (pts) with AS. Methods: This CTEP sponsored, investigator initiated, multi-center phase II study uses trebananib, in pts with AS having metastatic/unresectable AS and conducted through the Alliance for Clinical Trials in Oncology (Alliance A091103). Pts must have adequate performance status, organ function, and measurable disease (RECIST v1.1). Patients are treated with trebananib 30mg/kg d1, 8, 15, and 22 every 28 days until either progressive disease or unacceptable toxicity. The primary endpoint is objective overall response rate (ORR) via RECIST v1.1. Secondary endpoints include the evaluation of progression-free survival (PFS) and overall survival (OS). Translational objectives include correlation of ORR, PFS and OS with i. baseline and post-treatment expression of Ang2 and Tie2 by immunohistochemistry (IHC), ii. serum levels of Ang1 and Ang2, iii. baseline and post-treatment phospho-receptor tyrosine kinase (p-RTK) status of Tie2, VEGFR-2, PI3K, MEK and MAPK, and iv. mutational status of VEGFR-2 and amplification of MYC/FLT4. A Simon Optimal two-stage phase II study design is used and one confirmed response in the first 12 pts expands enrollment to 25. Pre- and post-treatment biopsies will be performed in up to 10 pts treated at MSKCC. Enrollment began in July 2012. As of January 2013, 7 pts have been recruited. Clinicaltrials.gov#: NCT01623869. Funded by the Alliance Clinical Trials in Oncology. NIH Grant CA-25224. Clinical trial information: NCT01623869.
A phase II study of oral ENMD-2076 administered to patients (pts) with advanced soft tissue sarcoma (STS).

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Background: The use of angiogenic and Aurora kinase inhibitors has been shown to abrogate tumour growth in STS. ENMD-2076 is an oral Aurora A and angiogenic kinase inhibitor that has demonstrated single-agent activity in sarcoma cell lines. Prior phase I dose escalation study has determined the maximum tolerated dose of ENMD-2076 to be 160mg/m², with a recommended starting dose of 275mg/day. In that study, one patient with STS experienced durable stable disease (21 months). Primary Objective: To determine the activity of ENMD-2076 in advanced STS (with ≤1 prior line of therapy) as defined by 6-month progression-free survival rate (PFSR). Secondary Objectives: (i) To determine the safety and tolerability of ENMD-2076, (ii) To determine the objective response rate (ORR) as per RECIST criteria and duration of response, (iii) To perform exploratory analysis of factors associated with survival. Study Design and Methodology: This is a single-center, open-labeled phase II study of ENMD-2076 in advanced STS. Pts are commenced on 275 mg daily dose on a 28 day cycle. Treatment-emergent adverse events will be assessed by the NCI-CTCAE (4.0). Radiographic or clinical tumour measurements will occur every 2 cycles. Sample Size Justification: It is assumed that ENMD-2076 shall be deemed non-efficacious in this population if the true 6-month PFSR probability is ≤15% (p0), whilst a 6-month PFSR probability ≥40% will be considered positive for activity. This translates to a minimum of 21 evaluable subjects required in the study, within which ≥6 patients need to have shown lack of progression at 6 months in order for this study to be considered positive. This design has a significance level of 10% and power of 90%. Methods: PFSR at 6-months will be estimated using the Kaplan-Meier method. ORR will be estimated and 2-sided 95% exact binomial confidence interval will be provided. Study Progress: At deadline for abstract submission, 3 patients have been enrolled onto this study. Clinical trial information: NCT01719744.

Alliance A091102: Phase II study of MLN8237 (alisertib) in advanced/metastatic sarcoma.

Mark Andrew Dickson, Michelle R. Mahoney, Benjamin T. Marchello, Mercedes M. Condy, William D. Tap, Gary K. Schwartz; Memorial Sloan-Kettering Cancer Center, New York, NY; Mayo Clinic, Rochester, MN; Montana Cancer Consortium, Billings, MT

Background: Approximately 13,000 cases of soft tissue and bone are diagnosed annually in the US. Despite primary surgery many patients develop recurrent disease. Response rates to chemotherapy are low and new agents are needed. Gene array studies have shown Aurora Kinase A (AURKA) commonly overexpressed. Inhibition of AURKA by shRNA or by a specific AURKA inhibitor blocks in vitro proliferation of multiple sarcoma subtypes. MLN8237 (alisertib) is a novel and oral, ATP-competitive, selective small-molecule inhibitor of AURKA. We hypothesize that alisertib will be an effective treatment for advanced/metastatic sarcoma.

Methods: This CTEP-sponsored, investigator-initiated, multi-center phase II study uses alisertib in patients with advanced/metastatic sarcoma and is conducted through the Alliance for Clinical Trials in Oncology (Alliance A091102). Patients must have adequate performance status, organ function, and measurable disease (RECIST v1.1). Patients are enrolled in one of five cohorts, depending on histology: 1) liposarcoma, 2) leiomyosarcoma, 3) undifferentiated sarcoma, 4) malignant peripheral nerve sheath tumor, or 5) other. Patients are treated with alisertib 50mg PO BID d1-d7 every 21 days until either progressive disease or unacceptable toxicity. The primary endpoint is objective overall response rate (ORR). Secondary endpoints include progression-free survival (PFS) and overall survival (OS). Translational objectives include correlation of ORR, PFS and OS with baseline and post-treatment markers of AURKA inhibition in tumor biopsies and baseline and post-treatment [F-18] FLT-PET scans. A Simon two-stage design is used for each of the 5 cohorts and one confirmed response in the first 9 patients expands enrollment in that cohort to 24. Enrollment began in December 2012. As of January 2013, 14 pts have been enrolled. Funded by the Alliance for Clinical Trials in Oncology. Clinical trial information: NCT01653028.
Phase I/II study of the safety, pharmacokinetics, and efficacy of pomalidomide in the treatment of Kaposi sarcoma in individuals with or without HIV.

Mark Niccolo Polizzotto, Thomas S. Uldrick, Kathleen Wyvill, Karen Aleman, Irini Sereti, Giovanna Tosato, Denise Whitby, Margaret Bevans, Frank Maldarelli, William Douglas Figg, Seth M. Steinberg, Robert Yarchoan; HIV/AIDS Malignancy Branch, CCR, National Cancer Institute, Bethesda, MD; HIV Pathogenesis Unit, LIR, National Institute of Allergy and Infectious Diseases, Bethesda, MD; Laboratory of Cellular Oncology, CCR, National Cancer Institute, Bethesda, MD; Viral Oncology Section, Frederick National Laboratory for Cancer Research, Frederick, MD; Clinical Center, National Institutes of Health, Bethesda, MD; Host-Virus Interaction Branch, HIV Drug Resistance Program, CCR, National Cancer Institute, Bethesda, MD; Molecular Pharmacology Section, National Cancer Institute, National Institutes of Health, Bethesda, MD; Biostatistics and Data Management Section, CCR, National Cancer Institute, Bethesda, MD

Background: Kaposi sarcoma (KS) is a multicentric angioproliferative tumor seen most frequently in people with HIV. It is caused by the gammaherpesvirus Kaposi-sarcoma associated herpesvirus (KSHV, or human herpesvirus 8) and is remarkable for its tendency to progress or regress based on host immune factors. Pomalidomide is an orally available third generation thalidomide derivative with immunomodulatory and antiangiogenic properties that may address unmet clinical needs in KS. Methods: The primary objective is to assess the safety, tolerability and pharmacokinetics of pomalidomide in subjects with KS, whether HIV associated or not, and to explore its antitumor effect at the tolerable dose once determined. This is the first assessment of this agent in patients with HIV and/or KS. Subjects with confirmed KS and no symptomatic pulmonay or visceral KS are eligible. Those with HIV must be compliant with HAART; have achieved an HIV viral load <10,000 copies/mL; and in the phase II portion have KS increasing despite HAART and HIV suppression for ≥2 months, or stable despite HAART for ≥3 months. In the phase I portion, up to 6 subjects will be treated with pomalidomide 5mg orally daily for 21 days of a 28 day cycle. Subject to evaluation of adverse events and tolerability, this may be deescalated to 3mg orally daily 21 of 28 days in a second cohort of up to 6 subjects. If either dose proves tolerable, the study will proceed to the phase II portion, and enroll up to 15 HIV positive and 10 HIV negative subjects. Antitumor activity will be assessed using modified ACTG KS response criteria in parallel with quality of life assessment. Key correlative studies include evaluation of immune responses including T cell numbers and activation in peripheral blood and tumor tissue and KSHV specific T-cell responses; HIV and KSHV activity and associated cytokines; and the first exploration of effects of pomalidomide pharmacokinetics when administered with common antiretroviral agents. Progress: The study opened to accrual in January 2012. The phase I portion is complete with no DLTs at the dose of 5mg 21 of 28 days. Phase II has accrued 11 subjects (4 HIV negative, 7 HIV positive) at this dose. Clinical trial information: NCT01495598.