Efficacy and safety of nivolumab and trabectedin in pretreated patients with advanced soft tissue sarcomas (STS): Results of a phase II trial of the German Interdisciplinary Sarcoma Group (GISG-15, NitraSarc).

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Background: Programmed death-1 (PD-1) inhibitors alone have modest activity in the treatment of most STS. A possible synergistic effect of combined trabectedin with PD-1 inhibitor nivolumab has been previously reported. Herein we evaluated the efficacy and safety of trabectedin plus nivolumab as a second-line treatment of patients with anthracycline-pretreated metastatic or inoperable STS. Methods: The prospective, explorative, two-group, non-randomized phase II NiTraSarc trial enrolled patients with advanced lipo- or leiomyosarcomas (Group A; GA) or with non-L-sarcomas (Group B; GB). Patients were initially treated with 3 cycles of trabectedin 1.5 mg/m², followed by the combination of trabectedin 1.5 mg/m² plus nivolumab 240 mg in a so-called “late combination cohort” (LCC) for up to 16 cycles. After positive results of a preplanned interim analysis, patients received the combination therapy already starting from Cycle 2 in an “early combination cohort” (ECC). Primary efficacy endpoint was progression-free survival rate after 6 months (PFSR6) according to RECIST v.1.1. A central pathological assessment (CPA) was done from tumor specimen from all patients. Updated results according to CPA are presented. Results: A total of 92 patients were recruited in the trial: 43 patients in GA and 49 in GB. In GA, 28 patients (63%) had leiomyosarcoma and 15 (37%) had liposarcoma. Most common sarcoma types in GB were pleomorphic (n = 12), spindle cell (n = 11), fibromyxoid (n = 6), synovial (n = 5) and epithelial (n = 4) sarcoma. After median follow up of 16.6 months, overall PFSR6 as per CPA in GA was 47.6% (60% in LCC vs 36.4% in ECC) and 14.6% in GB. Median PFS was numerically higher in GA compared to GB (5.5 vs 2.3 months) and even longer in LCC vs ECC (9.8 vs 4.4 months). Median overall survival was more than three times longer in GA vs GB (18.7 vs 5.6 months) and, again, longer in LCC vs ECC (24.6 vs 13.9 months). Safety trabectedin and nivolumab was consistent with the safety profiles of each drug alone with no relevant new findings for the combination between ECC and LCC. Conclusions: Our study confirms the activity of trabectedin plus nivolumab, particularly in patients with lipo- or leiomyosarcomas. There is a significant difference between ECC and LCC in terms of PFSR6, PFS and OS. The results in patients with non-L-sarcomas do not justify further investigation of this combination. Clinical trial information: NCT03590210. Research Sponsor: University Medicine Greifswald, Germany; PharmaMar, Bristol-Myers Squibb.
A single-arm, open-label phase 2 trial of doxorubicin plus zalifrelimab, a CTLA-4 inhibitor, with balstilimab, a PD-1 inhibitor, in patients with advanced/metastatic soft tissue sarcomas.

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Background: Doxorubicin (DOX) is the standard of care for unresectable soft tissue sarcomas (STS). DOX induces immunogenic cell death in numerous preclinical models. Immune checkpoint inhibitors (ICIs) including antibodies (ab) to PD-1 and CTLA-4 have shown modest activity, but most STS are immune “cold” tumors and do not respond. We hypothesized that concurrent DOX would improve immunogenicity of STS and boost efficacy of ICIs, including anti-CTLA-4 ab zalifrelimab (ZAL) and anti-PD-1 ab balstilimab (BAL).

Methods: We conducted a single arm Phase 2 trial of combination DOX/ZAL/BAL for patients (pts) with advanced/metastatic STS in the 1st/2nd treatment lines without prior DOX or ICI (NCT04028063). The study was a Simon minimax 2-stage design to accrue 28 pts evaluable for primary endpoint of progression-free survival rate at 6 months (PFS6mo) by RECIST 1.1. We aimed to improve PFS6mo by 20% with DOX/ZAL/BAL over null rate of 43.4% based on average PFS of 2 prior DOX monotherapy trials. Secondary endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS), duration of response (DOR), and adverse events (AEs). All pts received up to 6 DOX cycles with concurrent ZAL/BAL; pts on stage 1 began DOX at cycle 2 with ZAL/BAL at cycle 1, pts on stage 2 began DOX/ZAL/BAL at cycle 1. Imaging was obtained prior to the first dose of DOX (baseline), and then every 6 weeks (wks) to 6 mo, and thereafter every 9 wks. Tumor biopsies/peripheral blood were obtained at baseline, on-treatment, and progression for immune profiling.

Results: 35 patients were accrued as of 1/25/23. 25 pts are currently evaluable for primary endpoint of PFS6mo and 28 for efficacy (at least one post-treatment scan). PFS6mo is estimated at 52% (95%CI 31-72), with mPFS of 25.6 wks (24.0-44.9). ORR was 36% (19-56), and DCR was 86% (67-96). Median DOR was 12.8 wks (range 6 – 105). Most pts with PR who progressed did so on BAL after DOX completion. Responses were observed in pts with intimal sarcoma, angiosarcoma, MPNST, LPS, LMS, endometrial stromal sarcoma, UPS, and sclerosing epithelioid fibrosarcoma. Improved outcomes were observed in stage 1 pts compared to stage 2 pts, including PFS6mo (56.3% v. 25.0%), mPFS (31.7 v. 25.3 wks), ORR (56% v. 8.3%), and DCR (94% v. 75%). Toxicity was as expected with grade 3/4 TRAEs in 48% of 31 evaluable pts, primarily DOX-related hematologic AEs, and immune-related AEs requiring steroids in 19% of pts.

Conclusions: Combination DOX/BAL/ZAL led to meaningful efficacy, including favorable PFS6mo and responses in several STS subtypes unlikely to respond to DOX or ICI monotherapy. Further investigation is required to determine if the stage 1 priming dose of ZAL/BAL prior to DOX improved clinical outcomes. An ongoing cohort is exploring a next-generation CTLA-4 inhibitor, botensilimab in combination with DOX +/- BAL. Clinical trial information: NCT04028063. Research Sponsor: Agenus Bio; Cancer League of Colorado; University of Colorado Cancer Center.
ImmunoSarc2: A Spanish Sarcoma Group (GEIS) phase Ib trial of doxorubicin and dacarbazine plus nivolumab in first line treatment of advanced leiomyosarcoma.

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Background: The immunogenic death caused by certain chemotherapy agents consists of molecular changes in tumor dying cells that stimulate immunogenicity and enhance antitumor effects. Doxorubicin is one validated drug related to immunogenic death, mainly through calreticulin membrane translocation that elicits immunogenic signals as phagocytosis by dendritic cells. Doxorubicin+pembrolizumab was explored in a phase I/II trial treating patients with metastatic/unresectable sarcomas, achieving 22% PR, 59% SD, and 19% PD, with mPFS of 8.1 months superior to historical controls. We hypothesized that the addition of an anti-PD1 (nivolumab) would increase the antitumor activity of commonly used upfront polychemotherapy in leiomyosarcoma (LMS) of doxorubicin plus dacarbazine. We present here the phase Ib, cohort 7b of ImmunoSarc2 trial.

Methods: Adult patients (pts), with ECOG 0-1, naïve of previous anthracycline-containing treatments and with centrally confirmed diagnosis of advanced/metastatic leiomyosarcoma (LMS) were eligible. Initial dose level 0 (L0) was defined as doxorubicin (DOX) 75 mg/m²/d 20 min on D1 followed by dacarbazine (DAC) 400 mg/m²/d 60 min on D1 and 2, plus nivolumab (NIV) 360 mg on D2 after DAC Q3W with GCSF support. This combo would be given up to 6 courses of 21-day cycles, followed by 1-year NIV maintenance. A -1 dose level (L-1) was defined with the same regimen but with NIV 240 mg. A classic 3+3 phase 1 design was used to determine the MTD based on DLTs (main endpoint) observed during the first 21-day cycle. The cohort was foreseen to be extended with the RP2D up to 20 evaluable patients. Secondary endpoints included ORR and safety profile among others. Results: Between January 2022 and February 2023, 20 pts (M/F 6/14), ECOG 0/1 (15/5), with median age 54 years (31-72) were enrolled. All patients were treated with the initial L0 scheme and no DLTs were observed being L0 the RP2D. Grade 3-4 toxicities were neutropenia (20%), anemia (10%), febrile neutropenia, asthenia, and GGT increased (5% each). Four pts are not evaluable for efficacy (1 due to uncompliant dosing and 3 for not reaching the first tumor assessment yet). Of 16 efficacy-evaluable pts, RECIST ORR according to local clinical site assessment was 9 PR (56.2 %), 6 SD (37.5%), and 1 PD (6.3%) (2 SD cases had tumor size reductions > 20%). Five pts ended treatment due to progression (4 radiological, 1 clinical) and 15 pts remain under the trial therapy. mPFS for evaluable patients was 8.67 months (95% CI: 7.96-9.37) with a median follow-up of 8 months (2-12).

Conclusions: DOX 75 mg/m²/d on D1 followed by DAC 400 mg/m² on D1 and 2, plus NIV 360 mg on D2 after DAC Q3W, followed by 1-year NIV maintenance is a feasible and well-tolerated scheme. Clinical activity is encouraging improving historical efficacy outcomes in first line of advanced LMS, which deserves further testing in phase II trials. Clinical trial information: NCT03277924. Research Sponsor: Drug supply, shipping and insurances were provided by BMS and Pfizer. Operational expenses were in charge of GEIS group.
A multicenter phase II study of cabozantinib + nivolumab for patients (pts) with advanced angiosarcoma (AS) previously treated with a taxane (Alliance A091902).

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Background: Collectively, sarcomas have demonstrated less benefit from immunotherapy than many other cancers. Pts with AS have limited options, particularly after taxane chemotherapy. Although AS is a vascular malignancy, anti-VEGF therapies have minimal monotherapy clinical activity. Some cutaneous AS have a high UV damage signature, but other AS often do not. Cabozantinib (C) is a multikinase inhibitor that may alter PD-1 expression in regulatory T cells, promoting an immune permissive environment when combined with nivolumab (N), a fully human anti-PD-1 MAB. We hypothesize that the combination of C+N will be an effective therapy in AS, across AS subtypes.

Methods: This open-label multi-arm study enrolled pts with locally advanced/metastatic AS. Arm 3, reported here, enrolled pts who had received a taxane for AS (including adjuvant) prior to study enrollment. Pts were not restricted on number of prior lines, but prior anti-VEGF and immunotherapies were not allowed. Eligible pts received C (40 mg po daily) with N (480 mg IV every 4 wks). Treatment was permitted beyond progressive disease (PD) in the 1st 12 wks (4 wk confirmatory scan), but PD response was censored at 12 wks. The Simon 2-stage design (null and alternative overall response rate (ORR) were 10% and 35%, respectively) required ≥1 confirmed response in 9 pts in the 1st stage, and ≥4 of 18 pts (91.4% power, alpha 0.095) for the primary endpoint. Secondary endpoints were adverse events (AEs), progression free, overall survival (PFS, OS), and pt-reported outcomes (PRO).

Results: 21 eligible pts [median age 66 yrs (32-92), 10 female] received 1 dose of C+N. Primary disease sites: 12 cutaneous (scalp/face), 1 liver, 2 breast, 6 other. All pts received prior taxanes (11/21 = 52% as adjuvant therapy) and 5/21 (24%) had also received prior anthracycline (all relapsed AS). Primary endpoint: 13 of the first 18 evaluable patients (72%) experienced objective response (OR, 95%CI: 47%-90%). After a median follow-up of 11.2 mo, 13 of 21 pts achieved OR (11 partial response, 2 complete), for ORR 62% (95%CI: 38-82%). Responses were seen in pts with primary cutaneous disease 7/12 (58%) and noncutaneous disease 6/9 (67%). Median PFS was 9.6 mo (5.3-NR), and OS 20.5 mo (14.4-NR). Off treatment reasons include: progressive disease (14), comorbid condition unrelated to AS or study (1); 6 pts remain on study. Grade (G) 3 hypertension was the only possibly treatment related AE (TRAE) occurring in 310%. No G 4/5 TRAE were reported. Conclusions: C+N demonstrated significant antitumor activity in taxane-pretreated AS and was well tolerated without new safety concerns. Activity of the combination was seen across AS subtypes. PRO and exploratory analyses are ongoing. Support: U10CA180821, U10CA180882, U24 CA196171; U10CA180820; https://acknowledgments.alliancefound.org. U10CA180868; U10CA180888. NCT04339738. Clinical trial information: NCT04339738. Research Sponsor: U.S. National Institutes of Health.
Randomized phase II trial of cabozantinib combined with PD-1 and CTLA-4 inhibition versus cabozantinib in metastatic soft tissue sarcoma.

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A phase II study of cabozantinib and temozolomide in patients with unresectable or metastatic leiomyosarcoma and other soft tissue sarcomas.

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Background: Potentiation of chemotherapy, without increased toxicity, to improve outcome is an area of interest. Preclinical and clinical evidence shows simultaneous utilization of antiangiogenic agents and chemotherapy have a synergistic effect. We hypothesized that the dual targeting of VEGF and c-MET pathways with cabozantinib (CAB) would result in clinical benefit for patients with soft tissue sarcoma (STS) when combined with temozolomide (TMZ), an alkylating agent. Utilization of CAB/TMZ is anticipated to produce a synergistic antitumor effect worthwhile to explore in STS. Methods: A multicenter phase II study of CAB/TMZ in patients with unresectable/metastatic leiomyosarcoma (LMS) and other STS was conducted by the Midwest Sarcoma Trials Partnership. Age $\geq$ 18, adequate performance status, organ function, measurable disease (RECIST 1.1), and 0-5 prior chemotherapy regimens were required. CAB 40 mg PO daily plus TMZ 150-200 mg/m² PO 1-5 days were given in 28-day cycles until disease progression or unacceptable toxicity. Patients enrolled in 2 cohorts: 1. Uterine and non-uterine LMS 2. Other STS. The first 14 subjects to be enrolled in the study in either cohort served as a safety lead in. The primary endpoint was progression-free rate (PFR) at 12 weeks for cohort 1. Secondary endpoints include overall response rate (ORR), clinical benefit rate, median progression-free survival (PFS), overall survival, and safety and tolerability. The exploratory endpoint was to estimate the correlation of PFR and OS to expression levels of VEGF, amongst others. A Simon 2-stage design was used. Results: A total of 42 patients were enrolled in Cohort 1, and 30 in Cohort 2, across 5 sites. For Cohort 1, median age was 59 years (range 35-86), 85.7% were non-Hispanic, 73.8% were female, 61.9% had ECOG of 0. The PFR at 12 weeks was 45.9% (for 37 evaluable patient) with a median PFS of 6.4 months (95% CI 4.6-6.7). Five PR were observed for an ORR of 13.5%. For Cohort 2, median age was 63 (20-86), 83.3% were non-Hispanic, 36.7% were female, 53.3% had ECOG of 0. The PFR at 12 weeks was 50% (for 28 evaluable patients) with a median PFS of 3.2 months (95% CI 1.4-4.6). One PR was observed. Reported grade 3-4 adverse events attributed to one or both intervention drugs affecting $\geq$ 10% of patients (n = 70) included hypertension (10%), decreased neutrophils (18.7%), decreased platelets (31%). Conclusions: The combination therapy of CAB/TMZ in patients with unresectable or metastatic LMS exceeded its primary endpoint with a PFR at 12 weeks $> 39\%$. The PFS of 6.4 months in Cohort 1 exceeds rates achieved with second line tyrosine kinase inhibitors (TKIs) and alkylators in LMS patients. Treatment was feasible and did not reveal any previously unreported toxicities. The combination with CAB with TMZ demonstrated meaningful clinical benefit and is worth further exploration in LMS. Clinical trial information: NCT04200443. Research Sponsor: Exelixis.

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Background: The ISG-STS 1001 was an international, randomized, phase III, clinical trial for localized, high-risk, soft tissue sarcoma comparing neoadjuvant chemotherapy (ChT) with a standard regimen of epirubicin plus ifosfamide (EI) versus an histology-tailored regimen (HT) in five histologic types, within the context of an integrated multimodality strategy. In addition, in this study, a parallel group of patients (pts) was not randomized but just registered and treated with EI. Radiation-therapy (RT) could be delivered either pre-operatively (concurrent to ChT) or post-operatively, according to clinical judgement. Final results of ISG-STS 1001, published in 2020, showed a benefit in favor of EI, in terms of overall survival, in comparison to HT. Herein, we analyzed tolerability and activity of ChT with EI either in the standard arm of the trial or in the parallel group, whether alone and concurrent to RT. Methods: The EI regimen was made up of epirubicin 120 mg/m² plus ifosfamide 9 g/m². RT was delivered at a dose of 44-50 Gy pre-operatively or 60-66 Gy post-operatively. In the current analysis, toxicities related to EI were analyzed separately in the group receiving concurrent pre-operative ChT and RT and in the group treated with pre-operative ChT alone and receiving RT post-operatively. Surgical complications and radiological response according to RECIST were analyzed in the above mentioned two groups. Data on ChT dose-intensity will be provided. Results: Among the 548 pts (287 randomized and 261 registered) included in the ISG-STS 1001, 289 pts were considered for the current analyses (111 pts randomized in the EI arm and 178 pts just registered). 146 pts were treated with pre-operative RT and 143 with post-operative RT. In regard to toxicities, no statistically significant differences were found between pts treated with pre-operative concurrent ChT and RT and pts treated with pre-operative ChT alone. When surgical post-operative complications were considered, a higher number of wound dehiscence (9% vs 3.5%, respectively, p = 0.053) and seroma (10.5% vs 3%, respectively, p = 0.009) were observed in pts treated with pre-operative concurrent ChT and RT compared to pts treated with pre-operative ChT alone. Finally, a statistically significant association between RECIST response and pre-operative RT was found (p = 0.041), RECIST partial responses (PR) being 19% and 10% in pts receiving concurrent pre-operative ChT plus RT and in pts treated with pre-operative ChT alone, respectively. Conclusions: The concurrent administration of EI and RT was confirmed to be feasible and safe, resulting in an increased number of PR. Also given the final results of this randomized trial, favoring the EI arm, this combination may help when tumors are of borderline resectability or function preservation is a goal. Research Sponsor: None.
Efficacy of combination lurbinectedin (LURBI) + doxorubicin (DOX) from the phase 1B soft-tissue sarcoma (STS) lead-in to a randomized phase 2 trial in leiomyosarcoma (LMS).

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Background: Single agent or combination chemotherapy, typically Dox- or gemcitabine-based, are standard 1st- and 2nd-line therapies in patients (pts) with metastatic LMS; however, objective response rates (ORR), progression-free, and overall survival (PFS/OS) remain inadequate. Lurbi (PharmaMar S.A. / Jazz Pharmaceuticals) binds to DNA inhibiting transcription and inducing double strand breaks leading to apoptosis and delaying S/G2 progression. In a prior pilot study, we showed Lurbi+Dox is well-tolerated, with signs of activity, particularly in LMS. We designed this phase 1b to optimize dosing to lead into a randomized (1:1) phase 2 trial of Dox/-Lurbi in anthracycline-naïve LMS. Herein we provide updated efficacy and tolerability data for this Phase 1b cohort.

Methods: Pts > 18 yrs with locally advanced/metastatic, unresectable non-GIST STS (Phase 1b only) w/o prior anthracycline or Lurbi/trabectedin, ECOG PS < 3, RECIST 1.1 measurable, and normal organ function were eligible. The phase 1b followed a 3+3 design. Dosing included fixed Lurbi (3.2 mg/m² d1) with two Dox dose levels (DL; DL1: 25 mg/m² d1; DL2 25 mg/m² d1+8). All pts received GCSF prophylaxis. Tumor assessments were every 2 cycles. DL1 was chosen as RP2D and the phase 2 trial began accrual in Aug 2022 aiming to enroll 50 LMS pts randomized 1:1 (stratified by uterine LMS [uLMS] v. other LMS) with PFS as primary endpoint. Pts progressing on Dox are allowed to cross to Lurbi monotherapy.

Results: 10 patients were enrolled in Phase 1b. Histologies included 5 LMS (4 uLMS) and 1 each of myxofibrosarcoma (myxFS), undifferentiated pleomorphic sarcoma (UPS), dedifferentiated liposarcoma (DDLPS), endometrial stromal sarcoma (ESS), and solitary fibrous tumor (SFT). With a median follow-up of 344 days, 5/10 pts remain on treatment with median PFS of 357 days (95%CI 175-ND). 6 pts demonstrated partial response (PR; 5 confirmed), 3 with stable disease (SD), and 1 with progressive disease (PD, Table). Median time to PR was 81 days (range 46-207). Duration of response was over 132 days in all responders with 3 still on treatment. Treatment-related AEs were typical for Dox/Lurbi, including nausea, fatigue, and reversible LFT elevations/cytopenias. Updated safety and response data will be provided at the time of the meeting.

Conclusions: Lurbi+Dox is well-tolerated with efficacy in STS including 6/10 pts achieving PR, 9/10 pts staying on treatment for >120d, and 6/10 pts >200d. The randomized phase 2 study is currently enrolling.

Clinical trial information: NCT05099666. Research Sponsor: Jazz Pharmaceuticals.

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*PR on 1/30/2023 assessment; duration pending follow-up scans.
Safety and clinical activity of TTI-621 in combination with doxorubicin in patients with unresectable or metastatic high-grade leiomyosarcoma: Results from the low-dose expansion cohort.

Sujana Movva, Mihaela Druta, Lara E. Davis, Varun Monga, Mohammed M. Milhem, Howard Harry Bailey, Rashmi Chugh, Ingmar Bruns, Victoria E Allgood, Sant P. Chawla; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Sarcoma, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Knight Cancer Institute, Oregon Health & Science University, Portland, OR; Division of Hematology, Oncology, and Blood and Marrow Transplantation, University of Iowa Carver College of Medicine, Iowa City, IA; University of Iowa Hospitals and Clinics, Iowa City, IA; University of Wisconsin Carbone Cancer Center, Madison, WI; University of Michigan Rogel Comprehensive Cancer Center, Ann Arbor, MI; Pfizer Inc., Cambridge, MA; Sarcoma Oncology Center, Santa Monica, CA

Background: TTI-621 is a recombinant fusion protein combining the Fc region of human IgG1 with a fragment of human SIRPα, designed as a decoy receptor for CD47 on tumor cells to interrupt CD47-SIRPα signaling and promote macrophage-mediated phagocytosis of tumor cells as well as activation of NK cells. Preclinical studies suggest TTI-621 may enhance the response to doxorubicin in macrophage-rich tumors that express CD47, such as leiomyosarcoma (LMS). A phase 1/2 dose escalation study with high- and low-dose expansion cohorts evaluating TTI-621 + doxorubicin in patients (pts) with advanced LMS is ongoing (NCT04996004); results from the low-dose expansion cohort are presented. Methods: This open-label study enrolled anthracycline-naïve pts aged ≥18 y with evaluable unresectable or metastatic high-grade LMS and ≤1 prior line of therapy for advanced disease. Pts in the low-dose expansion cohort received TTI-621 0.2 mg/kg on Days 1 and 8 in combination with doxorubicin 75 mg/m² on Day 1 of 21-day cycles for a maximum 6 cycles, followed by TTI-621 monotherapy on Days 1 and 15 of 28-day cycles until objective disease progression. Primary objectives for the expansion phase were evaluation of safety and investigation of clinical activity via assessment of overall response and clinical benefit rates as defined by RECIST v1.1 criteria. Results: At data cut-off (Oct 3, 2022), 23 pts were evaluable for safety and 20 for clinical response. In the safety population, 39% had received prior treatment for advanced disease. Two pts (9%) experienced Grade ≥3 AE assessed as related to TTI-621 treatment: pancreatitis (n = 1, 4%) and platelet count decreased (n = 1, 4%). Seven pts (30%) experienced Grade ≥3 AE related to the combination of TTI-621 and doxorubicin, including two pts (9%) each with platelet count decreased and white blood cell count decreased and three pts (13%) with neutrophil count decreased. Grade ≥3 doxorubicin-related AEs were more common (n = 17, 74%); most frequent were neutrophil count decreased (n = 8; 35%), white blood cell count decreased (n = 7; 30%), and neutropenia (n = 6; 26%). One pt experienced an infusion-related reaction (Grade 1 chills) assessed as related to TTI-621. No pts attained complete response, but one pt had a complete resolution of all target lesions. Five pts (25%) attained partial response for an overall response rate of 25%; 11 pts (55%) attained stable disease for a disease control rate of 80%. Conclusions: Addition of TTI-621 to doxorubicin showed promising clinical activity and a favorable safety profile among pts with advanced LMS, including those with prolonged exposure to TTI-621 ( > 360 d). Clinical trial information: NCT04996004. Research Sponsor: Pfizer.
Molecular residual disease (MRD) detection using bespoke circulating tumor DNA (ctDNA) assays in localized soft tissue sarcoma (STS).

Abdulazeez Salawu, Elizabeth Demicco, Peter W. M. Chung, Jordan Feeney, Erik Spickard, Richa Rathore, Jasmine Lee, Philip Wong, Eoghan Ruadh Malone, Charles Catton, Limore Arones, Madeline J. Phillips, Peter Charles Ferguson, Jay Wunder, Tony Yin, Himanshu Sethi, Minetta C. Liu, David Benjamin Shultz, Alibiruni Ryan Abdul Razak; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, ON, Canada; Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Natera, Inc., Austin, TX; Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Department of Surgical Oncology, Princess Margaret Cancer Centre and Department of Surgery, Mount Sinai Hospital, Toronto, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: Surgery and (neo)adjuvant radiotherapy (RT) are the mainstay curative treatments for localized STS. Despite treatment, up to 50% of STS patients experience metastatic relapse, and routine use of adjuvant systemic therapy (AST) remains controversial. The presence of ctDNA following curative-intent treatment of STS is a potential biomarker for MRD and may identify patients who are likely to benefit from AST. Given the genomic heterogeneity of STS, a histology-agnostic approach to ctDNA detection in this population is desirable.

Methods: Patients (pts) with localized, high risk (size $\geq$ 5cm, grade $\geq$ 2) STS were enrolled prior to (neo)adjuvant RT and surgery. Pts who received (neo)adjuvant systemic treatment were excluded. Blood samples for ctDNA analysis were collected at diagnosis, post-RT, post-surgery and every 3 months for up to 2 years. Whole exome sequencing (WES) of archival tumor and matched normal were carried out to identify patient-specific, somatic, single nucleotide variants. Personalized and tumor-informed, multiplex PCR next generation sequencing-based ctDNA (Signatera) assays were then developed to track ctDNA in serially collected plasma samples. ctDNA levels were expressed as mean tumor molecules per milliliter (MTM/ml) of plasma. Radiologic surveillance was performed every 3 months following surgery. The primary endpoint was a ctDNA detection rate of >70% at diagnosis. Secondary endpoints included MRD detection after local therapy and correlation of ctDNA levels with disease relapse.

Results: A total of 140 plasma samples from 22 pts (18 male and 4 female; median age: 65 years, range: 30 – 84) were obtained. RT was preoperative in 19/22 pts. Of the 22 tumor samples, 20 had adequate tissue quality for WES to enable ctDNA assay design. Tumor histologic subtypes included undifferentiated pleomorphic sarcoma (n = 6), myxofibrosarcoma (n = 5), and liposarcoma (n = 9). A median of 7 plasma samples per patient (range: 2 – 10) were analyzed. ctDNA was detected in 80% of pts (16/20) at diagnosis, with median ctDNA level of 3.4 MTM/ml (range: 0.2 – 1393.9). Of these 16 pts, 15 (94%) became ctDNA negative at the immediate post-surgical timepoint. In addition, ctDNA was detected in 4 pts (80%) prior to or around radiologic relapse with a median lead time of 92 days. Conclusions: Personalized, tumor-informed ctDNA assays can detect MRD after definitive local therapy and/or prior to radiologic recurrence in patients with localized high-risk STS. As such, serial ctDNA monitoring provides prognostic value and may further identify patients that will benefit from AST treatment. Additional studies evaluating ctDNA as a predictive biomarker for AST benefit are ongoing. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; Natera.
Clinical Science Symposium

The clinical value of tumor-informed minimal residual disease detection in sarcoma.

Yiwei Fu, Jingnan Shen, Gang Huang, Changye Zou, Xianbiao Xie, Xiaoliang Shi, Qijie Jian, Jintao Huang, Fei Pang, Junqiang Yin; Department of Musculoskeletal Oncology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; Department of Stomatology, the Third Affiliated Hospital of Southern Medical University, Guangzhou, China; Shanghai OrigiMed Co., Ltd., Shanghai, China

Background: The high recurrence and metastasis rates lead to poor survival of patients with sarcoma. At present, circulating tumor DNA-based minimal residual disease (MRD) has been studied in various solid tumors and proved to be valuable in guiding treatment and predicting recurrence, but its application in sarcomas is rarely reported. Methods: Tumor tissue samples were used for whole exome sequencing (WES) and clonal mutations were selected for the customized MRD panel. Blood samples were collected for MRD detection. Experiments were conducted at OrigiMed, a College of American Pathologists accredited and Clinical Laboratory Improvement Amendments certified laboratory. Results: A total of 84 sarcoma patients including 47 bone tumor (BT), 32 soft-tissue sarcoma (STS), and 5 undifferentiated small round cell sarcoma (USRCS) patients were enrolled. Patients consisted of 49 (58.3%) males and 35 (41.7%) females, with a median age of 23 years old (1-85 years old). Based on WES, we found that 64% (4936/7715) of the mutated genes were unique to each patient, and 70.4% (859/1220) of selected tumor-informed single nucleotide variants (SNV) were variants with unknown significance, suggesting that tumor-informed MRD is superior to panel-based MRD in sarcomas. In this cohort, 78.6% (66/84) of patients successfully constructed MRD panels, including 85.1% (40/47) of BT patients, 75% (24/32) of STS patients, and 40% (2/5) of USRCS patients. The main reason for failure was the scarcity of SNVs detected. Preoperative MRD detection was performed on 6 cases and revealed a positive rate of 100%. MRD detection was performed twice on 2 patients during preoperative neoadjuvant therapy. For the patient with constant allele frequencies detected throughout the treatment course, imaging showed tumor enlargement; while for another patient with a trend of reduction in allelic frequency, imaging showed tumor shrinkage and necrotic tumor tissue was observed in surgery one month later. These two patients had not recurred after surgery at the time of analysis. Post-surgery MRD detection were performed on 27 patients, of which 1 STS and 7 B Ts were positive (30%, 8/27). Three of them confirmed recurrence by imaging at 12, 30, and 101 days after detection of positive MRD, respectively. However, there were still no imaging recurrence in the other patients so far, including the 5 remaining patients with positive MRD and 19 patients with negative MRD. Follow-up is still ongoing. Conclusions: MRD tests had been successfully performed in most of the sarcoma patients. Due to the heterogeneity of sarcomas, about 64% of mutated genes of sarcomas are unique individually, which may be more suitable for monitoring with tumor-informed MRD panel. Tumor-informed MRD could be used to predict the efficacy of preoperative neoadjuvant therapy and discover recurrence earlier than imaging in sarcoma. Research Sponsor: None.
Histopathological response (HR) after neoadjuvant chemotherapy (ChT) for high-risk soft tissue sarcomas (STS): A planned analysis of the ISG-STS-1001 trial.

Sandro Pasquali, Paola Collini, Cleofe Romagosa, Jean Michel Coindre, Sara Pizzamiglio, Paolo Verderio, Marta Barisella, Emanuela Palmerini, Vittorio Quagliuolo, Javier Martin Broto, Antonio Lopez-Pousa, Giovanni Grignani, Jean-Yves Blay, Iwona A. Lugowska, Valeria Fontana, Marta Sbaraglia, Silvia Bague, Paolo De Tos, Paolo G Casali, Alessandro Gronchi; Molecular Pharmacology, Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano, Italy; Department of Advanced Diagnostics, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; Vall d’Hebron University Hospital, Barcelona, Spain; Bergonié Institute, Bordeaux, France; Bioinformatics and Biostatistics Unit, IRCCS Fondazione Istituto Nazionale dei Tumori di Milano, Milano, Italy; Osteoncology, Bone and Soft Tissue Sarcomas and Innovative Therapies, Orthopaedic Institute Rizzoli, Bologna, Italy; Humanitas Clinical Institute, Milan, Italy; Fundacion Jimenez Diaz University Hospital and Health Research Institute-Fundación Jiménez Díaz University Hospital, Autonomous University of Madrid (IIS-FJD. UAM), Madrid, Spain; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Candido Cancer Institute, Candido, Italy; Centre Léon Bérard, Lyon, France; Institute of Mother and Child, Warsaw, Poland; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy; Department of Medicine, University of Padua School of Medicine, Padova, Italy; Pathology Department, Hospital De Sant Pau i la Santa Creu, Barcelona, Spain; Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; Sarcoma Service, Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori di Milano, Milan, Italy.

Background: HR after neoadjuvant ChT for high-risk STS has not been prospectively characterized and the prognostic implications remain unclear. This planned analysis of the ISG-STS-1001 trial, which compared neoadjuvant anthracycline plus ifosfamide (AI) and a histology-tailored (HT) ChT, was aimed at characterizing HR after neoadjuvant ChT and investigating association with the risk of recurrence.

Methods: Patients registered in the ISG-STS-1001 study (ID: NCT01710176) were included if they had the per-protocol assessment of HR in surgical specimens. The following morphological post-treatment changes were considered: residual stainable tumor cells, necrosis, hemorrhage, sclerosis, sclerohyalinosis, and fibrohistiocytic reaction with hemosiderin. Pathologists at each study site analyzed and expressed each of these changes as a rate within each tumor. Disease-free survival (DFS), which was the trial primary end-point, was the outcome variable.

Results: HR was assessed in 201 of 287 randomized patients (47 had re-excision, 7 did not have surgery, and 32 were not evaluable after wide excision), who were followed up for a median of 89 months (IQR 75-102 months). Presence (>1%) of stainable tumor cells (N=194, 96%) was not associated with DFS (HR=1.47, 95%CI 0.36–5.98, P= 0.591). Conversely, presence (>1%) of necrosis (N=169, 84%) was associated with shorter DFS (HR=3.11, 95%CI 1.36–7.14, P=0.007) and sclerohyalinosis >20% (N=42, 21%) was associated with a lower risk of recurrence (HR=0.51, 95%CI 0.28–0.94, P=0.031). These findings were confirmed when patients who had preoperative radiotherapy (N=32) were excluded. In patients randomized to AI with tumors evaluable for HR (N=98), sclerohyalinosis >20% (N=24, 24.5%) maintained the association with a lower risk of recurrence (HR=0.24, 95%CI 0.09 – 0.67, P=0.007). Finally, the prognostic value of necrosis and sclerohyalinosis for DFS held also when patients registered in the study (187/361 evaluable for HR) were selected in addition to randomized patients.

Conclusions: This is the first study that prospectively evaluated HR after neoadjuvant ChT in high-risk STS. Previous classifications of HR were based on expert consensus and had limited prognostic relevance. In this study residual stainable tumor cells, which is often considered the most relevant post-treatment change, did not stratify patient risk, while sclerohyalinosis (≥20%) singled out patients with the best outcome after neoadjuvant ChT. Clinical trial information: NCT01710176. Research Sponsor: Partially funded through a European Union grant (EUROSARC FP7 278472; A.G.) and PharmaMar (A.G.). The French sites were supported by awards to J.-Y. B. from NETSARC, LYRICAN (INCA-DGOS-INSERM 12563) and DEPGYN (RHU4).
Deep learning with whole slides images to predict histological response to neoadjuvant chemotherapy in patients with resectable high grade soft-tissue sarcomas: A multicenter study.

Benjamin Adjadj, Kathryn Schutte, Charles Maussion, Myriam Jean-Denis, Marie Karanian, Jean Michel Coindre, Antoine Italiano; OWKIN, Paris, France; Centre Léon Bérard, Lyon, France; Pathology Department, Centre Léon Bérard, Lyon, France; Bergonié Institute, Bordeaux, France; Early Phase Trials and Sarcoma Units, Institut Bergonié, Bordeaux, France

Background: Two recent randomized trials have confirmed the potential benefit of neoadjuvant anthracycline-based chemotherapy in patients with high-grade soft-tissue sarcomas (STS) (Issels et al 2018, Gronchi et al 2017). However, as for adjuvant chemotherapy, the main issue with neoadjuvant treatment of STS patients is the identification of predictive factors of response to chemotherapy that could avoid for a majority of patients ineffective and potentially toxic treatment with impaired quality of life. Histological response, defined as the percentage of stainable tumor cells on the surgical specimen, has been shown to be a reliable surrogate for metastasis-free survival and overall survival in bone but also in soft-tissue sarcomas (Crombe et al JCO Clin Inf 2021). Developing a tool to help medical oncologists predict the potential benefit of neoadjuvant chemotherapy prior to starting the treatment would be of great value for precision medicine in sarcomas. To address this need, we propose a deep learning-based approach to predict histological response to neoadjuvant chemotherapy patients from routine histological whole slide images sampled at diagnosis. Methods: A cohort of 220 patients with high grade limb and trunk wall STS enrolled in the NEOSARCOMICS study (NCT02789384, sponsor: Institut Bergonié, Bordeaux, France) was used to train a model to predict the binarized histological response from diagnostic biopsies. Responders are defined by a histological response inferior or equal to 10%. Digitized hematoxylin/eosin slides were preprocessed to segment the tissue and decompose the image into patches of smaller resolution. Features were extracted from each patch using a Vision Transformer pretrained in a self-supervised fashion on histology slides. A Multiple Instance Learning model was trained on the resulting features to compute a prediction at the patient level. The algorithm was trained and validated through a 5-fold, 5-repeat cross-validation scheme. Finally, external validation is performed on an unseen cohort from Centre Léon Bérard to assess the robustness of the model. Results: To predict histological response to neoadjuvant chemotherapy, a model using only diagnostic biopsies achieved an AUC of 0.69 (95% confidence interval, 0.60-0.76). External validation is ongoing and shows promising preliminary results with an AUC of 0.67 (95% confidence interval with bootstrapping, 0.45-0.89). Conclusions: This multi-center study demonstrates that deep-learning models can accurately predict the histological response to neoadjuvant chemotherapy from routine histological whole slide images sampled at diagnosis. This model could be used as a pre-screening tool to improve patient selection for neoadjuvant chemotherapy in STS. Research Sponsor: OWKIN.
Impact of pregnancy in women with desmoid fibromatosis: An international retrospective observational study.

Marco Fiore, Sylvie Bonvalot, Giulia Personeni, Chandrajit P Raut, Kelly Mercier, Rebecca Gladdy, Silva Ljevar, Dimitrios Tzanis, Enrica Rossi, Megan Sulciner, Harini Suraweera, Chiara Colombo, Mikhael Rabih, Marianna Coppola, Catherine Sarre-Lazcano, Sara Iadecola, Costanza Figura, Daniela Salvatore, Alessandro Gronchi; Sarcoma Service, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Institut Curie, Paris, France; Desmoid Foundation Italy, Milan, Italy; Brigham Women’s Hospital, Harvard Medical School, Boston, MA; Desmoid Tumor Research Foundation, Cary, NC; Mount Sinai Hospital and Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; Biostatistics for Clinical Research, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Sarcoma Service, Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori di Milano, Milan, Italy

Background: Desmoid fibromatosis (DF) often occurs during pregnancy/peripartum. Guidance for planning new pregnancies during active surveillance or following DF resection has been limited. Thus, we sought to evaluate outcomes and decision making in the peripartum. Methods: Women of child-bearing age with DF diagnosed between 2000 and 2020 were interviewed about procreation decisions, in a multicenter retrospective observational study (NCT05284305). Pregnancies simultaneous or after diagnosis were analyzed. Primary outcome was DF progression/recurrence within 1 yr postpartum. Secondary outcomes were spontaneous regression, switch to active treatment, and obstetric risks. To estimate probability of progression, a random intercept logistic model was fit to account for correlation of progression in multiple pregnancies in the same patient. Results: Of 483 pts interviewed, 120 (24.8%) postponed, 32 (6.6%) interrupted, and/or 232 (48%) avoided pregnancy (in 93.3%, 50%, and 72.9% of cases because of DF), respectively. 147 pregnancies in 131 pts were concurrent with or after diagnosis: 26 (17.7%, Group A) concurrent with diagnosis, 48 (32.7%, B) after DF resection, and 73 (49.7%, C) with DF on surveillance. Estimated probability of progression was 12.0% (CI 2.0 – 48.4) during pregnancy and 15.8% (5.6 – 37.5) postpartum; for pregnancies after diagnosis (Groups B and C), these rates were 5.1% (0.4 – 40.0) and 9.0% (1.8 – 35.0). On multivariate analysis, age at pregnancy and size of primary DF were significant risk factors for progression (Table). Estimated probability of spontaneous regression was 3.6% (CI 0.2-40.7) during pregnancy and 7.1% (CI 0.3 – 67.2) postpartum. 7/38 (18.4%) spontaneously regressed after pregnancy-related PD, 4/23 (17.4%) in Groups B and C. Treatment for progression was needed in 9/79 (11.4%) postpartum, in 4/63 (6.3%) in Groups B and C. Obstetric complications were comparable to population data in developed countries. Conclusions: After DF diagnosis, pregnancy is safe with a risk of progression of 5% during pregnancy and 9% postpartum. Treatment is needed in only 6%. Spontaneous regression is less common but occurs even after initial progression. Patients decision making about procreation appeared to be influenced by their DF diagnosis. This study supports counseling that fertility options should be fully explored with expert guidance as intervention rates are low. Research Sponsor: None.

Multivariable logistic model for progression of disease.

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Tumor volume and T2 hyperintensity changes from DeFi: A phase 3, randomized, controlled trial of nirogacestat in patients with desmoid tumors.

Thierry Alcindor, Bernd Kasper, Mrinal M. Gounder, Ravin Ratan, Winette T.A. Van Der Graaf, Breelyn A. Wilky, Richard F. Riedel, Noah Federman, Agnese Peruzzi, Stephanie Moody, Allison Lim, Brad Tumminello, Shivaani Kummar, Patrick Schöffski; McGill University Health Center, Montréal, QC, Canada; Universität Heidelberg, Mannheim Cancer Center (MCC), Mannheim, Germany; Memorial Sloan Kettering Cancer Center, New York, NY; University of Texas MD Anderson Cancer Center, Houston, TX; Netherlands Cancer Institute, Amsterdam, Netherlands; University of Colorado Anschutz Medical Campus, Aurora, CO; Duke Cancer Institute, Durham, NC; David Geffen School of Medicine UCLA, Los Angeles, CA; Medpace Inc, Cincinnati, OH; PharPoint Research, Durham, NC; SpringWorks Therapeutics, Stamford, CT; Division of Hematology & Medical Oncology, Oregon Health and Science University, Portland, OR; University Hospitals Leuven, Leuven, Belgium

**Background:** MRI tumor volume or T2 signal intensity changes may represent novel imaging techniques that could have a prognostic or predictive value for assessing response in desmoid tumors (DT). For example, hyperintense areas on T2-weighted images have been associated with active fibroblastic proliferation and ≥90% hyperintensity is associated with DT disease progression, whereas iso- or hypo-intense areas are associated with inactive sites of disease. In DeFi (NCT03785964), the novel gamma secretase inhibitor nirogacestat (n=70 patients) significantly improved the primary endpoint of PFS compared with placebo (n=72 patients; hazard ratio, 0.29 [95% CI, 0.15, 0.55; \( P < 0.001 \)) and significantly improved the secondary endpoint of ORR per blinded, independent central review (41% vs 8%; \( P = 0.001 \)). Complete responses were achieved in 7% with nirogacestat and 0% with placebo. Here, we present an exploratory analysis of MRI tumor volume and T2 signal intensity changes in DeFi. **Methods:** Eligible adults had histologically confirmed DT that had progressed ≥20% per RECIST v1.1 within 12 months of screening. Patients were randomized 1:1 to receive nirogacestat 150 mg or placebo twice daily taken continuously in 28-day cycles. Volumetric MRI and T2 hyperintensity of the largest target tumor were evaluated at screening and every 6 cycles during the double-blind phase. MRI T2 signal intensity is represented as the ratio of hyperintensity in total tumor volume to muscle background. A blinded, independent, central radiologist reviewed all MRI scans. **Results:** Nirogacestat treatment led to more substantial reductions versus placebo in tumor volume and T2 hyperintensity ratio (Table). At baseline, similar proportions of patients in each arm had a T2 hyperintensity ratio ≥90% (95% vs 97%). This ratio changed from ≥90% at baseline to <90% at any time after baseline in 34% of patients in the nirogacestat arm and 15% of those on placebo. **Conclusions:** In DeFi, nirogacestat demonstrated substantial reduction of tumor volume and T2 hyperintensity of the largest target tumors by MRI compared with placebo in adults with DT. These results are consistent with the significant improvement in ORR achieved with nirogacestat. These data suggest that volumetric MRI and T2 hyperintensity might provide additional information in the evaluation of treatment response in DT. The prognostic or predictive value of these imaging techniques in DT should be further studied. Clinical trial information: NCT03785964. Research Sponsor: SpringWorks Therapeutics.

<table>
<thead>
<tr>
<th>MRI tumor volume and T2 hyperintensity of the largest tumor.</th>
<th>Best % change from baseline at any time post-treatment</th>
<th>Median</th>
<th>Interquartile range (Q1, Q3)</th>
<th>Range (min, max)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor volume</strong></td>
<td>Nirogacestat (n=61)</td>
<td>-58.9</td>
<td>-84.7, -8.9</td>
<td>-100.0, 122.5</td>
<td>( P = 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=61)</td>
<td>13.8</td>
<td>-26.1, 58.5</td>
<td>-97.8, 339.0</td>
<td></td>
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<tr>
<td><strong>T2 hyperintensity ratio</strong></td>
<td>Nirogacestat (n=53)</td>
<td>-55.1</td>
<td>-75.5, -20.8</td>
<td>-100.0, 517.2</td>
<td>( P = 0.0001 )</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=60)</td>
<td>-19.8</td>
<td>-42.9, 6.2</td>
<td>-88.6, 441.7</td>
<td></td>
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</tbody>
</table>
RINGSIDE phase 2/3 trial of AL102 for treatment of desmoid tumors (DT): Phase 2 results.

Mrinal M. Gounder, Robin Lewis Jones, Rashmi Chugh, Mark Agulnik, Arun S. Singh, Brian Andrew Van Tine, Vladimir Andelkovic, Edwin Choy, Jeremy Howard Lewin, Ravin Ratan, Gary B. Gordon, Jonathan Yovell, Andres A. Gutierrez, Bernd Kasper; Memorial Sloan Kettering Cancer Center, New York, NY; Sarcoma Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom; Michigan Medicine, Ann Arbor, MI; City of Hope Comprehensive Cancer Center, Duarte, CA; University of California Los Angeles Translational Oncology Research, Santa Monica, CA; Washington University School of Medicine, St. Louis, MO; Princess Alexandra General Hospital, Boston, MA; Peter MacCallum Cancer Centre, Melbourne, Australia; University of Texas MD Anderson Cancer Center, Houston, TX; Ayala Pharmaceuticals, Highland Park, IL; Ayala Pharmaceutical, Wilmington, DE; Ayala Pharmaceuticals, Monmouth Junction, NJ; Universität Heidelberg, Mannheim Cancer Center (MCC), Mannheim, Germany

Background: For patients with desmoid tumors (DT, aggressive fibromatosis), systemic therapy that results in tumor regression, symptom improvement and durable tolerability is needed. Gamma secretase inhibitors (GSIs) have demonstrated antitumor activity against DT. AL102 is a potent, orally available, selective GSI under investigation for treatment of DT. Methods: RINGSIDE (AL-DES-01) is a Phase 2/3 study for patients with progressing DT. In the open-label Phase 2 study (Part A), adults with progressing DT ($\geq 10\%$ unidimensional growth within 18 months or DT-related pain requiring non-opioid medication) were randomized to three dosing regimens: 1.2 mg QD, 2 mg intermittent BIW (2 days on 5 days off), or 4 mg intermittent BIW. Patients who complete Phase 2 roll over into an open-label extension (OLE). RINGSIDE Phase 3 (Part B) is a double-blind, placebo-controlled study evaluating the chosen dose regimen from Phase 2 (1.2 mg once daily) utilizing PFS as the primary endpoint. We report updated efficacy and safety results from RINGSIDE Phase 2. Results: Enrollment of all 42 patients into Phase 2 was completed as of March 2022. As of January 3, 2023, median time on study was 10.5 months (range 0.8 – 14.7) and 30 patients (71.4%) were still on study, 10 (23.8%) of whom rolled over to the OLE. Mean age was 39.9 years, 73.8% were women and 69% had received prior desmoid cancer therapy. The best response in the evaluable population as assessed by blinded independent central review (BICR) was partial response (PR) in 6/12 patients (50%) for 1.2 mg QD, 3/13 patients (23.1%) for 4 mg BIW, and 5/11 patients (45.5%) for 2 mg BIW. Disease control rate was 100%, 91%, and 97% in these groups, respectively. A consistent pattern of deeper, more rapid and maintained response was observed with 1.2 mg QD. Median volume change (BICR) from baseline was -51.9% for 1.2 mg QD, -9.5% for 4 mg BIW, and -15.2% for 2 mg BIW at Week 16 and -76.4%, -35.5%, and -51.2%, respectively, at Week 28. Similar patterns were observed for % changes from baseline in T2 signal intensity, suggesting reduction of tumor cellularity. Consistent with the mechanism of action of GSIs, the five most common Grade 1-2 treatment-emergent adverse events (TEAEs) were diarrhea, nausea, fatigue, alopecia, and dry skin. Grade 3 drug-related TEAEs were reported in 26.2% of patients across all tested doses. There were no Grade 4, Grade 5, or serious TEAEs related to AL102 per investigator assessment. There were no new safety signals. Conclusions: In this Phase 2 study, AL102 was safe and generally well tolerated across all tested doses. The safety profile was consistent with the GSI class of drugs. Tumor response, volume reduction and T2 signal reduction were observed earlier in the 1.2 mg QD group, with deeper and maintained treatment responses. This dose was selected for study in RINGSIDE Phase 3, which is currently enrolling in multiple countries. Clinical trial information: NCT04871282. Research Sponsor: Ayala Pharmaceuticals.
A phase II basket trial of dual anti–CTLA-4 and anti–PD-1 blockade in rare tumors (DART) SWOG S1609: The desmoid tumors (cohort 27).

Young Kwang Chae, Megan Othus, Sandip Pravin Patel, Benjamin Powers, Chung-Tsen Hsueh, Rangaswamy Govindarajan, Silvana Z. Bucur, Liam Il-Young Chung, Christine McLeod, Helen X. Chen, Elad Sharon, Howard Streicher, Christopher W. Ryan, Charles David Blanke, Razelle Kurzrock; Northwestern University, Chicago, IL; Fred Hutchinson Cancer Center, Seattle, WA; UC San Diego Moores Cancer Center, La Jolla, CA; University of Kansas Medical Center, Kansas City, KS; Loma Linda University, Loma Linda, CA; University of Arkansas for Medical Sciences (UAMS), Little Rock, AR; St. Luke’s Mountain States Tumor Institute, Meridian, ID; Northwestern University Feinberg School of Medicine, Chicago, IL; SWOG Data Operations Center, Seattle, WA; National Cancer Institute, Bethesda, MD; National Cancer Institute/National Institutes of Health, Bethesda, MD; OHSU Knight Cancer Institute, Portland, OR; Division of Hematology and Medical Oncology, Oregon Health and Science University, and SWOG Group Chair’s Office, Portland, OR; Medical College of Wisconsin and WIN Consortium, Milwaukee, WI

Background: Dual inhibition with Anti-PD-1 and anti-CTLA4 checkpoint inhibitors is efficacious in many malignancies, but their potential role in numerous rare solid cancers is yet to be established. Desmoid tumors (DT; fibromatosis) are rare tumors of the soft tissue, and the mainstay of treatment is surgery (Richard Riedel, 2022). The utility of immunotherapy in this group of patients has not been explored. This study presents the first results of ipilimumab and nivolumab used in the DT cohort (#27) of the SWOG S1609 Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors (DART) trial. 

Methods: DART is a prospective, open-label, multicenter/multi-cohort phase 2 clinical trial of ipilimumab (1mg/kg intravenously every 6 weeks) plus nivolumab (240mg intravenously every 2 weeks). The primary endpoint includes objective response rate (ORR) (RECIST v1.1) (confirmed complete (CR) and partial responses (PR)). Secondary endpoints include progression-free survival (PFS), overall survival (OS), stable disease (SD) > 6 months, and toxicity. 

Results: Sixteen evaluable patients (median age 37) with desmoid tumors were analyzed. Location of the tumors are: 8, abdomen; 3, lower limb; 2, upper limb; 2, pelvis; and 1, neck. ORR was 18.8% with 3 patients attaining PR: 40% regression with ongoing duration of response (DoR) at over 30+ months; 83% regression (PFS 16 months); and 71% regression (PFS of 8.4 months). Of note, 3 patients had SD (3/16, 18.8%) with some shrinkage of the tumors and a durable response; 23% regression with PFS of 1820+ days; 6% regression with PFS of 902 days; 1% regression with PFS of 1147+ days. Overall clinical benefit rate (CBR; no progression > 6 months) was 62.5%. The median PFS was 17.9 months, 6-month PFS 69%, 1-year PFS 62%. All patients were alive at 1 years; median OS was not assessable as 14 patients are showing ongoing survival. The most common adverse events were fatigue (43.8%, n = 7), nausea (37.5%, n = 6), hypothyroidism (31.3%, n = 5), diarrhea, hyperthyroidism, headache, and adrenal insufficiency (25%, n = 4 each). There were 8 incidents (50%) of grade 3-4 adverse events. 7 adverse events led to discontinuation. There were no grade 5 adverse events. 

Conclusions: Ipilimumab plus nivolumab in treatment of desmoid tumors resulted in an ORR of 18.8% and CBR of 62.5% with durable responses seen. This is the first prospective study demonstrating efficacy of the combination in this rare disease. Correlative studies to determine response and resistance markers are ongoing. Expanded prospective studies in desmoid tumors are needed. Clinical trial information: NCT02834013. Research Sponsor: U.S. National Institutes of Health; Bristol-Myers Squibb.

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A pilot study of lenvatinib plus pembrolizumab in patients with advanced sarcoma.

Sujana Movva, Viswatej Avutu, Ping Chi, Mark Andrew Dickson, Mrinal M. Gounder, Ciara Marie Kelly, Mary Louise Keohan, Paul A. Meyers, Seth M. Cohen, Martee Leigh Hensley, Jason A. Konner, Alison M. Schram, Robert A Lefkowitz, Joseph Patrick Erinjeri, Li-Xuan Qin, Tiffany Salcito, Kenneth Seier, William D. Tap, Sandra P. D'Angelo; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Sarcoma Medical Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** New treatment options are needed for sarcomas. Lenvatinib (L) is an oral, multi-tyrosine kinase inhibitor with significant inhibitory activity against VEGF receptor (VEGFR) 1-3, FGF receptor (FGFR) 1-3, KIT, platelet-derived growth factor receptor (PDGFR) alpha/beta, and RET. Experimental models suggest that L can favorably alter the tumor immune environment, and the combination of L and pembrolizumab (P) has proven to be synergistic and effective across multiple solid tumor types, providing rationale for this study.

**Methods:** This is a pilot study evaluating the efficacy of L and P in select sarcomas. Patients who had at least 1 prior regimen but ≤ 3 were enrolled into one of five cohorts (n = 10 each): A: leiomyosarcoma (LMS); B: undifferentiated pleomorphic sarcoma (UPS); C: angiosarcoma and epithelioid hemangioendothelioma (EHE); D: synovial sarcoma (SS) and malignant peripheral nerve sheath tumor (MPNST); and E: osteosarcoma (OS) and chondrosarcoma (CS). Patients were treated with an initial 2-week run-in of L 20 mg orally daily. Subsequently, P was administered at 200 mg IV every 21 days. The primary endpoint for each cohort was the best objective response rate (ORR) documented by RECIST v1.1 by 27 weeks. The combination was considered worthy of further study if 2 or more responses were observed in a cohort. Secondary endpoints included progression-free survival (PFS), overall survival, duration of response, and safety of the combination. Archival tissue and on-treatment biopsies were collected. 

**Results:** As of January 31st, 2023, cohorts A, D and E have completed accrual. The best response in the LMS cohort was stable disease (SD). In cohort D there were 3 partial responses (PR): 2 SS; 1 radiation associated high grade MPNST. In cohort E one of 6 patients with OS had a PR. To date, of the 6 patients with angiosarcoma, there was 1 PR in a patient with adrenal primary that occurred after the prespecified 27-week timepoint. One of 5 evaluable patients in Cohort B had a PR. Among the 44 patients evaluable for safety, most common AEs were hypertension (56.8%), diarrhea (45.5%), proteinuria (45.5%), fatigue (40.9%), headache (36.4%) and nausea (36.4%). Most common grade 3 AEs were hypertension (13.6%), dyspnea (6.8%), non-cardiac chest pain (6.8%), syncope (6.8%). 

**Conclusions:** A signal of activity was noted in this pilot study for patients with OS, MPNST, angiosarcoma and SS. In the LMS cohort, there were no responses, and PFS was poor. Enrollment to cohorts B and C is ongoing. Clinical trial information: NCT04784247. Research Sponsor: Parker Institute for Cancer Immunotherapy, Sarcoma Foundation of America, Witherwax Fund, Linn Fund, EHE Foundation.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Subtype</th>
<th>Evaluable Disease (N)</th>
<th>Median Age, range</th>
<th>% Female</th>
<th>Best ORR at 27 weeks, % (N)</th>
<th>Median PFS (weeks), (95% CI)</th>
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<tbody>
<tr>
<td>A</td>
<td>LMS</td>
<td>10</td>
<td>50 (34-70)</td>
<td>90%</td>
<td>SD: 60% (6)</td>
<td>17.9 (9.8-22)</td>
</tr>
<tr>
<td>B</td>
<td>UPS</td>
<td>5</td>
<td>55 (29-72)</td>
<td>40%</td>
<td>PR: 20% (1)</td>
<td>25.5 (3.0-38)</td>
</tr>
<tr>
<td>C</td>
<td>Angiosarcoma, EHE</td>
<td>6</td>
<td>64 (30-74)</td>
<td>62.5%</td>
<td>SD: 75% (6)</td>
<td>40.9 (7.1-61.3)</td>
</tr>
<tr>
<td>D</td>
<td>SS, MPNST</td>
<td>6</td>
<td>36 (25-71)</td>
<td>44.4%</td>
<td>PR: 33.3%, 1, MPNST X 1</td>
<td>32 (4.3-51.1)</td>
</tr>
<tr>
<td>E</td>
<td>OS, CS</td>
<td>6</td>
<td>33 (18-61)</td>
<td>10%</td>
<td>SD: 70% (7)</td>
<td>20.7 (8-NR)</td>
</tr>
</tbody>
</table>

*1 PR after 27 weeks in a pt with angiosarcoma.
Interim results of a phase II trial of first line retifanlimab (R) plus gemcitabine and docetaxel (GD) in patients (pts) with advanced soft tissue sarcoma (STS).

Evan Rosenbaum, Li-Xuan Qin, Mark Andrew Dickson, Mary Louise Keohan, Mrinal M. Gounder, Ping Chi, Sujana Movva, Ciara Marie Kelly, Viswatej Avutu, Jason Earl Chan, Moriah Martindale, Travis Adamson, Camron Clark, Rhoena Desir, Matthew Biniakewitz, Grace Cho, Joseph Patrick Erinjeri, Robert A Letkowitz, William D. Tap, Sandra P. D’Angelo; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Sarcoma Medical Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: GD is an alternative to doxorubicin in the front line setting in advanced STS. In the Phase I portion of this study, the PD-1 antibody R, plus GD, was generally well tolerated. We hypothesized that R+GD would be more effective than historical controls treated with GD alone. Methods: This is an ongoing open-label single-center study of R+GD in pts with treatment-naive unresectable or metastatic high-grade STS. G (900 mg/m²) is administered on days 1 and 8 and D (75 mg/m²) on day 8, in 21-day cycles. R (375 mg flat dose) is administered on day 1 starting in cycle 2 and continued as monotherapy ‘maintenance’ after completion of 6 cycles of GD. Up to fifty pts can accrue into five histology-specific cohorts of 10 pts each. The primary endpoint is to estimate the progression-free survival (PFS) rate at 24 weeks. Secondary endpoints included safety, best overall response rate (RR) by RECIST 1.1, disease control rate (DCR), and duration of response (DOR). Subgroup analyses to evaluate all endpoints within each histology-specific cohort are preplanned. An early stopping rule for excessive toxicity will halt accrual if a prespecified severe adverse event rate is surpassed.

Results: As of January 11, 2023, 43 pts were enrolled and treated with R+GD. The leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma (UPS)/myxofibrosarcoma (MFS), dedifferentiated liposarcoma (DDLPS), and other STS cohorts (n = 10 pts each) were fully accrued. Three of 10 angiosarcoma (AS) pts were enrolled. Median age was 59.5 (range 21 – 81) and 27 (63%) were male. Two DDLPS patients were not yet evaluable for response. Of 41 evaluable pts, the best overall RR was 22% (95% confidence interval [CI]) 11 – 38). Confirmed responses were seen in UPS/MFS (n = 4), LMS (2), AS (2), and follicular dendritic cell sarcoma (1). Three pts (LMS, ossifying fibromyxoid tumor, AS) had an unconfirmed PR, for a best RR of 29% (95% CI 16 – 46). Median PFS was 32.7 weeks (95% CI 26.4 – not estimable [NE]) and median DOR was 24 weeks (95% CI 15 – NE). Safety was evaluated in all 43 pts and the early stopping rule was not triggered. Eighteen (42%) pts had at least one Grade (Gr) 3 or 4 treatment-related adverse event (TRAE). The most common ( > 5%) were anemia (16%), neutropenia (9%), febrile neutropenia (7%), lung infection (7%), and leukopenia (7%). Seven pts (16%) had pneumonitis: one Gr 1, four Gr 2, and two Gr 3. Six pts (14%) stopped treatment due to toxicity, including five with pneumonitis. Conclusions: The median PFS of R+GD appears promising compared to historical controls, although the primary endpoint analysis is pending completion of accrual. There was a higher incidence of pneumonitis with the combination compared to GD alone. Future studies of this combination will need to carefully consider the benefits and risks after the final efficacy and safety analyses are performed.

SARCO37: Results of phase I study of trabectedin given as a 1-hour (h) infusion in combination with low dose irinotecan in relapsed/refractory Ewing sarcoma (ES).

Patrick Grohar, Karla V. Ballman, Rachel Heise, John Glod, Mary Frances Wedekind, Leo Mascarenhas, Jenna Marie Gedminas, Steven G. DaBois, Robert G. Maki, Brian D. Crompton, Masanori Hayashi, Cody J. Peer, William Douglas Figg, Maria Liza Lindenberg, Esther Mena Gonzalez, Rochelle Bagatell, Theodore Willis Laetsch, Brigitte C. Widemann, Denise K. Reinke, Rashmi Chugh; Children’s Hospital of Philadelphia, Philadelphia, PA; Weill Cornell Medicine, New York, NY; Pediatric Oncology Branch, Clinical Center National Institutes of Health, Bethesda, MD; NIH / NCI, Bethesda, MD; Department of Pediatrics, Children’s Hospital Los Angeles, Los Angeles, CA; University of Iowa Stead Family Children’s Hospital, Iowa City, IA; Dana-Farber Cancer Institute, Boston, MA; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; University of Colorado at Denver - Anschutz Medical Campus, Aurora, CO; National Cancer Institute, Bethesda, MD; Molecular Imaging Program, CCR, NCI, NIH, Bethesda, MD; Molecular Imaging Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; Division of Oncology, Children’s Hospital of Philadelphia, and Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; University of Michigan, Ann Arbor, MI; University of Michigan Rogel Comprehensive Cancer Center, Ann Arbor, MI

Background: Recurrent ES carries a poor prognosis, and systemic therapies have limited efficacy. Preclinical models suggested that trabectedin (T) could achieve serum concentrations high enough to suppress the dominant oncogene of ES (i.e. EWS::FLI1 transcription factor), and that this effect is sustained by subsequent administration of low dose irinotecan (I). We conducted a phase I study of T+I in patients (pts) with ES. Methods: This multicenter dose escalation study employed a standard 3+3 design. T was given as a 1-h infusion on day (D)1 with low dose I intravenously on D2 and 4 of a 21D cycle. Dose limiting toxicities (DLTs) were evaluated in cycle one. Eligibility required confirmed EWS::FLI1 fusion transcript, age $\geq 10$ years, ECOG performance status $\leq 2$, adequate organ function and willing to have a research biopsy if safely accessible. Primary objectives were to determine the recommended dose (RD) and safety of T+I. Secondary objectives comprised efficacy of T+I and avidity of ES for 3'-Deoxy-3'18F Fluorothymidine (18F-FLT) PET. Results: 20 pts enrolled from 1/2021-12/2022 across 5 sites, 5F/15M, median age 18 years (range 10-59). Pts had received a median of 4 (range 2-9) prior therapy lines including irinotecan in 60% of pts. Grade (G) 3/4 treatment-emergent adverse events (TEAEs) occurring in $\geq 10\%$ of pts were: elevated ALT/AST, elevated creatinine phosphokinase, febrile neutropenia, anemia, lymphopenia, neutropenia, and thrombocytopenia. There were 2 G5 respiratory TEAEs. 18F-FLT PET scans were obtained in 5 pts. ES tumors were 18F-FLT PET avid. Dose level (DL)2 was the RD. At DL 2 and above, there were 4 PRs, 6 SD in 14 evaluable pts (Table). Conclusions: T+I can be safely administered to heavily pretreated pts with ES, demonstrating activity at the RD with 3 PRs (n=5 evaluable). The 18F-FLT PET may be useful to understand patterns of disease progression in ES. Correlative studies will be critical to understanding the mechanism of drug activity. Given the clinical benefit seen with T+I at RD, a phase II portion in pts with ES $\geq 6$ years old is actively accruing. Clinical trial information: NCT04067115. Research Sponsor: U.S. National Institutes of Health; 1 Million 4 Anna; Janssen Pharmaceuticals.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>No. Pts treated</th>
<th>DLTs observed</th>
<th>Best Response (No. of evaluable pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: T=0.8 mg/m$^2$ I=25 mg/m$^2$</td>
<td>4</td>
<td>-</td>
<td>3 PD (3)</td>
</tr>
<tr>
<td>2: T=1.0 mg/m$^2$ I=25 mg/m$^2$</td>
<td>6</td>
<td>-</td>
<td>3 PR, 1 SD, 1 PD (5)</td>
</tr>
<tr>
<td>3: T=1.1 mg/m$^2$ I=25 mg/m$^2$</td>
<td>4</td>
<td>G4 Neutropenia G1 Thrombosis</td>
<td>1 PR, 1 SD, 1 PD (3)</td>
</tr>
<tr>
<td>4: T=1.0 mg/m$^2$ I=30 mg/m$^2$</td>
<td>6</td>
<td>G2 Joint Infection G3 Fatigue</td>
<td>4 SD, 2 PD (6)</td>
</tr>
</tbody>
</table>

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SELISARC: A Spanish Sarcoma Group (GEIS) phase I/II trial of selinexor plus gemcitabine in selected sarcoma subtypes—Results of the phase I part.

Background: Selinexor (KPT-330) (S), a small-molecule inhibitor of the nuclear export mediator exportin-1 (XPO-1), is able to reduce mRNA and protein expression of DNA damage repair (DDR) gene products, being synergistic with DNA damage agents as gemcitabine (G) in preclinical experiments. We hypothesized that selinexor would have a synergistic effect with gemcitabine in selected sarcoma patients (pts).

Methods: Adult progressing pts, ECOG 0-1, with up to 2 previous systemic therapies for advanced disease (localized unresectable/metastatic) with centrally confirmed diagnosis of undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma (LMS), alveolar soft part sarcoma (ASPS), or osteosarcoma (OS) were eligible. S (days 1, 8, 15) and G (days 1, 8) were given in four dose levels, L1: S 60 mg + G 1,000 mg/m² 30 min, L2: S 60 mg + G 1,000 mg/m² (10 mg/m²/min), L3: S 60 mg + G 1,200 mg/m² (10 mg/m²/min), and L4: S 80 mg + G 1,200 mg/m² (10 mg/m²/min). A -1 level was defined with S 60 mg + G 800 mg/m² (30 min). A classic 3+3 design was used to determine the RP2D based on DLTs observed during the first 21-day cycle. In vitro research was performed in LMS and OS cell lines to test the synergy of the combination (MTS and flow cytometry assays).

Results: Between November 2020 and June 2022, 17 pts (M/F 9/8), ECOG 0/1 (14/3), median age 50 years (22-71) were recruited. The median of previous lines was 1 (1-2). Diagnosis was: 9 LMS (52.9%), 6 OS (35.3%), 1 ASPS and 1 synovial sarcoma (SS) (5.9%). Three pts were treated in each of the first 3 levels and 8 pts in L4 (2 pts were not evaluable for DLT due to improper dosing). Only one DLT was observed in L4 (G4 thrombocytopenia) and this level was selected as RP2D. G3/4 toxicity: Neutropenia (52.9%), thrombocytopenia (41.2%), febrile neutropenia (11.8%), anemia, nausea, asthenia, vomiting, alopecia, and lipase increased (5.9% each). There were 3 RECIST PR, 7 SD, and 7 PD. Median PFS for LMS was 7 months (95% CI: 3-11). No relevant clinical activity was observed in OS. In vitro cell viability studies shown that S+G was synergistic in the majority of LMS cell lines tested (combination index of 0.789 for CP0024, 0.791 for AA and 1.186 for IEC005). However, our results indicated antagonism of S+G in OS cell lines, with values for the combination index of 1.67 for MG63, 1.54 for SAOS2 and 1.23 for U2OS. Apoptosis assays by flow cytometry confirmed these observations in LMS and OS cells. Conclusions: At the RP2D, S 80 mg + G 1,200 mg/m² (10 mg/m²/min) is a feasible scheme with manageable toxicity. S+G has shown promising clinical activity for LMS, which warrants further investigation in a phase II. Preclinical studies shown the synergy and the antagonism of S+G in LMS and OS, respectively. Clinical trial information: NCT04595994. Research Sponsor: Spanish Group for Research in Sarcoma; Karyopharm.
A phase I study of nanoparticle albumin-bound sirolimus (NAB-S) combined with pazopanib (PAZO) in patients with advanced soft tissue sarcoma (STS).

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Background: NAB-S (ABI-009, nab-rapamycin) is approved for treatment of adults with unresectable or metastatic perivascular epithelioid cell tumors. Albumin binding improves sirolimus solubility and may target it to tumoral cells. mTOR inhibition may enhance PAZO activity directly and by overcoming resistance. We assess feasibility and safety of the combination.

Methods: Eligible patients (≥18y) had: advanced, unresectable, non-adipocytic STS progressing after 1-5 prior therapies; adequate end-organ function; ECOG performance status 0-1; measurable target lesions (RECIST v1.1); and no prior mTOR or angiogenesis inhibitor treatment. The study was conducted according to a 3+3 design. Initial cohorts received 800 or 400 mg PAZO daily and 60, 45 or 30 mg/m² of NAB-S on days 1 and 8 on a 21-day cycle. Subsequently, NAB-S was administered only on day 1 based on preliminary analysis of adverse events (AEs) and pharmacokinetics (PK). Primary endpoint was determination of maximally tolerated dose (MTD). Dose-limiting toxicities (DLT) were grade 3-5 adverse events (AE) during the first cycle not due to PAZO. Secondary endpoints included AE characterization (CTCAE v5.0), descriptive evaluation of responses and their duration, and correlative/PK studies.

Results: 19 patients were treated; initially, 13 received NAB-S on days 1 and 8. DLT included thrombocytopenia (TCP, n = 7), decreased WBC/neutrophils (n = 2), increased lipase (n = 1), and proteinuria (n = 1). Due to overlapping AEs or possible NAB-S/PAZO interaction, further cohorts received 400 mg PAZO daily and either 30 or 45 mg/m² NAB-S (n = 6). There were no DLTs in the 30 mg/m² cohort (n = 3). In the 45 mg/m² cohort, 2 out of 3 patients had TCP meeting DLT definition. Grade 3-4 AEs in more than 10% included: TCP (58%), neutropenia (11%), leukopenia (11%), lymphopenia (11%), and diarrhea (11%). Any grade AEs in >50% included: TCP (74%), mucositis (63%), fatigue (58%), and acneiform rash (53%). There was no grade 5 AEs. Of 19 treated, 11 (58%) discontinued due to disease progression, 3 (16%) due to AE (TCP-2, transaminitis-1), and 1 (5%) due to death from disease. Four (21%) remain on study as of 2/2023. 18 were evaluable for best response: 3 partial responses (PR; leiomyosarcoma, solitary fibrous tumor, spindle cell sarcoma), 13 stable disease (SD), 2 progressive disease. Clinical Benefit Rates (CBR = PR + SD) at 3 and 6 months were 72% (13/18) and 59% (10/17). Among the leiomyosarcoma subset, CBR at 3 and 6 months were 90% (9/10) and 80% (8/10). Correlative and pharmacokinetic results will be presented.

Conclusions: Thrombocytopenia was the most prominent DLT when studying the NAB-S/PAZO combination. 3 patients out of 19 discontinued therapy due to AEs; the remainder continued therapy after adjustment. MTD and RP2D is NAB-S 30 mg/m² day 1 and PAZO 400 mg days 1-21. Preliminary evidence of activity of the combination was observed. Clinical trial information: NCT03660930. Research Sponsor: Aadi Bioscience.
Multi-omic characterization of gastrointestinal stromal tumor (GIST) in a large real-world patient cohort.

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Background: Molecular knowledge of GIST is limited due to its rarity, few genes have been identified as relevant determinants of outcomes, tumor evolution and therapeutic targets. Therefore, we aimed to dissect the GIST molecular landscape in the largest series of real-world patients reported to date. Methods: 946 GIST patient samples (536 localized, 369 metastatic, 41 unknown) underwent next-gen sequencing of DNA (592-gene, N = 495; whole exome, N = 451) and RNA (whole transcriptome, N = 592) at Caris Life Sciences (Phoenix, AZ). Gene expression signatures of proliferation (Cristescu, 2021), cell cycle activation (CINSARC; Chibon, 2010), inflammation (T-cell inflamed; Ayers, 2017) and tumor microenvironments (MCP-counter; Becht, 2016) were examined. Statistical significance tested by $\chi^2$, Fisher’s exact, or Mann-Whitney U as appropriate. Results: GIST samples were comprised of 80% (N = 758) KIT mut, 8.1% (N = 77) PDGFRA mut, and 11.7% (N = 111) KIT/PDGFRA wild-type (WT), with 14.8% (N = 140) samples harboring a secondary KIT variant suggestive of TKI resistance. Overall median TMB was 2 mutations/MB (range 0-13). WT GIST were identified with mutations in NF1 (33.7%), DNA repair genes (16.7%), SDHX (8.2%), BRAF (6.3%), and PTEN (1.9%), along with NTRK3 fusions (3.1%). Primary KIT variants occurred in exons 11 (83.5%), 9 (13.9%), and 13 (2.6%), and secondary KIT variants (14.6% of total KIT mutations) were distributed across the ATP binding pocket (36.8%) and activation loop (63.2%). Primary PDGFRA mutations were in exons 18 (62.4%), 12 (11.0%), 14 (4.6%) and other (16.5%). KIT/PDGFRA mut GIST infrequently harbored RB1, TP53, SETD2, ARID1A, PIK3CA, PTEN, TSC1, BRCA1, or CHEK2 co-mutations (1-5% each). Copy number amplification (≥6 copies) was overall uncommon (≈2% for all genes). Proliferation and cell cycle activation signatures were higher in KIT exon 11 indels v. missense mut (1.2-fold, p < 0.05) and KIT resistant v. KIT primary (1.2-fold, p < 0.05), but not in KIT exon 11 557/558 v. others, nor between KIT v. PDGFRα v. WT subgroups. Deletion of tumor progression genes MAX (40.0%), CDKN2A (32.3%), and DEPDC5 (33.9%) was associated with increased proliferative gene expression (1.2-, 1.3-, and 1.2-fold, p < 0.05 each), while DMD deletion (52.5%) was not (1.1-fold, p = 0.37). Compared to KITmut and WT GIST, PDGFRA mut had increased abundance of several immune cell populations (range 1.2-3.7-fold, p < 0.05), along with enhanced inflammation signatures (1.1- and 1.2-fold, p < 0.05). Conclusions: This series provides unprecedented resolution of KIT/PDGFRA mut GIST with features of clinical aggressiveness associated with KIT exon 11 indels and resistance mutations, illustrating a specific cytogenetic genotype with more aggressive growth and malignant behavior. Identification of less common molecular alterations that drive kinase activation and impaired DNA damage repair warrant further investigation. Research Sponsor: Caris Lifesciences.
**Clinical efficacy of avapritinib in gastrointestinal stromal tumors (GIST) with different KIT genotypes: Post hoc analysis of the phase 1 NAVIGATOR and phase 1/2 CS3007-101 trials.**

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**Background:** Avapritinib, a novel KIT/platelet-derived growth factor receptor α (PDGFRA) kinase inhibitor, is approved in patients (pts) with GIST harboring PDGFRA activation loop (AL) exon 18 mutations, based on unprecedented clinical antitumor activity. Despite available treatments, there remains a great unmet medical need for pts with KIT-AL-mutant GIST receiving 2nd-line (2L) standard of care (SOC) sunitinib, and pts with primary KIT exon 9 (KIT 9)-mutant GIST receiving 4th-line (4L) SOC ripretinib. This post hoc analysis assessed the clinical benefit of avapritinib in pts with KIT mutations, especially with AL exons 17 and 18, or primary KIT 9 mutations. **Methods:** Tumor tissue and liquid biopsy samples were collected and analyzed to determine baseline molecular subgroups and outcomes were determined in pts with primary KIT mutations treated with oral avapritinib 300 mg once daily (starting dose) enrolled in the phase 1 NAVIGATOR (NCT02508532) and phase 1/2 (China bridging) trials (NCT04254939, CS3007-101). Pts with PDGFRA mutations and PDGFRA-KIT co-mutations were excluded. Progression-free survival (PFS) and objective response rate (ORR) were compared using Cox and logistic regression, respectively. **Results:** A total of 160 pts with KIT-mutant GIST were evaluated (NAVIGATOR, n = 131; CS3007-101, n = 29). At data cutoff (NAVIGATOR: March 31, 2021; CS3007-101: June 30, 2021), median follow-up duration was 22.0 months (95% CI 18.3–27.4). KIT-AL mutations were more frequently detected (n = 74, 46.3%) than KIT ATP-binding pocket (ABP) mutations (n = 34, 21.3%). Sixty pts (37.5%) had KIT-AL mutations without KIT-ABP mutations (ALposABPneg group); the remaining 100 pts were designated as KITOTHERS. Across all lines of therapy, the adjusted (inverse probability weighting of baseline characteristics) median PFS (mPFS) was longer for the ALposABPneg group than for the KIT OTHERS group (9.1 vs 3.4 months; HR 0.47, 95% CI 0.32–0.68; P < 0.0001), and the ORR was higher (31.4% vs 12.1%; odds ratio 3.31, 95% CI 1.44–7.58; P = 0.0047). mPFS and ORR in the KITALposABPneg group were 19.3 months and 38.5%, respectively, in the 2L setting (n = 13) and 11.0 months and 36.4%, respectively, in Chinese pts (3–9 lines, n = 11). In pts with KIT 9 mutations in the 4L (n = 14) and > 4L settings (n = 19), mPFS was 5.6 and 3.7 months, respectively. **Conclusions:** This post hoc analysis demonstrated significantly more robust avapritinib antitumor activity in pts with KIT ALposABPneg GIST versus pts with other KIT mutation profiles. The results suggest that avapritinib could confer meaningful clinical benefit in pts with GIST and specific KIT mutation types, especially KIT-AL or KIT 9 mutations. Avapritinib might be a potential 2L option for pts with KIT ALposABPneg GIST, and in later lines of therapy for pts with ALposABPneg or KIT 9 mutation profiles. Clinical trial information: NCT02508532, NCT04254939. Research Sponsor: CStone Pharmaceuticals.
Overall survival and long-term safety in patients with advanced gastrointestinal stromal tumor previously treated with imatinib: Updated analyses from INTRIGUE.

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**Background:** Ripretinib is a switch-control tyrosine kinase inhibitor approved for patients (pts) with gastrointestinal stromal tumor (GIST) who received prior treatment with ≥3 kinase inhibitors, including imatinib. Sunitinib is approved for advanced GIST after imatinib failure. In the first interim analysis (IA) for overall survival (OS) in the INTRIGUE trial, data were immature (OS event rate, 22.3%), and median OS was not reached in either arm for the KIT exon 11 intent-to-treat (ITT) and all-patient (AP) ITT populations (S Bauer, et al. *J Clin Oncol*. 2022). Additionally, ripretinib had a more favorable safety profile with fewer grade 3/4 treatment-emergent adverse events (TEAEs) than sunitinib. Here, we present the second IA of OS and updated safety from INTRIGUE. **Methods:** INTRIGUE is a global, open-label, phase 3 study that enrolled adult pts with advanced GIST who had disease progression on or intolerance to imatinib (NCT03673501). Randomization was 1:1 to ripretinib 150 mg once daily (QD) or sunitinib 50 mg QD (4 wks on/2 wks off) and was stratified by KIT mutational status and imatinib intolerance. OS was a key secondary endpoint; data cutoff for the second IA was Sept 1, 2022. **Results:** Of 453 pts in the AP ITT population, 444 received treatment; 51 remain on treatment (33/223 [14.8%] with ripretinib and 18/221 [8.1%] with sunitinib). Common reasons for treatment discontinuation were progressive disease (PD) assessed by independent radiologic review (55.4%), PD assessed by investigator (10.6%), clinical PD (5.9%), withdrawal of consent (5.4%), and adverse event (AE; 4.5%); fewer pts discontinued due to an AE for ripretinib vs sunitinib (2.7% vs 6.3%). Following study treatment discontinuation, 58 pts (25.6%) from the sunitinib arm received ripretinib; 139 pts (61.5%) from the ripretinib arm later received sunitinib. There were 185 OS events (40.8%) in the AP ITT population; median duration of follow-up was 28.7 and 28.5 months for ripretinib and sunitinib, respectively. OS was similar with ripretinib vs sunitinib in the AP ITT (median 35.5 vs 30.9 months; HR 0.88, 95% CI 0.66 to 1.18; nominal *P* = 0.39) and KIT exon 11 ITT populations (median 34.0 vs 31.5 months; HR 1.05, 95% CI 0.75 to 1.48; nominal *P* = 0.77). The updated safety profile was consistent with the primary analysis; fewer pts had grade 3/4 TEAEs with ripretinib vs sunitinib (95 [42.6%] vs 149 [67.4%]). Dose interruptions and reductions were lower with ripretinib vs sunitinib. The median (range) treatment duration was 7.9 (0.2–38.2) months for ripretinib and 6.5 (0.2–38.3) months for sunitinib. **Conclusions:** In the second IA from INTRIGUE, OS was similar between treatment arms. The safety profile remained consistent with additional data, and results demonstrate favorable safety with ripretinib in pts with advanced GIST previously treated with imatinib. Clinical trial information: NCT03673501. Research Sponsor: Deciphera Pharmaceuticals, LLC.
Two schedules of vincristine, irinotecan and temozolomide (VIT) for patients with relapsed or refractory Ewing sarcoma: A randomized controlled phase 2 trial.

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**Background:** Vincristine, irinotecan and temozolomide (VIT) has provided an effective regimen in relapsed or refractory Ewing sarcoma patients. Optimal dose schedule of VIT is still undefined. **Methods:** We did this phase 2 randomized controlled trial and included patients with relapsed or refractory Ewing sarcoma. They were randomly assigned (1:1) by random number table method to either shorter dx5 schedule (Irinotecan 50mg/m²/d D1,5, Vincristine 1.4mg/m² D1) or protracted dx5x2 schedule (Irinotecan 20mg/m²/d D1,5,8,12, Vincristine 1.4mg/m² D1,8) together with a fixed dose of temozolomide (100mg/m²/d D1-5) in both groups. Patients were treated every 3 weeks till progression or unacceptable toxic effects for up to eight cycles. The primary endpoint was objective response rate at 12 weeks (ORR 12w). The secondary endpoint was progression-free survival (PFS), overall survival (OS) and safety. The study was powered to detect a 30% improvement in the response rate from 20% of dx5 schedule to 50% of dx5x2 schedule (α = 0.1, 1-β = 0.9, one-sided test favoring dx5x2 schedule since the only difference of clinical importance was an improved response with the inconvenient schedule of dx5x2). A sample size of 30 patients per group (60 randomly assigned patients) was required to detect a significant improvement in ORR 12w. **Results:** Between May 21, 2020, and August 8, 2022, 24 patients were randomly assigned to dx5 schedule while 22 to dx5x2 schedule, respectively. Median follow-up was 10.7 months (IQR 9.7-13.9) in the dx5 group and 8.3 months (IQR 4.4-15.3) in the dx5x2 group. ORR 12w was lower in dx5 group than in dx5x2 group (5 [20.8%] of 24 patients vs 12 [54.5%] of 22; p = 0.019). There was no significant difference in PFS between the two groups (median PFS 2.3 months [95% CI 0.0-4.7] in dx5 group vs 4.3 months [2.7-6.0] in dx5x2 group; hazard ratio [HR] 0.956 [95% CI 0.84-1.09]; p = 0.434). Also, there was no significant difference in OS (median OS 14.8 months [95% CI 12.0-17.6] vs 12.8 months [95% CI 6.9-18.7]; HR 0.957 [95% CI 0.81-1.12]; p = 0.594). Patients in dx5 schedule reported more grade 3 and 4 adverse events (AEs) than dx5x2 schedule, including diarrhea/abdominal pain (23[23.7%] of 97 courses vs 8[8.4%] of 95 courses, p = 0.005), vomiting/nausea (6[6.2%] vs 1[1.15%], p = 0.035). Other common grade 3 and 4 AE (> 5%) were similar between two schedules (p > 0.05), including fatigue (24[24.7%] vs 14[14.7%]), leukopenia (6[6.2%] vs 8[8.4%]), neutropenia (5[5.2%] vs 8[8.4%]), and anemia (5[5.2%] vs 7[7.4%]). Unfortunately, the isolation policy of COVID-19 significantly restricted the speed of recruiting and the sponsor stopped following support to our study. **Conclusions:** Protracted dx5x2 VIT schedule showed superior efficacy and favorable tolerability compared with the shorter dx5 VIT schedule in patients with relapsed or refractory Ewing sarcoma. Clinical trial information: NCT03359005. Research Sponsor: This work was funded by Project (RDX2019-09) supported by Peking University People’s Hospital Scientific Research Development Funds.
Camrelizumab in combination with doxorubicin, cisplatin, ifosfamide, and methotrexate as neoadjuvant therapy for osteosarcoma: A single-arm, exploratory phase II trial.

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Background: Tumor necrosis rate after neoadjuvant therapy is one of the strongest predictors of long-term outcome for patients with osteosarcoma. Patients with good response (tumor necrosis rate ≥90%) have a substantially better survival than those with poor response (tumor necrosis rate < 90%), with 5-year overall survival of 75-80% and 55-65%, respectively. However, treatments for osteosarcoma have not yet shown much progress since the introduction of perioperative chemotherapy in 1970s. New neoadjuvant combinations are required to explored for osteosarcoma.

Methods: In this phase II trial (NCT04294511), patients aged 14-65 years with histopathologically confirmed osteosarcoma and Eastern Cooperative Oncology Group performance status of 0-1 received three 21-day cycles of neoadjuvant regimen (camrelizumab 200 mg on day 1 of each cycle; doxorubicin 37.5 mg/m² or liposomal doxorubicin 25 mg/m² on days 1-2 of cycles 1 and 3; cisplatin 100 mg/m² on day 2 of cycles 1 and 3; methotrexate 8-12 g/m² on day 12 of cycle 1; and ifosfamide 3 g/m² on days 1-4 of cycle 2). Surgery was scheduled 12-14 days after neoadjuvant therapy. Two weeks after surgery, patients received 6 cycles of adjuvant therapy (camrelizumab 200 mg on day 1 of each cycle; doxorubicin 37.5 mg/m² or liposomal doxorubicin 25 mg/m² on days 9-10 of cycles 1, 3, and 5; cisplatin 100 mg/m² on day 10 of cycles 1, 3, and 5; methotrexate 8-12 g/m² on day 2 of cycles 1, 3, and 5; and ifosfamide 3 g/m² on days 1-4 of cycles 2, 4, and 6). The primary endpoint was good response (tumor necrosis rate ≥90%) rate after neoadjuvant therapy.

Results: A total of 86 patients were screened and 75 patients signed informed consent from December 2019 to June 2022. By the data cutoff date on December, 2022, 8 patients did not complete neoadjuvant therapy and 2 patients refused surgery. 65 patients completed neoadjuvant therapy, one patient had disease progression before surgery, 64 received surgical resection and adjuvant therapy, and 44 completed adjuvant therapy. Thirty-one (48.4%, 95%CI: 36.6%-60.4%) of 64 patients showed good response. The most common grade 3-4 adverse events were decreased platelet count (44.0%), decreased white blood cell (37.3%), decreased neutrophil count (29.3%), oral mucositis (14.7%), increased alanine aminotransferase (12.0%), and increased aspartate aminotransferase (10.7%).

Conclusions: Camrelizumab combined with doxorubicin, cisplatin, methotrexate and ifosfamide in the perioperative treatment of osteosarcoma patients were safe and tolerable. Postoperative good response rate was similar to previously reported results. Survival follow-up is still ongoing to analyze the effect of perioperative immunotherapy combined with chemotherapy on long-term outcomes of patients with osteosarcoma. Clinical trial information: NCT04294511. Research Sponsor: None.
Background: Overall survival for patients (pts) with recurrent, unresectable osteosarcoma (OS) remains poor, and event free survival (EFS) based on historical benchmarks has been used to determine efficacy of investigational agents. HER2, a transmembrane receptor with kinase activity involved in cell signaling through the RAS pathway, is expressed in OS. T-DXd is a HER2 targeting antibody linked to DXd with preclinical in vitro studies demonstrating activity in OS correlating with the presence of HER2 expression. We report results of a Phase 2 study of T-DXd in adolescents and young adults with HER2 positive relapsed, unresectable OS.

Methods: Pts (12-39 yrs) with relapsed, unresectable OS were eligible for screening. The most recent available tissue sample was centrally evaluated for HER2 expression by immunohistochemistry. Pts with greater than 10% of OS cells with cytoplasmic or membranous HER2 expression of any intensity were eligible to receive T-DXd at 5.4mg/kg IV every 3 wks for up to 2 yrs. The proportion of pts with an EFS at 24 wks was the primary endpoint estimated using a 9+15 Simon’s optimal two-stage design assuming an unacceptable response rate of 12%, acceptable response rate of 40%, 5% type 1 error, and 90% power.

Results: 50 pts were screened for HER2, and 41 samples met the membranous or cytoplasmic HER2 expression inclusion criteria. A single pt had an assay failure and 8 pts had tumor samples with less than 10% HER2+ cells. Nine eligible pts were enrolled (7 male) between April 15th and November 11th of 2021 and received T-DXd. 2 pts were < 18 yrs old and the median age was 19.3 years. Seven pts received 2 cycles and had progressive disease (PD) at the first evaluation. A single pt withdrew consent before the first evaluation. The final pt was event free at wk 24, meeting the protocol specified criteria for a response. With a single pt having more than 24 wks of stable disease (SD) of the 9 planned in the first stage, this study did not meet criteria to progress to stage 2. The estimated response rate is 11.1% (1-sided 95% CI LB: 0.6%). The single responder with SD for 12 cycles had 15% HER2 positive OS cells and the remaining pts had 30-100% HER2 staining. A single cycle 1 DLT of thrombocytopenia (GR4) was observed. No unexpected or at least possibly related AE’s were observed. Grade 3-4 at least possibly related AE’s occurred in 3 of 9 patients and included nausea, vomiting, tumor hemorrhage, cytopenias (n = 3), wound infection, and hypertension.

Conclusions: T-DXd did not demonstrate sufficient response to expand enrollment to the planned second stage in pts with OS. None of the pts had significant HER2 membranous staining which may account for the limited efficacy. No new toxicities were observed. Further correlative studies including PK, anti-T-DXd analyses and circulating tumor DNA are ongoing. Clinical trial information: NCT04616560. Research Sponsor: U.S. National Institutes of Health.
Variations in the approach to lung metastases in osteosarcoma among pediatric and adult patients.

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Background: Osteosarcoma (OS) is most common in the pediatric (ped) and young adult population but can occur at any age. Amongst other factors, older age confers a worse prognosis, and it is uncertain whether this is due to inherent biologic differences or treatment approaches. Lung-only metastases (mets) is common, and metastasectomy is performed frequently to improve overall survival. Little is known about the differences in lung-only metastatic OS and approaches to metastasectomies between ped and adult populations. Methods: A single-institution retrospective chart review using a free-text search engine and keywords “osteosarcoma,” “lung mets” and “pulmonary mets”, generated 206 patients(pts) diagnosed from 2006-2021. Eligible pts had a diagnosis of lung-only metastatic disease, resection performed at the institution and at least one year of follow-up data. Data was analyzed in two cohorts based on age at OS diagnosis: ped (age < 18) and adult (age > 18 years), as well as with age as a continuous predictor. Results: Fifty pts (27F/23M) with lung only mets were eligible for analysis with a median follow up of 10.4 years. Median age was 23 yrs (range 6-77); 20 pts (40%) were ≤18 years old; 31 pts (16 ped, 15 adult) had an extremity primary site. Rates of metachronous (67% vs 60%) and bilateral (50% vs 40%) lung mets were similar in ped vs. adult pts, respectively. The median number of lung mets was 2 (range 1 to > 25) with 50% of patients (35) having 2-6 metastases (8 ped, 20 adult). The median size of lung metastasis was 1.2 cm (range 0.1-4.0 cm). 15 ped pts (75%) underwent metastasectomy, compared to 19 adult (63.3%) (OR 1.74, p = 0.39). Probability of metastasectomy decreased with age when used as a continuous predictor (p = 0.11). Ped pts were more likely to have an open procedure as compared to thoracoscopic (OR 12.75, p < 0.01). There was no significant difference in relapse-free survival between ped and adult pts who underwent metastatectomy (p = 0.84). Median overall survival following lung metastasis detection was 5.8 years for ped pts compared to 3 years for adult pts (p = 0.15 from Cox model). Conclusions: Multiple tumor and patient-specific factors affect the decision to undergo metastatectomy in lung-only OS. In our single-center study we learned that timing, pattern, and number of lung mets in ped vs. adult pts were similar, but younger pts were more likely to undergo an open procedure. Our data trended towards a lower chance of undergoing metastatectomy with older age. Larger studies are required to further understand decision-making and therapeutic outcome and a randomized study of open vs. thoracoscopic metastatecomy for lung-only OS mets is underway. In this small study, many patients with lung-only metastatic OS had long-term survival. We showed that relapse-free survival post-metastatectomy was similar in ped and adult patients. Research Sponsor: None.

Safia K. Ahmed, Odion Binitie, Mark D. Krailo, Allen Buxton, Daniel J. Indelicato, Alexandra Callan, Alexander Christ, Paul J. Chuba, Helen Ruth Nadel, Bruce Pawel, Richard Greg Gorlick, Damon R. Reed, Steven G. DuBois, Katherine A. Janeway, Patrick Leavey, Leo Mascarenhas, Nadia N. Laack; Mayo Clinic Arizona, Phoenix, AZ; Moffitt Cancer Center, Tampa, FL; Children's Oncology Group, Arcadia, CA; Public Health Institute, Monrovia, CA; Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL; UT Southwestern Medical Center, Dallas, TX; Children's Hospital Los Angeles, Los Angeles, CA; Ascension Macomb Oakland Hospital Webber Cancer Ctr, Warren, MI; Stanford University, Stanford, CA; Children's Hospital Los Angeles, Los Angeles, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Dana-Farber Cancer Institute, Boston, MA; University of Texas Southwestern Medical Center, Dallas, TX; Department of Pediatrics, Children's Hospital Los Angeles, Los Angeles, CA; Mayo Clinic, Rochester, MN

**Background:** To evaluate clinical characteristics and patterns of treatment failure in patients with localized Ewing sarcoma (ES) treated on AEWS1031 according to local control (LC) strategies, tumor size, and tumor site. **Methods:** AEWS1031 was a phase 3 randomized trial comparing two interval compressed chemotherapy regimens. Patients who completed LC on AEWS1031 were analyzed. LC was with surgery alone (S), definitive radiation therapy (RT), or surgery plus radiation (S+RT), and determined by the treating investigator. Local failure (LF) and distant failure (DF) were defined as recurrence at primary tumor site or distant site, respectively. Fine and Gray method was used to estimate cumulative incidence of LF and DF from time LC was completed. P-values were calculated using logrank or Gray's test, as appropriate. A two-sided p-value of ≤0.05 was considered significant. **Results:** 588 patients completed LC. Median age at enrollment was 13.0 years (range: 0.6-33.9 years). Tumor sites were categorized as extremity (230; 39%), axial (142; 24%), extraosseous (110; 19%), and pelvis (106; 18%). At diagnosis, tumor volume (TV) was ≥200 mL in 170 patients (31%) and maximum tumor dimension (MTD) was ≥8 cm in 289 patients (52%). LC was with S in 320 patients (54%), RT in 160 (27%), and S+RT in 108 (18%). Eight patients received preoperative RT. Fifty-three patients (13.1%) who received S+RT had an R1 resection. LC with S was more likely for extremity (58%), RT for pelvis (38%) and S+RT for axial (36%) and extraosseous (34%) primary tumors (p < 0.01). With median follow up of 67.6 months from LC, the 5-year cumulative incidences of LF and DF for the entire cohort were 6.0% (95% CI, 4.3-8.3%) and 11.0% (95% CI, 8.6-13.9%), respectively. Eleven patients experienced simultaneous LF and DF. LF incidence was 5.0% for S, 8.4% for RT, and 5.6% for S+RT (p=0.47). DF incidence was 2.6% for S, 6.4% for RT, and 16.1% for S+RT (p=0.06). LF incidence by tumor site was 3.6% for extremity, 8.7% for pelvis, 7.3% for axial, and 6.8% for extraosseous (p=0.08). LF incidence was higher for primary tumors ≥200 mL (11.3%) compared to tumors <200 mL (3.9%; p<0.01) and for tumors ≥8 cm (7.8%) compared to tumors <8 cm (4.4%; p=0.02). Tumor size was associated with a higher LF incidence for S and RT, but not for S+RT (Table). LF incidence was 4.0% for R0, 7.5% for R1 with RT, and 16.7% for R1 without RT (p=0.02). **Conclusions:** We report the lowest LF incidence to date for prospective ES trials conducted. Both larger TV and MTD were associated with higher LF. Future investigations will aim to evaluate the impact of chemotherapy dose-intensity on LC and identify risk-stratification variables for improved LC. Five-year LF incidence by LC and tumor size. Clinical trial information: NCT01231906. Research Sponsor: U.S. National Institutes of Health.

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ALMB-0168, a novel Cx43 hemichannel agonist monoclonal antibody, for metastatic or unresectable osteosarcoma after standard chemotherapy: A multicenter, open-label, single-arm, phase 1 study.

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Background: The treatment of metastatic or unresectable osteosarcoma after standard chemotherapy remains a significant clinical challenge. Connexin 43 (Cx43) hemichannel has been suggested to be a key regulator of bone homeostasis and represents a new target for bone and breast cancer. ALMB-0168, a first-in-class therapeutic antibody agonist for Cx43 hemichannel, has been shown to suppress the growth and migration of osteosarcoma and breast cancer bone metastases in preclinical studies.

Methods: Patients ≥16 years with histologically confirmed osteosarcoma who progressed after standard chemotherapy were eligible. This study consists of accelerated titration followed by a 3+3 design with 7 planned ALMB-0168 dose levels (1, 3, 6, 12, 18, 24, and 30 mg/kg) administered intravenously once every 3 weeks and then dose expansion at the potential recommended phase 2 dose (RP2D). Primary endpoints are safety and tolerability. Adverse events are rated according to the NCI CTCAE v5.0. Key secondary endpoints are overall response rate (ORR) and disease control rate (DCR) assessed using RECIST v1.1. Results: As of August 21, 2022, 14 patients (10 males, 4 females) with median age 27.5 years (range 16–38 years) were enrolled; ECOG PS was 0 in 7 patients (50.0%), 1 in 6 patients (42.9%) and 2 in 1 patient (7.1%). 5 patients received ≥2 prior lines of therapy. Six dose levels (1-24 mg/kg) have been completed in this ongoing study with no dose-limiting toxicities reported. Treatment related adverse events (TRAEs) of any grade occurred in 10 (71.4%) patients and were Grade 3 in 1 patient (infectious pneumonia); no events were Grade 4 or 5. Common TRAEs (>10%) were proteinuria (21.4%), anemia (21.4%), hematuria (14.3%), and increased aspartate aminotransferase (14.3%). No Cx43-related cardiac events or severe hepatic events were observed. A total of 13 patients were evaluable for response. ORR was 15.4% (2/13, 95% CI: 1.9–45.5%), including 2 partial responses (PR), 1 patient each at 6 mg/kg and 18 mg/kg. The patient at 6 mg/kg, who had ≥3 prior lines of therapy and lung metastases, achieved durable disease control with stable disease (SD) for 33 weeks followed by PR for 8+ weeks (at the time of analysis). The DCR was 53.8% (7/13, 95% CI: 25.1–80.8%) with 2 PRs and 5 SDs.

Conclusions: ALMB-0168 demonstrated encouraging efficacy and tolerable safety in patients with metastatic or unresectable osteosarcoma after standard chemotherapy in a phase 1 dose-escalation trial. Dose escalation is ongoing and dose expansion will start at the potential RP2D levels. Clinical trial information: NCT04886765. Research Sponsor: AlaMab Therapeutics (Shanghai) Inc.
ETCTN/NCI 10330: A phase 2 study of belinostat with SGI-110 (guadecitabine) or ASTX727 (decitabine/cedazuridine) for the treatment of unresectable and metastatic conventional chondrosarcoma.

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Background: Conventional chondrosarcoma (cCS) is the 2nd most common primary bone tumor and is resistant to chemotherapy and radiation. IDH1/2 mutations (m) occur in 50% of cCS. Both IDHm and wild-type (wt) cCS harbor epigenetic dysregulation. In preclinical models of IDHm and wt cCS, combination treatment with HDAC and DNMT inhibitors (i) suppressed growth in vitro and in vivo by reversing the hypermethylated state and inducing tumor suppressors, interferon response genes and apoptosis (Sheikh T, Schwartz G. Mol Cancer Ther 2021;20).

Methods: NCI 10330 is a single-arm, multicenter, phase 2 study evaluating the HDACi belinostat (B) with the DNMTi SGI-110 (S) or ASTX727 (A). A replaced S due to drug availability (pts were replaced). Pts had advanced cCS, ECOG PS ≤ 2 and could be treatment naïve. Progression was required for grade 1 cCS. Pts received B 1000mg/m² IV + S 45mg/m² SC both days 1-5 or B (same dosing) + A (cedazuridine 100mg/decitabine 35mg) PO both days 1-5, in 28-day cycles. 1° endpoint was objective response. A Simon 2-stage design was used. If ≥ 2/13 responses occurred in stage 1, the study would proceed to full accrual. Design had 85% power with α = 0.05 to test ORR 8% vs 28%. 2° endpoints included safety, PFS and OS. A safety lead-in was performed. Paired biopsies were collected.

Results: Stage 1 is complete. 19 pts were treated: 6 on B+S and 13 on B+A. Median age was 50 and 67 years, respectively. All pts had prior surgery. 17% (B+S) and 38% (B+A) had prior radiation. 33% (B+S) and 55% (B+A) were IDHm. 67% (B+S) and 75% (B+A) were histologic grade ≥ 2. There were no objective responses. Best response (at 8 weeks) was stable disease (SD) in 4/6 pts (67%) on B+S and 6/10 pts (60%) on B+A. mPFS was 4.2 mos (95% CI 1.97-NR) for B+S and 3.8 mos (95% CI 2.17-NR) for B+A. mOS has not been reached. For B+A, mPFS for IDHm vs wt pts was 4.7 and 3.1 mos, respectively (p=0.21). One pt with IDHm grade 2 cCS who progressed on FT-2102 (IDH1i) remains on B+A > 1 year. There were no DLTs during either safety lead-in. Grade 3/4 treatment-related adverse events (TRAEs) occurred in 17% (B+S) and 69% (B+A). For B+A, the most common grade 3/4 TRAE was neutropenia (54%) and the most common all-grade TRAEs were nausea (69%), leukopenia (61%), neutropenia (54%), anemia (46%) and fatigue (46%). Paired tumor biopsies are being evaluated with whole exome sequencing, RNAseq, methylation array and multiplex IHC with results forthcoming.

Conclusions: Combination HDACi + DNMTi was well-tolerated in advanced cCS. There were no objective responses; however, a subset of pts experienced prolonged SD with a trend towards improved mPFS in IDHm pts. Correlative work is ongoing with a focus on differential effects on IDHm tumors and whether modulation of the immune microenvironment might support combinations with immunotherapy. Support: UM1CA186689. Clinical trial information: NCT04340843. Research Sponsor: U.S. National Institutes of Health.

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Phase I study of the mutant IDH1 inhibitor ivosidenib: Long-term safety and clinical activity in patients with conventional chondrosarcoma.

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Background: Chondrosarcomas (CS) are rare primary bone malignancies for which there are no approved systemic therapies. 85% of CS are the conventional subtype. Mutations in the isocitrate dehydrogenase 1 (IDH1) gene occur in ~50% of conventional CS. In a phase 1 study in patients (pts) with IDH1-mutated advanced solid tumors, ivosidenib (IVO), an oral potent inhibitor of mutant IDH1, demonstrated manageable toxicity (without dose-limiting toxicities), suppression of the oncometabolite 2-hydroxyglutarate at dose levels $\geq 300$ mg/day, and disease control in pts with conventional CS. We report long-term safety, tolerability and efficacy of IVO in pts with conventional CS. Methods: In this phase I multicenter open-label dose-escalation and expansion study, IVO was administered orally (100 mg twice/day [BID] to 1200 mg once/day [QD]) in continuous 28-day cycles. Primary outcome was safety and tolerability; secondary outcomes included clinical activity (objective response rates [ORR, defined as complete response (CR) + partial response (PR)], stable disease [SD] and progression-free survival [PFS]). Adverse events (AEs) were assessed every visit and reported per the Common Terminology Criteria for Adverse Events (CTCAE version 4.03). Responses were assessed every other cycle using Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Results: 13 pts with advanced conventional CS were included in this analysis (data cut off 15 September 2022; women, n = 4; median age 54.0; AJCC tumor grade I [n = 2], II [n = 8], III [n = 1], unknown [n = 2]; 6 had received prior systemic therapy; received 100 mg IVO BID [n = 1], 400 mg QD [n = 1], 500 mg QD [n = 7], 800 mg QD [n = 2], and 1200 mg QD [n = 2]). Median treatment duration was 11.3 months (range: 0.5-92.6 months). Four pts (30.8%) have continued therapy for $> 6$ years (two of which were treated for $> 7$ years). Median relative dose intensity was 100%. The most frequent treatment emergent AEs (in 4 pts; mostly grade 1/2) were diarrhea (n = 5) and nausea (n = 5). Six pts experienced grade $\geq 3$ AEs. Three pts experienced serious AEs (none considered related to treatment). There were no discontinuations, dose reductions or deaths due to AEs. The ORR was 23.1%. Median duration of response was 42.5 months (range: 25.8-51.8 months). One pt with a base of the skull lesion achieved a CR (1200 mg IVO QD); two achieved PR (one 500 mg and one 1200 mg IVO QD); seven had SD (five received $\geq 500$ mg IVO QD) and two had PD (both received $\geq 500$ mg IVO QD). All responses occurred after $> 2$ years on treatment. Median PFS was 7.4 months (95% CI: 2.0-61.3). Conclusions: In pts with IDH1 mutated advanced conventional CS, IVO demonstrates manageable toxicity and durable disease control including long-term responses, extending several years for a proportion of pts. Future studies are warranted to better understand the efficacy of IVO in pts with advanced conventional CS. Clinical trial information: NCT02073994. Research Sponsor: This study was supported by Agios Pharmaceuticals, Inc. Servier Pharmaceuticals LLC has completed the acquisition of Agios’ oncology business.
A phase 2 study of an anti–PD-L1 antibody (atezolizumab) in dedifferentiated chondrosarcoma.

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Background: Chondrosarcoma (CS) is one of the most common bone malignancies in adults. Contrary to the indolent nature of low-grade CS, the dedifferentiated subtype (dCS), representing 5-10% of all CS, is known for aggressive behavior, high risk of relapse following resection, and poor prognosis. Expression of PD-L1 has been demonstrated in dCS samples and correlated with high numbers of tumor-infiltrating lymphocytes (Kostine, et al., Mod Pathol, 2016). Response to anti-PD1 therapy has not been evaluated prospectively. We report here the outcomes of a dCS cohort treated with the anti-PD-L1 agent, atezolizumab (atezo). Methods: Patients (pts) 2 years of age or older received intravenous atezolizumab 1200 mg (15 mg/kg with a 1200 mg cap in pediatric pts) once every 21 days. Prior immune checkpoint inhibitor therapy was not allowed. Primary objective was response rate (ORR). Imaging was carried out at the end of cycle 3 and then every two cycles; responses were evaluated per RECIST 1.1. The study employed a Simon two-stage design. If no responses were observed within 9 months of the ninth patient being enrolled, the cohort was to be terminated early. Research biopsies for immuno-pharmacodynamic (IO-PD) studies were collected at baseline, prior to C3D1, and optionally at progression. Results: Nine pts were enrolled to the dCS cohort. Three pts were female, 8 pts were White (1 unknown), all had an ECOG performance score ≤1, and their median age was 63 years (range, 53-85). Primary disease sites were pelvis (2); sternum (2); femur, hip, chest, scapula, and lung (1 each). Median duration of treatment for all pts was 9 weeks. Seven pts were evaluated for response, of whom 3 (42.9%) were documented to have stable disease (SD) as best response, lasting a median of 25.9 weeks (range, 15-38.3 weeks). Four pts had a best response of disease progression. Two pts died prior to first response assessment. No RECIST objective responses were observed; the cohort was closed due to futility. Reasons for treatment discontinuation included progression (n = 6), death (1, respiratory failure unrelated to treatment), withdrawal of consent (1), and SARS-CoV-2 infection (1). Treatment-related adverse events (TRAEs), grades 1-3, occurred in 7 pts (78%). Grade 3 TRAEs occurred in 2 pts (22%), included infusion reaction, myonecrosis, and anemia. IO-PD studies are ongoing to elucidate changes within the tumor microenvironment. Conclusions: Though objective response was not seen, atezo showed stabilization of disease in 1/3 of the patients with this aggressive tumor. IO-PD results will be critical to identify determinants of atezolizumab resistance within this dCS cohort and to identify possible partners for combination therapy. Funded by NCI Contract No. HHSN262201500003I. This project was also supported in with funding and drug supply from Genentech Inc (a member of the Roche group). Clinical trial information: NCT04458922. Research Sponsor: U.S. National Institutes of Health.
Prolonged 14-day continuous infusion of high-dose ifosfamide (14IFO) for relapsed/refractory high-grade osteosarcoma (R/R HOS): A retrospective multicenter cohort study.

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Background: The prognosis of patients (pts) with relapsed/refractory (R/R) High-Grade Osteosarcoma (HOS) remains dismal without an agreement on systemic therapy. The use of 14IFO with an external pump in outpatient setting (1g/sqm/day x 14 days every 21) in R/R HOS pts is limited. This is the first retrospective cohort study focused on 14IFO activity and toxicity in this setting (NCT04651569). Methods: Five Centers of the Italian Association of Pediatric Onco-Hematology and Italian Sarcoma Group participated to the study. Primary aim is to investigate 14IFO activity in pts with R/R HOS younger than 40 years. Secondary aim is to evaluate toxicity, according to CTCAE v.5, and clinical benefit. Progression Free Survival (PFS) and Overall Survival (OS) analysis are performed using the Kaplan Meier method with 95% confidence interval (CI). Results: Between 2012 and 2021, 26 R/R HOS pts were treated with 14IFO (median follow-up: 17,5 months, range: 4,6 – 83 months). Median age is 19 years at the beginning of 14IFO; eleven pts (42%) are < 18 years. Three pts (12%) have a localized HOS, twelve pts (46%) have pulmonary disease only and eleven pts (42%) have a pluri-metastatic HOS. Eleven pts (42%) have a relapsed HOS with a median disease-free interval (DFI) of 13 months before 14IFO, the remaining (58%) have a refractory disease to two or more treatments. Overall, thirteen pts (50%) receive 14IFO as second line therapy and fifteen pts (57%) are pre-treated with Ifosfamide in first line. Disease Control Rate is 57,5% (5 Partial Response + 10 Stable Disease). Seven pts (27%) receive a local treatment after 14IFO (5 surgery, 1 Radiotherapy (RT), 1 Carbon Ion RT). The median PFS is 4,1 months (95% CI 2.13, 7.37), 6-month and 1-year PFS are 38% (95% CI 24-63) and 8% (95% CI 2-29), respectively. The median OS is 13.7 months (95% CI 10.6 – 23.7). 1-year and 2-year OS are 51% (95% CI 35-75) and 22% (95% CI 9.5-49), respectively. Relapsed pts have both longer median PFS and OS compared to pts with a refractory disease (PFS: 7.33 months vs 2.13 months (p = 0.02); OS: 19.4 months vs 10.7 months (p = 0.1)). Sixteen pts (61%) receive at least 4 cycles and an amount of 101 cycles are evaluated for toxicity. Grade 4 hematological toxicity is reported in 15 cycles (14,8%) as follows: i) white-blood cell decrease in 6 cycles (6%); ii) neutropenia in 7 cycles (7%); iii) thrombocytopenia in 2 cycles (2%). One patient has one episode of febrile neutropenia. No grade 3-4 non hematological toxicities are reported. Conclusions: This trial shows a non inferiority activity of 14IFO compared to other treatments in this setting, despite the small number of pts. Therefore, 14IFO should be considered as a treatment option in R/R HOS, especially for its well tolerated toxicity profile and the home-administration that improve patient’s quality of life and it could significantly reduce cancer care cost. Clinical trial information: NCT04651569. Research Sponsor: None.
Survival outcomes in pediatric patients with metastatic Ewing sarcoma who achieve a rapid complete response of pulmonary metastases.

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Background: Twenty-five percent of patients with Ewing Sarcoma (EWS) have metastatic disease at diagnosis, most commonly in the lungs. Our objectives were to compare overall (OS) and pulmonary disease-free survival (PDFS) between patients with metastatic EWS at diagnosis who achieve rapid complete response (RCR), defined as radiographic resolution of all pulmonary nodules at the end of induction chemotherapy, and those with residual pulmonary nodules after induction chemotherapy (non-RCR).

Methods: This multi-center, retrospective cohort study included children under 20 years of age with metastatic EWS treated from 2007-2020 at 19 institutions participating in the Pediatric Surgical Oncology Research Collaborative. Chi-square tests were conducted for differences among groups, and p < 0.05 was considered significant. Kaplan-Meier curves were generated for OS and PDFS. Cox regression was performed for OS, controlling for whole lung irradiation (WLI), extrapulmonary metastases, and age.

Results: Among 153 patients with metastatic EWS at diagnosis, 61 (40%) achieved RCR, and 87 (57%) did not (5 unknown). The median number of pulmonary nodules was 3.5 in the RCR vs 5 in the non-RCR groups (p = 0.02), while bilateral disease was present in 44 (72%) RCR vs 75 (86%) non-RCR patients (p = 0.03). Pulmonary relapse occurred in 58 (38%) patients, including 18 (29%) in the RCR and 36 (41%) in the non-RCR groups (p = 0.14). Factors associated with pulmonary relapse in the univariate analysis include median age [15 years (IQR: 12-17) with pulmonary relapse vs 12 years (IQR: 9-16) without (p = 0.03)] and extrapulmonary metastases at diagnosis [24 (41%) patients with pulmonary relapse vs 26 (27%) patients without pulmonary relapse (p = 0.05)]. WLI was performed in 100 patients and was not associated with a reduction in pulmonary relapse (p = 0.93). Complete surgical clearance of pulmonary disease was attempted in 29 (19%) patients, including 17 of the patients who met the criteria for RCR. On Kaplan-Meier analyses, 5-year PDFS did not significantly differ based on RCR (67%) vs. non-RCR (53%, p = 0.13), or WLI (61%) vs. no WLI (54%, p = 0.32). However, 5-year OS did vary significantly between patients with RCR and WLI (85%), RCR without WLI (55%), non-RCR with WLI (60%), and non-RCR without WLI (25%; p < 0.01). In Cox regression analysis, RCR was associated with improved OS after controlling for WLI, extrapulmonary metastases, and patient age (HR 0.51, p = 0.03).

Conclusions: Patients with EWS who had pulmonary metastases at diagnosis had improved OS if they achieved RCR and received WLI, despite having no significant differences in rates of pulmonary relapse. Further research is needed to determine whether clearance of pulmonary disease achieved through surgical metastasectomy provides a comparable survival benefit and if any subsets of patients have a reduced risk of pulmonary relapse after resection. Research Sponsor: None.
Outcomes in patients with advanced gastrointestinal stromal tumor who did not have baseline ctDNA detected in the INTRIGUE study.

Jonathan C. Trent, Robin Lewis Jones, Suzanne George, Hans Gelderblom, Patrick Schöffski, Margaret von Mehren, John Raymond Zalcberg, Yoon-Koo Kang, Alibiruni Ryan Abdul Razak, Steven Attia, Axel Le Cesne, William Reichmann, Kam Sprott, Haroun Achour, Matthew L. Sherman, Rodrigo Ruiz-Soto, Jean-Yves Blay, Michael C. Heinrich, Sebastian Bauer, on behalf of the INTRIGUE Investigators; Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL; Sarcoma Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom; Dana-Farber Cancer Institute, Boston, MA; Leiden University Medical Center, Leiden, Netherlands; University Hospitals Leuven, Department of General Medical Oncology, Leuven Cancer Institute, KU Leuven, Leuven, Belgium; Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA; Monash University School of Public Health and Preventive Medicine and Department of Medical Oncology, Alfred Health, Melbourne, VIC, Australia; Asan Medical Center, University of Ulsan, Seoul, Korea, Republic of (South); Toronto Sarcoma Program, Princess Margaret Cancer Center, Toronto, ON, Canada; Mayo Clinic, Jacksonville, FL; Gustave Roussy, Villejuif, France; Deciphera Pharmaceuticals, LLC, Waltham, MA; Centre Léon Bérard, Lyon, France; Portland VA Health Care System and OHSU Knight Cancer Institute, Portland, OR; Department of Medical Oncology, Sarcoma Center/West German Cancer Center, University Hospital Essen, University Duisburg-Essen and German Cancer Consortium (DKTK), Partner Site University Hospital Essen, Essen, Germany

Background: Ripretinib is a switch-control tyrosine kinase inhibitor approved for patients (pts) with gastrointestinal stromal tumor (GIST) who received prior treatment with ≥3 kinase inhibitors, including imatinib. Exploratory baseline circulating tumor DNA (ctDNA) next-generation sequencing (NGS) analysis from INTRIGUE showed pts with second-line advanced GIST with primary KIT exon 11 mutations and secondary resistance mutations exclusively in KIT exons 17/18 derived clinical benefit from ripretinib but not sunitinib (Bauer S et al. J Clin Oncol. 2023; Abs 397784). Outcomes in pts with ctDNA-D had not been evaluated. Here, we present exploratory data from INTRIGUE in pts who had baseline ctDNA-ND vs ctDNA detected (ctDNA-D).

Methods: INTRIGUE is an open-label, phase 3 study that enrolled pts with advanced GIST who had disease progression on or intolerance to imatinib (NCT03673501). Pts were randomized 1:1 to ripretinib 150 mg once daily (QD) or sunitinib 50 mg QD (4 wks on/2 wks off) and stratified by mutation according to local pathology report. Baseline peripheral whole blood was analyzed by Guardant360, a 74-gene ctDNA NGS-based assay. Pts with ctDNA-D had ≥1 somatic alteration in the 74 genes analyzed.

Results: Pts with ctDNA-ND (82/362, 22.7%) were younger (median: 55.5 vs 62.0 years) and had smaller sums of longest diameters of target lesions (median [range]: 57.6 [11–459] vs 108.8 [15–418] mm) vs ctDNA-D (280/362, 77.3%). Progression-free survival (PFS) was longer in pts with ctDNA-ND vs ctDNA-D and numerically higher with ripretinib vs sunitinib in pts with ctDNA-ND (Table). Pts with ctDNA-ND categorized as not having a KIT exon 9 mutation at randomization (KIT exon 11, other KIT/PDGFRA, or KIT/PDGFRA wild-type; n = 71) had longer PFS with ripretinib vs sunitinib (median not estimable [NE] vs 11 months; HR = 0.56; 95% CI 0.28 to 1.12). Objective response rate (ORR) and overall survival (OS) were higher with ctDNA-ND vs ctDNA-D. Safety was similar between groups and consistent with the primary analysis.

Conclusions: Pts with ctDNA-ND had better efficacy outcomes vs pts with ctDNA-D in both treatment arms; PFS was numerically higher with ripretinib vs sunitinib in pts with ctDNA-ND. Although little is known about the biology driving ctDNA in GIST, these data suggest pts may have improved outcomes and different treatment sensitivity based on ctDNA detectability. Clinical trial information: NCT03673501. Research Sponsor: Deciphera Pharmaceuticals, LLC.

<table>
<thead>
<tr>
<th>Outcomes by ctDNA detection.</th>
<th>ctDNA-ND</th>
<th>ctDNA-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts, n</td>
<td>40 vs 42</td>
<td>135 vs 145</td>
</tr>
<tr>
<td>mPFS, months</td>
<td>16.6 vs 11.0</td>
<td>6.8 vs 6.9</td>
</tr>
<tr>
<td>HR (CI)</td>
<td>0.73 (0.39 to 1.39)</td>
<td>1.23 (0.92 to 1.64)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>25.0 vs 26.2</td>
<td>19.3 vs 15.9</td>
</tr>
<tr>
<td>Response difference, % (CI)</td>
<td>-1.2 (-19.6 to 17.5)</td>
<td>3.4 (-5.5 to 12.4)</td>
</tr>
<tr>
<td>mOS, months</td>
<td>NE vs NE</td>
<td>27.7 vs 29.5</td>
</tr>
<tr>
<td>HR (CI)</td>
<td>0.84 (0.25 to 2.75)</td>
<td>1.05 (0.75 to 1.47)</td>
</tr>
</tbody>
</table>

Data cutoff: *Sept 1, 2021; **Sept 1, 2022. CI, 95% confidence interval; HR, hazard ratio; m, median; R, ripretinib; S, sunitinib.
Safety, pharmacokinetics (PK), and clinical activity of bezuclastinib + sunitinib in previously-treated gastrointestinal stromal tumor (GIST): Results from part 1 of the phase 3 Peak study.

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Background: Patients with GIST often relapse after first line therapy with imatinib due to secondary resistance mutations in KIT. As the KIT mutation targeting profiles of bezuclastinib (type I TKI) and sunitinib are distinct and complementary, when combined they inhibit a broad spectrum of secondary KIT mutations. In a prior Phase 1b/2a study (NCT02401815), the combination of the original formulation (Form. A) of bezuclastinib + sunitinib had an acceptable safety profile and was associated with clinical activity at the RP2D (Wagner, JAMA Oncol 2021;7(9):1343-50). An optimized formulation (Form. B) of bezuclastinib with improved bioavailability was developed to reduce pill burden for GIST pts. PK and safety results from the Part 1a lead-in of Peak (NCT05208047) have been previously presented (Wagner, CTOS 2022, P320). Herein we intend to report comprehensive clinical results from Part 1a including duration of therapy, initial response assessment and updated safety.

Methods: Peak, a randomized Phase 3, open-label study, aims to evaluate efficacy and safety of bezuclastinib + sunitinib vs sunitinib in pts with imatinib-resistant or intolerant GIST. In Part 1a of the 3-part study, bezuclastinib (Form. B) dosing was escalated in serial cohorts based on PK results until the target exposure, comparable to those achieved at the RP2D established in the Phase 1b/2a study, was achieved. Key inclusion: adult with locally advanced, metastatic and/or unresectable GIST, 1 measurable lesion according to modified RECIST v1.1, and ECOG PS 0 to 2. Results: Part 1a enrolled 19 pts. Five pts (Cohort 1) received the starting dose of once daily (QD) bezuclastinib 300 mg + sunitinib 37.5 mg; dose was escalated to 600 mg with 14 pts receiving bezuclastinib 600 mg + sunitinib 37.5 mg. Median age - 60 yrs (range: 42-77); 68% male; 95% ECOG PS 0-1; 95% metastatic and 5% locally advanced. As of Sept 2022 data cutoff, the median (range) treatment duration was 6 weeks (3.1, 23.9). Due to AEs, one pt required dose reduction of bezuclastinib (Gr 3 diarrhea) and 1 pt discontinued (Gr 2 rash). The majority of TEAEs were low grade, with no ≥ Gr4. Most common TRAEs were diarrhea (37%), neutropenia (37%), ALT (32%) and AST (26%) increases. One pt experienced SAEs of Gr 2 neutropenia and pyrexia and Gr 3 thrombocytopenia. Steady state exposure in pts receiving QD doses of bezuclastinib 600 mg + sunitinib 37.5 mg in this study were similar to that at the RP2D established in the prior Phase 1b/2a study. Conclusions: Initial data from Peak shows an encouraging safety and tolerability profile with no unique safety signals when compared to the known safety profile for sunitinib monotherapy. A dose of bezuclastinib 600 mg QD + sunitinib 37.5 mg QD was confirmed for use in Peak study Part 2, for which enrollment is ongoing. Updated data from Part 1a, including response data, will be presented. Clinical trial information: NCT05208047. Research Sponsor: Cogent Biosciences.
Combination targeted therapy with avapritinib and sunitinib in patients with refractory gastrointestinal stromal tumors after failure of standard treatments: A small prospective pilot study.

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Background: There is currently no standard treatment after ripretinib beyond the fourth-line setting for refractory gastrointestinal stromal tumors (GISTs). A combination of tyrosine kinase inhibitors (TKIs) is rational to be potentially effective after failure of standard therapies. The objective of this study was to explore the efficacy and safety of avapritinib plus sunitinib in refractory GISTs. Methods: This was a prospective cohort study in part of a real-world trial (NCT05461664) exploring avapritinib in GIST patients (pts) after failure of standard treatments. Participants received avapritinib 100–200 mg once a day (QD) combined with sunitinib 25–37.5 mg QD continuously in 28-day cycles until disease progression (PD) or discontinuation from January 2022 to January 2023. Clinical outcomes including objective response rate (ORR), survival and safety were assessed. Results: A total of 11 pts with a median age of 57 years were enrolled. Median follow-up duration was 4.1 months (range, 1.4–12.8 months). Median sum of target lesions was 28.2 cm (range, 6.6–47.0 cm). Four pts had primary KIT exon 11 mutation, 6 had exon 9 and one had exon 17, secondary mutation KIT exon 13 was in 2 pts, exon 14 in one, exon 16 in 2 and exon 17 in 7 pts. Seven pts received more than 4 lines of prior TKIs, three received 3 and one had 2 lines of prior TKIs. One patient (9.1%) achieved partial response (PR) with 48.7% lesion length reduction, 9 (81.8%) had stable disease (SD) with 8 out of 9 pts achieving tumor shrinkage (median sum of lesion reduction of 20.8% [range, 9.8–27.3%]), and one (9.1%) had PD according to mRECIST1.1. Eight pts (72.8%) achieved PR, one (9.1%) had SD, and 2 (18.2%) had PD according to the Choi criteria. Until last follow-up, 4 pts progressed, one withdrew from the study and one discontinued treatment after surgery. Five pts were still receiving treatment, one exceeded 1 year with 26.3% lesion reduction in the seventh line setting. Progression-free survival and overall survival results were immature. ORR and lesion reduction trended favorably in those with KIT activation loop (AL) mutations, but this was not statistically significant. The dose of avapritinib (100–150 mg/d) and sunitinib (25–37.5 mg/d) could be tolerated. Common adverse events (AEs) were anemia, leukopenia, diarrhea, fatigue, periorbital and face oedema, and memory impairment. Common grade $\geq$3 AEs included anemia (54.5%), leukopenia (36.4%), diarrhea (36.4%), tumor hemorrhage (27.3%) and gastrointestinal hemorrhage (18.2%). Conclusions: The preliminary results from this study demonstrated meaningful clinical benefit with avapritinib plus sunitinib, achieving significant lesion reduction in refractory GISTs, especial those with KIT AL secondary mutations. Further studies are warranted to determine the optimal dosing regimen of two targeted drugs. Clinical trial information: NCT05461664. Research Sponsor: None.
Fluorine-18 fluorodeoxyglucose (\(^{18}\text{FDG}\))-uptake assessment of PDGFRA mutant gastrointestinal stromal tumors (GIST): A retrospective multicenter Italian study.

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**Background:** D842V PDGFRA mutation identifies a molecular subtype of GIST, primarily resistant to imatinib and characterized by higher indolent behavior and a prominent immune profile. Although functional imaging with \(^{18}\text{FDG-PET}\) plays a proven role in GIST, especially in early assessment tumor response, less is known about \(^{18}\text{FDG-uptake}\) according to the GIST molecular subtypes. Taking into account of clinical and molecular features of D842V mutant GIST, we assumed that this subset of GIST could also have a different \(^{18}\text{FDG-uptake}\). Therefore, the aim of the present study has been to investigate the degree of FDG uptake of PDGFRA mutant GIST, focusing on D842V ones, in order to better define the role of functional imaging in this rare and peculiar subset of GIST. **Methods:** Patients with PDGFRA mutant GIST underwent \(^{18}\text{FDG-PET}\) were retrospectively included from seven GIST Italian reference centers. Data on maximum standardized uptake (SUVmax) value of primary tumor or metastatic disease were collected. **Results:** 71 patients have been included: 37 (55.1%) with D842V PDGFRA mutant GIST (group A) and 34 (47.9%) with PDGFRA non-D842V mutant GIST (group B). Additionally, 30 patients with exon 11 KIT mutant GIST have been included, as control (group C). SUVmax values were obtained from primary tumor and metastatic lesions in 55 (54,4%) and 46 (45.6%) patients, respectively. Considering the whole population of 101 patients, the global median SUVmax was 3,7 (IQR 0-9.1), while the median SUVmax for group A, B, and C was 0, 3,6, and 10,4, respectively. The median SUVmax of PDGFRA mutant GIST was significantly lower than the median value of exon 11 KIT mutant GIST (p < 0.001). Notably, median \(^{18}\text{FDG-uptake}\) was significantly lower in D842V PDGFRA mutant GIST compared to PDGFRA non-D842V mutant ones (p = 0.021). **Conclusions:** PDGFRA D842V-mutant GIST present an overall lower \(^{18}\text{FDG-uptake}\) compared to other GIST subgroups. This feature could be related to their specific molecular background and is consistent with their higher tendency to an indolent behavior. Therefore, the role of functional imaging with \(^{18}\text{FDG-PET}\) in this subset of GIST is limited. Finally, the prognostic value of the \(^{18}\text{FDG-uptake}\) degree within all PDGFRA mutant GIST will be investigated in the future. **Research Sponsor:** None.
Antitumor activity of olverembatinib (HQP1351) in patients (pts) with tyrosine kinase inhibitor (TKI)–resistant succinate dehydrogenase (SDH)–deficient gastrointestinal stromal tumor (GIST).

Haibo Qiu, Zhi-wei Zhou, Ye Zhou, Xiangbin Wan, Ning Li, Kaixiong Tao, Yong Li, Xin Wu, Zi Chen, Lihui Liu, Lichuang Men, Hengbang Wang, Eric Liang, Cunlin Wang, Lixin Jiang, Dajun Yang, Rui-Hua Xu, Yifan Zhai; State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University, Guangzhou, China; Fudan University Shanghai Cancer Center, Shanghai, China; Henan Cancer Hospital, Zhengzhou, China; Union Hospital Medical College Huazhong University of Science and Technology, Wuhan, China; Guangdong Provincial People's Hospital, Guangzhou, China; Chinese People's Liberation Army General Hospital, Beijing, China; Ascentage Pharma (Suzhou) Co., Ltd., Suzhou, China; Ascentage Pharma Group Inc., Rockville, MD; State Key Laboratory of Oncology in South China Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China; Ascentage Pharma (Suzhou) Co., Ltd., Suzhou, China; Ascentage Pharma Group Inc., Rockville, MD

Background: Treatment of pts with GIST has been transformed by TKIs. However, treatment resistance is a challenge in managing locally advanced or metastatic disease. Pts with SDH-deficient GIST typically present with multifocal and multinodular disease that is insensitive to most TKIs. Olverembatinib is an investigational novel, potent, orally active third-generation TKI with promising activity against GIST in multiple preclinical models.

Methods: The aim of this study was to evaluate the safety and efficacy (per RECIST v1.1) of olverembatinib in pts with TKI-resistant metastatic SDH-deficient GISTS (confirmed by immunohistochemistry). Olverembatinib was administered orally once every other day (QOD) in 28-day cycles. Results: As of January 15, 2023, 20 pts with SDH-deficient GIST had received $1 dose of olverembatinib (median age, 30 [14-56] years), and 19 had received 1 to TKIs (50% of pts $\geq 3$; Table). The dose range of olverembatinib was 20 to 50 mg (50 mg cohort [n = 6]; 40 mg [n = 8]; 30 mg [n = 6]). The median (range) treatment duration was 7.8 (1.81-42.3) months. A total of 5 of 20 pts experienced partial response (PR) as the best response. Of 16 evaluable pts treated with $> 4$ cycles of olverembatinib, the clinical benefit rate (CBR; complete response + PR + stable disease > 4 cycles) was 93.8% (15/16); the longest treatment duration was 42 months. All pts experienced treatment-emergent adverse events (AEs; most, grade 1 or 2); 2 pts experienced grade 3 AEs; the only hematologic AE with an incidence rate $\geq 20\%$ was anemia (55%). A total of 15 (75%) pts experienced treatment-related AEs (grade 3 neutropenia [n = 1]). No treatment-related serious AEs were reported. Conclusions: Olverembatinib was well tolerated up to 50 mg QOD and showed antitumor activity in pts with TKI-resistant, SDH-deficient GIST. A total of 5 PRs were reported among 20 evaluable pts and 15 SDs among 16 pts treated for $\geq 4$ cycles (98.3% CBR). These promising findings warrant further investigation. Internal study identifier: HQP1351SJ003. Clinical trial registration: NCT03594422. Research Sponsor: Ascentage Pharma Group.

<table>
<thead>
<tr>
<th>Baseline characteristics.</th>
<th>No.</th>
</tr>
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<tbody>
<tr>
<td>Median age (range), y</td>
<td>30 [14-56]</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Primary tumor site, no. (%)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Stomach</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Prior TKI, no. (%)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>0</td>
<td>3 (15)</td>
</tr>
<tr>
<td>1</td>
<td>10 (50)</td>
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Clinical utility of liquid-based comprehensive genomic profiling (CGP) in gastrointestinal stromal tumors (GIST).

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Background: GIST is the most common mesenchymal cancer of the digestive tract. Beyond surgery, treatment for GIST focuses largely on tyrosine kinase inhibitors (TKI), whose selection and potential resistance depend on select mutations. We present the molecular landscape of GIST utilizing tissue and liquid biopsies with emphasis on the clinical utility of liquid biopsy in advanced GIST. Methods: Liquid (FoundationOne Liquid CDx [F1LCDx]) and tissue (FoundationOne CDx) CGP was performed by hybrid capture, targeted NGS at Foundation Medicine Inc. Tissue and liquid samples from 2,198 and 147 patients, respectively, were analyzed. A cohort of 27 paired tissue and liquid samples were also evaluated. The levels of circulating tumor DNA (ctDNA) in liquid biopsies was quantified by tumor fraction (TF), with a TF algorithm incorporating aneuploidy, variant allele frequency, and canonical alterations detected on F1LCDx.

Results: Tissue CGP (n = 2,198) revealed the following prevalence of primary driver alterations: KIT (77%), PDGFRA (8%), NF1 (6%), SDHA/B/C/D (SDHx, 3%) and BRAF (1%). Rates of molecular markers previously associated with worse prognosis included: CDKN2A (29%), RB1 (9%), TP53 (6%) and SETD2 (4%). 7% of cases had no reportable known pathogenic alterations in canonical GIST genes (wild-type GIST), while 2% of cases had a mutation in more than one driver. In a cohort of 147 liquid biopsies, TF was < 1% in 68.0%, 1-10% in 18.4%, > 10% in 13.6% of samples. In samples with elevated TF (> 10%), the prevalence of targetable driver alterations in KIT (89%), PDGFRA (4%), NF1 (4%) and BRAF (4%) was comparable to the tissue prevalence. In liquid, 58% (39/67) of samples with a KIT-driver mutation had a co-occurring imatinib-resistant KIT alteration. In addition, 4/147 patients (3%) were predicted to harbor a germline KIT mutation, including one patient (0.6%) with a potential imatinib-resistant KITD820G germine mutation and another with clinical suspicion of germline KITL576P mutation due to the presence of multiple primary GISTs, hyperplasia of myenteric plexus and dysplastic skin nevi. In paired tissue/liquid samples, liquid detected 2/2 driver mutations found in tissue when liquid TF was > 10%, and 5/6 in specimens with TF > 1%. In the overall cohort, the relative prevalence of KIT exon 13 and 17 mutations was comparable in tissue vs liquid, while imatinib-resistance KIT exon 13 and 17 mutations were enriched in liquid samples. Conclusions: Known driver and TKI-resistant mutations of both somatic and potential germline origin are identified in peripheral blood ctDNA of GIST patients. Liquid biopsy shows high concordance to tissue in identifying driver mutations in the presence of elevated TF and may exhibit TKI-resistant specific alterations. This study indicates that liquid biopsy may be useful in the molecular classification of GIST during the medical management of advanced GIST patients. Research Sponsor: Foundation Medicine, Inc.
Longitudinal follow-up and outcomes of pediatric and adult patients with SDH-deficient GIST.

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Background: Gastrointestinal stromal tumor (GIST) are gastrointestinal non-epithelial neoplasms most commonly driven by somatic mutations in KIT or PDGFRA. Approximately ten percent of GIST are due to germline mutations in SDHx or epigenetic loss of expression of SDHC. While KIT and PDGFRA driven GIST respond to treatment with tyrosine kinase inhibitors, effective systemic therapies for SDH-deficient GIST have not yet been identified. SDH-deficient GIST are indolent tumors that typically progress slowly over time. A better understanding of the natural history of patients with these neoplasms is critical to identify effective treatments and improve patient care. A cohort of patients with SDH-deficient GIST is followed at the NIH Clinical Center and through the NIH Pediatric and Wild-type GIST Clinic. The aim of this study is to characterize the long-term outcome of this cohort of patients. Methods: Data from patients with SDH-deficient GIST enrolled in a study Natural History and Biospecimen Acquisition for Children and Adults with Rare Solid Tumors (NCT03739827) from January 2019 through January 2023 at the NIH were evaluated. In addition to review of medical records and imaging, when available, tumors were characterized by sequencing of SDH genes. Germline analysis of SDH genes was offered to consenting patients and families. Results: Clinical information and specimens were collected from 77 GIST patients (median age at diagnosis 21.5, [range 7-57] years; 72.7% (56) female, 21.3% (21) male) were classified by molecular subtypes: 33.8% SDHC epimutation, 28.6% SDHA, 22.1% SDHB, 14.3% SDHC and 1.3% SDHD. Median age at presentation of SDHC epimutation was younger (14.5 years, range: 8-56) when compared to SDHA (27.5 years, range: 7-55), SDHB (22 years, range: 8-54), SDHC (18 years, range: 10-57) and SDHD (39 years, N = 1). Most commonly, patients had at least one surgery (55.8%) while a lower proportion had four or more (7.8%). Primary tumors occurred in the stomach with 26% having metastases at presentation the most common location being the liver (10.4%). Overall, 64.9% of patients were treated with imatinib, 39% were treated with sunitinib and 15.6% received other additional systemic therapies. Within the cohort there were 13% of patients with paragangliomas and 6.5% with chondromas while only 9.1% had a family history of GIST. Conclusions: Longitudinal follow-up of an SDH-deficient GIST patient cohort will allow for better understanding of the natural history including treatment history and survival of patients with this rare disease and will help to optimize strategies for treatment and follow-up of these patients. Research Sponsor: U.S. National Institutes of Health.
Efficacy and safety of ripretinib in Chinese patients with advanced gastrointestinal stromal tumors (GIST) as ≥4th line therapy: Long-term update from a single-arm, phase 2 trial.

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Background: In INVICTUS study (NCT03353753), ripretinib as ≥4th line (4L) GIST therapy significantly improved median progression-free survival (mPFS) versus placebo (hazard ratio 0.15, 95% confidence interval [CI] 0.09–0.25; mPFS 6.3 vs 1.0 months) with a satisfactory safety profile. In the primary analysis (data cut-off: 26 Feb 2021) of the bridging study (NCT04282980) of INVICTUS, ripretinib as ≥4L therapy showed consistent efficacy and safety profiles in Chinese GIST patients to those in INVICTUS, with mPFS of 7.2 months and objective response rate (ORR) of 18.4% (7/38 patients). The overall survival (OS) data was immature at the primary analysis. Here we report the long-term updates of this bridging study.

Methods: Patients received ripretinib 150 mg once daily continuously in 28-day cycles until progressive disease or other protocol-specified events for treatment discontinuation. The primary endpoint was progression-free survival (PFS) by independent radiologic review (IRR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 GIST-Specific Standard. Secondary endpoints included ORR by IRR, time to best response (TBR), duration of response (DOR), OS and safety. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

Results: Overall, 39 patients were enrolled. Thirty-eight patients received continuous ripretinib treatment and were included in the efficacy analysis set. All 39 patients received at least one dose of ripretinib and were included in the safety set. The updated data cut-off was 23 Aug 2022. The overall median follow-up (90% CI) was 23.00 (11.99, 24.87) months. In the efficacy analysis set, mPFS (90% CI) by IRR was 6.44 (2.89, 8.31) months and ORR was 21.1% (8/38 patients). Median TBR and median DOR for the 8 patients with confirmed partial response were 2.25 and 8.57 months, respectively. The median OS (95% CI) in the efficacy analysis set was 25.56 (11.73, not evaluable) months. In the safety set, 20.5% of patients experienced ≥1 grade 3/4 treatment-related treatment-emergent adverse events (TRAEs). Compared to the primary analysis, the increase in TRAEs and new TRAEs leading to dose modification were minimal after 18 months of additional follow-up.

Conclusions: After long-term follow-up, the more mature results continued to support the clinically meaningful benefit in PFS and also demonstrated clinically meaningful benefit in OS in Chinese ≥4L GIST patients, while the safety profile remained satisfactory. Clinical trial information: NCT04282980. Research Sponsor: Zai Lab (Shanghai) Co., Ltd.
Exploratory novel biomarker and resistance mechanism of milademetan, an MDM2 inhibitor, in amplified MDM2 intimal sarcoma from an open-label phase 1b/2 trial (NCCH1806/MK004).

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Background: Amplified Murine double minute 2 (MDM2) is found in >70% of intimal sarcoma, known as one of the ultra-rare sarcomas. Milademetan (DS3032, RAIN-32) is a novel, specific, small-molecule MDM2 inhibitor that disrupts MDM2 and the tumor suppressor protein p53 interactions in tumor cells. We conducted a phase 1b/2 trial (Trial registration No: JMA-IIA00402) in patients with amplified MDM2 wild-type TP53 intimal sarcoma as a sub-study under the nationwide large registry for rare cancers in Japan (MASTERKEY Project). Eleven patients were enrolled, and ten were included in the efficacy analysis. Two (20%) patients had durable responses for >15 months. Milademetan provided clinical benefits in patients with amplified MDM2 intimal sarcoma. Predictive biomarkers other than amplified MDM2 and acquired resistance mechanisms for milademetan are unknown.

Methods: Whole-exome and RNA sequencing analyses of pre-treatment tissue samples were conducted to identify determinants of response. Genomic alterations were analyzed for 10 patients, and gene expression was analyzed for 9 patients using their pre-treatment tissue samples. Targeted sequencing of cell-free DNA (cfDNA) samples (liquid biopsy) was also conducted sequentially at three points [before treatment with milademetan (baseline), at Cycle 2 Day1, and at the time of disease progression] to identify determinants of response and resistance. Results: From whole-exome and RNA sequencing analyses of pre-treatment tissue samples, we could not find any molecular pathways associated with the anti-tumor activity of milademetan. Focusing on 8 genes (CDK4, CDKN2A, CDKN2B, EGFR, ERBB3, MDM2, PDGFRA, TP53) known to be frequently affected in intimal sarcoma and 10 genes (AKT1, ATM, BBC3, CDKN1A, CDKN1C, CHEK2, MDM4, PMAIP1, PPM1D, TWIST1) reported to be associated with MDM2 inhibitor responses; we found that anti-tumor activity correlated with amplified TWIST1 (p-value = 0.028) and negatively with CDKN2A loss (p-value = 0.071). Eight of the 10 patients had their cfDNA collected sequentially at baseline, at Cycle 2 Day1 and disease progression; however, one did not consent to the exploratory analysis study using cfDNA, and one had cfDNA collected at baseline but not at disease progression due to ongoing treatment. Of the eight patients, TP53 mutations in cfDNA were detected in one and five patients at baseline and disease progression, respectively. The cfDNA allele frequency of TP53 mutations increased with disease progression. Conclusions: CDKN2A loss and amplified TWIST1 could be associated with the anti-tumor activity of milademetan in patients with amplified MDM2 intimal sarcoma. Acquired TP53 mutations were detected in sequential liquid biopsies as loss-of-function mutations, and these TP53 mutations might compromise the anti-tumor activity. Clinical trial information: JMA-IIA00402. Research Sponsor: None.
Large versus limited molecular profiling panel screening program in patients with metastatic sarcoma: An exploratory subgroup analysis from the ProfiLER 02 trial.

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**Background:** Profiler 02 (NCT03163732) is a multicentre, randomized molecular screening clinical trial aiming to evaluate the feasibility and the benefit of a large NGS (Next-generation sequencing) panel (FoundationOne Medicine NGS panel or FOne, 324 cancer-related genes) compared to a limited one (Control panel or CTRL, 87 cancer-related genes) in terms of clinical, quality of life and health economic outcomes. We present here the results of the patients with advanced/metastatic sarcoma included in the Profiler 02 trial. **Methods:** Patients (pts) were enrolled during their first-line of standard therapy for an advanced sarcoma. All sarcomas diagnosis were performed within the RRePS network (French pathology network of reference for sarcomas) and a central pathological review confirmed if quality and quantity of material were acceptable for molecular analysis. Patients were randomized within the two study arms (FOne versus CTRL) and DNA was analysed using both panels. The primary objective of the study was to compare the proportion of patients for whom a genomically driven recommended therapy (RT) could be initiated based on the FOne versus CTRL panels. A dedicated Molecular Tumour Board (MTB) reviewed tumour genomics data of both panels independently to propose a RT. **Results:** From January 2018 to July 2019, 39 pts with sarcoma (20F, 19M), with a median age of 54 years [21-81], were randomized between FOne Arm (17 pts) and CTRL Arm (22 pts). Pathological subtypes per arm are presented in the the table. Overall, 19 pts (49%) had at least one genomically driven RT, 11 according to both panels and 8 according to FOne panel exclusively (McNemar’s test, \( p = 0.01 \)). Main RT were CDK4/6 inhibitors \( n=5 \), PI3K/AKT/mTOR inhibitors \( n=4 \), and immunotherapy \( n=4 \). After the MTB, a RT was initiated for seven patients, four according to FOne panel only and three according to both panels. Importantly, a complete response was observed for a metastatic MPNST (Malignant Peripheral Nerve Sheath Tumor) with a high tumour mutational burden (TMB) detected by the FOne panel (37 mutations per megabase) and treated with durvalumab (anti-PDL1) + tremelimumab (anti-CTLA4). **Conclusions:** Although from an exploratory subgroup analysis, these results suggest that a large molecular profiling panel including TMB (FOne panel) might increase the number of RT and the number of sarcoma patients treated. Studies of precision medicine in rare cancers such as sarcomas are feasible, this approach could benefit to patients. Clinical trial information: NCT03163732. Research Sponsor: LYriCAN (INCa-DGOS-Inserm_12563), NetSARC (INCA & DGOS), InterSARC (INCA), LabEx DEweCan (ANR-10-LABX 0061), PIA Institut Convergence François Rabelais PLAsCan (PLASCAN, 17-CONV-0002) and EURACAN (EC 739521); ARC, La Ligue contre le Cancer, Roche.

### Pathological subtypes distribution

<table>
<thead>
<tr>
<th>Pathological subtype</th>
<th>FOne Arm</th>
<th>CTRL Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyosarcoma</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Undifferentiated pleomorphic sarcoma</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>MPNST</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Malignant fibrous tumor</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Synovial Sarcoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myofibroblastoma</td>
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<td>0</td>
</tr>
<tr>
<td>MPNST</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>CIC-rearranged sarcoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>17</td>
</tr>
</tbody>
</table>

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Alternative splicing (AS) regulation as a novel therapeutic target in soft-tissue sarcoma (STS).

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Background: There is an urgent clinical need to identify novel treatments for advanced STS, since all the clinical trials testing chemotherapy combinations have failed to improve survival compared to doxorubicin (dox) alone. AS deregulation has been associated with cancer initiation, progression and resistance to therapy. This deregulation can occur due to mutations or imbalanced expression or activity of splicing factors (SF). The alteration SF can alter thousands of pre-mRNAs, increasing cellular complexity and facilitating tumour progression. CDC-like kinases (CLK) that phosphorylate serine-arginine-rich SF (SRSFs), are key regulators of AS. SM09419 is an oral pan CLK/DYRK inhibitor that has been shown to inhibit SRSF phosphorylation, selectively modify spliceosome activity and decrease tumour growth by multiple mechanisms including the downregulation of Wnt/β-catenin signalling, a pathway that we reported to be important in sarcoma. Methods: A panel of 9 STS cell lines, including LMS (CP0024, IEC005, AA, SK-UT-1), LPS (93T449), synovial sarcoma (MCP037) and UPS (MCP016, MCP021, MCP025) were used to analyse the effect of SM09419 (provided by Biosplice) or PRI-724 (Wnt/β-catenin inhibitor) on cell viability (MTS assays). TOP flash β-catenin/TCF-responsive reporter assay was performed to evaluate the inhibition of the Wnt/β-catenin pathway in response to SM09419. In vivo experiments tested the combination of SM09419 (25mg/kg 5 days on and 2 off, for 21 days cycle) plus IP dox (5mg/kg once a week for 21 days cycle) in LMS (IEC005) and synovial sarcoma (FJD-SS-001) PDX models. Results: Our results showed that SM09419 had superior activity in STS cells compared to specific Wnt/β-catenin inhibitors with IC50 values starting at 29.8 nM in SK-UT-1 cell line, whereas PRI-724 IC50 values were clearly higher, starting from 5.18 μM in 93T449 cells. SM09419 treatment significantly inhibited the transcriptional activity of β-catenin by 40% in the MCP021 cells, demonstrating the regulatory activity of AS inhibitors on this pathway. In vivo studies confirmed the higher efficacy of SM09419 in monotherapy compared to dox, in inhibiting tumour growth (p < 0.05), which was potentiated when combined with dox. The combination was increasingly active in synovial sarcoma with tumour regressions in 3 out of 4 mice, including one complete response. Treatment schedule was adapted to a single IP administration of dox (5mg/kg) and 5 administrations of SM09419 (25mg/kg), to improve the tolerability of the combination. Conclusions: The effects of pan CLK/DYRK inhibition on growth and survival of STS cancer cell lines and PDX models, indicate that can STS may be therapeutically addressed with these AS-modulators. The combination of SM09419 with dox was active in STS preclinical models known for their resilience toward treatment. Based on these results, the exploration of such combinations in clinical trials is warranted. Research Sponsor: Foundation AECC - GEACC19007MA.
Novel genomic alterations and transcriptomic-based tumor microenvironment classification of sarcoma and their impact on treatment decision making.

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Background: Sarcomas are rare tumors of mesenchymal origin, with over 50 different histological sarcoma subtypes. The heterogeneous molecular and immunologic characteristics of sarcomas present many challenges for diagnostics and treatment plans. We aim to provide a more comprehensive molecular testing and immune profiling of sarcoma patients. **Methods:** The cohort consisted of samples from 200 patients diagnosed with sarcomas. WES and whole transcriptome analysis were performed on all samples. Tumor Portrait test identified genomic alterations of sarcomas and classified tumor microenvironment (TME) subtypes. The actual response to immune checkpoint inhibitor (ICI) treatment was determined using RECIST criteria and compared to response predictions by the Tumor Portrait test. **Results:** Across sarcoma subtypes, the most common mutations were in tumor suppressors including TP53, RB1, CDKN2A, and TSC1/2. We report fusions in 20.5% of cases, with commonly described diagnostic fusions accounting for 34/41 cases. In one case, the detection of the ZC3H7B-BCOR fusion suggested a change in diagnosis from uterine leiomyosarcoma to endometrial stromal sarcoma. Several previously unreported fusions were detected, including potentially targetable (ARID1A-NUDC, MICAL3-MAPK) and prognostic (YWHE-CIC) fusions. DNA damage response related genes were mutated in 12% of cases. Other less commonly detected targetable alterations were found in the following genes: MDM2, CDK4, SMARCBI, NF1, PIK3CA, NTRK1-3, FGFR1-4. Transcriptomic-based TME classification found that 52% of patients had an Immune-Enriched (IE) TME, with 26.5% and 25.5% grouped in the IE-Fibrotic and IE-non-Fibrotic subtype, respectively, which we previously showed is associated with good response to ICI treatment. In contrast, 48% of the patients presented with a Fibrotic (F, 30%) or Desert (D, 18%) subtype, are predicted to have a poor response to ICI treatment. Our classification of sarcomas based on TME subtypes conforms well with predicted responses of tumors to ICI therapy found in previous reports. Soft-tissue angiosarcomas, undifferentiated pleomorphic sarcoma, and myxofibrosarcomas presented TMEs of the IE subtype in 75% of cases, significantly more compared to 34% of the bone neoplasm cases, which are known for their favorable and unfavorable response to ICI therapy, respectively (Chi-squared test, p = 0.001). In retrospective chart review, we had response data on 24 patients who received ICI treatment. The disease control rate, defined as CR+PR+SD as best response, was significantly higher in the IE subtype compared to the F/D subtype (85.7% vs 20%, Chi-squared test, p < 0.003). **Conclusions:** Together, our findings identify actionable and diagnostic alterations in diverse mesenchymal tumors and suggest that ICI treatment may be beneficial in immune-enriched sarcomas. Research Sponsor: BostonGene Corporation.
Next generation sequencing reveals targetable mutations in multiple sarcoma histologies.

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Background: Sarcomas are a rare and heterogeneous group of cancers that arise from bone or soft tissue, and two thirds have poorly defined mutational profiles. Given their rarity, few comprehensive studies have fully characterized mutations and gene expression across sarcoma histologies correlated with clinical outcomes. Further studies are needed to determine the presence of targetable mutations that may improve patient outcomes. In this study, we explored the genomic landscape and clinical actionability of sarcoma mutations from patients enrolled in our CAUSAL (Cohort to Augment the Understanding of Sarcoma survivorship Across the Lifespan) study. Methods: Between 04/01/2022 and 01/01/2023, 481 participants, treated from 2012 – present with multiple sarcoma histologies were enrolled on CAUSAL. Next Generation Sequencing (NGS) was performed on primary or metastatic tumors from 76 patients to determine DNA mutations within a 648 gene panel. Whole transcriptome RNA sequencing (seq) provided expression profiles and RNA fusion products. Further analysis was performed using principal components analysis of RNA seq data to explore correlates amongst sarcoma subtypes. Tumor mutations were queried in ClinVar for relevance to known variants and were assigned to tiers I-IV based on the ESMO scale for clinical actionability of molecular targets (ESCAT). Tier I mutations have drug-mutation matched evidence of actionability while tier IV have only pre-clinical evidence.

Results: NGS has been completed on 76 tumor samples. Sequenced tumors represented 19 histologies, with the most common ones as follows: undifferentiated pleomorphic sarcoma (15.8%), liposarcoma (9.2%), gastrointestinal stromal tumor (9.2%), osteosarcoma (7.9%), and leiomyosarcoma (7.9%). Of 76 patients, 66 (87%) had at least one mutation detected with a mean frequency of 2.74. TP53 (20/66), RB1 (14/66), and ATRX (9/66) were most commonly mutated genes. Mean (std) tumor mutation burden (TMB) was 3.4 m/MB (3.5m/MB) and one tumor had TMB of 25.3 m/MB. Of the 76 samples, 68 had RNA expression and fusion data available, of which 42 (62%) had anomalous expression changes and 11 had RNA fusions. The most overexpressed genes were NY-ESO-1 (13), LAGE-1 (9), and RET (7); the most under-expressed genes were SMARCB1 (9) and MGMT (6). 30.2% (23 of 76) of patients had potentially actionable DNA mutations, 9 had ESCAT tier I DNA mutations, 3 had tier II, 10 had tier III, and 1 had tier IV. 29.4% (20/68) of patients had potential targets based on RNA expression. 51.3% (39/76) patients had either a potential DNA or RNA target, and 6.6% (5/76) had multiple RNA or DNA targets. Conclusions: NGS revealed potentially actionable targets in over half of sarcoma patients based on ESCAT criteria. With ongoing accrual and sequencing of additional tumor specimens future analysis of CAUSAL will focus on assessing the correlation between targetable mutations and clinical outcomes. Research Sponsor: U.S. National Institutes of Health.
Loss of the DNA repair gene RNase H2 and a unique subset of DDR-deficient leiomyosarcomas.

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Background: Targeting the DNA damage response (DDR)/Homologous Recombination (HR) pathway is an emerging therapeutic approach for leiomyosarcoma (LMS). Loss of RNase H2 decreases DNA repair via the Non-Homologous End-Joining (NHEJ) pathway, leading to increased double stranded breaks, replication stress, and increased cell death. Therefore, we developed an assay to screen for RNase H2 loss in STS patient samples to determine its prevalence and prognostic significance, particularly in LMS patients.

Methods: RNASEH2B homozygous deletion (HomDel) calls from TCGA samples were based on the Allele-Specific Copy number Analysis of Tumors (ASCAT2) algorithm. Immunohistochemistry (IHC) of RNase H2 was performed on tissue microarrays (TMAs) of uterine (U-LMS) and soft tissue (ST-LMS) leiomyosarcoma samples from MD Anderson Cancer Center (MDACC) using a selective antibody developed by Repare Therapeutics. RNase H2 loss was defined as < 10% cells without nuclear IHC staining and scored by experienced pathologists in 2 separate cohorts. Genomic analysis was performed using SNiPDx™, a targeted-NGS assay designed to detect biallelic loss of function in select DDR related genes and whole genome sequencing (WGS). MDACC TMA samples were clinically annotated by retrospective review.

Results: Using TCGA data, RNASEH2B HomDels were seen in 6% (5/80) of all LMS cases, with a higher proportion in U-LMS (15%; 4/27) as compared to ST-LMS (2%; 1/53). In a pan-tumor TMA, RNase H2 loss by IHC was found in 3.8% (32/843) of samples overall, and in 10% (9/88) of LMS samples. This proportion of RNase H2 loss was higher in a larger MDACC LMS cohort, where negative staining of RNase H2 was found in 30% (33/110) of U-LMS and 38% (39/102) of ST-LMS cases. 30 MDACC LMS cases (15 U-LMS and 15 ST-LMS) were analyzed for RNASEH2B HomDels by SNiPDx. In U-LMS, RNASEH2B HomDels were detected in 64% (7/11) of RNase H2 IHC loss cases vs. 0% (0/3) in RNase H2 IHC intact cases. In ST-LMS, RNASEH2B HomDels were detected in 60% (19/32) of RNase H2 IHC loss cases vs. 0% (0/1) in RNase H2 IHC intact cases. The median overall survival (mOS) of MDACC U-LMS patients (n = 109) was 4.3 years. No significant mOS difference was seen in RNase H2 IHC intact cases versus loss (mOS 4.4 v 3.3 years, p = 0.54). In a separate cohort, 4 U-LMS samples were screened by IHC; 22% (10/45) had RNase H2 loss. RNASEH2B HomDels were detected in 70% (7/10) of RNase H2 IHC loss cases using SNiPDx and confirmed using WGS. In contrast, RNASEH2B HomDels were detected in 3% (1/33) of RNase H2 IHC intact cases. In the combined U-LMS cohort with IHC and SNiPDx results (n = 71), the diagnostic accuracy, sensitivity and specificity of RNase H2 IHC for detecting RNASEH2B HomDels was 76%, 93% and 71% respectively.

Conclusions: RNase H2 loss via RNASEH2B HomDels is prevalent in U-LMS and is unique from other DDR pathway alterations. RNase H2 IHC is an effective screening tool and is being developed for future clinical trials targeting DDR in LMS. Research Sponsor: Repare Therapeutics.

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Aristolochic acid (AA) exposure and telomere maintenance mechanism in liver angiosarcoma (AS).

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Background: Liver AS has a grave prognosis and our previous study (Chen TW et al. Cancer 2022) showed that the incidence of liver AS is higher in Asia. We aimed to investigate the etiology of liver AS and its molecular characteristics.

Methods: We performed whole exome (WES) and transcriptome sequencing (RNA-seq) of AS (liver 10, scalp 5, breast 2, trunk 1, heart 1) and hepatocellular carcinoma (HCC, 9) from National Taiwan University Hospital (NTUH) and re-analyzed WES & RNA-seq of AS from the Count Me In Project (CMI, 46). Somatic mutations and copy number alternation were called by Mutect2 and Sequenza from tumor-normal matched WES. Non-negative matrix factorization was used to determine mutational signature profiles and the contributions of each signature to each sample. Telomere length was estimated using TelSeq.

Results: We identified four single-base-substitution (SBS) signatures using somatic mutations from 74 (AS/HCC 65/9) WES data. The dominated signature in liver AS had exceptionally high cosine similarity (93.08%) with COSMIC SBS22 (ver 3.2), which is related to AA exposure. The AA-mutation signature contributed significantly (adjusted p < 0.01) to the DNA mutations in 70% (7/10), 0% (0/9), 7% (3/46), and 56% (5/9) of liver AS (NTUH), nonliver AS (NTUH), CMI AS, and HCC (NTUH), respectively. TP53 (60% vs 22% vs 32%) and ATRX (40% vs 0% vs 11%) mutations were more common in liver than nonliver AS (NTUH) or CMI, while KDR mutation rates were similar (30% vs 44% vs 22%). Among TP53 mutations from liver AS with AA signature, 86% (6/7) showed the typical A:T > T:A mutation caused explicitly by AA-induced DNA damage. In liver vs nonliver AS, the median number of mutations and neoantigen burdens were 6.55 vs 0.98 (p = 0.0076) and 1572 vs 544 (p = 0.095), respectively. Although liver AS and HCC were highly associated with AA-mutation signature, liver AS had significantly longer telomeres in terms of tumor/normal telomere ratio (median 1.27 vs 1.16, p = 0.0009) but a significantly lower telomerase enzyme activity (p = 0.016). We did not find an association between ATRX mutation, or its mRNA expression level, with the extended telomere length in liver AS. Compared to nonliver AS, the activity of the telomere replication molecule BUB1 was significantly higher in liver AS (p = 0.0029).

Conclusions: Our study is the first to connect AA exposure to the etiology of liver AS. The high mutation rate and distinct telomere maintenance mechanism of liver AS provides insights into future treatments. Research Sponsor: National Taiwan University Hospital; Good Liver Foundation.
Phase 1 trial of avelumab with hypofractionated thoracic radiation therapy (HT-RT) in patients with metastatic soft-tissue sarcomas (mSTS).

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**Background:** Combining HT-RT with anti PD-L1 therapy may enhance local and distant tumour control in mSTS. This was a Phase 1 trial to evaluate the safety, tolerability, and efficacy of avelumab in patients with mSTS. **Methods:** This was a single centre phase 1 trial of avelumab with HT-RT in patients with mSTS (NCT03602833). Patients > 18 years with at least 2 pulmonary metastases, ECOG performance status 0-1 were eligible between Oct 2018-Apr 22. Patients received HT-RT (36 Gy in 12 fractions), with concurrent intravenous avelumab (10 mg/kg q14d) until disease progression. The primary end point was safety of avelumab with HT-RT. Secondary endpoints included local control rate at 3 months. Dose limiting Toxicity (DLT) assessed from start of HR-CT and avelumab up to Cycle 7 avelumab and defined as: ≥ G2 pneumonitis, ≥ G2 myelitis, ≥ G3 non-haem toxicity, ≥ any other G4 and/or HT-RT interruption > 5 days. Response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST). **Results:** 12 patients were treated in this trial. Histological subtypes: leiomyosarcoma (n = 2), undifferentiated pleomorphic sarcoma (n = 2), and spindle cell sarcoma (n = 2). The median age was 57.5 (37-68) years, 7 were female (58%). All patients had lung metastases. 1 previously received SBRT to the lung, and 5 (42%) patients had received prior systemic treatment. 12 patients received at least one cycle of avelumab, median 9 (range: 1-37), and treatment was discontinued in 11 (92%) patients; 10 (83%) stopping for progressive disease, 1 (8%) patient for G4 immune-mediated hepatitis after DLT period and 1 patient completed and continues on compassionate-use avelumab. Eleven (92%) completed radiotherapy (36 Gy, 12 fractions). No DLTs or treatment-related deaths were observed. HT-RT toxicity: 3 G2 acute (1 oesophagitis, 2 skin) noted up to 11 weeks. 13 G1 late toxicities (5 pneumonitis, 5 skin, 1 cardiac, 1 myelitis, 1 oesophagitis) reported. Avelumab toxicities: 2 G3 (1 ALT rise, 1 viral infection) and 3 G4 (1 AST rise, 1 hepatitis, 1 sepsis) reported after DLT observation period. The median follow-up was 21.8 (range 3.2-31.9) months with a 3-month local control rate of 50% (95% CI, 21%-74%). RECIST responses at 3 months were 0 CR, 1 (8%) PR, 5 (42%) SD and 5 (42%) PD. **Conclusions:** Avelumab in combination with thoracic radiotherapy was safe with encouraging anti-tumour activity in patients with metastatic soft-tissue sarcomas. Additional molecular biomarker analyses are in progress. Clinical trial information: NCT03602833. Research Sponsor: Merck Serono Ltd. (CrossRef Funder ID: 10.13039/100009945); Royal Marsden/Institute of Cancer Research London BRC.
Efficacy and safety of anlotinib combined with anthracycline and ifosfamide followed by anlotinib maintenance in advanced soft tissue sarcoma: A single-arm, phase 2 trial.

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Background: Anthracycline plus ifosfamide is the standard first line treatment regime for advanced soft tissue sarcoma (STS). Anlotinib, a multikinase angiogenesis inhibitor, has evolved as a standard second line treatment option in Chinese advanced STS patients. This study was performed to evaluate the efficacy and safety of anlotinib combined with anthracycline and ifosfamide followed by anlotinib maintenance in the first line treatment of patients with advanced STS. Methods: This prospective, open-label, single-arm, phase 2 trial was conducted in Shandong Cancer Hospital and Institute (ChiCTR2100054711). The key inclusion criteria included: (a) age was 18-70 years; (b) ECOG performance state of 0-1; (c) histologically confirmed high-grade STS; (d) unresectable or metastatic STS; (e) previously untreated, and sensitive to chemotherapy; (f) having measurable lesions according to RECIST 1.1. All patients received up to 6 cycles of anlotinib (12 mg QD on day 1-14, 21 days per cycle) combined with anthracycline (epirubicin 40mg/m²/d on day 1-2, 21 days per cycle; or liposomal doxorubicin 30mg/m²/d on day 1, 21 days per cycle) and ifosfamide (2g/m²/d on day 1-3, 21 days per cycle) followed by anlotinib maintenance until disease progression, unacceptable toxicity or death. Pegylated recombinant human granulocyte colony-stimulating factor was administered following chemotherapy. The primary endpoint was objective response rate (ORR). The secondary endpoints included progression-free survival (PFS), overall survival (OS), and adverse effect (AE). Results: From December 2021 to December 2022, 31 patients (median [range] age, 53 [18-69] years; 20 [64.5%] male) were enrolled. 29 were evaluable for objective response, and the ORR and DCR were 31.03% (95%CI, 17.28-49.23%) and 82.76% (95%CI, 65.45-92.4%), respectively. With a median follow-up duration of 6.3 months (range, 0.8–14.0), the median PFS for all 31 patients was 6.9 months (95% CI, 2.62-11.17). The median OS was not reached. Treatment-related AEs of any grade occurred in all patients. The most common AEs included nausea/vomiting (88.46%), anemia (23.08%), leukopenia (19.23%), venous thrombosis (15.38%), hand-foot syndrome (11.54%) and elevated alanine aminotransferase or aspartate aminotransferase (11.54%). The most frequent grade 3 AEs were leukopenia (11.54%) and thrombocytopenia (7.69%). 2 serious AEs (1 left heart failure and 1 intestinal obstruction) were recorded. No treatment-related death occurred. Conclusions: This study suggested that anlotinib combined with anthracycline and ifosfamide followed by anlotinib maintenance demonstrated encouraging efficacy with a manageable safety profile in the first line treatment of patients with advanced STS. Clinical trial information: ChiCTR2100054711. Research Sponsor: Beijing Lize Charity Foundation.
A phase Ia/Ib, dose-escalation/expansion study of the MDM2–p53 antagonist BI 907828 in patients (pts) with solid tumors: Safety and efficacy in patients with dedifferentiated liposarcoma (DDLPS).

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Background: Inactivation of p53 is a key mechanism which promotes tumor survival and proliferation. p53 inactivation can be due to mutations in TP53 or downregulation of wild-type (wt) p53 by the key negative regulator mouse double-minute 2 (MDM2). BI 907828 is a highly potent MDM2–p53 antagonist which has demonstrated preclinical antitumor activity, particularly in TP53-wt MDM2-amplified DDLPS models. In this phase I study (NCT03449381), BI 907828 monotherapy is being evaluated in pts with advanced solid tumors, including DDLPS. During dose escalation (phase Ia), BI 907828 had a manageable safety profile and the selected recommended dose for expansion (RDE) was 45 mg q3w. Here we report safety data in all pts who received the RDE of 45 mg q3w and present efficacy data in the subgroup of pts with DDLPS. Methods: In Phase Ia, pts received one of two BI 907828 dosing schedules: Arm A, day 1 of 21-day cycles (q3w); Arm B, days 1 and 8 of 28-day cycles. During Phase Ib (dose expansion), pts were enrolled to Cohort 1 (TP53wt, MDM2-amplified sarcoma) or Cohort 2 (other TP53wt, MDM2-amplified solid tumors). Here we focus on Cohort 1 (received BI 907828 45 mg q3w). The primary endpoint (phase Ib) was progression-free survival (PFS). Secondary endpoints/objectives included overall response rate (ORR) and grade ≥3 treatment-related AEs (TRAEs). Results: As of December 22, 2022, a total of 137 pts had been enrolled; 72 (52.6%) were male, 77 (56.2%)/59 (43.1%) had ECOG PS 0/1, and the median number of prior systemic therapies was 2 (range, 0–11). In the 73 pts who received the RDE of 45 mg q3w, the most common any-grade TRAEs were nausea (74.0%) and fatigue (61.6%). 33 (45.2%) pts had grade ≥3 TRAEs; the most common were thrombocytopenia (23.3%), neutropenia (21.9%), anemia (11.0%), and leukopenia (11.0%). 22 (30.1%) pts had TRAEs leading to dose reductions and 6 (8.2%) had TRAEs leading to treatment discontinuation. 20 pts (27.4%) had serious AEs; the most common were nausea, pulmonary embolism (each 4.1%), sepsis, small intestine obstruction, vomiting, thrombocytopenia, and pyrexia (each 2.7%). 50/73 pts who received 45 mg q3w had advanced DDLPS; all had MDM2-amplified disease. Of the 42 evaluable DDLPS pts, 8 achieved a confirmed PR (ORR 19.0%; locally assessed) and a further 29 achieved a best response of stable disease (including 2 with unconfirmed PR), giving a disease control rate of 88.1%. Preliminary median PFS was 8.1 months. Conclusions: BI 907828 demonstrated a manageable safety profile overall and encouraging preliminary efficacy was seen in pts with advanced MDM2-amplified DDLPS; Phase Ib is ongoing. BI 907828 is also being evaluated versus doxorubicin as first-line treatment for pts with advanced DDLPS in the ongoing Phase II/III Brightline-1 study (NCT05218499), for which the FDA has granted a Fast Track Designation. Clinical trial information: NCT03449381. Research Sponsor: Boehringer Ingelheim.
Results of SOC-2082 phase 2 study using metronomic gemcitabine, doxorubicin and docetaxel plus nivolumab as second/third-line therapy for advanced sarcoma.

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Background: Metronomic dosing of gemcitabine, doxorubicin and docetaxel causes less severe side effects than standard chemotherapy for advanced sarcoma. The addition of nivolumab to this regimen has potential to have synergistic effects and improve treatment outcomes. Methods: Primary objective: To assess progression-free survival (PFS); Secondary objectives: (1) To evaluate best overall response during treatment period confirmed in a 6-week follow-up, (2) PFS rate at 6 and 9 months, (3) Overall survival (OS) rate at 6, 12 months, and (4) Incidence of treatment-related adverse events (TRAEs). Inclusion criteria: Previously treated male and female subjects, $\geq 18$ years of age, pathologically confirmed diagnosis of locally advanced, unresectable, or metastatic sarcoma, measurable disease by RECIST v1.1, and acceptable hematologic and organ functions. Exclusion Criteria: History of autoimmune disorder. Treatment schedule: Metronomic doses of gemcitabine (600 mg/m2 max:1000 mg), doxorubicin (18 mg/m2; max: 32 mg), docetaxel (25 mg/m2; max:42 mg) on Day 1 and Day 8, and nivolumab (240 mg) on Day 1 only. Repeat treatment cycles are continued every three weeks if the toxicity grade is $\leq 1$. Results: This report on the modified intent-to-treat population (n=59). This population completed at least one treatment cycle and had a follow-up CT or MRI scan at week 6. Best Overall Response = 8 PR, 44 SD, 7 PD. The disease control rate (CR+PR+SD) was 88.1%. Median PFS was 5.1 (95% CI: 2.837-7.363) months; 6 month PFS rate 52.5%. Median OS, 15.3 (95% CI: 5.48-25.12) months, with 6-month OS 88%. Safety analysis: Grade 3/4 TRAEs include fatigue (n=18), nausea (n=13), neutropenia (n=10), thrombocytopenia (n=9), anemia (n=9), diarrhea (n=1). There were no unexpected adverse events. Conclusions: Taken together, the data suggests that nivolumab in combination with metronomic doses of gemcitabine, doxorubicin and docetaxel (1) may have synergistic activity, and (2) by indirect comparison, may be as effective as standard first line therapy for advanced sarcoma with manageable toxicity. Clinical trial information: NCT04535713. Research Sponsor: None.
Interstitial results of a phase 2 study using talimogene laherparepvec, nivolumab, and trabectedin for advanced leiomyosarcoma.

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Background: Intratumoral injection of Talimogene Laherparepvec (TVEC) has a local oncolytic effect and evokes a cytotoxic immune response. The combination of Trabectedin (T) and Nivolumab (N) is a safe and effective therapy in soft tissue sarcoma (STS). This study aims to determine the safety and efficacy of adding TVEC to the combination of T and N in advanced leiomyosarcoma (LMS). Methods: Objectives: Primary: To assess progression-free survival (PFS). Secondary: (1) To evaluate the best overall response, (2) PFS rate at 6 and 9 months, (3) Overall survival (OS) rate at 6, 9, and 12 months, (4) Incidence of conversion from unresectable to the resectable tumor, and (5) Incidence of treatment-related adverse events (TRAEs). Patients and Methods: Eligible patients included patients ≥ 18 years of age with locally advanced unresectable or metastatic LMS, measurable disease by RECIST v1.1, and at least one accessible tumor for TVEC intratumoral injection. N (3 mg/kg q2 weeks), T (1.2 mg/m2 q3 weeks), and TVEC (1x10e8 PFU/ml q 2 weeks depending on tumor size) were administered. A starting dose of TVEC (1x10e6 PFU/ml) was initially given, followed by a total dose of 1x10e8 PFU/ml q 2 weeks depending on tumor size) three weeks later. Results: Efficacy: Per protocol, there were 11 evaluable subjects (Modified Intention to Treat [mITT] patients who had completed at least one treatment cycle and had a follow-up CT scan). The median number of prior lines of therapy was 4 (range 1-8). Confirmed Best Overall Response (BOR) by RECIST v1.1 = 2 PR, 9 SD (BOR Rate 18.2%). The disease control rate (PR+SD) at week 6 was 100%. The median PFS was 7 months (range: 3- 18); 6-month PFS rate, 55%; median OS 18.2 months (range: 4- 32); 6-month OS rate, 91%. There was no conversion from unresectable to resectable tumor. Response was not related to PD-L1 positivity but both patients with PR were ER+/PR+ and had uterine LMS. There were 15 evaluable subjects for OS analysis under the Intention-to-Treat (ITT) population who received at least one dose of study drug. The median OS was 12 (range 0-32) months; 6-month OS rate, 60%. Safety: Eight of 15 (53.3%) patients experienced at least one > Grade 3 treatment-related adverse event (TRAE); Grade 3 TRAEs include anemia (n=3), thrombocytopenia (n=2), neutropenia (n=1), increased ALT (n=1), increased GGT (n=1), decreased LVEF (n=1), myalgia (n=1). Grade 4 TRAE include thrombocytopenia (n=1). The TRAEs were related to Trabectedin use. No new safety signals noted in this study. Conclusions: These results suggest that (1) By indirect comparison, the combination regimen using Talimogene laherparepvec, Nivolumab & Trabectedin may be more effective as second/third-line/fourth therapy for advanced leiomyosarcoma with manageable toxicity (Trabectedin alone for LMS= 4.3 mos; Dacarbazine alone = 1.6 mos; Demetri 2015), and (2) The best responders are patients with HR+ uterine LMS. Clinical trial information: NCT03886311. Research Sponsor: Amgen.
Metronomic dosing of selinexor in select soft tissue sarcomas (STS).

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Background: Selinexor (S) is a first-in-class, oral, selective inhibitor of nuclear export (SINE). S has a demonstrated anti-tumor activity in STS. However, the use of S can be associated with toxicities, such as nausea, anorexia and fatigue. A modified dosing schedule may improve the tolerability of S without compromising its efficacy. Methods: We evaluated S when given metronomically in patients (pts) with advanced metastatic leiomyosarcoma, endometrial stromal sarcoma, and malignant peripheral nerve sheath tumors. S was administered daily for 4-days in a row followed by 3-days break, repeated weekly in a 28-days cycle. Dose levels (DL) were escalated using a 3+3 design to determine maximum tolerated dose. DL included 2.5mg (DL1), 5mg (DL2), 7.5mg (DL3), 10 mg (DL4), 12.5 mg (DL5), 15 mg (DL6) and 17.5 mg (DL7). S was administered until unacceptable toxicities or disease progression. Imaging was performed every 8 weeks. Primary objectives were safety and tolerability as well as the determination of the recommended phase II dose. Secondary objectives were anti-tumor activity, toxicity profile, and pharmacokinetics (PK) profile. Results: Twenty-five pts (22 females/3 males, median age 59 years [range 35-84]) were enrolled at different DL (3, 3, 4, 6, 6, 3 pts at DL1 to DL6 respectively). The most common adverse events (AE) of any grade were constipation (n = 11, 50%), nausea (n = 11, 50%), and dysgeusia (n = 10, 45%). Eight (36%) pts experienced G3/4 AE while on trial; most were hematological toxicities seen in 3 (14%) pts (anemia, neutropenia, and leukopenia, n = 1 each). Non-hematological G3/4 AE were seen in 5 (23%) pts (Including: colonic obstruction, atrial fibrillation, and spinal cord compression, n = 1 each). Two Dose limiting toxicities were experienced, at DL4 (thrombocytopenia) and DL5 (transaminitis). Twenty-two pts were evaluable for response; 10 (45%) pts had stable disease (SD) as best response. Eight pts with SD had disease stability of > 4 months. Twelve pts (55%) had progressive disease. Median progression-free survival was 2.4 months (95% CI 1.7-5.3 months). PK data is awaiting final analysis. Conclusions: Metronomic S demonstrated tolerability in selected sarcoma pts. Signs of potential clinical benefit was seen in the form of SD. Further data comparison with historical controls and PK analysis are needed to put this finding into perspective. Clinical trial information: NCT04811196. Research Sponsor: University Health Network, Toronto.
Results from phase I/II study of NY-ESO-1-specific TCR gene-transduced T cell therapy (TBI-1301, mipetresgene autoleucel) in patients with advanced synovial sarcoma.

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**Background:** Synovial sarcoma is one of malignant soft tissue tumors with a poor prognosis. A cancer-testis antigen NY-ESO-1 is expressed in the tumors of 50-80% synovial sarcoma patients. The purpose of this study was to evaluate the safety and the efficacy of gene engineered autologous T cell product with NY-ESO-1 siTCR retroviral vector which expressed affinity-enhanced NY-ESO-1-specific TCR and siRNA to silence endogenous TCR (TBI-1301).

**Methods:** This was an open label phase I/II study to evaluate safety, appearance of replication competent retrovirus (RCR), appearance of clonality, in vivo cell kinetics and clinical responses. TBI-1301 were manufactured from each subject’s leucocytes stimulated with anti-CD3 antibody and Retronectin and transduced with NY-ESO-1 siTCR retroviral vector. TBI-1301 was infused at split dose of 5 x 10^9 cells following cyclophosphamide treatment at 750 mg/m^2 for two days to HLA-A*02:01 or HLA-A*02:06 positive subjects with synovial sarcoma expressing NY-ESO-1, which were surgically unresectable and refractory to anthracycline therapy.

**Results:** Eight subjects were enrolled and treated with TBI-1301. The objective response rate was 50.0% with best overall partial response in 4 of 8 subjects according to RECIST v1.1/irRECIST and the median overall survival was 650 days. Cytokine release syndrome (CRS) occurred in 50.0% (4/8) and consisted of 1 subject with grade 1 CRS and 3 subjects with grade 2 CRS. All subjects who developed CRS recovered with prespecified treatment, in which 2 subjects were treated with symptomatic therapy, 1 subject was treated with tocilizumab and corticosteroid. No subjects had immune effector cell- associated neurotoxicity syndrome (ICANS). RCR and clonal dominance were not detected in any subjects throughout the study period. **Conclusions:** Adoptive immunotherapy with TBI-1301 to selectively target NY-ESO-1 positive tumors will become a promising treatment for advanced or recurrent synovial sarcoma with acceptable toxicity. Clinical trial information: NCT03250325. Research Sponsor: Takara Bio Inc.
Background: TGCT is a rare type of locally aggressive neoplasm that is mainly caused by overexpression of colony-stimulating factor 1 (CSF1) gene. Pimicotinib is an oral, highly potent, and selective small-molecule antagonist of CSF-1R with minimum inhibition of c-Kit and PDGFR, and has been granted Breakthrough Therapy Designation for TGCT by FDA in Jan 2023. Here, we report the updates from 50 mg QD cohort as well as the preliminary data from 25 mg QD cohort in TGCT pts. Methods: The study (NCT04192344) is to evaluate the safety and preliminary antitumor activity of Pimicotinib at 50 mg QD and 25 mg QD in TGCT pts not amenable to surgical resection. Results: As of December 31, 2022, 49 TGCT pts were enrolled, including 37 pts treated with 50 mg QD and 12 pts with 25 mg QD. Median age was 39 y (range: 19-76) and 40.8% were male. The tumor location was mainly in knee (53.1%), hip (18.4%) or ankle (12.2%). Thirty-one pts received at least one prior surgery, and 1 pt received prior exploratory systemic therapy (Anlotinib). Median treatment duration was 7.9 mos (range: 0.4-12.5), and 89.8% remained on treatment. The ORR was 77.4% (24/31, including 2 CR) in 50 mg QD and 40% (4/10, including 1 CR) in 25 mg QD by IRC based on RECIST 1.1. Most responses were achieved within 25 wks and median DOR in both cohorts was not reached. Average improvement of flexion range of knee at wk 13 from baseline was 30.2 degrees (n = 13, range: 2, 105) in 50 mg QD and 4.8 degrees (n = 5, range: -12, 24) in 25 mg QD. Proportion of responders based on BPI-30 at wk 25 was 66.7% (16/24) in 50 mg QD and 60% (3/5) in 25 mg QD, along with a similar trend of stiffness. Most TEAEs were Gr 1 or 2. Four Gr 3/4 TEAEs were reported (2 drug-related), including 1 Gr 3 serious TEAE. Most common TEAEs (≥20%) include LDH increase (75.5%), CPK increase (67.3%), a-HBDH increase (63.3%), AST increase (42.9%), amylase increase (26.5%), ALT increase (24.5%), pruritus (20.4%) and rash (20.4%). No hair color changes or serious liver injuries were reported. CPK and transaminase elevations were asymptomatic, on-target and quickly recovered after drug interruptions. Under steady-state, 50 mg QD resulted in ~ 2-fold higher C max and C trough compared to 25 mg QD, in sync with findings from escalation phase. Significant PD changes were observed in both cohorts, such as increase in plasma CSF-1 levels, decrease in non-classical monocytes and C-terminal telopeptide(CTx). Changes from baselines in both CSF-1 and CTx showed a correlation with pimocetinib plasma concentrations. Conclusions: Pimicotinib has demonstrated a significant antitumor activity, favorable safety, and PK profiles at both 50 mg QD and 25 mg QD with no apparent hepatotoxicity. The changes in PD biomarkers indicate significant CSF-1R inhibition in TGCT pts. Updated data from 50 mg QD cohort showed higher ORR and continuous improvement over a longer treatment time, which supports the further evaluation of Pimicotinib in a phase 3 study. Clinical trial information: NCT04192344. Research Sponsor: Abbisko Therapeutics Co, Ltd.
Evaluation of hyperprogression in patients with sarcoma treated with targeted therapy and/or immunotherapy in early-phase clinical trials.

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Background: Hyper-progressive disease (HPD) is an adverse outcome with acceleration of tumor growth, often accompanied by clinical deterioration. This phenomenon is described with immunotherapy (IT) but its incidence in sarcoma and/or in the context of targeted therapy (TT) remains unknown. Tumor growth rate (TGR) allows for dynamic evaluation of tumor volume change over time and may complement RECIST. We evaluated HPD in sarcoma patients (pts) treated in early-phase trials by assessing TGR and describing their subsequent clinical outcomes. Methods: We retrospectively reviewed medical records from advanced soft tissue sarcoma (STS) pts enrolled in early phase trials at the Princess Margaret Cancer Centre between January 2012 and December 2022. TGR was calculated based on tumor measurements taken at pre-baseline, baseline, and on-treatment CT scans. We used the Champiat formula (Clin Cancer Res 2017) to calculate TGR ratio. Primary objective was to describe the incidence of HPD, defined as a TGR ratio of ≥ 50%. Secondary objective was to investigate the correlation between HPD with progression-free survival (PFS) and overall survival (OS). Results: We identified a total of 192 pts involved in STS early phase trials from 2012-2022. Most common histology was leiomyosarcoma seen in 72 pts. Eighty-four pts (43.8%) received TT, 75 (39%) pts received IT-based, and the rest had combined TT/IT regimens (n = 33, 17.2%). The incidence of HPD was 6.8% (n = 13), including IT-based (n = 9) and non-IT-based (n = 4) regimens. HPD was associated with a worse PFS, and OS compared to non-HPD pts (median PFS 1.6m vs 4.6m HR: 5.5, 95%CI 2.8-10.6, P < 0.001; median OS 5.5 vs 16.1 months; HR: 3.7, 95%CI: 2.0-7.1, P < 0.001). On multivariable analysis, only IT was significantly associated with HPD (OR 3.9, 95%CI: 1.1-13, P = 0.021). There was no association between HPD and new lesions or sarcoma histology subtype. Conclusions: HPD occurs in a small subset of sarcoma patients undergoing clinical trials with TT or IT. Exploring TGR provides clinically meaningful data as it pertains to HPD as it predicts OS and PFS in sarcoma patients undergoing early-phase clinical trials. Research Sponsor: None.
Novel MRI scoring system to assess osseous malignancy in patients with soft tissue sarcoma following radiotherapy.

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**Background:** Although radiotherapy is an important component of STS management, radiation induced changes such as radiation osteitis are commonly identified on magnetic resonance imaging (MRI). These imaging findings may be concerning for malignancy and sometimes require biopsy for investigation. This study proposes a novel MRI scoring system to assess osseous lesions and predict potential for malignancy based on MRI score in STS patients who received radiotherapy. **Methods:** The MRI score consisted of 3 parameters: morphology, signal intensity, and progression. Interobserver reliability between the total score of MRI examinations scored by two senior musculoskeletal radiologists were analyzed with Cohen’s kappa coefficient. Receiver operating curve (ROC) analysis was performed to determine a predictive MRI score for malignancy. **Results:** 156 MRI’s from 30 STS patients who received radiotherapy were retrospectively reviewed. Two (6.7%) patients developed regional osseous metastasis identified on MRI. The kappa coefficient of the scoring system was 0.785 demonstrating substantial interobserver agreement (p<0.001). ROC analysis demonstrated that the optimal cut-off value for malignant lesion on MRI was 5.5 (area under the curve 0.998 (95% CI 0.993-1.000) p<0.001). **Conclusions:** This novel MRI scoring system recommends lesions with a score of six and above to be biopsied to distinguish if malignancy is present. We believe this scoring system can be utilized by multidisciplinary care teams to guide clinical recommendations for patients with STS and MRI findings concerning for malignancy versus radiation induced changes. Research Sponsor: None.
HH2853, an EZH1/2 inhibitor, in patients with epithelioid sarcoma: Preliminary results from the phase 1 part of a first-in-human phase I/II study.

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Background: Epithelioid sarcoma (ES) is a rare and aggressive subtype of soft-tissue sarcoma. Over 90% of tumors have lost INI1 expression, leading to oncogenic dependence on the transcriptional repressor EZH2. Tazemetostat (an EZH2 inhibitor) has been approved by FDA for clinical use in ES. HH2853 is a novel selective EZH1/2 dual inhibitor, which has demonstrated superior anti-tumor efficacy to tazemetostat in INI1-loss preclinical models. Methods: This is a first-in-human, open-label, multi-center, Phase (Ph) I/II study in patients (pts) with relapsed/refractory non-Hodgkin lymphomas or advanced solid tumors. Ph I is composed of two parts: dose escalation and dose extension part. Local pathologically documented, advanced recurrent or metastatic ES pts who received prior systemic anti-tumor therapies or have no standard therapy are eligible. HH2853 was administered orally twice daily (BID) on a continuous 28-day treatment cycle. Safety and clinical activity of HH2853 were assessed in pts with ES from the Ph I part. Results: Between Dec 2, 2021 and Nov 7, 2022, 32 pts with pre-treated ES were enrolled to three dose levels (400, 600, and 800 mg BID) from 4 sites in China. Median prior lines of therapy was two. 12 (37.5%) pts received ≥3 lines of prior therapies. 30 (93.8%) pts had documented loss of INI1 expression by local immunohistochemical analysis. There were 18 (56.3%) pts with proximal subtype. As of Jan 4, 2023, at a median treatment duration of 124 days, the most common treatment-related adverse events (TRAEs) were diarrhea (59.4%), blood bilirubin increased (43.8%), white blood cell count (WBC) decreased (34.4%), rash (31.3%), anemia (25.0%), hypokalemia (21.9%), and platelet count (PLT) decreased (21.9%). TRAEs of Grade 3 included diarrhea, WBC decreased, anemia, hypokalemia, and neutrophil count decreased (6.2%, each), and blood bilirubin increased, PLT decreased, blood creatine phosphokinase increased, and hyperglycemia (3.1%, each). TRAEs leading to dose interruption or reduction were reported in 21.9% and 12.5% pts, respectively. No TRAE led to dose discontinuation or death. Tumor responses were observed from 400 to 800 mg BID. Overall response rate (ORR) was 15.6% (5/32) per investigator assessment according to RECIST 1.1. Three pts had unconfirmed response waiting to be confirmed at the next scheduled assessment, expecting to bring the total ORR to 25% [95% CI 11.5 – 43.4]. Median time to response was 1.9 months. One patient with complete response (CR) has responded for 222 days from the initial response. Disease control rate (DCR) (DCR = CR + partial response + stable disease at 6 weeks) was 78.1% [95% CI 60-90.7]. Conclusions: HH2853 showed an acceptable safety profile and promising anti-tumor activity in heavily pretreated ES pts with a wide therapeutic window, providing evidence for further investigation. Clinical trial information: NCT04390737. Research Sponsor: Haihe Biopharma Co., Ltd., Shanghai, China.
The SPEARHEAD-1 trial of afamitresgene autoleucel (afami-cel [formerly ADP-A2M4]): Analysis of overall survival in advanced synovial sarcoma.

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Background: Afami-cel is an autologous, T-cell receptor (TCR) T-cell therapy to treat human leukocyte antigen (HLA) A*02–eligible patients (pts) with advanced solid tumors positive for the cancer testis antigen melanoma-associated antigen A4 (MAGE-A4). The efficacy and safety of afami-cel in pretreated pts with advanced/metastatic synovial sarcoma or myxoid/round cell liposarcoma are being evaluated in the Phase 2, two-cohort, open-label, SPEARHEAD-1 (NCT04044768) trial. Here we report interim overall survival (OS) data in the pts with advanced synovial sarcoma in Cohort 1. Methods: Pts who were HLA-A*02 positive with advanced synovial sarcoma (with evidence of clinical/radiological progression) received afami-cel after lymphodepleting chemotherapy containing fludarabine and cyclophosphamide. The primary endpoint was overall response rate per RECIST v1.1 by independent review. Secondary endpoints included OS and progression-free survival (PFS), estimated utilizing the Kaplan-Meier method. Results: As of August 29, 2022, 44 pts with synovial sarcoma received afami-cel (2.68–9.99 × 10⁹ transduced T-cells) in Cohort 1. The median age was 41 years (range: 19–73 years), 50% of pts were female, 89% of pts were white, 96% of pts were typed as HLA-A*02:01P, and median tumor MAGE-A4 expression H-score was 257 (132–300). Pts were heavily pre-treated with a median of 3 prior lines of therapy (range: 1–12). The median follow-up time at the data cut-off was 20.8 months. Median PFS was 3.8 months (95% CI: 2.8, 5.8) and 4.1 months (95% CI: 2.8, 6.9) by independent and investigator review, respectively. Median OS by independent review was 15.4 months (95% CI: 10.9, not estimable) with 52% of pts censored at the data cut-off. The 12-month OS probability was 60% and 24-month OS probability was 40%. Twenty-one pts received additional therapy during long term follow up (systemic therapy, n = 20; radiation, n = 6; other, n = 4). In the 17 pts who had a RECIST response by independent review, the median OS was not reached, the 12-month OS probability was 60% and 24-month OS probability was 40%. Conclusions: Pts with advanced synovial sarcoma treated with afami-cel in SPEARHEAD-1 had encouraging survival, especially those pts with a RECIST response. Clinical trial information: NCT04044768. Research Sponsor: This study was sponsored by Adaptimmune. Writing/editorial support was provided by Excel Scientific Solutions and was funded by Adaptimmune.
Impact of nirogacestat on pain, a key symptom in patients with desmoid tumors (DT): Results from the phase 3 DeFi study.

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Background: Pain reduction is a key treatment goal in DT (aggressive fibromatosis): 60% of patients (pts) experience chronic pain. In the phase 3 DeFi trial, nirogacestat (NIRO; n = 70) significantly improved progression-free survival compared with placebo (PBO; n = 72) in pts with progressing DT (HR: 0.29 [95% CI, 0.15–0.55]; P < 0.001). Also as previously reported, NIRO significantly reduced pain severity by 1.50 points (on a 10-point scale) compared with PBO at cycle 10 (28-day cycles; P < 0.001) per the prespecified secondary endpoint of “worst pain” from the Brief Pain Inventory Short Form (BPI-SF). Additional aspects of pain were collected in DeFi to further characterize treatment impact and consistency across multiple pain assessment tools.

Methods: In DeFi, pts completed 3 prespecified pain assessment tools through end of treatment: BPI-SF (worst pain), GODdesmoid Tumor Research Foundation DEsmoid Symptom Scale (GODDESS-DTSS pain scale: worst pain, dull pain, shooting pain), European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ-C30 pain scale: pain, pain interference with daily activities). Change from baseline (BL) in pain scores was compared between arms; analyses included mixed models for repeated measures to compare change from BL and stratified Cochran-Mantel-Haenszel to compare proportions of pts with clinically meaningful pain reduction (defined using prespecified thresholds) at cycle 10. Cycle 10 was preselected to allow adequate time for a treatment effect to be observed. Results: Statistically significant and clinically meaningful pain reductions were observed with NIRO compared with PBO at cycle 10 across all assessment tools; statistically significant differences between arms occurred as early as cycle 2 and were sustained throughout treatment. At cycle 10, NIRO reduced mean BL pain per GODDESS-DTSS (0–10 range) by 1.78 points (SE = 0.26) and PBO increased pain by 0.32 points (SE = 0.27; P < 0.001). At cycle 10, NIRO reduced mean BL pain per QLQ-C30 (0–100 range) by 22.05 points (SE = 3.38) and PBO increased pain by 7.19 points (SE = 3.64; P < 0.001). Clinically meaningful pain reduction (by ≥2.0 points) by BPI-SF worst pain (0–10 range) was achieved by 72% of pts with NIRO vs 29% of pts with PBO at cycle 10 (P < 0.001). Per GODDESS-DTSS, clinically meaningful pain reduction (by ≥1.9 points) was achieved by 62% of pts with NIRO vs 19% of pts with PBO at cycle 10 (P = 0.002). Conclusions: Rapid, sustained, and consistent reductions in different aspects of pain were observed with NIRO compared with PBO across multiple assessment tools in pts with DT. Furthermore, a significantly greater proportion of pts achieved clinically meaningful reductions in pain with NIRO than with PBO. As pain is the most commonly reported symptom, pain reduction should be a key clinical trial endpoint and a key treatment goal in DT. Clinical trial information: NCT03785964. Research Sponsor: SpringWorks Therapeutics, Inc.
A phase II trial with safety lead-in to evaluate the addition of sotigalimab, a CD40 agonistic monoclonal antibody, to standard-of-care doxorubicin for the treatment of advanced sarcoma.

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Background: Immune checkpoint inhibitors have limited efficacy in soft tissue sarcoma (STS) due to insufficient T-cell activation and infiltration by immunosuppressive macrophages. Sotigalimab (S), a high-affinity humanized monoclonal antibody for CD40, promotes antigen presentation, stimulates T-cell responses, and reprograms immunosuppressive macrophages. Preclinical studies with CD40 agonists revealed efficacy in immune “cold” tumor types and synergy with chemotherapy. Standard first-line doxorubicin (D) provides objective response rate (ORR) < 15% and median progression-free survival (mPFS) of 4-6 mos in advanced STS. We therefore conducted this first-in-human study of D+S in STS. Methods: An open-label, single-arm, multi-center, phase 2 study evaluated D+S in advanced STS. Pts had ECOG PS ≤ 1 and any number of prior lines (but were anthracycline-naïve). The study initially enrolled all STS subtypes (except KS and GIST) but was amended in 12/2020 to limit enrollment to dedifferentiated liposarcoma (DDLPS), leiomyosarcoma (LMS), and undifferentiated pleomorphic sarcoma (UPS). Pts received D 75 mg/m² IV D1 + S 0.3 mg/kg IV D1 for eight 21-day cycles, followed by S monotherapy. A safety lead-in was performed (first 6 patients). Primary endpoint was ORR. Secondary endpoints included PFS and safety. A Simon two-stage design was used. If ≥ 7/32 responded overall, the treatment would be considered promising (85% power, α = 0.05). A subset of patients underwent paired tumor biopsies. Results: 32 pts have enrolled (median age 62; 10 LMS, 10 UPS, 9 DDLPS, 3 other). 4 pts remain on treatment with median follow-up of 2.8 mos (1 UPS pt has not reached first imaging). D (75 mg/m²) + S (0.3 mg/kg) was safe and tolerable without dose limiting toxicity. Overall ORR was 16% (5/31). Objective responses occurred in UPS (2), LMS (1), other LPS (1), and epithelioid hemangioendothelioma (1). Overall mPFS was 7.5 mos (95% CI 5.6-14.9 mos) and PFS rate at 6 and 12-mos was 55% and 31%, respectively. mPFS by STS subtype was 11.9 mos (95% CI: 10.3 – NE) for DDLPS, 7.5 mos (95% CI: 1.4—NE) for UPS and 5.6 mos (95% CI: 1.3 – NE) for LMS. Overall, 17/31 (55%) pts experienced grade 3 or 4 adverse events (AEs): most commonly, neutropenia (32%), febrile neutropenia (19%), and anemia (16%). 16% of pts experienced cytokine release (all low-grade). Correlative analysis of biopsies with high-definition spatial proteomics is ongoing. Conclusions: D (75 mg/m²) + S (0.3 mg/kg) every 21 days is safe and tolerable in STS. Final analysis of the primary endpoint awaits further follow-up on recently enrolled patients. Subtype-specific analysis suggests improvement in median PFS for DDLPS over historical controls: 11.9 mos vs 4 mos (Stacchiotti S. Ann Oncol 2020; Livingston M. Sci Rep 2017). An expansion of the DDLPS cohort is planned. Clinical trial information: NCT03719430. Research Sponsor: Apexigen, Inc.
A phase II clinical trial of chidamide in combination with toripalimab in patients with advanced soft tissue sarcoma.

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Background: Chidamide is an oral subtype-selective histone deacetylase inhibitor which is effective on the patients with hematological tumors and reported to enhance the efficacy of checkpoint blockade therapies and regulate the host immune response. Here, we report preliminary results of Chidamide in combination with Toripalimab in soft tissue sarcoma (STS) patients. Methods: An open, single arm, phase II study of Chidamide with Toripalimab in patients with advanced soft tissue sarcoma after failure of standard treatment was conducted. Eligible patients could have any number of prior therapies, excluding HDAC inhibitors and immune checkpoint inhibitors treatment. All patients received Chidamide orally at 30mg twice weekly in combination with intravenous Toripalimab 240mg every 21 days until progression or unaccepted toxicity. The primary endpoint was RECIST1.1 objective response rate (ORR). The secondary endpoint included progression free survival (PFS), overall survival (OS), disease control rate(DCR) and safety. Results: Forty-six patients with advanced soft tissue sarcoma were enrolled. The median age of the patients was 47 years and the median prior lines of therapy were 3. The main subtypes included leiomyosarcoma (30.4%), well/dedifferentiated liposarcoma (30%), myxoid/round cell liposarcoma (7%), undifferentiated sarcoma(9%), and osteosarcoma (7%). Treatment was well tolerated with the most common adverse events mainly in grade I and grade II, including thrombocytopenia (43.5%), nausea(28.3%), neutropenia(23.9%), fatigue (17.4%) and hypothyroidism(15.2%). Among 46 efficacy-evaluable patients, the overall response rate and disease control rate were 23.9% and 80.4%, respectively. The median time to an initial response was 3 months (range, 2 to 14), and the 3-mon and 6-mon progression-free survival rate were 92.7% and 58.9%, respectively. Conclusions: Chidamide with Toripalimab every 21 days was well tolerated and showed promising efficacy in patients with advanced STS. Clinical trial information: NCT04025931. Research Sponsor: Shenzhen Chipscreen Biosciences Co.,Ltd. and Shanghai Junshi Biosciences Co.,Ltd.

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Immune correlates of outcome in patients with leiomyosarcoma (LMS) treated with durvalumab plus olaparib or cediranib: Transcriptome analysis from the DAPPER study.

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Background: Immune checkpoint blockade (ICB) as monotherapy has not shown clinical benefit in non-inflamed (cold) tumors such as LMS. Combining ICB with angiogenesis, or poly-ADP ribose polymerase (PARP) inhibitors may increase tumor immunogenicity by altering the immune cell composition of the tumor microenvironment (TME). In the DAPPER trial [NCT03851614], advanced LMS pts were randomized to receive ICB (Durvalumab 1500mg IV q4w) with either angiogenesis- (Cediranib 20mg qd PO on 5 days/week) or PARP inhibition (Olaparib 300mg bid PO) until unacceptable toxicity or disease progression (Ayodele et al, J Clin Oncol, 2021). Here, we present the results of transcriptomic and immune biomarker analyses of patients (pts) in the whole cohort.

Methods: Radiologic responses were assessed using RECISTv1.1 and survival analysis performed by Kaplan-Meier method. Transcriptome analysis by RNAseq was performed on fresh tumor biopsies obtained from all pts at screening. Relative fractions of 22 immune cell subsets in the TME were inferred from gene-expression profiles using CIBERSORT v1.06. Gene set variation analysis (GSVA) to identify transcriptomic signatures associated with progression-free (PFS) or overall survival (OS) benefit was performed using GSVA R package v1.42. For comparison with an independent cohort, GSVA was also performed using transcriptome data from LMS pts (n = 104) in the cancer genome atlas (TCGA) dataset. Results: Among 28 response-evaluable pts, 1 (3.6%) had partial response; 10 (35.7%) had stable disease (SD); and 17 (60.7%) had progressive disease. Median PFS and OS were 2.8 months (95% CI, 2.8 – 5.4) and 14.6 months (95% CI 10.7 – NR), respectively. RNAseq data of adequate quality was available for 17 pts. Using the median CIBERSORT score as cut-off, pts with high M1 macrophage levels at baseline had significantly longer OS (p = 0.0019). High M1/M2 macrophage ratio score was also associated with longer OS (p = 0.05). GVSA identified 7 immune- and angiogenesis-related signatures that were associated with significantly longer OS. After false discovery rate correction, 1 signature comprising genes reflective of high overall B-cell activity remained significant. No transcriptomic signatures were associated with OS in the TCGA LMS cohort where pts did not receive ICB. Conclusions: Transcriptomic analysis shows that macrophage presence in the TME is associated with longer OS. Association of the B-cell activity signature with longer OS in LMS pts on the DAPPER trial, but not in the ICB treatment-naïve TCGA cohort suggests that high B-cell activity may identify pts who are more likely to have favorable outcomes with ICB and supports previous reports in sarcoma (Petitprez et al, Nature, 2020). Our results support ongoing further evaluation and integration of these biomarkers in LMS. Clinical trial information: NCT03851614. Research Sponsor: University Health Network; AstraZeneca.
Intratumoral INT230-6 (cisplatin, vinblastine, shao) alone or with ipilimumab prolonged survival with favorable safety in adults with refractory sarcomas.

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Background: Sarcomas are a rare and diverse group of solid tumors from mesenchymal cells; chemotherapy provides limited benefit for metastatic disease. INT230-6 is a novel formulation of cisplatin (CIS), vinblastine (VIN) and a tissue dispersion enhancer (SHAO) designed for intratumoral (IT) delivery. The drug diffuses into cancer cells, causes apoptosis and recruits dendritic and T-cells to the tumor. Adding ipilimumab (IPI) appears to improve INT230-6 responses in models and clinically. The study evaluated INT230-6 for safety and efficacy alone and with intravenous (IV) IPI. Previously reported results showed INT230-6 alone induced tumor regression, T-cell influx and abscopal effects in uninjected lesions1,2.

Methods: IT-01 is an open-label phase1/2 study in adults with locally advanced, unresectable or metastatic solid tumors, including sarcoma. INT230-6 dose was set by tumor diameter or volume. INT230-6 was dosed IT Q2W for up to 5 doses alone or with IPI at 3mg/kg Q3 weeks for 4 doses. Maintenance INT230-6 dosing was Q9W. Results: The study enrolled 29 sarcoma patients with 11 subtypes (mainly leiomyosarcoma, liposarcoma, pleomorphic, chondrosarcoma and chordoma). The maximum INT230-6 dose at a single visit was 175 mL (87.5 mg of CIS, 17.5 mg VIN) in 1 or more tumors, an amount that exceeds an IV dose of VIN or CIS. PK analysis shows that >95% of VIN stays in the tumor. The >20% treatment-related adverse events (TRAEs) in evaluable monotherapy patients (n=15) were localized pain (80%), nausea (40%), fatigue (33%), decreased appetite (27%), and vomiting (20%). The >20% TRAEs in evaluable IPI/INT230-6 patients (n=14) were fatigue (39%), localized pain (39%), nausea (31%), pruritus (23%), rash (23%) and vomiting. G3 TRAEs occurred in 20% and 7% of patients in the INT230-6 and combination arms respectively with no grade 4 or 5 events in either arm. RECIST metrics are confounded by IT injections due to the large volume of highly retained INT230-6 and the influx of immune infiltrates. Analysis of median overall survival (mOS) for INT230-6 alone (n=15) was 649 days. For INT230-6 dosed at a volume/total tumor burden (TTB) ratio of >40%, the mOS was 715 days. The mOS of the combination has not been reached with over 1 year of median follow-up. OS data compare favorably to a synthetic control (mOS of 205 days) based on historical data3. The hazard ratios of INT230-6 alone or with IPI for OS to the synthetic control were 0.446 and 0.270, p-values <0.01. Conclusions: INT230-6 dosed IT alone or with IPI was well-tolerated in diverse sarcomas. INT230-6 use was associated with immune infiltration and favorable mOS as compared to a synthetic control, particularly when >40% of the TTB was injected. A randomized phase 3 trial vs. SOC in selected sarcoma subtypes with an OS endpoint is planned. References: 1. Oncoimmunology. 2019 Jul 16;8(10). 2. ASCO 6/2022. 3. Sci Rep. 2016;6:35448. Clinical trial information: NCT03058289. Research Sponsor: Intensity Therapeutics.
Phase I/II study to evaluate penpulimab combined with anlotinib and epirubicin in the first-line treatment of soft tissue sarcoma: Updated.

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Background: Anthracycline-based chemotherapy regimens are the cornerstone of first-line treatment of recurrent/metastatic unresectable soft tissue sarcoma (STS), while the efficacy was not satisfactory (the median PFS: 4-8 months). Anti-angiogenesis TKI hypothetically can improve the efficacy of chemotherapy by remodeling the immunosuppressive TME. We conducted this trial to explore the safety and efficacy of PD-1 antibody Penpulimab (P) plus anlotinib (A) and epirubicin (E) in the first-line treatment of STS. The results of the phase I study were reported (2022 ESMO), We updated the latest efficacy and safety data. Methods: This ongoing phase I/II, open-label trial (ChiCTR2100048014) enrolled patients (pts) aged 16-75 years old with pathologically confirmed metastatic or unresectable locally advanced STS. Pathologic types are moderately sensitive or above to anthracycline chemotherapy. Pts who met the inclusion criteria were treated with phase I dose results (E 60 mg/m2 + A 10 mg and P 200 mg; E: IV, D1-3, Q3W, A: PO, QD, D1-14, Q3W, P: IV, Q3W ) for a total of 6 treatment cycles (3 weeks each). A+P was maintained for 2 years until progressive disease or unacceptable toxicity. The primary endpoint was PFS (progression-free survival) and secondary endpoints were ORR (objective response rate), DCR (disease control), OS (overall survival), 2-year OS and PFSR at 3 and 6 months. The response to treatment was evaluated according to RECIST version 1.1. In addition, adverse events were evaluated by CTCAE v5.0. Results: From September 2021 to December 2022, 32 pts (14 males and 18 females) were enrolled with the median age is 53.5 (range 29-73) years old. Pathological types included liposarcoma (DDLPS 14, PLS 1, n = 15), undifferentiated sarcoma (n = 4), leiomyosarcoma (n = 5), angiosarcoma (n = 3), fibrosarcoma (n = 2), and others (n = 3). At the data cut off date on December 20, 2022, Median follow-up time was 3.5 months (range 0.03-15.38), Median PFS was 10.55 months [95%CI 4.60, 14.59]. Median OS was not reached. The PFS at 3 months and 6 months was 86.76%, 68.16%, respectively. and the OS at 12 months was 92.64%. 24 pts were eligible for the evaluation of tumor response, the objective response rate (ORR) was 12.50% (4/32) and the disease control rate (DCR) was 86.76% (14/24). The incidence of treatment-related adverse events of grade 3 was 31.25%, with a higher incidence of hypertriglyceridemia (9.38%), Neutrophil count decreased (6.25%), palmar-plantar erythrodysesthesia syndrome (6.25%), febrile neutropenia (6.25%), respectively. The incidence of Severity Adverse Event was 12.5%. 50 pts are expected to be enrolled in the study, and the data will be mature after the follow-up is completed. Conclusions: Penpulimab (P) plus anlotinib (A) and epirubicin (E) has shown encouraging activity as first-line treatment for STS, which significantly prolong the PFS with well tolerance. Clinical trial information: ChiCTR2100048014. Research Sponsor: None.
A phase II study of talimogene laherparepvec (T-VEC) and pembrolizumab in patients with advanced sarcoma: Results of expansion cohorts.

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Background: The open-label, single-center phase II study of T-VEC and pembrolizumab in patients with advanced sarcoma met its primary endpoint and demonstrated a best objective response rate of 30% at 24 weeks per RECIST v1.1 (Kelly CM, et al, Jama Oncology, 2020). Responses were seen in undifferentiated pleomorphic sarcoma (UPS), myxofibrosarcoma (MFS), epithelioid sarcoma (ES), cutaneous angiosarcoma (AS), and undifferentiated sarcoma not otherwise specified. Here, we report the efficacy observed in three histology specific expansion cohorts: 1) UPS/MFS, 2) cutaneous AS and 3) ES. Methods: Patients refractory to ≥ 1 prior line of systemic therapy or declined standard of care systemic therapy received pembrolizumab intravenously and intratumoral T-VEC injections on day 1 of a 21-day cycle. The primary endpoint was best objective response (ORR, complete and partial responses per RECIST v 1.1) by 24 weeks estimated for each subtype-specific cohort. Secondary objectives included: adverse events (AEs, TRAEs), median PFS and correlatives. Results: Twenty-one patients enrolled in the expansion cohorts: median age 72 years (range: 39-85), male 57%, ≤ 1 prior line of therapy (43%). Treatment was well tolerated in twenty patients; one patient discontinued study therapy due to grade 3 immune mediated hepatitis. Nineteen patients were evaluable for efficacy (one patient withdrew from the study and another discontinued treatment before week 24). Subtype specific best ORR by 24 weeks per RECIST v 1.1: UPS/MFS – 11% (n = 1/9)[95% CI: 0.0-0.48]; AS – 43% (n = 3/7)[95% CI: 0.1-0.82]; ES – 0% (n = 0/3). The best ORR overall for the AS cohort was 71% (n = 5/7)[95% CI: 0.03-0.95]. Median PFS (weeks) was 14.9 [CI: 7-111] for UPS/MFS and 54 [95% CI: 3- not reached] for AS (Table). Conclusions: TVEC and pembrolizumab demonstrated acceptable safety and promising anti-tumor activity in cutaneous AS (head & neck (n = 4) and Stewart-Treves syndrome involving the upper extremity (n = 1)). Five AS patients experienced a partial response with durable disease control, remaining on study for 1-2 years or more. Two delayed responses were observed in the AS cohort after the pre-specified 24-week criteria. One AS responder progressed on immune checkpoint inhibition prior to study entry. Correlative analyses are ongoing. Clinical trial information: NCT03069378. Research Sponsor: Merck and Amgen; Cycle for Survival; from NIH/NCI Cancer Center Support Grant p30 CA008748; Angiosarcoma Awareness, Inc foundation provided funding for travel reimbursement for angiosarcoma participants in the expansion cohort.

<table>
<thead>
<tr>
<th></th>
<th>UPS/MFS (n = 9)</th>
<th>Cut. AS (n = 8)</th>
<th>ES (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range[years])</td>
<td>69 (48-81)</td>
<td>80 (72-85)</td>
<td>63 (39-70)</td>
</tr>
<tr>
<td>Prior treatment (%)</td>
<td>≤ 2 regimens</td>
<td>7 (70)</td>
<td>4 (50)</td>
</tr>
<tr>
<td></td>
<td>≥ 3 regimens</td>
<td>3 (30)</td>
<td>4 (50)</td>
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<tr>
<td>Prior immunotherapy (%)</td>
<td>2 (20)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
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<tr>
<td>≥ Grade 3 TRAE (%)</td>
<td>0 (0)</td>
<td>1 (12.5%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Best ORR at 24 weeks n (%)[CI]</td>
<td>1 (11) [0.0-0.48]</td>
<td>3 (43) [0.1-0.82]</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Best ORR overall n (%)</td>
<td>1 (11)</td>
<td>5 (71)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clinical benefit rate (%)</td>
<td>6 (67)</td>
<td>5 (71)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Median PFS (weeks)</td>
<td>14.9 (CI: 7-110)</td>
<td>54 (CI: 3- NR)</td>
<td>—</td>
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</tbody>
</table>

*One patient was evaluable for toxicity but not evaluable for efficacy because they came off study prior to week 24.
Trabectedin (T) versus adriamycin plus dacarbazone (A-DA) in advanced solitary fibrous tumor (SFT): Results from a phase II randomised clinical study (STRADA).

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Background: T and A-DA showed antitumor activity in a PDX model of dedifferentiated-SFT (D-SFT) and a few cases of activity in advanced SFT pts have been reported. The efficacy of these agents in advanced typical- (T-)/malignant- (M-)SFT is unclear. A phase 2 randomised (R) study was conducted within the Italian Sarcoma Group (ISG) to investigate the activity of T and A-DA in advanced T-, M- and D-SFT (Clin-Gov: NCT03023124).

Methods: An Italian, multicentre, investigator-initiated prospective open-label, R, non-comparative, phase 2 trial was started in July 2017 involving 6 ISG sites, to evaluate the activity of front-line T (1,5-1,3 mg/sqm at investigator’s discretion, day 1 every 3 wks; arm A) vs A-DA (A 75 mg/sqm day 1 + DA 400 mg/sqm days 1,2 every 3 wks; arm B) in > 18 years-old pts with advanced SFT (T-SFT, M-SFT, D-SFT) until progression or limiting toxicity; in arm B, a maximum number of 6 cycles was foreseen, given the constrain of the maximum tolerated dose of A. Eligible pts had to show RECIST progression in the 6 mos prior to study entry. Centralized pathologic and radiologic review was performed. Pts were randomly assigned to Arm A or Arm B (1:1 ratio), with cross over in case of progression (PD) or unacceptable toxicity prior to the completion of the 6 cycles (arm B in case of randomization to arm A and vice versa). An interim analysis was pre-planned after reaching 10 evaluable pts in each arm, and at least 1 response in arm A was required to continue the study. Primary end-point was the overall response rate (ORR) by RECIST; secondary end-points ORR by Choi, progression-free survival (PFS), overall survival (OS).

Results: Enrolment for the interim analysis was completed in September 2022. 30 pts were screened and 23 were enrolled (7 screening failure): T-SFT = 7, M-SFT = 14, D-SFT = 2. All pts were naïve; 3 pts are ongoing, 20 completed their treatment, (12 = PD, 8 = other). All pts were evaluable for RECIST. No responses by RECIST were seen in each arm (ORR 0%), while stable disease (SD) and PD were 9 (45%) and 1 (5%) in arm A and 8 (40%) and 2 (10%) in arm B, respectively. At a 15.9-mo (I.Q. range 11.3-29.0) m-FU, m-PFS by RECIST was 9.2 (2.7-not assessable) mos in arm A and 8.0 (1.1-not assessable) mos in Arm B, with 29.6% progression-free pts at 1 year in arm A and 18.7% in arm B. Median OS was 34.3 (9.3-not assessable) mos in arm A, 31.5 (4.2-31.5) mos in arm B. Conclusions: No responses were seen neither to T nor to A-DA across all SFT subtypes; therefore, the study was closed to enrolment for T-SFT and M-SFT after the interim analysis. Noteworthy, both T and A-DA stabilised the disease in about 40% of previously progressive pts, and nearly 30% of pts treated with T were free from progression at 1 year. On the other hand, no conclusion can be drawn yet on the activity of T / A-DA in this SFT subtype, since D-SFT cases who entered the study were only 2 and the enrolment of D-SFT is still ongoing. Clinical trial information: NCT03023124. Research Sponsor: Pharmamarr.
Efficacy of eribulin administered in combination with an immune checkpoint inhibitor (ICI) and anlotinib as salvage treatment for patients (pts) with advanced adult soft tissue sarcoma (STS).

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Background: Eribulin combined with a multi-targeted antiangiogenic tyrosine kinase inhibitor has shown efficacy in STS. ICIs have also exhibited improved survival in some STS subtypes. We investigated the efficacy and safety of triple combination therapy with eribulin, an ICI and anlotinib in the treatment of advanced STS in an adult Chinese population. Methods: This study retrospectively analyzed data from patients diagnosed with advanced STS who received combination therapy with eribulin, an ICI and anlotinib at the Department of Oncology, Zhongshan Hospital affiliated to Fudan University. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR) by RECIST v1.1, disease control rate (DCR), and treatment-related adverse events (TRAEs) by CTCAE v5.0. Results: Medical records from 32 pts treated between August 15, 2020 and January 31, 2023 were included; the median age was 56 years, 71.8% (23/32) were female, 75.0% (24/32) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and 25.0% (8/32) had an ECOG PS of 2. Pts had received a median of 2 (range 0-6) prior regimens and the median follow-up was 4.1 months. Among the patients, 50.0% (16/32) had liposarcomas (including 1 with pleomorphic liposarcoma and 15 with dedifferentiated liposarcoma [DDLPS]), 31.3% (10/32) had leiomyosarcomas (LMS), 3 had undifferentiated pleomorphic sarcoma (UPS), and 1 each had angiosarcoma, rhabdomyosarcoma and desmoplastic small round cell tumor. In a preliminary analysis, 29 pts were evaluable for clinical activity; partial responses (PRs) were achieved in 3 pts (2 DDLPS, 1 UPS), the ORR and DCR were 10.3% (3/29) and 62.1% (18/29) respectively, and the median PFS was 5.7 months (95% CI 2.7-9.8). Of the 15 pts with DDLPS (median 1 prior line of therapy; median follow-up 6.3 months), 13 were evaluable for clinical activity; a PR was achieved by 15.4% (2/13), the DCR was 61.5% (8/13), the median PFS was 9.8 months (95% CI 1.8-28.5) and treatment was ongoing in 46.7% of pts (n = 7). Among the 9 evaluable pts with LMS, 0 achieved a PR, the DCR was 44.4% (4/9), median PFS was 3.9 months and 3 pts were still receiving treatment. In the overall cohort (n = 32), TRAEs of any grade occurred in 56.3% of pts (n = 18), the most common were myelosuppression (28.1%), fatigue (15.6%), fever (12.5%) and rash (12.5%). Grade 3/4 TRAEs occurred in 12.5% of pts, with no grade 5 events. Conclusions: This study demonstrates the potential efficacy of combination therapy with eribulin, an ICI and anlotinib in patients with advanced STS, especially in those with the DDLPS subtype. Our data suggest that this combination has good tolerability and a prospective trial is warranted. Clinical trial information: ChiCTR2100053594. Research Sponsor: None.
Trabectedin failure-free survival (TFFS) after resuming trabectedin (T) in advanced myxoid liposarcoma (MLPS) patients.

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Background: To explore the time to trabectedin failure-free survival after resumption of T in advanced MLPS patients who were stable or responding to T at the time of discontinuation.

Methods: We retrospectively collected the cases of all patients with advanced MLPS treated with T at our institution from September 2002, highlighting those who were free from progression (according to RECIST) after 6 cycles of T. Trabectedin failure-free survival (TFFS) was defined as time from the first cycle of T to progression (PD) or death, whichever occurred first. Survival analyses were performed using the Kaplan-Meier method.

Results: Since September 2002, 75 patients with recurrent myxoid liposarcoma received T at our institution. A total of 56 patients were free from progression (according to RECIST) after 6 cycles of T and were included in this analysis. Among them, 25/56 (45%) interrupted their treatment in absence of progression, while 31/56 (55%) patients received T until progression of disease. In the former group, 11/25 had surgery of their residual disease, 3/25 received radiotherapy, 5/25 interrupted T for toxicity and 6/25 patients shared the decision to stop with the clinician. Among patients who received surgery, 2/11 had monofocal disease (longest diameter \( \geq 5 \) cm), 4/11 had monofocal disease (longest diameter between 10-18 cm) and 5/11 had plurifocal disease. The interruption of T in these 25 patients occurred after a median of 12 cycles (interquartile range = 9-14). Median TFFS was 43.4 months (95% CI 38.7-NA). In the concurrent group of patients who received T continuously, the median TFFS was 14.2 months (95% CI: 10.8-21.9).

Conclusions: While the longer TFFS of patients undergoing discontinuation cannot be compared with the shorter of those who did not interrupt, the former group being biased favorably (feasibility and exploitation of surgery, other likely determinants of physician’s decision to stop), we speculate that there may be a subgroup of selected patients with advanced myxoid liposarcoma primarily responding to T, who could benefit from a “stop and go” policy, thus prolonging the overall time interval within which T remains active. Prospective studies in selected subgroups of MLPS patients on optimization of treatment strategy with T are worthwhile.

Research Sponsor: None.
Outcome of patients (PTS) with advanced epithelioid hemangioendothelioma (EHE) after failure on sirolimus (S).

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Background: EHE is an ultra-rare sarcoma, showing a highly variable clinical behavior, from indolent to very aggressive. Systemic agents available for treatment of sarcoma have marginal activity in EHE. S showed antitumor effect in PDX models and pts affected by advanced EHE. However, clinical data on S in EHE are only retrospective and uncontrolled. This makes it difficult to interpret if the median progression-free survival (m-PFS) of 13 mos and the m-overall survival (m-OS) of 18.8 mos observed in the 38 progressive pts included in the largest series available (Stacchiotti et al, doi:10.1002/cncr.33247) were attributable to the antitumor effect of S or to EHE natural history. To fill this gap, we reviewed the outcome of pts included in this series who went off S.

Methods: Clinical data of all EHE pts included in the above-mentioned retrospective study and treated with S for advanced disease between 2010 and 2019 were reviewed, focusing on pts who discontinued S for any reason. Progression was retrospectively categorized by RECIST 1.1 progressive disease (PD) and as “clinical progression” (CP), CP being defined as worsening of systemic symptoms and/or serosal effusion without criteria for RECIST PD. Survival analyses were performed by Kaplan-Meier method. OS was defined as the time from S start until death or last follow-up (FU), post-discontinuation OS (pOS) as the time from S discontinuation until death or last FU, post-discontinuation PFS (pPFS) as the time from S discontinuation until first evidence of progression (PD or CP) or death, post-re-challenge PFS (pR-PFS) as the time from S re-challenge until first evidence of progression (PD or CP) or death.

Results: Of the 38 pts, 24 stopped S and were included in this analysis (median age = 47 yrs; serosal effusion yes/no = 9/15; S discontinuation due to: RECIST PD = 12, CP = 3, toxicity = 7; other = 2). After S discontinuation all pts had an event (PD or CP or death), and 13/24 (54%) pts did not receive further treatments, while 11/24 (46%) started again a systemic treatment. In particular, 6/24 (25%) restarted S (all after interval progression, PD or CP) with a new stable disease in 5/6 cases. At last FU, 6/24 (25%) pts were alive, 18/24 (75%) dead. At 62.2-mo m-FU (IQR 46-124), m-OS was 14.3 mos (95% CI, 7.3-21.2). Overall m-pPFS was 3.02 mos (95% CI, 1.6-4.4), m-pOS was 7.15 mos (95% CI, 4.4-9.9). m-PFS of pts who discontinued S without evidence of progression (PD or CP) was also 3.02 mos (95% CI, 2.9-3.1). m-PFS following the re-challenge of S (m-pR-PFS) was unreached; 1 pt died following PD after 19 mos, 1 pt was alive and showed CP at 40 mos, 4 were alive and progression-free after 27, 31, 55, 94 mos.

Conclusions: In our study the outcome of EHE pts who discontinued S was poor, with a m-pPFS of 3 mos and a m-pOS of 7 mos. However, pts who discontinued S for reasons other than progression benefited from S re-challenge, suggesting that in advanced EHE there is a subset of long-responders to S. Research Sponsor: None.
Risk stratification tools to help decide on adjuvant chemotherapy usage in resected soft tissue sarcomas: A 10 year review of an Irish sarcoma centre experience.

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Background: Soft tissue sarcoma (STS) is comprised of 80 pathologic subtypes based on a combination of distinctive morphological, immunohistochemical and molecular features. Adult-type soft tissue and visceral sarcomas are rare, with an estimated incidence of 4-5/100,000/year in Europe. The National Comprehensive Cancer Network (NCCN) guidelines recommend consideration of neo-adjuvant or adjuvant systemic treatment in resectable stage III (high grade tumours which are >5cm) and also in those who need to undergo an amputation or radical resection with adverse functional outcomes. The Sarculator risk prediction tool has identified a threshold of risk above which the administration of chemotherapy may provide an overall survival benefit. This can be applied to the most common histologic subtypes. Patients affected by these subtypes and with a 10-year predicted OS likelihood <60% are considered as high risk and therefore, should be considered for adjuvant chemotherapy. Alternatively, tumours considered at high risk of recurrence based on size >5cm and high grade histology, may benefit from adjuvant chemotherapy. Therefore, the aim of this project is to review the outcomes of resected extremity/trunk soft tissue sarcoma and assess the prognostic accuracy of these risk prediction methods. 

Methods: All new patients with resected STS discussed in the STS MDT in Cork University Hospital between Jan 2012 – Dec 2021 were identified. The histology and imaging of the identified patients were reviewed. Data regarding demographics, histology, treatment and outcomes was collected. Risk assessment using AJCC and Sarculator score was done on all patients with an extremity or trunk sarcoma. Overall survival was recorded and assessed including Kaplan Meier method for time to event analysis. 

Results: 200 patients were identified as having an STS resected - 134 of these were located on the trunk or extremities representing 24 different histological subtypes. Sarculator score was calculated for 60 of these (well differentiated liposarcomas, desmoid tumours, and dermatofibrosarcoma protuberans were excluded). 3 patients received adjuvant chemotherapy and 4 patient neoadjuvant chemotherapy. Overall survival data is presented below. Conclusions: Our cohort is representative of the broad histological subtypes expected in sarcoma. Sarculator score results correlate with international outcomes, with higher scores associated with increased mortality. In our cohort, sarculator score was more predictive of outcome than tumour grade/size alone. Research Sponsor: None.

<table>
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<tr>
<th>Sarculator score – risk assessment</th>
<th>No. patients</th>
<th>No. of deaths</th>
<th>5 yr OS rate (n = 30)</th>
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<tbody>
<tr>
<td>High risk</td>
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<td>8 (42.1%)</td>
<td>60.2%</td>
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<tr>
<td>Low risk</td>
<td>41</td>
<td>6 (14.6%)</td>
<td>87.1%</td>
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<tr>
<td>AJCC staging – risk assessment</td>
<td>No. patients</td>
<td>No. of deaths</td>
<td>5 yr OS rate (n = 30)</td>
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<tr>
<td>High risk</td>
<td>25</td>
<td>8 (32%)</td>
<td>67.6%</td>
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<tr>
<td>Low risk</td>
<td>35</td>
<td>6 (17%)</td>
<td>86.3%</td>
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</table>
Clinical implications of recurring mutations in myxoid liposarcoma (MLS).

Prapassorn Thirasast, Heather Y. Lin, Elise F Nasisif, Wei-Lien Wang, Dejka M. Araujo, Robert S. Benjamin, Anthony Paul Conley, J Andrew Andrew Livingston, Joseph Aloysius Ludwig, Shreyaskumar Patel, Ravin Ratan, Vinod Ravi, Maria Alejandra Zarzour, Xiao Zhou, Neeta Somaiah; University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Department of Sarcoma Medical Oncology, Houston, TX

Background: MLS is a subset of liposarcoma characterized by a translocation, (t(12;16), FUS-DDIT3 or less frequently t(12;22), EWSR1-DDIT3). Additional mutations have been reported in TERT promoter, PIK3CA, and PTEN and some were associated with the more aggressive round cell phenotype. Our study aimed at analyzing the clinical significance of these recurring mutations. Methods: MLS patients (pt) with available next-generation sequencing (NGS) data (any clinical grade) between Jan 2014 to Oct 2022 were included. Baseline characteristics, chemotherapy (CMT) response (partial response [PR] and stable disease [SD]), and survival were collected for doxorubicin-ifosfamide (AI), doxorubicin-dacarbazine (ADIC), trabectedin (T), and eribulin (E). Binary logistic regression was used to evaluate mutations associated with response. Cox proportional-hazard regression was used to investigate associations of variables with progression-free survival (PFS) and overall survival (OS). The Kaplan-Meier method was used to estimate survival and log-rank tests were used to compare survival between groups. Results: Of 18 MLS pt included, median age at diagnosis was 42 years (R 30-65). Majority were male (12/18, 67%), had localized disease at diagnosis (13/18, 72%), and had lower extremities as primary location (10/18, 56%). Eight (44%) had round-cell > 5% and 15 (83%) had primary tumor > 5 cm. Somatic mutations were reported in 15 pt (83%); the most common were TERT promoter (61%), PTEN (28%), PIK3CA (22%), and TP53 (17%). None showed significant association with clinical factors (age, sex, size, stage, round cell > 5%, primary location). Forty-eight records (18 AI, 6 ADIC, 19 T, and 5 E; 3 pt received AI and T twice for different recurrences), were evaluated for PFS and 47 records had response data available. For AI, ADIC, T, and E, PR rate was 39% (7/18), 17% (1/6), 32% (6/19), and 40% (2/5), while clinical benefit (CBR: PR + SD > 3 mo) was 67% (12/18), 50% (3/6), 63% (12/19), and 80% (4/5), respectively. PR or CBR were not associated with the common mutations for any regimen. Median follow up (FU) from start of CMT was 4 mo (R 0.5-31). PFS (95%CI) was 11 (6.7- Not Reached [NR]), 1.2 (1.1-NR), 23 (6.3-NR), and 8 (1.3-NR) mo for AI, ADIC, T, and E, respectively. PIK3CAwt (n = 15) was associated with improved PFS with CMT (PFS [95%CI]: PIK3CAwt 7.8 [6.3-11.2] vs. PIK3CAm 23 mo [1.3-NR]; multivariate hazard ratio [HR] 0.23, p= 0.036, adjusted by gender and ADIC regimen). This appeared to be mainly driven by the PIK3CAm/TERTwt (n = 8, HR 0.07, p= 0.006). For T, PIK3CAm/TERTwt (n = 3) showed a trend for lower PFS (1.3 mo) in contrast to other groups (23 mo). Conclusions: TERT promoter mutation was the most frequent mutation but was not associated with outcome in our small series. PIK3CAm suggested PFS benefit from CMT while, on the contrary, dual PIK3CAm/TERTwt showed a trend towards shorter PFS with T. The predictive and prognostic role of these mutations in MLS warrant further study. Research Sponsor: None.
DCK expression by RNAseq as a potential biomarker of gemcitabine response in sarcoma.

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Background: Deoxycytidine kinase (DCK) is responsible for activation of gemcitabine by phosphorylation of gemcitabine to its monophosphate form. Studies have suggested that DCK expression may be correlated to response to gemcitabine in various solid tumors, and that downregulation of DCK may be at least partly responsible for gemcitabine-resistance in vitro. However, the significance of DCK expression in sarcomas as a biomarker of response to gemcitabine remains poorly characterized.

Methods: Participants enrolled in the prospective Electronic Health Record (EHR)-Based Comprehensive Bone and Soft Tumor Registry (NCT02677961) at The Ohio State James Cancer Center who had received gemcitabine-based chemotherapy for the treatment of bone and soft tissue sarcoma were eligible for this study. A total of 179 patients were identified who had received at least one cycle of gemcitabine-based chemotherapy, between January 1st, 2014, to December 31st, 2022. Whole exome RNASeq expression data was available for 36 of these patients who had received gemcitabine-based chemotherapy in the setting of active disease.

Results: Of the 36 patients included in this study, 22 were female and 14 were male. Nine different main disease types were identified in the patient subset. These include angiosarcoma (8), chondrosarcoma (1), leiomyosarcoma (16), liposarcoma (3), malignant peripheral nerve sheath tumor (1), myxofibrosarcoma (2), osteosarcoma (2), undifferentiated pleomorphic sarcoma (3), and undifferentiated spindle cell sarcoma (1). The median time to treatment discontinuation (TTD) among all patients was 178 days. Among DCK low-expressors (n = 16), the median TTD was 86 days; among high-expressors (n = 16), the median TTD was not reached. Differences between groups did not reach statistical significance (HR = 0.55, p = 0.14).

Conclusions: DCK expression by clinical RNASeq is a potential biomarker of gemcitabine-response in sarcoma, but larger studies are necessary to evaluate the potential clinical significance and possible role of DCK expression in identifying patients most likely to benefit from gemcitabine-based chemotherapy. Research Sponsor: Ohio State University, Division of Medical Oncology Research Award.
AOST2031: An in-progress COG phase 3 randomized controlled trial comparing open vs thoracoscopic management of pulmonary metastases in patients with osteosarcoma.

John J Doski; University of Texas Health Sciences Center at San Antonio, San Antonio, TX

Background: Pulmonary metastasectomy is considered a necessary component of curative therapy in pulmonary metastatic osteosarcoma, however the optimal surgical approach is unknown. Two approaches include open surgery (OSY) including thoracotomy or sternotomy and minimally invasive surgery (MSY) by thoracoscopy. No randomized trial has been completed comparing these approaches in patients with osteosarcoma, however randomized controlled trials in other cancers have not identified superior outcomes in patients undergoing OSY. OSY allows for direct palpation of all lung surfaces and more pulmonary metastatic nodules can be identified during OSY compared to the number predicted by pre-operative imaging. MSY offers the benefit of faster patient recovery, improved quality of life and potential for equivalent surgical control of relevant metastatic disease. Given wide variability in surgical approach and willingness of both surgical oncology and patient advocacy communities to participate in a randomized trial, AOST2031 was developed to address this clinical equipoise.

Methods: Eligibility for AOST2031 includes patients ≥ 50 yrs with a histological diagnosis of osteosarcoma and evidence of pulmonary metastases at initial diagnosis or at first recurrence. Patients must have oligometastatic lung metastasis considered resectable by either OSY or MSY, with rapid central review of chest CT images to confirm eligibility. Systemic therapy considered equivalent to methotrexate, cisplatin and doxorubicin is required to be ongoing in newly diagnosed and completed in patients with recurrence. Exclusion criteria include unresectable primary disease, metastatic disease requiring anatomic lung resection, pleural or mediastinal lesions or pleural effusions, progression while receiving initial therapy, extra-pulmonary metastases and prior chest surgery for pulmonary metastases. Patients are randomized 1:1 to either OSY or MSY, with randomization stratified by disease status and risk. The primary outcome is thoracic event free survival, defined as intrathoracic tumor recurrence or death that results from the procedure or a complication related to the procedure. Two-hundred and twenty-five eligible patients are anticipated to answer the primary objective. Secondary objectives include event free, overall survival and . Exploratory objectives include surgical complication rates, patterns of recurrence, use of surgical localization techniques, comparison of CT findings to pathology of resected specimens, and patient reported outcomes. Biologic objectives include the collection of metastatic tissues to facilitate the study of metastatic disease and serial blood samples for future tumor profiling, germline and circulating tumor DNA studies. AOST2031 opened to enrollment at NCTN sites in February 2022. Clinical trial information: NCT05235165. Research Sponsor: U.S. National Institutes of Health.
A randomized, open-label, phase 2 study evaluating abemaciclib in combination with irinotecan and temozolomide in participants with relapsed or refractory Ewing sarcoma.

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Background: Ewing's sarcoma (ES) is the second most common malignant bone tumor affecting children and young adults. Patients with relapsed disease have a poor prognosis and need effective therapies. EWS-FLI1, the most common ES fusion gene (90-95% of cases), is an oncogenic transcription factor that downregulates intrinsic cyclin-dependent kinase (CDK) inhibitors, CDKN1A and CDKN1C, which promote cell cycle arrest and upregulates CDK4, which drives entry into the cell cycle. This provides a biological rationale for the clinical evaluation of CDK4/6 inhibitors in ES. Abemaciclib is a selective CDK4/6 inhibitor approved for the treatment of breast cancer. It is approximately 14 times more potent against CDK4/cyclin D1 than CDK6/cyclin D3 in enzymatic assays and has the advantage of continuous dosing schedule without breaks for neutrophil recovery. Abemaciclib is currently also in clinical development for paediatric patients with relapse/refractory solid tumors in combination with irinotecan and temozolomide (JPCS study, NCT04238819). This study, NCT05440786, will evaluate the potential benefit of adding abemaciclib to irinotecan plus temozolomide for the treatment of relapsed/refractory ES.

Methods: This randomized, open-label, Phase 2 study is part of the CAMPFIRE master protocol. It is enrolling paediatric and young adult patients (1–39 years) with relapsed/refractory ES or ES-like tumors. Approximately 45 patients will be randomized 2:1 between 2 arms: irinotecan and temozolomide with or without abemaciclib. Stratification factors include age, pulmonary/non-pulmonary site of metastases, and time to recurrence from initial diagnosis. Patients will receive irinotecan (50 mg/m²/day intravenously) and temozolomide (100 mg/m²/day orally) on days 1-5. Abemaciclib will be administered orally twice-daily on a continuous 21-day cycle. The abemaciclib dose will be 55mg/m² BID for patients < 18 years and 100mg BID for those ≥ 18 years. Besides 25 and 50mg tablets, abemaciclib will be available as 2.5mg granules allowing administration of doses as low as 10mg to patients with a body surface area lower than 0.2m². Treatment continues until disease progression or other discontinuation criteria are met. The primary endpoint is progression-free survival (PFS) determined by a blinded independent review committee using Response Evaluation Criteria in Solid Tumors, Version 1.1. Key secondary endpoints include overall survival, objective response rate, duration of response, disease control rate, PFS determined by investigator assessment, safety, and pharmacokinetics. Additional analysis includes exploratory biomarker testing. This study is open and actively enrolling in Australia, Europe, Japan, and United States. Clinical trial information: NCT05440786. Research Sponsor: Eli Lilly and Company.
Background: Outcomes for relapsed osteosarcoma (OS) remain poor and there are no systemic therapies that have been shown to provide a survival benefit. Chimeric Antigen Receptor (CAR) T cell immunotherapy involves the adoptive transfer of T-lymphocytes that have been engineered to recognize tumor-specific antigens, resulting in targeted lysis of malignant cells. Folate receptors (FR) are membrane-bound surface proteins that bind folates with high affinity. FRs are overexpressed in OS and have very limited expression in normal tissue. UB-TT170 (Umoja Biopharma) is a small molecule bispecific “adapter” consisting of folate conjugated to fluorescein (FL). It penetrates tumors in minutes and is retained for long periods of time due to high affinity for the FR, while unbound UB-TT170 rapidly clears from the blood and from FR- tissues. We hypothesize that administration of fixed dosing anti-FL (FITC-E2) CAR T cells followed by escalating doses of UB-TT170 will deliver personalized immunotherapy to OS patients. In addition, this approach offers an attractive safety mechanism since administration of NaFL should reverse CAR T cell reactivity. Methods: We designed a Phase I study for young adult (15-30 yr) patients with recurrent/refractory OS to examine the safety and feasibility of administering autologous, peripheral blood-derived T cells that have been genetically modified to express a 2nd generation FL-specific CAR in combination with intra-subject dose escalation of UB-TT170. The primary objective is to identify a recommended dose escalation sequence of UB-TT170 to move forward in clinical development. A 3+3 design will be used to investigate 3 possible dosing sequences. The trial opened in July 2022. As of January 5, 2023, 5 subjects have enrolled and one subject has been treated on dose regimen 1. T cell products have been successfully manufactured for all enrolled subjects. The trial remains open to enrollment. Clinical trial information: NCT05312411. Research Sponsor: Umoja Pharma; Seattle Children’s Therapeutics.
INSIGHT: A phase 3, randomized, multicenter, open-label study of ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib harboring KIT exon 11 + 17 and/or 18 mutations.

Suzanne George, Jean-Yves Blay, Ping Chi, Robin Lewis Jones, Cesar Serrano, Neeta Somaiah, William Reichmann, Kam Sprott, Haroun Achour, Matthew L. Sherman, Rodrigo Ruiz-Soto, Michael C. Heinrich, Sebastian Bauer, on behalf of the INSIGHT Study Investigators; Dana-Farber Cancer Institute, Boston, MA; Centre Léon Bérard, Lyon, France; Memorial Sloan Kettering Cancer Center, New York, NY; Sarcoma Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom; Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; The University of Texas MD Anderson Cancer Center, Houston, TX; Deciphera Pharmaceuticals, LLC, Waltham, MA; Portland VA Health Care System and OHSU Knight Cancer Institute, Portland, OR; Department of Medical Oncology, Sarcoma Center/West German Cancer Center, University Hospital Essen, University Duisburg-Essen and German Cancer Consortium (DKTK), Partner Site University Hospital Essen, Essen, Germany

Background: Gastrointestinal stromal tumor (GIST) is the most common gastrointestinal sarcoma, with approximately 80% of cases driven by KIT mutations. Most patients (pts) with advanced GIST develop disease progression following first-line treatment with imatinib due to KIT secondary resistance mutations occurring most commonly in the ATP-binding pocket (exons 13/14) and/or activation loop (exons 17/18). Sunitinib is approved as second-line therapy for advanced GIST. Ripretinib is a switch-control tyrosine kinase inhibitor approved for pts with GIST who received prior treatment with 3 or more kinase inhibitors, including imatinib. In the phase 3 INTRIGUE study (NCT03673501) in second-line advanced GIST, ripretinib was not superior to sunitinib in terms of progression-free survival (PFS); however, a more favorable safety profile was observed with ripretinib vs sunitinib (Bauer S et al. J Clin Oncol. 2022). Exploratory mutational analysis from INTRIGUE using baseline circulating tumor DNA (ctDNA) demonstrated that pts harboring primary KIT exon 11 mutations with secondary resistance mutations exclusively in KIT exons 17 and/or 18 derived PFS benefit with ripretinib vs sunitinib (median, 14.2 vs 1.5 months; HR = 0.22, 95% CI 0.11 to 0.44, nominal P < 0.0001; Bauer S et al. J Clin Oncol. 2023; abstract 397784). Here, we describe a planned phase 3 study for pts with advanced GIST previously treated with imatinib harboring KIT exon 11 + 17 and/or 18 mutations.

Methods: INSIGHT is a phase 3, randomized, open-label study that aims to evaluate the efficacy of ripretinib vs sunitinib in pts with advanced GIST previously treated with imatinib and who harbor KIT exon 11 + 17 and/or 18 mutations. Eligible pts must be ≥18 years old with histologically confirmed GIST and co-occurring KIT exon 11 + 17 and/or 18 mutations confirmed by ctDNA analysis. Pts must also have advanced disease with ≥1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (mRECIST) v1.1, radiologic progression on imatinib, and an Eastern Cooperative Oncology Group Performance Status ≤2. Key exclusion criteria include a KIT exon 9, 13, or 14 mutation via ctDNA at screening and prior treatment with another line of therapy in addition to imatinib for advanced GIST. A total of 54 pts will be randomized (2:1) to receive ripretinib 150 mg once daily (QD; continuous) or sunitinib 50 mg QD (4 weeks on/2 weeks off) in 6-week cycles. The primary endpoint is PFS by independent radiologic review (IRR) per mRECIST v1.1; key secondary endpoints are objective response rate by IRR using mRECIST v1.1 and overall survival. Safety and patient-reported outcome measures will also be assessed. Pts randomized to the sunitinib arm may cross over to the ripretinib arm upon disease progression. Clinical trial information: NCT05734105. Research Sponsor: Deciphera Pharmaceuticals, LLC.
ENVASARC: A pivotal trial of envafolimab and envafolimab in combination with ipilimumab in patients with advanced or metastatic undifferentiated pleomorphic sarcoma or myxofibrosarcoma who have progressed on prior chemotherapy.

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Background: Metastatic undifferentiated pleomorphic sarcoma (UPS) and the genetically related myxofibrosarcoma (MFS) are soft tissue sarcoma (STS) subtypes with poor prognoses. While responses to first-line chemotherapy can approach 20%, efficacy remains limited in the 2nd-line setting and beyond. Pazopanib, the only FDA approved treatment in the refractory setting, has demonstrated an objective response rate (ORR) of 4%. Envafolimab is a single domain PD-L1 antibody administered by rapid subcutaneous (SQ) injection that is approved for the treatment of microsatellite instability-high (MSI-H) cancer in China. The activity of envafolimab appears to be similar to other PD-1 antibodies administered intravenously (i.v.). Envafolimab demonstrated a 32% ORR in MSI-H colorectal cancer patients with progressive disease following three approved chemotherapeutics, similar to the ORR of 28% and 33% with nivolumab and pembrolizumab in these patients, respectively. The rationale for the ENVASARC is based on envafolimab activity in STS in phase 1 trials and previously reported activity of checkpoint inhibition in UPS/MFS: single-agent pembrolizumab demonstrated a 23% ORR, while the combination of nivolumab and ipilimumab demonstrated a 29% ORR in refractory UPS/MFS. Methods: ENVASARC (NCT 04480502) is a pivotal multicenter (at 30 U.S. and U.K. centers) open-label, randomized, non-comparative, parallel cohort study of envafolimab 600 mg every 3 weeks by SQ injection (n = 80) or envafolimab 600 mg every 3 weeks by SQ injection combined with ipilimumab 1 mg/kg every 3 weeks i.v. for four doses (n = 80) in patients with locally advanced, unresectable or metastatic UPS/MFS with disease progression on one or two lines of prior therapy. The primary objective of each of parallel cohort is to demonstrate an ORR with a lower limit of the 95% confidence interval that excludes 5.0% in each cohort. If ≥ 9 responders are observed among the 80 patients enrolled in each cohort, then the lower bound of the 95% confidence interval will exclude 5.0%. Secondary endpoints include duration of response, PFS and OS. Key inclusion criteria: ≥ 2 prior lines of therapy ([neo]adjuvant therapy excluded), ECOG ≤ 1. Clinical trial information: NCT04480502. Research Sponsor: TRACON Pharmaceuticals.
Alliance A092104: A randomized phase 2/3 study of olaparib plus temozolomide versus investigator’s choice for the treatment of patients with advanced uterine leiomyosarcoma after progression on prior chemotherapy.

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Background: Uterine leiomyosarcoma (uLMS) is an aggressive sarcoma subtype with frequent metastatic relapse. Advanced uLMS is treated with gemcitabine/docetaxel or anthracycline-based regimens. After failure of initial chemotherapy, remaining options provide limited benefit (trabectedin: objective response rate (ORR) 11%, median progression-free survival (mPFS) 4.0 months (mo); pazopanib: ORR 11%, mPFS 3.0 mo; dacarbazine: ORR 9%, mPFS 1.5 mo). 18-23% of uLMS harbor deleterious alterations in homologous recombination (HR) DNA repair genes. HR-deficient cancers are unable to effectively repair double-stranded DNA breaks and may be sensitive to poly ADP-ribose polymerase (PARP) inhibitor-based strategies. In preclinical studies, the combination of temozolomide (T), an alkylating agent, and olaparib (O), a PARP inhibitor, markedly suppressed proliferation of uLMS models. Among 22 uLMS patients with median 3 prior lines, O+T demonstrated mPFS 6.9 mo and ORR 27% (Ingham M. et al. ASCO 2021: #11506). In correlative analysis, alterations in HR genes including PALB2 and RAD51B or absence of RAD51 foci formation by a functional assay were observed in patients with prolonged PFS (Bose S. et al. ASCO 2022: #11509). Based on these results, we designed a randomized phase 2/3 study to further evaluate O+T in advanced, pretreated uLMS. Methods: Alliance for Clinical Trials in Oncology A092104 is a randomized, open-label phase 2/3 clinical trial of O+T versus investigator’s choice in advanced uLMS. Eligible patients have ECOG performance status ≤2, progression on ≥2 prior treatment lines and measurable disease. Patients are randomized 1:1 to receive T 75 mg/m2 orally daily + O 200 mg orally twice daily on days 1-7 in 21-day cycles (Arm 1) or investigator’s choice of trabectedin 1.5 mg/m2 over 24 hours every 21 days or pazopanib 400-600 mg orally daily (Arm 2). For phase 2, the primary endpoint is PFS. The design evaluates for an improvement in PFS from 4 mo to 8 mo, requires 70 patients, and yields 90% power and 1-sided alpha 0.10. If phase 2 is positive, phase 3 will enroll. For phase 3, the primary endpoint is overall survival (OS). The design evaluates for an improvement in OS from 13 mo to 23 mo, requires 165 patients (including 70 from phase 2) and yields 90% power with 1-sided alpha 0.025. Secondary endpoints include ORR, duration of response, safety and patient-reported outcomes. Archival tissue will be collected and evaluated with a RAD51 foci formation assay. Genomic sequencing results will be obtained where available. The study opened to accrual in 1/2023. Support: U10CA180821, U10CA180882, U24 CA196171; https://acknowledgments.alliancefound.org. Clinical trial information: NCT05633381. Research Sponsor: U.S. National Institutes of Health.
A phase 2, open-label, adaptive, dose-ranging study with long-term extension to evaluate the safety, tolerability, efficacy, and pharmacokinetics of intra-articular AMB-05X injections in patients with tenosynovial giant cell tumor.

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Background: CSF1R is a clinically validated target for Tenosynovial Giant Cell Tumor (TGCT). CSF1 is overexpressed in TGCT and, via action at the colony-stimulating factor 1 receptor (CSF1R), leads to the proliferation of synovial-like mononuclear cells and recruitment of multinucleate giant cells, foam cells, siderophages, and inflammatory cells, which compose the bulk of the neoplasm. Although nonmetastatic in nature, TGCT can develop into locally destructive lesions that cause significant local tissue injury, loss of joint function, and impaired quality of life. When complete resection is achievable without significant morbidity, the standard of care for patients with TGCT is surgical resection. Recurrence after surgery occurs in up to 30% of patients with localized TGCT and 83% of patients with diffuse TGCT (Mastboom 2019, Patel 2017). Repeat surgeries may be necessary but often leads to further morbidity, complications, and reduced function of affected joints. A safe, effective, and convenient pharmacotherapy is a desirable addition to the therapeutic armamentarium for TGCT. AMB-05X is a potent and selective anti-CSF1R monoclonal antibody in development for local treatment of TGCT. Intra-articular (IA) injection of AMB-05X enables high drug concentration at the tumor site while minimizing systemic exposure and toxicity. A proof-of-concept study of IA AMB-05X for TGCT found clinically meaningful improvement in objective response rate, functional (pain, stiffness, range of motion) and quality of life measures after 12 weeks of therapy with no serious and a low number of adverse events associated with targeting CSF1R. This phase 2 study aims to establish the optimal dosing regimen and local administration of AMB-05X and confirm the efficacy and safety of 24 weeks and longer treatment.

Methods: AMB-051-07 (NCT05349643) is an open-label, multicenter, phase 2 study of AMB-05X in patients with TGCT. The trial is being conducted at multiple sites in North America, Europe, and Australia. The dosing schedule includes an injection interval of every 4 weeks and longer, including an extended dosing period. Adult patients with histologically confirmed symptomatic TGCT with one joint involvement whether surgically amenable or non-amenable with measurable disease and adequate organ function are being enrolled. After the initial cohort of patients with TGCT of the knee, other joints may be enrolled pending evaluation by the DMC. The primary study outcome measures are objective response rate (ORR) per RECIST v1.1 by central radiology review and safety. Secondary outcome measures include ORR per modified RECIST and Tumor Volume Score, duration of response, time to response, PRO/QOL (including range of motion, stiffness, pain), pharmacodynamics and pharmacokinetics. Clinical trial information: NCT05349643. Research Sponsor: AmMax Bio, Inc.
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Pembrolizumab and Cabozantinib in Patients with Advanced Sarcomas.

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Background: Despite optimal treatment, up to 40% of patients with sarcomas will develop locoregional and/or distant relapse and median survival in this setting is less than two years. There are very few options in the treatment of undifferentiated pleomorphic sarcomas whereas there is no specific treatment regimen established for recurrent osteosarcoma (OSS) and Ewing sarcoma (ES). Innovative strategies are therefore urgently needed in these settings. In preclinical studies, while immune checkpoint inhibitors were insufficient in controlling tumour growth, combining them with M2 macrophage or angiogenesis targeting resulted in superior tumour control (Mao et al, Clin Cancer Res 2016; Zhu et al, Cancer Res 2014). Combining both antiangiogenic and MET inhibition properties, cabozantinib has shown both preclinical and clinical activity, notably in osteosarcoma and Ewing sarcoma (Italiano et al. ESMO 2018). Interestingly, cabozantinib has also recently been shown to trigger an innate immune response in a preclinical model (Patnaik et al, Cancer Discov 2017). Altogether, these findings pave the way for studies assessing the impact of targeting angiogenesis, MET and immune response in soft-tissue and bone sarcomas. Methods: PEMBROCABOSARC (NCT05182164) is a multi-stratum, three single-arm phase 2, multicenter, open-label study investigating pembrolizumab combined with cabozantinib in patients with advanced selected sarcomas: undifferentiated pleomorphic sarcoma (stratum 1), osteosarcoma (stratum 2), Ewing sarcoma (stratum 3). Strata 1 and 2 will enroll ~32 patients and stratum 3 ~55 patients, respectively. Each stratum phase II will be conducted using a Simon's optimal two-stage design. Eligible and consented patients must be ECOG PS 0–1, have measurable and progressive disease according to RECIST 1.1 and have received less than 3 previous lines of systemic therapy for advanced disease and consent also to baseline and per treatment biopsies. Cabozantinib will be administered orally, once daily at a fixed dose of 40 mg, continuously. Pembrolizumab will be administered by intravenous infusion every 3 weeks on Day 1 of each cycle, at a fixed dose of 200 mg. Both treatments will start on Day 1 (of cycle 1). The primary endpoint is 6-months non progression rate as per RECIST 1.1. Secondary endpoints include adverse events (AEs)/serious AEs, best overall response, and progression-free survival. Pharmacodynamic and other biomarkers will be explored on blood and tumor tissue. The first patient received study drug on May, 31, 2022; 8 of planned 119 patients have been enrolled and 5 sites across France among the planned 10, are currently enrolling patients. Clinical trial information: NCT05182164. Research Sponsor: IPSEN PHARMA; French DGOS.
SARCO41: A phase 3 randomized double-blind study of abemaciclib versus placebo in patients with advanced dedifferentiated liposarcoma.

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Background: Recurrent or metastatic dedifferentiated liposarcoma (DDLS) remains a difficult disease to treat. Available agents such as doxorubicin, eribulin, trabectedin, ifosfamide, dacarbazine, or gemcitabine-based regimens are associated with low response rates and only modest improvements in progression free or overall survival. The oncogene CDK4 is ubiquitously amplified in this disease and represents a rational therapeutic target. In single-arm phase 2 studies, treatment with selective CDK4 inhibitors resulted in clinical benefit (12-week progression-free survival (PFS) of 57% with palbociclib and 74% with abemaciclib). We hypothesize that treatment with abemaciclib will improve PFS compared to placebo in patients with recurrent or metastatic DDLS. Methods: This is a phase 3 randomized double-blind study of abemaciclib versus placebo. Eligible patients have recurrent or metastatic dedifferentiated liposarcoma (purely well-differentiated liposarcoma excluded), progression of disease by RECIST 1.1 in the 6 months prior to study entry, any number of prior systemic therapies, and adequate organ function and performance status. Patients are stratified by number of prior lines of therapy (0 vs 1 or more) and randomized 1:1 between abemaciclib 200 mg PO twice a day and matching placebo. Patients are followed with scans every 6 weeks (every 12w after 36w) and those with progression of disease on placebo may cross over to open label abemaciclib. The primary endpoint is PFS. Target enrollment is 108 evaluable patients which provides 80% power with two-sided 10% significance level to detect a hazard ratio of 0.6. Secondary endpoints include response rate, PFS and response rate after crossover, and overall survival. Archival tissue will be collected to explore potential biomarkers. As of Feb 1, 2023, 43 patients have been accrued at 9 participating centers. Clinical trial information: NCT04967521. Research Sponsor: Eli-Lilly.
Engagement of patient participation in genomics research by the Osteosarcoma and Leiomyosarcoma Count Me In Projects of the Cancer Moonshot funded PE-CGS Network.

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Background: Osteosarcoma (OS) and Leiomyosarcoma (LMS) are sarcomas with complex genomes for which there has been limited progress in identifying new treatments and improving outcomes. Slow progress in OS and LMS is partially due to insufficient characterization of the genomic landscape. Generating large genomic datasets in OS and LMS is challenging because of the rarity of these sarcomas and recruitment barriers such as care fragmentation between institutions and specialties. The OS and LMS Project research studies aim to: 1) establish a network of engaged pediatric and adult participants with OS and LMS who will co-create a shared database of clinical, genomic, molecular, and patient reported data to enable research; 2) define the clinicogenomic landscape of OS and LMS; and 3) optimize the approach to direct patient engagement in cancer research. Methods: Count Me In, a research initiative with prior success in angiosarcoma, working with patients and advocates created websites (OSProject.org and LMSProject.org) where patients register and consent to participation. Projects were launched in September, 2022. After 5 months of accrual, 306 patients age 6-79 from 149 Institutions have consented. Blood and saliva are collected from consented participants, tumor samples are obtained from pathology departments and medical records are requested from treating hospitals. WES and WGS of tumor and normal, and RNASeq of tumor is performed. ctDNA is obtained and sequenced. Results are shared with patient, advocacy, physician and research communities in several ways. Individual participants receive a shared learning report describing the somatic variants identified in their tumor from paired tumor-normal WES and are offered genetic counseling and clinical germline testing. Registered participants receive updates via email and Project websites. There are regular pre-publication data releases to the genomic data commons and to cBioPortal. A physician engagement committee meets regularly to discuss clinical insights and conundrums from shared learning reports and germline testing. Patient accrual over the next 3 years is anticipated to result in sequencing of 750 tumor-normal pairs and 500 ctDNA samples. Research Sponsor: U.S. National Institutes of Health.
Phase 1 dose-expansion study of oral TP-1287, a cyclin-dependent kinase 9 (CDK9) inhibitor, in patients with Ewing sarcoma (EWS).

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Background: Cyclin-dependent kinase 9 (CDK9) blockade inhibits tumor growth and progression by impairing the transcription of key oncogenes, such as myeloid cell leukemia-1 (MCL-1) and c-MYC. CDK9 overexpression has been observed in sarcoma patients (pts), and CDK9 has emerged as a potential therapeutic target in pts with sarcoma. TP-1287 is an investigational orally delivered phosphate prodrug of the CDK9 inhibitor alvocidib. In preclinical studies, TP-1287 has been shown to decrease MCL-1 expression and phosphorylation of RNA polymerase II (RPB1), and inhibit tumor growth in an Ewing sarcoma (EWS) mouse model. Phase 1 dose-escalation in solid tumors has completed and TP-1287 is being investigated in a dose expansion cohort in pts with EWS (NCT03604783). The design of the expansion part of the trial in pts with EWS is herein described.

Methods: Up to thirty pts with EWS will be enrolled in this dose expansion cohort. Key eligibility criteria are age ≥18 years (≥12 years, if weight ≥40 kg); histologically confirmed locally advanced or metastatic unresectable EWS; received 1 to 5 prior lines of treatment including an anthracycline; one or more measurable tumors per the RECIST v1.1; ECOG performance status of ≤1; acceptable liver and renal function, and acceptable hematologic and coagulation status; no treatment with surgery, chemotherapy, or investigational therapy within 28 days or 5 half-lives. Eligible pts will be treated with oral TP-1287 monotherapy RP2D established from the dose escalation part (11 mg BID, continuous dosing in a 28-day treatment cycle) and will continue treatment until treatment-related adverse event or disease progression. Assessments will be performed on Day 1 and Day 15 of each cycle. Tumor response assessment will be done after Cycle 2 and at the end of every other cycle thereafter. The primary objectives are objective response rate (ORR) and clinical benefit rate (CBR); secondary objectives are median progression-free survival (PFS), PFS rate at 16-weeks and 24-weeks and safety; and exploratory objectives include evaluation of systemic exposure and pharmacodynamics. Safety data will be reviewed on an ongoing basis and a Bayesian approach will be used to assess the efficacy data. Statistical analysis for safety and efficacy parameters will be primarily descriptive in nature. EWS dose expansion cohort is currently recruiting in the United States. Clinical trial information: NCT03604783. Research Sponsor: Sumitomo Pharma Oncology.
A phase II study of palbociclib combined with retifanlimab in patients with advanced dedifferentiated liposarcoma.

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Background: Dedifferentiated liposarcoma (DDLPS) is characterized by near universal amplification of the cyclin-dependent kinase 4 (CDK4) gene. Palbociclib (P) is a selective CDK4/6 inhibitor that has demonstrated promise in phase II studies of DDLPS. Anti-PD-1 therapy has also shown signals of efficacy, with an approximate overall response rate of 10% in DDLPS patients. CDK4/6 inhibitors upregulate antigen processing and presentation, suppress regulatory T cells, and increase inflammation within the tumor microenvironment. Combined with anti-PD-1 blockade, they can induce an inflamed T cell phenotype and tumor regression in pre-clinical models. We hypothesize that P combined with the anti-PD-1 inhibitor retifanlimab (R) will be safe and tolerable and have synergistic activity leading to activation of T cells and resultant clinical responses. Methods: NCT04438824 is a phase II study of P plus R with a safety lead-in phase. Patients with unresectable or metastatic DDLPS who have received any number of prior therapies are eligible to enroll. On the safety lead-in phase, 6 patients received P (125 mg once daily orally for 21 days followed by 7 days off) plus R (500 mg IV flat dose), repeated in 28-day cycles. P was initiated as monotherapy two weeks prior to initiation of R. The primary endpoint of the safety lead-in was to confirm the recommended phase two dose of the combination. Accrual to the safety lead-in has been completed and a pre-planned phase II expansion portion was opened to accrual. A study amendment was passed that revised the treatment schedule on the expansion cohort to start both P and R concomitantly on day 1 of each cycle. This revised schedule was based on recent data demonstrating the superior safety of a concurrent, rather than staggered, dosing schedule. The primary endpoint of the expansion phase is to estimate the best overall response rate (ORR) by RECIST 1.1. Secondary endpoints include describing the safety and estimating clinical benefit rate, duration of response, progression-free, and overall survival. A total of 30 patients treated with the revised dosing scheme will be enrolled onto the expansion phase. Twelve patients have been enrolled to date. An ORR of 5% will be considered not promising, while an ORR of 25% will be considered promising. The null hypothesis will be rejected if 4 or more patients have a confirmed objective response to treatment. This design has a type I error rate of 0.06 and a type II error rate of 0.04. Mandatory pre- and on-treatment biopsies will be performed for correlative analyses. Clinical trial information: NCT04438824. Research Sponsor: Incyte; U.S. National Institutes of Health.