10000 Oral Abstract Session

Efficacy and safety of entrectinib in children with extracranial solid or primary central nervous system (CNS) tumors harboring *NTRK* or *ROS1* fusions.

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Background: Entrectinib previously yielded durable responses in children with *NTRK*or *ROS1*-fusion-positiveextracranial solid or primary CNS tumors in STARTRK-NG (NCT02650401). We present updated data from STARTRK-NG, TAPISTRY (NCT04589845) and STARTRK-2 (NCT02568267): pediatric patients from these trials were combined to enable an integrated efficacy and safety analysis on a larger cohort than previously. **Methods:** Eligible patients were TRK or ROS1 inhibitor naïve and aged <18 years, had locally advanced or metastatic extracranial solid or primary CNS tumors harboring an *NTRK* or *ROS1* fusion, and had measurable or evaluable-only disease. Once enrolled, patients received $\geq$1 daily dose of oral entrectinib until disease progression, unacceptable toxicity, or consent withdrawal. Tumor responses were confirmed by blinded independent central review (BICR) per RECIST v1.1 or RANO criteria. Patients were included if they had been followed for $\geq$6 months. The primary endpoint was confirmed objective response rate (ORR) per BICR. Key secondary endpoints included ORR in patients with baseline measurable disease per BICR, duration of confirmed response (DoR), time to confirmed response (TTR), clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** At clinical cutoff (16 July 2023), out of 91 safety-evaluable patients (regardless of fusion), 44 patients in the *NTRK*cohortand 20 patients in the *ROS1*cohort were efficacy evaluable. Median duration of survival follow-up was 24.2 months (*NTRK*: range 1–66) and 27.6 months (*ROS1*:range1–73). The ORR was 68.2% (95% CI 52.4–81.4) in the *NTRK* cohort and 65.0% (95% CI 40.8–84.6) in the *ROS1* cohort. In patients with baseline measurable disease, the ORR was 77.8% (*NTRK*: n = 28/36; 95% CI 60.9–89.9) and 62.5% (*ROS1*: n = 10/16; 95% CI 35.4–84.8). Efficacy outcomes are shown in the Table. The most common adverse events were pyrexia (50.5%), vomiting (40.7%) and anemia (40.7%). **Conclusions:** Entrectinib continued to yield rapid and durable responses in pediatric patients with extracranial solid or primary CNS tumors harboring an *NTRK* or *ROS1* fusion. The safety profile of entrectinib was in line with previous reports. Clinical trial information: NCT02650401/NCT04589845/NCT02568267. Research Sponsor: F. Hoffmann-La Roche Ltd.

Efficacy	*NTRK* (n = 44)	*ROS1* (n = 20)
Confirmed ORR*, % (95% CI)	68.2 (52.4, 81.4)	65.0 (40.8, 84.6)
Complete response	45.5 (30.4, 61.2)	15.0 (3.2, 37.9)
Partial response	22.7 (11.5, 37.8)	50.0 (27.2, 72.8)
Confirmed ORR per investigator, % (95% CI)	79.5 (64.7, 90.2)	65.0 (40.8, 84.6)
Median confirmed DoR*, months (95% CI)	NE (25.4, NE)	NE (16.2, NE)
Median TTR*, months (range)	1.9 (1.1, 7.4)	1.9 (1.6, 4.0)
CBR*, % (95% CI)	81.8 (67.3, 91.8)	80.0 (56.3, 94.3)
Median PFS*, months (95% CI)	NE (23.1, NE)	NE (21.8, NE)
Median OS, months (95% CI)	NE (35.7, NE)	NE (NE, NE)

*Per BICR; CI, confidence interval; NE, not evaluable.

10001 Oral Abstract Session

Phase IB study of tovorafenib for children with relapsed/recurrent low-grade gliomas and other MAPK pathway activated tumors.

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Background: LGGs present a therapeutic challenge often occurring in areas of brain and spine not amenable to resection and carrying high morbidity with currently available therapies. The majority harbor alterations in the MAPK pathway. Our study (NCT03429803) aimed to establish the recommended phase 2 dose (RP2D) and assess the safety, tolerability and preliminary efficacy of type II RAF-inhibitor tovorafenib in such tumors. **Methods:** Eligible patients were > 1 year and < 25 years old with radiographically recurrent/progressive MAPK pathway-altered tumors. We applied a novel 2S-Sub-TITE design to determine a RP2D with posterior probability of toxicity closest to the 20% target for patients with BSA ≤1.5 and > 1.5 m^2 based on preliminary exposure-efficacy data. Toxicities were graded according to CTCAE version 5. Patients with complete response (CR), partial response (PR) or stable disease (SD) were designated responders. **Results:** We treated 35 eligible patients, including 20 *KIAA1549:BRAF*-, 9 BRAF V600E- and 1*FGFR1*-altered tumors; 5 possessed novel *RAF* fusions. Histologically, there were 27 grade 1 gliomas, 3 anaplastic pleomorphic xanthoastrocytomas, 3 pilomyxoid astrocytomas, 1 high-grade glioma and 1 soft tissue sarcoma. There were 6 grade 3 DLTs (2 fatigue, 3 rash, 1 menorrhagia) in 30 evaluable patients: 3 in each BSA subgroup, all at 530 mg/m^2/dose. Using AAP guidelines for minimum pubertal peak growth velocities (GV) in males (7 cm/year) and females (6 cm/year), decreased GV (median 0.09 cm/year; range 0.02-0.3) was an unexpected, related AE observed in all 13 of 13 pre-pubertal females < 14 or males < 16 years of age receiving >6 months of protocol 1B therapy. Three of 13 patients with decreased GV were treated at 420 mg/m^2. Three of the remaining 10 patients with decreased GV originally treated at 530 mg/m^2 were dose reduced for other toxicities and hence, 6 of 13 patients with decreased GV were treated at the RP2D. For patients with follow-up data available, GV appears to show recovery off drug. The 2S-Sub-TITE model recommended 530 mg/m^2 for BSA ≤1.5m^2 and 420 mg/m^2 for BSA > 1.5m^2. Dose modifications were required in 8/22 versus 1/13 patients treated at 530 and 420 mg/m^2, respectively. Twenty-seven of 35 patients were evaluable for objective response performed by an independent single reader. Overall, 25 patients had SD, PR or CR with median duration of response of 11.3 months (range 0.03-35.4) at data cutoff. **Conclusions:** Oral weekly tovorafenib is well tolerated and shows preliminary efficacy. Decreased GV was observed in pre-pubertal patients on drug and warrants further investigation to understand the mechanism of action. Based on the number of dose modifications required for toxicity, the chosen RP2D for weekly oral dosing of tovorafenib was 420 mg/m^2. Clinical trial information: NCT03429803. Research Sponsor: None.

10002 Oral Abstract Session

Efficacy and safety of erdafitinib in pediatric patients with advanced solid tumors and FGFR alterations in the phase 2 RAGNAR trial.

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Background: Erdafitinib is an oral selective pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor approved in the US for adult patients (pts) with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* genetic alterations, as determined by an FDA-approved companion diagnostic test, whose disease has progressed on or after ≥1 line of prior systemic therapy. Primary analysis of the RAGNAR study Broad Panel Cohort demonstrated tumor agnostic efficacy in pts with solid tumors harboring predefined *FGFR* mutations or fusions (Pant 2023). Here we report on Final Analysis of efficacy and safety results from the Pediatric Cohort of the RAGNAR study. **Methods:** Pediatric pts ≥6 years with advanced solid tumors and any *FGFR* mutation, fusion, or tandem duplication received oral erdafitinib. Starting doses were 8 mg, 5 mg, and 3 mg daily for ages > 15 years, 12 to < 15 years, and 6 to < 12 years, respectively, in 21-day cycles with possible individualized up-titration based on serum phosphate and adverse events (AEs). The primary endpoint was objective response rate (ORR) (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 or Response Assessment in Neuro-Oncology [RANO]) by independent review committee (IRC). Secondary endpoints included ORR by investigator, duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS). **Results:** 11 pts (median age 13 years; range, 6-16; 64% female) received erdafitinib. Median follow-up was 9.7 months at data cutoff. Histologies included low-grade glioma (LGG-6 pts); high-grade glioma (HGG-3 pts); soft tissue sarcoma (1 pt), and temporal neurocytoma (TNEURO-1 pt). 7, 1, and 3 pts had *FGFR1*, *FGFR2*,and *FGFR3* alterations, respectively. 6, 4, and 1 pts had *FGFR* fusions, mutations, and tandem duplication, respectively. Pts had a median of 1 prior line of systemic treatment; 6 (55%) had prior radiotherapy. At data cutoff, 1 of 3 pts (33%) with HGG and an *FGFR1-TACC1* fusion achieved a partial response based on investigator assessment with a response duration of 19.8 months. Investigator-assessed objective responses were not observed in the other tumor types. DCR and CBR were 100% in pts with LGG and 67% in pts with HGG. Most common treatment-emergent adverse events (TEAEs) included hyperphosphatemia (64%), diarrhea (64%), pain in extremity (45%), alanine transaminase increased (36%), nausea (36%), and onycholysis (27%). No central serous retinopathy events occurred; related serious adverse events (SAEs) occurred in 4 (36%) pts, including 1 SAE of epiphysiolysis; there were no related TEAEs leading to death. **Conclusions:** In this small pediatric population comprising primarily refractory HGG and LGG with any *FGFR* alteration, erdafitinib demonstrated limited objective responses but promising disease control with acceptable safety. Clinical trial information: NCT04083976. Research Sponsor: None.

10003 Oral Abstract Session

Impact of an objective scoring system on initiation of therapy in patients with International Neuroblastoma Risk Group Staging System (INRGSS) stage MS neuroblastoma: A report from the Children's Oncology Group.

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Background: A subset of children with INRGSS Stage MS neuroblastoma (NBL) may be observed without treatment, while others have rapidly evolving symptoms that can be life-threatening. ANBL1232 adapted a previously developed semi-quantitative objective scoring system (OSS) to assign a numeric value to symptoms and laboratory abnormalities. The goal was to standardize monitoring, therapy initiation, and treatment duration in this cohort. **Methods:** Patients with newly diagnosed Stage MS NBL were eligible for this prospective trial. An OSS score (OSSS) was assigned at enrollment; the total number was based on scoring in 5 systems: gastrointestinal (GI), respiratory, circulatory, renal, and hepatic. Within the 5 systems, individual clinical and laboratory parameters were scored as not present = 0, mild/moderate = 1 [Grade 2 CTCAEv4.0 adverse event (AE)] or severe = 2 (Grade $\geq$3 AE). The OSSS was the sum of highest score within each organ system (maximum score: 2 per system, 10 total). Asymptomatic MS patients with an OSSS $<$ 2 who were either $<$ 3 months (mo) of age without hepatomegaly or 3-18 mo of age with favorable biology tumors were eligible for observation without initial treatment. Observed patients underwent monthly physical examinations and laboratory assessments for the first 6 mo following diagnosis. Tumor imaging was performed every 3 mo for 1 year, then every 6-12 mo through 36 mo. An OSSS $\geq$2 or a protocol-defined increase in primary tumor size prompted initiation of therapy. **Results:** From July 2014 to February 2021, 89 eligible and evaluable patients with newly diagnosed stage MS NBL enrolled. Among these, 18 (20.2%; 5 male and 13 female) were eligible for observation. Observed patients were older at diagnosis (median age: 2.87 vs. 1.81 mo, p = 0.23) and more likely to have primary tumors without image-defined risk factors (62.5% vs. 30.0%, p = 0.0166) than those assigned to therapy up front. Nearly all observed patients (17/18) had abdominal/adrenal primaries. The initial OSSS was 0 in all observed patients. Median reported observation time was 36 mo (range: 1-36 mo); 13 patients completed all required monthly assessments for the first 6 mo. No patients in the observation cohort required initiation of therapy for an increase in OSSS. One patient with OSSS = 1 at mo 3 had complete GI symptom resolution by mo 5. **Conclusions:** An OSSS of 0 at diagnosis can aid in identifying a favorable group of patients with stage MS NBL who can be safely observed. No patients in the observation cohort developed evidence of organ dysfunction or OSSS $>$ 1 despite frequent physical examination and comprehensive laboratory testing, suggesting that follow up may be safely liberalized in this population over time. Clinical and laboratory criteria implemented at diagnosis could be used to identify patients requiring prompt treatment. Clinical trial information: NCT02176967. Research Sponsor: Children's Oncology Group; U.S. National Institutes of Health; U10CA180886; U.S. National Institutes of Health; U10CA180899.

10004 Oral Abstract Session

A pilot study of post-consolidation chemoimmunotherapy for high-risk neuroblastoma (ANBL19P1): A report from the Children's Oncology Group.

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Background: Post-consolidation anti-GD2 antibody-based immunotherapy has improved survival for newly diagnosed patients (pts) with high-risk neuroblastoma (HRNBL). However, nearly half of newly diagnosed pts relapse. Based upon the efficacy of anti-GD2 antibody dinutuximab given with chemotherapy (chemoimmunotherapy) in the relapse setting, we hypothesized that post-consolidation chemoimmunotherapy may further improve frontline outcomes. ANBL19P1 first assessed the feasibility of delivering chemoimmunotherapy after tandem high-dose chemotherapy with autologous stem cell transplant (ASCT). **Methods:** Pts <31 years old with HRNBL who received 4-6 cycles of Induction chemotherapy +/- up to 4 cycles of post-Induction chemotherapy or chemoimmunotherapy, underwent tandem ASCT, had no evidence of progressive disease (PD), and met organ function criteria were eligible. Therapy, administered every 28 days, consisted of temozolomide and irinotecan on Days 1-5, dinutuximab on Days 2-5, and sargramostim on Days 6-12 during Cycles 1-5; isotretinoin on Days 8-21 during Cycles 1-6. Therapy was deemed feasible if the 95% confidence interval (CI) placed on the percentage of pts that completed 5 cycles of dinutuximab + chemotherapy without PD within 30 weeks contained 75%, and if the interim monitoring rules for feasibility and excessive toxicity were not triggered. Event-free (EFS) and overall survival (OS) were determined from time of enrollment. **Results:** From 11/30/20-6/30/23, 40 eligible pts enrolled and started protocol therapy. 87.5% (n=35) were ≥18 months old and 97.5% (n=39) had INRG Stage M disease, at diagnosis. 87.5% (95% CI 73.9%, 94.5%) completed 5 cycles of dinutuximab + chemotherapy without PD within 30 weeks, exceeding the feasibility benchmark of 75%. Feasibility and monitoring rules were not triggered. Five pts were removed from protocol therapy prior to Cycle 4 [physician determination (n=2), pt/parent refusal of further therapy (n=2), and PD (n=1)]. No unacceptable toxicities or deaths on protocol therapy were reported. Toxicities of interest are summarized (Table). One-year EFS and OS were 90.0±5.0% and 97.5±2.7%, respectively (median follow-up time for pts without event=1.2 years). **Conclusions:** Administration of post-consolidation chemoimmunotherapy in pts who underwent tandem ASCT is tolerable and met pre-defined feasibility criteria. The impact of this approach on survival outcomes will be studied in a future COG trial. Clinical trial information: NCT04385277. Research Sponsor: NCTN Operations Center Grant; NCTN Statistics & Data Center Grant; St. Baldrick's Foundation.

CTCAE v5 Grade ≥3 Adverse Event	C1 (N=40) % (n)	C2 (N=40) % (n)	C3 (N=38) % (n)	C4 (N=35) % (n)	C5 (N=35) % (n)	C6 (N=34) % (n)
Febrile neutropenia	7.5 (3)	2.5 (1)	5.3 (2)	2.9 (1)	-	-
Diarrhea	2.5 (1)	2.5 (1)	-	-	5.7 (2)	-
Anorexia	7.5 (3)	2.5 (1)	5.3 (2)	2.9 (1)	-	-
Dehydration	7.5 (3)	2.5 (1)	-	-	-	-
Enterocolitis infectious	-	10 (4)	-	-	-	-
Sepsis	-	5 (2)	7.9 (3)	5.7 (2)	2.9 (1)	2.9 (1)
Infections & infestations - Other	-	5 (2)	2.6 (1)	-	2.9 (1)	-

C=Cycle.

10005 Oral Abstract Session

Preliminary experience of ex-vivo expanded allogeneic universal donor TGFβi NK cell infusions in combination with irinotecan, temozolomide, and dinutuximab in patients with relapsed or refractory neuroblastoma: The Allo - STING trial.

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Background: Neuroblastoma (NBL) is the most common extra-cranial solid tumor in children and outcomes for children with relapsed/refractory (RR) NBL remain dismal. While the combination of chemoimmunotherapy (CIT) with the anti-GD2 antibody dinutuximab as per COG protocol ANBL1221 has improved responses, this regimen is still not curative. Dinutuximab can recruit NK cells for anticancer activity, however, NK cells are depleted in NBL patients undergoing chemotherapy. We devised a method to expand allogeneic NK cells ex vivo to improve effector function and render the NK cells resistant to TGFβ-induced suppression (TGFβi). These TGFβi NK cells are expanded from a universal donor (UD) pool, enabling multiple cycles of "off-the-shelf" high-dose therapy. We hypothesize that adoptive transfer of UD-TGFβi NK cells to patients with RR NBL sequentially following CIT is safe and improves outcomes compared to CIT alone. **Methods:** This Phase I/II study evaluates the safety and tolerability of UD-TGFβi NK cells in combination with CIT and compares anti-cancer efficacy to CIT alone. Eligibility includes age < 30 years, RR or progressive NBL, and prior treatment with at least 4 cycles of induction chemotherapy. The treatment protocol consists of 21-day cycles of CIT as per COG protocol ANBL1221 with UD-TGFβi NK cells ($1x10^8$ cells/kg) infused on day 8. Up to six cycles of treatment are permitted. Overall response rates are defined using the Revised International NBL Response Criteria, with 95% confidence intervals compared to the results from ANBL1221. Progression-free and overall survival will be estimated by the Kaplan Meier method. **Results:** Four subjects (7 – 11 years) have been enrolled. All patients presented with high risk NBL: three with relapsed disease and one with refractory disease. All received at least one prior salvage therapy. Three patients have completed all 6 cycles of protocol therapy, and one remains on treatment. 20 NK cell infusions have been administered to date. All NK cell infusions occurred within the protocol specified window. One subject experienced grade 1 fever with two NK cell infusions. There have been no other adverse events attributable to the NK cells. Adverse events attributable to CIT were similar to those described in COG ANBL 1221. Treatment delays for cytopenias due to CIT occurred in two patients. Three patients achieved a partial response. A fourth patient attained prolonged stable disease (9 months) but experienced a skeletal recurrence. **Conclusions:** UD allo-TGFβi NK cells can be safely and feasibly administered to children with RR NBL after treatment with CIT, with early objective responses observed in the preliminary cohort of patients. Ongoing studies will assess markers of response, NK cell persistence, pharmacokinetics and pharmacodynamics. Clinical trial information: NCT04211675. Research Sponsor: Nationwide Children's Hospital.

10006 Oral Abstract Session

Outcome of children and young adults with localized extremity rhabdomyosarcoma treated on Children's Oncology Group trials.

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Background: Extremity rhabdomyosarcoma (RMS) accounts for 15-20% of patients with localized RMS. The long-term survival and associated prognostic factors of extremity RMS patients treated on the contemporary Children's Oncology Group (COG) trials have not been reported. **Methods:** Patients with localized extremity RMS enrolled on the D9602, D9803, ARST0331 and ARST0531 COG trials were analyzed. The Kaplan-Meyer method estimated event-free (EFS) and overall survival (OS). The Log-rank test and Cox regression were used to estimate the prognostic significance of age at diagnosis, sex, race, tumor site & size, IRS group, stage, histology, *FOXO1* fusion status, anaplasia, lymph node involvement, delayed primary excision (DPE) and radiation on survival. **Results:** We identified 159 patients with localized extremity RMS; 108 (68%) were $<$10 years at diagnosis, 84(53%) had primary tumor $>$ 5 cm, and 35 (22%) and 98 (62%) had IRS group II and III disease. Histology was alveolar in 106 (67%), and 43 (27%) had regional lymph node involvement on imaging or pathology. Seventeen were treated on low-risk (LR) studies D9602 (N = 10) and ARST0331 (N = 7), whereas 142 were treated on intermediate-risk (IR) trials D9803 (N = 85) and ARST0531 (N = 57). Eighty patients (50%) underwent primary surgical excision and 121 (76%) received radiotherapy. DPE was attempted in 60 patients (38%), resulting in an R0 (microscopically negative) margin in 48 (80%). Relapse/progression occurred in 52 patients: metastatic 26 (50%), local 22 (42%), and combined 3(6%). The 5-year EFS and OS of the whole cohort were 62.6% (95% CI: 54%-71.2%) and 78.7%% (95%CI: 71.4%-85.9%). LR patients treated on D9602 and ARST0331 trials had comparable 5-year EFS (70% vs. 71.4%, p-0.90) and OS (90% vs. 85.7%, p-0.54), respectively, while IR patients had significantly better 5-year EFS (68.9% vs. 51%, p-0.023) and OS (86.2% vs. 64.4%, p-0.007) on D9803 trial than ARST0531 trial. The 5-year EFS and OS of IRS group III patients with DPE with R0 margins were comparable to IRS group II patients (70.4% vs. 66.6%) & (86.5% vs. 84.6%), respectively. On univariable analysis, age at diagnosis and sex were associated with EFS, while age at diagnosis, sex, tumor size, IRS group, stage and fusion status were associated with OS ($p < 0.05$). None of the analyzed factors demonstrated independent statistical association with EFS, whereas female sex was the only factor independently associated with OS [Hazard ratio (HR): 0.4, 95% CI 0.20-0.85)]. **Conclusions:** IR localized extremity RMS patients treated on ARST0531 had suboptimal outcome. Survival of IRS group III patients with R0 DPE was comparable to IRS group II patients. Females with localized extremity RMS had better OS than males. Clinical trial information: NCT00354835; NCT00003958; NCT00075582; NCT00002995. Research Sponsor: National Cancer Institute.

10007 Oral Abstract Session

Radiation dose escalation and local control for intermediate-risk rhabdomyosarcoma on ARST1431: A report from the Children's Oncology Group

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Background: The objective of this study was to evaluate local failure (LF) rates for patients with intermediate-risk rhabdomyosarcoma (IR-RMS) treated on the Children's Oncology Group (COG) ARST1431 clinical trial. To improve local control, the radiation therapy (RT) dose was increased to 59.4 Gy for patients with tumors > 5cm at diagnosis and residual gross disease at the time of RT. **Methods:** The297 patients randomized on ARST1431 were included. LF was defined as progression or relapse at the primary tumor site. Gray's test was used to compare the cumulative incidence of LF across variables. **Results:** There was a trend for lower 3-year LF in group III patients with fusion-positive disease (11.1%, 95% confidence interval (CI) 4.5%-21.1%) compared to patients with fusion-negative disease (21.8%, 95% CI 15.8%-28.4%), p = 0.09.There was no difference in the 3-year LF rate for patients who underwent proton RT (16.3%, 95% CI 9.6%-24.7%) compared to photon RT (16.2%, 95% CI 10.2%-23.6%;), p = 0.8. The 3-year LF rate for all patients with tumors > 5cm at diagnosis (24.9%, 95% CI 18.6%-31.7%) was significantly higher than that of patients with tumors ≤5cm at diagnosis (9.9%, 95% CI 5.2%-16.4%), p < 0.01. Of 81 patients with tumors > 5cm and residual gross disease after induction chemotherapy who went on to receive RT, 62 (76.5%) received the protocol-specified boost to 59.4 Gy. Patients who received the boost had a 3-year LF rate of 32.1% (95% CI 20.1%-44%), while patients who did not undergo an RT boost had a 3-year LF rate of 16.1% (95% CI 3.8%-36.2%), p = 0.3. For patients with group III, non-parameningeal disease, those who underwent delayed primary excision (DPE) had a significantly lower LF rate compared to those who did not undergo DPE (3-year rate of 5.6% (95% CI 1.4%-14.0%) vs. 22.0% (95% CI 14.5-30.7%), p < 0.01). **Conclusions:** On ARST1431, larger tumors (> 5cm at diagnosis) were associated with increased risk of LF. Dose escalation to 59.4 Gy did not improve local control for patients with tumors > 5cm at diagnosis with residual gross disease at the time of RT. For a select group of non-parameningeal, group III patients who underwent DPE followed by RT, local control was improved. Clinical trial information: NCT02567435. Research Sponsor: None.

10008 Oral Abstract Session

RMS13: A phase II trial using risk adapted focal proton beam radiation and/or surgery with the addition of maintenance chemotherapy in intermediate risk rhabdomyosarcoma.

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Background: European trials have demonstrated improved outcomes in SIOP high-risk/COG intermediate risk (IR) rhabdomyosarcoma (RMS) when 6 months of maintenance therapy (MTC) was added to ifosfamide, vincristine (VCR), dactinomycin (DAC) +/-doxorubicin chemotherapy. The effectiveness of MTC integrated with VCR, DAC and cyclophosphamide (CYC), standard North American chemotherapy, remains unclear. **Methods:** RMS13 is a phase II multicenter trial evaluating the safety and efficacy of risk adapted proton radiation therapy (RT) and the addition of MTC in patients with IR RMS (embryonal stage 1, Group III non-orbit, and stage 3 Group I, II were not eligible for MTC). Patients received 12 cycles of VCR (1.5mg/m^2 weekly), DAC (0.045mg/kg q3weeks), and CYC (1200mg/m^2 q3weeks) (VAC) followed by MTC with 4 cycles of oral CYC (50mg/m^2 daily), bevacizumab (15mg/kg) q3wks, and sorafenib (90mg/m^2 bid) (CBvSor). RT was prescribed based on local tumor status at the time of RT (Table 1). Five-year disease-free survival (DFS) using the Kaplan-Meier method and the cumulative incidence (CI) of primary site local failure (LF) was described. **Results:** 46 patients were enrolled (Table 1). One patient refused further therapy and was removed from the analysis. 5-year DFS for the entire cohort was 67.5% with a median follow up of 54 mo. The trial was halted since $<$ 75% of enrolled patients received all prescribed CBvSor MTC. Of the 35 who were eligible for MTC, 24 initiated MTC and 18 completed protocol-directed MTC. Three pts received vinorelbine/CYC MTC after enrollment was stopped. Reasons for not completing CBvSor MTC included: progression prior (6), toxicity (5), refusal (3). The 5-year DFS for the 24 patients that started cycle 3 was 70.3%. When limited to patients classified as high-risk in RMS2005 trial, the 5-year DFS was 81.4%. No patients experienced LF after margin negative surgery. The CI of LF was: 0% following 36GyRBE RT for microscopic residual disease, 8% for patients with unresected tumors $<$ 5cm receiving standard dose RT (50.4GyRBE), and 10% for patients with unresected tumors $>$ = 5cm receiving dose escalated RT (59.4GyRBE). 5/6 patients with alveolar N1 disease recurred. **Conclusions:** Local control with risk adapted dose-escalated RT was excellent in IR patients. Those with nodal involvement fared poorly. While 4-cycles of MTC with CBvSor was not feasible, those who underwent at least 3 cycles experienced enhanced DFS outcomes, aligning with the positive results seen in other trials incorporating MTC. Clinical trial information: NCT01871766. Research Sponsor: None.

	N (%)
Age (yrs, median)	4.9 (0.3-21.5)
Age Group (yrs)	-
< 1	5 (11)
1-10	30 (67)
> 10	10 (22)
Histology	-
Alveolar (Fusion +)	9 (20)
Embryonal	34 (76)
Other	2 (4)
IRS Stage	-
1	9 (20)
2	9 (20)
3	27 (60)
Group	-
II	3 (7)
III	42 (93)
Primary Site	-
Bladder/Prostate	7 (16)
Extremity	7 (16)
Parameningeal	16 (35)
Other	15 (33)
RT Dose (GyRBE)	-
0	7 (17)
36	12 (29)
50.4	12 (29)
59.4	10 (25)

10009 Oral Abstract Session

Uptake of germline cancer genetic services in a randomized trial of remote telehealth services as compared to usual care: A report from the Childhood Cancer Survivor Study (CCSS).

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Background: Limited access to genetic services in community practices, leaves many childhood cancer survivors who are genetic carriers unidentified and at risk for subsequent malignant neoplasms (SMNs) due to therapy or an inherited cancer predisposition. The **ENG**aging and **A**ctivating cancer survivors in **Ge**netic services (ENGAGE) study evaluated the effectiveness of an in-home, collaborative PCP (primary care provider) model of remote centralized telehealth services to increase uptake of cancer genetic services in survivors compared to usual care. **Methods:** 414 survivors were randomized to remote services by phone or videoconference (n = 281) or usual care (n = 133). The primary outcome was uptake of genetic counseling or testing at 6 months. In secondary analyses we evaluated baseline characteristics and patient reported outcomes associated with uptake of services. We used Fisher's Exact tests, Chi-squared tests, and T-tests for analyses. **Results:** Participants were identified through the NCI-funded Childhood Cancer Survivor Study and included 189 (45.7%) male, 88 (21.1%) nonwhite participants with mean age 52 years (SD 0.65), recruited from over 40 states with a history of CNS tumors (n = 190, 46%), sarcoma (n = 116, 28%), or SMN or a family history of cancer (n = 108, 26%). At 6 months, 40% (n = 113) of survivors in the remote telehealth services arms utilized genetic services as compared to 16% (n = 21) in the usual care arm ($p < 0.001$). Factors associated with uptake of services included lower baseline genetic knowledge score (31.0, SD 5.8 without uptake versus 29.7, SD 5.1 with uptake, p = 0.025), having more relatives with cancer (1.6, SD 1.5, without uptake versus 2.0, SD 1.8 with uptake, p = 0.019), having a higher perceived risk of cancer on a Likert scale (3.6, SD 1.0 without uptake versus 3.9, SD 0.8 with uptake, p = 0.011), having a history of internet use (35% uptake with use versus 0% without use, p = 0.040), and not having a high deductible plan (30% uptake with high plan versus 42% without, p = 0.025). Having a higher positive attitude toward genetic testing score (e.g. higher perceived value, lower perception of high cost and lower anticipated distress) was associated with uptake of services (29.5, SD 4.3 without uptake versus 31.2, SD 4.4 with uptake, $p < 0.001$). **Conclusions:** These data suggest that offering remote centralized telehealth genetic services increases the uptake of genetic services in survivors of childhood cancer across the US using a collaborative PCP model. Although uptake was higher than usual care, barriers to uptake of genetic services remain, including concerns about cost and negative perceptions about genetic testing. Strategies to address multi-level barriers to genetic services are needed to realize the potential of genetic testing in childhood cancer survivors and patients in community practices. Clinical trial information: NCT04455698. Research Sponsor: National Cancer Institute.

10010 Oral Abstract Session

A stepped wedge trial of a healthcare provider–focused intervention to increase human papillomavirus (HPV) vaccine initiation among survivors of childhood cancer.

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Background: Childhood cancer survivors are at increased risk for human papillomavirus (HPV)-related cancers. HPV vaccination is highly protective against HPV acquisition. However, we have previously shown that initiation rates among survivors are low, primarily due to lack of healthcare provider recommendation for the vaccine. **Methods:** We conducted a stepped wedge trial from 2021 to 2023 to evaluate the effectiveness of an evidence-based healthcare provider-focused intervention (HPV PROTECT; NCT04469569) in increasing HPV vaccine initiation rates 1y following implementation. The intervention includes provider communication training to enhance vaccine recommendation skills, audit/feedback regarding clinic vaccination rates, and patient-directed resources in multiple languages tailored to pediatric oncology settings. We measured the effectiveness of the intervention in a racially, ethnically, and geographically diverse sample of HPV vaccine naïve childhood cancer survivors, aged 9-17y, and ≥1y post-completion of therapy returning to pediatric oncology clinics for follow-up care at 6 sites. The primary outcome of interest was HPV vaccine initiation rates (abstracted from state vaccine registries) at end of each study year. Baseline data were collected for all sites in Y1, three sites were randomly selected to receive the intervention in Y2, and the remaining three in Y3. The intervention effect was tested using a longitudinal logistic regression model for initiation with intervention as the main fixed effect, adjusting for survivor age, cancer diagnosis, time off-therapy, sex, race, ethnicity, and receipt of hematopoietic cell transplantation. The secular trend (estimated using pre-intervention data from Y1 and Y2) was included as an offset, and site was included as a random effect. The intervention effect was reported as odds ratio (OR) for initiation with 95% confidence intervals (CI). **Results:** A total of 1779 unique vaccine naïve survivors (47.1 % leukemia; 55.1% male; 51.5% non-Hispanic white) completed 2689 clinic visits across 6 sites. Median (range) age at diagnosis was 5.1y (0-16.5), at study entry was 12.3y (9-17.9), and median time off-therapy was 5.5y (1.0-17.3). Overall incident HPV vaccine initiation was 16.0% at baseline. The adjusted odds of vaccine initiation were 1.3-fold (95% CI, 1.03-1.6; p = 0.03) higher post-intervention vs. pre-intervention, accounting for secular trend OR of 1.1. Overall prevalence of vaccine initiation increased from 51.9% pre-intervention to 61.3% post-intervention. **Conclusions:** The improvement in childhood cancer survivor HPV vaccine initiation rates in a diverse sample following implementation of a healthcare provider-focused intervention underscores the potential for pediatric oncology providers to positively impact HPV vaccine uptake in this vulnerable population. Clinical trial information: NCT04469569. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U01CA246567.

10011 Oral Abstract Session

Communicating cardiovascular health information and improving coordination with primary care: A Childhood Cancer Survivor Study randomized trial.

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Background: Childhood cancer survivors are at risk of early cardiovascular disease (CVD). We conducted a survivorship care plan (SCP)-based counseling intervention to improve CVD risk factor control in adult-aged survivors. **Methods:** Randomized (1:1) trial of survivors at high CVD risk based on history of anthracycline or chest radiotherapy exposures with undertreated hypertension (≥130/80 mmHg), dyslipidemia (LDL ≥160 mg/dL or triglyceride ≥200 mg/dL), and/or glucose intolerance (threshold varied if history of pre-diabetes or diabetes) based on in-home testing. Approximating a survivorship clinic visit, the intervention consisted of a remotely delivered session with an advanced practice provider to review results, a SCP with personalized CVD risk information, and an action plan to help manage CVD risk factors. A remote booster session was provided 4 months later with the action plan updated. Control participants only received a copy of their in-home results with abnormalities noted and written encouragement to follow-up with their primary care provider (PCP). Blood pressure, lipid profile, and glucose tolerance were retested after 1y. For both groups, all participant materials were sent to PCPs throughout the study, and PCP medical records were abstracted at study completion. Logistic regression assessed the odds ratio (OR) for undertreatment at 1y associated with the intervention, adjusting for pre-specified variables (sex, current age, time since cancer, insurance status, recent history of survivorship clinic visit, and undertreated CVD risk factor). **Results:** Among 644 survivors who completed in-home testing, 347 met inclusion criteria and were randomized (175 intervention; overall 52% male, mean age 40y, 31y since cancer diagnosis); 264 with 1y follow-up (126 intervention). At baseline, rates of hypertension, dyslipidemia, and glucose intolerance were 53%, 52%, and 49%, respectively; 43% had > 1 undertreated condition. Although the intervention achieved > 95% satisfaction, it was not associated with reduced undertreatment vs control (OR 0.9, 95% CI 0.7-1.3). Notably, 48% of intervention and 44% of control participants had less undertreatment after 1y. In secondary analysis, greater internal locus of control was associated with less undertreatment at 1y (OR 0.7, 95% CI 0.6-0.9). The intervention group was more likely than controls to have CVD risk (+10 vs -1%), SCP (+17 vs -2%), and some late effects surveillance plan (+8 vs +2%) documented within PCP records at 1y vs baseline ($p < 0.05$ for all). **Conclusions:** While a remotely delivered counseling intervention did not reduce CVD risk factor undertreatment compared with provision of test results alone, both study arms had > 40% reduction in undertreatment. These results suggest that simply providing a formal CVD risk assessment to high-risk cancer survivors and their PCPs may be effective. Clinical trial information: NCT03104543. Research Sponsor: U.S. National Institutes of Health; R01 CA204378.

10012 Oral Abstract Session

Access for adolescents and young adults with hard-to-cure cancer to PROFYLE: The pan-Canadian precision oncology pipeline.

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Background: Cancer is the most common cause of disease-related death in children, adolescents and young adults (CAYA). Approximately, 1.5% of patients with cancer in Canada are adolescents and young adults (AYAs) (age 15-29). AYAs often present with advanced disease and limited access to clinical trials including genomic testing. The PRecision Oncology For Young peopLE (PROFYLE) national, collaborative program, was created to provide equitable access to molecular profiling to identify novel targeted treatment options for CAYA with hard-to-cure cancers. The AYA node of PROFYLE aims to enhance the inclusion of AYAs across Canada at pediatric and adult centers while raising awareness of improving cancer outcomes of this underserved population. **Methods:** Building upon 3 pre-existing regional precision oncology programs, PROFYLE was implemented as the first pan-Canadian precision oncology pipeline. The PROFYLE study is multi-centred, non-randomized, interventional, and qualitative. Inclusion criteria: ≤29y; treatment at a Canadian center; diagnosis of a hard-to-cure cancer. It includes genomic and transcriptomic sequencing of paired germline and cancer fresh/frozen samples. Actionable findings, potential targeted therapy options including available clinical trials, clarification of diagnosis, and genetic counseling recommendations are provided to the clinical care team. **Results:** To date, > 1,200 CAYA are included from all provinces. Of these, 33% were AYAs. Cancer diagnoses included: 47% sarcoma, 15% leukemia/lymphoma, 13% CNS tumor, 25% other. Of the AYAs enrolled, 53% had ≥1 significant tumour profiling finding (48% specific mutations/fusions; 6% DNA repair defect signature, hypermutation, microsatellite instability, chromosomal instability; 3% predictors of therapeutic resistance; 5% outliers in gene expression). 71% had potentially useful findings (15% diagnostic; 9% prognostic; 59% therapeutic; 2% etiologic; 15% cancer predisposition; 2% secondary germline; 0.5% pharmacogenetic). 23% had a pathogenic/likely pathogenic germline variant. 60% had ≥1 potentially actionable somatic alteration. 64% of clinicians indicated that molecular findings impacted clinical management (12% diagnostic; 6% prognostic, 60% therapeutic; 16% germline genetic). 24% indicated a change in treatment planning in response to these findings. **Conclusions:** The goal of developing a national precision oncology pipeline that provides equitable access to molecular profiling in a clinically relevant timeframe has been realized through the establishment of PROFYLE. Findings demonstrate that the sequencing platform provided medically informative results in the majority of enrolled AYAs. The success of PROFYLE underscores the importance of the continuing efforts to increase the access to this precision oncology initiative for all AYAs with cancer in Canada. Research Sponsor: None.

10013 Oral Abstract Session

CINSARC score use in pediatric non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) in the Children's Oncology Group (COG) studies ARST0332 and ARST1321.

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Background: Despite genomic and histologic heterogeneity, limited risk stratification is used in the treatment of NRSTS (grade, size, presence of metastases, and extent of surgical resection). Genomic signatures including CINSARC score and Genomic Index (GI), both measures of genomic instability, have been shown to be prognostic in retrospective studies, but are not routinely used clinically. Here we evaluated the association of these scores with EFS and OS on two consecutive, prospective COG NRSTS studies, ARST0332 and ARST1321. **Methods:** All patients enrolled to ARST0332 or ARST1321 with sufficient banked tumor in the COG biospecimen repository were included in this analysis. Whole exome and transcriptome sequencing was performed on DNA and RNA from banked FFPE and flash frozen specimens. Raw WES reads were mapped to hg38 using BWA. The base qualities of the aligned reads were recalibrated and realigned by GATK. RNAseq data was aligned to hg38 by STAR. Differential expression analysis was performed by DESeq2. Stratified log rank and proportional hazards models were used to evaluate the association of CINSARC score and GI above or below the median with EFS and OS. **Results:** Tumors from 197 patients yielded sufficient DNA and 166 sufficient RNA, of which 177 and 142, respectively, passed sequencing quality metrics and were included. Demographics of these patients were generally representative of overall trial enrollment with most patients between ages 10-17 years (53%) with localized disease (77-80%). The most common histologic diagnoses were synovial sarcoma (35-37%) and MPNST (9-12%). Median follow-up was 6 years. CINSARC high vs low was associated with worse EFS (5-year 52.1% vs 74.6%, $p < 0.01$) and OS (5-year 66.2% vs 83.6%, $p < 0.01$). Accounting for sex and presence of metastatic disease, the hazard ratio for CINSARC high was 2.4 for EFS and 2.7 for OS ($p < 0.01$). CINSARC maintained the association with EFS among patients with non-metastatic disease ($p = 0.017$), and with OS among patients with metastatic disease ($p = 0.031$). GI analysis is ongoing and will be reported. **Conclusions:** In this analysis from the largest prospective North American pediatric NRSTS studies to date, CINSARC score was prognostic for EFS and OS. Further analysis including additional clinical prognostic factors (tumor size, grade, and extent of resection) is ongoing and will be reported. Use of CINSARC score for risk stratification should be considered on future NRSTS clinical trials. Clinical trial information: NCT00346164, NCT02180867. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; St Baldrick's Foundation.

10014 Oral Abstract Session

Comparison of immunoglobulin high-throughput sequencing MRD in bone marrow and peripheral blood in pediatric B-ALL: A report from the Children's Oncology Group AALL1731.

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Background: Minimal (measurable) residual disease (MRD) at end of induction (EOI) therapy is a strong predictor of outcome in pediatric B-ALL. Currently, EOI MRD is assessed in bone marrow (BM). We hypothesized that the highly sensitive assay, high-throughput sequencing (HTS) of immunoglobulin loci, can effectively monitor MRD in peripheral blood (PB) and may provide a less invasive way to track therapy response. **Methods:** We conducted HTS MRD on paired EOI BM and PB samples from 808 NCI standard risk (SR) pediatric B-ALL patients enrolled on Children's Oncology Group study AALL1731 (NCT03914625). We determined the correlation between BM and PB HTS MRD via Spearman's rank correlations. We calculated the BM/PB MRD ratio and compared these by subgroup using Kruskal-Wallis tests. We defined subgroups by cytogenetics (cyto) (*ETV6::RUNX1*, double trisomies of chromosome 4 and 10 (DT), Unfavorable (hypodiploidy, iAMP21, or *KMT2A*-rearranged), or Neutral (lacking *ETV6::RUNX1*, DT, or unfavorable)), and risk group (SR-average (AVG) and SR-High). Flow cytometry-defined EOI BM MRD was $< 0.01\%$ for all SR-AVG patients (N = 623) and $\geq 0.01\%$ for selected SR-High patients (N = 185). **Results:** There was strong correlation between PB and BM HTS MRD with an overall correlation coefficient of 0.75 ($P < 0.001$). Correlation was similar by cytogenetics: *ETV6::RUNX1*, 0.69 (N = 63; $P < 0.001$), DT, 0.75 (N = 147; $P < 0.001$), Neutral, 0.74 (N = 580; $P < 0.001$), and Unfavorable, 0.66(N = 18; P = 0.003). For risk groups, correlation for SR-AVG was 0.67 ($p < 0.001$) and SR-High, 0.64 ($p < 0.001$). Of the 591 SR-AVG patients with detectable BM HTS MRD, PB HTS MRD was detectable in 474 (80.2%), undetectable in 94 (15.9%) and indeterminate (no leukemic cell detected and $< 500{,}000$ total cells in sample) in 23 (3.9%). Among 182 SR-High patients with detectable BM HTS MRD, 175 (96.2%) had detectable PB HTS MRD. Disease burden was higher in the BM than PB with a significantly higher BM/PB ratio in SR-High compared to SR-AVG patients (median 16.5 vs 2.6, $P < 0.001$). The median BM/PB ratio also varied by cytogenetics with those with Unfavorable cyto having the highest ratio (15.3 vs 6.3 in DT, 3.8 in *ETV6::RUNX1*, 3.1 in Neutral; P = 0.013). **Conclusions:** This is the largest analysis of paired B-ALL BM/PB HTS MRD to date. We show strong correlation between PB and BM across risk and cytogenetic groups. The ratio of BM/PB MRD varied and was highest among patients with Unfavorable cyto suggesting BM tropism. Importantly, PB MRD was detectable in nearly all patients with flow EOI BM MRD $\geq 0.01\%$, a threshold warranting therapy intensification. However, most patients with EOI BM flow MRD $< 0.01\%$ also had detectable PB HTS MRD. Thus, PB HTS MRD may provide a useful adjunct for screening and clinical management of B-ALL patients. Defining a PB HTS MRD threshold useful for risk stratification will require correlation with outcome. Research Sponsor: None.

10015 Oral Abstract Session

Vincristine (VCR) pharmacokinetics (PK) in infants dosed using a body surface area (BSA) banded dosing table and in older children dosed based on BSA: A pediatric early phase clinical trial network study (PEPN22P1).

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Background: The Children's Oncology Group developed and implemented a unified method of dosing anticancer drugs in infants and small children with a BSA < 0.6 m^2. The dosing tables use BSA-based dose banding and account for deliverable doses/volumes of the drugs. We studied the PK of VCR (1.5 mg/m^2 dose level) in infants and children to determine whether this new infant dosing method achieves uniform drug exposures across the pediatric age span. **Methods:** We designed a sampling strategy to limit the blood volume required by focusing on the elimination (β) phase of the VCR concentration-time curve, which accounts for $>$ 80% of the total area-under the curve (AUC). Duplicate samples to detect contamination were drawn at 3 post-infusion time points (2, 6-8 and 18-24 hr) through a central venous catheter (CVC) after a 90 min flush. VCR concentrations were measured at the Children's Hospital of Philadelphia using a validated high-pressure liquid chromatography/tandem mass spectrometry method with a lower limit of quantitation (LLQ) of 0.25 ng/mL. A one-compartment model was fit to the concentration-time data using population PK methods (Phoenix NLME). The AUCβ was derived from the dose and clearance for each patient. Patients were accrued in 4 age groups ($\leq$6 mo, goal n = 20); $>$ 6 mo to $\leq$12 mo, goal n = 10; $>$ 12 mo to $\leq$36 mo, goal n = 10; and $>$ 36 mo to $\leq$12 yr, goal n = 10) to focus on infants and ensure representation across the pediatric age range. **Results:** 52 eligible patients have been enrolled and 39 are evaluable for PK analysis, including 9 $\leq$6 mo, 8 $>$ 6 mo and $\leq$12 mo, 12 $>$ 12 mo and $\leq$36 mo, and 10 $>$ 36 mo and $\leq$12 y,. The median (range) age is 13.5 mo (1.15-112 mo). VCR was quantifiable in all samples, and there was no evidence of contamination in the duplicate samples drawn through the CVC. The mean $\pm$ SD AUCβ in the 39 evaluable patients was 54.7 $\pm$ 19.8 ng·h/mL. As shown in the Table, the AUCβ is similar in patients with a BSA < 0.6 m^2 dosed according to the BSA-banded infant dosing table and patients with a BSA ≥ 0.6 m^2 dosed by multiplying their BSA times 1.5 mg/m^2 ($p = 0.53$, Mann Whitney test). **Conclusions:** The VCR BSA-banded infant dosing table appears to provide uniform VCR exposure for infants and young children compared to conventional BSA-based dosing in older children. The study design and sampling strategy facilitated rapid accrual of a young population and generated more VCR PK data in infants within a year than has been published since the drug was approved in 1963. This study demonstrates the feasibility of systematically studying other anticancer drugs in infants and other special populations to ensure they are receiving safe and effective doses. VCR AUCβ by dosing method. Clinical trial information: NCT05359237. Research Sponsor: None.

	Dosing Table (< 0.6 m^2)	Calculated (BSA x 1.5 mg/m^2) (≥0.6 m^2)
n	25	14
Median (range) Age [mo]	9.0 (1.2 – 29.2)	51.8 (25.7 – 112)
Mean ± SD AUCβ [ng·h/mL]	52.5 ± 16.9	58.7 ± 24.4

10016 Oral Abstract Session

Evolution of tisagenlecleucel use for the treatment of pediatric and young adult relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL): Center for International Blood & Marrow Transplant Research (CIBMTR) registry results.

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Background: Tisagenlecleucel is an autologous CD19-directed chimeric antigen receptor (CAR) T-cell immunotherapy indicated for patients (pts) up to 25 y of age with B-ALL that is refractory or in second or later relapse. Since the pivotal ELIANA trial, pt characteristics now include pts < 3 y, pts with isolated central nervous system relapse, and pts with leukemia burden < 5%. Here we examine the impact of tisagenlecleucel on the pt treatment journey since FDA approval in 2017. **Methods:** Data were collected as a part of a noninterventional, prospective, longitudinal study using the CIBMTR registry. Pts were treated in the United States, Canada, Korea, or Taiwan. **Results:** As of May 4, 2023, 974 pts received tisagenlecleucel. Primary disease history has evolved since 2017. Notably, disease burden prior to infusion has decreased (≥50% blasts: 18% in 2018, 4% in 2022) and a higher proportion of pts received tisagenlecleucel while in morphological complete remission (34% in 2018, 51% in 2022). Between 2018 and 2022, the proportion of pts who were in third or greater relapse decreased (14% vs 2%, respectively). Pts ≥18 y had more prior exposure to blinatumomab and inotuzumab compared with pts < 18 y: 27% vs 16% and 17% vs 7%, respectively. The proportion of pts undergoing ≥1 hematopoietic stem cell transplantation (HSCT) before tisagenlecleucel infusion decreased (37% in 2018, 15% in 2022), coinciding with the use of tisagenlecleucel in earlier lines of therapy. Reporting of B-cell recovery was suboptimal. In total, 34.5% (314/911) of pts received postinfusion HSCT (reasons for HSCT were not captured for most pts); 8.5% (77/911) of pts received postinfusion HSCT to treat relapse, persistent/progressive disease, or positive minimal residual disease. Although the overall rate of postinfusion HSCT did not change, pts with high-risk cytogenetics showed a decrease in HSCT frequency. Previously, most pts < 3 y with *KMT2A* rearrangement received a HSCT. Since 2017, only 16% (12/75) of pts < 3 y received a prior HSCT despite 72% (54/75) having a *KMT2A* rearrangement. Furthermore, of the pts with rearrangement, only 43% (23/53) received a HSCT postinfusion. With censoring for HSCT, median RFS improved: 18 mo in 2018, 27 mo in 2020, and not estimable in 2021. OS was not substantially affected by HSCT censoring; 36-mo probabilities (95% CI) with and without censoring were 66 (61-71) and 62 (57-66), respectively. **Conclusions:** Pediatric and young adult pts with r/r B-ALL are receiving tisagenlecleucel earlier in the course of their disease treatment, reducing the use of HSCT for r/r disease, and prolonging RFS. As both real-world and clinical trial data supporting the curative potential of tisagenlecleucel grow, the use of HSCT in pts with remission after CAR-T should be carefully evaluated. Research Sponsor: Novartis Pharmaceutical Corporation.

10017 Oral Abstract Session

Brigatinib monotherapy in children with R/R *ALK*+ ALCL, IMT, or other solid tumors: Results from the BrigaPED (ITCC-098) phase 1 study.

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Background: Brigatinib is a potent ALK inhibitor (ALKi), with good CNS penetration and durable efficacy in adults with *ALK*-positive (*ALK*+) non-small cell lung cancer at 180 mg/day after a 7-day lead-in at 90 mg/day. This report presents the results of a pediatric phase 1 study (NCT04925609) in patients (pts) with *ALK*+ malignancies. The study is sponsored by the Princess Máxima Center and supported by Takeda Pharmaceuticals International Co. **Methods:** This multicenter, non-randomized, open-label phase 1 study enrolled pediatric pts aged ≥ 1 to < 18 years, with *ALK*+ newly diagnosed unresectable/metastatic or relapsed/refractory (R/R) IMT, R/R ALCL, or other solid tumors. *ALK*+ ALCL pts who were MRD positive after one course of frontline chemotherapy were considered refractory disease. A proven *ALK* gene aberration was required, except in ALCL, where ALK+ by immunohistochemistry was sufficient. Pts had to be able to swallow tablets and to weigh more than 10 kg at trial entry. Brigatinib was administered as tablets once daily in 28-day cycles, and was dose-escalated according to the rolling-six design to a maximum of 3 dose levels (DL). Dose limiting toxicities (DLTs) were evaluated during 35 days (1st cycle preceded by a 7-day lead-in phase), to determine the RP2D. Pts were assessed for safety, pharmacokinetics (PK) and efficacy. **Results:** Ten pts were enrolled (5 centers, 2 countries) over 12 months, including 9 ALCL, and 1 sarcoma NOS, with an *ALK*fusion. Median age was 9 years (range: 6-17) and 2 pts were pretreated with another ALKi. No pts less than 6 years were included due to the lack of age-appropriate formulation (AAF). At database cut-off, a median of 13 cycles (range 4-17) were administered. No DLTs were observed on DL1 (n = 4), and only 1 on DL2 (N = 6, grade (G)3 neutropenia $>$ 7 days). Common treatment related adverse events (AE) were (n any G; n $\geq$G3): abdominal pain (6;0), CPK increase (7;1), nausea/vomiting (6;0), AST/ALT elevation (4;0). Reported AEs of special interest included ophthalmological events (3;0) and weight gain (2;1), no brigatinib related pulmonary toxicity or endocrine AEs were observed. PK exposure at DL2 was equivalent to that reported in adults at the approved dose. The sarcoma patient had progressive disease after 12 cycles. All 9 ALCL patients are still on therapy with an ongoing response. **Conclusions:** The RP2D of brigatinib was established at DL2, corresponding to 150 mg (18-40 kg), or 240 mg ($>$ 40 kg) once daily. In general, the drug was well tolerated, with no instances of patients discontinuing dosing due to safety concerns. Brigatinib monotherapy demonstrated promising preliminary signs of efficacy in pediatric ALCL, although follow-up is still limited. The phase 2 part of this study has recently opened for accrual, and an AAF will soon be available for smaller children to define the RP2D in this population. Clinical trial information: NCT04925609. Research Sponsor: Takeda Pharmaceuticals International Co.

10018 Rapid Oral Abstract Session

Association of elevated ctDNA burden following one cycle of chemotherapy with inferior outcomes for patients with metastatic Ewing sarcoma: A report from the Children's Oncology Group (COG).

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Background: All patients with Ewing sarcoma (EWS) currently receive the same intensive chemotherapy and novel risk-adapted approaches to therapy are needed. We have previously shown that elevated baseline ctDNA burden is prognostic among patients with EWS. Here we investigate the prognostic impact of on-treatment ctDNA burden in patients with metastatic EWS treated on COG AEWS1221. **Methods:** AEWS1221 was a randomized phase 3 trial evaluating ganitumab plus interval compressed chemotherapy (vincristine/doxorubicin/cyclophosphamide alternating with ifosfamide/etoposide given every 2 weeks) for patients with newly diagnosed metastatic EWS. We evaluated 680 serial blood samples and data from 273 patients enrolled to AEWS1221. We utilized a custom NGS hybrid-capture assay for ctDNA quantification that detects *EWSR1* and *FUS*fusions. We used log rank tests to compare event-free survival (EFS) from the designated timepoint according to ctDNA burden post cycle 1 of VDC (planned day 14) and post cycle 2 VDC+IE (planned day 28) of chemotherapy. We dichotomized patients by ≥0.5% ctDNA at each timepoint. A *P*-value of ≤0.05 was considered evidence of a significant association. **Results:** Of 298 eligible patients with metastatic EWS, 273 provided blood samples for ctDNA analysis. Three patients had non-FET-ETS family fusions (*CIC::DUX4*, *EWSR1::WT1* and *EWSR1::GTDC1*) and were excluded from further analysis. Eighty-five percent of patients were < 21, 56% were male, 33% had pelvic bone primary tumors, and 40% had lung only metastatic disease. ctDNA was ≥0.5% in 86% of patients at baseline (median 25%, range 0-113%, n = 264), in 53% (median 0.53%, range 0-15%, n = 34) after 1 cycle (median day 14, range 11-20), and in 14% (median 0, range 0-53%, n = 130) after 2 cycles (median day 29, range 25-36). Baseline ctDNA burden ≥0.5% was associated with an increased risk of EFS-event (3-year EFS 35% [95% CI 29-41%] vs. 61% [95% CI 43-76%], HR = 2.2, *P*= 0.002). ctDNA ≥0.5% after cycle 1 was also associated with an increased risk of EFS-event (3-year EFS 6% [95% CI 0.4-22%] vs. 56% [95% CI 29-76%], HR = 6.0, *P*< 0.0001). ctDNA ≥0.5% after cycle 2 was not associated with an increased risk of EFS-event (28% [95% CI 10-49%] vs. 34% [95% CI 25-43%], HR = 1.2, *P*= 0.55). **Conclusions:** ctDNA burden ≥0.5% following one cycle of chemotherapy identifies patients highly likely to relapse, albeit in a small cohort with available data at that timepoint. Conversely, ctDNA at a cutpoint of ≥0.5% after two cycles of chemotherapy was not prognostic, suggesting either more sensitive assays are needed or the prognostic value of ctDNA burden is diminished following additional therapy. These findings will enable novel trials of risk-adapted therapy focused on baseline and early ctDNA burden. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; National Cancer Institute/U.S. National Institutes of Health; U10CA180886; QuadW; National Cancer Institute/U.S. National Institutes of Health; U10CA180899.

10019 Rapid Oral Abstract Session

A multi-assay liquid biopsy approach to improve detection of bone and soft tissue sarcomas.

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Background: Bone and soft tissue sarcomas are among the most common extra-cranial solid tumors of childhood, yet advances in liquid biopsies lag behind what has been achieved across adult cancers. Solid tumors that lack recurrent genetic mutations or translocations, such as bone and soft tissue sarcomas, are more difficult to detect in circulation using established assays, such as ddPCR. We have developed a pipeline to analyze cell-free DNA (cfDNA) using two molecular profiling techniques that we hypothesized would improve detection of circulating tumor DNA at diagnosis for patients with bone and soft tissue sarcomas. **Methods:** cfDNA was isolated from plasma of patients with osteosarcoma (OS) (n = 36) and fusion-negative rhabdomyosarcoma (FN-RMS) (n = 7) at multiple timepoints. Methods for detecting tumor DNA in cfDNA included ultra-low coverage whole genome sequencing (ULC-WGS, 0.5x) and ultra-deep targeted sequencing (UDP, ~1000x) using a panel of 11 and 22 tumor-associated genes for OS and FN-RMS, respectively. ULC-WGS data underwent ichorCNA analysis to define percent tumor content of each sample. UDP analysis identified somatic variants through variant callers, Mutect2, Lancet, strelka, and DELLY2, with ClinVar to annotate and define tumor-specific variants in each sample. Combining ULC-WGS and UDP data, an integrated tumor score was developed and assessed in diagnostic samples. **Results:** 136 OS and 30 FN-RMS cfDNA samples were collected during the patients' disease courses. Circulating tumor material was detected in 18/23 (78%) OS and7/7 (100%) FN-RMS samples at diagnosis. The most frequent copy number aberrations were seen in the region of chromosome 8q containing the cMYC gene. cMYC amplification was found in 11/23 (48%) of diagnostic OS samples and 2/7 (29%) of diagnostic FN-RMS samples. UDP analysis identified variants in 17/23 (73%) and 7/7 (100%) of diagnostic OS and FN-RMS samples respectively. The most commonly detected variants included TP53, BRCA2, MET, and BRAF. Of the 23 diagnostic OS samples, four had TP53 translocations. The integrated tumor score detected the presence of tumor associated material within diagnostic samples with a sensitivity of 25/30 (83%), compared to the sensitivity of ULC-WGS or UDP alone, which was 15/30 (50%) and 24/30 (80%) respectively. **Conclusions:** A multi-assay liquid biopsy has promise to improve disease detection and monitoring for patients with solid tumors that lack recurrent driver mutations. We plan to integrate additional molecular profiling technologies to improve the sensitivity and specificity of our cfDNA assays and aim to adapt our pipeline across additional cancers. Research Sponsor: None.

10020 Rapid Oral Abstract Session

iCatalog: An open-source, collaborative platform for precision oncology studies.

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Background: Genomic profiling of patient (pt) tumors using next-generation sequencing (NGS) has become an integral part of precision oncology (PO). To address the need for a streamlined, interoperable approach to clinical and NGS data management, interpretation, and reporting for a multi-institution pediatric PO study we developed iCatalog (iCat), a clinical decision support system for a multi-institution pediatric PO study. **Methods:** iCat was developed by the University of Chicago (UChicago) and Dana-Farber Cancer Institute to create clinical interpretation reports for the iCat2/Genomic Assessment Informs Novel Therapy Consortium (GAIN) study. It is a web-based application using the Python Django framework using open-source software and runs on virtual machines (VM) behind a secure firewall. iCat manages user and administrative permissions according to role and site. It securely stores, manages, and integrates genomic and clinical information as well as internal and external genomic knowledge on a patient level. Data types available during interpretation and report generation include pt demographics, specimen-level information such as diagnosis from pathology reports, and molecular data. iCat can host molecular data from different NGS test types. These data are entered through web interfaces and API calls. Genomic knowledge accessible in iCat is a combination of information brought in from external resources and gene and variant-level pediatric-specific curations completed in iCat by curators. Editable study-specific patient reports are generated for each test. **Results:** As of January 10, 2024, iCat has generated reports for 902 tests and stores information for an additional 217 tests for the 742 pts enrolled in the GAIN study. Of the 217 tests, 25 tests have reports in progress and 192 tests had reports generated manually before iCat was developed. Genomic data are from 11 different test types and clinical data are from patients with 92 rare pediatric solid tumor diagnoses. A total of 108 pts have received iCat clinical interpretation reports integrating genomic data from more than one NGS test type. The knowledge base contains pediatric-specific research-team authored curations for 561 genes, 2114 unique SNVs, 268 unique CNVs, and 227 unique structural variants. Test-specific, variant-level therapeutic recommendations have been made on 666 reports for 502 pts. Diagnostic or hereditary risk associations have been made on 729 reports for 537 pts. **Conclusions:** iCat is an academically developed open-source platform for PO studies that integrates clinical and genomic data, supports gene and variant interpretation, and facilitates the generation of an individualized genomic report with relevant clinical information for treating physicians. We developed and tested iCat for a pediatric precision oncology study and propose it as a customizable, collaborative platform for future precision oncology research. Research Sponsor: Dana-Farber/Harvard Cancer Center; Hyundai Hope on Wheels.

10021 Rapid Oral Abstract Session

Impact of breaks in therapy on survival for pediatric patients with relapsed or refractory solid tumors: A single-center study.

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Background: Relapsed or refractory (R/R) solid tumors remain a significant cause of mortality for children. While upfront therapies have been well-studied, the cumulative effects of multiple relapses and salvage regimens is unknown. We describe the disease trajectory in these patients, from the time of first R/R event (on-therapy progression/refractoriness or off-therapy relapse) to time of death or last follow-up. We also analyze whether breaks ($>$ 30 days) between diagnosis of events and initiation of subsequent therapies have an impact on survival. **Methods:** We reviewed data from electronic medical records for patients with primary, malignant R/R extracranial solid tumors treated at Texas Children's Hospital between 2005-2023. Descriptive analysis was performed along with univariate chi-square, one-way ANOVA, and independent sample t-tests. Cox regression analysis was used to evaluate time from first event to death or last known follow-up for each variable described. Analysis was performed with SPSS v29. **Results:** We reviewed data for 466 patients with R/R solid tumors (female: 47%; median age: 8.66 years; median follow-up after first event: 12.9 months). Most common diagnoses were neuroblastoma (21.5%), rhabdomyosarcoma (19.1%), and osteosarcoma (16.1%). Patients had a median of 3 (interquartile range [IQR]: 1-4) R/R events with a median of 93 (IQR 52-200) days between each event. The most common post-event therapy regimens were intravenous chemotherapy alone (21.4%) or in combination with surgery and/or radiotherapy (19.9%). Deceased patients (n = 339) had a median of 291 (IQR: 127-549) days from first event to death. Increased time from first R/R event to death was associated with a break in disease-directed therapy; type of diagnosis; non-metastatic stage at original diagnosis; type of first event; type of first salvage regimen; and receiving phase 1 therapy. Of 438 patients who received $\geq$1 salvage therapy regimen, 116 (26.5%) took $\geq$1 break between an R/R event and subsequent therapy. Reasons for breaks varied relatively evenly between intentional/goal-concordant (e.g., to seek second opinion, to focus on quality of life), and unintentional (e.g., care coordination, care access issues). In a multivariable Cox regression model, taking a $>$ 30 day break in disease-directed therapy was associated with prolonged survival, even after adjusting for number of events and significant covariates ($p < 0.05$). **Conclusions:** The prognosis for children with R/R solid tumors is poor. Most children experience multiple R/R events and therapy regimens without a break in therapy. Presence of a $>$ 30 day break between an R/R event and subsequent therapy did not negatively impact survival, implying that time between therapy regimens can safely be offered to some patients to promote quality of life, exploration of goals of care, and thoughtful decision-making, without compromising survival. Research Sponsor: None.

10022 Rapid Oral Abstract Session

Safety and efficacy of selpercatinib in pediatric patients with RET-altered solid tumors: Updated results from LIBRETTO-121.

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Background: Selpercatinib is a highly selective and potent CNS-penetrant oral RET inhibitor, approved for treatment of *RET*-driven thyroid cancer in adult and adolescent patients (pts), and lung or other solid tumors in adult pts. Here we present updated results from LIBRETTO-121, the first trial to assess the safety and efficacy of a selective RET inhibitor in pediatric and adolescent pts with *RET*-altered solid tumors. **Methods:** LIBRETTO-121 (NCT03899792) is a multicenter phase 1/2 trial in pts 0.5-21 yrs of age with advanced, *RET*-altered solid tumors. Enrollment began in June 2019 and is ongoing. To confirm the recommended phase 2 dose for selpercatinib, dosing started at 92 mg/m^2 BID, expecting to result in equivalent exposure to 160 mg BID in adults.The primary objectives were to evaluate safety and dose limiting toxicities (DLTs) in phase 1 and determine the ORR per RECIST 1.1 by independent review in the phase 2 population. **Results:** At the data cut-off (January 13, 2023), 27 pts aged 2-20 yrs were treated with selpercatinib. Tumor types included *RET*-mutant medullary thyroid cancer (MTC, n = 14), *RET* fusion-positive papillary thyroid cancer (PTC, n = 10), or other (n = 3). The most common *RET* alterations were a M918T mutation (71.4% [10/14] of MTC pts) or *NCOA4-RET* fusion (50% [5/10] of PTC pts). Pediatric and adolescent patients treated at 92 mg/m^2 (up to 160 mg BID) had a similar exposure as adults treated with 160 mg BID at steady state on cycle 1 day 8. Time on selpercatinib ranged from 0.4 to 40.8 mo and 22 pts remain on treatment. There were no treatment discontinuations due to DLTs or TEAEs; 2 pts (7.4%) experienced a dose reduction due to TEAEs (elevated ALT and reduced neutrophil count). The most common TEAEs observed ($\geq$25% of pts) were diarrhea, headache, coronavirus infection, nausea, vomiting, elevated ALT, elevated AST and pyrexia. The most common TEAEs $\geq$ G3 included constipation, reduced neutrophil count, vomiting and weight gain, each occurring in 2 pts (7.4%). One pt (age 15 yrs) experienced a TEAE $\geq$ G3 of epiphysiolysis, a risk for selpercatinib in this population based on pre-clinical data. In pts with RECIST measurable disease at baseline, the ORR was 83.3% (10/12), while 1 pt had stable disease (SD) and 1 pt had progressive disease (PD). Among pts with measurable disease at baseline, PTC pts had an ORR of 100% (5/5), and MTC pts had an ORR of 83.3% (5/6), while 1 MTC pt had SD. No PTC or MTC pts had PD. Responses were durable, with a 24 mo DOR rate of 100% (95% CI: NE, NE). With a median follow up of 18 mo, the mPFS among all pts has not yet been reached, and the 24 mo rate of PFS was 92.4% (95% CI: 73.0% - 98.1%). **Conclusions:** Selpercatinib's safety profile remains consistent with prior reports from adult trials. These results, including more robust efficacy and PK data, continue to support the use of selpercatinib in pediatric and adolescent pts with *RET*-altered solid tumors. Clinical trial information: NCT03899792. Research Sponsor: Loxo@Lilly, a wholly owned subsidiary of Eli Lilly and Company.

10023 Rapid Oral Abstract Session

Interpretable artificial intelligence-based analysis for morphologic classification of neuroblastic tumors.

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Background: Rapid and accurate identification of morphologic features of neuroblastic tumors (NTs) is critical for risk stratification and therapeutic decision making. The prognostic value of features like neuroblast differentiation, mitosis-karyorrhexis index (MKI), and Schwannian stromal presence is well established. Deep learning permits objective histopathological analysis, streamlining workflows for pathologists, notably in rare cancers. In rare cancers, our method minimizes bias and optimizes limited data using transfer and self-supervised learning (SSL) for feature extraction, with improved explainability. Here, we used an artificial intelligence-based model to morphologically classify NT tumors and *MYCN*-amplification. **Methods:** Annotated H&E-stained slides of diagnostic NT tumor biopsies from the University of Chicago and the Children's Oncology Group were digitalized. Pathologists defined three binarized measures including diagnostic category (ganglioneuroblastoma/neuroblastoma), grade (differentiating/poorly differentiating), and MKI (low and intermediate/high). *MYCN* status was abstracted from patient records (amplified/non-amplified). Using Slideflow, our open-source pipeline, we developed an attention-based multiple instance learning model with features extracted by CTransPath, a SSL model pretrained on pan-cancer images from The Cancer Genome Atlas. For each measure, model performance was evaluated using 5-fold cross validation by aggregating k-fold model predictions across multiple metrics. Patients were excluded from a model if the measure of interest was unknown. Feature significance was assessed visually using Class Activation Mapping (Grad-CAM). **Results:** The mean age of the study cohort (n = 172) was 3.66 years. Of patients with clinical information, 84 of 138 (60.2%) had metastatic disease and 94 of 133 (70.7%) were high-risk. Of the 148 tumors with a diagnostic category of neuroblastoma, 93.2% were poorly differentiated and 25% had high MKI. Of the 135 tumors with known *MYCN* status, 40 were amplified (29.6%). The final models excelled across all outcomes, performing best for diagnostic category, grade, and *MYCN* status (Table 1). Physician review of the attention-based heatmaps for all measures highlighted biologically relevant regions such as neuropil. **Conclusions:** We created a deep learning pipeline for auto-characterization of digitized H&E-stained NT pathology slides. Our approach may also aid in identifying molecular features including *MYCN*-amplification. Review of heatmaps showed pertinent biological tissue, boosting model reliability. Research Sponsor: University of Chicago Cancer Center; P30CA014599; Burroughs Wellcome Fund; Children's Oncology Group; U24CA196173.

Model performance for aggregate predictions.

Outcome Measure	Specificity	Sensitivity	Precision	F-1 Score	AUPRC	AUROC
Diagnostic Category	0.92	0.93	0.99	0.95	0.99	0.96
Grade	0.70	0.80	0.97	0.88	0.99	0.85
MKI	0.60	0.77	0.85	0.81	0.88	0.71
MYCN	0.73	0.75	0.87	0.80	0.89	0.77

10024 Rapid Oral Abstract Session

Comparing the impact of insufficient physical activity on cardiovascular disease in survivors of childhood Hodgkin lymphoma and sibling controls: A report from the Childhood Cancer Survivor Study (CCSS).

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Background: Survivors of childhood Hodgkin lymphoma are at increased risk of cardiovascular disease (CVD) from anthracycline and radiation exposures. Whether the treatment-induced risk can be mitigated with physical activity is not known. We aimed to compare the impact of insufficient physical activity on CVD in Hodgkin lymphoma survivors and controls. **Methods:** Participants in the Childhood Cancer Survivor Study (CCSS) reported physical activity, which was translated into metabolic equivalent of task hours/week (MET) and categorized as 0, 1-8, or ≥9 METs. We estimated rate ratios (RR) for new onset (incident) congestive heart failure and any CVD (including heart attack, congestive heart failure, arrhythmia, and valvular disease requiring interventions) during follow-up, accounting for age, sex, race/ethnicity, smoking, risky drinking, overweight/obesity, and treatment exposures (survivors only). Then we calculated population attributable fractions (PAF) for insufficient physical activity (< 9 METs). The attributable relative rate (ARR) was calculated by multiplying the PAF in survivors with the RR for CVD incidence in survivors compared to controls, resulting in an ARR for survivors that was compared to the PAF in controls. **Results:** In 2,357 Hodgkin survivors [50% female; [mean (SD)] 14.3 (4.1) years at diagnosis; 31.6 (5.8) years at start of follow-up, and 17.8 (7.6) years from diagnosis] and 3,949 sibling controls, 233 survivors and 19 controls developed congestive heart failure. 462 survivors and 95 controls developed any CVD. The PAF for congestive heart failure attributable to insufficient physical activity was larger in controls (38.0%) than survivors (22.3%). However, with RR 20.3 (95% CI 12.6-32.5) for congestive heart failure for survivors compared to controls, the ARR in survivors (452.1%) revealed a 12 times higher incidence of congestive heart failure attributable to insufficient physical activity in Hodgkin survivors than in controls (452.1%/38.0%). The ARR indicates that 4.5 of the 20-fold higher risk of congestive heart failure in survivors vs. siblings is attributable to insufficient physical activity in the survivors. For any CVD, the PAFs were comparable in survivors (13.7%) and controls (11.7%). With RR 10.2 (95% CI 8.2-12.7) for any CVD for survivors compared to controls, the ARR for any CVD in survivors (139.7%) was also 12 times higher than the incidence attributable to insufficient physical activity in controls (139.7%/11.7%). **Conclusions:** Our results suggest that the magnitude of treatment-induced CVD risk that can be mitigated by physical activity is considerable. This offers a modifiable target and provides rationale for exercise interventions aimed at reducing CVD in survivors at high risk. Research Sponsor: None.

10025 Rapid Oral Abstract Session

Tamoxifen for breast cancer prevention among survivors of pediatric lymphoma previously treated with chest radiation: Clinical benefits, harms and tradeoffs.

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Background: Survivors of pediatric lymphoma previously treated with chest radiation are at high risk for subsequent breast cancer. Although early initiation of breast cancer screening is recommended, the clinical benefits and harms of adding tamoxifen to reduce breast cancer deaths among these women are unknown. **Methods:** We adapted a Cancer Intervention and Surveillance Modeling Network (CISNET) breast model using data from the Childhood Cancer Survivor Study (CCSS) to reflect the elevated risks for breast cancer and competing mortality for 5-year survivors previously treated with chest radiation (RT). Breast cancer risk was based on age, chest RT field, timing of RT relative to menarche, menopause status, anthracycline exposure, and family history. Premature menopause risk varied by cumulative ovarian RT and alkylator dose. Based on the US Preventive Services Task Force 2019 Evidence Summary, we assumed tamoxifen (20mg daily for 5 years) reduced estrogen receptor positive (ER+) breast cancer risk by 42% (RR = 0.58 [0.42-0.81]) for 20 years and increased risks for venous thromboembolism, deep vein thrombosis, coronary heart disease, stroke and endometrial cancer during treatment. Strategies included no screening or tamoxifen, annual screening with mammography and MRI starting at age 25, annual screening with mammography and MRI starting at age 25 with the addition of tamoxifen at ages 25, 30 or 35. Model outcomes included cumulative breast cancer risk, number of childbearing years before age 45 (defined as years menstruating without tamoxifen use or a breast cancer diagnosis or having survived breast cancer for at least 3 years), and number of tamoxifen-related side-effects. **Results:** Among a cohort of 20-year-old 5-year lymphoma survivors previously treated with mediastinal RT without primary ovarian failure, an estimated 20% were projected to develop breast cancer and 2.6% would die from the disease before age 50 in the absence of screening or tamoxifen use. Survivors would have on average 22 childbearing years before age 45. Early initiation of breast cancer screening at age 25 would reduce breast cancer deaths before age 50 by 56.3%. Depending on age at initiation, tamoxifen would further reduce breast cancer deaths by 8.0 to 9.6 percentage points for an overall 64.3% to 65.9% reduction and reduce the average number of childbearing years by 17% to 21%. For each breast cancer death averted, a reduction of 1950 to 3740 childbearing life years and 11 to 20 side-effects would occur and varied by the tamoxifen start age compared to mammography and MRI screening. **Conclusions:** Tamoxifen use for primary breast cancer prevention among pediatric lymphoma survivors may further reduce breast cancer deaths but decisions might depend on survivor preferences for side effects vs. avoiding breast cancer and consideration of timing for childbearing. Research Sponsor: National Cancer Institute; R01CA261874.

10026 Rapid Oral Abstract Session

Treatment modifications and mortality among female patients with subsequent breast cancer: A report from the Childhood Cancer Survivor Study (CCSS).

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Background: Childhood cancer survivors are at high risk for developing subsequent breast cancer with higher mortality than females in the general population with primary breast cancer. Whether therapeutic tradeoffs in treating primary versus subsequent breast cancer alter survival is unknown. **Methods:** Breast cancer treatment data were abstracted from medical records for female survivors from the CCSS and a multi-institutional sample of females with primary breast cancer matched one-to-one by demographics, diagnosis age/year, and breast cancer characteristics. Survivors' excess mortality risk was evaluated as hazard ratios (HRs), adjusting for receipt of historically-appropriate guideline-concordant treatment established for primary breast cancer. **Results:** Subsequent breast cancers were diagnosed between 1981-2016 among 431 survivors, with a median diagnosis age of 40 years (IQR: 35-44). Most subsequent breast cancers were invasive (77%), with hormone receptor profiles similar to the general population (78% ER-positive; 26% HER2-positive). Guideline-concordant breast cancer treatment did not differ between survivors and controls (N = 688; 94% versus 93%), but treatment selection differed, reflecting survivors' complex clinical history and guidelines' multiple treatment options. Anthracyclines were used in 47% of survivors (controls 66%), mastectomy in 81% of survivors (controls 60%), and radiotherapy in 18% of survivors (controls 61%). In the subgroup treated with surgery and chemotherapy (survivors 31%, controls 26%), survivors did not have greater likelihood of dose reductions or omissions, treatment delays, or hospitalization for fever and neutropenia, but they were more likely to experience hematological toxicities (21% vs. 9%, $p = 0.033$) and other organ system-specific toxicities (36% vs. 11%, $p < 0.001$). Over one-third (38%) of survivors died during follow-up (median follow-up 9 years, IQR 6-14) after breast cancer. Strikingly higher all-cause mortality was observed among survivors than controls (HR = 3.5, 95% CI 2.2-5.6), especially after in situ disease (HR = 9.9, 95% CI 2.2-44.2). Among survivors with invasive disease, breast cancer accounted for most deaths (51%), followed by other subsequent malignancies (15%) and cardiovascular diseases (15%). Other health conditions accounted for 67% of deaths following in situ disease. **Conclusions:** Childhood cancer survivors with subsequent breast cancer generally receive guideline-concordant breast cancer treatment. While the treatments survivors receive differ from females with primary breast cancer, they do not experience higher rates of on-therapy treatment modifications. Despite this, they face excess mortality, primarily driven by other health conditions. Managing comorbidities is critical to enhancing long-term survival for this high-risk population. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; K08 CA234232, LM Turcotte, principal investigator; U24 CA55727, GT Armstrong, principal investigator; American Lebanese Syrian Associated Charities.

10027 Poster Session

Precision genome profiling for pediatric leukemia with a software-controlled enrichment method using nanopore sequencer.

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Background: The real-time nature of nanopore sequencing allows for simultaneous basecalling of DNA sequences during sequencing. This unique capability enables adaptive sampling (AS), a software-controlled targeted sequencing method. AS is notable for its ability to rapidly and flexibly enrich multiple genes with long fragment reads and detect various modalities of genetic aberrations in a single run. However, the feasibility and significance of AS for cancer have not been previously reported. **Methods:** We performed AS on a GridION sequencer using samples from 28 pediatric leukemia patients (10 acute myeloid leukemia, 13 B-cell acute lymphoblastic leukemia, and 5 T-cell acute lymphoblastic leukemia). Target regions were comprised of 466 genes associated with hematologic malignancies and included 30-kilo base pairs of flanking regions. After 3 days of sequencing, single-nucleotide variants (SNVs), structural variations (SVs), and copy number variations (CNVs) were determined. In 21 samples, variant calling accuracy was evaluated using short-read-based whole genome sequencing (WGS). **Results:** In the on-target regions, mean depth was 21.0× and N50 was 11,191 bps at the median. Of the 13 samples with genetic alterations previously detected through clinical testing for diagnostic classifications, all were reconfirmed by AS. Detecting *DUX4* rearrangement needed an additional analysis pipeline because of its structural complexity. Among the 15 remaining samples whose genetic alterations had not been determined by clinical diagnostic testing, AS identified putative driver aberrations in 14 samples. All of these genomic abnormalities were structural variations (SVs) or copy number variations (CNVs), most of which were not encompassed within the genes or regions targeted in clinical diagnostic testing. Detected SVs were described with accurate genomic breakpoints, enabling the efficient detection of gene rearrangements and deletions of the entire region of an exon or a gene. Regarding CNVs, both chromosomal-level CNVs, such as high-hyperdiploid, and focal CNVs, such as *CDKN2A* deletion, were detectable using genome-wide low-coverage reads in the off-target regions. In the other case with acute myeloid leukemia in which genetic abnormalities were not detected either by clinical testing or AS, WGS identified an *NPM1* frameshift deletion located outside of known hotspots. Among variants identified by WGS, AS detected 60.9% of the SNVs, 17.6% of the small indels, and 89.2% of the SVs, with a tendency of poor detection efficiency for variants with low variant allele frequency. **Conclusions:** AS provides a rapid and precise description of the genomic profile of pediatric leukemia, particularly advantageous for identifying SVs and CNVs, which are difficult to detect by capture-based short-read sequencing. Research Sponsor: Japan Agency for Medical Research and Development; JP23ck0106876; Japan Leukemia Research Fund.

10028 Poster Session

Accelerated aging among survivors of childhood leukemia and lymphoma: Estimates of early onset and excess morbidity from the COMPASS model.

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Background: Cohort studies have detected an increased risk of accelerated aging among survivors of childhood cancer but the timing and magnitude are not known. **Methods:** To predict the clinical course of diseases of aging— cancer and cardiovascular disease — among survivors of childhood leukemia and lymphoma compared to the general population, we developed the Cancer Outcomes Microsimulation: Pediatric and Adolescent SurvivorShip (COMPASS) model. The model simulates 8 severe, disabling or life-threatening chronic health conditions (CHCs), including 4 subsequent cancers (breast, colorectal, glial tumors, sarcomas) and 4 cardiovascular diseases (heart failure, myocardial infarction/coronary artery disease, valvular disease, stroke), and excess mortality risks among survivors diagnosed between 1970 and 1999 over the course of their lifetimes. Treatment-related risks varied by patient characteristics (sex, age at diagnosis, diagnosis) and treatment exposures (chemotherapy, radiation dose) and were based on data from the Childhood Cancer Survivor Study (CCSS). Age-related risks and competing mortality were based on national databases (SEER, NHLBI, CDC Wonder). We used model calibration to identify parameter sets that generated outcomes consistent with observed data. Model outcomes included cumulative CHC risk. For comparisons to the general population, age-, sex, and diagnosis year-matched individuals who faced only age-related risks were simulated. **Results:** Among survivors representative of CCSS participants, the model estimated that 45% of leukemia and 65% of lymphoma survivors will develop at least 1 of the 8 CHCs by age 65. Compared to the estimated 20% cumulative risk for the general population, this represented a two- to three-fold excess morbidity risk among survivors. The age at which 20% of survivors developed at least 1 CHC was 51 years for leukemia and 42 years for lymphoma, suggesting an early onset of 14 and 21 years compared to the general population. Outcomes varied by diagnosis and treatment era due to competing risk changes. Among leukemia survivors diagnosed in the 1990s vs. 1970s, cumulative late recurrence mortality by age 40 (11% to 1%) declined. This combined with a reduction in radiation exposure (79% to 24%) resulted in a greater proportion living into adulthood and developing CHCs by age 65 (38% to 48%). In contrast, among lymphoma survivors, the proportion projected to develop a CHC by age 65 remained stable during the same period (62% to 65%) as late recurrence mortality risk declined (8% to 1%), but almost half still received radiation (90% to 49%). **Conclusions:** Despite improvements in therapy, leukemia and lymphoma survivors are projected to experience CHC early onset and excess morbidity, underscoring the importance of prevention-focused survivorship care and continued efforts to develop more targeted therapies. Research Sponsor: National Cancer Institute; R01CA227576.

10030 **Poster Session**

Preclinical efficacy of BRG1/BRM ATPase inhibitor in B lymphoblastic leukemia.

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Background: Acute lymphoblastic leukemia (ALL) is the most common blood cancer in children and young adults. While ALL has a high cure rate, approximately 20% of patients who initially respond to treatment relapse and prognosis post relapse remains poor. New therapeutic treatments are needed to reduce relapse rates in B-ALL pediatric patients and to minimize the toxic side effects seen with current therapies. We and others have previously shown that BRG1/BRM ATPase inhibitors have efficacy in targeting acute myeloid leukemia (AML) and one, FHD-286, is currently being evaluated for its use in AML in an ongoing clinical trial (NCT04891757). BRG1 and BRM are the ATP-dependent catalytic subunits of the SWI/SNF chromatin remodeling complex which has a critical role in controlling gene expression, cell growth and survival of AML cells. Our prior work revealed that BRG1/BRM ATPase inhibition leads to selective transient reduction of normal B cells. Further, data from Depmap also nominates *SMARCA4*, the gene encoding BRG1, as a dependency in B-ALL cell lines, leading us to hypothesize that BRG1/BRM inhibition may be an effective therapy for B-ALL. **Methods:** We treated B-ALL cell lines with varying genetic lesions (*KMT2A*-rearranged: RS4;11, KOPN-8, SEM; *ETV6::RUNX1* fusion: REH and *DUX4*-rearranged: Nalm6) with dose titrations of FHD-286 and measured cell growth over the course of six days. In addition, at 48- and 72-hours post-treatment, we assayed cells for viability, cell cycle kinetics, and apoptosis induction via flow cytometry to provide insight into FHD-286's mechanism of action in B-ALL. **Results:** We found that FHD-286 treatment resulted in decreased cell growth in a dose-dependent manner across all B-ALL cell lines. While all cell lines were displayed reduced proliferation at nanomolar doses, sensitivity varied. Nalm6, REH and SEM cells were the most sensitive with low nanomolar IC50s (2-7nM). In contrast, two of the *KMT2A*r B-ALL lines, RS4;11 and KOPN-8, required higher doses to achieve growth inhibition (40-70nM). To better understand the mechanism by which FHD-286 is affecting cell growth, we evaluate whether FHD-286 is targeting cell growth through the apoptotic pathway or through cell cycle arrest. Our preliminary data indicates cell growth inhibition is only slightly attributable to cell cycle arrest and apoptosis induction, leading us to explore terminal differentiation as a mechanism of slowed proliferation. **Conclusions:** Our results show FHD-286 can strongly inhibit B-ALL cell growth in vitro, indicating FHD-286 as a potential therapeutic agent to treat B-ALL. In vivo validation is ongoing. Further directions include defining the effect of FHD-286 on chromatin remodeling, gene expression, and exploring efficacy in combination therapy, which has been shown to increase FHD-286 efficacy against AML. Our data may ultimately justify inclusion of B-ALL patients in clinical studies of BRG1/BRM inhibitors. Research Sponsor: None.

10031 Poster Session

Racial disparities in pediatric patients with acute myeloid leukemia.

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Background: Leukemia is a cancer of the blood and bone marrow characterized by the rapid and uncontrolled production of abnormal white blood cells. Acute myeloid leukemia (AML) makes up 15–20% of all childhood acute leukemias (1). The purpose of this study is to use the National Cancer Database (NCDB) to provide an updated investigation of racial disparities in survival in pediatric patients with AML. Investigating the different factors associated with poor outcomes provides valuable information when allocating resources and understanding where policies will be useful to improve patient outcomes. **Methods:** Pediatric (0-19 years old) AML patients were identified in this retrospective cohort study via the 2004-2020 NCDB. Chi square analysis, Fischer's exact test, and t-tests were used to analyze demographic variables. Kaplan Meier survival analysis was used to compare mean survival across race categories which was repeated with demographic variables of interest using a multivariate Cox regression. **Results:** A total of 4765 patients were identified in this study. Most patients were male (53.5%), White (73.0%), held private insurance (52.3%), and resided in metropolitan areas (82.0%). The mean age at diagnosis was 8.1 years old. There was no significant difference in age at diagnosis and time to treatment start across racial categories. Black patients had lower mean survival compared to White patients (131 vs 148 months, $p<0.001$). When controlling for age, sex, metropolitan status, comorbidity status, income, education, and insurance status as covariates, Black race independently portended a poorer prognosis compared to White race (hazard ratio: 1.174, 95% confidence interval: 1.003-1.376, $p=0.046$). Black patients were more likely to be uninsured (4.1%) compared to White patients (2.8%) ($p<0.001$). Black patients were more likely to reside in zip codes with lower incomes (36.0% vs 17.6%, $p<0.001$) and lower education attainment (38.7% vs 27.8%, $p<0.001$) compared to White patients. Black patients were more likely to have comorbidities with a Charlson-Deyo score of >1 than White patients (11.2% vs 6.2%, $p<0.001$). Black patients were also more likely to be from metropolitan areas than White patients (90.5% compared to 83.9%, $p<0.001$). **Conclusions:** This study indicates that Black AML patients experience lower survival rates and are subject to more predictors of poor outcomes. Black patients were more likely to be uninsured, have comorbidities, live in zip codes with lower incomes and lower education attainment. 1. Morais, R. V. de et al (2021). *J De Pediatria*, *97*(2), 204–210. https://doi.org/10.1016/j.jped.2020.02.003. Research Sponsor: None.

10032 Poster Session

Naxitamab-related adverse events within and across treatment cycles in patients with relapsed/refractory (R/R) high-risk neuroblastoma.

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Background: Anti-GD2 monoclonal antibodies, including naxitamab, for the treatment of high-risk neuroblastoma (HRNB) are associated with adverse events (AEs), though few studies have characterized their frequency and patterns of presentation. A practical understanding of AEs can help clinicians expect and manage those requiring intervention. In this post hoc analysis, we report the frequency and severity of naxitamab-related AEs across infusions and treatment cycles, based on data from a prespecified interim analysis of Trial 201. **Methods:** Trial 201 (phase 2, NCT03363373) is investigating naxitamab plus granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with R/R HRNB with residual disease in bone/bone marrow only. Patients with soft tissue or actively progressing disease were excluded. Naxitamab was infused at 3 mg/kg/dose IV on Days (D) 1/3/5 with GM-CSF administered SC on Days -4 to 5 (monthly cycles [C]). Patients (N=74) were evaluated for safety (CTCAE v4.0), with frequency defined as % of patients reporting >1 events. Frequency of AEs of Grade ≥3 were evaluated for C1-C5. **Results:** Most (81%) naxitamab-related AEs were Grade 1 or 2. Grade ≥3 AEs reported in ≥10% of patients were hypotension (60% of patients), pain (54%), urticaria (19%), bronchospasm (18%), and abdominal pain (16%). The frequency of related hypotension Grade ≥3 (Grade 4, n=3) decreased across cycles, from C1 (47%) to C5 (33%) and across infusions, from C1D1 (43%) to C1D3 (18%) and C1D5 (11%). Similar decreases were seen during C2 to C5. Among patients with Grade ≥3 hypotension, 73% had their first event C1D1, of whom 34% and 31% had their second event C1D3 or C2D1, respectively. The frequency of related pain Grade 3 AEs (all preferred terms with word "pain") decreased from C1 (53%) to C2 (37%), generally stabilizing thereafter with frequencies consistent across infusions. Most (77%) had their first event C1D1, of whom 82% had a second event C1D3. The frequency of related bronchospasm Grade 3 (no Grade 4 AEs) was relatively stable around 7% from C1 to C3, decreasing to 4% and 2% in C4 and C5, respectively. Patients generally experienced these events on D1 infusions with few reported D3 or D5. No consistent pattern was seen for Grade 3 urticaria. None of the Grade ≥3 AEs of hypotension, urticaria, pain or bronchospasm resulted in treatment discontinuation. **Conclusions:** The frequency of naxitamab related Grade ≥3 AEs changed over the course of therapy. Hypotension was most frequent C1D1, decreasing across infusions and cycles. Pain frequency peaked C1 and decreased in subsequent cycles, remaining stable across infusions. Bronchospasm events, though relatively rare, generally occurred D1 and decreased across infusions. The results underline the importance of initial and ongoing monitoring within and across cycles to ensure appropriate and timely management. Clinical trial information: NCT03363373. Research Sponsor: Y-mAbs Therapeutics, Inc.

10033 Poster Session

Patterns of improvement following initial response in patients treated with naxitamab for relapsed/refractory high-risk neuroblastoma.

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Background: Treatment of high-risk neuroblastoma (HRNB), the most common extracranial solid tumor in pediatric patients, is associated with suboptimal efficacy outcomes. While monitoring responses to naxitamab and other anti-GD2 monoclonal antibodies is essential, there is limited evidence on the timing and magnitude of improved responses following first assessment. Here, we report the patterns of improvement following the initial response to naxitamab therapy, based on the results of a prespecified interim analysis of Trial 201. **Methods:** Trial 201 (phase 2, NCT03363373) is investigating naxitamab plus granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with refractory/relapsed HRNB with residual disease in bone and/or bone marrow (BM) only. "Refractory" and "relapsed" disease comprised those with an incomplete response (partial response [PR], minor response [MR], or stable disease [SD]) per International Neuroblastoma Response Criteria (INRC) to induction therapy or to treatment for actively progressing or relapsed disease, respectively. Patients with soft tissue or actively progressing disease were excluded. Naxitamab was infused at 3 mg/kg/dose IV on Days 1/3/5 with GM-CSF administered SC on Days -4 to 5 (monthly cycles [C]). The primary endpoint was overall response rate (ORR), comprising those with a complete response (CR) or PR per INRC. Response assessments occurred between C2 and C3 and at prespecified timepoints thereafter. **Results:** The ORR in Trial 201 was 50% (26/52). At first assessment, the ORR was 37% (n=19), with 14 patients achieving CR. An additional 6/26 patients (23%) achieved a CR or PR after C3, of whom 4 went from MR to CR, and 2 from SD to PR. (One patient whose disease was not evaluable at first assessment and who later had a PR was included in the ORR but excluded from this response improvement analysis.) In addition to the 6 patients who achieved a CR or PR after C3, 2 patients with PR at initial assessment later achieved a CR, and 1 patient with initial SD achieved MR, totaling 9 patients with improved post-C3 responses, or 17% of the overall efficacy population. Among those with baseline disease in bone, post-C3 responses in the bone compartment improved in 6/50 patients (12%). Of these 6 patients, 5 had initial SD in bone and achieved a post-C3 CR or PR. Post-C3 responses in the BM compartment improved in 6/23 patients (26%) with baseline BM disease, of whom 5 had initial SD in BM and achieved a post-C3 CR. Naxitamab safety (N=74) has been reported previously. **Conclusions:** A considerable proportion (23%) of patients achieved a CR or PR only after C3. Among these patients, most had initial SD within specific bone or BM compartments before achieving a post-C3 CR/PR. Taken together, the results support the rationale for continued treatment of patients not achieving CR/PR at first assessment. Clinical trial information: NCT03363373. Research Sponsor: Y-mAbs Therapeutics, Inc.

10034 Poster Session

Phase I trial of chidamide, an oral HDAC inhibitor, in combination with oral etoposide in patients with refractory/recurrent neuroblastoma.

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Background: Chidamide, an oral subtype-selective histone deacetylase (HDAC) inhibitor, has been shown to be effective in adult patients with hematological tumors. However, there is no data on its safety and efficacy in pediatric cancer patients. Combination of HDAC inhibitors and etoposide have shown synergistic anti-tumor effects in preclinical studies of neuroblastoma. We conducted a phase I trial in pediatric patients with recurrent or refractory neuroblastoma to determine the maximum tolerable dose (MTD) of chidamide combined with oral etoposide treatment. **Methods:** Daily oral etoposide 35 mg/m^2/dose was administered on days 1–21 in combination with escalating doses of chidamide (14 and 17 mg/m^2/d) twice weekly in each 28-day cycle using the standard 3 + 3 design. Patients with response or stable disease after two cycles would maintain treatment until disease progression or unacceptable toxicity occurred. Chidamide pharmacokinetic testing was performed. **Results:** 31 patients were enrolled in this study. The median age was 7 years (range 3 – 18). 14 patients were included in the dose escalation phase (Ia), 17 patients in the expansion cohort (Ib). The MTD of chidamide was 14 mg/m^2/d, with dose limiting neutropenia and thrombocytopenia observed at 17 mg/m^2/d. Median number of cycles completed was 2.5 (range 1–11). A total of 19 patients (61.3%) experienced treatment-related grade 3/4 hematologic toxicity, and no grade 3/4 non-hematological toxicity was observed. No objective responses were seen. **Conclusions:** In children with refractory/recurrent neuroblastoma, chidamide is well-tolerated at 14 mg/m^2/d twice weekly when combining with oral etoposide 35 mg/m^2/d daily. Prolonged disease stability achieved in patients with minimal residual diseases deserves further investigation. Clinical trial information: NCT05338541. Research Sponsor: None.

10035 Poster Session

Testicular germ cell tumor survival among children, adolescents, and young adults: A population-based retrospective cohort study.

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Background: While testicular germ cell tumor (TGCT) overall survival (OS) exceeds 90%, some patient groups, such as adolescents, have inferior event free survival (EFS) outcomes. There is a paucity of granular, population-derived data about outcomes in children, adolescents, and young adults (CAYA) with TGCT, limiting a deeper understanding of the factors that impact their survival. **Methods:** All male CAYA (ages 11-21 years) in Ontario, Canada diagnosed with TGCT between 1992-2021 were identified using provincial cancer registries. Detailed disease and treatment characteristics were chart abstracted for ~2/3 of the cohort and determined through health administrative databases for the remainder. We assessed 5-year OS and EFS (first of death, recurrence/progression, or subsequent malignant neoplasm [SMN]) using Kaplan-Meier analysis and the log rank test. Follow-up started at TGCT diagnosis, except for survival after SMN or recurrence, where follow-up started at event date. **Results:** 748 TGCT patients were identified; 521 were chart abstracted and thus had EFS data available. Median age at diagnosis was 19 years (interquartile range:18-21) and 83.6% had non-seminoma histology. OS and EFS ± standard error (SE) were (94.7 ± 0.8 %, n=748) and (76.4 ± 1.9%, n=521), respectively. Among patients with chart abstracted data, OS and EFS differed by cancer extent at diagnosis and were lowest among CAYA with non-lung organ metastases (Table). Patients who underwent retroperitoneal lymph node dissection (RPLND) for initial treatment (91/521) had higher survival than those who did not (OS 96.6 ± 1.9% vs 93.7 ± 1.2%, p=0.04; EFS 87.6 ± 3.5 % vs 74.1 ± 2.1 %, p=0.0008), particularly CAYA with lung-only organ metastases. OS post SMN (n=28) was 77.3 ± 8.2%, with lower OS after non-TGCT SMN (50.8 ± 14.4%, n=13) than second primary TGCT (100 ± 0%, n=15), p=0.002. OS after recurrence/progression (n=116) was superior in the 59 who did not receive chemotherapy at initial diagnosis (89.7 ± 4%) compared to the 57 who had initial chemotherapy (65.9 ± 6.4%; p=0.0001). **Conclusions:** CAYA with TGCT have low EFS, consistent with previous studies. The extent of metastasis is a significant predictor. Efforts are needed to improve the survival outcomes of young TGCT patients with organ metastasis at diagnosis, and those who recur or develop a non-TGCT SMN. Research Sponsor: Canadian Institutes of Health Research (CIHR). RA is supported by the Ontario Graduate Scholarship (OGS) through the University of Toronto and the Research Training Competition (RESTRA-COMP) award through the Hospital for Sick Children.

5-year survival ± SE (%).

Cancer Extent n=512	OS/EFS By Cancer extent		OS/EFS by Initial RPLND for Each Cancer Extent Category					
	EFS*	OS*	EFS			OS		
			No	Yes	p	No	Yes	p
No mets n=377	81.9 ± 2.0	97.6 ± 0.8	80.1 ± 2.2	97.4 ± 2.6	**0.002**	97.3 ± 0.9	100 ± 0	0.1
Lymph node mets only n=34	90.9 ± 5.0	97.0 ± 3.0	88.9 ± 7.4	93.3 ± 6.4	0.5	100.0 ± 0	93.3 ± 6.4	0.9
Lung only organ mets (± lymph) n=68	57.2 ± 6.0	88.2 ± 3.9	45.0 ± 7.7	76.9 ± 8.3	**0.006**	80.8 ± 6.1	100.0 ± 0	**0.008**
Other organ mets (± lymph/lung) n=33	39.4 ± 8.5	63.6 ± 8.4	29.2 ± 9.3	66.7 ± 15.7	**0.03**	58.3 ± 10.0	77.8 ± 13.9	0.2

*p<.0001.

10036 Poster Session

Type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma (pLGG): Reversible decreases in growth velocity in the phase 2 FIREFLY-1 trial.

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Background: Tovorafenib is an investigational, selective, CNS-penetrant, type II RAF inhibitor. Results from the ongoing FIREFLY-1 (NCT04775485) phase 2 study (1) in *BRAF*-altered pLGG showed clinically meaningful tumor responses and a manageable safety profile with tovorafenib monotherapy. Decreased growth velocity (GV) was observed; this is an update on changes in GV in skeletally immature children receiving tovorafenib. **Methods:** A planned safety analysis was completed on August 8, 2023 and included 137 patients (Arm 1: 77 & Arm 2: 60) treated with ≥1 dose of tovorafenib in FIREFLY-1. This report provides additional follow-up on all cases of decreased growth velocity (GV), an adverse event of special interest (AESI), reported to the Sponsor's global safety database (GSDB) as of January 19, 2024. **Results:** Decreased GV was reported in 40 (29.2%) of 137 patients; 26 (19%) had GV reduction ≥50% from baseline (BL). Of those with decreased GV, 30 (75.0%) had pre-existing neuromuscular or endocrine comorbidities that may affect normal growth, including 6 (15%) with precocious puberty being treated with a gonadotropin-releasing hormone analogue, and 9 (22.5%) with BL heights 2 standard deviations above or below average for age and sex. Nineteen of the 40 patients with this AESI had on-treatment bone age assessments; none showed advancement of bone age from BL or premature closure of growth plates. No osteopenia or abnormal fractures were reported. Of the 35 patients with growth hormone (GH) testing, only 2 had signs of GH deficiency (both had optic pathway tumors; 1 had GH deficiency at BL, the other, a new tumor-associated GH deficiency). Post-treatment heights ≥3 months off treatment were reported for 10 of 40 patients who had interrupted or discontinued treatment for any reason (mean follow up: 5.8 months), including 2 (1.5%) permanent discontinuations and 3 (2.2%) interruptions due to decreased GV. All 10 showed post-treatment recovery in annualized GV (AGV) (average on-treatment AGV 1.1 cm/y vs. average post-treatment AGV 8 cm/y), in some cases exceeding expected average AGV for age. One additional 4-year-old boy with on-treatment AGV of 1.2 cm/y had an off-treatment AGV of 12.3 cm/y after 2 months of off-treatment follow-up. Decreased GV was reported to the GSDB for 5 (11.4%) of 44 patients who received above the maximum dose of tovorafenib used in FIREFLY-1 in an ongoing investigator-initiated study. Four of the 5 patients from this study had ≥3 months of off-treatment follow-up reported; all 4 showed evidence of GV recovery. **Conclusions:** Decreased GV has been observed in patients treated with tovorafenib. Early follow-up data from patients whose treatment was interrupted show consistent evidence for GV recovery and preservation of growth potential on bone age studies. 1. Kilburn LK, et al. *Nat Med.*2023. Clinical trial information: NCT04775485. Research Sponsor: Day One Biopharmaceuticals, Inc.

10037 Poster Session

Naxitamab chemo-immunotherapy regimens other than with irinotecan/temozolomide for patients with relapsed/refractory high-risk neuroblastoma.

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Background: Patients with relapsed/refractory (R/R) high-risk neuroblastoma (HR-NB) have dismal prognosis with chemotherapy-only salvage regimens. Naxitamab, a humanized anti-GD2 monoclonal antibody (mAb), when combined with Irinotecan and Temozolomide (I/T), has demonstrated clinically meaningful efficacy in R/R HR-NB patients (NCT03189706). We aimed to investigate the potential synergy of naxitamab with other cytotoxics. **Methods:** In this retrospective analysis, we examined patients treated at SJD with chemo-refractory disease, who received naxitamab in combination with chemotherapeutics other than I/T. Each cycle comprised naxitamab 2.25 mg/kg/day IV over 30 minutes, days 2, 4, 9 and 11 (total 9 mg/kg or 270 mg/m2 per cycle), and GM-CSF 250 mg/m2/day subcutaneously, days 6-10 combined with either a) cyclophosphamide (250mg/m2) and topotecan (0.75mg/m2) D1 to D5 (C/T), b) ifosfamide (1500mg/m2), etoposide (100mg/m2) D1-D3 and carboplatin (400mg/m2) D1 (ICE) or c) doxorubicin 37.5mg/m2 D1-D2 and cyclophosphamide (250mg/m2) D1-D3 (C/D). Toxicity was measured by CTCAE v4.0 and responses by INRC. **Results:** Twenty-nine patients received naxitamab plus GM-CSF with C/T (n=23), ICE (n=6) and C/D (n=1). One patient received both ICE and C/T. Seventeen patients had a variable number of prior relapses (1 n=14, 2 n=1, and 3 n=2). Twelve patients had refractory disease, most having received additional therapy post-induction. All but 4 patients had received naxitamab and I/T (n=20), and/or ICE (n=3/n=1), and dinutuximab-beta and I/T (n=1). Toxicities of the new regimens included myelosuppression expected with chemotherapy, and pain and hypertension expected with naxitamab. Hemorrhagic cystitis occurred in 2 patients treated with C/T, BK infection documented in one. A total of 113 cycles (median 2; 1-8) were administered, outpatient. Out of the 30 treatments, 5 achieved complete response (CR), 2 partial response (PR), and 2 mixed response (MR), providing an objective response (OR) of 30%. Eight patients achieved stable disease (SD) and 13 progressed on treatment. Disease control rate (DCR) (OR or SD) after 2 cycles was 56.6%. Patients who never responded with prior chemo-immunotherapy progressed through the new combinations. Contrary, patients who showed initial stabilization with I/T or ICE but ultimately progressed, switching drugs resulted in 60% DCR and 30% OR. Most favourable OR (75%) was seen in patients who achieved CR with prior chemoimmunotherapy and relapsed (3 out of 4). **Conclusions:** Naxitamab-based chemo-immunotherapy with regimens other than I/T exhibited similar and manageable toxicity profiles. Switching chemotherapeutics provided objective responses only to patients who had previously shown efficacy with I/T chemo-immunotherapy. Research Sponsor: None.

10038 Poster Session

Revealing and targeting metabolic drivers contributing to treatment escape in diffuse midline glioma.

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Background: Diffuse midline glioma (DMG) is an aggressive pediatric brain tumor that predominately affects children, with a median survival of 9-11 months. DMGs are driven by self-renewing, stem-like glioma cells that have been stalled in an oligodendrocyte precursor cell (OPC)-like state and that highly express *PDGFRA*. This overexpression of *PDGFRA* has been shown to be pivotal in DMG development. Thus, targeting PDGFRA may serve as a viable treatment approach for DMG. In our previous studies, we revealed that avapritinib, a next generation tyrosine kinase inhibitor of PDGFRA, is highly effective in DMG cells. While a subset of patients receiving treatment with avapritinib experienced a promising clinical response, all patients eventually experienced tumor progression due to treatment escape. In this study, we investigated which mechanisms DMG cells use to escape avapritinib treatment, and how we can therapeutically exploit these resistance mechanisms. **Methods:** Transcriptomic profiling and functional assays were performed on patient-derived DMG cell lines. A combinatorial drug screening identified drug candidates evaluated in this study. **Results:** Bulk RNA sequencing analysis of two patient derived DMG cell lines revealed an upregulation of genes associated with both fatty acid metabolism and oxidative phosphorylation (OXPHOS) following avapritinib treatment. Functional assays confirmed elevated OXPHOS in avapritinib-treated cells with significant increases in mitochondrial energy transduction, palmitate- (a product of fatty acid metabolism) driven oxygen consumption rates, and incorporation of palmitate-derived carbons into the tricarboxylic acid (TCA) cycle. CRISPR-Cas9-mediated knockout of *PDGFRA*in one DMG cell line confirmed the metabolic changes observed following avapritinib treatment. Analysis of bulk RNA sequencing data revealed an upregulation of key fatty acid- related transcription factors in avapritinib-treated DMG cells. Specifically, Peroxisome Proliferator-Activated Receptor alpha (PPAR-alpha), Sterol Regulatory Binding Element Binding Transcription Factors 1 and 2, and Fatty Acid Synthase (FASN) were most prominently upregulated. To determine which therapies could target the dependency of avapritinib-treated cells on fatty acid metabolism, we performed a combinatorial drug screening and found three lipid pathway inhibitors that have synergistic cytotoxic effects with avapritinib. Specifically, a FASN inhibitor, cholesterol pathway inhibitor, and PPAR-alpha inhibitor. **Conclusions:** In this study, we revealed metabolic drivers that may contribute to avapritinib resistance in DMG cells, and identified compounds capable of inhibiting these drivers that demonstrate synergy with avapritinib. We now intend on testing these combination therapies *in vivo* as we aim to provide a long-term clinical benefit to DMG patients receiving avapritinib. Research Sponsor: The Physician Scientist Support Foundation.

10039 Poster Session

Harmonizing cancer care delivery for AYAs with osteosarcoma: Comparison of pediatric and medical oncology approaches in a single center.

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Background: Osteosarcoma (OS) has a peak incidence amongst adolescents and young adults (AYA). Nuances in chemotherapeutic regimens are largely influenced by the training of pediatric or medical oncologists. MAP is the standard chemotherapy regimen used by pediatric oncologists. Chemotherapy regimens used by medical oncologists vary; our center uses preoperative doxorubicin/cisplatin (AP) followed by either doxorubicin/ifosfamide (AI) or a combination of HD methotrexate and HD ifosfamide. We undertook this analysis to characterize the treatment response, toxicity, and survival outcomes for AYAs with OS treated with pediatric vs medical oncology regimens as an initial step towards harmonizing our institutional approach to the treatment of AYA patients with bone sarcomas. **Methods:** We retrospectively reviewed the records of AYAs with OS receiving primary treatment at our center. Clinicopathologic characteristics and outcomes for patients treated with MAP vs. AP+ were compared. Progression-free survival (PFS) was defined as the time from either MAP/AP+ initiation or surgery to the time of first recurrence or death. Overall survival was defined as the time from MAP/AP+ initiation or surgery to death. The distributions of PFS and overall survival were estimated by the Kaplan-Meier method. Log-rank test was performed to test the difference in survival between groups. Regression analyses of survival data based on the Cox proportional hazard (PH) model were conducted on the time to event outcomes. **Results:** Between 2016-2022, 209 OS patients were seen at our center for initial diagnosis and treatment recommendations including 124 AYAs (59%). Amongst AYAs, 41 patients (median age 22y, range 14-38y) initiated and received the majority of their chemotherapy at our center and were included in analysis. Of the 41 AYAs, 17 were treated on MAP; 24 were treated using AP+. Ten patients $<$ 20 years received MAP; one patient $>$30 years received MAP. The median time from initiation of therapy to surgery for those receiving MAP was 87.5 days vs 95.5 days for AP ($p = 0.0052$). Percent tumor necrosis varied widely with both regimens (range 0-99%) and was not statistically different ($p = 0.11$). There was no statistically significant difference in PFS between AYAs treated with MAP as compared to AP+ (Three-year PFS rates 80% vs 66%, $p = 0.40$). Evaluation of treatment related toxicity and late effects is ongoing. **Conclusions:** We had insufficient data to compare survival outcomes in this limited retrospective series. This limited retrospective study did not show a statistically significant difference in PFS for AYA patients with OS treated with a standard pediatric vs. adult type regimen containing at least 3-drug chemotherapy. Further study is needed to refine treatment for this patient population. These data support prospective efforts to harmonize AYA treatment paradigms in osteosarcoma. Research Sponsor: None.

MRI compared to ^{123}I-MIBG scan for detection of central nervous system relapse in neuroblastoma.

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Background: Neuroblastoma (NB) relapsing in the central nervous system (CNS), though uncommon, is historically incurable. However, a multimodality approach has improved long term survival (1). Timely detection of CNS relapse may reduce or prevent morbidity and mortality. In most centers, surveillance for NB includes whole-body MIBG scans but does not require dedicated anatomical brain imaging. At Memorial Sloan Kettering Cancer Center (MSK), head MRI at regular intervals is standard. The objective of this retrospective study was to determine the optimal imaging modality for detecting CNS relapse in NB. **Methods:** After MSK IRB approval, records of patients with CNS NB seen at MSK from 2004-2023 were evaluated. In most cases, relapse was diagnosed at other institutions before referral to MSK. Analyzed data included symptoms and findings on brain CT/MRI and MIBG scans. **Results:** Of 206 patients with MIBG-avid CNS NB, 7 were excluded because they had CNS disease at diagnosis. For the remaining 199 patients, median time to CNS relapse from diagnosis was 18 months. 132 (66%) patients had CNS relapse at a median of 9.8 months after achieving complete remission. In 67 patients with prior systemic progression, median time to CNS relapse was 10.9 months from the last relapse. Relapse was isolated to CNS in 130/199 (65%) patients. 118 (59%) patients had neurological symptoms at time of CNS disease; 81(41%) were asymptomatic, relapse being detected on surveillance scans. Multiple (>1) parenchymal lesions were noted in 74 (37%), diffuse leptomeningeal disease without parenchymal involvement in 15 (7%) and solitary lesions in 110 (55%) patients. Median diameter of the largest lesion was 2.7 (range <0.5-6.8) cm. Anatomical imaging was performed with MRI (65%), CT (14%) or both (34%). Of those undergoing both scans, CNS relapse was missed on CT in 4/67 (6%) patients. 137 patients had MIBG scans before resection of CNS relapse. All sites of CNS disease noted on MRI/CT were positive by MIBG in 46 (33%) patients. However, MIBG scan was either totally or partly negative in 69 (50%) and 22 (16%) patients, respectively. Even for lesions ≥2cm in diameter, MIBG was completely negative in 27/57 (47%). MIBG positivity did not correlate with age, size >2cm, *MYCN* amplification or *ALK* mutation status ($p>0.05$ for each). Lesions <1cm and infratentorially located were more likely to be negative on MIBG scan ($p<0.05$). Lesions in symptomatic patients, dural lesions and hemorrhagic lesions were more likely to be positive on MIBG scan ($p< 0.05$). **Conclusions:** CNS relapse is isolated to the brain in most patients. MIBG scan has poor sensitivity for the detection of CNS NB, regardless of size or location. Although CT or MRI are both effective in detecting CNS relapse, the former can miss some lesions. We recommend brain MRI for surveillance of high-risk NB for ≥2 years after initial diagnosis or last systemic relapse. 1. J. Neurooncology 97:409, 2010. Research Sponsor: None.

10041 Poster Session

Demographic factors of prognosis in pediatric neuroblastoma.

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Background: Neuroblastoma is a rare type of pediatric tumor derived from neural crest progenitor cells. It can arise anywhere along the sympathetic chain but is most commonly found in the retroperitoneum from the adrenal glands. At diagnosis, approximately 50% of patients have hematogenous spread of metastases and so timely, aggressive treatment may be life-saving. The National Cancer Database (NCDB) is an oncology database that collects data from over 1500 cancer centers in the United States. This study will utilize the NCDB to analyze how demographic factors may impact prognosis in patients with pediatric neuroblastoma. **Methods:** We conducted a retrospective analysis using the National Cancer Database (NCDB) and identified patients diagnosed with pediatric neuroblastoma under the age of 18 between 2004-2020 with ICD code 9500/3 (n = 2323). Multivariate Cox regression analysis was used to calculate hazard ratios (HR) analyzing race, Spanish/Hispanic origin, facility type, education, income, insurance status, age at diagnosis, distance traveled to the facility, and urban characteristics of the facility on prognosis. **Results:** The median age at diagnosis was one year-old. Patients aged greater than one year-old composed 48% of the sample and had a less favorable prognosis compared to patients younger than one-year old (HR 1.99, 95% CI 1.69-2.35, $p < 0.001$). The median distance to the facility was 21.4 miles. 50% of the sample patients lived greater than 21.4 miles of their chosen facility and had a poorer prognosis compared to patients who lived closer (HR 1.25, 95% CI 1.06-1.47, p = 0.008). Conversely, patients with private insurance composed 59% of the sample and had a more favorable prognosis (HR 0.54, 95% CI 0.30-0.99, p = 0.046) compared to patients with no insurance. **Conclusions:** To our knowledge, this study provides the most updated analysis on how demographic factors impact prognosis in patients with pediatric neuroblastoma. We highlight potential barriers to care including age, distance to facility, and insurance. We hope this study may serve as a foundation for further investigation into the systemic barriers that affect patients with pediatric neuroblastoma. Research Sponsor: None.

10042 Poster Session

Institutional review of pediatric oncology patients participating in early phase clinical trials.

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Background: Phase 1 or phase 1/2 trials are a first step in pediatric cancer drug development with a primary objective of evaluating safety and dosing of new therapies or new combinations. They most commonly enroll patients with relapsed/refractory or very rare cancers and currently there is a paucity of information regarding outcomes for pediatric patients enrolled on phase 1/2 trials. Thus, we sought to describe clinical outcomes of pediatric patients enrolled in phase 1 clinical trials over a 9-year period at a single institution. **Methods:** We queried our clinical trials management system to generate a list of all pediatric patients who were enrolled and treated on phase 1 or phase 1/2 trials from 2011-2019. We reviewed the electronic medical record to collect baseline demographic and clinical data. We also collected key efficacy and safety endpoints post-enrollment including: time to death (if applicable); objective response to trial therapy; duration on therapy; need for dose modification; and occurrence of DLT. Overall survival was calculated using Kaplan-Meier methods. **Results:** A total of 224 unique patients accounted for 258 enrollments and 253 episodes of treatment on trial. The median age at trial enrollment was 11 years (range 0-27 years) and 56.2% were male. The majority of patients were white (85.7%) and non-Hispanic (88.2%). English was the primary language for 86.3% of patients and 65.8% of patients had private insurance. Solid tumors were the most common malignancy at 41.0%, followed by brain tumors (34.1%), and hematologic malignancies (24.9%). The majority of patients (60%) had metastatic disease at time of first enrollment. Among episodes of treatment, 51.4% received targeted monotherapy. Median overall survival from first enrollment for 210 patients treated with available vital status was 12.8 months. Among episodes of treatment, 25.2% of patients had an objective response to trial therapy. Stratified by disease type, objective response was documented for 52.9% of patients with hematologic malignancies, 20.5% of patients with CNS tumors, and 15.8% of patients with solid tumors. Patients on trials with cytotoxic-only treatment had the highest objective response (47.5%), while patients treated with cytotoxic plus targeted therapies combinations had the lowest rate (18.9%). The median duration of therapy was 1.5 months. Twenty-seven patients (11.0%) required dose modification and 22 patients (9.0%) had DLT. **Conclusions:** We present clinical outcomes for a recent cohort of pediatric patients treated on early phase clinical trials. We identified differential response rates to phase 1 therapy by disease and trial-type in a single-center cohort treated over the past decade. These data are immediately informative to discussions between providers and patients/parents regarding expected phase 1 trial outcomes. Research Sponsor: None.

10043 Poster Session

AI/ML-derived mechanistically interpretable whole-genome biomarkers of patient survival in pre-treatment primary neuroblastoma tumors and whole blood.

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Background: Prediction, understanding, and management, of neuroblastoma (NBL) outcomes, from spontaneous regression to relapse and death, remain limited, and rely mostly on the International Neuroblastoma Staging System (INSS) stage, age, and the one-gene test for *MYCN* amplification. The entire multi-ome affects every aspect of the disease. But typical artificial intelligence and machine learning (AI/ML) cannot discover effective biomarkers from real-life, small-cohort, multi-omic, and noisy data. **Methods:** We use our AI/ML to identify two whole-genome biomarkers from open-source pre-treatment NBL patient-matched primary tumor and whole blood DNA copy numbers, and primary tumor mRNA expression. Our data-agnostic, unsupervised algorithms extend the mathematics that underlies quantum mechanics to overcome the limitations of typical AI/ML [1,2]. Our platform- and reference genome-agnostic biomarkers in astrocytoma, including glioblastoma, and lung, ovarian, and uterine adenocarcinomas, were mathematically discovered, and computationally and experimentally validated, repeatedly, in federated, imbalanced datasets from as few as 50–100 patients [3]. **Results:** We discover the biomarkers in "skinny" datasets of minimally preprocessed ≈3M-bin whole-genome sequences from tumors and blood of a set of 101 patients. Blindly, i.e., label-free, we separate both biomarkers from the normal X chromosome-number variation, demonstrating sex-agnostic learning. Combined, the biomarkers are statistically independent of all standard-of-care indicators, with the univariate Cox hazard ratio of 4.0 (log-rank *P*-value=2.3×10^{-5}) within the 95% confidence intervals of the bivariate ratios. The risk that the tumor's whole genome confers upon outcome, as is reflected by the bivariate ratios, is greater than that conferred by all standard-of-care indicators, including DNA ploidy, the Children's Oncology Group (COG) risk, and the mitosis-karyorrhexis index (MKI), except for histopathology. We validate the biomarkers in ≈10K-bin target-capture sequences of a mutually-exclusive set of 419 patients, demonstrating generalizability as well as site-, platform-, and protocol-agnostic transfer learning. At 73–80% concordance, in both the tumor and blood profiles of both the discovery and validation sets, the biomarkers combined are more accurate than *MYCN*. We show that the biomarkers identify known and previously unrecognized disease mechanisms and druggable gene alterations, including co-amplification of *MYCN* with genes encoding for extra-embryonic transcripts, as well as the hijacking of embryonic development toward aneuploidy, which can spontaneously regress via embryonic self-correction. **Conclusions:** Our AI/ML is uniquely suited for personalized medicine. 1. doi: 10.1063/1.5099268 2. doi: 10.1073/pnas.0530258100 3. doi: 10.1063/1.5142559. Research Sponsor: NIH/National Cancer Institute (NCI) Physical Sciences in Oncology Project; U01 Project CA-202144.

10044 Poster Session

Efficacy and safety of the use of dinutuximab in newly diagnosed or relapse high risk neuroblastoma: Single arm systematic review and meta-analysis.

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Background: Patients with high-risk Neuroblastoma have a poor prognosis, with 43% experiencing a 3-year survival rate in newly diagnosed cases and a 21% 1-year event-free survival in relapsed patients. Dinutuximab, an immunotherapy targeting anti-disialoganglioside (GD2), emerges as a promising treatment for high-risk Neuroblastoma. This single arm meta-analysis aims to assess the efficacy and safety of dinutuximab, providing insights into its impact on survival rates among neuroblastoma patients. **Methods:** We systematically searched Pubmed, Cochrane and EMBASE for clinical trials between 1988 to 2023 utilizing Dinutuximab (ch14.18 or ch14.18/CHO) in patients with newly diagnosed or relapsed/refractory high-risk neuroblastoma. We pooled the prevalence and the 95% confidence intervals (CI) for the outcomes of interest: overall survival (OS), event-free survival (EFS) and progression-free survival (PFS), objective response rate (ORR), and treatment-emergent adverse events (TEAE). Heterogeneity was assessed using I^2 analysis and all statistical analyses were employed using R software version 4.3.2 and a random-effects model. **Results:** The analysis included 2214 patients from 13 clinical trials, comprising four phase III trials and six phase II. Six studies included Interleukin 2 (IL-2). Among the patients, 364 (16.5%) had relapsed or refractory disease. Dinutuximab was applied as post-consolidation treatment in 1809 patients (81.1%). The age of patients ranged from 1 to 21 years. In a pooled analysis, the 3-year OS rate was 69% (CI 0.62-0.76; I^2 = 85%), and the 3-year EFS rate was 61% (CI 0.52-0.69; I^2 = 77%). In the group of newly diagnosed patients, the 3-year EFS rate was 62% (CI 0.58-0.66; I^2 = 52%) and 3-year OS rate of 74% (CI 0.69-0.79; I^2 = 71%). Among patients with relapse, there was a 3-year OS rate of 57% (CI 0.50-0.64; I^2 = 0%). The overall ORR was 47% (CI 0.37-0.57; I^2 = 69%), of which 38 newly diagnosed patients using Dinutuximab during induction chemotherapy showed an ORR of 86%. TEAEs of grade $\geq$ 3 were 70% (CI 0.44-0.88; I^2 = 94%), and in the subgroup without IL-2 use, it was 43% (CI 0.29-0.57; I^2 = 85%). **Conclusions:** This single-arm meta-analysis suggests that both newly diagnosed or relapsed/refractory high-risk Neuroblastoma patients benefit from Dinutuximab, with a promising impact on 3-year OS and EFS. Dinutuximab appears to be a safer option; however, concomitant use of IL2 is associated with a higher rate of adverse effects. Research Sponsor: None.

10045 Poster Session

Diffuse midline gliomas in children: Does changing strategies change results?

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Background: The prognosis of children with diffuse intrinsic pontine gliomas (DIPG)/diffuse midline glioma (DMG) is dismal. Radiotherapy (RT) is considered the standard of treatment. We previously published results of our center, where patients receiving temozolomide or other chemotherapy after radiotherapy (RT) had a better survival than those receiving RT alone (1). This study aims to evaluate a larger cohort of children with DMG in a single center. **Methods:** We retrospectively reviewed demographic, clinical characteristics and treatment outcome of children with DMG diagnosed and treated at Istanbul University, Oncology Institute between Feb1999-Feb 2023. We compared the groups that received only radiotherapy (Group 1, only RT, n=19), the ones that received RT with concomitant and adjuvant temozolomide po (Group 2-n= 38 TMZ 75 mg/m2/day for 6 weeks concomitant (c.) with RT, followed by TMZ (200 mg/m2/day) for 5 days every 28 days until progression or for 12 cycles), and the ones that received RT with c. TMZ, followed by other systemic agents (Group 3 n= 18 RT c.TMZ, followed by nimotuzumab containing regimens; Group 4 the rest 26 received other agents such as bevacizumab, CCNU, ONC201 and other). The ones that progressed on group 2, received nimotuzumab containing or other regimens. **Results:** 114 children (49 female, 65 male) with a mean age of 7± 4 years (6 months-16 years) were analyzed. The most frequent clinical findings were ataxia, strabismus and motor weakness. 108 had diffuse intrinsic pontine gliomas (DIPG). In total 106 patients received RT, 54-60 Gy to the tumor site. The overall survival (OS) in all patients at 2 years, 3 years and 5 years were 25.6%,15% and 11.5% respectively. The 2 years, 3 years and 5 years OS in group1 were 0.79%, 0% ,0% respectively; in group 2 they were 38.4%, 27.9%, 16%respectively ; in group 3 they were 17.6% , 0 % ,0% respectively, in Group 4 they were 10.3%, 0.34%, 0% respectively, The OS in Group 2 or3 or 4 were significantly higher than group 1 (only RT) (P =0.002, p=0.004, $p<0.001$,respectively). There was no major side effect due to TMZ, nor nimotuzumab. Seven patients were re-irradiated at progression. The number of patients undergoing biopsies and molecular testing increased to 50% of the patients after 2016 versus only in two patients previously. **Conclusions:** In our series, the overall survival was significantly superior in patients who received RT with concurrent and adjuvant temozolomide and/or adjuvant nimotuzumab containing regimens or other adjuvant systemic treatment in comparison to patients that received RT alone, suggesting that adding systemic treatment after RT (poTMZ or iv nimotuzumab containing regimens or other) may help extend survival. Oral temozolomide may be easier to use as first line treatment after radiotherapy especially in resource limited settings, switching to nimotuzumab containing or other chemotherapy and/or re-radiotherapy at progression. 1. Kebudi R, 2013. Research Sponsor: None.

10046 Poster Session

Targeted treatment in inflammatory myofibroblastic tumors in children.

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Background: Inflammatory myofibroblastic tumors (IMTs) and epithelioid inflammatory myofibroblastic sarcoma (EIMS)-a variant of IMT, are rare mesenchymal neoplasms in children. Surgical resection has been the mainstay of treatment, however it may cause morbidities due to the size, location, invasiveness of the tumor. With the identification of targetable molecular alterations, targeted treatment has begun to be used in inoperable/relapsed/refractory cases. **Methods:** Files of children with IMT diagnosed and treated between 1990-2023 were retrospectively evaluated for demographic, clinical, molecular characteristics, treatment and outcome. **Results:** The mean age of 8 patients (5 male, 3 female) at diagnosis was 9 years (8 months-17 years). Six had IMT and two EMS. Tumor localization was intestine, retroperitoneum, lower extremity in two patients each; liver and back in one each. None had metastatic at diagnosis. Three of the six patients (one EMS) who underwent only surgical resection had negative surgical margins (one after re-resection) and are under follow-up with no evidence of disease (NED). Molecular analysis was performed in six patients. ALK was positive in the tumor tissue of five patients. One patient with an inoperable local recurrence received chemotherapy, had a life-threatening infection and resistant hypercalcemia. The molecular analysis by next-generation sequencing revealed a YWHAE-ROS fusion and she was treated by ceritinib, after which a significant (>90%) tumor shrinkage occurred and hypercalcemia resolved. She is currently in remission and continuing treatment. The patient with a positive surgical margin experienced local and metastatic (lung, liver) recurrences during follow-up and was treated with chemotherapy containing vincristine, actinomycin-D, and cyclophosphamide, the patient died due to progressive disease. In a patient with an unresectable tumor and ALK positivity, crizotinib treatment was initiated. After a treatment duration of seven months with crizotinib, the tumor completely regressed and treatment was stopped. On follow-up, local recurrence was detected after two months of cessation of crizotinib, crizotinib was restarted, considering the infiltrative appearance of the tumor and possible morbidities if operated. Two months after readministering crizotinib, complete response was achieved once again. The patient is continuing treatment with crizotinib. Thus, 7/8 patients are alive with NED for a median of 99 (9-174) months. **Conclusions:** Inflammatory myofibroblastic tumor and epithelioid inflammatory myofibroblastic sarcoma are rare in children. Surgery is the mainstay of treatment. The effectiveness of chemotherapy is yet unclear despite its use in inoperable cases. Molecular analysis of tumor tissue is highly recommended as targets such as ALK rearrangements or ROS fusions may enable the use of targeted treatments with fewer side effects. Research Sponsor: None.

10047 Poster Session

Phase I dose escalation and pharmacokinetics clinical trial of mitoxantrone hydrochloride liposome in children with relapsed and refractory solid tumors.

Junting Huang, Mingqing Ji, Hui Li, Yanpeng Wu, Ruiqing Cai, Juan Wang, Suying Lu, Jia Zhu, Feifei Sun, Zijun Zhen, Yizhuo Zhang; Sun Yat-sen University Cancer Center, Guangzhou, China; Sichuan Cancer Hospital, Chengdu, China; Wuhan Children's Hospital, Wuhan, China; The Fifth Affiliated Hospital, Guangzhou, China; Yuexiu District, Guangzhou, China

Background: Compared with solvent-based mitoxantrone, mitoxantrone hydrochloride liposome has been found to reduce bone marrow toxicity. This open-label, muti-center, single-arm phase I clinical trial aims to evaluate the safety and efficacy of mitoxantrone hydrochloride liposome in pediatric with solid tumors. **Methods:** The study was divided into Phase Ia and Ib. Phase Ia was the dose escalation study, with a "3+3" design. Patients received mitoxantrone hydrochloride liposome at three dose levels (16 mg/m^2, 20mg/m^2, 24mg/m^2, d1) in combination with irinotecan (50mg/m^2, d1-5) and vincristine (1.5mg/m^2, d1) every 3 weeks. Pharmacokinetic studies were conducted simultaneously. The primary endpoint of Phase Ia was the maximum tolerated dose (MTD). In phase Ib, patients received the combination therapy of mitoxantrone hydrochloride liposome at the MTD dose. The primary endpoint of Phase Ib was the incidence and severity of hematological adverse events. Secondary endpoints in both phases included objective response rate (ORR), pharmacokinetic (PK) parameters, and others. **Results:** From October 2022 to January 2024, a total of 51 pediatric patients with relapsed and refractory solid tumors were enrolled, 28 patients in Phase Ia and 23 patients in Phase Ib. The median age was 10.0 years (range: 3, 21). All Patients could be evaluated for toxicity and 40 for efficacy. The MTD of mitoxantrone hydrochloride liposome was determined to be 24mg/m^2. The results of pharmacokinetic analysis were not returned. Highest incidence of hematological and non-hematological adverse events (AEs) were anaemia (88.2%), diarrhea (84.3%). The newly found or aggravated TnIUtra, BNP value abnormality and lower LV function after medication were 4 (11.8%), 5 (14.3%) and 0 (0.0%), respectively. The overall ORR and DCR were 50.0% (95% CI: 33.8% - 66.2%) and 90.0% (95% CI: 76.3% -97.2%). 13 patients (25.0%) treated with mitoxantrone hydrochloride liposome combination regimen received the opportunity of surgery. **Conclusions:** The mitoxantrone hydrochloride liposome combination regimen has demonstrated an acceptable toxicity profile and promising clinical efficacy in pediatric patients with solid tumors, especially in sarcomas. Clinical trial information: NCT05620862. Research Sponsor: None.

10048 Poster Session

Clinical and molecular characteristics and targeted therapy of pediatric non-infantile fibrosarcoma NTRK rearrangement–related tumors.

Junting Huang, Mengjia Song, Suying Lu, Yu Zhang, Shan Wang, Yanpeng Wu, Ruiqing Cai, Juan Wang, Jia Zhu, Feifei Sun, Zijun Zhen, Yizhuo Zhang; Sun Yat-sen University Cancer Center, Guangzhou, China; Yuexiu District, Guangzhou, China; Sun Yat-sen University, Guangzhou, China; Children's hospital of Chongqing Medical University, Chongqing, China; The Fifth Affiliated Hospital, Guangzhou, China

Background: Neurotrophic tyrosine receptor kinase (NTRK) rearrangement is rare in tumors and relevant to targeted therapy. Pediatric NTRK rearrangement-related tumors have distinct clinical and molecular features compared to adults, and previous studies on pediatric NTRK rearrangement-related tumors has focused on infantile fibrosarcoma (IFS), the most common subtype. However, the clinical behaviors and molecular profiles of other subtypes of pediatric NTRK rearrangement-related tumors are largely unknown. **Methods:** In this study, we evaluated the molecular features, treatment response, and prognosis of 28 pediatric patients with non-IFS NTRK rearrangement-related tumors. Next-generation sequencing was performed in 21 patients to identify the NTRK fusion types and their co-occurring alterations, and pathway enrichment analysis was performed to explore the potential mechanisms involving NTRK rearrangement and resistance to tyrosine receptor kinase (TRK) inhibitors. **Results:** The NTRK fusion partners were diverse and tumor-specific. Several novel NTRK fusions were identified, including SNIP1-NTRK1, AGAP1-NTRK2, CRCT1-NTRK1, ZBTB7B-NTRK1, and SLC6A15-NTRK3. RTK-RAS, NOTCH, TP53, and WNT pathways were top 4 significantly enriched in tested samples. Twelve of 17 patients (70.6%) received TRK inhibitors as salvage treatment achieved complete or partial response. Patients who did not develop DDR, NOTCH, or TP53 pathway-related gene mutations had a high objective response rate of 82%, 82%, and 83%, respectively. **Conclusions:** Our findings may have important implications for the diagnosis and treatment of non-IFS NTRK fusion-positive tumors in pediatric patients. We also provide potential therapeutic targets for tumors resistant to TRK inhibitors. Clinical trials with TRK inhibitors, either alone or in combination, are required to establish the optimal treatment regimen and sequence in large-cohort pediatric patients with non-IFS NTRK rearrangement-related tumors. Clinical trial information: NCT05076071. Research Sponsor: None.

10049 Poster Session

Evaluating antitumor activity and response determinants to trastuzumab deruxtecan in pediatric solid tumors.

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Background: Trastuzumab deruxtecan (T-DXd) is an anti-HER2 antibody-drug conjugate (ADC) linked to a topoisomerase inhibitor FDA-approved for several indications, including the treatment of HER2+ breast and gastric cancer. Although HER2 amplification is uncommon in pediatric cancers, recent demonstration of T-DXd efficacy in HER2-low breast cancer patients prompted us to examine the potential clinical relevance of T-DXd in pediatrics by evaluating HER2 expression and activity of T-DXd in preclinical pediatric solid tumor models. **Methods:** Cell viability was assessed in a panel of histologically diverse pediatric solid tumor cell lines and 2 HER2-amplified adult cancer cell lines treated with T-DXd, payload (DXd), and a control IgG-ADC. HER2 protein expression in patient-derived xenograft (PDX) tumors was evaluated by immunohistochemistry (IHC) using 5 clinically validated anti-HER2 antibodies. RNAseq was performed on clinical (n=290) and PDX (n=184) tumors to determine relative expression of ERBB2. *In vivo* activity of T-DXd was evaluated in osteosarcoma (OS, n=10), Wilms tumor (WT, n=1) and malignant rhabdoid tumor (MRT, n=1) PDX models and a desmoplastic small round cell tumor (DSRCT) cell line xenograft model. Differences in tumor volume and time to disease progression was assessed and compared across treatments and models. Responses were correlated with HER2 expression by IHC. **Results:** *In vitro*, HER2-amplified control cell lines demonstrated a >30-fold reduction of IC50 when comparing T-DXd to ADC control. In contrast, the ADC control IC50 was nearly identical to T-DXd across all pediatric cancer cell lines, consistent with the absence of HER2 amplification in these models. We observed focal and membranous staining of HER2 by IHC in PDXs but was quite variable across antibodies tested: WT 0-17% HER2+ cases (n=6), MRT 0-40% (n=5), DSRCT 0-33% (n=24), OS 0-7% (n=30). ERBB2 gene expression was highest in DSRCT followed by WT, OS and MRT. *In vivo* efficacy studies demonstrated complete and partial responses in OS, WT, and DSRCT and improved disease control rates (OS: 67%, p=0.006, Mann-Whitney; WT: 100%; DSRCT: 100%). However, T-DXd and ADC control demonstrated similar activity in all tumor types with no consistent correlation between *in vivo* response and HER2 expression. Consistent with these preclinical studies, 4 patients with progressive DSRCT were treated with T-DXd via compassionate/off-label access with signs of clinical and radiographic responses. **Conclusions:** T-DXd shows significant preclinical antitumor activity across multiple pediatric solid tumors but little correlation with HER2 expression suggesting a mechanism of action similar to the clinical activity observed in HER2-low breast cancer. Xenograft efficacy studies and preliminary clinical experience with T-DXd in DSRCT patients warrant formal clinical trial investigation in this largely incurable disease. Research Sponsor: None.

10050 Poster Session

Clinical characteristics, prognosis, and immunotherapy outcome in pediatric melanoma: Analysis from a large Chinese cohort.

Juan Wang, Mengjia Song, Yingxia Lan, Junting Huang, Jia Zhu, Suying Lu, Feifei Sun, Zijun Zhen, Yi Que, Wanming Hu, Yu Zhang, Yizhuo Zhang; Yuexiu District, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen Univeresity Cancer Center, Guangzhou, China; Sun Yat-sen University, Guangzhou, China

Background: Malignant melanoma in children and adolescents is rare, with limited data on Chinese populations.To assess the clinical characteristics, survival, prognostic factors, and the efficacy of immunotherapy in a real-world cohort of Chinese pediatric patients with melanoma. **Methods:** This is a retrospective, cohort study included pediatric melanoma patients between February, 2005 and May, 2021, with a median follow-up time of 76.7 months. Data analyses were conducted in May, 2023. This study enrolled patients from Sun Yat-sen University Cancer Center, the biggest cancer institution in South China for cancer prevention, diagnosis and treatment. Inclusion criteria for this study were as follows: 1) histopathologically confirmed diagnosis of melanoma; 2) Age ≤18 year; 3) with complete clinical data on sex, age, histopathological features, etc. The exclusion criteria was secondary malignant melanoma. Main outcomes and measures were patient's OS and EFS. **Results:** 43 patients were enrolled, with median age of 138.9 (range 13.1-215.0) months, including 30 cutaneous melanoma, 7 meningeal melanoma, 5 mucosal melanoma, and 1 uveal melanoma. The frequency of BRAF V600E mutation was 16.7% (4/24). Mismatch repair proteins were normally expressed (7/7), and the positive rate of programmed cell death ligand 1 expression was 55.6% (5/9). The event-free survival and overall survival of cutaneous, mucosal and meningeal melanoma were 46.7±9.1% vs 75.0±21.7% vs 16.7±15.2% (P = 0.010), 65.5±8.9% vs 75.0±21.7% vs 16.7±15.2% (P< 0.001), respectively. Survival of cutaneous melanoma were associated with pathological type, ulceration, Clark level, disease spread, sentinel lymph node status, tumor stage and Ki-67 expression. 5 of 9 patients who were treated with PD-1 inhibitors (5 with PD-1 inhibitors alone, 3 with PD-1 inhibitors plus angiogenesis inhibitors, 1 with combination of anti-PD1, anti-angiogenic inhibitors plus chemotherapy) were evaluable with the overall response rate of 20%. The most common immune-related adverse event was hypothyroidism. **Conclusions:** This is the largest real-world study in pediatric melanoma patients in Asia. The prognosis of mucosal melanoma was favorable, followed by cutaneous melanoma, and meningeal melanoma had the worst prognosis. PD-1 antibody combined with angiogenesis inhibitors maybe a promising choice in pediatric melanoma. Research Sponsor: None.

10051 Poster Session

Pediatric cancer registry in Turkey 2002-2023: 22 years of achievement (TPOG & TPHD).

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Background: The survival rates for childhood cancer have seen significant improvements in high-income countries over the past few decades. However, in low- and middle-income countries, it remains a substantial challenge. Access to care remains a significant barrier to improving survival rates in low- and middle-income countries (LMICs). The pediatric cancer registry is a crucial component of pediatric cancer control efforts. In this context, we present the findings from 22 years of the pediatric cancer registry in Turkey. **Methods:** The present pediatric cancer registry was established by Turkish Pediatric Oncology Group and Turkish Pediatric Hematology Association in 2002. The childhood cancer cases registered between 2002-2023 was included in this analysis. International Childhood Cancer Classification System was used for the classification. Essential demographic findings, ICD-O-3 morphology and topography codes were recorded for each case. **Results:** During the 22 years from 2002 to 2023, 50887 cases were registered. For all cases, median age was 6.5 year (0-19; M/F 28641/22233, 6 hermaphrodite, 7 unknown). Age distribution was 0-4 yrs, 41.1%; 5-9 yrs, 24.7%; 10-14 yrs, 23.1%; 15-19 yrs, 11.0%) The distribution of the tumor types were [number of cases, percentage of total, median age yrs, M/F]: Leukemia (14633, 28.8%, 5.6, 8510/6123); Lymphoma & other RES tumors (8958, 17.6%, 9.2, 5956/3000, 2 unknown); CNS [brain & spinal] (7299, 14.3%, 7.0, 4066/3232, 1 unkown); Sympathetic system (3783, 7.4%, 2.4, 1951/1831, 1 hermaphrodite); Retinoblastoma (1444, 2.8%, 1.5, 752/692); Renal (2310, 4.5%, 3.1, 1140/1168, 1 hermaphrodite & 1 unknown); Liver (732, 1.4%, 2.1, 428/304); Malignant bone (3122, 6.1%, 12.5, 1747/1375); Soft tissue sarcomas (3675, 7.2%, 7.3, 2047/1628); Germ cell (2933, 5.8%, 8.9, 1077/1849, 4 hermaphrodite, 3 unknown); Carcinoma & other malignant epithelial (1628, 3.2%, 13.1, 783/845); Other/non-specific malignant (370, 0.7%, 7.8, 184/186). Five-year survival rate was found as 71.1%. **Conclusions:** The survival rates for children and adolescents have improved to 70%, a figure comparable to that of other middle-income countries and reflective of the quality of pediatric cancer care in Turkey. This represents a successful pediatric cancer registry from a middle-income country, covering a period of over 20 years. It has become a valuable resource for stakeholders at both the national and international levels. Research Sponsor: None.

10052 Poster Session

N9: Pilot study of novel shortened induction for high-risk neuroblastoma.

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Background: N9 induction for high-risk neuroblastoma was designed to limit non-hematological toxicity (especially ototoxicity) and to prevent relapse in the central nervous system (CNS). N9 builds on 2 novel regimens: high-dose cyclophosphamide-topotecan-vincristine (CTV) and ifosfamide-carboplatin-etoposide (ICE), each with good penetration across the blood-brain barrier. **Methods:** N9 is a pilot study (Clinicaltrials.gov.NCT04947501) to assess feasibility and safety. Secondary/exploratory objectives include response, collection of peripheral blood stem cells (PBSCs; $\geq 5x10^6$/kg CD34(+) cells sufficient for ≥ 2 rescues), tumor resection, and assessment of central nervous system relapse. Early stopping rules centered on excessive delay in timing of chemotherapy. Eligibility criteria included age >1-to-<13 years; 1 prior chemotherapy cycle was allowed. CTCAE Version 5.0 and International Neuroblastoma Response Criteria are used.N9 comprises 4 cycles of chemotherapy. Cycles start after absolute neutrophil count is >500/μL, platelets >100,000/μL, and non-hematologic toxicities grade ≤2. Intervals of 21-28 days between start of cycles are foreseen. PBSC collection and surgery follow >3 cycles. Cycles #1 and #4 (CTV): cyclophosphamide 70mg/kg/day, days 1-2, topotecan 2mg/m^2/day, days 1-4, and vincristine 0.067mg/kg, day 1. Cycle #2 (ICE): ifosfamide 1500mg/m^2/day, days 1-5, carboplatin 400mg/m^2/day, days 1-2, and etoposide 100mg/m^2/day, days 1-5. Cycle #3: cyclophosphamide (as in CTV) and 72-hr infusions of doxorubicin 75mg/m^2 and vincristine 0.067mg/kg. **Results:** The target number of 15 patients were enrolled: 10/2021-9/2023; age 1.5–9.8 (median 3.3) years; 14 stage M, 1 stage L2; and 10 post-1 cycle of other chemotherapy. They completed N9 without undue toxicity: all cycles started on time, organ functions remained intact, 11/11 patients tested had no ototoxicity, and acute toxicities were typical for myelosuppression (including uncomplicated fever/neutropenia). Responses were complete (n=6), partial (n=5), and stable disease (n=4). The target number of PBSCs was collected in 12 patients (9-75, median 14 x10^6/kg CD34(+) cells), 4x10^6/kg in 2 patients, and pending in 1. All patients had gross total resections of the primary tumor. Post-N9, patients did not undergo transplant, but proceeded to immunotherapy (naxitamab) or chemo-immunotherapy (naxitamab+irinotecan-temozolomide). Of 9 with residual disease post-N9, 7 achieved CR (median of 5.6 months from study entry) and 1 achieved metabolic CR (16 months), though 3 subsequently relapsed (no CNS). **Conclusions:** N9 shows promise for reducing chemotherapy and long-term toxicity. Less chemotherapy without compromising survival is a realistic goal by virtue of the advances with anti-G_{D2} monoclonal antibodies which, in combination with GM-CSF+low-dose chemotherapy, are highly effective against chemo-resistant disease in bone/bone marrow. Clinical trial information: NCT04947501. Research Sponsor: Memorial Sloan Kettering Cancer Center.

10053 Poster Session

Clinical application of individualized tumor-informed circulating tumor DNA for therapeutic response and relapse prediction in patients with neuroblastoma.

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Background: Patients with high-risk neuroblastoma (NB) generally present with widely metastatic disease and often relapse despite intensive therapy. At present, circulating tumor DNA (ctDNA)-based minimal residual disease (MRD) has been studied in various tumors and proven to be valuable in guiding treatment and predicting recurrence, but its application in NB has rarely been reported. This study aimed to assess the effectiveness of tumor-informed ctDNA monitoring for evaluating the response to induction therapy in NB patients, as well as its role in predicting the risk of relapse. **Methods:** We conducted a prospective cohort study of NB patients. Primary tumor samples were collected at baseline and blood samples were collected sequentially from baseline until disease progression or the last follow-up. Tumor tissue samples were subjected to whole exome sequencing (WES), and clonal mutations were selected for the individualized MRD panel. Sequencing was conducted at OrigiMed, a College of American Pathologists accredited and Clinical Laboratory Improvement Amendments certified laboratory. **Results:** Our cohort included 43 individuals diagnosed with NB, with a median age of 3.5 years (0.42-40 years). WES revealed that 75% (2054/2753) of the mutated genes were unique to each patient, and 98.9% (704/712) of the selected tumor-informed single nucleotide variants were variants of unknown significance, suggesting that individualized tumor-informed MRD (n = 23) is superior to fixed tumor-agnostic panel (n = 20) MRD in NB. A successful individualized MRD panel was constructed for 53.5% (23/43) of patients, with a remarkable 92.3% success rate for those older than 5 years ($p < 0.01$). The initial positivity rate for ctDNA detection was 68%, with the initial positivity rate being associated with the stage ($p < 0.01$). During treatment and follow-up, 0/6 of the patients whose ctDNA levels remained negative experienced a relapse, whereas 2/5 patients who had a negative conversion or an increase in positivity experienced a relapse. In addition, ctDNA changes matched radiological evaluations in 94% of patients. Notably, ctDNA was detected prior to radiological relapse, with a lead time of 6 months in one patient. Patients can be divided into four groups according to the mutation landscape: ALK mutation, MYCN amplification, chromosome amplification, and other groups. Among them, the rate of ctDNA clearance was the highest in the chromosome amplification group, indicating that patients in this group were the most sensitive to chemotherapy. **Conclusions:** Individualized tumor-informed ctDNA monitoring shows promise for evaluating therapeutic response and forecasting relapse in NB patients. This approach proves more effective than fixed tumor-agnostic panel-based MRD due to high genetic mutation uniqueness. Clinical trial information: NCT05076071. Research Sponsor: None.

10054 Poster Session

Overall survival prediction and risk stratification in patients with neuroblastoma through machine learning in the large multi-institutional PRIMAGE cohort.

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Background: Neuroblastoma (NB) is the most prevalent solid cancer in childhood in which imaging plays a pivotal role at every step of the patient's journey. This investigation aimed to develop a machine learning model using clinical, molecular (MycN amplification), and magnetic resonance (MR) radiomics features at diagnosis to predict patient's overall survival (OS) and improve their risk stratification. **Methods:** A database comprising clinical, molecular, and International Neuroblastoma Risk Group (INRG) staging on 513 patients with accessible MR imaging (discovery cohort) was employed for model training, validation, and testing. An additional 22 patients from non-discovery cohort hospitals served as an external validation group. Tumor segmentations of NB were manually and semi-automatically performed on corresponding T2-weighted MR images by an experienced radiologist. In total, 107 radiomics features were extracted and harmonized across MR scan manufacturers and magnetic field strengths using the nested ComBat methodology to correct both batch effects. These radiomics features, combined with clinical and molecular data, were utilized as input for the models. A nested cross-validation approach was employed for model development to determine the optimal preprocessing, machine learning algorithm, and model configuration. **Results:** The discovery cohort yielded a C-index of 0.788 ± 0.049 in the test partitions, with a random survival forest (RSF) exhibiting the best performance. In the validation cohort, a C-index of 0.934 was achieved. Interpretability analysis identified lesion heterogeneity, size, and molecular variables as crucial factors in OS prediction. The model demonstrated superior predictive performance and patient stratification compared to conventional staging systems in both cohorts. **Conclusions:** The RSF predictive model exhibited high performance, emphasizing the significant contribution of radiomics features and alignment with established clinical and molecular variables. The model stratified NB patients into low-, intermediate-, and high-risk categories and suggests that radiomics features potentially could improve current risk stratification systems. Additional external validation is warranted as this may present new evidence for enhancing patient care and clinical decision-making for NB patients. Research Sponsor: European Commission H2020 (H2020-SC1-DTH-2018-1 call).

10055 Poster Session

PP2A activation as a new therapeutic strategy in neuroblastoma: Making sense out of senescence.

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Background: Neuroblastoma (NBL) is the most common extracranial solid tumor in children, accounting for 15% of all pediatric cancer deaths. The five-year survival rate for children with high-risk disease is less than 50%, with the primary reasons for mortality being refractory and relapsed disease. One hypothesis for the poor response to therapy and propensity for recurrent disease in high-risk patients is treatment-induced senescence (TIS). Protein phosphatase 2A (PP2A) is a known tumor suppressor that is downregulated in NBL. PP2A activation has been shown to reverse cellular senescence in non-cancerous pathologies, therefore we hypothesized that reactivation of PP2A using novel small molecule activators would function as a novel senotherapeutic in NBL. **Methods:** We employed *MYCN*amplified, SK-N-BE(2), and non-amplified, SK-N-AS, established human NBL cell lines. Topotecan, a common NBL chemotherapeutic, known to induce senescence, and ATUX-1215, a small molecule PP2A activator, were utilized. NBL cells were treated with topotecan and ATUX-1215 alone, as well as in combination. Colorimetric assays detected cell viability and proliferation. Immunoblotting identified proteins of interest including γ-H2AX and CCL2. TIS was detected by S-β galactosidase (Sβgal) assay. **Results:** We found increased expression of the senescence marker, histone γ-H2AX, and increased Sβgal-positive tumor cells supporting the ability of topotecan to generate TIS in NBL. Following treatment with PP2A activator in combination with topotecan, markers of TIS are decreased in both *MYCN* amplified and non-amplified NBL cells. Further, and importantly, PP2A activation reversed the effects of topotecan TIS and acted in a synergistic fashion to decrease NBL cell viability. **Conclusions:** Activation of PP2A with a novel small molecule ameliorates topotecan-induced TIS in NBL cells irrespective of *MYCN* status. These results are promising, providing a potential novel therapeutic adjunct to children who are most in need of innovative interventions. Research Sponsor: U.S. National Institutes of Health.

10056 Poster Session

Real-world experience of larotrectinib in children, adolescents and young adults with TRK fusion solid tumors in France.

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Background: Larotrectinib is an FDA and EMA approved TRK inhibitor for TRK fusion solid tumors in patients with locally advanced or metastatic disease, or where surgical resection is likely to result in severe morbidity. Here we report the real-world activity and safety data on compassionate use and post-marketing authorization of larotrectinib collected in the SACHA-France study (NCT04477681), following the French Health Technology Assessment institution (HAS) request. **Methods:** All larotrectinib prescriptions made in France outside clinical trials since April 2019 for patients' < 25 years-old were registered in the SACHA-France study. Safety and activity data were collected, with data cut-off of 23/01/2024. SACHA-France is open in all 31 French Society of Pediatric Oncology (SFCE) centers, it is approved as a real-world data source by the HAS and supported by the French National Agency for the Safety of Medicines and Health Products (ANSM). **Results:** 21 patients were included (4 compassionate use, 17 post-marketing authorization). Main cancer types were soft-tissue sarcomas (n=13, of them 7 infantile fibrosarcoma), followed by central nervous system (CNS) tumors (n= 7), and other solid extra-CNS tumors (n=1). All patients except one had a TRK fusion tumor: *NTRK3* (n=10), *NTRK2* (n=6, all CNS tumor) and *NTRK1* (n=4). Median age at start of larotrectinib was 2.8 years (range: 0.2 -21.1). Ten patients had received no prior systemic therapy. Main reasons to start larotrectinib were to avoid mutilating surgery (n=9) and disease progression (n=9). Best objective response was reported as partial response in 13 out of 19 patients with evaluable disease (10/12 patients with soft tissue sarcomas, 2/6 patients with CNS tumors), with median time to response of 57 days. Of them, five patients with soft tissue sarcomas achieved a complete response after non mutilating surgery. Median treatment duration was 219 days (range: 10-1368, 5 patients still on therapy). Seven patients with soft tissue sarcomas stopped larotrectinib, after a median duration of 242 days (range: 122-1190), three of them after tumor surgery; none presented with tumor recurrence (follow-up: 350 days; range 40-636). At data cut-off, 8 patients had disease progression on-therapy (5/7 CNS tumors, 3/13 soft tissue sarcomas), with a NTRK resistance mutation identified in 2 out 3 patients with tumor biopsy. Adverse drug reaction (ADR) were reported in 2/21 patients (9%), including a grade 2 weight gain and a grade 3 neutrophil count decreased (1 patient each). Both ADRs were expected and required neither corrective treatment nor action on larotrectinib. **Conclusions:** Our real-world data confirm the favorable safety profile of larotrectinib with rapid and durable tumor-agnostic efficacy. Research Sponsor: Imagine for Margo; Association Hubert Gouin; Fondation du Leem; Bayer.

10057 Poster Session

The role of immune checkpoint blockade in children, adolescents, and young adults: A systematic review and meta-analysis.

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Background: Immune checkpoint blockade (ICB) has changed the treatment landscape for many types of adult cancer. However, while certain subsets of cancer in children, adolescents, and young adults (CAYA) are ICB-responsive, ICBs are less routinely used in clinical practice, thus clinical experience lags behind that of adults. Therefore, we performed a systematic review and meta-analysis to evaluate the safety and efficacy of ICB in the CAYA population. **Methods:** PubMed, Cochrane and Embase libraries were systematically searched for clinical trials evaluating ICB therapies for cancer in CAYA patients. We excluded reviews, case reports, observational studies, retrospective studies, studies with overlapping populations, trials with no outcomes of interest, and studies enrolling the adult populations (>40 years). We pooled the prevalence of treatment-related adverse events (TRAE), objective response rate (ORR), stable disease (SD), and their corresponding 95% confidence intervals (95% CI). For ORR and TRAE endpoints, we performed a subgroup analysis of each drug (PD-1, PD-L1 and CTLA-4) and each tumor type. A comparative analysis of the reported median overall survival (OS) and progression-free survival (PFS) was also completed. Statistical analysis was performed using R software version 4.3.1 and heterogeneity was evaluated through I^2 statistics. **Results:** From 3,753 initial studies, 15 clinical trials were included, comprising 797 patients with median age ranging from 6.5 to 16.0 years (1-30 years) and multiple types of hematologic and solid malignancies. An all-grade TRAE rate of 66% was found (95% CI 60-71), while the proportion of grade 3/4 TRAE was 19% (95% CI 13-27). In the tumor type subgroup analysis for all-grade TRAE and grade 3/4 TRAE, solid tumors had the highest rates; 92% (95% CI 41-99) and 50% (95% CI 14-42), respectively. Central nervous system tumors had all-grade and grade 3/4 TRAE rates of 61% (95% CI 53-68) and 21% (95% CI 12-33), respectively. Fatigue, anemia, and nausea were the most frequently reported TRAE. The ORR was 13% (95% CI 5-27) (82 of 531 patients). For drug class and tumor type subgroup analysis, PD-1 inhibitors and lymphoma presented the highest proportion of ORR, with 25% (95% CI 8-56) and 59% (95% CI 23-87), respectively. SD was noted in 21% (95% CI 14-30) of patients (97 of 467 patients). Median OS, available for 300 patients, ranged from 4.4 to 23.7 months, while median PFS, available for 299 patients, ranged from 1.2 to 6.2 months. **Conclusions:** This study suggests that ICB is well tolerated in CAYA patients with different cancer types. As previously reported in the literature, certain subsets of CAYA cancer are ICB-responsive. This pooled safety data supports the continued investigation of ICB in CAYA patients most likely to benefit from ICB therapy, including advancing ICB into combination strategies. Research Sponsor: None.

10058 Poster Session

Feasibility of tumor-informed circulating tumor DNA (ctDNA) for molecular residual disease (MRD) assessment in pediatric patients with solid tumors.

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Background: Circulating Tumor DNA (ctDNA) is a noninvasive biomarker which has been validated as a prognostic tool in multiple adult cancers. There is evolving evidence that ctDNA may be prognostic in pediatric solid tumors, but experience with commercially available assays in pediatric patients is scarce. Signatera is a ctDNA assay which utilizes whole exome sequencing of tumor and whole blood to identify 16 tumor-specific, clonal, somatic variants. These variants are then monitored in plasma as a molecular residual disease (MRD) assessment. **Methods:** From November 2021 through August 2023, 30 patients were enrolled on a single center study evaluating the feasibility and utility of Signatera MRD monitoring in pediatric patients with solid tumors. Patients 6 months to 25 years of age with any malignant extracranial solid tumor including lymphoma were eligible. Peripheral blood has been collected every 3 weeks to 3 months while on therapy and every 3 to 6 months while off therapy for up to 2 years. A minimum of 22mL of blood was required for the first draw, and 16mL for subsequent draws. Timing of blood draws was aligned with standard of care blood draws when possible. Results of ctDNA MRD were compared with imaging obtained for disease response and surveillance as standard of care. **Results:** The cohort consisted of 6 cases of neuroblastoma, 6 osteosarcomas, 4 Wilms tumors, 4 carcinomas, 3 soft tissue sarcomas, 2 Ewing sarcomas, 2 germ cell tumors, 2 lymphomas, and one hepatoblastoma. Of 30 patients enrolled, a tumor-informed ctDNA assay was successfully created for 27 (90%). Of 25 patients who had radiographic evidence of disease at any time of monitoring, 23 (92%) had simultaneous detectable ctDNA. Seven patients have had disease recurrence, of whom all seven had detectable ctDNA at or preceding time of recurrence. **Conclusions:** Signatera tumor-informed ctDNA assay is a feasible noninvasive tool which may be utilized in parallel with standard of care imaging to monitor for disease recurrence in pediatric patients with extracranial solid tumors. Additional analysis of a larger patient cohort is needed to identify tumor types and clinical scenarios for which its application is most useful. Research Sponsor: None.

10059 Poster Session

Intravitreal chemotherapy (IVC) in retinoblastoma: A study of clinical variables and ocular preservation outcomes.

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Background: Retinoblastoma, a primary intraocular malignancy, poses unique challenges in preserving life and vision. This retrospective study aims to analyze the impact of IVC in a population of retinoblastoma patients. The primary objective to avoid external radiotherapy, a recognized risk factor for second neoplasms, particularly in germline retinoblastoma cases. **Methods:** We conducted an analysis of retinoblastoma patients from 2011 to 2024. Clinical variables, including sex, age, laterality, intraocular retinoblastoma staging, and therapies employed, were prospectively documented. **Results:** The study included 59 patients (37 male; 22 female). Thirty-three percent of patients had unilateral tumors and an average age of 28 months at diagnosis, and 67% had bilateral tumors with an average age of 15 months. Sixty-one eyes were treated and classified at diagnosis as follow: 6 (9.8%) in groups A and B, 10(18%) in group C, 37(64%) in group D, 6(11%) in group E, and 2(3%) without initial information. IVC was administered as part of a multimodal treatment approach. A total of 203 cycles of IVC were performed, averaging 3.4 cycles per patient. Melphalan was used in 39% of cycles, followed by the combination of melphalan and topotecan in 35%, and topotecan alone in 26%. Seven of 61 (11.5%) were enucleated. Three of 61 eyes (4.9%) received radiotherapy. Control of vitreous seeds and vision preservation were achieved in 57/61 eyes (93%). No grade 3 or 4 adverse events occurred. **Conclusions:** IVC emerges as a crucial component in the management of retinoblastoma, offering a viable alternative to external radiotherapy. The analysis highlights the importance of this approach in preserving ocular integrity, thereby avoiding enucleation and reducing the risk of second neoplasms, particularly in germline retinoblastoma patients. Research Sponsor: TUCCA.

10060 Poster Session

Survival outcomes in patients with high-risk neuroblastoma (HRNB) in remission after relapsed or refractory treatment receiving eflornithine (DFMO) maintenance.

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Background: Five-year overall survival in newly diagnosed HRNB patients is around 50%, with relapse as the primary cause of mortality. While survival for newly diagnosed HRNB has improved with new treatment advances, relapsed or refractory (R/R) patients continue to have poor outcomes, with a high risk of subsequent relapse even among those who achieve remission, underscoring the need for treatments to improve EFS in this group. DFMO has been evaluated as a chemopreventative therapy in a single arm phase 2 study designed to compare Event Free Survival (EFS) and Overall Survival (OS) outcomes with published data for HRNB. The results of patients treated after standard therapy have been previously published. We now present an analysis of EFS/OS for patients with R/R disease, who historically have had a two-year EFS of approximately 10%. **Methods:** A total of 140 HRNB patients were enrolled, prospectively divided into two strata. S1 included patients in initial remission after upfront therapy, whereas S2 included patients who had either relapsed or had disease refractory to standard induction chemotherapy but achieved remission with additional therapy. Patients received 2 years of continuous treatment with oral DFMO 750 $\pm$250 mg/m^2 BID and were followed for up to 7 years. **Results:** A total of 35 patients withR/R disease who had achieved remission after additional therapy were enrolled onto S2, including 28 patients in remission after one or more prior relapses and 7 refractory patients in remission after subsequent therapies. Of the relapsed patients, 23 had one prior relapse, while 5 patients had two or more relapses prior to enrollment; only one previously relapsed patient had received chemoimmunotherapy prior to enrollment in the study. For the entireS2 cohort, two-year EFS was 46% (95% CI 29%, 61%) with the lower confidence interval above the 10% historical control estimate. Four-year EFS was 46% (95% CI 29%, 61%) and OS 62% (95% CI 44%, 76%), with no relapses occurring after 18 months. For patients enrolled with refractory disease only (n=7) the four-year EFS was 85.7%. In the 28 relapsed patients, the four-year EFS was 35.7%, with single relapse patients (n=23) having an EFS rate of 39.1% and multiple relapsed patients (n=5) 20.0%. **Conclusions:** Patients in remission after chemotherapy for relapsed or refractory HRNB and treated with DFMO had improved EFS compared to the best historical estimate available at the time of the study. Although the number of patients is too small to support clear conclusions, the subgroup of refractory patients had outcomes that trended better than the relapsed subgroup with an EFS rate that was unexpectedly similar to prior reports of DFMO-treated S1 patients in remission after standard upfront therapy. Clinical trial information: NCT02395666, NCT00026312. Research Sponsor: Beat Childhood Cancer Research Consortium; USWM, LLC.

10061 Poster Session

Biomarker development from functional precision medicine datasets via explainable machine learning.

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Background: Genomics precision medicine, deployed via tumor panel sequencing, now assists in deploying targeted therapies to cancer patients. Numerous clinical trials have investigated the utility and benefit of genomics precision medicine in multiple cancer indications. Current large-scale studies report actionability rates from ~35% to ~60%, although clinical benefit rates have been shown to be closer to 10%. While this has positively impacted patients in need, the gap between actionability and benefit remains a clinical challenge attributed to multiple factors including the complex, multi-factorial relationship between molecular status and response to therapy. These differences go beyond simple disease states and may be reflective of multiple clinically relevant features including age, sex, and race/ethnicity. **Methods:** We implemented a functional precision medicine (FPM) program where patients with advanced pediatric cancers were prospectively profiled via high-throughput drug sensitivity testing (DST) of FDA-approved agents on patient-derived tumor cells as well as genomics testing. The objective was to investigate the clinical utility and benefit of FPM guidance in the treatment of pediatric cancer and elucidate the relationship between molecular status of patients' diseases and treatment responses. We generated DST data (n = 21 patients) and genomic profiling data (n = 20 patients) on pediatric cancer patients in Miami, FL, as well as post-hoc whole exome and transcriptome sequencing data (n = 13 patients) and investigated three specific relationships. **Results:** We analyzed the relationship between racial/ethnic background and functional response to anti-cancer agents, determining potential differences in response to therapeutic classes. Next, we examined relationships between functional response and cancer type, identifying an unanticipated lack of clustering between disease indications in patients with advanced pediatric cancers. Finally, we applied an explainable machine learning (xML) framework to the functional genomic dataset to develop multi-omics biomarker hypotheses for the chemotherapy agent idarubicin, pinpointing a potential multi-cancer relationship between response to idarubicin and known disease mechanisms in acute myeloid leukemia (AML), the sole indication where idarubicin is approved. We further present additional proof-of-concept studies generating biomarker hypotheses via xML, demonstrating a framework for development of multi-omics biomarkers. **Conclusions:** We are now expanding our pan-pediatric cancer functional genomics dataset through an NIMHD-funded expansion cohort (NCT05857969, n = 65 patients) to further investigate multi-omics relationships between functional and molecular characteristics and understand the role of race/ethnicity in the complex relationship. Research Sponsor: NIMHD; U54MD012393; Florida Department of Health Live Like Bella Pediatric Cancer Research Initiative; 8LA05.

10062 Poster Session

Central pathological review and molecular classification of medulloblastoma in countries with limited resources: A commitment to equitable access.

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Background: Medulloblastoma, the most common malignant pediatric brain tumor, exhibits molecular heterogeneity influencing prognosis and treatment decisions. This study focuses on feasibility the pathological review and molecular classification with cost-effective methods. **Methods:** From December 2018 to November 2023, we analysed samples of patients referred to our laboratory. Data were collected on patient demographics (age, gender, origin), pathological review and specific medulloblastoma subtypes identified. The study was performed without costs for parents or institutions. **Results:** During the study period, 146 patients were included. The predominant age groups being 0 to 4 years (20.1%) and 5 to 9 years (36.1%) The mean age was 10.2 years. 55.6% of patients were female and 43.8% were male. Ninety-three patients were from Brazil and 7% from Latin America. Of the 117 samples that could be analyzed, 43% was classified as group 4, 37% were sonic hedgehog (SHH) group, 10% were group 3 and 4% were WNT group. Five percent of the samples had inconclusive results, with two patients had diagnoses other than medulloblastoma. Seventy percent of samples had a turnaround time for molecular classification results around 30 days. **Conclusions:** This study highlights the importance of central review pathology and molecular classification in medulloblastoma management. Our results emphasize the feasibility of centralized pathology review and molecular classification in countries with limited resources and provide equity for all patients. Based on this experience, we have expanded for other brain and pediatric tumors. Our effort contributes to ensuring that every patient benefits from the advancements in personalized medicine and this represents a real step to offer the same chances of cure for everyone. Research Sponsor: TUCCA.

10063 Poster Session

Effect of oncolytic herpes simplex virus on fusion-positive rhabdomyosarcoma to radiotherapy.

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Background: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children. Despite multimodal interventions including surgery, chemotherapy, and radiotherapy, nearly a third of patients with localized disease will experience tumor recurrence. Patients with tumors harboring an oncogenic *FOXO1* fusion are at greater risk of relapse and are most in need of novel therapies. Oncolytic viruses are being explored as treatments for pediatric tumors, and data suggest that oncolytic viruses may enhance responses to chemoradiotherapy. M002 is a genetically engineered oncolytic herpes simplex virus (oHSV) that exhibits aneurovirulence in normal cells. M002 selectively replicates in malignant cells, eliminating these cells through cellular burst during the lytic cycle. In the present study, we explored the efficacy of the M002 virus alone and in combination with low-dose ionizing radiotherapy in a human patient-derived xenograft (PDX) model of fusion-positive RMS (FP-RMS). **Methods:** A human FP-RMS PDX was established and maintained by injection into the quadriceps femoris muscle of athymic nude mice under Institutional Animal Care and Use Committee guidelines (IACUC-09363). Tumors were dissociated and cells were treated with increasing multiplicity of infection (MOI) of either the oHSV, R3659 or its genetically engineered variant, M002. A colorimetric assay evaluated the cytotoxicity of oHSV treatments on the RMS PDX cells after 24, 48, and 72 hours of infection. In separate experiments, cells treated with vehicle (control) or infected with M002 were exposed to irradiation (2 Gy), and viability was determined at 24, 48, 72, and 96 hours. **Results:** Treatment with M002 or its parent construct, R3659, significantly reduced RMS PDX cell viability in a dose-dependent manner at all time points. M002 showed slightly higher cytotoxicity than R3659 as measured by lethal dose 50% (LD50, 37 ± 1.25 vs 44 ± 0.95 PFU/cell, M002 vs R3659, at 24 hours, $p=0.02$). When sub-lethal doses of M002 were combined with low-dose irradiation, RMS PDX cell viability was significantly decreased compared to cells treated with either M002 or irradiation alone (26% decrease at 10 PFU/cell). **Conclusions:** Our pre-liminary data highlight that M002 exhibits cytotoxicity in a PDX model of FP-RMS. Treatment with M002 further increased the cytotoxicity of ionizing radiation compared to individual treatments, suggesting that oHSV sensitized the cells to radiotherapy. Future studies *in vivo* may provide more pre-clinical evidence for the radio-sensitizing and therapeutic potential of M002 in FP-RMS. Research Sponsor: National Pediatric Cancer Foundation.

10064 Poster Session

Evaluation of kidney function and body composition in adult survivors of unilateral, non-metastatic, non-syndromic Wilms tumor: A report from the St. Jude Lifetime Cohort Study.

Daniel M. Green, Kendrick Li, Sue C. Kaste, Kirsten K. Ness, Matthew J. Krasin, Lu Xie, Carmen L Wilson, Deo Kumar Srivastava, Andrew M. Davidoff, Rima S Zahr, Siddhant Taneja, Kyla C. Shelton, Jennifer Q. Lanctot, Stephanie B Dixon, Matthew J. Ehrhardt, Daniel A. Mulrooney, Chelsea Goodliffe Goodenough, Gregory T. Armstrong, Leslie L. Robison, Melissa M. Hudson; St. Jude Children's Research Hospital, Memphis, TN; Department of Pediatrics, University of Tennessee Health Sciences Center, Memphis, TN

Background: The relationships among treatment exposures, body composition and estimated glomerular filtration rate (eGFR) in adult survivors of childhood have not been well studied. **Methods:** We evaluated body composition with dual energy x-ray absorptiometry (DXA) and eGFR with the Kidney Disease International Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD) in 149 adults previously treated for non-syndromic, non-metastatic, unilateral Wilms tumor at St. Jude Children's Research Hospital between 1964 and 2004 with chemotherapy and with [(whole abdomen (WA) radiation therapy (RT) – 41 patients; median dose 12.5 Gray (Gy), Interquartile Range (IQR) 12.5 – 20.0 Gy); (hemiabdomen (HA) RT – 30 patients; median dose 12.0 Gy, IQR 10.8 – 20.1 Gy)] or without (78 patients) RT. z-scores for DXA variables were calculated using data from the National Health and Nutrition Survey (1). **Results:** The study population [56 males (37.6%), 109 whites (73.2%)] was a median of 3.1 years of age at diagnosis (IQR: 1.7-4.3) and 23.4 years at evaluation (IQR: 23.4-35.5). Relative total and relative trunk lean mass, and eGFR were significantly decreased among those who received WART compared to unirradiated patients. Linear regression demonstrated that WART was significantly associated with a lower eGFR (p = 0.012) and higher value of creatinine (p = 0.013). **Conclusions:** Relative total and relative trunk lean mass, and eGFR are decreased in survivors of unilateral, non-metastatic, non-syndromic WT following WART. Although eGFR was in the normal range, eGFR may be inaccurate due to loss of lean mass. Assessments using non-secreted molecules may more accurately measure the magnitude of kidney function loss among WART treated WT survivors. 1. PLoS ONE 2009; 4(9):e7038. Research Sponsor: None.

	z-score [mean (Standard Deviation)]			
	RTotLM	RALM	RTruLM	RTruFM
No RT	-0.27(1.10)	-0.44 (1.12)	0.07 (1.15)	0.16 (1.08)
HART	-0.42 (1.37)	-0.10 (1.29)	-0.57 (1.58)	-0.12 (1.41)
WART	-1.02 (1.57)*	-0.30 (1.40)	-1.73 (1.54)**	-0.60 (1.31)
	eGFR (ml/min/1.73m^2) [mean (standard deviation)]			
No RT	103.83 (16.75)			
HART	96.38 (17.72)			
WART	94.39 (17.54)***			

HART - hemiabdomen radiation therapy; WART - whole abdomen radiation therapy; RTotLM - relative total lean mass; RALM - relative appendicular lean mass; RTruLM - relative trunk lean mass; RTruFM - Relative trunk fat mass; *p = 0.018; **p < 0.001; ***p = 0.005 (WART vs None).

10065 Poster Session

Evaluating scholastic achievement in pediatric brain tumor survivors compared to healthy controls.

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Background: Radiotherapy (RT) causes cognitive deficits in pediatric brain tumor survivors (PBTS). This has traditionally been measured using exams such as serial IQ tests administered after diagnosis. Scholastic data provides pre-diagnostic measurements and is practical for patients and families. In our state, testing in reading and mathematics is mandated annually for grades 3-11. We sought to evaluate scholastic achievement in PBTS pre- and post-RT treatment. **Methods:** With IRB approval, we retrospectively analyzed scholastic achievement in children ($<$21) with primary brain tumors treated with RT at our institution. Eligible children all resided within the state of the institution and were treated 2007-2020. The state's Department of Education (DOE) provided test scores, school grades, and accommodations, which were matched to institutional clinical data. The other scholastic outcome of interest was Achievement Level (range 1-5 where 5 reflects highest achievement) from state-mandated standardized assessments in Mathematics and Reading, tested annually in grades 3-11. The DOE also provided scholastic data on healthy children matched 3:1 to treated patients by year, district, age, and whether the child was eligible for free or reduced lunch. A general linear mixed-effects model was performed with the above dependent variables and independent variables grade, time (a binary value being pre- or post-time of RT), and treatment (a child being treated or healthy). The interaction term of time*treatment was the outcome of interest, with α=0.1 for this pilot. Odds ratios (ORs) are reported. **Results:** A total of 200 students were available for analysis: 50 recruited patients and 150 matched controls identified by the DOE with median age 11.6 years at treatment and 7 years median follow-up. Fifty-two percent were eligible for free or reduced lunch. Fifty-six percent received craniospinal irradiation. Thirty-seven (60%) children had post-treatment scholastic data with 179 annual observations available. Of those, there were 10 (6%) physical education waivers, 32 (18%) testing accommodations, and 6 (3%) academic retentions. Compared to matched controls, treated patients were significantly more likely to receive accommodations (OR=31; p=0.001) and significantly less likely to receive a standard grade promotion (OR=0.57; p=0.005) or passing Mathematics scores (OR=0.47; p=0.05). **Conclusions:** We present the first reporting of scholastic data for United States PBTS. We demonstrate a novel method using existing state mandated school performance testing to evaluate academic performance in PBTS receiving RT. Compared to matched healthy children, we noted significantly increased needs and worse scholastic performance for PBTS. Evaluating scholastic success is an unmet need for PBTS, and we demonstrate the feasibility of using school performance as a novel patient-centered metric. Research Sponsor: None.

The dose-response relationship between cumulative alkylating agent exposure and sperm concentration in adult survivors of childhood cancer: A report from the St. Jude Lifetime (SJLIFE) cohort study.

Daniel M. Green, Kendrick Li, Raymond W. Ke, Angela Delaney, Christine Yu, Lu Xie, Deokumar Srivastava, Wiliam H Kutteh, Megan Elizabeth Ware, Kyla C. Shelton, Siddhant Taneja, Kirsten K. Ness, John Thomas Lucas, Gregory T. Armstrong, Leslie L. Robison, Melissa M. Hudson; St. Jude Children's Research Hospital, Memphis, TN; Fertility Associates of Memphis, Memphis, TN

Background: Male survivors of childhood cancer treated with alkylating agents (AA) are at risk for azoospermia; however, the long-term dose-response relationship is unknown. **Methods:** Of the 685 male SJLIFE participants treated with AA but no radiation therapy, 387 (56.5%) provided an evaluable semen sample (mean age at diagnosis: 8.3 years, mean age at evaluation: 28.6 years, and mean years from diagnosis to evaluation: 20.3 years). 73 had one or more subsequent semen analyses (median interval between semen analyses 5.4 years; interquartile range 4.2 – 6.6 years). Survivors were categorized as azoospermia, oligospermia (sperm concentration $>$ 0 and $<$ 15 million/ml), or normospermia (sperm concentration $\geq$ 15 million/ml). AA exposure was estimated using the cyclophosphamide equivalent dose (CED). Risks were estimated using the odds ratio (OR) and 95% confidence intervals (CI) from multinomial logistic regression analyses. **Results:** Among survivors 22.5% had azoospermia, 26.6% oligospermia, and 50.9% normospermia (Table). Motility and progressive motility were not associated with increasing CED categories among normospermic or oligospermic participants. Multinomial logistic regression including CED, age at diagnosis and at follow-up demonstrated that, for each 1,000 mg/m^2 increase in CED, the odds of azoospermia increased by 1.14 (95% CI 1.09, 1.20), and the odds of azoospermia and oligospermia increased by 1.22 (95% CI, 1.14, 1.30). Azoospermia and oligospermia were best distinguished from normospermia using a CED cutoff of 7,000 mg/m^2 based on the Youden Index. Nearly all participants initially identified with azoospermia (24 out of 25) maintained this diagnosis upon later evaluation. **Conclusions:** Nearly half of adult childhood cancer survivors who received alkylating agents without radiation therapy experience impaired sperm production, either low sperm count (oligospermia) or no sperm at all (azoospermia). The association increases with increasing CED. Recovery of spermatogenesis is unlikely among those who present azoospermic. CED = 7,000 mg/m^2 is the optimal cutoff for differentiating risk for oligo- or azoospermia from normospermia. Research Sponsor: None.

Outcome	Number	Cyclophosphamide Equivalent Dose (mg/m^2)				
		Mean	SD	Range	Median	Inter-Quartile Range
Azoospermia	87	11,194	7,368	1,000 – 41,308	9,644	6,315 – 11,375
Oligospermia	103	8,342	5,208	983 – 31,894	7,443	5,233 – 9,771
Normospermia	197	5,728	3,706	602 – 29,602	5,171	3,129 – 7,202

10067 Poster Session

AMH levels after initial cycles of chemotherapy in female adolescents with Ewing sarcoma and implications for preservation of fertility.

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Background: Anti-Müllerian hormone (AMH) has been recommended as the primary surveillance modality for evaluation of ovarian insufficiency in females. Patients with Ewing sarcoma receive VDC-IE chemotherapy which is estimated high risk of gonadotoxic injury. Previous studies have shown that only a small part of female patients with Ewing sarcoma show signs of ovarian recovery during long-term follow-up, similar to those treated with SCT or abdominal radiotherapy. Time to start preservation of fertility should be defined in this group of patients. **Methods:** In this observational study, we prospectively investigated AMH as a measure of ovarian function in female adolescents (less than 18 years old) with Ewing sarcoma who received initial chemotherapy in our hospital. Patients previously treated with systemic treatment were excluded. Serum levels of AMH were measured at the laboratory of Peking University People's Hospital. Blood samples were collected at the first day of the initial two cycles of VDC-IE treatment, before local therapy including surgical resection and radial radiation, and at the end of chemotherapy. All statistical analyses were performed using SPSS 19.0 version. **Results:** A total of 53 female adolescents with Ewing sarcoma who received initial chemotherapy in our hospital were analyzed from February 1, 2021 to December 31, 2023, including 35 patients aging from 6 to 12 (group 1), 18 patients aging from 12 to 18 (group 2). 255 blood samples from unique time points were measured. The baseline mean AMH were 4.16 (90% CI, 1.88 – 9.42) ng/mL in all patients, 3.58 (90% CI, 1.40 – 6.91) ng/mL for group1 and 5.28 (90% CI, 3.10 – 9.48) ng/mL for group 2. The mean AMH level after first cycle of chemotherapy was 0.43 (90% CI, 0.03 – 0.81) ng/mL in all patients, 0.40 (90% CI, 0.03 – 0.69) ng/mL and 0.47 (90% CI, 0.12 – 1.09) ng/mL for each group at a mean time of 16.5 days after initial chemotherapy. The mean AMH level before local therapy was 0.17 (90% CI, 0.03 – 0.37) ng/mL and 0.07 (90% CI, 0.01 – 0.32) ng/mL at the end of chemotherapy. **Conclusions:** Female adolescents with Ewing sarcoma treated by VDC-IE regimen showed a rapid reduction of AMH after initial cycles. Methods for preservation of fertility should be implemented as soon as possible but not at the same time of local therapy.
Research Sponsor: None.

Effects of cardiac radiation on sleep and psychological distress in adult survivors of pediatric Hodgkin lymphoma without breathing sleep disorders.

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Background: Adult survivors of childhood Hodgkin lymphoma (HL) are at higher risk for excessive sleepiness, fatigue, and other morbidities that affect long-term quality of life (QoL). The relationship between radiation dose to the heart delivered during treatment and self-reported sleep quality, fatigue, QoL, and psychological distress in survivors of HL has not been explored. This study examines clusters of cardiac dosimetry and sleep quality and associated symptoms of insomnia, fatigue, QoL, and psychological distress in a subset of adult survivors of pediatric HL without breathing sleep disorders. **Methods:** Survivors completed standardized surveys of sleep quality (Pittsburg Sleep Quality Index, PSQI), insomnia (Insomnia Severity Index), fatigue (FACIT-F), QoL (SF36 short survey), and psychological distress (BS18). Two consecutive nights of in-home polysomnography were completed with at least 4 hours of recorded sleep in one night. Analyses were conducted on 95 survivors (mean[SD] age=36[7.2] years, 55 female) who demonstrated at least average sleep efficiency (>85%) and demonstrated no evidence of sleep apnea (Apnea-Hypopnea Index <5, or AHI >5 and <15 with no daytime sleepiness as defined by the American Society of Sleep Medicine). Radiation dose to the heart was estimated using dose reconstruction methods for therapeutic radiation exposure developed by the MD Anderson Cancer Center. Radiation/Sleep clusters were found using a silhouette analysis and K-means algorithm. Linear regression associations between clusters and outcomes were adjusted by age and body mass index. Statistical analyses were computed in the statsmodels toolbox for Python3. **Results:** Sleep and radiation were not correlated (ρ=0.03, p=0.67). Considering good sleep as PSQI<5, three main Radiation/Sleep clusters were found indicating a low-radiation/middling-sleep group (22%; RT = 251[250.7] cGy, PSQI = 7[2.7]), a high- radiation/better-sleep group (46%; RT = 2012[406.8] cGy, PSQI = 4[1.5]), and a high-radiation/worst-sleep group (32%; RT = 2072[472.3] cGy, PSQI = 11[2.5]). Survivors in high-radiation/worst-sleep group demonstrated worse fatigue (β=-12.3, p=0.001) and insomnia (β=9.52, p<0.001). This group was associated with poor Mental Health (β=-2.1, p<0.001) but not Physical Health QoL (β=-0.4, p=0.154). This latter group also indicated more psychological distress (depression β=11.6, p=0.001, somatization β=11.8, p<0.001), but not anxiety (β=4.6, p=0.241). **Conclusions:** Our results highlight the burden of symptoms associated with higher radiation dosimetry in the heart including poor sleep quality, insomnia, fatigue, and increased psychological distress. Understanding the mechanisms of sleep quality and fatigue in HL survivors is warranted as some survivors demonstrate poor sleep quality and fatigue due to factors other than clinical sleep disorders. Research Sponsor: National Cancer Institute; CA215405 to KRK & BM; CA195547 to MMH and KKN; National Cancer Institute/U.S. National Institutes of Health; T32CA225590 to KRK; American Lebanese Syrian Associated Charities (ALSAC).

Mapping aging phenotypes in childhood cancer survivors: A report from the St. Jude Lifetime Cohort.

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Background: Childhood cancer survivors experience accelerated aging manifest as physical, cognitive and/or emotional impairments. Aging populations respond to behavioral interventions that address impairment combinations. We aimed to identify and characterize phenotypes (classes) of physical, cognitive and emotional impairments in childhood cancer survivors to inform targets for future intervention. **Methods:** Factor analysis using St. Jude Lifetime Cohort data (N=4051, 52.2% male, mean [SD] age at diagnosis 8.7 [5.7], assessment 33.9 [10.1] years) generated 9 impairment domains (Table) using 40 items from the Neurocognitive Questionnaire, Brief Symptom Inventory 18 and NHIS Health Status/Limitation of Activities. Latent class analysis estimated impairment patterns and class membership probabilities. Descriptive statistics characterized survivors by class for deficit accumulation index (DAI) score (range 0-1, >0.25 frail), Fried Frailty (FF) score (range 0-5, ≥3 frail), diagnosis and treatment exposures. Logistic regression comparing emotional or cognitive impairment class to the physical impairment class examined associations between survivor characteristics and class membership, adjusting for diagnosis and assessment ages, sex and race/ethnicity. **Results:** Three classes (phenotypes) differentiated survivors reporting only physical from those reporting both physical and cognitive or emotional impairments. Mean [SD] DAI (cognitive 0.40 [0.10], emotional 0.56 [0.16], physical 0.16 [0.11]) and FF scores (cognitive 1.5 [1.0], emotional 1.8 [1.0], physical 0.9 [0.9]) were highest in the emotional impairment class. Compared to solid tumor survivors (17.1%), brain tumor (33.7%, OR 3.5; 95% CI 2.7-4.4) and leukemia (21.7%, OR 1.5; 95% CI 1.2-1.8) survivors were more likely to be in the cognitive impairment class. Leukemia (OR 1.4; 95% CI 1.1-1.7) and lymphoma (OR 1.4; 95% CI 1.1-1.9) diagnoses increased risk for emotional impairment class membership. Cranial radiation was associated with cognitive (OR 1.8; 95% CI 1.5-2.2) or emotional (OR 1.3; 95% CI 1.1-1.6) impairment class membership. Chest radiation (1.4; 95% CI 1.2-1.7) was associated with emotional impairment class membership. **Conclusions:** These data provide foundational information for development and testing of targeted behavioral interventions to remediate accelerated aging in survivors. Research Sponsor: U.S. National Institutes of Health; U01CA195547; U.S. National Institutes of Health; P30CA021765; ALSAC.

Domain	Number Impaired	Physical + Cognitive Class N=849 Row %	Physical + Emotional Class N=625 Row %	Physical Only Class N=2577 Row %
Task efficiency	1048	62	36	2
Emotional regulation	1579	34	32	34
Organization	1112	43	30	28
Memory	1565	46	29	25
Depression	944	19	60	20
Somatization	688	14	62	24
Anxiety	600	2	83	16
Physical limitation	1053	32	32	36
Limited in instrumental activities of daily living	682	43	38	18

10070 Poster Session

Risk of low bone mineral density in young pediatric cancer survivors with sarcopenia.

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Background: Required treatments to cure pediatric cancer at such a young age increase the risk of later health-related complications. Early exposure to DNA damaging agents, during a vital period of active skeletal growth, interferes with accrual of bone mass. Treatments not only impair bone health, but also affect skeletal muscle function and mass. Long-term pediatric cancer survivors present these limitations due to myofibrillary atrophy caused by degradation of myosin heavy chain and decrease in myosin synthesis death. Muscle weakness (both muscle strength deficits and low lean mass hereafter referred to as sarcopenia) and low areal bone mineral density (aBMD) have been observed to coexist in adult survivors of paediatric cancer. However, in young pediatric cancers survivors, associations between sarcopenia and low aBMD are not well described. Therefore, this study aimed to examine the risk of low aBMD in young pediatric cancer survivors with sarcopenia confirmed/probable, compared to not having sarcopenia. **Methods:** This cross-sectional study included 116 pediatric cancer survivors (12.1±3.3 years old; 42% female) enrolled on a randomized controlled trial designed to improve bone health (iBoneFIT project). Handgrip strength was used to assessed muscle strength. Dual-energy X-ray absorptiometry estimated aBMD (g/cm^2) at the total body (less head), lumbar spine, total hip and femoral neck, and appendicular lean mass index (ALMI, kg/m^2). Sarcopenia status was determined using age and sex specific international reference data from a healthy population. "No sarcopenia" was defined when muscle strength was >decile 2. "Sarcopenia probable" was defined when muscle strength was ≤decile 2 and ALMI Z-score was > -1.5 standard deviation (SD). "Sarcopenia confirmed" was defined when muscle strength was ≤decile 2 and ALMI Z-score ≤-1.5 SD. Logistic regression, adjusted for time from treatment completion and radiation exposure, was used to evaluate the risk of low aBMD (age-, sex- and race-specific aBMD Z-score < -1.0) by sarcopenia status. **Results:** More than one-third of survivors met criteria for sarcopenia confirmed (37.9%); 19.0% met criteria for sarcopenia probable. Survivors with sarcopenia confirmed had higher risk of low aBMD at the total body (odd ratio [OR]: 6.91, 95% confidence interval [CI]: 2.31-24.15), total hip (OR: 2.98, 95% CI: 1.02-9.54) and femoral neck (OR: 4.72, 95% CI: 1.72-14.19) than those without sarcopenia. Survivors with sarcopenia probable had higher risk of having low aBMD only at the total body (OR: 4.13, 95% CI: 1.04-17.60) than those without sarcopenia. **Conclusions:** Over one-third of young paediatric cancer survivors presented sarcopenia confirmed with higher risk of low aBMD. These findings suggest that interventions to mitigate osteosarcopenia in this population should be implemented at early stages after treatment completion. Research Sponsor: None.

10071 Poster Session

Social support dynamics within parent-AYA cancer survivor dyads in a rural, socioeconomically disadvantaged, majority Hispanic/Latino region.

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Background: Childhood cancer survivors and their parents often face psychological, financial, and informational challenges as survivors transition to adolescent/young adult (AYA) age, which can be exacerbated by socioeconomic disparities. Social support can positively impact the trajectory of AYA survivors and their parents by facilitating post-traumatic growth and well-being and reducing psychological distress. The aim of this study was to examine social support dynamics within AYA-parent dyads by comparing their support needs and gaps. **Methods:** This qualitative study was conducted in collaboration with a community-based organization (CBO) serving a predominately socioeconomically disadvantaged, Hispanic/Latino (H/L), and rural population of families affected by childhood cancer in California. English- and Spanish-speaking AYA childhood cancer survivors (≥15 years old, ≥5 years from diagnosis) and parents were interviewed. Transcripts were analyzed qualitatively using applied thematic analysis. **Results:** Seven AYA-parent dyads (6 H/L) participated in the study. AYAs (6 male, 1 female) were median (min-max) age 19 (16-23) and 14 years post diagnosis (6-17). Parents (1 male, 6 female) were predominantly Spanish-speaking (5/7). Forms of social support fell into emotional, instrumental (i.e. tangible assistance such as financial help), and informational domains. Although family and faith were shared sources of emotional support for parents and AYAs, parents were more likely to discuss fractured family support structures and unmet emotional needs. In contrast AYAs universally identified their parents as consistent sources of emotional support. Parents also more commonly discussed gaps in instrumental support, which were exacerbated by being a single parent and lacking a local extended family network after immigrating to the United States. Parents were frequently the primary source of informational support for their children and AYAs often lacked knowledge regarding their cancer diagnosis and treatment course. Two AYAs expressed ambivalence about receiving more survivorship-focused information due to it bringing up negative emotions around fear of recurrence. Parents frequently expressed worry about their child's readiness to transition to adult care. **Conclusions:** Parents experienced gaps in emotional and instrumental social support that were not noted by AYAs, suggesting that parents protected their children from these experiences. Parents continued to serve as primary sources of informational support for AYAs even as they transitioned out of pediatric care. Our findings demonstrate the opportunity to build upon supportive parent-AYA relationships through dyad-focused education and counseling, which may improve readiness to transition to adult-focused survivorship care. Research Sponsor: Stanford Maternal and Child Health Research Institute.

10072 Poster Session

Factors associated with fertility status assessment among female survivors of childhood cancer.

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Background: Female survivors of childhood cancer with prior gonadotoxic treatment are at risk for infertility. As such, fertility status assessment (FSA) with ovarian reserve assessment and antral follicle count in consultation with a fertility specialist may be indicated to evaluate options for biological parenthood. FSA is underutilized in this population. This study explored psychosocial, developmental, and clinical factors associated with FSA. **Methods:** Female survivors (aged 18-29 years, diagnosis $<$ 21 years, $>$ 1 year from treatment completion, prior gonadotoxic treatment) were recruited from four cancer centers in the U.S. Participants reported sociodemographics (race, sexual orientation, gender identity, relationship status), developmental milestones (living and financial independence, full-time employment), reproductive concerns (modified Reproductive Concerns Scale), knowledge of reproductive health, decisional factors, and history of FSA. Clinical characteristics (cancer diagnosis, treatment-related risk for infertility, hormonal testing, clinical encounter with pediatric reproductive health subspecialist [gynecology, endocrinology]) were abstracted from the medical record. Multivariate logistic regression was performed to calculate odds ratios (OR) and 95% confidence intervals (95%CI) for factors associated with FSA. **Results:** Of 325 participants, N = 260 completed all survey items of interest. Participants were an average of 23.7$\pm$3.1 years, 74% non-Hispanic white, 79% heterosexual and cisgender, and 48% in a committed relationship. Compared with those without FSA (N = 164), participants who completed an FSA (N = 96) reported greater attainment of developmental milestones (OR 2.20, 95%CI: 1.10-3.85, p = .027), greater desire for reproductive information (OR 1.86, 95%CI: 1.2-2.77, p = .001), greater knowledge regarding fertility-related procedures (OR 4.12, 95%CI: 2.36-7.57, p $<$ .001) and fertility preservation (OR 1.76, 95%CI: 1.31-2.44, p $<$ .001), having made an informed decision to pursue FSA (OR 1.82, 95%CI: 1.30-2.59, p = .001), clinical encounter with pediatric reproductive subspecialist (OR 3.37, 95%CI: 1.1-10.9, p = .032), and less knowledge regarding family building options (OR 0.47, 95%CI 0.27-0.79, p = .006). Diagnosis, infertility risk, and hormonal evaluation were not associated with FSA completion. **Conclusions:** Among emerging adult survivors, psychosocial factors associated with FSA completion include developmental milestones and knowledge of reproductive health. Clinical encounters with pediatric reproductive subspecialists may provide an opportunity for survivors to learn about and receive referrals to a fertility clinic. Psychoeducation is warranted to support survivors' pursuit of FSA. Integration and consideration of survivor development and knowledge in these clinical encounters should potentiate optimal uptake of FSA. Research Sponsor: NIH/NINR; K23NR020037.

10073 Poster Session

Experiences of underrepresented adolescent and young adult (AYA) cancer survivors engaging in research-related activities.

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Background: Adolescent and young adult (AYA) cancer survivors are an age-defined cohort (15-39 years at diagnosis) confronting unique biopsychosocial needs throughout their cancer experience. Underrepresented (sexual and gender minority [SGM] and/or Black, Indigenous, and People of Color [BIPOC]) AYAs face additional challenges associated with discrimination, mistrust of providers, and culturally incongruent services. As a result, many underrepresented AYAs experience suboptimal oncological care and disparate outcomes when compared to cisgendered heterosexual and/or white peers. This study explored the experiences of underrepresented AYA cancer survivors engaging in research-related activities. **Methods:** This study is part of a larger Patient Centered Outcomes Research Institute (PCORI)-funded project that is evaluating multilevel facilitators and barriers to oncological care and research for underrepresented AYA cancer survivors. With support from five academic cancer centers and five community-based organizations supporting AYAs across the US, we have assembled an intersectional community advisory panel (CAP) of 10 AYAs who identify as BIPOC and/or SGM. Together with the CAP, a semistructured interview guide was developed, and from January to February 2024, we conducted video interviews. Data were analyzed using thematic analysis of verbatim transcribed interview scripts. The CAP assisted the investigative team in the analyses and interpretation of data. **Results:** Of the 20 participants interviewed, roughly 70% identified as BIPOC, 40% as SGM, and 10% as both BIPOC and SGM. Participants included underrepresented AYA cancer survivors who, prior to this specific study, had or had not participated in cancer-related research. Three major themes affecting underrepresented AYAs and engagement in research-related activities were discovered, and included: 1) Layering of identities, culture, and stigma; 2) The role of trusted conduits in facilitating engagement; and 3) Beyond compensation: reasons of pursuance. **Conclusions:** The resultant themes illuminate multilevel facilitators and barriers to research engagement among underrepresented AYA cancer survivors. Findings will assist in guiding researchers, oncology care providers and program administrators both in academic and community settings in the design of inclusive and equitable cancer care delivery programs for underrepresented AYA cancer survivors. Research Sponsor: Patient-Centered Outcomes Research Institute (PCORI); EACB-26540.

10074 Poster Session

The effects of oral nutritional supplements on functional outcomes and body composition in patients with solid cancer undergoing systemic chemotherapy: A pilot study.

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Background: Cancer cachexia is a complex syndrome characterized by significant weight loss and depletion of skeletal muscle mass. Despite its profound impact on the well-being of cancer patients, the effective management of cancer cachexia remains a challenging and underexplored aspect of oncology. This study aims to investigate the potential benefits of oral nutritional supplements (ONS) to cancer patients undergoing chemotherapy. **Methods:** This is single-arm, prospective pilot study. Patients with cancer cachexia undergoing chemotherapy were included. Patients received ONS twice a day for 8 weeks. The ONS contained 200 kcal, 22.5 gram of carbohydrates, 7.5 gram of fat, and 12.5 gram of protein per 200 mL. Primary endpoints were improvements of lean body mass and physical performance. The secondary endpoints were changes of health-care related quality-of-life (HRQoL), nutritional status, and gut microbiomes profiles. EORTC-QLQ-C30 questionnaire, body composition analysis, 4-meter-walk test, hand grip strength test, and fecal microbiome analysis were conducted at baseline and after 8 weeks. The bacterial 16S rRNA gene (V3 and V4 region) was amplified using PCR and sequenced on the Illumina MiSeq platform. The QIIME 2 pipelines were used to analyze the raw data. **Results:** From January 2023 to October 2023, total of 10 patients were included. There were no significant differences of the mean daily energy intake (p=0.62) and calf-circumferences (p=0.2) between baseline and after 8 weeks. However, participants exhibited a statistically significant improvement in hand-grip strength (p=0.002) and 4-meter walk test (p=0.021) after 8 weeks. In the body composition analysis using dual-energy X-ray absorptiometry, no differences were observed in body weight (p=0.43), fat mass (p=0.62), fat-free mass (p=0.27), and fat-free mass index (p=0.38). Also, no significant differences were detected in the results of HRQoL survey (p=0.85). In the microbiome analysis, no differences of microbiome composition at phylum and genus levels, α-diversity, and β-diversity were observed between baseline and after 8 weeks. **Conclusions:** While ONS have shown potential in enhancing physical functions of patients with cancer cachexia undergoing chemotherapy, this did not correlate with the anticipated microbiome changes or improvements in body composition. The absence of expected microbiome alterations, despite enriched protein and dietary fiber, underscores the complexity of cachexia and indicates that its management may extend beyond nutritional supplementation alone. Further research should explore the broader context of cachexia, including nutrition, metabolic processes, and the impact of chemotherapy. Research Sponsor: None.

10075 Poster Session

Cost-effectiveness of single-day intravenous fosaprepitant versus three-day oral aprepitant anti-emetic regimen in pediatric patients receiving highly-emetogenic chemotherapy.

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Background: The non-inferiority of single-dose fosaprepitant to a three-day oral aprepitant-based anti-emetic regimen for pediatric patients receiving high emetogenic chemotherapy (HEC) has not been demonstrated. The cost-effectiveness of these regimens with respect to each other in India and the United States (US) is unknown. **Methods:** Individual patient data from an investigator-initiated, open-label, non-inferiority randomized control trial was used to estimate health states. The total costs and quality-adjusted life years (QALY) were calculated from the patient's perspective in India and the US. The incremental-cost utility ratio (ICUR) and net-monetary benefit (NMB) were calculated. One-way sensitivity analysis was done by varying the cost of medications, hospitalization and utility values by ±25%. **Results:** The fosaprepitant arm had a total QALY of 0.0116 compared to 0.0118 in the aprepitant arm. The use of fosaprepitant led to an incremental cost of $14.21 in India and a cost reduction of $193.81 in the US. The total cost of medication in the fosaprepitant arm was higher in India and lower in the US compared to the aprepitant arm. The cost of hospitalisation was lower in the fosaprepitant in both India and the US. The ICUR was -$59,974.86/QALY in India and $817,737.23/QALY in the US. The ICUR for India was located in the north-west quadrant of the cost-effectiveness plane, for the US it was located in the south-west quadrant below the willingness the pay threshold for the US. The ICUR estimate was most sensitive to the cost of fosaprepitant in India and the utility value of the complete protection health state in the US. **Conclusions:** Fosaprepitant was not found to be cost-effective versus aprepitant in India, comparatively it was cost-saving and cost-effective in the US. These findings highlight the necessity of region-specific considerations when evaluating the cost-effectiveness of anti-emetic regimens. Research Sponsor: None.

Cost comparison and economic outcomes in India and the United States.

	India			United States		
Parameter	**Fosaprepitant Arm**	**Aprepitant Arm**	**Difference***	**Fosaprepitant Arm**	**Aprepitant Arm**	**Difference***
Average Cost of Fosaprepitant (USD)	29.56	0	29.56	42.56	0	42.56
Average Cost of Aprepitant (USD)	0	14.54	-14.54	0	88.17	-88.17
Average Cost of Ondansetron (USD)	2.17	2.19	-0.02	483.49	489.09	-5.6
Average Cost of Dexamethasone (USD)	1.83	1.85	-0.02	19.33	19.55	-0.22
Average Cost of Rescue Medication (USD)	0.01	0.01	0	0.11	0.1	0
Average Cost of Hospitalisation (USD)	0.38	1.14	-0.76	70.43	212.82	-142.38
Average Total Cost (USD)	33.94	19.73	14.21	615.92	809.73	-193.81
ICUR (USD/QALY)		-59,974.86			817,737.23	
NMB (USD)		-15.59			179.12	

ICUR: Incremental Cost-Utility Ratio; NMB: Net Monetary Benefit; USD: United States Dollars.
*Differences have been rounded to two decimal places so may not be exact.

10076 Poster Session

Personal symptom ecosystem predicts progression of chronic health conditions (CHCs) in adult survivors of childhood cancer: A report from the St. Jude Lifetime Cohort study (SJLIFE).

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Background: Survivors of childhood cancer experience a range of interconnected symptoms, forming a personal symptom ecosystem with unique structures and dynamics. Unlike prior research analyzing the main effect of each symptom, we created *personal symptom networks* to predict the onset/worsening of CHCs for cancer survivors. **Methods:** We analyzed data collected from 2007-2020 among 4044 adult survivors of childhood cancer enrolled in SJLIFE. At baseline and follow-up (FU), individual CHCs were clinically assessed, severity-graded (CTCAE), and classified into organ-based groups: cardiac, pulmonary, musculoskeletal and neurological. Progression of CHCs from baseline to FU was defined as onset (grade 0-1 to grade 2-4) or worsening (grade 2 to 3-4; grade 3 to 4). Baseline symptoms in 9 domains (cardiac, pulmonary, sensation, nausea, movement, pain, fatigue, anxiety, depression) and personal factors (age, sex, education, smoking) were self-reported; neighborhood adversity was assessed by the Social Vulnerability Index (SVI); treatment data were sourced from medical records. The Ising model incorporating personal/treatment/SVI factors as covariates was used to develop personal symptom ecosystems. The effect of symptoms on the CHC progression included both the influence of a symptom domain (mean main effect) and its interaction with other symptom domains (ecosystem effect). These effects were examined using LASSO regularized logistic regressions on the progression of CHC groups. **Results:** The mean age of survivors at baseline was 30.3±8.6 years, 52.2% were male; the mean years from baseline to FU were 4.3±1.7. Survivors with lower education, smoking, and living in poorer neighborhoods reported interconnected pain-depression (effect size [ES] 0.35), anxiety-fatigue (ES 0.57), and cardiac-fatigue (ES 0.35) symptom domains. Symptom domains significantly impacting the progression of CHC groups were cardiac symptoms on the pulmonary (OR 1.2) and neurological CHC groups (OR 1.5); movement symptoms on the musculoskeletal (OR 1.4) and neurological CHC groups (OR 1.7); pain (OR 2.4) and fatigue (OR 1.8) on the neurological CHC group. Significant ecosystem effects of symptom domains impacting the progression of CHC groups were pain on the cardiac CHC group (OR 1.2); pulmonary symptoms on the pulmonary CHC group (OR 1.2); cardiac symptoms on the musculoskeletal CHC group (OR 1.4). The 95% confidence intervals were omitted since LASSO does not estimate standard deviation for variables identified as significant. **Conclusions:** The symptom network approach shows promising ecosystem effects of individual symptom domains beyond its main effects on CHC progression. This study improves our understanding of dynamic, interconnected symptoms underlying CHC progression, and highlights avenues for future intervention research. Research Sponsor: National Cancer Institute; R01CA238368; National Cancer Institute; R01CA258193; National Cancer Institute; U01CA195547.

TPS10077 Poster Session

TAZNI: A phase I/II combination trial of tazemetostat with nivolumab and ipilimumab for children with INI1-negative or SMARCA4-deficient tumors.

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Background: The prognosis for children with INI1-negative cancers is dismal, with historic 5-year overall survival <30%. These cancers (including malignant rhabdoid tumors [MRT], atypical teratoid rhabdoid tumors [ATRT], epithelioid sarcomas [ES], and poorly differentiated chordomas) have few novel treatment options. These tumors exhibit a heightened dependence on the Polycomb Repressive Complex, whereby EZH2 is the catalytic subunit. Two recent pediatric phase 1/2 trials with EZH2 inhibitor tazemetostat (EZH-102, NCT02601937 and APEC1621C, NCT03213665) demonstrated 17% overall objective response rate, with 19% response in ATRT patients and higher response rates in patients with chordoma and ES. One patient had PR on the phase 2 Pediatric MATCH study and 5 patients had prolonged SD. Studies of INI1-deficient tumors have shown significant immune infiltration, including T-cells with high levels of inhibitory checkpoint receptors. As EZH2 has a role in tumor immunity and tazemetostat increases MHC presentation and immune signaling, we hypothesized that combining EZH2 inhibitor with checkpoint inhibitors may provide benefit for pediatric patients with INI1- or SMARCA4-deficient tumors. **Methods:** TAZNI is a phase 1/2, multi-center trial of Tazemetostat, Nivolumab and Ipilimumab for children with INI1- or SMARCA4-deficient tumors after upfront therapy. All patients receive standard pediatric nivolumab and ipilimumab doses/dosing schedule with continuous tazemetostat dosing determined by disease strata: Stratum A- subjects with ATRT; Stratum B for all other (non-ATRT) INI1/SMARCA4-deficient tumors. Each stratum is subdivided by disease status: A1/B1- subjects with refractory disease after upfront therapy; A2/B2- subjects with relapsed disease; and A3/B3: subjects with no evidence of disease (NED) after upfront therapy. The study is conducted in 2 parts: Part 1 will be two concurrent "rolling six" phase 1 studies to identify the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) by disease stratum. Starting dose level 1 for Stratum A is 900mg/m^2 orally BID and for Stratum B: 520mg/m^2 orally BID, with one dose escalation and one dose de-escalation planned. Part 2 will be two phase 2 studies to estimate the overall response rate (ORR) in Substrata A1 and A2 (with refractory disease or with relapse, respectively), based on a primary endpoint of ORR (CR+PR) in a Simon's 2-stage design at the RP2D. All other substrata will be descriptive analyses. Patients may receive up to 26 cycles of therapy. Key inclusion/exclusion criteria include INI1 loss by immunohistochemistry (IHC) or molecular confirmation; age between 6 mo and 21 yo; no prior immunotherapy; limited corticosteroid; and no history or concern for hematologic malignancy. To date, 4 patients have enrolled, and the study is ongoing in the United States. Clinical trial information: NCT05407441. Research Sponsor: None.

TPS10078 **Poster Session**

Impact of molecular therapy on radioactive iodine uptake in patients with oncogene-driven metastatic differentiated thyroid cancer.

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Background: Targetable kinase fusions and mutations are common in pediatric and young adult patients with papillary thyroid cancer (TC) and are associated with metastatic disease and lack of response to radioactive iodine therapy (RAI). While survival outcomes are excellent, less than 20% of children with metastatic TC achieve a complete response to standard treatment with surgery and radioactive iodine (RAI). Thus, repeated RAI therapy is common, increasing the risk of pulmonary fibrosis and secondary malignancies. Targeted kinase inhibitors are highly effective at shrinking oncogene-driven TC. Preliminary data suggest that these targeted therapies can improve tumor differentiation and RAI sensitivity. However, optimal integration of targeted therapy with standard of care RAI for TC remains uncertain. The objective of this study is to evaluate if targeted inhibitors in patients with metastatic, oncogene-driven differentiated TC will improve or restore tumor RAI uptake and ultimately induce durable clinical responses in patients with metastatic differentiated TC. **Methods:** Patients with TC lung metastases, both RAI naïve and refractory, with an identified targetable molecular driver (Table) and intent to start oncogene-specific targeted therapy are eligible for this study. Patients who received a prior oncogene-specific targeted therapy are excluded. A RAI-whole body scan (WBS) is performed at baseline and after 4 weeks of targeted therapy. Patients will be followed for up to 5 years to monitor clinical response. Response parameters include structural (CT, WBS, and/or neck US) and biochemical (thyroglobulin, thyroglobulin antibodies) evaluation. The primary endpoint is the change in RAI avidity between baseline and 4 weeks of treatment. This will be calculated as the ratio of RAI uptake in the lungs/disease sites versus the whole body for each subject at each time point. Secondary endpoints include progression free survival and the proportion of patients who achieve a complete response to the combination of targeted therapy and RAI. Five of 32 patients have been enrolled. Clinical trial information: NCT05024929. Research Sponsor: National Institute of General Medical Sciences of the National Institutes of Health; TW Laetsch receives funding from the US Department of Defense, Grant Number W81XWH2210654.

Example selection of oncogene drivers and targeted inhibitors.

Mutation	Inhibitor
***NTRK* fusion**	Larotrectinib, entrectinib, and repotrectinib
***RET* fusion**	Selpercatinib and pralsetinib
***ALK* fusion**	Crizotinib, lorlatinib, entrectinib, repotrectinib, and alectinib
***BRAF* V600E**	Dabrafenib with or without trametinib

TPS10079 Poster Session

A multicohort platform trial to improve drug access for pediatric cancer patients in Japan: The PARTNER trial (NCCH2220).

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Background: In Japan, there are no pediatric regulations that encourage drug development for pediatric cancer, such as Pediatric Investigation Plans (PIPs) which are mandated in Europe, or the RACE Act in the U.S. Therefore, there are fewer early-phase clinical trials and approved drugs for pediatric cancer than in Western countries. In addition, because there is no rapid compassionate use program, there are delays when using an unapproved drug. According to a report from the Japanese cancer genome profiling (CGP) testing data center, C-CAT, 51.3% of pediatric patients with solid tumors had targetable genetic abnormalities. However, only 5.8% of them had access to the recommended molecular targeted therapy (Tanimura K. et al., presented at the Japanese Society of Pediatric Hematology and Oncology annual meeting 2022). Thus, Japanese pediatric patients with relapsed or refractory solid tumors have limited access to novel drugs, even if they have druggable mutations. Therefore, we designed a platform study (NCCH2220, PARTNER trial) to rapidly deliver molecularly targeted drugs based on CGP testing. **Methods:** This study has two objectives: first, to administer some drugs to pediatric patients that are not approved for pediatric cancer in Japan. These drugs have been shown to be safe in pediatric patients in foreign countries and are expected to be effective. Second, to evaluate the safety and efficacy of the drug in Japanese pediatric patients and, if necessary, its pharmacokinetics. These data will be used for potential future regulatory filings. This is an open-label, multicenter, multicohort study. Eligible patients are aged 0–29 years with diseases having no standard therapy, which are refractory, or when there is intolerance to standard therapy. The study drug must be recommended for the patient by CGP testing or approved for pediatric use for their disease in the U.S. or Europe, or approved in Japan for use in adults only. The drugs are used as monotherapy in the study. The study schedules follow a master protocol. Up to 30 patients can be enrolled in each cohort. The primary endpoint is the incidence of dose-limiting toxicity in each cohort. The secondary endpoints are the incidence of adverse events, the overall response rate, and, if necessary, the pharmacokinetics in each cohort. As of January 2024, the study had five treatment cohorts with the following agents: imatinib, pazopanib, ruxolitinib, trametinib, and atezolizumab. Additional cohorts will be added. We started planning the study in November 2022, and enrollment began on January 18, 2024. This platform trial has enabled us to deliver drugs to patients more quickly and efficiently than by conducting individual early-phase trials for each drug. Clinical trial information: jRCTs031230544. Research Sponsor: None.