

Tisagenlecleucel (tisa-cel) in pediatric and young adult patients with high-risk (HR) B-cell acute lymphoblastic leukemia (B-ALL) and minimal residual disease (MRD) at the end of frontline consolidation (EOC).

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Background: Persistent MRD portends a high risk of relapse in B-ALL. In the Children's Oncology Group (COG) AALL0232 frontline trial for HR B-ALL, children and young adults with MRD $\geq 0.01\%$ at the EOC had poor 5 y disease-free survival (DFS) of 39% (Borowitz, *Blood*, 2015). We report the primary analysis of a phase 2 trial, in collaboration with COG, of tisa-cel, a CD19-directed chimeric antigen receptor (CAR) T cell therapy, in this very high-risk (VHR) population. **Methods:** COG AALL1721/CASSIOPEIA (NCT03876769) is a global (34 sites in the US/Canada, 10 sites in EU/UK) phase 2 study of tisa-cel in patients (pts) aged 1-25 y with National Cancer Institute HR B-ALL and persistent MRD $\geq 0.01\%$ by flow cytometry at EOC. A single dose of tisa-cel ($0.2-5 \times 10^6$ CAR+ T cells/kg for pts ≤ 50 kg or $0.1-2.5 \times 10^8$ CAR+ T cells for pts > 50 kg) was given after standard lymphodepleting chemotherapy. Reinfusion was available for pts with B-cell recovery within 6 mo and/or MRD $\geq 0.01\%$ at any time. Primary endpoints were 4 y overall survival (OS) and 5 y DFS, defined as time from first infusion to morphologic relapse, secondary malignancy, or death, without censoring for new anticancer therapy, including stem cell transplant (SCT). Secondary endpoints included DFS with censoring, MRD negative rate (MRD $< 0.01\%$) at 3 mo, and safety. **Results:** The primary analysis included 121 infused pts; 1 pt was not infused due to adverse event. Median age was 14 y (range: 1-24 y), 67% were male, 6% had trisomy 21. As of August 20, 2025, median time from infusion to last follow-up was 38 mo. OS at 4 y was 85% (95% CI: 76-90%). DFS (95% CI) at 3 y and 5 y without censoring for new therapy was 71% (61-79%) and 64% (53-73%). DFS (95% CI) at 3 y and 5 y with censoring was 69% (55-79%) and 62% (46-74%). MRD negative rate at day 29 and 3 mo post infusion was 95% and 86%. Relapse occurred in 31 pts, of which 7 occurred after new therapy/SCT. 41 (34%) pts received a second infusion. 58 (48%) pts received new anticancer therapy/SCT without prior relapse. Median duration of B-cell aplasia was 5.6 mo. Probability (95% CI) of ongoing remission and B-cell aplasia at 3, 6, and 12 mo was 76% (67-83%), 47% (38-56%), and 31% (23-41%). Following first infusion, cytokine release syndrome (CRS) occurred in 37% (grade ≥ 3 , 2%), immune effector cell-associated neurotoxicity syndrome (ICANS) in 3% (grade ≥ 3 , 1%). There were 18 deaths, all post new therapy/SCT and/or relapse. **Conclusions:** Durable remissions, with very low rates of severe CRS/ICANS, were achieved with tisa-cel in a VHR population with persistent MRD in frontline therapy, who historically have low 5 y DFS. Nearly 50% of pts received new anticancer therapy, including SCT, without prior relapse. Longer follow-up is needed to confirm 5 y DFS. Clinical trial information: NCT03876769. Research Sponsor: Novartis Pharmaceuticals.

SPARTO: A phase I study of PD-1 inhibitor spartalizumab (PDR001) in combination with low dose of pazopanib in pediatric relapsed/refractory tumors.

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Background: The initial results of immunotherapy in children with refractory/relapsed tumors have been disappointing. Modulation of angiogenesis with anti-VEGF may enhance immunotherapy penetration and promote lymphocytes T infiltration. In this context, we propose combining immunotherapy with low doses of pazopanib to enhance therapeutic efficacy in pediatric patients. **Methods:** Pediatric part of the SPARTO trial (NCT05210413) was a multi-center, open-label, dose-finding phase I clinical trial conducted in France. Pediatric patients with recurrent/refractory solid tumors were eligible to receive pazopanib at a fixed low dose of 225 mg/m²/d combined to anti-PD1 spartalizumab at three candidate doses (2, 3, 4 mg/kg/q4w). Dose-finding was guided by Bayesian Optimal Interval design based on dose-limiting toxicities (DLTs) in cycle 1, with a target toxicity level of 25%. Recommended phase 2 dose (RP2D) was determined on the basis of DLTs and blood exposure of pazopanib and spartalizumab. Toxicities were evaluated using CTCAE v5.0 and responses were evaluated by clinical and radiologic assessment (RECIST1.1 or RANO for brain tumors). **Results:** From May 2022 to June 2025, 41 patients were enrolled at 8 sites (median age: 13.9y; range: 7-25). Among 39 evaluable patients, 4 DLTs occurred in 1/9 patients at 2 mg/kg of spartalizumab (DL0), 1/6 patients at 3 mg/kg (DL1) and 2/24 patients at 4 mg/kg (DL2). Three patients experienced macrophagic activation syndrome (grade 3 at DL0 and DL2, grade 4 at DL1) and one patient experienced liver enzymes increase grade > 3 at DL2. A total of 58 grade 3-4 adverse events were reported in 26 patients, predominantly hepatic and hematologic toxicities. Median area under the serum concentration-time of spartalizumab from 0 to 28 days post-infusion at cycle 1, were 12.9 g.h/L (IQR 10.7-15.8), 17.2 g.h/L (IQR 15.5-20.0) and 19.5 g.h/L (IQR 16.9-23.6), respectively for DL0, DL1 and DL2. Median trough concentration of pazopanib was 23.1 mg/L (IQR 15.8-32.1). DL2 was identified as the RP2D. Of 40 evaluable patients, one patient with osteosarcoma presented complete response, 4 had partial responses (2 osteosarcoma, 1 chondroma, 1 carcinoma) and 8 had stable disease (including 4 for more than 4 months). The median duration of treatment was 68 days (IQR 57-106); one patient completed 24 cycles and two were still on treatment at data cut-off (at cycle 16 and cycle 23). **Conclusions:** Spartalizumab combined with low dose pazopanib was well tolerated leading to a RP2D of 4 mg/kg/q4w. The regimen shows evidence of anti-tumor activity in pediatric sarcoma, especially osteosarcoma. Further investigations are ongoing to select the sub-population who could benefit of this combination. Funded by INCa and ARC Foundation (call for project CLIP2 "Novartis Innovative Molecules, INCa-ARC_14820"). Clinical trial information: NCT05210413. Research Sponsor: Institut National du Cancer (INCa) et Fondation ARC.

Targeting metastatic sites with radiation and outcomes in high-risk pediatric rhabdomyosarcoma.

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Background: Outcomes for pediatric patients with metastatic rhabdomyosarcoma (RMS) remain poor despite therapy intensification and novel agents. RMS13 (NCT01871766) was a phase II prospective multicenter trial evaluating a response-based approach to metastatic site radiotherapy (RT). We report outcomes related to metastatic disease management in this high-risk (HR) population. **Methods:** Event-free survival (EFS) and metastatic site control were analyzed for HR patients treated with interval compressed chemotherapy, risk-adapted RT to primary and metastatic site, and maintenance therapy. EFS was defined from therapy start to relapse, progression, death or last follow-up. Metastatic RT was delivered between interval-compressed and maintenance therapy for non-bone marrow metastatic sites without complete response (CR). RT omission criteria included PET negativity, lesion size <1 cm, or complete surgical resection with negative margins. Metastatic RT used protons: 25 Gy in 5 or 50.4 Gy in 28 fractions, by lesion size. Primary tumor control consisted primarily of proton RT, with limited use of surgery plus adjuvant RT. **Results:** From 2015 to 2020, 39 HR patients were enrolled (median age 9.5 years). Most patients were FOXO1 fusion-positive (64%), had nodal involvement (74%), and an Oberlin score >1 (67%). Median follow-up was 23.1 months overall (78.5 months for non-progressors). Five-year EFS was 31.6% (95% CI, 19.7–50.6%), differing by Oberlin score >1 – 16.2% (95% CI, 6.6–39.8%), ≤1 – 61.5% (95% CI, 40–94.6%). Twenty-six patients relapsed: 22 had distant failure (DF), 6 had local failure (LF), and 2 had both DF and LF. The 5-year cumulative incidence of LF was 14.4% (95% CI, 5–28), and 54% for DF (95% CI, 36–69), establishing DF as the predominant pattern of failure. Twenty-six patients reached the protocol window for metastatic-site RT (weeks 47–54): 11 soft-tissue metastases, 6 bone, 8 both, and 1 bone marrow only, with a 5-year EFS of 42.3% (95% CI 23.3–61.3%). Among 21 patients achieving CR at metastatic sites without RT, 5-year EFS was 38.1% (95% CI 17.3–58.9%), and cumulative incidence of any DF was 57.1% (95% CI 35.9–78.3%). Seven patients (33%) recurred at initially involved metastatic sites, primarily soft tissue. In-site recurrence occurred in 7/17 (41%) non-irradiated soft-tissue sites versus 1/12 (8%) bony sites. Only one recurrence occurred among irradiated soft-tissue sites. **Conclusions:** Soft-tissue metastatic sites in CR that were not irradiated had high recurrence rates, while bony sites achieved durable control without RT. Future trials should consider consolidative RT for soft-tissue metastases regardless of response in HR RMS. Clinical trial information: NCT01871766. Research Sponsor: None.

Recurrence by metastatic site.

	CR, no RT (N)	Recurrence, non-RT, N(%)	PR, RT (N)	Recurrence, No RT, N (%)
Bone metastases (n=14)	12	1 (8)	2	0
Soft-tissue metastases (n=19)	17	7 (41)	2	1 (5.9)

CR, complete response; PR, partial response; RT, radiotherapy.

Digital health intervention for comorbid insomnia and neurocognitive impairment in adult survivors of childhood cancer: Results from a randomized clinical trial.

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Background: Survivors of childhood cancer are at risk of developing both insomnia and cognitive impairment, which may persist decades following treatment. Cognitive behavioral therapy for insomnia (CBT-I) is the gold-standard treatment for insomnia, yet the impact of improved sleep on comorbid cognitive dysfunction has not been evaluated in survivors.

Methods: Survivors enrolled in the Childhood Cancer Survivor Study (CCSS; median age 44 [range 23–66] years; 73% female; 37% leukemia, 23% lymphoma, 18% sarcoma, 14% Wilms, 8% neuroblastoma) with comorbid insomnia and neurocognitive impairment were randomized 1:1 to 9-week digital CBT-I vs. online sleep education (SE). Insomnia severity index (ISI), neurocognitive problems (CCSS-Neurocognitive Questionnaire [NCQ]), emotional health (Patient Health Questionnaire/Generalized Anxiety Disorder), and quality of life (PROMIS) were measured at baseline and 9-week and 6-month follow-ups. Intent-to-treat models estimated treatment effects for ISI (mean difference [MD] between CBT-I and SE of change from baseline to follow-ups) adjusted for age, sex, and cranial radiation. Cohen's *d* estimated effect size. Additional models estimated treatment effects on secondary outcomes and mediation by improved ISI. **Results:** 439 of 541 randomized survivors completed baseline assessments and started the intervention (82% CBT-I; 81% SE); 353 of those completed 9-week (76% CBT-I; 85% SE) and 305 completed 6-month (61% CBT-I; 78% SE) post-intervention assessments. Survivors randomized to CBT-I reported improved ISI scores at 9 weeks (MD=-2.4[95% CI -3.4, -1.4]; Cohen's *d*=0.50) and 6 months post-intervention (MD=-3.5[-4.6, -2.4]; *d*=0.72) vs. SE (both *p*'s<0.001). Survivors randomized to CBT-I reported greater improvement in memory (9wks: MD=-0.3SD [-0.5, -0.1], *p*=0.003; 6mos: MD=-0.5SD [-0.7, -0.3], *p*<0.001) and task efficiency (9wks: MD=-0.3SD [-0.5, -0.1], *p*=0.003; 6mos: MD=-0.5SD [-0.7, -0.3], *p*<0.001) vs. SE. Effects of CBT-I on cognitive function were mediated by improved ISI scores (42–65% mediated, all *p*'s <0.001). Insomnia responders (those who reported a change in ISI from >8 [mild to severe insomnia] to <8 [no insomnia]) also reported improved quality of life (9wks: mental beta=1.7[95%CI 0.4, 3.0], physical=2.1 [1.0, 3.1]; 6mos: mental=3.5 [2.0, 5.0], physical=3.3 [2.1, 4.5]), and emotional health (9wks: anxiety beta=-1.3 [-2.1,-0.5], depression=-1.8[-2.6, -1.0]; 6mos: anxiety=-1.8 [-2.7, -0.8], depression=-2.4 [-3.4, -1.4]). **Conclusions:** Use of a fully automated digital health treatment of insomnia confers immediate and long-term benefits to comorbid cognitive impairment and quality of life in survivors of childhood cancer. Given its efficacy and availability, digital CBT-I should be considered for the behavioral treatment of insomnia and comorbid symptoms in survivors. Clinical trial information: NCT04317742. Research Sponsor: National Cancer Institute; R01 CA239689.

The ASPIRES study: Promoting colorectal cancer surveillance in childhood cancer survivors—A randomized intervention trial from the Childhood Cancer Survivor study (CCSS).

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Background: Survivors of childhood cancer exposed to abdominal, pelvic, spinal, or total-body radiotherapy (RT) are at elevated risk for subsequent treatment-related colorectal cancer (CRC). However, adherence to recommended CRC surveillance screening is only ~37%, leaving survivors vulnerable to potentially preventable cancer. Innovative interventions are needed to improve screening uptake. **Methods:** We conducted a three-arm randomized controlled trial comparing mHealth-based patient activation (PA) and patient plus primary care provider activation (PA+PCP) with a control arm that received a survivorship care plan with screening recommendations. Nested within the CCSS, eligible participants were 5-year survivors diagnosed before age 21 who had received abdominal, pelvic, spinal, or total-body radiotherapy and were not up to date with surveillance. Participants (n = 300) were randomized in a 1:1:1 ratio, stratified by age at enrollment (30–44 vs ≥45 years). The primary outcome was the proportion of participants who completed CRC surveillance within 12 months. Each intervention arm was compared with the control in an intent-to-treat analysis using the Cochran-Mantel-Haenszel test ($\alpha = 0.025/\text{comparison}$). In secondary analyses, logistic regression, adjusted for age at enrollment, was used to estimate odds ratios (ORs) to identify moderators of the relationship between the intervention (grouping PA with PA+PCP) and the outcome. **Results:** Participants were 45% male and 8% non-white, with a median age of 41 years (range: 30 – 67 years). At 12 months, survivors in the PA group were significantly more likely than controls to have completed surveillance screening: 32/99 (32%) vs 14/102 (14%) [$p = 0.003$]. Surveillance screening completion was also higher in the PA+PCP group than in controls, but this difference did not meet the prespecified α (0.025): 26/99 (26%) vs 14/102 (14%) [$p = 0.041$]. Secondary analyses suggested the intervention was more effective among survivors without a chronic health condition (without: OR = 3.6; 95%CI 1.5, 10.1 vs. with: OR=1.9; 95%CI 0.8, 4.8) and with ≤ high school education (≤ high school OR=4.4; 95%CI 1.3, 20.2 vs. > high school OR=2.2; 95%CI 1.1, 4.7). **Conclusions:** An mHealth-based patient activation intervention more than doubled adherence to CRC surveillance compared with a survivorship care plan with surveillance recommendations alone. While patient plus PCP activation showed improvement, adding PCP activation did not confer a significant benefit compared with the control. Intervention effectiveness varied across subgroups, underscoring the importance of tailored approaches. As digital technologies continue to advance, mHealth strategies offer a promising and scalable pathway to improving surveillance screening among high-risk survivors of childhood cancer. Clinical trial information: NCT05084833. Research Sponsor: National Cancer Institute R01CA255269; National Cancer Institute U24CA55727.

Prediction of anthracycline-related cardiomyopathy in long-term childhood cancer survivors: The power of survivor-specific polygenic risk score—A COG-ALTE03N1 study.

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Background: Cardiomyopathy is a major dose-limiting toxicity of anthracyclines in the treatment of childhood cancer. Inter-patient variability in cardiomyopathy risk suggests an underlying genetic susceptibility, providing an opportunity to identify survivors at high risk and enable personalized interventions. We evaluated whether addition of a curated survivor-specific PRS for anthracycline-related cardiomyopathy (PRS-S) or general population PRSs for heart failure (PRS-G) to a clinical model improved cardiomyopathy risk classification in CCS.

Methods: In a matched case-control study of CCS (COG-ALTE03N1: matched on cancer diagnosis and year of diagnosis; controls followed at least as long as cases), anthracycline-exposed non-Hispanic White CCS were randomly split (80/20) into training (cases: n=106; controls: n=180) and test (cases: n=27; controls: n=44) sets. From >100 published genetic variants associated with anthracycline-related cardiomyopathy, we selected a prioritized list of 8 independently validated variants with demonstrated biologic plausibility (reduced drug efflux [ABCC2], altered drug metabolism [SLC22A17, SLC28A3, UGT1A6], reduced antioxidant capacity [HAS3], impaired TOP2B-mediated DNA damage response [RARG], alternative splicing of TNNT2, reducing cardiac pumping efficiency [CELF4], and cardiac profibrotic pathway [ROBO2]) to construct a standardized weighted survivor-specific PRS (PRS-S). Area under the receiver operating characteristic curve (AUC) was used to compare the performance of a clinical model (age at cancer diagnosis, sex, anthracycline dose, chest radiation (Y/N)) v combined models incorporating either PRS-S or PRS-Gs. All models included PRS × anthracycline dose interaction terms and adjusted for matching variables. Risk scores derived from training model were applied to the test set for risk classification. **Results:** Median age at cancer diagnosis was 7.1y for cases and 8.6y for controls. Cases received higher anthracycline doses (median: 330 v 240 mg/m²) and were more likely to have received chest radiation (24.8% v 19.2%). In the test set, PRS-S combined model significantly outperformed the clinical model ($AUC_{clin+PRS-S}=0.70$, 95% CI=0.57–0.82 v $AUC_{clin}=0.63$, 95% CI=0.50–0.76, $p=0.04$); 85% of all cases were classified as high risk and the adjusted negative predictive value was 95.1%. Importantly, none of the 11 PRS-G combined models (AUCs: 0.60–0.65) out-performed the clinical model. **Conclusions:** Integrating a survivor-specific PRS derived from a parsimonious set of biologically plausible genetic variants with readily-available clinical factors informs cardiomyopathy risk classification in CCS and provides an opportunity to develop personalized screening recommendations and behavioral/therapeutic interventions. Research Sponsor: U.S. National Institutes of Health; UG1CA189955; U.S. National Institutes of Health; U10CA180886; U.S. National Institutes of Health; U10CA180899; St Baldrick's Foundation.

Primary breast malignancies in adolescents and young adults: The MD Anderson Cancer Center experience.

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Background: Primary malignancies of the breast rarely affect adolescents and are uncommon in young adults. Limited information is available about their clinicopathologic characteristics and outcomes. The 5-year overall survival (OS) for women with breast cancer, not including ductal carcinoma in situ, exceeds 90%. However, it remains unclear whether adolescents and young adults experience similar outcomes compared with older patients. **Methods:** We conducted a retrospective study of all patients aged 0–25 years with primary breast malignancies seen at MD Anderson Cancer Center between 2000 and 2024. Demographics, histology, staging, treatment, and outcome data were collected. Event-free survival (EFS) and OS were estimated using the Kaplan–Meier method. Log-rank test was used to analyze patient outcomes by histology. **Results:** A total of 110 patients were identified. Median age at diagnosis was 23.9 years (range, 15.7–25.5). Two patients were male, 44.9% were White, 27.7% Hispanic, and 15.9% Black. The most common tumor histology was invasive ductal carcinoma (n=83, 75.5%), followed by sarcoma and malignant phyllodes tumors (n=14, 12.7%), carcinoma in situ (n=7, 6.4%), and rare histologic subtypes (n=6, 5.5%). Family history of breast cancer was present in 53.6% of patients and ovarian cancer in 9%. Of 81 patients with germline genetic testing, 25 (30.9%) had a cancer predisposition syndrome: Li-Fraumeni (n=9), BRCA1 (n=8), BRCA2 (n=4), ATM (n=2), other (n=2). Eleven patients (10%) had metastatic disease at presentation to bone, lung, distant lymph nodes, and liver. Among the 96 carcinoma cases, 36 (37.5%) were estrogen or progesterone receptor-positive and HER2-negative; 25 (26%) were HER2+, and 32 (33%) were triple-negative. Of the 110 patients, 69 (62.7%) received neo-adjuvant chemotherapy, 37.6% of whom achieved a pathologic complete response, and 46.3% a partial response. Most patients (92.7%) had surgery (mastectomy 87.2% or lumpectomy 9.8%), 67.2% received radiotherapy, and 25.4% targeted therapy. Following treatment, 56 (51%) patients received adjuvant endocrine therapy. The 5-year EFS and OS for the cohort were 30% (95% CI, 22.6–39.9) and 71.8% (95% CI 62.9–82), respectively, and are presented by histology in the table. EFS (p=0.023) but not OS (p=0.36) was associated with histologic type. **Conclusions:** Primary breast malignancies in adolescents and young adults have distinct characteristics with a high frequency of family history and genetic predisposition syndromes and appear to be associated with lower survival compared with breast cancer in older patients. Research Sponsor: None.

Histology	No. of patients	5-year EFS (%) (95% CI)	5-year OS (%) (95% CI)
Invasive ductal carcinoma	83	31.3 (22.8, 43.1)	68 (57.9, 80)
Sarcoma and malignant phyllodes tumors	14	28.6 (12.5, 65.4)	82.1 (62.1, 100)
Carcinoma in situ	7	42.9 (18.2, 100)	100 (100, 100)
Rare histologic subtypes	6	NA	100 (100, 100)

Characteristics and survival of 4N and non-4N metastatic neuroblastoma across treatment eras: A report from the International Neuroblastoma Risk Group Task Force.

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Background: Patients with metastatic neuroblastoma confined to distant lymph nodes (4N) were identified as a subgroup with superior outcomes to those with metastases to other sites. Over the past two decades, outcomes for high-risk neuroblastoma have improved from increasingly effective and intense therapy, while intermediate-risk patients have maintained excellent outcomes with biology and response-based therapy. We aimed to determine if 4N patients remained a favorable subgroup with contemporary therapy. **Methods:** Patients with International Neuroblastoma Staging System (INSS) stage 4 disease in the International Neuroblastoma Risk Group Data Commons diagnosed between 1990–2020 were evaluated. Those with metastases only to the distant lymph nodes were defined as 4N. All other patients were defined as non-4N. Treatment eras included: 1999 and prior, 2000–2009, 2010 and later which correspond to standardization of multimodal therapy, stem cell transplant, and anti-GD2 immunotherapy for high-risk patients. Differences between 4N and non-4N patients were assessed with chi-square, Wilcoxon rank sum, and t-tests. Five-year Kaplan-Meier estimates of survival with 95% confidence intervals and multivariable Cox proportional hazards modeling were used to evaluate event-free (EFS) and overall (OS) survival. **Results:** The analytic cohort included 107 4N and 5976 non-4N patients. There were no clinical differences between 4N and non-4N patients apart from unfavorable histology (74.2% [4N] versus 60.1% [non-4N]; $p=0.02$). 5-year EFS and OS were higher for 4N compared to non-4N patients ($p=0.001$ and 0.001 , respectively). Though survival estimates for 4N were higher in each era, the difference was not statistically significant for patients diagnosed from 2000–2009 nor 2010 and beyond; (1999 and prior: EFS 58.7% (40.9–72.7%) versus 31.8% (29.7–33.9%) $p=0.001$; OS, 66.2% (48.1–79.3%) versus 37.9% (35.7–40.1%) $p=0.002$, 2000–2009: EFS, 47.9% (34.0–60.5%) versus 36% (34.1–37.9%) $p=0.179$; OS, 55.4% (40.7–67.8%) versus 45.1% (43.1–47.1%) $p=0.122$, and 2010 and later: EFS, 63.6% (29.7–84.5%) versus 42.8% (39.9–45.6%) $p=0.178$; OS, 71.6% (35.0–89.9%) versus 52.3% (49.2–55.3%) $p=0.207$). Log-rank calculations may have been underpowered in part due to small sample sizes ($n=39$, 56 , and 12) of each 4N subgroup, respectively. 4N patients had superior EFS ($HR=0.48$; $p=0.0004$) and OS ($HR=0.49$; $p=0.0009$) in a model which included age, MYCN-amplification status, treatment era, ferritin, and LDH. A sensitivity analysis using only high-risk patients age >18 months yielded similar results. **Conclusions:** Patients with stage 4N neuroblastoma are a rare subgroup which appears to continue to have favorable outcomes with contemporary therapy. Additional studies to identify opportunities to reduce therapy intensity for this subgroup are warranted. Research Sponsor: None.

Real-world experience of a pediatric precision oncology protocol utilizing paired somatic and germline sequencing at a single institution: Interim analysis.

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Background: While most pediatric oncology patients are cured with upfront therapy, outcomes for patients with metastatic and relapsed/refractory disease remain poor. Salvage therapy is toxic and has marginal success rates, necessitating novel, personalized approaches. We established our pediatric precision oncology program based on integrative clinical sequencing (ICS) in 2012 and present an interim outcomes analysis of this single institution cohort. **Methods:** Pediatric and AYA oncology patients (age 0–25 years) underwent paired somatic and germline sequencing, including whole exome and transcriptomic analysis. Results were annotated with longitudinal clinical data extracted from the medical record using the NCI-supported tool EMERSE, which has been enhanced by the addition of a beta version of a large language models (LLM) integrated “Chatbot” to implement more efficient data abstraction from clinical notes. **Results:** Of the 1000 patients enrolled, 925 (92.5%) were sequenced successfully. We present interim analysis of the first 435 patients. Within this interim cohort, 233 (53.56%) of patients were male and 79.8% were non-Hispanic white. Hematologic malignancies accounted for 110 (25.3%) diagnoses, brain tumors 75 (17.2%), and non-brain solid tumors 250 (57.5%). ICS succeeded for 400/435 (92.0%) patients. Overall, 471 actionable alterations (AA) were discovered in 266 (66.5%) patients (mean 1.77 AA/patient). These included 62 actionable germline alterations in 60 patients (15%). There were 195 single nucleotide variants (SNV) in 142 patients, 69 gene fusions in 62 patients, and 145 copy number alterations (CNA) in 92 patients. Actionable findings guided the use of targeted therapies (TT) supported by NCI-MATCH criteria in 116 patients (29.0%) with a total of 209 targeted therapies given (mean 1.80 /patient). Thirty-two patients (8.0%) enrolled on therapeutic clinical trials featuring an identified targeted therapy. Sixteen (4.0%) patients without AAs received 22 TTs based on clinician preference. Additionally, 166 patients (41.5%) did not receive TT despite at least one AA due to lack of availability of a suitable formulation, pursuit of alternative therapy, or death prior to therapy initiation. Repeat ICS (range 1–4) was completed for 115 patients (28.8%), among which 8 (7.0%) had additional AAs identified and 5 (4.4%) received TT based on repeat ICS. **Conclusions:** This study highlights the importance of ICS based precision oncology with 67% of patients having AAs and 29% receiving TTs. Analyses are ongoing to study the most frequently altered signaling pathways, frequency of targeted agents used, impact of ICS and TT on the clinical outcomes for these patients, barriers in receiving TT despite having AAs, role of longitudinal sequencing, and the impact of LLM based “Chatbot” on data extraction efficiency. Research Sponsor: U.S. National Institutes of Health; Hyundai Hope on Wheels; Children's Foundation of Michigan.

Harnessing OMOP-CDM for multisite collaborations to measure cardiovascular risk factors and cardiovascular disease in the early survivorship period for children, adolescents, and young adults.

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Background: The Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM) is an international effort to leverage data standards to cultivate multi-institutional collaborations and generate reproducible evidence using real-world data. Four institutions mapped their electronic health records data to the OMOP-CDM. Cardiovascular risk factors (CVRFs) and their impact on risk for cardiovascular disease (CVD) among survivors of childhood cancer merit further investigation into cardiotoxicity during the early survivorship period.

Methods: Eligible patients from Seattle Children's with at least one condition contained within the ancestor concept "malignant neoplastic disease" (concept ID 443392) and an index date defined as the initial administration of a medication contained within the ancestor concept "antineoplastic agents" (concept ID 21601387) were included. Clinically computable phenotypes from OMOP-CDM data were constructed in alignment with the Common Terminology Criteria for Adverse Events (version 6.0) for hypertension, diabetes, obesity, and hyperlipidemia within one year of the index date. The primary outcome was CVD, defined as the incidence of cardiomyopathy, heart failure, atrial fibrillation, and ventricular arrhythmias within 1-5 years of the index data. **Results:** Among 1195 survivors, the incidence rate of any CVD from non-cardiotoxic therapy was 0.11 per 100-person-years (95% Confidence Interval 0.04-0.25), compared to 0.43 (95% CI 0.25-0.71) and 1.6 (95% CI 0.08-7.88) for survivors treated with cardiotoxic therapy and cardiotoxic therapy plus targeted or immunotherapy, respectively. Validation of results and sharing of coding for multi-site meta-analysis is ongoing. **Conclusions:** OMOP-CDM represents a feasible approach to explore CVRFs and CVD in the early survivorship period among contemporary cohorts treated with traditional cardiotoxic chemotherapy, targeted therapy, and immunotherapy. Research Sponsor: None.

CVD and CVRF among survivors.

	Non-cardiotoxic Chemotherapy N=677	Cardiotoxic chemotherapy N=493	Cardiotoxic and Targeted Immunotherapy N=25
Age (in years)	6.6 (5.1)	8.6 (5.3)	9.4 (4.9)
Cancer Type			
CNS	240 (35.5%)	0 (0.0%)	0 (0.0%)
Hematologic	267 (39.4%)	285 (57.8%)	23 (92.0%)
Solid Tumor	160 (23.6%)	208 (42.2%)	2 (8.0%)
Sex (Female)	310 (45.8%)	243 (49.3%)	10 (40.0%)
Race			
Asian	54 (8.0%)	36 (7.3%)	2 (8.0%)
Black/African American	22 (3.2%)	13 (2.6%)	0 (0.0%)
Hispanic	131 (19.4%)	101 (20.5%)	4 (16.0%)
White	351 (51.8%)	259 (52.5%)	14 (56.0%)
Other or Unknown	119 (17.6%)	84 (17.0%)	5 (20.0%)
CVRFs (<1 year)			
Hypertension	111 (16.4%)	103 (20.9%)	5 (20.0%)
Diabetes	100 (14.8%)	78 (15.8%)	8 (32.0%)
Hyperlipidemia	87 (12.9%)	61 (12.4%)	8 (32.0%)
Obesity	214 (31.6%)	143 (29.0%)	4 (16.0%)
CVD (1-5 years)			
Any	2 (0.3%)	12 (2.4%)	1 (4.0%)

Association of neighborhood-level vulnerability with health behavior patterns in survivors of childhood cancer: A report from the St. Jude Lifetime Cohort (SJLIFE).

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Background: Childhood cancer survivors face elevated risks for chronic health conditions and premature mortality. Engaging in healthy behaviors may mitigate these risks, yet neighborhood-level vulnerability may constrain survivors' ability to adopt or sustain them.

Methods: Among survivors (n=3,303) and community controls (n=652) in SJLIFE, neighborhood-level vulnerability was measured using census tract level overall and domain-specific (i.e. socioeconomic status, household composition, minority status, housing type and transportation) Social Vulnerability Index (SVI) scores, with higher values indicating higher vulnerability, and the U.S. Department of Agriculture's persistent poverty measure. Health behaviors, including sedentary time/physical activity, smoking, alcohol, and illicit drug/marijuana use, were categorized as healthy, moderately unhealthy (1–2 unhealthy behaviors), and unhealthy (≥ 3 unhealthy behaviors). Multinomial logistic regression evaluated associations between neighborhood-level vulnerability at enrollment and health behavior patterns at most recent evaluation among survivors, adjusted for sociodemographic and cancer treatment factors as determined by backward selection. Interaction models compared associations between survivors and controls. **Results:** Survivors were 53.1% male, 82.5% non-Hispanic White, with a median age of 31.0 years (interquartile range: 23.5 – 38.5) at health behavior assessment. The most common childhood cancer diagnosis was acute lymphoblastic leukemia (28.8%). Survivors in the highest vs. lowest SVI tertile had higher odds of reporting moderately unhealthy (Odds Ratio [OR]: 1.46, 95% Confidence Interval [95% CI]: 1.08 – 1.98) or unhealthy (OR: 1.70, 95% CI: 1.13 – 2.56) behavior patterns, compared to a healthy behavior pattern. Socioeconomic and housing type SVI domains drove these associations, with survivors in the highest tertiles more likely than those in the lowest to have an unhealthy rather than healthy behavior pattern (Socioeconomic OR: 1.55, 95% CI: 1.02 – 2.35; Housing type OR: 1.53, 95% CI: 1.03 – 2.27). Persistent poverty was associated with greater odds of a moderately unhealthy behavior pattern (OR: 1.70, 95% CI: 1.09 – 2.66) in survivors. Housing type vulnerability was associated with disproportionately higher odds of an unhealthy behavior pattern among survivors compared to controls (ratio of ORs: 2.80, 95% CI: 1.19 – 6.60). **Conclusions:** Neighborhood-level vulnerability was associated with higher likelihood of unhealthy behavior patterns in childhood cancer survivors with housing type vulnerability having a greater impact on health behaviors in survivors compared to controls. Effective interventions to improve survivors' health behaviors should incorporate neighborhood-level factors. Research Sponsor: National Cancer Institute; U01 CA195547; National Cancer Institute; P30 CA21765; American Lebanese-Syrian Associated Charities.

Thematic game intervention as a novel psychosocial support to reduce sedation needs and anxiety in pediatric neuro-oncology patients during radiotherapy: A prospective cohort study (2020–2025).

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Background: Pediatric neuro-oncology patients undergoing radiotherapy frequently require sedation/anesthesia due to severe anxiety (mYPAS >15 in >80% cases) and treatment non-compliance. Conventional psychosocial interventions show limited efficacy in reducing sedation dependence, which incurs costs and clinical risks (e.g., respiratory depression). **Methods:** A prospective cohort study (2020–2025) of 246 children (3–5 years) receiving varied radiotherapy regimens (average course: ~30 fractions). Non-randomized allocation with propensity score matching for age, tumor stage, and sedation history: 1. Intervention group (n=122): Structured game-based intervention ("Radiation Warrior Training Camp"). 2. Control group (n=124): Standard psychological support. Primary outcomes: mYPAS anxiety scores, sedation/analgesia usage, treatment compliance, and cost savings (calculated at ¥376/session). **Results:** Sedation avoidance rate : 0% in intervention group vs. 41.1% in controls (OR=0.08, 95% CI [0.03–0.22], $p<0.001$). mYPAS score (median): 8.5 [6.8–3] vs. 17.1 [14.2–19.8] ($\beta=-7.9$, [-9.5, -6.3], $p<0.001$). Cost savings: ¥5,512/patient (derived from 82% relative sedation reduction $\times$ 30 fractions $\times$ ¥376/session). Treatment duration deviation reduced by 29% ($p=0.011$). **Key Findings:** 1. 92% of intervention patients completed radiotherapy without sedation. 2. Dose-dependent efficacy: Anxiety reduction correlated with gameplay duration ($r=-0.71$). 3. Developmental gradient: 5-year-olds achieved 9.2-point mYPAS reduction vs. 6.5-point in younger children. **Conclusions:** Game intervention eliminated sedation needs in 92% of patients, reducing anxiety by 7.9 mYPAS points and yielding ¥5,512/patient cost savings. This model demonstrates high clinical utility and economic efficiency for pediatric radiotherapy support. Research Sponsor: None.

Alrizomadlin (APG-115) alone or in combination with lisaftoclax (APG-2575) for the treatment of pediatric patients with relapsed/metastatic rhabdomyosarcoma (RMS) or other soft-tissue sarcomas (STSs).

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Background: Pediatric tumors rarely harbor *TP53* mutations but often overexpress antiapoptotic BCL-2 family proteins (BCL-2, BCL-XL, MCL-1), making MDM2 and BCL-2 inhibitors attractive therapeutic approaches. Preclinical data have shown that dual targeting these proteins results in synthetic lethality, which may overcome chemoresistance in pediatric patients with STSs. The study evaluated the safety and preliminary efficacy of alrizomadlin alone or combined with lisaftoclax in heavily pretreated relapsed/metastatic pediatric RMS, neuroblastoma (NB) and other STSs. **Methods:** This Chinese multicenter trial (NCT05701306; APG115XC103) assessed alrizomadlin ($\pm$ lisaftoclax) in children with heavily pretreated relapsed/metastatic RMS, Ewing sarcoma (EWS), NB, or other STSs; Lansky or Karnofsky PS $\geq$ 50; and no CNS metastases. Alrizomadlin alone was administered orally at 30, 60, or 90 mg/m² QOD (2 weeks on, 1 week off). When combined with lisaftoclax (250, 375, or 500 mg/m² oral QD), alrizomadlin dose was 90 mg/m² QOD in 21-day cycles until progression or toxicity. The primary endpoints were safety and RP2D for the combination. ORR was assessed per INRC for NB or RECIST v1.1 for other solid tumors. **Results:** As of January 16, 2025, 16 pediatric patients received alrizomadlin monotherapy at 30 (n = 5), 60 (n = 4), or 90 mg/m² (n = 7). No DLT was observed; the recommended dose was 90 mg/m² when combined with lisaftoclax. Most common TRAEs were gastrointestinal and hematologic. Grade $\geq$ 3 TRAEs included thrombocytopenia (42.9%) and neutropenia (28.6%). One patient (14.3%) experienced treatment-related SAEs (thrombocytopenia, febrile neutropenia, and leukopenia). No treatment-related discontinuation or death occurred. In the combination arm, 18 patients were treated with alrizomadlin (90 mg/m²) combined with lisaftoclax at 250 (n = 13) or 375 mg/m² (n = 5). No DLT was observed. Most common TRAEs were gastrointestinal and hematologic. Grade $\geq$ 3 TRAEs included thrombocytopenia (38.9%), neutropenia (33.3%), leukopenia (27.8%), and anemia (27.8%). One (5.6%) treatment-related SAE of thrombocytopenia was reported. No treatment-related discontinuation or death occurred. In monotherapy, 1 patient with refractory RMS achieved CR; 2 patients with STSs maintained stable disease. In the combination arm, 10 patients were evaluable for response, showing 1 CR (EWS), 1 PR among 4 patients with RMS, and 1 PR among 3 patients with NB. ORR (CR + PR) was 30% and DCR 80%. **Conclusions:** Alrizomadlin alone or in combination with lisaftoclax showed a manageable safety profile, with preliminary antitumor activity in heavily pretreated R/R RMS, EWS, and NB. The potential mechanisms, safety, and efficacy of alrizomadlin combined with lisaftoclax for pediatric RMS and other STSs warrant further investigation. Clinical trial information: NCT05701306. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

RAPID: A pilot feasibility study of rapid dinutuximab infusion in patients with relapsed/refractory (RR) high-risk neuroblastoma (HRNBL).

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Background: Dinutuximab is a key component of therapy for HRNBL and is widely used in the RR setting. Standard administration requires inpatient infusions of ~10 hours daily. Emerging pediatric and adult data support shorter infusion durations. Evaluating rapid infusion of dinutuximab (RID) with chemotherapy may reduce pain, facilitate outpatient delivery, and decrease healthcare burden. **Methods:** This prospective, single-institution pilot study enrolled patients from 11/2022-12/2025 following IRB approval. Eligible patients included those ≥ 1 year old with RR-NBL, adequate organ function, and prior dinutuximab exposure. Patients received chemoimmunotherapy consisting of dinutuximab 17.5 mg/m²/day for 4 days (over 2-4 hours) combined with irinotecan/temozolomide (ITD) or cyclophosphamide/topotecan (CTD) for up to 6 cycles. Outpatient administration was permitted after cycle 1 if tolerated. The primary feasibility endpoint was successful dinutuximab administration over ≤ 5 hours with ≤ 1 patient experiencing unacceptable toxicity (UT) during cycle 1 in a 10-patient cohort. Secondary and exploratory endpoints included infusion duration, serial pain scores assessed during and post-infusion, opioid use in morphine milligram equivalents (MME), toxicity, feasibility of outpatient administration, pharmacokinetics (PK) and human anti-chimeric antibody (HACA). Changes in MME were compared using a one-sample t-test. **Results:** Eleven patients (median age 14 years, range: 3-24) received ITD (n=6) or CTD (n=5). All patients met the primary feasibility endpoint. Median infusion time was 2 hours (range 2-4) across all cycles. One patient (3 years old), enrolled in the early post-transplant period developed UT (grade 3 ventricular dysfunction). The protocol was amended to exclude patients within 6 months of transplant, require dinutuximab tolerance within 2 months, and extend cycle 1 infusion to 4 hours for patients < 12 years of age; this patient was replaced per protocol. Across cycles 1-6, mean pain score was 0.4 (SD 0.46), and mean opioid usage was 0.04mg/kg MME (SD 0.07), reflecting a 78% reduction of opioid use in cycle 1 RID compared to the pre-enrollment standard-infusion cycle ($p < 0.001$). Outpatient RID was administered in seven patients without hospital admission; 1 patient was admitted for chemotherapy-related toxicity, 3 patients remained inpatient (social reasons). RID showed expected PK levels; HACA was noted in 1 patient. Most common grade 3 toxicities (27%): increased ALT and hypokalemia; 1 patient (with UT) had grade 4 toxicity (dyspnea, hypocalcemia). **Conclusions:** RID was feasible and well tolerated, including in the outpatient setting. Pain control was achieved with standard premedication and significantly reduced opioid requirements compared with standard infusion. These data support planned multi-institutional evaluation of RID. Clinical trial information: NCT05421897. Research Sponsor: United Therapeutics.

Interim analysis of CaboMain: A prospective, single-arm phase 2 clinical trial of cabozantinib as maintenance therapy for patients with “ultra-high-risk” pediatric solid tumors.

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Background: There are patients with pediatric solid tumors, including those with relapsed/refractory disease, with “ultra-high” risk (UHR) disease (1-year progression free survival (1-yr PFS) <25%) even when achieving disease control. Most pediatric solid tumors do not have a therapeutically-targetable oncogenic driver, limiting treatment options for maintenance therapy. Cabozantinib is a multitargeted tyrosine kinase inhibitor with demonstrated activity against many solid tumors, with a defined safety profile and dosing in pediatric and young adult patients. We hypothesize that use of cabozantinib for 1 year, after achieving disease control, can improve 1-yr PFS to $\geq 45\%$. **Methods:** We are performing a multisite, open-label, single-arm Phase 2 clinical trial for patients with pediatric solid tumors with 4 strata; Stratum A, primary stratum for analysis, enrolls patients with UHR disease. Patients must have completed prior therapy at least 4 weeks and no longer than 12 weeks before enrollment with stable disease or better at time of enrollment. Enrolled patients receive cabozantinib as per dosing nomogram at 40 mg/m²/day, taken for up to 365 days from start of therapy. Primary outcome is 1-yr PFS, with Bayesian time-to-event optimal phase 2 design for analysis. Interim analysis follows the rules: assuming a Beta (0.25,0.75) prior distribution for efficacy and 88% statistical power, at interim at least 5/18 evaluable patients must have achieved 1-yr PFS to justify ongoing enrollment. Interim analysis reporting has been recommended by the Data Safety and Monitoring Committee. **Results:** We report the interim results as of 11/1/2025, which includes all enrolled patients on Stratum A who have reached 1 year after start of therapy (n=13). Eight of thirteen patients reached 1-yr PFS; by diagnosis, neuroblastoma (NBL) = 2, Ewing sarcoma (EWS)= 3, osteosarcoma (OST)= 3. Of those not reaching the one-year time point, 2 patients progressed after voluntarily discontinuing cabozantinib (1 NBL, 1 month after discontinuation; 1 OST, 5 months after discontinuation), 1 NBL elected radiation therapy and was removed from study, and 2 OST progressed on study treatment. Having reached the interim analysis benchmark, enrollment continues. Three additional strata (metastatic EWS, metastatic OST, and fusion-positive metastatic rhabdomyosarcoma, each at end of 1st line therapy) also continue to enroll, as secondary endpoints. Longer-term PFS and overall survival, patient reported outcomes, and exploratory biological measures continue to be tabulated for later analysis. **Conclusions:** Use of cabozantinib as maintenance therapy, after prior treatment and achievement of stable disease or better response, has been determined to be feasible to demonstrate improvement of 1-yr PFS by at least 20%, and ongoing enrollment is justified. Clinical trial information: NCT05135975. Research Sponsor: Exelixis, Inc.

Phase II trial of olaparib and ceralasertib in patients with recurrent osteosarcoma: Lung-only resectable cohort efficacy and correlative biomarker results.

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Background: Patients with osteosarcoma recurrence have limited treatment options and poor outcomes. The observed response to cisplatin in osteosarcoma, in vitro susceptibility of osteosarcoma cell lines to ATR and PARP inhibitors, and the presence of mutations in genes involved in DDR served as the basis for the development of this trial. **Methods:** We conducted a phase II trial of olaparib and ceralasertib in patients aged 12–40 with recurrent osteosarcoma. The primary endpoint for patients with resectable disease limited to the lung (Cohort 2) was submission of paired pre- and post-treatment tumor samples. Secondary endpoints for Cohort 2 included event-free status at 12-months, event-free survival (EFS) and overall survival (OS). Patients received Olaparib 150mg twice a day on days 1–28 and ceralasertib 80mg twice a day on days 1–14 of a 28-day cycle. Patients with unilateral disease received 2 cycles of treatment prior to surgery. Patients with bilateral disease had one side resected, then received 2 cycles of treatment followed by surgery of the contralateral side. Tumor, blood and plasma samples were obtained from Cohort 1 (measurable unresectable disease, efficacy results previously reported) and Cohort 2 patients for correlative studies. **Results:** Between 3/2021–9/2024, 10 patients from 4 centers were enrolled in Cohort 2. Four patients had bilateral and six had unilateral lung metastases. Median age was 19.3 (range 15.7–24.6). Patients had received a median of three prior therapy regimens. Seven patients (70%, 95%CI: 35%–93%) underwent planned thoracic surgery and had paired pre- and post-treatment tumor samples submitted for correlative studies. Four patients (40%, 95%CI: 12%–74%) were event-free at 12 months and received >12 cycles of olaparib and ceralasertib. The 12-month EFS $\pm$ SE and OS $\pm$ SE were 40 $\pm$ 15.5% and 90 $\pm$ 9.5%, respectively. Initial review of clinical sequencing on a subset of Cohort 1 and 2 patients suggests therapy resistance may be associated with high-risk genomic features, like MYC amplification. **Conclusions:** Patients with recurrent resectable osteosarcoma limited to the lung parenchyma can be included as a separate cohort in phase II trials of novel agents. In this cohort, it is feasible to incorporate pre-surgical treatment with experimental agents followed by surgical resection of pulmonary nodules and collection of pre- and post-treatment tumor samples, enabling correlative biology. 12-month EFS was 40% but with a wide confidence interval crossing the confidence interval of historical 12-month EFS of 20% from prior COG studies. Sequencing and ctDNA analyses for all enrolled patients (both cohorts) with available samples (N=40 patients with tumor samples and N=48 patients with ctDNA samples) are underway to further assess potential biomarkers of treatment response. Clinical trial information: NCT04417062. Research Sponsor: St. Baldrick's Foundation; Osteosarcoma Institute; Alex's Lemonade Stand.

Characterization and validation of a methylation signature as a prognostic marker in osteosarcoma.

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Background: Despite extensive research efforts, outcomes for patients with osteosarcoma have not substantially improved since the 1980s. Moreover, no prognostic features are used clinically to risk adapt therapy. Here, we performed methylation and RNA sequencing of pre-treatment osteosarcoma tumor samples to identify distinct features of tumor biology and to generate and validate a prognostic signature. **Methods:** All patients diagnosed with osteosarcoma at the Children's Hospital of Philadelphia (CHOP) before March 15, 2024 with tissue available for analysis were eligible. Of the 100 eligible patients, three were excluded for lack of clinical data and one for initial diagnostic uncertainty. Methylation and RNA sequencing were performed on DNA and RNA extracted from FFPE or frozen tumor. Unsupervised analyses characterized global methylation structure and differential methylation analyses compared differences between progression groups. Tumor and immune cell fractions were estimated using a reference-based deconvolution algorithm. CpGs were filtered using an unsupervised variability criterion (top 20% MAD) and a ridge-penalized Cox model was used to derive a methylation risk score as a linear predictor. The publicly available TARGET-OS cohort was used for validation with median-based risk stratification defined in the CHOP cohort. **Results:** Of 96 patients, 44 patients had pre-treatment samples that passed methylation QC and 13 passed RNA sequencing QC. Within the CHOP cohort, 34/44 (77%) had localized disease with a median age of 13 years. Variability in methylation profiles was driven by leukocyte infiltration, supported by strong correlations between global methylation levels and mitotic index estimates. Tumors from patients with progressive disease displayed 12,338 significantly different CpGs ($FDR < 0.01$) and enriched for hypomethylated CpGs. A methylation-derived risk score was established for overall survival (OS) in the CHOP cohort. In multivariable Cox models, the methylation risk score remained significantly associated with OS (HR 1.54 [1.05–2.26]; $p = 0.026$) together with metastatic status (HR 5.13 [2.49–10.59]; $p < 0.001$), yielding improved model discrimination (C-index 0.77 [0.70–0.83]). This was replicated in event-free survival (EFS, HR 2.49 [1.49, 4.19], $p < 0.01$). In the TARGET-OS cohort, after adjustment for metastatic status, methylation risk score remained independently associated with EFS (HR 1.6 [1.15, 2.23], $p = 0.005$). and OS (HR 1.54 [1.05, 2.26], $p = 0.003$). **Conclusions:** In this single-institution cohort analysis, a methylation-based risk score predicts survival and adds prognostic value when combined with metastasis status. Integration of CpG methylation with downstream pathway activation via RNA sequencing is ongoing and will be reported. Further validation of this prognostic signature should be considered in future osteosarcoma trials. Research Sponsor: Connor Initiative (Philanthropy); National Cancer Institute; 1R50CA305079; National Human Genome Research Institute; 5T32HG009495; Conquer Cancer, the ASCO Foundation; Abramson Cancer Center, University of Pennsylvania; Rally Foundation for Childhood Cancer Research,.

Dexamethasone-free antiemetic prophylaxis with olanzapine in children and adolescents receiving highly emetogenic chemotherapy: A multicenter, phase III non-inferiority randomized trial.

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Background: Dexamethasone, with a 5-HT₃ receptor antagonist and a neurokinin-1 antagonist, is the guideline-recommended prophylaxis for chemotherapy-induced nausea and vomiting (CINV) in children and adolescents receiving highly emetogenic chemotherapy (HEC), but is associated with clinically relevant toxicities. The role of olanzapine as a dexamethasone-sparing agent for pediatric CINV prophylaxis remains uncertain. **Methods:** This investigator-initiated, multicenter, open label, phase III randomized non-inferiority (NI) trial (INPHOG-SUPP-22-03) enrolled patients aged 4–18 years receiving single or multi-day HEC. Patients were randomized 1:1 (single chemotherapy cycle) to receive dexamethasone, palonosetron, and fosaprepitant (DEX; standard-of-care) or olanzapine, palonosetron, and fosaprepitant (OLANZ; dexamethasone-free). The primary endpoint was complete response (CR) to vomiting (no vomiting and no rescue anti-emetics) during the overall period (0–120 h after the last chemotherapy dose). A NI margin of –15% was prespecified based on adult dexamethasone-sparing trials. Assuming a control CR rate of 70% from prior pediatric studies, 310 patients provided 80% power at a one-sided α of 0.025, allowing for 5% dropout. Absolute differences in CR rates were analyzed using the Miettinen–Nurminen method; NI was concluded if the lower bound of the 95% confidence interval (CI) was above –15%. **Results:** Between December 2022 and January 2026, 310 patients were randomized (DEX, n=156; OLANZ, n=154). The per-protocol (PP) population included 299 patients (DEX, n=151; OLANZ, n=148). Median age was 13 years; 62.2% were male, and 56.8% received multi-day HEC. In the PP population, the CR rate for vomiting during the overall period was 56.9% in the DEX arm and 63.5% in the OLANZ arm (absolute difference, 6.6%; 95% CI, –4.5% to 17.7%). Non-inferiority was demonstrated, as the lower 95% CI (–4.5%) was above –15%. Results were consistent in the intention-to-treat population. For secondary endpoints, CR to vomiting during the acute period (0–24 h) was 64.2% vs 68.9%, and during the delayed period (24–120 h) 78.8% vs 79.1%, in the DEX and OLANZ arms, respectively. CR to nausea during the overall period was 54.3% vs 53.4%, during the acute period 59.6% vs 59.5%, and during the delayed period 69.5% vs 68.9%, respectively. Grade ≥ 2 non-hematologic and hematologic laboratory toxicities were uncommon and similar between arms. Any-grade somnolence was significantly higher with OLANZ than DEX (52.0% vs 25.8%), with all events being $\leq$ grade 2. **Conclusions:** A dexamethasone-free antiemetic regimen was non-inferior to standard dexamethasone-based prophylaxis for prevention of vomiting in children and adolescents receiving HEC. These findings support the use of olanzapine as an effective steroid-sparing alternative. Clinical trial information: CTRI/2022/08/045009. Research Sponsor: CanKids KidsCan, the National Society for Change For Childhood Cancer In India.

Integrating genomics, imaging, and clinical data for late-onset cardiomyopathy prediction in pediatric cancer survivors: A multi-modal machine-learning comparison using St. Jude Cloud.

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Background: Pediatric cancer survivors face substantial risk of anthracycline- and radiation therapy (RT)-related cardiomyopathy (CM). Current risk stratification using clinical factors alone demonstrates suboptimal discriminative capacity. We hypothesized that integrating multi-modal data (clinical, genomic, and cardiac imaging/electrocardiography) would enhance predictive accuracy for late-onset CM beyond single-modality models. **Methods:** We analyzed data from 1,217 adult survivors of childhood cancer enrolled in the St. Jude Lifetime Cohort (SJLIFE), accessed via St. Jude Cloud. The primary endpoint was CM, defined as left ventricular ejection fraction (LVEF) <50% or ≥10% absolute decline from baseline. Four progressively complex feature sets were evaluated: (1) Clinical-Only (anthracycline/RT dose, age at diagnosis, sex); (2) Clinical+Genomic (adding 31 protective variants from PeCan); (3) Clinical+ECG/Imaging (adding 86 signal-processed ECG features and global longitudinal strain [GLS]); and (4) Multi-Modal (comprehensive integration). Logistic regression, random forest (RF), and extreme gradient boosting (XGBoost) algorithms were compared using 5-fold stratified cross-validation. Model interpretability was assessed via SHapley Additive exPlanations (SHAP) analysis. **Results:** Clinical-Only models demonstrated limited discrimination (AUC 0.70; 95% CI, 0.65-0.75). Incremental addition of genomic data (AUC 0.85) or ECG/GLS parameters (AUC 0.89) substantially improved performance. The Multi-Modal XGBoost model achieved superior predictive accuracy (AUC 0.93; 95% CI, 0.90-0.95; sensitivity 0.88; specificity 0.89), marginally outperforming RF (AUC 0.91). SHAP analysis identified GLS as the dominant predictor, followed by cumulative anthracycline dose and protective genomic variants, demonstrating synergistic contribution of multi-modal features. **Conclusions:** Multi-modal machine learning integration using open-source St. Jude Cloud data enables highly accurate prediction of late-onset CM in pediatric cancer survivors (AUC 0.93). The demonstrated superiority over single-modality approaches supports a paradigm shift toward comprehensive risk stratification. This XGBoost-based model could facilitate precision survivorship care, enabling risk-adapted surveillance intensification and early cardioprotective intervention for high-risk patients. Research Sponsor: None.

Comparative performance of machine learning models for 10-year cardiomyopathy risk prediction.				
Model Type	Algorithm	AUC (95% CI)	Sensitivity	Specificity
Clinical-Only	Log. Reg.	0.70 (0.65-0.75)	0.62	0.66
Clinical + Genomic	Random Forest	0.85 (0.81-0.89)	0.79	0.82
Clinical + ECG/GLS	XGBoost	0.89 (0.86-0.91)	0.78	0.81
Multi-Modal (Full)	XGBoost	0.93 (0.90-0.95)	0.88	0.89

Longitudinal genomic characterization of pediatric acute myeloid leukemia at diagnosis and relapse.

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Background: Relapse remains the leading cause of treatment failure and mortality in pediatric acute myeloid leukemia (pAML). In AML, relapse is common and is increasingly recognized as a consequence of therapy-driven clonal evolution rather than mere persistence of the diagnostic clone. This study aimed to delineate mutational trajectories from diagnosis to relapse and identify relapse-associated genomic alterations of potential clinical relevance. **Methods:** This prospective study was conducted from July 2021 to December 2025. Bone marrow or peripheral blood samples were collected from children ≤ 18 years at diagnosis and relapse. Genomic DNA from paired samples was sequenced exomically to identify somatic mutations. Longitudinal comparative analyses assessed clonal persistence, emergence of relapse-specific mutations, and pathway-level enrichment. **Results:** A total of 100 children with AML were enrolled. Paired longitudinal analysis ($n=18$) identified 133 mutated genes. Seventy-nine (59.4%) were shared between diagnosis and relapse, forming a conserved truncal genomic backbone. Fifty genes (37.6%) were exclusive to diagnosis, while only four (3.0%) were exclusive to relapse, suggesting strong therapeutic selection pressure rather than widespread genomic diversification. At diagnosis, missense variants predominated (88.4%), followed by in-frame insertions/deletions (6.5%), nonsense (2.4%), and frameshift alterations (2.5%). Relapse samples showed further enrichment of missense variants (90.5%) and a relative depletion of truncating events, consistent with selection for functionally adaptive mutations. Truncal alterations were consistently observed in epigenetic regulators TET2 and KMT2C, supporting their role as early leukemogenic events. In contrast, relapse samples showed enrichment of signaling and transcriptional regulators, including FLT3 and PTPN11, along with relapse-exclusive emergence of WNT pathway components (FZD7, LEF1) and the PI3K regulator PIK3R1. Functional enrichment analysis revealed that diagnostic samples were primarily enriched for DNA damage response, p53 signaling, apoptosis, and cell-cycle checkpoint pathways ($p<0.05$). At relapse, these core programs persisted alongside marked enrichment of oncogenic signaling pathways (WNT, PI3K-AKT, FLT3) and metabolic processes, including glycolysis and ATP generation. Reactome analysis highlighted convergence on FLT3- and AKT-driven signaling, TP53-mediated DNA repair, and escape from apoptosis. **Conclusions:** Longitudinal genomic profiling demonstrates that pAML relapse is driven by the persistence of early truncal mutations, coupled with the selective expansion of signaling- and metabolism-adapted subclones. Enrichment of WNT, PI3K-AKT, and FLT3-associated pathways at relapse reveals potential targets for relapse-directed precision strategies. Research Sponsor: Indian Council of Medical Research.

Distinct immunologic vs progenitor landscapes in myeloid leukemia recurrence: Adaptive immune persistence in pediatrics vs niche exhaustion in adults.

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Background: Recurrent myeloid leukemia remains a therapeutic challenge with distinct clinical trajectories across age groups. While our parallel study identified a "universal adipogenic shift" in the marrow stroma common to all ages, the specific cellular drivers distinguishing pediatric from adult relapse remain undefined. We hypothesized that against this shared stromal background, the mechanism of recurrence diverges: the pediatric marrow mounts an adaptive immune response, whereas the aging adult marrow suffers from hematopoietic reservoir depletion. **Methods:** We analyzed the tumor microenvironment (TME) of 2,378 myeloid leukemia samples (2,007 primary, 371 recurrent) using xCell transcriptomic deconvolution. The cohort was stratified into Pediatric (< 18y, n = 2,071) and Adult (≥ 18y, n = 307) subgroups to control for ontogenic baselines. We compared differential expression rankings between primary and recurrent states using Mann-Whitney U tests with Bonferroni correction (P_{adj}) to identify age-specific dominance in TME remodeling. **Results:** Comparative analysis revealed divergent TME landscapes between age groups. In pediatrics, recurrence was characterized by an "Immune-Adaptive" program; CD4+ Memory T-cells were the dominant signature (rank 4, p < 10⁻²⁷), alongside significant increases in Preadipocytes (p < 10⁻⁴⁹) and pro-B cells. Conversely, adult recurrence exhibited "Niche Exhaustion," primarily losing hematopoietic progenitors (CMP/GMP, p <10⁻⁷) and mesenchymal stem cells (MSC, p < 10⁻⁹). While CD4+ Memory T-cells increased in adults, the signal was less prominent (rank 18, p < 10⁻⁵). Both groups shared significant vascular collapse (Pericyte loss, p < 10⁻⁷), identifying it as a universal hallmark of relapse. **Conclusions:** Myeloid leukemia recurrence is driven by age-distinct microenvironmental remodeling. Pediatric relapse is defined by immune adaptation and adipogenesis, while adult relapse is characterized by progenitor and niche exhaustion. Vascular collapse represents a universal therapeutic target. These findings suggest that immunotherapy and niche-directed treatments must be tailored to the patient's age-specific TME landscape to improve outcomes. Research Sponsor: None.

Top age-specific trends in recurrent vs. primary myeloid leukemias.				
Cohort	Cell Type	Direction	Mean Diff (Rec - Pri)	P _{adj}
Pediatric (<18y)	Pericytes	Primary- High	-0.085	P < 0.05
	Preadipocytes	Recurrence- High	+0.064	P < 0.05
	MSC	Primary- High	-0.099	P < 0.05
	CD4+ Memory T-cells	Recurrence- High	+0.849	P < 0.05
	pro-B cells	Recurrence- High	+0.301	P < 0.05
Adult (≥18y)	MSC	Primary- High	-0.165	P < 0.05
	Pericytes	Primary- High	-0.078	P < 0.05
	CMP	Primary- High	-0.526	P < 0.05
	Smooth muscle	Primary- High	-0.094	P < 0.05
	GMP	Primary- High	-0.765	P < 0.05
	CD4+ Memory T-cells*	Recurrence- High	+1.184	P < 0.05

*Manually added row for comparison purposes.

The burden of childhood cancers in the South Asian Association for Regional Cooperation (SAARC) region: A GLOBOCAN 2022 analysis.

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Background: Countries of the South Asian Association for Regional Cooperation (SAARC) are home to approximately 600 million children aged 0–14 years, representing a quarter of the global child population. We report incidence and mortality for childhood cancers among South Asia's eight nations to inform priority setting for research, programming for health services, and policy for childhood cancers. **Methods:** Incidence and mortality of new childhood cancer diagnoses for all cancers combined and for selected leading diagnostic groups were retrieved from the GLOBOCAN 2022 database of Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka. Age-standardized incidence rates (ASR) and mortality-to-incidence ratios (MIR) were calculated, together with statistical examination of cross-country variation in diagnostic structure and survival trends. **Results:** In SAARC nations, 37,716 new childhood cancer diagnoses and 17,700 deaths were estimated in 2022. India contributed 68.7% of subregional cases (25,939), and Pakistan contributed 20.8% (7,841). Age-standardized rates differed and were greatest in Sri Lanka (10.4/100,000) and Pakistan (10.1) and lowest in Bhutan (2.3) and Bangladesh (3.7). Boys represented 60% of cases overall, with significant cross-country variation in sex distribution ($\chi^2=18.0$, $p=0.012$). Leukemia was the most common cancer in all countries (35–50%), followed by central nervous system (CNS) tumors. MIR ranged from 0.30 (Sri Lanka) to 0.57 (Afghanistan), reflecting extreme survival differences, with CNS tumors demonstrating disproportionately high mortality relative to incidence. **Conclusions:** SAARC childhood cancer trends reflect both population size influences and health system capacity, with a preponderance of leukemia but alarming survival gaps, particularly for CNS cancers. These findings highlight actionable priorities, including strengthening population-based childhood cancer registries, centralizing care pathways for CNS tumors, expanding standardized leukemia treatment protocols with abandonment-prevention strategies, and improving equitable access to specialty care through subregional collaboration. Research Sponsor: None.

A capacity assessment of pediatric oncology research biorepositories across a regional collaborative group in the Middle East, North Africa, and Asia.

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Background: Biobanks advance translational research in pediatric oncology. Understanding the existing biobanking infrastructure is critical for fostering collaboration and improving research capacity in low- and middle-income countries (LMICs). **Methods:** A previous research capacity survey within institutions of the Pediatric Oncology East and Mediterranean (POEM) Group collaborative network identified 26 out of 69 institutions across 23 countries, with access to clinical tissue specimens for research use. We surveyed these centers regarding sample/data management, patient population, governance, standard operating procedures (SOPs), quality systems, and funding. This study was determined non-human subjects research by the Stanford IRB. Biobanking capacity and participation were evaluated using descriptive statistics (medians, ranges, and frequencies). **Results:** Fifteen of the 26 (58%) institutions confirmed that they have a research-specific biobank; 10 of 15 (67%) participated. All surveyed biobanks collect cancer samples using broad consent, and have ongoing funding through institutional support, external collaborations or both. Principal investigators lead 20% of the biobanks, the others are institution-based and led. A median of 7 staff are involved in biobanking activities per institution (range, 3–28). Most institutions (80%) rely on Microsoft Excel for sample tracking. A quality management system is implemented in 7 of 10 (70%) of institutions, with most adhering to ISBER best practices. Five of 10 (50%) of the biobanks lack disaster management SOPs. Eight of 10 (80%) biobanks are capable of sharing samples and associated clinical data with other institutions through material/data sharing agreements. A median of 3500 samples (range, 368–6000) are stored yearly with a median of 300 samples (range, 100–1000) released for authorized research. While most biobanks viewed their national legal frameworks as supportive, 2 biobanks (20%) indicated that national regulations constrain biobanking activities. All the respondents indicated a need to improve their national regulation to support ethical biobanking practices – specifically need for improved regulation for cross-border collaborations, data privacy, and intellectual property (60%, 40% and 30%, respectively). **Conclusions:** Biobanks exist in 21.7% (15 of 69) centers within the POEM group. Biobanks in the region have robust consenting and sample collection procedures. Significant opportunities exist to enhance capacity through implementation of international quality standards, and improved disaster preparedness. Further understanding of the determinants of successful initiation and maintenance of these biobanking efforts in LMICs will guide targeted initiatives to further expand regional biobanking infrastructure and augment research collaborations. Research Sponsor: None.

Cancer outcome among adolescents in Canada.

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Background: Adolescents and young adults (AYA) with cancer, commonly defined as patients aged 15–39 years at diagnosis, experience higher morbidity and mortality compared with other age groups. In this study, we compared outcomes of adolescents with newly diagnosed cancer treated at Canadian pediatric oncology centers with those of younger children. **Methods:** We conducted a retrospective cohort study using the population-based CYP-C database, including children aged 1–18 years with newly diagnosed cancer across Canada (2015–2020). Event-free survival (EFS) and overall survival (OS) were compared between adolescents (15–18 years) and younger children (1 to <15 years) across cancer subtypes using Kaplan–Meier analyses and univariable and multivariable Cox proportional hazards models. **Results:** Of the 6,794 patients, adolescents aged 15–18 years comprised 16% (n=1,075) of the cohort. Median age at diagnosis was 16 years (IQR: 15.7–17.2), and among those with solid tumors, 26% (n=150) had metastatic disease at diagnosis. The most frequent adolescent cancers were Hodgkin lymphoma (20%), gliomas and other glioneuronal tumors (12%), acute lymphoblastic leukemia (11%), osteosarcoma (6%), thyroid carcinoma (6%), malignant extracranial germ cell tumors (5%), and Ewing sarcoma (4%). Adolescents with leukemia had comparable 5-year EFS (71% vs. 79%; p=0.06) and OS (83% vs. 89%; p=0.07) to younger children, as did those with non-central nervous system (CNS) solid tumors for EFS (65% vs. 65%; p=0.55) and OS (74% vs. 75%; p=0.23). Among patients with sarcomas, adolescents had similar 5-year EFS (50.7% vs. 52.0%, p=0.55) and OS (55.6 vs. 59.7%, p=0.14) to younger children. Adolescents with CNS tumors had superior EFS (83% vs. 66%; p=0.005) and OS (89% vs. 73%; p=0.006), primarily driven by ependymoma and choroid plexus tumors, and other gliomas/glioneuronal tumors excluding pilocytic astrocytoma. **Conclusions:** Although AYA with cancer are often reported to have poorer outcomes, adolescents aged 15–18 years treated exclusively in Canadian pediatric oncology centers did not have inferior outcomes to younger children, underscoring the effectiveness of pediatric treatment approaches. Research Sponsor: None.

5-year EFS and 5-year OS of adolescents (≥15 years-old) vs. younger children (1 to < 15 years old) across major cancer categories.

	Adolescents 5-year EFS (%) [95% CI]	Younger children 5-year EFS (%) [95% CI]	p-value	Adolescents 5-year OS (%) [95% CI]	Younger children 5-year OS (%) [95% CI]	p-value
All cancers	76.4 [72.8-79.9]	72.6 [70.8-74.3]	0.12	84.7 [81.4-87.4]	81.1 [79.6-82.7]	0.13
Leukemias	71.2 [58.7-80.5]	79.0 [75.8-81.9]	0.06	83.2 [73.3-89.7]	88.6 [86.2-90.6]	0.07
Lymphomas	88.5 [82.6-92.5]	87.3 [82.6-90.7]	0.63	96.2 [91.9-98.3]	95.5 [92.7-97.3]	0.50
Non-CNS solid tumors	65.4 [58.6-71.3]	65.2 [61.8-68.3]	0.55	73.5 [66.7-79.0]	74.8 [71.5-77.9]	0.23
CNS tumors	83.1 [74.2-89.1]	66.3 [62.5-69.8]	0.005	89.1 [82.0-93.5]	72.5 [68.8-75.9]	0.006

Beyond translation: Leveraging interpreter expertise to enhance clinician training and language equity in pediatric oncology.

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Background: Medical interpreters play a critical role in pediatric oncology beyond translation by guiding conversations, interpreting cultural and emotional cues, and ensuring families with limited English proficiency (LEP) can access medical information. Yet few clinician training resources focus on interpreter-mediated communication. This study aimed to (1) identify communication best practices and challenges from the perspective of professional medical interpreters and (2) develop an educational toolkit for clinicians to promote equitable, patient-centered communication for families with LEP. **Methods:** We conducted semi-structured individual interviews and a focus group with Spanish medical interpreters from six freestanding children's hospitals across the United States between 12/2024-10/2025. Verbatim transcripts were thematically analyzed in Dedoose, and resulting themes directly informed creation of an educational toolkit. **Results:** Sixteen interpreters (15 female, 1 male) who provide in-person interpretation participated. Benefits of in-person professional interpretation included perceiving non-verbal communication cues, serving as patient/family advocates, providing cultural and linguistic tailoring, explaining idiomatic or metaphorical clinical language, and continuity of interpreters across visits. Challenges included fragmented communication across medical teams, limited clinician understanding of cultural nuance, exclusion of parents from conversations, and remote interpreting. Based on these themes, we developed recommendations for clinicians focused on building collaborative relationships with interpreters, allowing time for interpretation, and actively checking patient and family understanding. We then designed a toolkit comprising three resources for clinicians working with interpreters: a badge reference card with a pre-, during-, and post-visit checklist; a decision-making learning module with case-based, first-person scenarios navigating interpreter-mediated encounters; and a self-paced modular course with structured lessons for in-depth learning. **Conclusions:** Interpreters identified concrete practices that enhance patient-centered care, with particular strengths evident during in-person interpretation, and challenges that undermine equitable communication. These insights informed a clinician-facing educational toolkit to improve interpreter-clinician encounters. Future studies will pilot the toolkit with ongoing, iterative refinement guided by interpreter input. Research Sponsor: Conquer Cancer, the ASCO Foundation; 2023CDA-5176592918.

Immunogenicity profiles in pediatric extra-cranial rhabdoid tumors: A framework for future risk stratification.

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Background: Malignant rhabdoid tumors (MRTs) are highly aggressive pediatric cancers driven by SMARCB1 loss. Emerging evidence suggests that the tumor immune microenvironment may influence the biological behavior of tumors. However, data on immune patterns in extra-cranial MRTs remain extremely limited, particularly in low- and middle-income settings. This study characterizes immune marker expression and immune phenotypes in a large single-center cohort to explore their potential relevance for future risk stratification. **Methods:** Formalin-fixed paraffin-embedded specimens from pediatric extra-cranial MRTs were evaluated for CD4⁺, CD8⁺, and CD68⁺ immune infiltrates using immunohistochemistry. Marker expression was categorized as high or low. Tumor immune phenotypes were subsequently classified based on the balance of infiltrating populations into: (immune-cold (uniformly low), mixed (variable across markers), and inflamed (uniformly high). Associations between immune phenotypes, clinicopathologic features, and survival trends were explored to determine whether immune architecture could serve as a biologically meaningful correlate of clinical behavior. **Results:** Individually, none of the immune markers (CD4, CD8, CD68) showed statistically significant correlation with overall survival. However, higher CD4⁺ and CD8⁺ T-cell infiltration demonstrated a consistent trend toward improved clinical outcomes. The most informative observation emerged at the phenotype level: tumors with a mixed immune profile exhibited more favorable survival trends and delayed progression compared with immune-cold tumors, whereas fully inflamed tumors were rare. These findings suggest that the equilibrium and interaction of immune infiltrates—rather than absolute immune cell density—may shape clinical behavior. **Conclusions:** Pediatric extra-cranial MRTs demonstrate distinct immune microenvironment patterns that are readily identifiable using routine immunohistochemistry. Although individual immune markers did not independently predict survival, immune-cold versus mixed phenotypes reflected meaningful biological divergence and aligned with clinical outcomes. Integrating immune phenotyping into diagnostic workflows may provide a pragmatic foundation for future risk stratification and help identify patients most likely to benefit from emerging immuno-epigenetic treatment strategies. **Statement of Clinical Significance:** Immune profiling using routine immunohistochemistry can classify pediatric extra-cranial rhabdoid tumors into clinically relevant immune phenotypes. Identifying immune-cold versus mixed tumors may support future risk stratification and guide biologically informed treatment selection. **Research Sponsor:** None.

Peptide receptor radionuclide therapy with ^{177}Lu -DOTATATE in pediatric, adolescent, and young adult neuroendocrine tumors: A single-center experience from Bambino Gesù Children's Hospital.

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Background: Neuroendocrine tumors (NETs) in pediatric, adolescent, and young adult (AYA) patients are rare and often associated with hereditary syndromes such as Von Hippel Lindau (VHL) and type 1 neurofibromatosis (NF1). Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu -DOTATATE is well established in adults with somatostatin receptor-positive NETs, but data in younger populations remain limited. We report our single-center experience evaluating feasibility, safety, and efficacy of PRRT in this age group. **Methods:** We retrospectively analyzed patients <20 years treated with ^{177}Lu -DOTATATE at Bambino Gesù Children's Hospital between 2019 and 2025. Eligibility required somatostatin receptor expression confirmed by PET-DOTA imaging (Krenning score ≥ 2). Data included demographics, age at diagnosis and PRRT, tumor characteristics, prior therapies, PRRT cycles, cumulative dose, toxicity, and best response per RECIST. Follow-up status was assessed at last visit. **Results:** Six patients (median age at diagnosis 11 years, range 7–16; median age at PRRT 15 years, range 10–19) received PRRT for metastatic or unresectable NETs (pheochromocytoma/paraganglioma, n=5; bronchial carcinoid, n=1). All completed 4 cycles of ^{177}Lu -DOTATATE (median cumulative dose ~30 GBq). Prior treatments included surgery, chemotherapy (temozolomide), and MIBG therapy. No grade ≥ 3 hematologic or renal toxicity occurred; treatment was well tolerated. Best responses: 4 partial responses (PR), and 2 stable disease (SD). At a median follow-up of 18 months, all patients were alive: one in complete remission after surgery, others with stable disease or ongoing therapy. Genetic predisposition was present in 3 patients (VHL, NF1). SUVmax on baseline PET ranged from 1.2 to 43.8, correlating with Krenning score ≥ 2 in all cases. **Conclusions:** PRRT with ^{177}Lu -DOTATATE is feasible and well tolerated in pediatric, adolescent, and young adult patients with somatostatin receptor-positive NETs, achieving meaningful disease control with minimal toxicity. This single-center experience supports PRRT as a valuable option in selected cases and highlights the need for prospective studies and age-specific guidelines. Research Sponsor: None.

Clinical impact of panel-based next-generation sequencing in a real-world cohort of neuroblastoma patients.

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Background: Neuroblastoma is a malignant childhood tumor with a low somatic mutation rate, making targeted therapy challenging. Using a targeted NGS panel in a large real-world cohort, we identified recurrent variants and assessed the clinical impact of NGS for this disease. **Methods:** A real-world cohort of 185 peripheral neuroblastic tumor samples from 181 patients were sequenced with a targeted NGS assay (OncoPanel). Samples were either obtained at baseline ("diagnostic") or at relapse/progression ("relapse"). Variants include SNVs, CNAs, and SVs and were manually curated for pathogenicity. Recurrently altered genes were those curated as Pathogenic/Likely Pathogenic and occurring in more than 4% of samples. Clinically impactful findings were those with therapeutic implications (e.g., targetable *ALK* aberration) and those with prognostic implications at diagnosis (e.g. *MYCN* amplifications or segmental chromosomal aberrations (SCAs) included in the Children's Oncology Group (COG) risk stratification system). SCAs were defined as regions of loss or gain of at least 3Mb. Mutual exclusivity analyses utilized false-discovery rate corrected Fisher exact tests. **Results:** All COG risk groups were represented. At time of last follow-up (median 65.9 months), 103 (59%) were alive with no disease, 31 (18%) were alive with disease or unknown disease status, and 41 (23%) were deceased. Of the diagnostic cohort (n=144), 78 (54%) had at least one clinically impactful alteration (n=42 prognostic only, n=13 therapeutic only, n=23 both). Of the relapse cohort (n=41), 14 (34%) had a therapeutically impactful variant. Recurrently altered genes in the diagnostic samples included *MYCN*, *ALK*, *ATRX* and *MYCN*, *ALK*, *ATRX*, *BRAF*, *CREBBP*, *MLH3*, *PHOX2B* and *TERT* in the relapse samples. The most commonly observed SCA was 17q gain. Among the 144 diagnostic samples, no patients were observed to have both *MYCN* amplification and an *ATRX* variant nor *MYCN* amplification and 11q loss; this mutual exclusivity was statistically significant for *MYCN* amplification and 11q loss (adjusted p <0.001). **Conclusions:** Targeted NGS panels provided clinically impactful results in a majority of cases in a real-world cohort of children with neuroblastoma. Future analyses will include survival analysis by genomic features and comparison of NGS to standard clinical testing. Research Sponsor: None.

Key genomic findings across clinical cohorts.

	Diagnosis (n=144)	Relapse (n=41)	High-risk (HR)(n=53)	Non-HR(n=62)
<i>ALK</i> variant	29 (20.1%)	8 (19.5%)	14 (26.4%)	9 (14.5%)
<i>ATRX</i> variant	7 (4.9%)	3 (7.3%)	5 (9.4%)	1 (1.6%)
<i>BRAF</i> variant	1 (0.7%)	3 (7.3%)	0 (0%)	1 (1.6%)
<i>PHOX2B</i> variant	5 (3.5%)	2 (4.9%)	4 (7.5%)	1 (1.6%)
<i>MYCN</i> amplification	27 (18.8%)	10 (24.4%)	16 (30.2%)	3 (4.8%)
17q gain	87 (60.4%)	27 (65.9%)	33 (62.3%)	39 (62.9%)
1p loss	17 (11.8%)	11 (26.8%)	12 (22.6%)	3 (4.8%)
11q loss	35 (24.3%)	12 (29.3%)	14 (26.4%)	17 (27.4%)

Results of a phase II trial of nivolumab and ipilimumab in children and young adults with relapsed or refractory INI1-deficient cancers.

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Background: Several aggressive pediatric and young adult cancers are characterized by loss of INI1 expression, including malignant rhabdoid tumor, ATRT, epithelioid sarcoma and poorly differentiated chordoma. These cancers have a poor prognosis and limited effective treatments for relapsed or refractory disease. Prior data nominated immune checkpoint inhibition as a potential strategy for INI1-deficient tumors. **Methods:** In this phase II multicenter trial of nivolumab and ipilimumab, patients 6 months to 40 years with relapsed or refractory INI1-deficient cancers were enrolled in two strata: extracranial solid tumors (Stratum 1) and CNS tumors (Stratum 2). The primary endpoint was objective response $\geq$ partial response (PR) by RECIST v1.1 (Stratum 1) or RANO (Stratum 2). Secondary endpoints included progression-free survival, overall survival and 12-month disease control rate. Patients received nivolumab 3mg/kg and ipilimumab 1mg/kg every 3 weeks for 4 cycles followed by nivolumab 3mg/kg every 2 weeks for up to 1 year. A Simon’s two-stage design targeted a response rate $>25\%$, with each stratum assessed separately. Interim analysis at Stage 1 required ≥ 1 of 10 patients to have response $\geq$ PR to proceed to Stage 2; at Stage 2, ≥ 3 of 20 patients with response $\geq$ PR for evidence of efficacy. Evaluable patients received study treatment and were assessed for response or had progressive disease. **Results:** Thirty patients from six centers enrolled across both Strata from 8/2020 to 5/2025 and 27 were evaluable for the primary endpoint. Three inevaluable Stratum 1 patients were replaced per protocol. In Stratum 1, 1 patient (with poorly-differentiated chordoma) of 20 evaluable patients had $\geq$ PR (ORR: 5%; 95% CI: 0.1–25%). In Stratum 1 (n=20), the 3-month EFS $\pm$ SE and OS $\pm$ SE were 20% $\pm$ 9% and 60% $\pm$ 11%, respectively, and the proportion of patients who were progression-free at 12-months was 5% (95%CI=0.1%–25%). Stratum 2 closed early with 7 patients enrolled, too few for Stage 1 interim analysis. No Stratum 2 patients had $\geq$ PR [ORR: 0% (n=7)]. Patients received a median of 2 cycles of study treatment. The most common $\geq$ grade 3 treatment-related adverse events were decreased lymphocyte count (n=3), increased AST (n=3) anemia (n=2), and pneumonitis (n=2). **Conclusions:** The study did not meet the predetermined threshold for efficacy for Stratum 1. Immune checkpoint inhibitor therapy could warrant further exploration in poorly differentiated chordoma. Clinical trial information: NCT04416568. Research Sponsor: Gateway for Cancer Research; Alex’s Lemonade Stand Foundation for Childhood Cancer.

Patient characteristics (n=27 evaluable patients).	
	Median (Range)
Age at enrollment (years)	7.1 (0.6-37.6)
Lines of prior therapy	2 (1-7)
	n (%)
Age group	
<18 yrs	24 (89%)
≥ 18 yrs	3 (11%)
Sex	
Male	15 (56%)
Female	12 (44%)
Cancer diagnosis	
Stratum 1	20 (74%)
Malignant Rhabdoid Tumor	12 (60%)
Poorly Differentiated Chordoma	3 (15%)
Epithelioid Sarcoma	2 (10%)
Other	3 (15%)
Stratum 2	7 (26%)
Atypical Teratoid Rhabdoid Tumor	7 (100%)

Safety and feasibility of cabozantinib (CABO) in combination with cisplatin, doxorubicin, and high-dose methotrexate (MAP) in patients with newly diagnosed high-risk osteosarcoma (OS).

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Background: CABO is a multi-targeted kinase inhibitor of VEGFR2, c-MET, AXL and RET and has shown clinical evidence of activity in two prior studies of adult and pediatric patients with advanced OS. We report results of a feasibility cohort of CABO + MAP chemotherapy in patients with newly diagnosed high-risk OS. **Methods:** Patients <40 years, body surface area $\geq 0.8 \text{ m}^2$ and new diagnosis of high-grade OS with metastatic disease and resectable primary tumor were eligible. Patients were enrolled to two CABO dose levels (Dose Level 1 (DL1) 25 mg/m²/day, maximum 40 mg/day; Dose Level 2 (DL2) 35 mg/m²/day; maximum 60 mg/day) using a modified IQ 3+3 design. CABO was orally administered concomitantly with six 35-day cycles of MAP (cisplatin 60 mg/m² on days 1-2 (cycles 1-4), doxorubicin 37.5 mg/m² on days 1-2 (with dexrazoxane), methotrexate 12 g/m² on days 22, 29) and for 24 weeks as maintenance monotherapy. CABO was held after 7 weeks and resumed during 4th MAP cycle to allow for primary tumor resection and metastatic surgeries. Dose-limiting toxicities (DLT) were assessed during weeks 1-6 of treatment; additional monitoring for post-surgical complications was conducted through completion of 4th MAP cycle. The primary endpoint for this cohort was feasibility of combination therapy. **Results:** Ten patients (median age 11.5 years, 70% male) were enrolled and treated with CABO + MAP (DL1, n=4; DL2, n=6). Median cumulative doses of all MAP agents were maintained throughout treatment with no dose reductions. Concomitant dosing of CABO with MAP was tolerated with no protocol-specified DLTs occurring during the evaluation period. DL2 (35 mg/m²) was established as the recommended dose for further study of combination therapy. Commonly reported adverse events included hematologic toxicities, febrile neutropenia, and alanine/aspartate aminotransferase (AST/ALT) elevation. Interruption of CABO was required in 6 patients for Grade 3+ AST/ALT elevation following methotrexate (n=3), wound complications (n=3), and Grade 3 pneumothorax (n=1). Wounds included two Grade 3 port site events and one Grade 1 primary tumor resection site; two patients later resumed CABO after healing without wound recurrence. Dose reduction of CABO was required in one patient for Grade 4 amylase elevation. **Conclusions:** The combination of CABO + MAP is feasible with no protocol-specified DLTs during the evaluation period. Generalizability is limited based on cohort size. Further evaluation of CABO + MAP is ongoing in a phase II/III randomized efficacy study in newly diagnosed standard and high-risk patients using CABO dose of 35 mg/m²/day (max 60 mg), with delayed initiation of CABO in patients with port placement and early safety monitoring for wound-related events, as well as full study monitoring of dose delivery, wound complications and systemic toxicity. Clinical trial information: NCT05691478. Research Sponsor: Children's Oncology Group.

Long term effects of treatment with dabrafenib (D) and/or trametinib (T) in pediatric patients with MAPK pathway-activated tumors.

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Background: Studies have shown the clinical benefits of D and T, in combination and as monotherapy, to treat adult and pediatric patients with *BRAF* V600 mutation-positive cancers. Here, we report the interim results from a long-term, follow-up study for patients from previously completed clinical trials that assessed the use of D and/or T in pediatric patients with MAPK pathway-activated tumors. **Methods:** This ongoing, global, open-label, multi-center study evaluated the long-term effects (general health, growth and development) of D and/or T in pediatric patients with tumors with MAPK pathway activation from previous studies that assessed (1) safety, tolerability and pharmacokinetics of D in solid tumors (NCT01677741); (2) pharmacodynamics and clinical activity of T or D+T in cancer or plexiform neurofibromas (NCT02124772); and (3) safety and efficacy of D+T in glioma (NCT02684058). The patients in this study followed the same treatment as at the end of the parent study. The duration of this study is 7 years after the first patient first visit (FPFV) (November 2019). The primary objective is to assess the long-term safety of the treatment. **Results:** Of a total 165 patients, 157 received the study treatment (D [n=28], T [n=21], D+T [n=108]) and 8 patients were for observation only. Most patients with low-grade glioma (LGG) and high-grade glioma (HGG) had *BRAF* V600 mutation (n=129). The median duration of exposure was approximately 21 months. From FPFV to the data cut-off (October 2024), most of the patients (94.3%) experienced at least one adverse event (AE) with 28% patients experiencing serious AEs. The most common AE was pyrexia (36.9%). AEs leading to treatment discontinuation occurred in 3.8% of total patients (D [3.6%], T [9.5%], D+T [2.8%]). One on-treatment death was reported in the D+T arm due to convulsion (not related to the study treatment). No clinically meaningful changes were observed in hematological or biochemical parameters in the D+T arm. Grade ≥ 3 abnormalities were infrequent and were reported in <2% of patients, except creatine kinase increase (5.7%). Assessment of vital signs, growth, electrocardiography, bone age and Tanner staging did not reveal any new safety signals. In the D+T arm, as per investigator assessment, overall response (complete + partial) was 27.7% for patients with *BRAF* V600E mutation positive LGG (stable disease: 63.9% patients) and 41.2% for patients with *BRAF* V600E mutation positive HGG. The median progression-free survival and median overall survival were not reached. **Conclusions:** In this long-term study, reported AEs were in line with established safety profile of D and/or T. Except more than normal increase in weight, no significant impact of D and/or T was observed on growth, sexual maturation and skeletal development. The benefit-risk remained favorable toward D and/or T therapy in pediatric patients with MAPK pathway-activated tumors. Clinical trial information: NCT03975829. Research Sponsor: Novartis Pharma AG.

Comprehensive genomic landscape of osteosarcoma: Systematic review and analysis of 1,058 patients across 20 studies with therapeutic implications from the Fight Osteosarcoma Through European Research (FOSTER) Consortium.

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Background: Osteosarcoma exhibits profound genomic complexity, complicating biomarker discovery. Although advances in multi-omics profiling have improved biological understanding, genomic data remain fragmented across heterogeneous cohorts, and actionable alterations are rarely reported. **Methods:** A systematic review identified 20 studies published between 2005 and 2022, spanning heterogeneous sequencing technologies (whole-genome/exome/RNA sequencing, methylome, and targeted gene panels) and reporting genetic drivers and/or potentially actionable mutations. Mutation data were manually extracted from the published results (e.g., tables, figures, oncoplots) and integrated into a binary Mutation Annotation Format - like matrix (1,041 samples, 471 genes) to provide a comprehensive overview of variants reported to date. **Results:** 1058 patients were included, with tissue derivation (primary, metastatic, recurrent) described in about 10% of the cases. 3816 germlines or somatic SNVs, CNVs or structural alterations were reported in 471 genes. *TP53* (40%), *RB1* (18%), and *CDKN2A/B* (17%) were the most frequently altered genes, alongside with recurrent changes in cell cycle regulators (*CCND* family) and angiogenesis-related genes (*VEGFA*). Potentially actionable variants were less common: *MYC* (13%, all amplifications), *CDK4* (10%), *PDGFRA* (8%); single agent activity against such targets is either lacking or not yet available. Potentially actionable epigenetic targets were rarely identified: *TET2* (0.2%), *IDH2* (0.3%), *DNMT3A* (0.7%). TCGA-based pathway analysis revealed consistent involvement of *TP53*, cell cycle, RTK-RAS, PI3K, and *MYC* signaling. Co-occurrences detected were *TP53* with *MAP2K4*, *RICTOR*, *PTPRD* and *RB1* genes, and structural rearrangements affecting RTK-RAS and PI3K pathways. There was relative exclusivity between mutations of *RB1* and *CDK4*. **Conclusions:** The analysis identifies a small number of recurrently mutated genes and a large number of rarely affected, though potentially actionable, mutations, encoding proteins involved in cell surface, nuclear and epigenetic interactions. Lack of harmonization in data processing, mutation calling and definition of 'over' and 'under' expression, together with absent descriptions of tissue derivation hamper effective large scale analysis and phenotypic subgrouping. *TP53* mutation co-occurrences such as *RICTOR* or *RB1* were also identified, with potential therapeutic implications including *WEE1* and mTOR inhibitors. Tumors with overactive *CDK4/6* typically have functional *RB1* and might be sensitive to CDK inhibitors. Harmonization of multi-omic methods and collaborative international analyses are essential to advance precision medicine in osteosarcoma and to inform future trials. Research Sponsor: None.

Association of response with survival in patients with relapsed/refractory high-risk neuroblastoma: A report from NANT Consortium.

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Background: Patients with relapsed/refractory (RR) high-risk neuroblastoma (HR-NB) have poor survival. Tumor response may be an early predictive endpoint, though response may not reflect long term survival. We evaluated the association between NANT Response Criteria (NANTRC) v1.2/2.0 with event-free survival (EFS) and overall survival (OS) in patients with RR-NB treated on contemporary NANT Phase 1/2 trials. **Methods:** Patients enrolled on 8 NANT trials from 2013 to 2022 were included. For patients enrolled on more than one trial, the first trial data was included. NANTRC were utilized to grade individual response components (soft tissue [ST], bone/MIBG, bone marrow [BM]) and overall response (complete [CR], partial [PR], minor [MR] response, stable disease [SD], or progressive disease [PD]). Patient/tumor characteristics, prior therapy and relapse, and disease at enrollment were analyzed for association with best overall response (BOR). Component and BOR were analyzed for association with EFS and OS from trial treatment initiation. EFS and OS were compared with the log-rank test and estimated by the Kaplan-Meier methods. **Results:** Among 244 patients, 3-year OS was 52% (95% confidence interval [CI] 46-58%), and EFS was 22% (95% CI 14-32%). OS differed significantly by best overall response ($p < 0.001$), driven primarily by inferior outcomes of patients with PD. The 3-year OS was 16% (95% CI 9-29%) for patients with PD. Patients achieving objective response (CR/PR/MR) had an OS of 63% (95% CI 55-74%) and EFS 25% (95% CI 15-43%), while those achieving disease control (CR/PR/MR/SD) had very similar OS of 63% (95% CI 57-71%) and EFS 29% (95% CI 20-43%). Among patients with response of CR, PR, MR, or SD, OS and EFS were not significantly different. For individual components, a similar impact on OS was seen for PD vs no PD (all $p < 0.001$), with BOR of PD in MIBG/bone and ST having OS $< 10\%$. Patients lacking either BM or bone/MIBG involvement (but not ST) at baseline and remained not involved in those components demonstrated superior OS (both $p < 0.001$). Patients with BOR of PD had shorter time from diagnosis to first progression (median of 1.4 vs 1.8 years, $p = 0.035$), and higher incidence of MYCN-amplified disease (46% vs. 14%, $p < 0.001$) and prior history of progression (95% vs 73%, $p < 0.001$). **Conclusions:** In RR-HRNB treated on contemporary NANT trials, BOR of PD is associated with inferior OS. Patients achieving disease control (CR/PR/MR/SD) experienced comparable outcomes regardless of response achieved. These findings support disease-control as a clinically meaningful efficacy endpoint for early-phase neuroblastoma trials. Research Sponsor: National Cancer Institute; P01 CA217959; V Foundation for Cancer Research; St. Baldrick's Foundation; United Therapeutics; Pfizer; Band of Parents; Anonymous.

3-year survival by component response.

Component	Response	N	OS % (95% CI)	EFS* % (95% CI)
BM	Non-PD	100	47 (38, 58)	17 (7, 38)
	PD	18	29 (14, 61)	-
Bone/MIBG	Non-PD	180	59 (52, 66)	22 (13, 35)
	PD	30	7 (2, 26)	-
ST	Non-PD	142	61 (53, 70)	28 (18, 44)
	PD	35	9 (3, 25)	-

*EFS censored at time of new therapy.

HopeMove: Feasibility and acceptability of a mobile exercise app for pediatric patients undergoing cancer treatment.

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Background: Cancer related fatigue and reduced physical activity are common during pediatric cancer treatment and negatively affect daily functioning and quality of life. Although exercise is recommended as supportive care, maintaining regular physical activity during active treatment is challenging. Digitally delivered exercise programs may offer flexible and safe supportive care options. This study evaluated the feasibility, acceptability, usability, and safety of the HopeMove mobile exercise app and explored preliminary changes in fatigue among adolescents undergoing cancer treatment. **Methods:** This prospective, single center pilot feasibility study included adolescents aged 13–18 years undergoing active cancer treatment (N=15). Participants completed 45 minute video guided exercise sessions at least three times per week for eight weeks. The intervention was developed through a multidisciplinary collaboration involving pediatric oncology clinicians, pediatric nurses, physiotherapists, and engineers. Exercise sessions included warm-up, aerobic, strengthening, flexibility, and cool down components, with seated and standing options tailored to individual clinical needs. Prior to patient implementation, the HopeMove mobile application was evaluated by 10 clinical experts using the Mobile Application Usability Scale (MAUS). Feasibility outcomes included recruitment, retention, adherence, and technical performance. Adherence was defined as completing at least 75% of planned exercise sessions. Participant satisfaction was measured with a Visual Analog Scale (VAS). Before the intervention, adolescents completed brief application evaluation questions. Fatigue was assessed before and after the intervention using a validated pediatric oncology specific fatigue scale. Safety was monitored throughout the study. **Results:** All eligible adolescents agreed to participate and completed the intervention, resulting in 100% recruitment and retention. Twelve participants (80%) met adherence criteria. The application showed high usability (mean MAUS score 6.55 ± 0.49) and high satisfaction (VAS mean 6.66 ± 0.48). Participants reported the application to be easy to use and age appropriate. Fatigue scores improved significantly after the intervention, increasing from 100.06 ± 22.28 at baseline to 139.26 ± 18.89 post-intervention ($p < 0.001$). Significant improvements were observed across fatigue subdomains (all $p < 0.01$). No exercise related adverse events, injuries, falls, or treatment interruptions were reported. **Conclusions:** HopeMove was feasible, acceptable, and safe for adolescents undergoing active cancer treatment. High adherence, favorable usability, and improved fatigue outcomes suggest that mobile, video guided exercise interventions may support supportive care in pediatric oncology. Larger controlled studies are warranted. Clinical trial information: NCT07274358. Research Sponsor: None.

Concurrent RNA- and DNA-NGS testing for the detection of clinically-relevant fusions in pediatric solid-tumor patients.

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Background: Identifying structural rearrangements and gene fusions is critical to providing high quality, precision-driven clinical care for many types of pediatric cancers. RNA next-generation sequencing (NGS) provides a functional readout of the genome that enables superior detection of chimeric transcripts and novel driver fusions, particularly when genomic break-points reside in complex intronic regions. This study demonstrates the benefit of concurrent DNA- and RNA-NGS for fusion detection in a real world pediatric cohort of 1,050 patients, one of the largest such studies to date. **Methods:** We used the Tempus de-identified multimodal database to select a cohort of pediatric solid tumor cancer patients (all stages) who received successful DNA (Tempus xT, 648 gene panel with enhanced detection of structural variants [SVs] in 22 genes) and RNA (Tempus xR, whole-transcriptome) NGS sequencing. All patients had a minimum tumor purity of 20% and were aged 0–21 at the time of sample collection (n=1,050). All assessed fusions appeared on clinical reports. **Results:** Overall, we detected a fusion in 35.1% of patients (n=369). The top 3 cancer types in our cohort were soft tissue sarcoma (n=321), brain/CNS cancer (n=280), and bone cancer (n=120), and fusion prevalence in these types was 53% (n=170), 30.4% (n=82) and 30% (n=36), respectively. The fusion types with the highest overall prevalence were: EWSR1 (9.0%, n=95), BRAF (6.1%, n=64), PAX3-FOXO1 (2.7%, n=28), ALK (2.2%, n=23), and RET (2.0%, n=21) fusions. In assessing the subset of genes that appear on both the DNA-NGS and RNA-NGS panel, 303 patients harbored one of these fusions and 38.6% (117/303) of those fusions were detected only via RNA-NGS. Among fusions with highest prevalence, the percentage detected only via RNA-NGS ranged from 3.1% (EWSR1 fusions) to 100% (PAX3-FOXO1); BRAF (53/64, 82.8%) and ALK (4/23, 17.4%) fusions both had comparatively high proportions detected only via RNA-NGS. RNA-NGS alone detected gene fusions in 65 additional patients where neither partner appears on the DNA-NGS panel. Considering only fusions associated with an indication-matched FDA-approved targeted therapy, we observed a prevalence of 9.0% (94/1050), and of these, 46.8% (44/94) were detected only by RNA-NGS. Overall, 49.3% (182/369) of fusion-positive patients would have been missed if RNA-NGS were not performed, representing 17.3% of the total cohort. **Conclusions:** Pediatric solid tumors are frequently driven by structural rearrangements and gene fusions that are difficult to characterize using DNA sequencing alone. This study demonstrates that performing combined DNA-NGS and RNA-NGS substantially improves the identification of patients with a clinically relevant fusion in a large real-world data set. Research Sponsor: None.

Precision oncology in practice: Real-world multicenter experience with larotrectinib in pediatric extracranial NTRK fusion–positive tumors.

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Background: Gene fusions involving *NTRK1/2/3* represent actionable oncogenic drivers across a spectrum of rare pediatric solid tumors. Larotrectinib, a highly selective TRK inhibitor, has demonstrated robust efficacy and a favorable safety profile in clinical trials. However, real-world data from middle-income countries remain limited. We report a national multicenter real-world experience evaluating outcomes of pediatric patients with NTRK fusion–positive tumors treated with larotrectinib in Türkiye. **Methods:** This retrospective, descriptive multicenter study included pediatric patients (0–18 years) with histologically confirmed solid tumors harboring NTRK gene fusions, treated with larotrectinib for ≥ 1 month between August 2023 and April 2025. Clinical data were collected from 15 tertiary pediatric oncology centers. Treatment response was assessed using RECIST v1.1 or tumor-specific pediatric criteria. Adverse events were graded per CTCAE v5.0. Survival outcomes were analyzed descriptively. **Results:** Twenty-two patients were included; median age at diagnosis was 3 months (range, 1 day–182 months), and 59% were female. Infantile fibrosarcoma (IFS) was the most common diagnosis ($n=16$, 72.7%), followed by rhabdomyosarcoma (RMS), epithelioid sarcoma (ES), desmoplastic small round cell tumor (DSRCT). Six patients (27.3%) had metastatic disease at diagnosis. Larotrectinib was initiated due to disease progression or inadequate response to prior therapy in 86% of patients, treatment-related toxicity in 9%, and as maintenance therapy in one patient. After a median follow-up of 24 months, 10 patients achieved complete response, 6 had partial response or stable disease, and 4 experienced progression; 3 patients later relapsed. One patient died due to progressive disease. The 24-month overall survival rate was 95.5%, and 82% of patients remained event-free. No treatment-limiting adverse events were observed. **Conclusions:** In this national real-world cohort, larotrectinib demonstrated high efficacy, durable disease control, and an excellent safety profile in pediatric patients with NTRK fusion–positive solid tumors, particularly IFS. These findings support early integration of molecular diagnostics and TRK inhibition into routine pediatric oncology practice and provide valuable real-world evidence from a middle-income country setting. *Larotrectinib was provided through the early access to medicines program for humanitarian purposes and the data reflects real world data and does not reflect phase research data. The pharmaceutical company did not provide any kind of support in the planning/reporting/publication of the study. Research Sponsor: None.

Dinutuximab beta in combination with chemotherapy in patients with refractory or relapsed neuroblastoma: A national prospective study (2020/ABM/01/00055).

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Background: The ChIm-NB-PL phase IIa trial (EudraCT: 2021-003832-96) evaluated the safety and efficacy of dinutuximab beta (DB) combined with chemotherapy (Cht) in children with relapsed or refractory high-risk neuroblastoma (RR-HRNB), a population with limited therapeutic options and poor prognosis. **Methods:** Twenty-eight patients aged 1–18 years with RR-HRNB received DB combined with temozolomide/irinotecan (TemIri) or with N5/N6 chemotherapy of the German Pediatric Oncology and Hematology Group (GPOH) protocol. DB was administered as a 5-day continuous infusion (10 mg/m²/day) every 21 days, concurrently with TemIri or sequentially after GPOH. Treatment allocation and number of cycles were individualized based on prior therapy, disease dynamics, metastatic burden, and toxicity. Responses were assessed after 3 and 5–7 cycles. The primary endpoint was safety and best response (complete or partial response); secondary endpoints included progression-free survival (PFS) and overall survival (OS). **Results:** Between 2021 and 2025, 28 patients were enrolled (25% female). Median follow-up was 28.4 months. Median age was 40.9 months at diagnosis and 51.0 months at study entry. Eleven patients had refractory disease (Group 1), while 17 had relapsed or progressive disease (Group 2; 12 early and 5 late relapses). MYCN amplification was present in 9 patients, and 12 had involvement of more than one metastatic compartment. In Group 1, best response rate (BRR) was 91.7%, end-of-treatment response rate 75.0%, and metastatic complete response 58.3%; 1-year PFS was 0.67 ± 0.13 . In Group 2, BRR was 87.5% (CR 56.3%, PR 31.3%), with higher BRR in late versus early relapse (100% vs 80%); 1-year PFS was 0.81 ± 0.09 . Overall, 71.4% of patients were alive at last follow-up; 1-year PFS and OS were 0.75 ± 0.08 and 0.82 ± 0.07 , respectively. Grade ≥ 3 non-hematologic toxicities occurred 42 times with TemIri and 35 times with GPOH (CTCAE v4.0). Neurotoxicity, pain, capillary leak syndrome, and cytokine release syndrome were comparable between regimens and consistent with DB monotherapy. **Conclusions:** DB combined with TemIri or GPOH chemotherapy demonstrates high antitumor activity with acceptable and manageable toxicity in children with RR-HRNB. Response-adapted sequencing and individualized chemotherapy selection may improve disease control, including metastatic responses, in this high-risk population. Clinical trial information: 2021-003832-96. Research Sponsor: Medical Research Agency; 2020/ABM/01/00055.

A study of the safety, efficacy, and pharmacokinetics of SPJ-101CA as maintenance therapy for newly diagnosed high-risk neuroblastoma.

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Background: Isotretinoin (ISO), an oral vitamin A derivative, induces differentiation of neuroblastoma (NB) cells and is used as maintenance therapy. SPJ-101CA (Sun Pharma Ltd.), a novel ISO formulation developed with microparticle technology to enhance absorption, is designed to achieve adequate systemic exposure at 80% of the conventional dose. As ISO is an off-label treatment for NB worldwide, the present, registration-directed clinical trial was conducted to evaluate the safety, efficacy, and pharmacokinetics (PK) of SPJ-101CA in pediatric patients. **Methods:** This open-label, multicenter phase 2 trial enrolled 16 patients aged 1-18 years with newly diagnosed, high-risk NB who had completed the standard, multidisciplinary therapy without progression. Eligibility required an ECOG performance status of 0-2 and adequate organ function. The exclusion criteria were other active malignancies, gelatin allergy, pregnancy or breastfeeding, psychiatric disorder, and intolerance to the study treatment. Written informed consent was obtained from the patients' legal guardians, and assent was provided by the patients when appropriate. The patients received oral SPJ-101CA 64 mg/m² twice daily for 14 days in each, 28-day course for a total of six courses. Dinutuximab was permitted only before or after, but not during, SPJ-101CA administration. The primary endpoint was the incidence of serious adverse events (AEs). The secondary endpoints included 1-year event-free and overall survival, the AE incidence, and PK properties. Blood samples were collected on day 14 of the first course at predefined intervals to measure the plasma concentration of ISO and 4-oxo-isotretinoin, and the standard PK parameters were evaluated. **Results:** All 16 patients were included in the full analysis and per-protocol sets. Three serious AEs related to SPJ-101CA occurred in three patients (two and one case of hypertriglyceridemia and hypercalcemia, respectively), for a total incidence of 18.8%. Common, non-serious AEs included upper respiratory inflammation (75.0%), dry skin (62.5%), hypercalcemia (56.3%), eczema (50.0%), hypertriglyceridemia (43.8%), cheilitis (37.5%), pruritus (31.3%), and neutropenia (31.3%). The 1-year event-free survival rate was 93.8%, and the overall survival rate was 100%. PK analysis of 15 patients found that the mean T_{max} of ISO was 3.9 hours and that the 4-oxo-isotretinoin level remained constant and exhibited no distinct peak. The mean ISO C_{max} was approximately 2.3 µg/mL, with a half-life of about 5 hours; 4-oxo-ISO had a higher C_{max} and longer half-life. **Conclusions:** SPJ-101CA was well-tolerated and effective as maintenance therapy following multidisciplinary treatment for high-risk NB. The PK findings were consistent with the known profile of ISO and indicated good absorption of the formulation. Clinical trial information: JRCT2031220687. Research Sponsor: Sun Pharma Japan Ltd.

Phase I study of the LiViT regimen (liposomal irinotecan, vincristine, and temozolomide) in pediatric patients with relapsed/refractory solid tumors.

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Background: Relapsed or refractory solid tumors in children and adolescents remain a major therapeutic challenge with limited effective options. Liposomal irinotecan provides prolonged systemic exposure compared to conventional irinotecan and may offer improved efficacy and tolerability. We conducted a phase I trial to determine the recommended phase II dose (RP2D), safety, and preliminary antitumor activity of the LiViT regimen in patients aged 2–18 years.

Methods: This single-center, open-label phase I study enrolled patients aged 2–18 years with relapsed/refractory solid tumors. The LiViT regimen consisted of vincristine (1.5 mg/m² IV day 1; max 2 mg), temozolomide (150 mg/m²/day IV days 1–5) and liposomal irinotecan at escalating doses of 40, 50, 65, 80, or 100 mg/m² (IV day 1) every 3 weeks. A standard 3+3 dose-escalation design was used (Ia), followed by an expansion cohort (Ib). **Results:** Twenty-nine patients were enrolled (Ia: 18; Ib: 11). Diagnoses included rhabdomyosarcoma (n=12), neuroblastoma (n=9), desmoplastic small round cell tumor (n=3), Ewing sarcoma (n=2), and others (n=3). In phase Ia, liposomal irinotecan was administered at escalating doses of 40, 50, 65, 80, and 100 mg/m². At 80 mg/m², 1 of the first 3 patients experienced a dose-limiting toxicity (DLT) (grade 3 diarrhea lasting >3 days despite loperamide); the cohort was expanded to 6 patients, and no additional DLTs or other grade 3–4 toxicities were observed. No DLTs occurred among patients treated at 100 mg/m² during Ia (n=3) or in the Ib expansion cohort (n=11). The MTD was not reached, and 100 mg/m² was selected as the RP2D based on safety in 14 patients. Across all dose levels, the only grade ≥3 treatment-related adverse event was the single episode of grade 3 diarrhea at 80 mg/m²; all other toxicities were grade 1–2. Among 27 evaluable patients, 5 achieved partial response (PR) and 12 had stable disease (SD), yielding an objective response rate (ORR) of 18.5% and a disease control rate (DCR) of 63.0%. **Conclusions:** The LiViT regimen is feasible with a manageable safety profile in pediatric patients with relapsed/refractory solid tumors. The MTD was not reached, and liposomal irinotecan at 100 mg/m²—the highest tested dose—was established as the RP2D. Promising preliminary activity supports phase II evaluation. Clinical trial information: NCT06710821. Research Sponsor: None.

Changes in the incidence of second malignant neoplasms in neuroblastoma over time: An updated SEER database analysis.

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Background: To investigate changes in the incidence of second malignant neoplasms (SMN) for patients with neuroblastoma in the era of anti-GD2 immunotherapy, we analyzed patients from the SEER database according to four treatment eras (1: 1975–1989, 2: 1990–1996, 3: 1997–2010, 4: 2011–2018) corresponding to the introduction of multi-agent chemotherapy, risk-based treatment, stem cell transplant, and GD2-directed immunotherapy. We hypothesized that while the GD2-directed immunotherapy would not increase the incidence of SMNs for patients with neuroblastoma, the standardization of tandem autologous transplant would.

Methods: The SEER database was assessed for patients younger than 30 years of age with neuroblastoma (ICD-O-3 9500) or ganglioneuroblastoma (ICD-O-3 9490). Patient demographic information and characteristics were assessed, including age at diagnosis, sex, race, histology, year of diagnosis, and extent of disease. Data about delivery of chemotherapy or radiotherapy were collected when available. Statistics including the cumulative incidence of SMN, standardized incidence ratios (SIRs), and rates of SMNs between patients in different eras were calculated. **Results:** The analytic cohort included 4,491 patients. Eighty-four patients (1.9%) developed a SMN with a median latency of 10 years. The SIR of all SMNs was 5.5 (95% CI 4.4–9.0). The majority of SMNs were hematologic (n=23; SIR 18.5, 95% CI 11.7–87.0), followed by kidney cancer (n=14; SIR 28, 95% CI 15.2–309.1) and thyroid cancer (n=12; SIR 11.2, 95% CI 5.8–58.6). Patients who developed a SMN were more likely to have received radiation than those who did not (39.3% versus 24.7%; p=0.002). There was no significant difference in median age, sex, race, or ethnicity between patients who did or did not develop a SMN. The cumulative incidence of SMN at 30 years from diagnosis for high-risk patients was 4.1% (95% CI 2.63–5.56) compared to 1.6% (95% CI 1.07–2.12) in non-high-risk patients. There was a trend toward increasing SIRs over time; in Era 1: the SIR was 3.4, with a 95% CI 2.2–7.0; in Era 2: the SIR was 3.2, with a 95% CI 1.4–9.9; in Era 3: the SIR was 8.7, with a 95% CI 6.3–20.3; and in Era 4: 9.2, 95% CI 4.8–42.1. **Conclusions:** High-risk neuroblastoma patients continue to suffer from high rates of SMNs compared to non-high risk neuroblastoma patients in the current era of GD2-directed immunotherapy. Using standardized incidence ratios, there is a trend toward increasing rates of SMNs in our cohort compared to the general population. This increase may be due to the continued addition of cytotoxic therapy. Ongoing monitoring and research into treatment-associated toxicities is needed for neuroblastoma survivors in the modern era of therapy.

Research Sponsor: None.

Interrogation of fibrolamellar cancer to provide clinically relevant insights into therapeutic vulnerabilities.

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Background: Fibrolamellar carcinoma (FLC) is a rare disease that primarily afflicts young adults. Systemic therapy with surgery is the only curative intervention for advanced disease with 5-year survivals of 45%. We examined 3-dimensional tissue explants from FLC patients to measure the efficacy of cytotoxics, targeted agents and novel combinations. **Methods:** Of 41 FLC specimens; 17 female, 24 male, median age 26 (14–60), 36 (88%) were previously treated, 18/36 (50%) Oxaliplatin & Gemcitabine–Lenvatinib (GEMOX–LEN), 11 (31%) 5FU & Interferon and 18 (50%) Nivolumab. Samples were examined by Ex Vivo Analysis of Programmed Cell Death (EVA/PCD) as previously described. Following disaggregation and 72-hour drug exposures, 5-point dose-response curves were interpolated to provide lethal concentration 50% (LC50) for comparison with 10,000 prior human tumor explant analyses. Drug synergy was evaluated by the method of Chou & Talalay (Chou TC. *Cancer Res* (2010)15;70(2):440–6). Of 24 drugs and combinations selected for testing, FLC yields were sufficient for 18/24 (75%) to be fully analyzed. To explore mechanisms of response/resistance, single agent LC50's compared drug activity against all solid tumors by Z-score. **Results:** By rank order the highest activity for single-agents identified Vorinostat (HDAC), followed by Phenformin (Mitochondrial Complex I) and 6-Diazo-5-Oxo-L-norleucine (Glutaminolysis), then Cobimetinib (MEK) Regorafenib (TKI), KAT (Hexokinase) Lenvatinib (TKI) and Irinotecan (TOPO I). The lowest activity was found for Navitoclax (BH3) followed by Celecoxib (NSAID) and Quercetin (Natural product). Z scores for drug combinations favored GEMOX and 5FU & Interferon compared with other solid tumors. Previously treated tumors were more drug resistant. GEMOX combined with LEN proved synergistic in 40% of samples. Despite low single agent activity, Quercetin showed synergy with Lenvatinib. **Discussion:** We have previously described the ex vivo study of small molecules as probes of human tumor biology. As FLC uniformly expresses the DNAJB1–PRKACA gene-fusion, we used drugs with known mechanisms of action to interrogate operative pathways and vulnerabilities of the FLC phenotype associated with the DNAJB1–PRKACA genotype. We have previously shown that Vorinostat and Phenformin activities correlate with the MYC-directed BRD-inhibitor JQ1 while Protein Kinase A is known to regulate MYC and glutaminolysis is an established hallmark of MYC activation. **Conclusions:** The results suggest that the DNAJB1–PRKACA reprograms FLC toward a metabolic phenotype that is vulnerable to epigenetic modulation, mitochondrial targeting and glutaminolysis inhibition. The study met its objective to establish a database for the future management of FLC patients. This will allow each patient's tissue to be used to craft novel therapies predicated upon new insights into the biology of FLC. Research Sponsor: None.

Prognostic significance of CD8+T lymphocytes and CD68+ macrophages in assessing pathologic response in pediatric soft tissue sarcomas.

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Background: The tumor immune microenvironment (TIME) plays a critical role in treatment response in pediatric oncology. Conventional clinical and demographic parameters often fail to accurately predict individual therapeutic outcomes. Increasing evidence suggests that the phenotype and spatial distribution of immune cells within the tumor may provide valuable prognostic information. This study evaluated the prognostic significance of immune markers (CD4, CD8, CD20, CD68) and their localization in predicting therapy-induced pathomorphologic response in pediatric soft tissue sarcomas (STS). **Methods:** A retrospective analysis was conducted in 98 pediatric patients with embryonal and alveolar STS. Immunohistochemical profiling was performed to assess the status, density, and spatial localization (intratumoral vs peritumoral) of CD4+, CD8+, CD20+, and CD68+ immune cells. Treatment response was evaluated based on the degree of therapy-induced pathomorphosis (grades I–IV) and standard imaging criteria. Statistical analysis included Spearman correlation and chi-square testing. **Results:** Intratumoral immune-cell infiltration demonstrated stronger prognostic value than demographic or clinical characteristics. A significant association was observed between CD8+ T-cell positivity and higher grades of pathomorphologic response (grades III–IV; $p=0.001$). CD68+ macrophage infiltration was also significantly correlated with tumor regression ($p<0.001$). Intratumoral localization of CD8+ ($p=0.002$) and CD68+ ($p=0.021$) cells was significantly associated with improved therapeutic response compared with peritumoral localization. No significant associations were identified for age ($p=0.771$), sex ($p=0.775$), or histologic subtype ($p=0.960$). **Conclusions:** Intratumoral CD8+ T lymphocytes and CD68+ macrophages are key predictors of therapeutic response in pediatric STS. These findings support the integration of immunohistochemical profiling into routine clinical practice for response stratification. The results also provide a rationale for combining standard chemotherapy with immunomodulatory strategies to enhance intratumoral immune infiltration. Clinical trial information: B2023.2.DSc/Tib856. Research Sponsor: None.

Utilization and outcomes of minimally invasive resection in patients with neuroblastoma and Wilms tumor in a national cohort.

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Background: Tumor resection is a cornerstone of therapy for neuroblastoma (NB) and Wilms tumor (WT). Minimally invasive surgical approaches such as laparoscopic or robotic tumor resection hold promise to reduce surgical morbidity while maintaining excellent oncologic outcomes. This study aims to determine the utilization and outcomes of laparoscopic and robotic resection of NB and WT among children in a national cohort, hypothesizing that utilization is increasing over time and outcomes are not inferior to open resection. **Methods:** A retrospective cohort analysis of patients <18 years old in the 2020–2023 National Cancer Database who underwent resection of NB or WT was performed. Surgical approach trends were assessed via Cochran–Armitage tests. Conversions to open surgery, length of stay (LOS), and readmissions were compared between approaches using Kruskal–Wallis, Chi-square, and Fisher’s exact tests. **Results:** Among 1,262 children who underwent resection of NB (n=581) or WT (n=681), open procedures were most common (83.4%), followed by laparoscopic (13.9%), and robotic (2.7%). Utilization of each approach was stable over time aside from increased robotic resection of NB from 0% to 4% (p=.024). Approach did not vary by patient age (Table 1). Median WT size and lymph node yield were similar between approaches (both p>.05). In NB, laparoscopic procedures were performed on smaller tumors than open or robotic (p<.001). There were no robotic conversions to open; 11.4% of laparoscopic procedures were converted without change over time or difference between NB and WT (both p>.05). Median LOS was greater for open procedures than laparoscopic or robotic (p<.001). Readmission rates (p=.64) and margin status (p=.63) were similar between approaches. Outcomes did not vary by diagnosis. **Conclusions:** Utilization of minimally invasive approaches for NB or WT resection remains low despite noninferior or improved outcomes. Efforts to safely increase utilization are needed, especially for robotics, so that survivorship can be improved through reduced surgical morbidity. Research Sponsor: None.

Differences in patient characteristics and outcomes by surgical approach.

Characteristic or Outcome	Open	Laparoscopic	Robotic	p value
Age in years (median, IQR)	3 (1, 4)	3 (1, 5)	3 (1, 7)	0.08
% female	53%	53%	44%	0.59
NB tumor size in mm (median, IQR)	72 (50, 101)	47 (35, 71)	70 (51, 86)	<0.001
WT tumor size in mm (median, IQR)	110 (75, 140)	115 (93, 150)	93 (54, 125)	0.10
% metastatic disease	33%	30%	15%	0.07
% neoadjuvant therapy	35%	27%	22%	0.014
% conversion to open	n/a	11%	0%	0.05
Negative margins	86%	83%	96%	0.63
# Lymph nodes assessed in WT (median, IQR)	5 (3, 8)	6 (3, 10)	4 (3, 9)	0.62
LOS in days (median, IQR)	5 (4, 7)	4 (2, 6)	4 (1, 5)	<0.001
% readmission	15%	14%	9%	0.64

Impact of central review process on response rates in neuroblastoma clinical trials: A report from NANT Consortium.

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Background: Accurate and reproducible response assessment is critical for evaluating efficacy in clinical trials. Central response review is frequently used to reduce inter-site variability but is resource intensive and may delay data availability. Whether centralized review meaningfully alters response endpoints compared with remote source verification of site assessment remains unclear. **Methods:** We evaluated response assessments from eight NANT phase 1–2 trials conducted between February 2013 and December 2022 in relapsed/refractory high-risk neuroblastoma. Initial investigator-assessed response, remote source-verified response (remote review of radiology/bone marrow [BM] reports), and centrally-reviewed responses (review of radiographic images and BM biopsy slides) were assessed. Each patient's best overall response (BOR) and individual component responses (BM, MIBG/bone, and soft tissue [ST]) at time of BOR as determined by these three review methods were assessed. Only patients with MIBG-avid disease were included in bone response. **Results:** Among 244 evaluable patients, concordance between remote source-verified response and central review response exceeded the concordance between initial investigator-assessed response and central review response (BOR: 89% vs 79%, BM: 91% vs 74%, MIBG/bone: 92% vs 83%, ST: 82% vs 74%). Concordance between initial investigator-assessed response and remote source-verified response was 86% for BOR and similar for component response (BM: 83%, MIBG/bone: 91%, ST: 86%). Remote source-verified assessment compared to central review demonstrated higher level of concordance than initial investigator assessment for complete response (CR) (90.0% vs 81.0%), partial response (PR) (85.7% vs 72.7%), minor response (MR) (80.6% vs 71.0%), and stable disease (SD) (92.1% vs 86.7%), indicating improved response classification consistency across all major BOR categories. Overall, the initial investigator-assessed response for CR, PR, and MR agreed with central review 74.0% of the time, while remote source-verified agreed 84.7%. Most discordance reflects relabeling within adjacent categories (e.g., CR vs PR or PR vs MR). A change in response from CR/PR/MR to SD/PD when compared to central review was uncommon: 9.4% for initial investigator-assessed response, and decreased with remote source verification down to 7.1%. A change from CR/PR to MR/SD/PD was more frequent but also improved with remote source verification (from 20% to 11.3%). **Conclusions:** Remote source verification substantially improves agreement with central review and reduces responder misclassification. These findings demonstrate that structured remote source verification improves response assessment reliability and harmonization with central review, reinforcing its role as an important quality-control mechanism in multicenter trials. Research Sponsor: National Cancer Institute; P01 CA217959; V Foundation for Cancer Research; St. Baldrick's Foundation; United Therapeutics; Pfizer; Band of Parents; Anonymous.

Evaluating satisfactory testing versus transcript grade performance between childhood cancer survivors and healthy controls.

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Background: Substantial evidence suggests that survivors of childhood cancer are at increased risk for poor academic performance including receiving poor or failing course grades. There is a paucity of primary data as many contributing studies have relied on parental reporting of school performance. In the state of Florida, a high school student graduating with a standard diploma must successfully pass required biology and math classes. These classes require taking a standardized state-wide test which constitutes 30% of their final course grade. Our team sought to evaluate the concordance of state testing and course grade performance between pediatric brain tumor survivors and matched healthy controls from Florida. **Methods:** Children who received radiotherapy for intracranial tumors between 2007–2020 who reside in Florida were recruited to this IRB-approved study (N=37). Electronic medical record data was linked to scholastic data provided by the Florida Department of Education. Scholastic data included state testing scores and grade transcripts. For every patient enrolled, the state provided scholastic data matched at a 3:1 ratio (healthy control to survivor), based on age, grade, school district, and eligibility for free or reduced lunch (ERFL). We used Fisher's Exact test to perform an analysis of association of test scores and course grades between survivors and controls based on state-set pass/fail criteria. **Results:** Mean age of survivors was 14 years. Fifty-one percent of the survivors were female, 81% white, 8% Black, and 14% Hispanic. The majority received chemotherapy and were ERFL. Approximately 55% of survivors and controls received satisfactory math test scores (Table 1). However, survivors with unsatisfactory math scores were significantly more likely to pass their math class compared to controls (67% vs 51%; $P<0.01$). For biology, 79% of survivors vs 45% of controls had a satisfactory state test score; however, survivors with unsatisfactory biology scores were significantly more likely to pass their biology class compared to controls (80% vs 73%; $P=0.007$). **Conclusions:** We present the first US-based evaluation of primary evidence of childhood cancer survivors' performance in schools looking at transcripts. Our results demonstrate a discordance that if a survivor or control performed unsatisfactorily on the state test, the survivor was significantly more likely to pass the actual course required for a standard diploma. Further work inviting stakeholder participation, including students, caregivers, and educators is needed. Research Sponsor: Florida Department of Health; 21L09.

Comparison of standardized math test score and math course grades.			
State Test	Number (%)		P-value
Unsatisfactory test	Control (n=61)	Survivor (n=21)	P<0.01
Passing course	31 (51)	14 (67)	
Failing course	30 (49)	7 (33)	
Satisfactory test	Control (n=73)	Survivor (n=26)	
Passing course	71 (97)	26 (96)	
Failing course	2 (3)	1 (4)	

Neurosensory deficits and functional outcomes in childhood cancer survivors: A report from the Childhood Cancer Survivor Study (CCSS).

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Background: Survivors of childhood cancer are at risk for neurosensory deficits secondary to their disease and treatment. Previous research has characterized system-specific (e.g., visual) impairments; however, the prevalence of multisystem neurosensory deficits and their functional impact remain unknown. **Methods:** Adult 5-year survivors (n=20037, median age 36 [range 18–69] years, 53.4% male) and sibling controls (n=4121) reported neurosensory deficits related to vision, hearing, vestibular, and neuropathy. Comorbidities were graded using modified CTCAE v5 and defined as having at least one grade 1 neurosensory deficit in one, two, and three/four systems. Survivors reported neurocognitive function (CCSS Neurocognitive questionnaire; impairment: <10th %ile of sibling distribution), emotional distress (BSI-18; impairment: T score ≥63), quality of life (SF-36; impairment: T score <40), and functional independence. Multivariable models estimated the prevalence of neurosensory comorbidities, adjusted for age, sex, and race. Multivariable models further adjusted for other chronic conditions and neurotoxic therapies examined associations between comorbidities and functional outcomes in survivors. **Results:** Survivors had higher prevalence of neurosensory deficits in one (31% vs. 24%; prevalence ratio [PR] 1.4, 95% confidence interval [CI] 1.3–1.5), two (14% vs. 8%; 2.2, 1.9–2.5) and three/four systems (9% vs. 3%; 3.3, 2.9–4.1) than siblings. Neurosensory comorbidities were associated with greater risk of neurocognitive impairment (task efficiency and memory), emotional distress (anxiety) and poor quality of life (physical and social function) in a dose-dependent manner in survivors (Table). Similar effects were observed for indicators of functional independence: assistance with personal care/routine needs (one system: relative risk [RR] 2.7, 95% CI 2.2–3.3; two systems: 4.1, 3.3–5.0; three/four systems: 6.5, 5.4–7.9), interference with job/school (2.5, 2.2–3.0; 3.8, 3.2–4.5; 6.1, 5.2–7.1), no driver's license (1.5, 1.3–1.8; 2.4, 2.1–2.8; 3.8, 3.2–4.4), and non-independent living (1.3, 1.2–1.4; 1.8, 1.6–2.0; 2.1, 1.9–2.4). **Conclusions:** Adult survivors of childhood cancer have high rates of comorbid neurosensory deficits that have a dose-dependent impact on functional outcomes. Survivors with multisystem deficits should be prioritized for interventions to support functional independence. Research Sponsor: National Cancer Institute.

Relative risk (95% CI) of impaired outcomes in survivors with neurosensory comorbidities.					
Neurosensory comorbidities (# organ systems)	Memory	Task Efficiency	Anxiety	Physical Function	Social Function
0 (ref.)	-	-	-	-	-
1	1.6 (1.4-1.8)	1.8 (1.6-2.0)	2.6 (2.2-3.1)	2.2 (1.9-2.6)	1.9 (1.7-2.1)
2	2.2 (2.0-2.5)	2.4 (2.2-2.7)	3.4 (2.8-4.1)	3.1 (2.7-3.5)	2.5 (2.2-2.8)
3/4	3.1 (2.7-3.4)	3.3 (3.0-3.7)	5.2 (4.4-6.3)	4.4 (3.8-5.0)	3.2 (2.9-3.7)

Comparison of different metrics for estimating kidney radiation exposure during treatment for childhood cancer: A report from the St. Jude Lifetime Cohort Study.

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Background: Risk for impaired kidney function varies with radiation therapy (RT). We compared different methods for quantifying RT. **Methods:** Kidney function was graded in 2753 survivors (>10 years post-diagnosis, age ≥ 18 years) and 806 community controls (CC) per the Kidney Disease International Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD). Multivariable logistic regression was used to evaluate the associations between grades 3–5 CKD and demographics and treatment exposures. RT was expressed as percentage of total kidney volume treated with 5 Gray (Gy) or more (V5), 10 Gy or more (V10) Gray, Children's Oncology Group (COG) abdominal RT, or total body irradiation (TBI)/whole abdomen RT (WA). Model discrimination was assessed using area under the receiver operating characteristic curve (AUC). **Results:** 2.1% of survivors had stages 3 to 5 CKD, compared to 0.12% of CC (Odds Ratio (OR): 17.0 (95% confidence interval (CI) 2.9, 682.8), $p < 0.001$). Significant associations between higher risks of grades 3–5 CKD and demographic and treatment exposures were identified in separate regression models (Table). AUCs were 0.891, 0.888 and 0.896 for V5, V10, and TBI/WA, models respectively. **Conclusions:** TBI/WA is a more readily available exposure designation than V5 or V10. These results inform identification of survivors at highest risk for CKD. Research Sponsor: None.

Predictors	V5		V10		COG		TBI/WA	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Race (White vs non-White)	1.68 (0.81 – 3.30)	0.144	1.71 (0.82 – 3.35)	0.133	1.80 (0.89 – 3.44)	0.086	1.71 (0.85 – 3.28)	0.116
Age at evaluation	1.09 (1.04 – 1.13)	<0.001	1.09 (1.05 – 1.13)	<0.001	1.09 (1.05 – 1.13)	<0.001	1.10 (1.05 – 1.14)	<0.001
Hypertension	8.21 (4.12 – 17.61)	<0.001	8.27 (4.15 – 17.71)	<0.001	8.61 (4.41 – 18.02)	<0.001	8.61 (4.42 – 17.97)	<0.001
Nephrectomy (yes/no)	2.44 (0.88 – 6.12)	0.069	2.68 (0.97 – 6.72)	0.044	4.23 (1.81 – 9.48)	0.001	3.42 (1.36 – 8.01)	0.006
Ifosfamide (per 1000 mg/m ²)	1.04 (1.02 – 1.06)	<0.001	1.04 (1.02 – 1.05)	<0.001	1.04 (1.03 – 1.06)	<0.001	1.04 (1.03 – 1.06)	<0.001
Cisplatin (per 100 mg/m ²)	1.46 (1.26 – 1.68)	<0.001	1.46 (1.26 – 1.67)	<0.001	1.47 (1.27 – 1.68)	<0.001	1.49 (1.29 – 1.70)	<0.001
Carboplatin (per 100 mg/m ²)	1.03 (1.00 – 1.06)	0.024	1.03 (1.00 – 1.06)	0.027	1.03 (1.00 – 1.06)	0.012	1.03 (1.00 – 1.06)	0.012
Calcineurin inhibitor (yes/no)	7.29 (1.86 – 26.92)	0.003	7.9 (1.94 – 30.52)	0.003	14.79 (4.32 – 48.28)	<0.001	9.31 (2.43 – 33.77)	0.001
Doses Abelcet and/or Ambisome	1.02 (0.94 – 1.06)	0.516	1.02 (0.94 – 1.06)	0.513	1.02 (0.95 – 1.06)	0.469	1.02 (0.94 – 1.06)	0.555
Doses amphotericin B	1.00 (0.95 – 1.03)	0.990	1.00 (0.95 – 1.03)	0.998	1.00 (0.96 – 1.03)	0.981	1.00 (0.95 – 1.03)	0.936
V5 (per 10%)	1.14 (1.04 – 1.24)	0.004						
V10 (per 10%)			1.12 (1.01 – 1.23)	0.021				
COG abdominal radiation therapy (yes/no)					1.49 (0.76 – 2.85)	0.235		
TBI or WA (yes/no)							2.73 (1.08 – 6.61)	0.029

Opportunities for breast cancer prevention among pediatric lymphoma survivors treated with chest radiation: Projected gap in breast cancer deaths with real-world uptake rates.

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Background: For survivors of pediatric lymphoma previously treated with chest radiotherapy (RT), the Children's Oncology Group recommends initiation of breast cancer screening with mammography and MRI starting at age 25. The National Comprehensive Cancer Network also recommends risk-reducing medications (e.g. tamoxifen) for breast cancer prevention in high-risk women. While low uptake among survivors has been described, the missed opportunity in terms of avoidable breast cancer deaths remains unknown. **Methods:** Using a Cancer Intervention and Surveillance Modeling Network model adapted to reflect the elevated breast cancer risk and competing mortality among 5-year lymphoma survivors previously treated with mediastinal RT, we estimated the number of breast cancer deaths by age 65 versus no screening or tamoxifen for a 20-year-old cohort under three scenarios: i) optimal uptake and adherence (100%) to early initiation of recommended screening (mammography with MRI) at age 25 and standard dose tamoxifen for 5 years at age 25; ii) real-world uptake of screening alone based on Childhood Cancer Survivor Study data (18% at age 25, increasing over time to 60% by age 35, with 50% reporting MRI within 1 year of mammogram); iii) real-world screening uptake as described in scenario 2, plus real-world tamoxifen use based on published estimates (16%). We assumed tamoxifen reduced breast cancer risk for a minimum of 20 years based on follow-up data from clinical trials. Breast cancer deaths averted were calculated as the difference in breast cancer deaths between each scenario and a baseline of no screening or tamoxifen. **Results:** In the absence of screening or tamoxifen, 53.2 breast cancer deaths per 1000 female survivors were projected by age 65. Under optimal uptake, screening averted 28.5 deaths per 1000 women (54%); screening plus tamoxifen increased the number averted to 31.6 deaths per 1000 (59% total reduction). Under real-world uptake, the number of breast cancer deaths averted was only 11.7 per 1000 women with screening alone and 12.6 for screening plus tamoxifen, suggesting only a 19-24% mortality reduction. **Conclusions:** Low real-world uptake of screening and tamoxifen represents a substantial missed opportunity to prevent breast cancer deaths among survivors of pediatric lymphoma treated with chest RT. Strategies to increase uptake are needed to fully realize the mortality benefits of breast cancer control in this high-risk population. Research Sponsor: National Cancer Institute; R01CA261874, U01CA199218, U24CA55727.

Modeled breast cancer mortality at age 65 under optimal and real-world uptake scenarios.			
Scenario	Breast Cancer Deaths per 1000	Breast Cancer Deaths Averted per 1000	% Breast Cancer Deaths Averted
No screening or tamoxifen	53.2	-	-
Optimal (100%)			
Mammo/MRI	24.8	28.5	54%
Mammo/MRI + tamoxifen	21.7	31.6	59%
Real-world			
Mammo/MRI	41.5	11.7	19%
Mammo/MRI + tamoxifen	40.7	12.6	24%

Early-onset chronic and metabolic morbidity among survivors of childhood acute lymphoblastic leukemia: Evidence from Middle Eastern real-world data.

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Background: Survivors of childhood acute lymphoblastic leukemia (ALL) are at increased risk of long-term morbidity; however, limited data describe the *early* onset of metabolic and chronic conditions in contemporary cohorts or their association with treatment intensity in real-world settings. Existing evidence largely reflects European or North American populations, historical treatment eras, and fragmented healthcare systems. Data from Middle Eastern populations, particularly within a national health insurance framework enabling longitudinal follow-up across childhood and adulthood, are scarce. This study addresses these gaps by evaluating early-onset metabolic and chronic morbidity among childhood ALL survivors treated across multiple therapeutic eras within Israel's integrated healthcare system. **Methods:** We conducted a retrospective cohort study using electronic health records from Clalit Health Services, Israel's largest integrated payer-provider healthcare system. Five-year survivors of childhood ALL (diagnosed <19 years between 1980–2018) were matched 1:6 to cancer-free controls by age and sex. Chronic conditions were ascertained longitudinally using validated diagnosis codes. Multivariable Cox and logistic regression models estimated associations between ALL survivorship and chronic health outcomes. Among survivors, additional analyses examined associations with treatment intensity, treatment protocol era, and cranial radiation exposure (dose-specific). **Results:** The cohort included 437 childhood ALL survivors and 2,622 matched controls; survivors were 74.6% Jewish, 18.3% Arab, and 7.1% other ethnicities. Compared with controls, ALL survivors had significantly increased risks of central nervous system conditions (HR 3.65, 95% CI 1.71–7.80), thyroid disorders (HR 2.18, 95% CI 1.55–3.05), cardiovascular disease (HR 2.09, 95% CI 1.35–3.22), diabetes (HR 1.83, 95% CI 1.05–3.21), obesity (HR 1.58, 95% CI 1.31–1.91), and metabolic syndrome (OR 2.09, 95% CI 1.53–2.80). No ethnic differences were found across all chronic conditions. Excess morbidity occurred within the first 2-years of survivorship and persisted through 5- years, except for endocrine that became apparent later. Higher treatment intensity, earlier treatment protocols, and hematopoietic stem cells were associated with greater burden. **Conclusions:** Childhood ALL survivors experience early and disproportionate accumulation of chronic conditions, at young ages. Leveraging real-world data, this study provides novel evidence that treatment intensity and protocol era strongly shape early survivorship risk; unrelated to type of healthcare or ethnicity. These findings highlight the need for early, risk-adapted surveillance and targeted metabolic prevention strategies in contemporary ALL survivorship. Research Sponsor: The Jos and Fanny Sphon Foundation.

Symptom-based individual risk prediction for late mortality: A report from the Childhood Cancer Survivor Study (CCSS).

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Background: Survivors of childhood cancer face a higher risk of late mortality than the general population. Yet no prior study has integrated patient-reported symptoms and social determinants of health with treatment exposures to predict late mortality risks. **Methods:** A total of 9,569 survivors from the CCSS cohort who completed two surveys (baseline [T1], follow-up [T2]) reported 37 symptoms spanning 10 domains (cardiac, pulmonary, sensory, musculoskeletal, nausea, pain, fatigue, memory, anxiety, depression) at T1 and T2. Additional predictors included sociodemographic and lifestyle factors, address-linked Area Deprivation Index, and treatment exposures. Standardized mortality ratios (SMRs) were calculated, stratified by individual symptoms and domains at T2 and T1-T2 change, to compare mortality rates between survivors and the general population five years after T2. Multivariable Cox proportional hazards models with LASSO regularization were used to predict 5-year health-related and cause-specific late mortality (cardiac, pulmonary, subsequent neoplasm) after T1 and T2. The dataset was randomly split into training and test datasets in a 7:3 ratio, and prediction performance was assessed using the area under the receiver operating characteristic curve (AUC). **Results:** Among 9,569 survivors (52.4% female), the median age at T1 and T2 was 27.1 and 36.9 years; median years from diagnosis to T1 and T2 were 16.6 and 26.3, respectively. Acute lymphoblastic leukemia (31.3%) and Hodgkin lymphoma (15.3%) were the most frequently observed primary diagnoses. Compared with the sex/age/race/calendar year-matched general population, survivors had significantly higher health-related mortality 5 years after T2, with SMR of 4.21 (95% CI 3.76-4.70). Presence of cardiac and pulmonary symptom domains at T2, and their persistence and worsening from T1 to T2, were associated with >10-fold higher SMRs. Presence, persistence, and worsening of individual symptoms, including angina pectoris, chronic cough, and trouble breathing, were also associated with SMRs >10. For 5-year health-related mortality after T2, the symptom-based model yielded an AUC of 0.79 (95%CI 0.75-0.84), surpassing the symptom-agnostic model (AUC 0.76, 95%CI 0.71-0.81) and the T1 model (AUC 0.73, 95%CI 0.67-0.79). Cause-specific models also showed strong prediction performance, with symptom-based AUCs of 0.87 for cardiac, 0.89 for pulmonary, and 0.78 for subsequent neoplasms mortality. **Conclusions:** Adult survivors of childhood cancer experience elevated SMRs, with the greatest excess late mortality observed in those reporting cardiopulmonary symptoms. Longitudinal symptom-based models yielded the highest predictive performance, outperforming single-time-point and symptom-agnostic models. Incorporating symptom data can strengthen mortality prediction and inform targeted survivorship care. Research Sponsor: U.S. National Institutes of Health; U24 CA55727.

Perceptions of Medicaid coverage and care experiences among long-term survivors of childhood cancer: Qualitative interviews from the Childhood Cancer Survivor study (CCSS).

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Background: Childhood cancer survivors require lifelong, risk-based follow-up care. Survivors insured by Medicaid may face barriers to coverage and care unique to this type of insurance. We identified barriers and facilitators related to coverage, access to quality primary and specialty care, and survivor-provider interactions among Medicaid-insured survivors. **Methods:** Between May–November 2024, we conducted 23 in-depth interviews with adult survivors in CCSS currently also enrolled in Medicaid or with Medicaid coverage within the prior two years. Participants were recruited using stratified purposive sampling by state Medicaid expansion status, race/ethnicity, and age group. Interviews were audio-recorded, transcribed, and analyzed using thematic analysis. **Results:** Participants lived in 10 states (6 expansion, 4 non-expansion), 52% rural. At interview, 91% were enrolled in Medicaid. Mean age was 39 years (median 39; range 28–55); 26% were Hispanic and 35% non-Hispanic Black. Cancer types included blood cancers (n=9), brain tumors (n=7), and other solid tumors (n=7). When asked about maintaining coverage, survivors reported barriers including burdensome application/renewal requirements (e.g., in-person processes, extensive documentation); limited navigation guidance; and coverage instability tied to changes in disability status or income. Facilitators included assistance from knowledgeable staff (e.g., social worker), renewal reminder, and auto-renewal tied to Supplemental Security Income eligibility. Survivors expressed a need for hands-on help with application/renewal paperwork. When asked about care access, survivors reported difficulty finding specialists and primary care providers (PCPs) who accept Medicaid and are equipped to address survivor-specific needs (e.g., implement recommended tests in survivorship care plans), appointment delays, and transportation/geographic barriers. Facilitators included long-term relationships with PCPs and effective PCP–specialist communication. When asked about interactions with providers, survivors valued being heard, clear explanations, adequate visit time, and shared decision-making. However, many reported negative specialist encounters—feeling rushed or dismissed, including when new symptoms were repeatedly attributed to childhood cancer history without clear explanation, undermining trust. **Conclusions:** Medicaid-insured survivors reported challenges in maintaining coverage and accessing primary and specialty care. Streamlining enrollment/renewal, strengthening navigation supports, and improving survivor-centered care within Medicaid are critically needed amid the evolving Medicaid policy landscape. Findings inform a larger study designed to quantify policy-relevant gaps in coverage among aging survivors. Research Sponsor: NIH/NIMHD; K01MD018637; National Cancer Institute/U.S. National Institutes of Health; U24CA55727.

Effects of delayed sodium thiosulfate on cisplatin-induced ototoxicity in pediatric and adolescent patients with cancer: Results from the Japanese Children's Cancer Group STS-J01 study.

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Background: Cisplatin is a cornerstone of therapy for pediatric, adolescent, and adult solid tumors but frequently causes irreversible, dose-dependent ototoxicity. Delayed administration of sodium thiosulfate (PEDMARK) has demonstrated otoprotection in Western trials. STS-J01 evaluated the efficacy, safety, and pharmacokinetics of delayed sodium thiosulfate anhydrous in Japanese pediatric and adolescent patients. **Methods:** STS-J01 was an open-label, single-arm phase II study enrolling patients aged 0–18 years with localized solid tumors receiving cisplatin-based chemotherapy. Sodium thiosulfate (12.8 g/m²) was administered intravenously 6 hours after completion of each cisplatin dose. The primary endpoint was incidence of hearing loss by American Speech-Language-Hearing Association (ASHA) criteria in patients aged ≥3 years, compared with the observational cohort of ACCL0431. Secondary endpoints included hearing loss by Brock classification, tumor response, safety, and pharmacokinetics. **Results:** Thirty-one patients were enrolled, including 25 evaluable patients in the primary cohort (Table). Hearing was preserved in the majority of patients, with 76% free of ototoxicity by ASHA criteria and 84% with no hearing loss by Brock classification, representing a significant reduction versus historical controls (relative risk 0.42; 95% CI 0.20–0.82; P=0.007). Antitumor efficacy was preserved, with an objective response rate of 95.8% and there was no evidence of treatment interference from sodium thiosulfate. Pharmacokinetic analyses demonstrated no clinically meaningful impact of sodium thiosulfate on cisplatin exposure. No serious adverse events were attributed to sodium thiosulfate transient electrolyte abnormalities were manageable and reversible. **Conclusions:** Delayed administration of sodium thiosulfate significantly reduced cisplatin-induced ototoxicity without compromising antitumor efficacy in Japanese pediatric and adolescent patients, confirming reproducibility of sodium thiosulfate otoprotection across populations. Clinical trial information: jRCT2061220018. Research Sponsor: Japan Agency for Medical Research and Development; Fennec Pharmaceuticals.

Summary of STS-J01 trial.

Age at diagnosis (years)		3–6 (N=4)	7–14 (N=17)	15–18 (N=4)	Total (N=25)
No Hearing Loss by ASHA Disease		2/4(50%)	13/17 (76.4%)	4/4 (100%)	19/25 (76.0%)
	Hepatoblastoma	1/2 (50%)	-	-	1/2 (50.0%)
	Germ Cell Tumors	1/1 (100%)	6/6 (100%)	1/1(100%)	8/8 (100%)
	Bone and Soft Tissue Tumors	-	6/8 (75.0%)	3/3 (100%)	9/11 (81.8%)
	Medulloblastoma	0/1 (0%)	0/1 (0%)	-	0/2 (0%)
Chemotherapy	Others	-	1/2 (50.0%)	-	1/2 (50.0%)
	Responder*	4/4 (100%)	16/16 (100%)	3/4 (75.0%)	23/24 (95.9%)

*One case was unevaluated for treatment response.

Olanzapine for weight gain in children undergoing chemotherapy for solid-organ malignancies: An investigator-initiated, open-label, multicenter, phase III randomized controlled trial (SNOWMAN).

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Background: Children receiving intensive chemotherapy for solid-organ malignancies frequently experience deterioration in nutritional status. Olanzapine improves nutritional outcomes in adults with advanced cancer and is guideline-endorsed. Its use in pediatric oncology has been limited by safety concerns and lack of robust data. We conducted this trial to evaluate the efficacy and safety of olanzapine for weight gain in children undergoing chemotherapy for solid-organ malignancies. **Methods:** In this open-label, investigator-initiated, multicenter, phase III randomized trial (CTRI/2024/03/064371), children aged 2–18 years with newly diagnosed solid-organ malignancies were randomized 1:1 to receive olanzapine (1.25–2.5 mg once daily, weight-based) plus standard dietary counseling (SDC) or SDC alone for 12 weeks, stratified by nutritional status. The primary endpoint was the proportion of participants achieving $\geq 5\%$ weight gain at 12 weeks. Secondary endpoints included changes in appetite scores (visual analog scale), anorexia-related quality of life (QoL) (Peds-FAACT), anthropometric measures (weight, body-mass index, and mid-upper arm circumference), dietary intake, health-related QoL (PedsQL Cancer Module v3.0), and safety outcomes (CTCAE v5.0). Exploratory endpoints included longitudinal changes in body composition, using air-displacement plethysmography and skeletal muscle mass assessed by computed-tomography derived L3–L4 psoas muscle area. **Results:** A total of 130 participants were randomized (median age of 11.1 years; 13.9% undernourished), of whom 117 (60 olanzapine plus SDC, 57 SDC) had evaluable outcomes. At 12 weeks, 21/60 (35%) in olanzapine plus SDC and 22/57 (38.6%) in SDC group achieved the primary endpoint, with no significant difference between groups (OR 0.86, 95% CI 0.40–1.82; $p=0.69$). Longitudinal analyses showed no significant differences between groups in appetite scores, anthropometric measures, dietary intake, and QoL. Exploratory analyses showed no differential impact on skeletal muscle mass or fat proportions. Rates of grade ≥ 3 adverse events were similar between groups. No extrapyramidal symptoms were observed, and no participant required dose modification or discontinuation of olanzapine due to sedation or QTc prolongation. **Conclusions:** The addition of olanzapine to SDC does not increase the proportion of children achieving clinically meaningful weight gain over 12 weeks. The impact of pharmacological nutritional modulation may be limited by the physical hurdles posed by highly intensive pediatric chemotherapy protocols. Olanzapine was well tolerated and these data provide reassurance regarding its short-term safety for other supportive care indications in pediatric oncology. Clinical trial information: CTRI/2024/03/064371. Research Sponsor: CanKids KidsCan National Society for Change for Childhood Cancer in India.

Neuropsychiatric symptom and biomarker changes with electroacupuncture in adolescent and young adult (AYA) cancer survivors: Results from a randomized controlled trial.

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Background: Electroacupuncture (EA) shows promise for managing neuropsychiatric symptoms, yet its role in adolescent and young adult (AYA) cancer survivors remains unclear. We conducted a randomized, controlled, patient- and assessor-blinded pilot trial comparing two EA regimens to evaluate effects on neuropsychiatric symptoms and associated biomarkers in AYA cancer survivors (ClinicalTrials.gov: NCT05283577). **Methods:** AYA cancer survivors aged 16–39 years who self-reported cognitive impairment, fatigue, insomnia, or psychological distress were randomized (1:1) to receive ten weekly EA sessions targeting either neuropsychiatric-specific acupoints (nEA) or non-neuropsychiatric-specific acupoints (sham EA; sEA). Blood collection, neurocognitive testing (CANTAB), and patient-reported outcomes (FACT-Cog, MFSI-SF, EORTC QLQ-C30) were obtained at four timepoints. Sixteen plasma cytokines were measured using ProcartaPlex immunoassays, and brain-derived neurotrophic factor (BDNF) concentrations were quantified using ELISA. Between-group effects were evaluated with linear mixed models and expressed as Cohen's d (positive values favor nEA). Adverse events (AEs) were graded using CTCAE v5.0. **Results:** Thirty-four AYAs participated (mean age 20.9 ± 3.5 years; 59% Hispanic/Latino; 59% hematologic and 21% CNS cancers). Most (82%) reported ≥ 2 neuropsychiatric symptoms at baseline. Completion of all EA sessions was comparable between study arms (nEA: 64.7%; sEA: 70.6%). A positive dose-response relationship was observed, with approximately half reporting at least one improved symptom after 5 weeks of treatment (nEA: 53.8%; sEA: 60.0%) and $>80\%$ reporting improvement at 4 weeks post-treatment (nEA: 80.0%; sEA: 92.3%). At 4-week follow-up, greater improvement in self-reported cognitive function favored sEA ($d = -1.017$, $p < 0.05$), accompanied by between-group differences in BDNF ($d = -1.073$, $p < 0.05$), IL-10 ($d = 1.378$, $p < 0.05$), and RANTES ($d = 1.058$, $p < 0.05$). All AEs were grade ≤ 2 ; tremors and pain were the most commonly reported. **Conclusions:** AYAs across both EA regimens demonstrated meaningful improvements in neuropsychiatric symptoms, accompanied by corresponding biomarker changes. However, maximal benefit occurred among participants who completed all scheduled sessions, underscoring the importance of strategies to optimize EA session adherence in this population. These findings support the feasibility of EA in AYAs and inform the design of larger trials. Clinical trial information: NCT05283577. Research Sponsor: University of California Irvine.

Barriers and enablers to pediatric palliative care integration in low- and middle-income countries: A systematic review and meta-synthesis.

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Background: Globally around 21 million children require pediatric palliative care yearly of whom more than 97-98% of the children in greatest need live in low- and middle- income countries. Nevertheless, presently, only around 5-10% of children and their families in those situations receive palliative care while the development of pediatric-specific palliative care frameworks and services remains very much less developed than adult palliative care in many health systems. **Methods:** A systematic search was performed in PubMed database, Embase database and Global Health for studies published between 2015 and 2025 using PRISMA guidelines. Inclusion criteria: Original research on the models of PPC, access to opioids or educational interventions in the context of LMICs. Articles were screened for inclusion by two independent reviewers and were evaluated for quality using the MMAT. Data have been synthesized with the help of a thematic framework. **Results:** Out of the 427 identified records, 48 studies in 32 countries met the inclusion criteria. Important barriers identified were restrictive legislation, and 68% of the studies mentioned "opiophobia" and legal barriers to access of pediatric morphine, median morphine consumption in LMICs less than 1% of high income countries. While workforce deficit only of 12% of LMIC children's or pediatric doctors (pediatricians) reported some type of formal training in PPC during residency. Also, financial toxicity: End-of-life care financial costs for families in LMIC often outweigh cost up to, or more than, 50% of their yearly income. On the other hand, successful enablers were task-shifting to community health workers and integration of PPC into existing oncology protocols. Quantitative synthesis demonstrated the use of integrated hospital in-home models to decrease emergency room visits by 35% in the last month of life. **Conclusions:** Large disparities still exist in PPC provision in LMICs, which is related to regulatory and educational gaps. But some localized "hub-and-spoke" models provide an outline of how to integrate in a sustainable fashion. For ASCO's global mission, these findings indicate that "Zero Pain" initiatives require pediatric specific legislative reform and mandatory oncology palliative training to address the gap in quality of survival. Research Sponsor: None.

Development and early implementation of a statewide comprehensive childhood cancer network to support pediatric oncology care and research.

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Background: Although pediatric cancer survival has improved substantially, families continue to face fragmented access to navigation, clinical trials, survivorship care, and psychosocial support. Florida's pediatric oncology system is geographically dispersed and resource-variable, highlighting the need for coordinated statewide infrastructure. **Methods:** The Live Like Bella Comprehensive Childhood Cancer Network (CCCN) was established as a statewide, multi-institutional initiative to address gaps in access, care coordination, and research participation. Phase 1 activities emphasized infrastructure development, stakeholder engagement, and needs assessment. A caregiver survey was distributed to 2,478 families who received pediatric cancer support services between April 2024 and August 2025. Descriptive analyses evaluated barriers to care, information gaps, survivorship education, and clinical trial awareness. Missing survey responses were handled using complete-case analysis for each item, with denominators reported per question. In parallel, CCCN convened children's hospitals, academic centers, advocacy organizations, and researchers to develop collaborative frameworks, digital navigation tools, and consortium-based initiatives. **Results:** Over 170 caregivers responded. Eighty percent reported significant non-clinical care challenges (e.g., housing, utilities, transportation), 67% reported work-related disruptions, and 52% identified unmet caregiver support needs. Thirty-three percent reported difficulty locating services. Only 50–53% rated information about childhood cancer and diagnosis-specific education as comprehensive. Forty-eight percent of families reported being offered a clinical trial; among those, 71% participated. Survivorship education gaps were common, with 22.7% and 26% reporting limited or no information on post-treatment and survivorship care. CCCN established leadership and advisory governance, launched development of a digital navigation and clinical trial matching portal, hosted a statewide research symposium (>250 participants), and initiated multi-institutional grant proposals focused on precision oncology and navigation workforce development. **Conclusions:** Early CCCN implementation demonstrates the feasibility of a statewide, family-centered model to identify care gaps, support research participation, and align pediatric oncology stakeholders. Ongoing evaluation will assess impacts on access, survivorship, and clinical trial engagement. Research Sponsor: Florida Cancer Innovation Fund.

A phase 1b study of xaluritamig (a STEAP1 x CD3 T-cell engager) in pediatric, adolescent, and adult patients with relapsed/refractory (R/R) Ewing sarcoma.

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Background: Ewing sarcoma (EWS) is an aggressive tumor of the bone and soft tissue primarily affecting adolescents and young adults. For patients with recurrent disease, outcomes remain poor with 5-year survival rates of 10%–15%, highlighting the need for novel approaches. STEAP1 is highly expressed in EWS cell lines, xenograft models, and patient tumor samples¹ and is transcriptionally regulated by *EWSR1::FLI1*, the main oncogenic driver in EWS. Xaluritamig, a humanized bispecific XmAb 2+1 T-cell engager targeting STEAP1 and CD3, has demonstrated potent, antigen-dependent T-cell-mediated lysis of STEAP1-expressing EWS cell lines¹ and induced robust in vivo antitumor activity in EWS xenograft models with concomitant CD8+ T-cell activation. In metastatic castration-resistant prostate cancer, another STEAP1-expressing solid malignancy, xaluritamig has shown meaningful antitumor activity and a manageable safety profile² supporting its clinical evaluation in R/R EWS. **Methods:** This ongoing, phase 1b, single-arm, open-label, two-part, multicenter study (NCT07297979) is evaluating xaluritamig in pediatric, adolescent, and adult patients with a histologic diagnosis of EWS and an *EWSR1::ETS* fusion gene locally confirmed by next-generation sequencing. Patients must have R/R EWS following ≥ 1 line of systemic therapy and Karnofsky or Lansky performance status ≥ 70 . Part 1 (dose confirmation) consists of cohort 1 (age ≥ 12 years) and cohort 2 (age ≥ 2 to < 12 years), and part 2 (dose expansion) includes patients aged ≥ 2 years with no upper age limit at enrollment. This study includes a 21-day screening period, a treatment period, a safety follow-up period, and a long-term follow-up period. Patients receive xaluritamig every 2 weeks once reaching the target dose until radiographic disease progression per RECIST v1.1, clinical disease progression, unacceptable toxicity, initiation of other anticancer therapy not permitted per protocol, withdrawal of consent, death, or end of study as determined by the sponsor, whichever is earlier. Primary endpoints are safety, tolerability, and determination of recommended dose(s) for expansion. Secondary endpoints are pharmacokinetics, preliminary antitumor activity, and immunogenicity. Biomarker evaluation as an exploratory endpoint includes assessment of serum cytokines, other pro-inflammatory markers, immune-cell subsets, circulating tumor DNA, STEAP1 protein expression, and tumor genomic profile and their association with safety and efficacy. CRS mitigation plan includes step-up dosing, steroid premedication, and administration of interleukin-6 inhibitors as needed. Site activation commenced in January 2026 and enrollment is ongoing. 1. Nolan-Stevaux O. *Cancer Res.* 2020;80(16_Suppl):DDT02–03. 2. Kelly WK, Danila DC, Lin CC, et al. *Cancer Discov.* 2024;14(1):76–89. Clinical trial information: NCT07297979. Research Sponsor: Amgen Inc.

Feasibility study of prolonged administration of naxitamab, irinotecan, and temozolomide for patients with relapsed or refractory neuroblastoma.

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Background: Neuroblastoma is a malignant childhood tumor of the sympathetic nervous system. Cure rates are unsatisfactory for patients with high-risk disease (approximate 3-year EFS 50%) with current standard of care therapy. For patients who relapsed, anti-GD2 based chemoimmunotherapy has become standard, though it often requires in-hospital administration. Naxitamab, a humanized anti-GD2 monoclonal antibody (mAb), is FDA approved for patients with relapsed or refractory (R/R) high-risk neuroblastoma (HR-NB) with metastatic disease restricted to bone or bone marrow (BM), and who have stable disease or minor/partial response to previous therapies. With an infusion duration of 30-60 minutes, grade 3 pain and infusion-related reactions are common (72% and 68% of patients respectively) and necessitate extensive nursing and provider resources that may preclude administration at many centers. Slowing the rate of infusion of naxitamab and other anti-GD2 mAbs is generally associated with lower rates and severity of acute toxicity. We have therefore opened a phase I feasibility trial of prolonged administration of naxitamab in combination with irinotecan and temozolomide.

Methods: This is a phase 1, single treatment arm, modified 3+3 prospective trial in patients with R/R or progressive HR-NB. The primary objective is to identify a recommended safe and feasible prolonged infusion duration of naxitamab in combination with irinotecan and temozolomide, with a goal of still allowing outpatient administration. Patients are enrolled at the starting total infusion duration of 4 hours, with an escalating infusion rate at pre-defined timepoints; the total infusion duration will be extended or shortened in cohorts of 3-6 patients based on safety and adverse events (AEs) observed in the first cycle. Individual patients will be eligible for duration escalation or de-escalation depending on AEs observed. An expansion cohort will be enrolled at the recommended infusion time. Key eligibility criteria include diagnosis of R/R or progressive HR-NB or ganglioneuroblastoma, age 1-30 years at enrollment, documentation of disease per revised International Neuroblastoma Response Criteria (INRC), adequate performance level, and adequate organ function including BM. Key exclusion criteria include prior receipt of naxitamab, untreated CNS metastatic disease, and discontinuation of prior GD2 immunotherapy due to unacceptable toxicity other than allergic reaction. Secondary endpoints include response rate per revised INRC and survival outcomes. Correlative and exploratory investigations embedded within the trial include PK profiling of prolonged naxitamab infusion durations and evaluation of circulating biomarkers including circulating tumor DNA, tumor cells, and GD2 in the study population during anti-GD2 therapy. Clinical trial information: NCT07027748. Research Sponsor: None.