10000 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Treatment of pediatric lymphocyte predominant Hodgkin lymphoma (LPHL): A report from the Children's Oncology Group.

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Background: LPHL, an uncommon subtype of HL, typically presents with low stage disease and responds to regimens used for classical HL. Recurrence is uncommon, but second malignant neoplasms (SMN) or development of non-Hodgkin lymphoma (NHL) can occur. Therefore, reducing radiation exposure may be of benefit. We report the results of a prospective trial in which a selected subset of patients had surgery alone and the remainder were treated with limited chemotherapy +/- involved-field radiation therapy (IFRT). **Methods:** Patients ages 0-21 years with newly diagnosed, low risk LPHL were eligible for AHOD03P1. Low risk was defined as clinical Stage IA or IIA without bulk disease (mediastinal mass $>$ 1/3 of the thoracic diameter or nodal aggregate $>$ 6 cm). Patients with Stage IA LPHL with an unresected node or more than a single involved node or Stage IIA were treated with 3 cycles of AV-PC (doxorubicin/vincristine/prednisone/cyclophosphamide). Patients with Stage IA LPHL in a single node that was completely resected were initially observed without further therapy; those who recurred after surgery with low risk LPHL received AV-PC x 3. Patients with $<$ complete response (CR) to AV-PC x 3 received 2100 cGY IFRT. **Results:** 180 eligible patients with low risk LPHL were enrolled and completed study therapy. 52 patients underwent initial surgery alone; their 3 year EFS = 81.5%. 137 patients received AV-PC x 3; 128 were treated at diagnosis and 9 upon relapsing after surgery alone. 11 patients receiving AV-PC had $<$ CR and received IFRT. 12 first events occurred among these 137 patients (11 relapses and 1 SMN, a NHL). One relapse occurred in a patient who received IFRT. The median follow-up among the 125 remaining patients is 39 (range 3 -76) months. Current 4-year EFS estimate is 88.1% (95% CI: 79.5%-93.3%) for these 137 patients. 4 year EFS for the entire cohort of 180 patients = 86.2%; their overall survival (OS) is 100%. **Conclusions:** Pediatric LPHL patients have an excellent EFS with chemotherapy that is less intensive than standard regimens; $>$90% of patients can avoid RT. NHL as a first event may be related to the underlying LPHL and not an effect of treatment. The salvage rate for the few relapses is high, and OS to date is excellent. Clinical trial information: NCT00107198.

10001 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Assessment of end induction minimal residual disease (MRD) in childhood B precursor acute lymphoblastic leukemia (ALL) to eliminate the need for day 14 marrow examination: A Children's Oncology Group study.

Michael J. Borowitz, Brent L. Wood, Meenakshi Devidas, Mignon L. Loh, Elizabeth A. Raetz, Eric Larsen, Kelly W. Maloney, Andrew J Carroll, Alison M. Friedmann, Julie M Gastier-Foster, Nyla A. Heerema, Leonard A. Mattano, James B. Nachman, Naomi Joan Winick, William L. Carroll, Stephen Hunger; The Johns Hopkins Hospital, Baltimore, MD; University of Washington, Seattle, WA; Children's Oncology Group, Gainesville, FL; University of California, San Francisco, San Francisco, CA; New York University Langone Medical Center, New York, NY; Maine Children's Cancer Program, Scarborough, ME; Children's Hospital Colorado, Aurora, CO; Children's Hospital of Alabama, Birmingham, AL; Massachusetts General Hospital, Boston, MA; Nationwide Children's Hospital, Columbus, OH; The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; MSU/KCMS, Kalamazoo, MI; The University of Chicago, Chicago, IL; The University of Texas Southwestern Medical Center; Center for Cancer and Blood Disorders, Children's Medical Center Dallas, Dallas, TX; University of Colorado Denver Health Science Center, Aurora, CO

Background: Response to initial therapy is a powerful prognostic factor in pediatric ALL. Traditionally, slow early response (SER) has been defined by marrow morphology 8 or 15 days after start of induction therapy. More recently, MRD has been identified as the most important predictor of adverse outcome. The value of morphologic assessment of response in the setting of MRD has not been established. **Methods:** In COG studies AALL0331 (for NCI Standard Risk (SR) B ALL patients (pts)) and AALL0232 (High Risk (HR) B ALL pts), SER was defined by morphology as either ≥5% blasts in a day 15 marrow, or by flow cytometry as ≥0.1% MRD in a d29 marrow (SER MRD). Assignment to treatment arms also depended upon cytogenetic findings and extramedullary disease; each protocol had randomized treatment questions. SER pts were non-randomly assigned to receive augmented BFM therapy (ABFM) with 2 interim maintenance and delayed intensification phases (and CNS radiation for HR SER pts only). All pt treatment groups were combined for these analyses. Rapid early responders (RER) had a better outcome than SER pts (Table). However, pts who were SER only by morphology had a 5y DFS that was not significantly different from that of RER pts, and superior to that of pts who were SER MRD, or SER by both morphology and MRD. In multivariate analysis, SER by morphology was not an adverse prognostic factor after adjusting for risk group and MRD, or separately in SR or HR pts after adjusting for MRD. However, pts with .01-.1% MRD who were SER by morphology had a better 5y DFS than the.01-.1% MRD pts who were RER (90±6%, n=91 vs 77±3%, n=592). Only the former group received ABFM, suggesting intensification based on response rescues some poor risk pts. We conclude that a day 15 marrow is not needed to assess response if MRD is measured at end induction, provided that SER MRD is defined using a .01% cutoff, the threshold for intensifying therapy in current COG ALL trials. Clinical trial information: NCT00103285, NCT00075725.

Pt group	N	5 y DFS	P value vs RER
RER	6419	89±1%	--
SER all	1011	79±2%	<.0001
SER by morphology only	339	91±3%	.48
SER MRD only	485	72±4%	<.0001
SER by morphology and MRD	187	77±6%	<.0001

10002 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Effect of dexamethasone (DEX) dose modification on osteonecrosis (ON) risk associated with intensified therapies for standard risk acute lymphoblastic leukemia (SR-ALL): A report from the Children's Oncology Group (COG) study AALL0331.

Leonard A. Mattano, Meenakshi Devidas, Alison M. Friedmann, Elizabeth A. Raetz, Stephen Hunger, Naomi Joan Winick, William L. Carroll, Kelly W. Maloney, Children's Oncology Group; Bronson Methodist Hospital, Kalamazoo, MI; Children's Oncology Group, Gainesville, FL; Massachusetts General Hospital, Boston, MA; New York University Langone Medical Center, New York, NY; University of Colorado Denver Health Science Center, Aurora, CO; The University of Texas Southwestern Medical Center; Center for Cancer and Blood Disorders, Children's Medical Center Dallas, Dallas, TX; Children's Hospital Colorado, Aurora, CO

Background: ON is a known toxicity of childhood ALL therapy, particularly in patients (pts) >9 years (y). Intensified use of DEX, methotrexate (MTX), and asparaginase (ASNase) may increase the risk of developing ON among B-precursor NCI SR-ALL pts despite their younger age. **Methods:** Newly diagnosed SR-ALL pts 1-9y enrolled on AALL0331 between 4/05 and 5/10 were prospectively monitored for symptomatic ON within three treatment cohorts risk-stratified by clinical, cytogenetic, and early response criteria. ON sites were confirmed by imaging. SR-Low (SRL) pts were randomized to standard therapy +/- 4 additional doses of PEG-ASNase. SR-Average (SRA) pts were randomized (2x2) to standard therapy +/- an intensive consolidation (IC) +/- an augmented interim maintenance/delayed intensification (AIM/ADI). SR-High (SRH) pts all received IC and two AIM/ADI phases. After 6/08, alternate week DEX (AWD, days 1-7/15-21) replaced continuous DEX (days 1-21) during DI, and escalating-dose MTX replaced oral MTX during IM. All pts received DEX days 1-28 during induction and 5-day pulses every 4 weeks during maintenance. **Results:** Overall ON cumulative incidence (CI) at 5y was 2.7% (133/5261), correlating with sex (F 3.7%, M 1.9%, $p<0.0001$), age (1-2y 0.8%, 3-4y 2.0%, 5-6y 3.3%, 7-9y 7.8%, $p<0.0001$), and risk group (SRL 2.6%, SRA 2.9%, SRH 5.7%, $p=0.0009$). Before 6/08, ON CI was higher for SRA pts given intensive vs standard consolidation (5.8% vs 1.9%, $p=0.002$), and trended higher for SRL pts given additional PEG-ASNase (4.0 vs 2.3%, $p=0.09$). Use of AWD significantly reduced ON CI at 3y among SRH pts (7.4% vs 1.5%, $p=0.003$) and further reduced ON events in SRL/SRA pts. **Conclusions:** Young children receiving intensified therapy for SR-ALL therapy are at risk for ON. Extended exposure to PEG-ASNase is a likely contributing factor, possibly by potentiating DEX exposure during DI. ON risk can be significantly reduced by using AWD during DI, which is now COG standard of care. Clinical trial information: NCT00103285.

10003 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Bortezomib reinduction therapy to improve response rates in pediatric ALL in first relapse: A Children's Oncology Group (COG) study (AALL07P1).

Terzah M. Horton, Xiaomin Lu, Maureen Megan O'Brien, Michael J. Borowitz, Meenakshi Devidas, Elizabeth A. Raetz, Patrick Andrew Brown, Hui Zeng, Hao W. Zheng, Stephen Hunger, James Whitlock, Children's Oncology Group; Baylor College of Medicine, Houston, TX; Children's Oncology Group, Gainesville, FL; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; The Johns Hopkins Hospital, Baltimore, MD; New York University Langone Medical Center, New York, NY; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Dept of Biostatistics, Colleges of Medicine, Public Health & Health Professions, University of Florida, Gainsville, FL; University of Colorado Denver Health Science Center, Aurora, CO; Hospital for Sick Children, Toronto, ON, Canada

Background: Bortezomib (bortez) is a reversible inhibitor of the 26S proteasome. Promising results have been reported adding bortezomib to reinduction chemotherapy in patients (pts) with ALL in 2nd or later relapse (Messinger, Blood 2012). **Methods**: This was a phase 2 study of bortez with reinduction chemotherapy in 1st relapse pediatric ALL that enrolled pts with pre-B ALL (relapse $<$36 months (m) from diagnosis). This report summarizes results from 61 evaluable pre-B ALL pts $\leq$21 yrs old, either $<$18m (stratum 1) or 18-36m (stratum 2) from diagnosis. Therapy consisted of bortez (1.3 mg/m^2, days 1, 4, 8, and 11) with reinduction chemotherapy (vincristine, prednisone, PEG-asparaginase, doxorubicin). Complete response (CR2) rates and minimal residual disease (MRD) were determined at the end of the first 5-week therapy block. AALL07P1 utilized a stratified 2-stage design (London 2005) with the primary objective of comparing CR2 rates at the end of block 1 of therapy to historical control CR2 rates (AALL01P2). Block 2 included cyclophosphamide, etoposide, and bortez followed by 5g/m^2 methotrexate. Biology studies included assessment of NF-κB activity. **Results**: 61 evaluable pre-B ALL pts were assessed. Toxicities were similar to AALL01P2, including 10 Grade 3- 4 hypotension, 4 Grade 4 hypertriglyceridemia, 3 Grade 3-4 typhlitis, and 2 Grade 3-4 enterocolitis. There were 2 deaths due to infection. Although Grade 3-4 infections were not infrequent (13 in block 1 and 7 in block 2) there were no reports of respiratory distress syndrome or Grade 4 peripheral neuropathy. 42 of the 61 patients enrolled (18/28 (64%) in Stratum 1 and 24/33 (73%) in stratum 2) attained CR2 at the end of Induction I. Based on CR2 response rate compared to historical controls, the study met its primary response objective. The number of pts in CR2 with MRD $<$0.1% also improved from AALL01P2; among pts achieving CR2, MRD was $<$0.1% in 41% (16/39) in AALL01P2 vs. 71% (25/35) ($p = 0.073$, Fisher's exact test). **Conclusions**: Based on response rates in the very early and early first relapse pre-B ALL, AALL07P1 met its predefined efficacy benchmark. We conclude that bortezomib is worthy of further study in pediatric ALL. Clinical trial information: NCT00873093.

10004 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Hyaluronidase synthase 3 (*HAS3*) variant and anthracycline-related cardiomyopathy: A report from the Children's Oncology Group.

Can-Lan Sun, Xuexia Wang, Wei Liu, Saro Armenian, Hakon Hankonarson, Lindsey Hageman, Yan Ding, Wendy Landier, Frank G. Keller, Joseph Philip Neglia, Sunil J. Desai, Charles A. Sklar, Sharon M. Castellino, Irene Cherrick, Zoann Dreyer, Yutaka Yasui, Mary V. Relling, Smita Bhatia; City of Hope, Duarte, CA; University of Wisconsin-Milwaukee, Milwaukee, WI; University of Alberta, Edmonton, AB, Canada; Children's Hospital of Philadelphia, Philadelphia, PA; Children's Healthcare of Atlanta-Egleston, Atlanta, GA; University of Minnesota, Minneapolis, MN; Stollery Children's Hosp, Edmonton, AB, Canada; Memorial Sloan-Kettering Cancer Center, New York, NY; Wake Forest University, Winston-Salem, NC; Upstate Medical University, Syracuse, NY; Baylor College of Medicine, Houston, TX; St. Jude Children's Research Hospital, Memphis, TN

Background: The strong dose-dependent association between anthracyclines and cardiomyopathy limits the therapeutic potential of this extremely effective class of agents, demanding identification of those at highest risk, such that anthracycline exposure may be tailored. **Methods:** In a two-stage design, we investigated host susceptibility to anthracycline-related cardiomyopathy in cancer survivors by using the ITMAT/Broad/CARe cardiovascular SNP-array to profile common SNPs in 2100 genes considered most relevant to *de novo* cardiovascular disease. All cases of cardiomyopathy fulfilled American Heart Association (AHA) criteria for cardiac compromise and were confirmed echocardiographically. **Results:** Using a matched case-control design (93 cases, 194 controls, all non-Hispanic white survivors of childhood cancer) we identified a common SNP rs2232228 in hyaluronan synthase (*HAS3*) gene that exerts a substantial modifying effect on anthracycline dose-dependent risk of cardiomyopathy. Among individuals with GG genotype, cumulative anthracycline exposure was not associated with cardiomypathy risk at any dose. Individuals with AA genotype, exposed to $>250 mg/m^2$ anthracyclines, had an 8.5-fold increased cardiomyopathy risk (95%CI, 2.0-35.6, $p=0.004$). Replication in an independent set of 76 patients (adult-onset and childhood cancer; all races) with anthracycline-related cardiomyopathy revealed the odds of cases with AA genotype in the high-dose anthracycline group to be 4.5-times higher (95%CI, 1.1-18.4, $p=0.04$). Hyaluronan (HA) – produced by *HAS3* – is a ubiquitous component of extracellular matrix (ECM). ECM is involved in tissue remodeling; the extent of cardiac remodeling/repair after anthracycline-induced cardiac injury is possibly modulated by variability in HA production. **Conclusions:** The significant modifying effect of *HAS3* genotype on the dose-dependent association between anthracycline and cardiomyopathy risk suggests that, upon confirmation in prospective studies, genotyping *HAS3* may be considered when evaluating risk of anthracycline-related cardiomyopathy.

10005 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Genetic variations in cytarabine pathway genes as determinants of outcome in acute myeloid leukemia.

Jatinder Kaur Lamba, Stanley Pounds, Xueyuan Cao, Kristine Radomski Crews, Susana Raimondi, Dario Campana, Sharyn D. Baker, Raul Correa Ribeiro, Jeffrey E. Rubnitz; University of Minnesota, Minneapolis, MN; St. Jude Children's Research Hosiptal, Memphis, TN; St. Jude Children's Research Hospital, Memphis, TN; St. Jude Children's Resrch Hosp, Memphis, TN; National University of Singapore, Singapore, Singapore; St Jude Children's Resch Hosp, Memphis, TN; St Jude Children's Rsch Hosp, Memphis, TN

Background: Cytarabine (ara-C), a key component of AML therapy, is a prodrug that requires activation to ara-CTP, which inhibits DNA/RNA synthesis and triggers leukemic cell death. Thus, cellular pathways involved in ara-CTP metabolism and/or cell death are likely to influence treatment response. **Methods:** In the present study, we used a pathway-directed approach to identify the genetic predictors of ara-C response in 187 pediatric patients enrolled in the St. Jude AML02 trial. Patients were randomized to receive the first course of remission induction therapy containing either high- or low-dose ara-C, combined with daunorubicin and etoposide. SNPs in 14 key ara-C pathway genes were genotyped and screened for association with multiple endpoints, such as in vitro ara-C LC50 in diagnostic leukemic cells, minimal residual disease levels (MRD), event-free survival (EFS), overall survival (OS), and rate of relapse. Because AML is a very heterogeneous disease with multiple clinical, cytogenetic, and molecular features that are associated with response, we also evaluated SNPs in ara-C PK genes in the context of prognostic factors of proven clinical utility. **Results:** Ara-C pathway SNPs were significantly associated with clinical outcome. Known variables such as treatment, core-binding factor leukemia, MRD after one course of therapy, age at diagnosis, 11q23 rearrangements, megakaryoblastic leukemia without t(1;22), and *FLT3*-ITD accounted for 18.7% of variability in EFS. Additional variation in EFS could be explained by individual SNPs or a combination of SNPs within ara-C pathway genes. For instance, our analysis showed that incorporation of a DCTD SNP into existing model could enhance the percent total variation in EFS explained from 18.7% to 22.9%. Inclusion of all DCTD SNPs in the model increased the percent total variation in EFS explained from 18.7% to 29.7% **Conclusions:** Overall our results indicate that genetic variation in the ara-C pathway genes had a prognostic relevance that was similar to that of well-known factors. Understanding this variation can provide additional insights into the factors influencing treatment response and could lead to the identification of new prognostic markers.

10006 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Long-term survival after alternative donor transplantation in children with acute leukemia.

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Background: Most reports describing long-term survival after allogeneic transplantation are in adults after transplantation of bone marrow (BM) from HLA-matched siblings. This report compares long-term survival after transplantation of unrelated donor BM to that after umbilical cord blood (UCB) in children with acute leukemia. **Methods:** Included were patients aged less than 18 years with acute myeloid or lymphoblastic leukemia, alive and leukemia-free for at least 1 year after transplantation. Transplants occurred 2000-2009. Patients received BM grafts that were HLA-matched (N = 205) or mismatched at 1-HLA locus (N = 112) and UCB grafts that were matched (N = 55) or mismatched at 1 (N = 160) or 2 HLA-loci (N = 134). Multivariate Cox regression models were constructed to explore differences in survival between groups. UCB transplants were treated as a single group as there were no significant differences between HLA-matched and mismatched UCB grafts. Multivariate models held 3 treatment groups: HLA-matched BM, HLA-mismatched BM and UCB grafts. **Results:** The disease characteristics of the three groups were similar. There were differences in patient and transplant characteristics. Recipients of UCB transplants were younger, more likely non-Caucasian, and more likely to have received a non-irradiation-containing conditioning regimen, in-vivo T-cell depletion and GVHD prophylaxis with cyclosporine and either prednisone or mycophenolate. In multivariate analysis, the risks of long-term mortality were not significantly different after UCB and HLA-matched BM transplants (HR 0.83, p=0.41). Mortality risks were significantly higher after HLA-mismatched BM transplants compared to UCB (HR 1.66, p=0.03) and HLA-matched BM transplants (HR 2.00, p=0.008). In this cohort, surviving disease-free at least 1-year after transplantation, the 8-year probabilities of overall survival after UCB, HLA-matched and HLA-mismatched BM transplants were 78%, 81% and 68%. **Conclusions:** This is the first report to document long-term durability of UCB grafts. The data continue to support the use of UCB grafts either in the absence of an HLA-matched donor or when transplantation is needed urgently for children with acute leukemia.

10007 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Cytological and molecular remissions with blinatumomab treatment in second or later bone marrow relapse in pediatric acute lymphoblastic leukemia (ALL).

Lia Gore, Gerhard Zugmaier, Rupert Handgretinger, Franco Locatelli, Tanya M. Trippett, Susan R. Rheingold, Peter Bader, Arndt Borkhardt, Todd Michael Cooper, Maureen Megan O'Brien, Christian M. Zwaan, Anja Fischer, James Whitlock, Arend von Stackelberg; University of Colorado Cancer Center, Aurora, CO; Amgen Research (Munich) GmbH, Munich, Germany; University of Tuebingen, Department of Pediatric Oncology, Tübingen, Germany; Ospedale Pediatrico Bambino Gesu, Roma, Italy; Memorial Sloan-Kettering Cancer Center, New York, NY; Children's Hospital of Philadelphia, Philadelphia, PA; University of Frankfurt, Frankfurt am Main, Germany; University of Düsseldorf, Düsseldorf, Germany; Children´s Healthcare of Atlanta, Atlanta, GA; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Erasmus MC-Sophia Children's Hospital, Rotterdam, Netherlands; Hospital for Sick Children, Toronto, ON, Canada; Humboldt-University Berlin, Berlin, Germany

Background: Pediatric B-precursor acute lymphoblastic leukemia (ALL) in second or later relapse is an aggressive malignancy that needs therapeutic approaches with new mechanisms of action. Blinatumomab, a bispecific T-cell engaging (BiTE) antibody, has shown a hematological remission rate of 69% in adult patients with relapsed/refractory ALL. In order to establish a recommended dose in pediatric patients, a phase I multicenter trial was initiated. **Methods:** The primary endpoint is to determine the maximum tolerable dose defined by $\leq$1 of 6 patients experiencing dose limiting toxicity (DLT) within the 1st course of treatment. Up to 6 different dose levels of blinatumomab are being evaluated. Eligible patients must be $<$18 years old and have B-precursor ALL that is refractory or in second or later bone marrow relapse, or in any marrow relapse after allogeneic hematopoetic stem cell transplantation (HSCT). Blinatumomab is administered by continuous IV infusion over 28 days followed by a 14-day treatment-free interval (up to 5 cycles). To date, 3 dose levels have been explored (Table). **Results:** Seventeen patients have been treated thus far with a total of 32 cycles. One DLT (gastrointestinal hemorrhage) at dose level 2 (15 μg/m^2/d) and two DLTs at dose level 3 (30 μg/m^2/d; both cytokine release syndrome) with 1 death have been observed. One patient had generalized seizures on the 3rd day of the 2nd treatment cycle at the first dose level of 5 μg/m^2/d, which was completely reversible. The patient successfully underwent an allogeneic HSCT after blinatumomab. Eight (47%) of the 17 patients reached a cytological complete remission in bone marrow and a molecular remission defined as MRD by PCR $<10^{-4}$. **Conclusions:** A phase I trial of blinatumomab in patients with relapsed/refractory pediatric ALL has shown hematological and molecular remissions. Dose-limiting cytokine release syndrome has been noted. Alternative dosing regimens are being explored in current cohorts to refine the recommended dose of blinatumomab in this patient population. Clinical trial information: NCT01471782.

Cohort	Dose level μg/m^2/d	Patients treated n	DLTs n	Bone marrow CR/MR (Jan 2013)
1	5	5	0	2 / 2
2	15	7	1	4 / 4
3	30	5	2	2 / 2
Total		17	3	8 / 8

10008 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Autologous-collected anti-CD19 chimeric antigen receptor T cells (19CARTs) for pediatric acute lymphocytic leukemia (ALL) and non-Hodgkin lymphoma (NHL): Clinical activity and cytokine release without graft versus host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT).

Daniel Warnell Lee, Nirali Shah, Maryalice Stetler-Stevenson, Marianna Sabatino, Kelly Richards, Cindy Delbrook, James Kochenderfer, Steven A. Rosenberg, Dave Stroncek, Crystal Mackall, Alan S. Wayne; National Cancer Institute, National Institutes of Health, Bethesda, MD; Laboratory of Pathology, NCI, NIH, Bethesda, MD; National Institutes of Health, Bethesda, MD; Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; Department of Transfusion Medicine, National Institutes of Health, Bethesda, MD; National Cancer Institute, Bethesda, MD

Background: Despite intensive chemotherapy and HSCT, outcomes in relapsed/refractory pediatric B cell ALL and NHL are poor. To treat children with or without prior allogeneic-HSCT and quickly deliver therapy, we developed a Phase I trial of 19CARTs for both HSCT-naive and post-allo-HSCT patients where autologous-collected T cells are manufactured in 11 days. **Methods:** T cells collected on Day -11 by lymphopheresis were positively selected and activated using anti-CD3/CD28 beads then transduced with the CD19-CAR gene via retrovirus. Cells were infused after 7 additional days of expansion. Patients (Pt) received fludarabine and cyclophosphamide prior to receiving 1e6 19CARTs/kg. **Results:** A 59-65 fold expansion of 19CARTs with 39-65% transduction efficiency was achieved in Pt 1 and 3 (ALL, NHL). Pt 1 achieved a complete response (CR). Mild cytokine release syndrome was observed (Gr 3 fever, Gr 2 hypotension) correlating with mild elevation in IL6, GM-CSF, INFg and C reactive protein (CRP; Table). No other non-hematologic, CAR-related Gr $\geq$3 toxicities were observed. Pt 2 (ALL) received 2.8% of the targeted cell dose due to lack of cell expansion likely from recent prior chemotherapy but experienced a transient CR with significant 19CART expansion (15% blood, 5% marrow, 6% CSF). Importantly, 19CARTs were well tolerated without evidence of GVHD in these post-allo HSCT patients. **Conclusions:** Autologous-collected allogeneic derived 19CART cells can be rapidly manufactured and safely administered to children with ALL and NHL. Clinical activity can be achieved without GVHD despite inflammatory cytokine generation. 19CARTs offer a potentially effective strategy to treat post-HSCT relapse warranting further study. Clinical trial information: NCT01593696.

	Pt 1				Pt 2				Pt 3			
Day	IL6 (pg/mL)	TNFa (pg/mL)	GM-CSF (pg/mL)	CRP (<3mg/L)	IL6 (pg/mL)	TNFa (pg/mL)	GM- CSF (pg/mL)	CRP (<3mg/L)	IL6 (pg/mL)	TNFa (pg/mL)	GM- CSF (pg/mL)	CRP (<3mg/L)
0	3	10	3		2	7	2	4	>2500	119	91	274
4	4	8	1		1	6	1	3	987	283	42	55
7	53	16	59	112				5	10	12	2	56
9				261								82
14	2	9	2	16	2	9	2	4	>2500	457	38	90
21									236	167	15	107
28	9	7	1	2	1	7	2	2				

10009 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

IQ change within three years of radiation therapy in pediatric brain tumor patients treated with proton beam radiation therapy versus photon radiation therapy.

Lisa Kahalley, M. Fatih Okcu, M. Douglas Ris, David Grosshans, Arnold Paulino, Murali M. Chintagumpala, Bartlett Moore, Heather Stancel, Robert Wickham, Paras Mehta, Anita Mahajan; Baylor College of Medicine, Houston, TX; Baylor Coll of Medcn Texas Children's Cancer Ctr, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; The Methodist Hospital, Houston, TX; University of Houston, Houston, TX

Background: Radiation therapy (RT), an essential treatment for pediatric brain tumors, increases the risk of cognitive impairment. Advanced RT techniques reduce the volume of normal tissues receiving radiation dose. Proton beam radiation therapy (PBRT) minimizes irradiation to surrounding healthy brain tissue, with the potential to preserve cognitive function better than photon radiotherapy (XRT). We examined change in IQ over time between patients treated for pediatric brain tumors with PBRT versus XRT. **Methods:** IQ scores obtained in the first 3 years post-RT were abstracted for pediatric brain tumor patients treated with PBRT or XRT. **Results:** Baseline and follow-up IQ scores were available for 53 survivors (31 PBRT, 22 CRT). A linear regression model predicted follow-up IQ scores controlling for baseline IQ, age-at-RT, time-since-RT, and craniospinal irradiation (CSI), $F(7,45)=23.4$, $p<.001$. Follow-up IQ scores were significantly lower in the XRT group compared to the PBRT group ($p<.05$). The XRT group lost 10.3 IQ points on average with each additional year post-RT ($p<.01$), while the PBRT group remained stable, losing only 0.1 points per year on average ($p<.05$). CSI was associated with IQ decline in both groups ($p<.05$), while age-at-RT was not in either group ($p=.154$). Total RT dose was not associated with IQ with the above variables in the model. **Conclusions:** Findings suggest significant cognitive risk is associated with XRT, with IQ scores declining by more than half a standard deviation with each additional year post-RT. In contrast, IQ remained stable in the PBRT group. Preliminary findings suggest that PBRT may spare cognitive functioning in the first 3 years post-RT. Future research should replicate these findings with a larger sample and should study longer-term cognitive outcomes in patients treated with PBRT versus XRT.

	PBRT		XRT	
	n	%	n	%
Tumor histology				
Medulloblastoma/PNET	9	29.0	11	50.0
Germ cell	10	32.3	1	4.5
Glioma	7	22.6	4	18.2
Ependymoma	0	0.0	4	18.2
Other	5	16.1	2	9.1
Infratentorial	9	29.0	10	45.5
CSI	17	54.8	11	50.0
	Mean	Range	Mean	Range
Age at RT (yrs)	10.3	3.1-16.6	7.5	3.3-14.8
	Median	Range	Median	Range
Total RT Dose (Gy)	50.4	30.0-60.0	55.8	48.6-59.4

10010 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Elevated risk of second malignant neoplasms in pediatric germ cell tumor patients.

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Background: The probability of cure is very high for children with germ cell tumors (GCT), but late effects from cisplatinum can be quite significant. In addition to the immediate effects of oto-, neuro and nephrotoxicity, data from men treated for testicular cancer shows that the rate of second malignant neoplasm (SMN) is doubled and that a man treated before age 20 has a 50% chance of SMN by age 75. This study was designed to assess the risk of SMN among individuals treated for malignant GCT during childhood. **Methods:** We included all patients 0-19 years old with a primary diagnosis of malignant GCT registered in the Surveillance, Epidemiology and End Results (SEER) in the period 1973-2008. We analyzed tumors occurring at least 12 months after the first primary. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) were calculated using SEER Stat, version 8.0.1. **Results:** The cohort comprised 1997 patients (798 women and 1,199 men); 86.3% had primary gonadal tumors (91% in men and 79.5% in women). The median age at diagnosis of the primary malignancy was 17 years (17 for males ; 15 for females), and for second malignancies was 27 (27 for males; 30 for females). Fifty eight SMNs were observed (21 in females; 37 in males). Among women, higher risk was observed to developing breast cancer (n=5; SIR=1.29; 95% CI= 0.42-3.02), thyroid cancer (n=5; SIR= 3.40; 95% CI= 1.1-7.93) and brain cancer (n=3; SIR= 9.19; 95% CI=1.89-26.85). Twenty-seven out of 37 second primary tumors observed in men were contralateral testicular tumors, conferring a 16.2 fold higher risk of developing this neoplasm (95% CI= 10.67-23.58). When the analysis excluded testis as a second site, a higher risk was noted for the development of pancreatic cancer (SIR=19.06; 95% CI=2.31-68.83) and leukemia (SIR=3.55; 95% CI=0.43-12.81). **Conclusions:** Rates of SMN are elevated in both men and women treated as children for pediatric germ cell tumors. Men need to be made aware of risk in contralateral testicle. The rates of SMN may continue to rise with longer follow up. The attribution of treatment type to risk of SMNs is not possible due to the lack of this information in SEER database.

10011 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Impact of socioeconomic status on extent of disease at diagnosis and cancer and ocular outcomes in retinoblastoma: A population-based analysis.

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Background: The strong correlation between early diagnosis and improved outcomes has been consistently reported for retinoblastoma; extent of disease and eye preservation are associated with delayed diagnosis. In this study, we aimed to analyze the impact of socioeconomic status (SES) and ethnicity on extent on disease and cancer and ocular outcomes. **Methods:** All retinoblastoma cases (0-9 years) recorded in 18 SEER registries between 2000-2009 were included. The county-based disparity variables analyzed included poverty level, education attainment, language isolation, crowding, and percentage of immigrants. The cut-off values were defined as the median values for the cohort of patients. We also analyzed the impact of gender, race, and ethnicity. We tested for the association between SES and ethnicity with the percentage of extraocular disease and enucleation. Relative survival was calculated using Ederer II method; estimates were compared using Z-score. **Results:** We identified 753 cases. Percentage of extraocular cases was consistently higher in US counties with low SES indicators: higher vs. lower poverty status (29.3% vs. 22.1%, $p=0.028$); lower vs. higher education attainment (30.6% vs. 22.7%, $p=0.003$); higher vs. lower crowding (33.2% vs. 18.1%, $p<0.001$); higher vs. lower language isolation (32.2% vs. 19.3%, $p<0.001$); higher vs. lower percentage of immigrants (30.1% vs. 21.4%, $p=0.008$). Hispanic patients had significantly higher percentage of extraocular disease (35.2% vs. 20.9%, $p<0.001$). Poor ocular outcomes, reflected by high percentage of enucleation, were associated with counties with low education attainment ($p=0.025$), and with Hispanic origin ($p=0.019$). Decreased survival was associated with language isolation ($p=0.016$), but not with Hispanic origin or other SES indicators. **Conclusions:** Our study highlights significant disparities in the care and outcome of children with retinoblastoma. A low SES negatively impacts extent of disease, presumably by limiting access to primary care and delaying diagnosis. Hispanic patients have more advanced disease and higher enucleation rates, although survival is not significantly different.

10012 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Evaluation of early response by anatomic imaging to predict survival among patients with group III rhabdomyosarcoma: A report from the Children's Oncology Group.

Douglas S. Hawkins, Abby R. Rosenberg, Elizabeth Lyden, James Robert Anderson, David A. Rodeberg, Suzanne L. Wolden, Simon C Kao, David Parham, Carola A. S. Arndt, Children's Oncology Group; Department of Pediatrics, Seattle Children's Hospital, University of Washington, Seattle, WA; Department of Pediatrics, Seattle Childrens Hospital, University of Washington, Seattle, WA; University of Nebraska College of Medicine, Omaha, NE; College of Public Health, University of Nebraska Medical Center, Omaha, NE; East Carolina University, Greenville, NC; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Iowa College of Medicine, Iowa City, IA; University of Oklahoma Health Sciences Center, Oklahoma City, OK; Mayo Clinic, Rochester, MN

Background: The prognostic significance of response to induction therapy for rhabdomyosarcoma (RMS) by anatomic imaging (computerized tomographic [CT] or magnetic resonance imaging [MRI] scan) is controversial. We previously reported no relationship between early response and failure-free survival (FFS) for patients on IRS-IV. We repeated the same analysis using an independent cohort of patients with non-metastatic, initially unresected RMS treated on a more recent clinical trial. **Methods:** A total of 338 patients enrolled in Children's Oncology Group study D9803 met the following inclusion criteria for this analysis: 1) non-metastatic, initially unresected (Group III); 2) embryonal (ERMS) or alveolar (ARMS) histology; 3) documented response to induction chemotherapy (excluding progressive disease) based on anatomic imaging; and 4) documented therapy beyond week 12. Response at week 12 was determined by the treating institution as complete response (CR, complete resolution), partial response (PR, decrease of $>=$ 50% of the sum of the products of maximum perpendicular diameters), or no response (NR, between 50% reduction and 25% increase in the sum of the products of maximum perpendicular diameters). FFS was estimated using the Kaplan-Meier method, and comparisons between groups were made using the log-rank test. **Results:** Overall objective response rate (CR+PR) at week 12 of therapy was 85%, with similar responses for ERMS and ARMS. FFS was similar among all patients with CR, PR, or NR ($p=0.49$). Restricting the analysis to either ERMS or ARMS, there was no difference in FFS by histology ($p=0.20$ and $p=0.45$, respectively). **Conclusions:** These findings provide additional evidence that anatomic imaging assessment of early response to therapy among RMS patients does not predict outcome and should not be used to tailor subsequent therapy. Clinical trial information: NCT00003958.

Week 12 response	n (%)	5-year FFS (95% CI)
All patients	(N=338)	
CR	95 (28)	74% (64%, 82%)
PR	193 (57)	75% (68%, 80%)
NR	50 (15)	64% (49%, 76%)
ERMS	(N=245)	
CR	56 (23)	87% (75%, 94%)
PR	145 (59)	79% (72%, 85%)
NR	44 (18)	69% (52%, 81%)
ARMS	(N=95)	
CR	39 (41)	55% (38%, 69%)
PR	50 (53)	61% (46%, 73%)
NR	6 (6)	33% (5%, 68%)

10013 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Survival in metastatic Ewing sarcoma (EWS) and rhabdomyosarcoma (RMS) following consolidation immunotherapy with autologous lymphocyte infusion, dendritic cell vaccines ± CYT107 (rhIL-7).

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Background: Higher lymphocyte levels correlate with better survival in a variety of cancers, but it remains unclear whether there is a causal relationship between immune function and survival in cancer patients. A pilot study in high-risk pediatric sarcomas was undertaken to determine if a regimen designed to enhance immune reconstitution following standard cytotoxic therapy could improve survival. **Methods:** Forty-four patients (median 16 yrs, range 5-33) enrolled following a diagnosis of metastatic or late recurrent pediatric sarcoma, and underwent apheresis to collect mononuclear cells and tumor biopsy to generate tumor lysate, then received standard therapy at their home institution. After standard therapy, 29 patients received immunotherapy, comprising a single infusion of autologous lymphocytes depleted of $CD4^+CD25^+$regulatory T cells, plus dendritic cell vaccines pulsed with autologous tumor lysate and keyhole limpet hemocyanin (KLH, Q14d x 6). After the first 5 patients, CYT107 (rhIL-7, 20 mcg/kg SQ Q14d x 4) was added to the regimen. Intensive biologic analyses measured global and regulatory T cell immune reconstitution and vaccine responses. **Results:** This outpatient regimen was well tolerated with toxicities limited to rash, low-grade fever and mild constitutional symptoms. CYT107 dramatically enhanced global immune reconstitution and diminished regulatory T cell frequency. All patients developed immune responses to KLH and 31% developed immune responses to tumor lysate. Intent-to-treat analysis of all patients enrolled shows 56% 5-yr OS, with immunotherapy recipients having a 64% 5-yr OS (median f/u 30 mos, range 23-65). Intent-to-treat analysis of the subset of patients enrolled at the time of a new diagnosis of metastatic EWS or RMS shows 83% 5-yr OS and 54% 5-yr EFS (n=13, median f/u 35 mos, range 24-63), which is superior to previous outcomes reported for this population. **Conclusions:** A low intensity immunotherapy regimen focused on enhancing immune reconstitution following standard therapy may diminish recurrence in newly diagnosed metastatic EWS and RMS. Clinical trial information: NCT00923351.

10014 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Prognostic implications of gain of 1q in favorable histology Wilms tumor: A report from the Children's Oncology Group.

Eric J. Gratias, Lawrence J Jennings, James Robert Anderson, Jeffrey Dome, Paul Edward Grundy, Elizabeth Perlman; T.C. Thompson Children's Hospital, Chattanooga, TN; Ann and Robert H. Lurie Children's Hospital, Chicago, IL; College of Public Health, University of Nebraska Medical Center, Omaha, NE; Children's National Medical Center, Washington, DC; Stollery Children's Hosp, Edmonton, AB, Canada

Background: Wilms tumor is the most common childhood renal tumor. While the majority of patients with favorable histology Wilms Tumor (FHWT) have good outcomes, many patients still experience recurrence and death from disease. This study's goal was to determine if chromosome 1q gain is associated with event-free (EFS) and overall survival (OS) in FHWT. **Methods:** Unilateral FHWT samples were obtained from patients enrolled on National Wilms Tumor Study-4 and Pediatric Oncology Group 9046, "A Molecular Genetic analysis of Wilms Tumor." 1q gain, 1p loss, and 16q loss were determined using multiplex ligation-dependent probe amplification (MLPA). **Results:** The eight-year EFS was 87% (95% CI 82%, 91%) for the entire cohort of 212 patients. Tumors of 58/212 patients (27%) displayed 1q gain. A strong relationship between 1q gain and 1p/16q loss was observed. The eight-year EFS was 76% (95% CI 63%, 85%) for those with 1q gain and 93% (95% CI 87%, 96%) for those lacking 1q gain ($p=0.0024$). The eight-year OS was 89% (95% CI 78%, 95%) for those with 1q gain, and 98% (95% CI 94%, 99%) for those lacking 1q gain ($p=0.0075$). Gain of 1q did not correlate with disease stage ($p=0.16$). After stratification for stage, 1q gain was associated with a significant increase in the risk of failure (risk ratio estimate: 2.72, $p=0.0089$). **Conclusions:** Gain of 1q is associated with inferior EFS and OS in FHWT and may provide a new and valuable prognostic marker to stratify therapy for patients with FHWT. A confirmatory study is necessary before this biomarker is incorporated into risk stratification schema of future therapeutic studies.

10015 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Metastatic neuroblastoma confined to distant lymph nodes (stage 4N) to predict outcome in patients with stage 4 disease: A study from the International Neuroblastoma (NB) Risk Group (INRG) Database.

Daniel Alexander Morgenstern, Wendy B. London, Derek Stephens, Samuel Louis Volchenboum, Barabara Hero, Andrea Di Cataldo, Akira Nakagawara, Hiroyuki Shimada, Peter F Ambros, Katherine K. Matthay, Susan Lerner Cohn, Andrew DJ Pearson, Meredith Irwin; The Hospital for Sick Children, Toronto, ON, Canada; Dana-Farber Cancer Institute/Harvard Cancer Care/Children's Hospital Boston, Boston, MA; University of Chicago, Chicago, IL; University Children's Hospital, Köln, Germany; University of Catania, Catania, Italy; Chiba Cancer Research Institute, Chiba, Japan; Children's Hospital Los Angeles, Los Angeles, CA; Children's Cancer Research Institute, St. Anna Kinderspital, Vienna, Austria; University of California, San Francisco, San Francisco, CA; The University of Chicago, Chicago, IL; Institute of Cancer Research and Royal Marsden Hospital, Sutton, United Kingdom

Background: Patients with metastatic NB typically have a poor prognosis; however case series have suggested that those with 4N disease may have improved outcomes. **Methods:** Retrospective analysis of data from INRG database for patients diagnosed 1990–2002. 4N patients (INSS stage 4 disease confined to distant lymph nodes) were compared to the balance of stage 4 patients ('non-4N'), excluding those with missing metastatic site data. 5-yr estimates of overall (OS) and event-free survival (EFS) were calculated ± standard error (Kaplan-Meier method). Patient characteristics were compared by Mann-Whitney or Fisher's exact/Chi-square tests. **Results:** 2,250 INSS stage 4 patients with complete data were identified, of whom 146 (6%) had 4N disease. For 4N patients, EFS and OS (5-yr: 77% ± 4%, 85% ± 3%), were significantly better than EFS and OS (5-yr: 35% ± 1%, 42% ± 1%) for non-4N stage 4 patients ($p<0.0001$). 4N patients were more likely to be younger (median age at diagnosis 1.2 yr vs 2.5 yr for non-4N; $p<0.0001$) and have tumors with favourable International Neuroblastoma Pathologic Classification (INPC) (63% vs 26%, $p<0.0001$), differentiating grade (21% vs 8%, $p=0.006$), lower MKI ($p=0.0011$) and non-MYCN amplified tumors (89% vs 69%, $p<0.0001$). Within subgroups defined by age at diagnosis and MYCN status, 4N pattern of disease remained significantly associated with improved outcomes. For patients aged ≥547 days at diagnosis and MYCN non-amplified, 5-yr EFS for 4N patients ($n=42$) was 63% ± 8% vs 27% ± 2% for non-4N ($n=785$); OS 74% ± 7% vs 38% ± 2% (both $p<0.0001$). Within this subgroup, favourable INPC and differentiating grade remained more frequent in the 4N vs non-4N patients (45% vs 10%, $p<0.0001$; 45% vs 8%, $p=0.0017$, respectively). **Conclusions:** 4N represents a subgroup of metastatic patients with better outcome than other INSS stage 4 patients. These findings indicate that the biology and response to treatment of 4N tumors differs from other stage 4 tumors, and different therapies should be considered for this cohort. Future exploration of biological factors determining pattern of metastatic spread and response to therapy is warranted.

10016 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Topotecan-vincristine-doxorubicin in metastatic neuroblastoma with insufficient response to rapid COJEC: Results of a SIOPEN Group study.

Loredana Amoroso, Dominique Valteau-Couanet, Victoria Castel, Penelope Brock, Andrew DJ Pearson, Ruth Lydia Ladenstein, Alberto Garaventa; Giannina Gaslini Children's Hospital, Genoa, Italy; Pediatric and Adolescent Oncology, Gustave Roussy Institute, Universite Paris-Sud, Villejuif, France; Pediatric Hematology and Oncology, Pediatric Oncology Unit Hospital La Fe Valencia, Valencia, Spain; Great Ormond Street Hospital, London, United Kingdom; Institute of Cancer Research and Royal Marsden Hospital, Sutton, United Kingdom; St. Anna Children's Hospital and Research Institute, Vienna, Austria

Background: This study evaluated the activity and toxicity of a topotecan-vincristine-doxorubicin (TVD) combination administered to patients with stage 4 neuroblastoma failing to achieve adequate metastatic remission after induction therapy (rapid COJEC) according to the HR-NBL-1 SIOPEN protocol. **Methods:** Patients above 1 year of age with stage 4 neuroblastoma, who failed to achieve adequate metastatic remission with rapid COJEC were eligible. Topotecan was administered at 1.5 mg/m^2/day for 5 days, followed by a 48-hour infusion of vincristine, 2 mg/m^2 and doxorubicin, 45 mg/m^2. Tumour response was assessed after 2 TVD courses, according to the INSS criteria. Patients achieving CR or VGPR (metastatic CR) or PR ($\leq$ 3 skeletal MIBG spots and cytomorphological CR on 2 bone marrow aspirates) underwent myeloablative therapy (MAT) followed by PBSC rescue. Patients who failed to achieve PR after 2-4 TVD courses, or developed PD were withdrawn from the study and were treated at physicians' discretion. Results were recorded in the SIOPEN-R-NET database. **Results:** Sixty-eight patients who did not achieve CR or VPGR after rapid COJEC were enrolled in the study. Responses of 68 assessable patients after 2 TVD courses included 4 CR, 13 VPGR, 26 PR, 7 MR, 14 NR, 2 PD, 2 missing data (major response rate 65 %). Twenty-five patients who achieved CR or VGPR or PR (metastatic CR) received MAT according to protocol. Thirty-three/68 patients are presently alive, no toxic deaths occurred. Toxicity was mostly hematopoietic. Fifty-three patients experienced grade 4 neutropenia, 47 grade 4 thrombocytopenia and 12 grade 4 anemia after the first course. Forty-nine patients developed grade 4 neutropenia, 41 grade 4 thrombocytopenia and 12 grade 4 anemia after the second course. Twenty-six patients required hospitalisation for systemic antibiotic therapy after the first course, and 19 patients after the second. Grade 3-4 stomatitis requiring a liquid diet or TPN was observed in 17 patients after the first cycle and 9 after the second. **Conclusions:** This TVD combination was active and tolerable in patients with metastatic neuroblastoma after treatment with rapid COJEC. Clinical trial information: 2006-001489-17.

10017 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

The RIST design: A molecularly targeted multimodal approach for the treatment of patients with relapsed and refractory neuroblastoma.

Selim Corbacioglu, Daniel Steinbach, Holger N. Lode, Bernd Gruhn, Michael Fruehwald, Mechthild Broeckelmann, Meinolf Suttorp, Gabriele Escherich, Gunnar Cario, Karoline Ehlert, Bernhard Meister, Thorsten Simon, Klaus-Michael Debatin, Michaela Kuhlen, Isa Feddersen; University Hospital Regensburg, Regensburg, Germany; University Hospital Ulm, Ulm, Germany; University Hospital Greifswald, Greifswald, Germany; University of Jena, Jena, Germany; Hospital of Augsburg, Augsburg, Germany; Hospital of Bielefeld, Bielefeld, Germany; University Hospital of Dresden, Dresden, Germany; University Hospital of Hamburg, Hamburg, Germany; University Hospital of Kiel, Kiel, Germany; University Hospital of Muenster, Muenster, Germany; University Hospital of Innsbruck, Innsburck, Austria; University Hospital of Koeln, Koeln, Germany; University of Ulm, Ulm, Germany; University Hospital of Düsseldorf, Düsseldorf, Germany; Hospital of Trier, Trier, Germany

Background: The prognosis for children with recurrent or refractory neuroblastoma (rNB) remains dismal. Novel therapeutic approaches are urgently needed. **Methods:** Based on promising in vitro data unselected patients with rNB were treated as compassionate use according to a multimodal approach (RIST design). The treatment consisted of metronomic courses of Rapamycin/Dasatinib (R/S) for 4 days followed by 5 days of Irinotecan and Temozolomide (I/T). Twenty-one patients (median age: 38 months) with stage IV (n=19) and stage III (n=2) disease, 5 with refractory disease, 8 with 1^{st} and 8 with 2^{nd} and 3^{rd} relapses were included. Seven patients presented within 18 months after diagnosis (median age: 28 months). 18 patients were MIBG positive, 4 MYCN amplified. Dissemination was present in the bone in 15, bone marrow in 11 and lymph nodes in 6 patients, respectively. **Results:** The patients received a median of 16 courses of R/S (4 to 72) and 7 courses of I/T (4 to 65). 19 patients (90%) showed an initial response according to imaging criteria after a median of 7 R/S and 4 I/T courses (median treatment duration 12 weeks): CR in 12 (57%), a PR in 3 (14%) and a SD in 4 (19%). The median PFS was 90 weeks. The OS after a median of 148 weeks was 43% with 7 patients in CR, 1 VGPR and 1 in PR. There were no toxic deaths in this highly pretreated population. Grade III and IV toxicities (CTC 3.0) were thrombocytopenia in 81%, leukopenia in 76%, anemia in 71%, and diarrhea in 71% respectively. **Conclusions:** This RIST treatment design applied as a multimodal approach in a compassionate use setting exhibited very promising results considering the adequately long follow-up period of 3 years. This molecular targeted therapy design for rNB warrants confirmation in a prospective clinical trial.

10018 Poster Discussion Session (Board #35A), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Second non-ocular tumors among survivors of retinoblastoma treated with proton therapy.

Roshan V Sethi, Helen Alice Shih, David Kim, Beow Y. Yeap, Kent Mouw, Karen Chayt Marcus, Eric Grabowski, Torunn I. Yock, Nancy Tarbell, Shizuo Mukai, Shannon M. MacDonald; Harvard Medical School, Boston, MA; Massachusetts General Hospital, Boston, MA; Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA; Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; Children's Hospital Boston, Boston, MA; Department of Pediatric Hematology and Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: The leading cause of death for patients with hereditary retinoblastoma is second malignancy. Proton radiation allows for significant sparing of non-target tissue. We sought to determine the risk of second malignancy for the largest and oldest cohort of retinoblastoma patients treated with proton therapy. **Methods:** We performed a retrospective review of patients treated at the Massachusetts General Hospital (MGH) between 1986 and 2011. **Results:** Fifty-two patients were identified (see Table). Forty-four patients (85%) were hereditary survivors. Patients were followed for a median of 6.9 years from the start of radiation therapy (range, 11.3 months to 24.4 years). The median age at follow-up was 9.0 years (range, 31.3 months to 24.5 years). Fifteen patients had more than 10 years of follow-up from the start of radiation therapy, and 20 patients were more than 10 years old at last follow-up. With 417.2 person-years of follow-up, we identified one secondary malignancy, an osteosarcoma of the distal femur. The cumulative incidence of second tumor was 5% at 10 years. No radiation-associated malignancies were reported. **Conclusions:** Retinoblastoma is highly responsive to radiation. The central objection to the use of radiation—the risk of second malignancy—is founded on studies of patients treated with relatively non-conformal techniques. We present the first series of patients treated with the most conformal of current available modalities. While longer follow up is necessary, our preliminary data suggest that the risk of radiation-associated malignancy is minimal with proton therapy.

Patient characteristics.

Variable	Number of patients (%) n=52
Sex	
Male	22 (42)
Female	30 (58)
Age at diagnosis	
Median (range)	6.9 months (6 days – 11.9 years)
<12 months	26 (50)
>12 months	16 (31)
Unknown	10 (19)
Laterality at diagnosis and history	
Bilateral with family history	12 (23)
Bilateral, no/unknown family history	30 (58)
Unilateral with family history	2 (4)
Unilateral, no/unknown family history	8 (15)
Treatment	
Chemotherapy and radiation	30 (58)
Radiation alone	22 (42)
Median dose (range) (Gy[RBE])	44 (34-46.8)
Age at treatment	
Median (range) (months)	14.9 months (27 days – 12.1 years)
<12 months	19 (37)
>12 months	33 (63)

10019 Poster Discussion Session (Board #35B), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Chronic medical conditions in adult survivors of retinoblastoma.

Danielle Novetsky Friedman, Joanne F. Chou, Kevin C. Oeffinger, Jennifer Ford, Charles A. Sklar, Yuelin Li, Mary S. McCabe, Leslie L. Robison, Ruth Kleinerman, Brian Marr, David H. Abramson, Ira J. Dunkel; Memorial Sloan-Kettering Cancer Center, New York, NY; St. Jude Children's Research Hospital, Memphis, TN; National Cancer Institute, Rockville, MD

Background: Increased risk of second malignant neoplasms (SMN) in retinoblastoma survivors (RBS) is well documented, but little is known about their long-term burden of chronic non-visual morbidity. **Methods:** RBS treated in NYC were asked to complete a comprehensive questionnaire, adapted from the Childhood Cancer Survivor Study (CCSS) surveys; frequencies of chronic conditions, excluding SMN, in 470 RBS and 2,377 CCSS siblings were calculated. A severity score, based on the NCI CTCAE v4 (ranging from grade 1 [mild] to grade 4 [disabling/life-threatening]) was assigned to each condition. Logistic regression was used to estimateodds ratios of chronic condition risk in RBS vs CCSS siblings, adjusted for age, sex, and race/ethnicity, reported as relative risks (RR) and 95% confidence intervals (CIs). **Results:** RBS and CCSS siblings were mean ages of 43 years (SD 11) and 38 years (SD 9), respectively, at the time of questionnaire completion. 53.6% of RBS had bilateral disease. After excluding SMN, 70.2% of RBS had at least one non-visual chronic condition while 14% had a grade 3-4 condition. The adjusted RR of a non-visual chronic condition in a survivor compared to siblings was 1.5 (95% CI, 1.2-1.8); for a grade 3-4 condition, the risk was 1.5 (95% CI, 1.1-2.1). The most common grade 3-4 non-visual conditions in RBS were hearing loss (3.6%; bilateral 5.6%, unilateral 1.3%, p=0.023) and thyroid nodules requiring partial or full thyroidectomy (3.4%; bilateral 5.6%, unilateral 0.9%, p=0.008). Rates of grade 3-4 thyroid nodules and hearing loss did not differ significantly when stratified by treatment received. Rates of all conditions in RBS are reported in the Table. **Conclusions:** RBS have a modestly increased risk of non-visual chronic conditions when compared to individuals of comparable age, sex and race/ethnicity.

RBS and siblings with a chronic condition (excluding SMN).

Condition	Survivors (N=470)	Siblings (N=2377)	RR (95%CI)
No. (%)			
Any condition			
Grades 1-4	330 (70.2)	1,323 (55.7)	1.5 (1.2-1.8)
Grades 3-4			
Nonvisual*	66 (14.0)	148 (6.2)	1.5 (1.1-2.1)
Including visual	320 (68)	174 (7.3)	23.4 (18-31)
Multiple conditions			
≥ 3	148 (31.5)	370 (15.5)	1.7 (1.4-2.2)

* Nonvisual excludes cataracts, glaucoma, blindness, and other eye conditions.

10020 Poster Discussion Session (Board #35C), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Comprehensive profiling of cardiac dysfunction in asymptomatic childhood cancer survivors (CCS) treated with anthracyclines.

Saro Armenian, Sarah Gelehrter, Tabitha Vase, Rajkumar Venkatramani, Wendy Landier, Karla Wilson, Claudia Herrera, Leah Reichman, John David Menteer, Leo Mascarenhas, David Robert Freyer, Kalyanasundaram Venkataraman, Smita Bhatia; City of Hope, Duarte, CA; C.S. Mott Children's Hospital, Ann Arbor, MI; Children's Hospital Los Angeles, Los Angeles, CA

Background: Anthracyclines are associated with left ventricular (LV) dysfunction in CCS with inevitable progression to congestive heart failure (CHF). Use of ejection fraction (EF) to identify LV dysfunction precludes intervention, because EF decline is a late event in the progression to CHF. Further, better understanding of pathogenesis at the cellular level could facilitate development of targeted interventions. **Methods:** Study design: Cross-sectional; Biomarkers: Echocardiographic (echo), and blood biomarkers in asymptomatic individuals exposed to anthracyclines $\geq$300mg/m^2 (high-risk [HR]: n=100) compared with: i) CCS exposed to $<$300 mg/m^2 (low-risk [LR]: n=50): and ii) matched healthy controls (Con: n=50). Pathogenesis: Metabolomic analyses (351 plasma metabolites; 64 pathways). **Results:** Time from dx to study was comparable for HR (12.0y) vs. LR (13.2y, p=0.8). All CCS had EF$\geq$50%. Echo: HR had lower LV chamber thickness-dimension (T-D) ratio (Z-score: -0.62) compared with LR (-0.03) and Con (-0.02; P$<$0.01) as well as increased LV wall stress ([ESWS] HR: 66 g/cm^2, LR: 58 g/cm^2, Con: 55 g/cm^2, p$<$0.01) and higher myocardial performance index ([MPI] HR: 0.51, LR: 0.46, Con: 0.46; P$<$0.01). Blood biomarkers: HR had higher plasma NT-pro BNP (HR: 71 pg/dL, LR: 37 pg/dL, Con: 26 pg/dL; P$<$0.01); there were no differences in troponins, Galectin-3 or ST-2. Metabolomics:Individuals with LV dysfunction ($>$2 SD ESWS) had reduced plasma carnitine levels (relative ratio [RR]: 0.88, p$<$0.01) contributing to altered fatty acid β-oxidation and accumulation of cardiotoxic long-chain (docosadienoate [RR=1.26], adrenate [RR=1.29]; p$<$0.05) and essential fatty acid intermediates (dihomo-linolenate [RR=1.27], eicosapentaenoate [RR=1.23], docosapentaenoate [RR=1.46]; p$<$0.05). **Conclusions:** Comprehensive profiling of anthracycline-exposed CCS with preserved EF revealed dose-dependent echo (LV ESWS, T-D ratio, MPI) and blood (NT-ProBNP) abnormalities 10+years from dx; metabolomic studies demonstrated the role of carnitine in the pathogenesis of LV dysfunction. Taken together, these findings may facilitate early detection and targeted interventions in CCS at highest risk for CHF.

10021 Poster Discussion Session (Board #35D), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Pulmonary function after treatment for embryonal brain tumors on SJMB03 that included craniospinal irradiation.

Daniel M. Green, Thomas E. Merchant, Catherine A Billups, Dennis C Stokes, Alberto Broniscer, Ashok Srinivasan, Murali M. Chintagumpala, Timothy E Hassall, Eric Bouffet, Sridharan Gururangan, Stewart J Kellie, David M Ashley, Richard J Cohn, Michael J. Fisher, Amar J. Gajjar; St. Jude Children's Research Hospital, Memphis, TN; Pediatric Pulmonary, Le Bonheur Children's Medical Center, Memphis, TN; Baylor College of Medicine, Houston, TX; Haematology and Oncology, Royal Children's Hospital, Brisbane, Australia; The Hospital for Sick Children, Toronto, ON, Canada; Division of Pediatric Hematology-Oncology, Duke School of Medicine, Durham, NC; Paediatrics & Child Health, Children's Hospital, Westmead, Sydney, Australia; The Andrew Love Cancer Centre, Melbourne, Australia; Centre for Children's Cancer and Blood Disorders, Sydney Children's Hospital, Sydney, Australia; Children's Hospital, Philadelphia, PA

Background: Treatment of children with embryonal brain tumors (EBT) includes craniospinal irradiation. There are limited data regarding the effect of radiation therapy (RT) on pulmonary function. **Methods:** Protocol SJMB03 enrolled patients 3 to 21 years of age with EBT. Pulmonary function tests (PFTs) [forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) by spirometry, total lung capacity (TLC) by plethysmography and diffusing capacity of the lung for carbon monoxide (DLCO)] were obtained following completion of RT, prior to each of four courses of high-dose chemotherapy (cumulative cyclophosphamide dose, 16 g/m^2), and 24 months after completion of treatment (ACT). Differences between PFTs obtained following the completion of RT and 24 months ACT were compared using exact Wilcoxon signed rank tests. **Results:** 303 eligible patients were enrolled between June 24, 2003 and March 1, 2010, 258 of whom had at least one PFT. Median age at diagnosis - 8.9 years (range, 3.1 to 20.4 years). Median spinal RT dose - 23.4 Gy (range, 23.4 to 50.4 Gy). Median cyclophosphamide dose was 16.24 g (range, 0 to 34.38 g). 24 months ACT, DLCO was $< 75\%$ predicted in 23% (27/115 evaluated), FEV1 was $< 80\%$ predicted in 21% (32/150 evaluated), FVC was $< 80\%$ predicted in 27% (46/168 evaluated) and TLC was $< 80\%$ predicted in 18% (24/135 evaluated) of patients. DLCO was significantly decreased 24 months ACT compared to the end of RT (median difference (MD) in % predicted, - 3.00%; $p = 0.035$). Race and cumulative cyclophosphamide dose were not significant predictors of DLCO. DLCO was significantly higher among males ($p = 0.037$) than females in a model that included time point, sex, RT dose group, RT dose*time interaction and age at diagnosis. The differences in FEV1 ((MD, - 1.00%), FVC (MD, 0.00%) and TLC (MD, -2.00%) were not statistically significant. **Conclusions:** Among patients with EBT treated with spinal RT, DLCO was significantly decreased 24 months after completion of treatment compared to immediately post-RT. TLC was decreased 24 months ACT, suggesting that a significant minority of patients have restrictive lung disease. Continued monitoring of this cohort to five years ACT is planned. Clinical trial information: NCT00085202.

10022 Poster Discussion Session (Board #35E), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Global fitness in adult survivors of childhood acute lymphoblastic leukemia (ALL).

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Background: The extent to which adult survivors of childhood ALL may have impaired fitness has not been well documented. This study compared clinically assessed fitness between childhood ALL survivors and matched controls, and examined risk factors for impaired fitness among survivors**. Methods:** 365 survivors of childhood ALL diagnosed from 1980-2002, treated at St. Jude Children's Research Hospital (SJCRH), 10+ years from diagnosis, and 18+ years old completed questionnaires, fitness testing and physical activity assessment (accelerometry). 365 friends/relatives of current SJCRH patients, frequency matched on age, race and sex, were recruited as controls. Data from fitness measures were combined into a composite (SJFIT) using factor analysis. Individual measures and SJFIT scores were compared between survivors and controls with two sample t-tests. Among survivors, associations between demographic, lifestyle, treatment variables and poor fitness, i.e. scoring in the lowest 10th percentile of controls on the SJFIT, were evaluated with logistic regression. **Results:** Survivors were 52% male (mean age 28±7 years, mean diagnosis age 6±5 years, mean survival 21±5 years), and scored lower than controls on individual fitness measures (Table) and the SJFIT composite. Female sex (OR 9.4, 95%CI 3.4-26.1) and fewer daily minutes of moderate and vigorous physical activity (OR 0.95, 95% CI 0.92-0.99) were associated with poor fitness after adjusting for diagnosis age, current age, cranial radiation, body fat and smoking. **Conclusions:** Childhood ALL survivors, particularly females, have fitness impairments when compared to matched controls. Poor fitness is associated with physical activity levels. Interventions to address impairments need to be tested and implemented.

	Survivors	Controls	P
	Mean±SD	Mean±SD	
Peak oxygen uptake (mg/kg/min)	24.2±6.2	27.5±8.3	<.001
Strength			
Hand grip (kg)	40.3±13.5	42.0±12.7	0.09
Quadriceps- (Nm/kg)			
60°/s	148.7±55.4	173.3±59.4	<.001
180°/s	93.6±36.0	109.8±41.0	<.001
300°/s	65.9±26.4	78.9±32.3	<.001
Flexibility			
Ankle dorsiflexion (°)	7.2±7.6	11.8±6.3	<.001
Sit-reach (cm)	21.7±10.7	27.1±9.2	<.001
Balance			
Sensory Organization Test (%)	79.1±8.1	80.2±6.3	0.04
SJFIT T score	47.3±9.7	50±10	<.001

10023 Poster Discussion Session (Board #35F), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Implementation and evaluation of clinical exome sequencing in childhood cancer care: The BASIC^3 study.

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Background: Advances in sequencing technologies allow for provision of genome-scale data to oncologists and geneticists caring for pediatric cancer patients. The goal of the BASIC^3 (Baylor Advancing Sequencing into Childhood Cancer Care) study is to determine the clinical impact of incorporating CLIA-certified tumor and constitutional exome sequencing into the care of children with newly diagnosed solid tumors. **Methods:** Blood and frozen tumor samples obtained at initial surgery are submitted for clinical exome sequencing (target enrollment 280 patients). Results are deposited into the electronic medical record and disclosed to families by their oncologist and a genetic counselor. Identification of germline cancer susceptibility mutations is compared with standard testing practices. Oncologists are surveyed on prioritization of treatment options in the hypothetical event of tumor recurrence before and after receiving tumor exome results. Patients will be followed for two years to assess the clinical utility of exome data. Preferences for reporting this complex information are obtained by interviews and audiorecording of disclosure visits. **Results:** Initial results reveal that41 of 49 (84%) ethnically diverse families have consented to enroll on study. Adequate tumor samples were available from 35 of 41 patients (85%), including 11 of 15 (73%) patients with CNS tumors and 24 of 26 (92%) with non-CNS tumors. Pathogenic germline cancer susceptibility mutations (*TP53, MSH2*) were reported in 2 of the first 11 patients, with a medically-actionable mutation in a gene (*SCN5A*) unrelated to cancer in 1 patient and 0-4 (median of 2) recessive carrier mutations per patient. Between 9 and 33 protein altering mutations (median of 11) have been identified in tumors, including known cancer genes such as *TP53* and others with no known link to pediatric cancer. **Conclusions:** A robust clinical pipeline for exome sequencing of blood and tumor samples has been successfully developed with significant parental interest. Data assessing the clinical utility of both the tumor and constitutional exomes and the preferences of oncologists and parents for reporting of these results are under study. Supported by NHGRI 1U01HG006485.

10024 Poster Discussion Session (Board #35G), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Pleuropulmonary blastoma: The causative role of germ-line *DICER1* mutations.

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Background: Pleuropulmonary blastoma (PPB) is a rare, aggressive childhood lung cancer that is often the first manifestation of the PPB-*DICER1* familial tumor predisposition which includes other benign and malignant conditions. The initial genetic mutation is inherited by a germ-line loss of function of *DICER1* gene which was discovered by Hill et al. It is proposed that loss of *DICER1* expression alters miRNA regulation of key regulatory cellular mechanisms which promote tumor growth. PPB can progress from the purely cystic, curable Type I to a high-grade Type III having a dismal prognosis. We sought to determine the frequency of *DICER1*mutation in the largest cohort of PPB patients to date. **Methods:** We obtained germ-line DNA from saliva or blood samples from 113 PPB patients collected from 2005-2012. DNA was extracted using the Maxwell 16 Research System (Promega Corporation, Madison WI). Sample quality and quantity was checked using the Nanodrop 2000 (Thermo Scientific, Wilmington, DE). Sequencing was performed using the Sanger sequencer. For a subset of cases we used targeted sequencing services or full gene sequence analysis (Ambry Genetics, Aliso Viejo, CA). **Results:** Seventy-four (65.5%) PPB patients were found to have deleterious *DICER1*germ-line mutations. The most common mutation type found was small insertion/deletions. These 74 samples were composed of 7 (9.5%)Type Ir PPBs, 22 (29.7%)Type I PPBs, 24 (32.4%) Type II PPBs, and 21 (28.4%)Type III PPBs. The following Table shows a summary of mutation types identified. **Conclusions:** Our results confirm that *DICER1* germline mutations are the most common genetic alterations in PPB making it critical for genetic testing to be performed at diagnosis. Additionally, this underscores the need for important correlative studies to describe the genotype-phenotype relationship in order for appropriate screening guidelines to be developed and implemented to allow for early detection. While a majority of cases are explained by germline *DICER1* mutations using current sequencing methods, further investigation is warranted to elucidate other possible mechanisms in the development of PPB.

Mutation type	Number detected	Percentage
Indel	35	47.3
Nonsense	27	36.5
Missense	6	8.1
Splice	6	8.1
Total	74	100%

10025 Poster Discussion Session (Board #35H), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Role of IGF-1R inhibition on an Src-family kinase bypass resistance pathway: A rational basis for cotargeting IGF-1R and Src kinase in pediatric sarcomas?

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Background: Dysregulation of IGF signaling plays a fundamental role in oncogenesis in pediatric sarcomas. We recently completed a Phase II study targeting the IGFI receptor signaling pathway in refractory Ewing's and other sarcomas. We demonstrated an objective response rate of 16 percent, but most responses were transient lasting less than 18 weeks. The majority of patients, even those with initial responses, do not have long term benefit from IGFIR blockade, indicating the presence of an innately resistant tumor mass or the recruitment of compensatory pathways allowing for continued growth. To improve on these responses, we have been probing these tumors to identify other critical pathways that might allow combined targeting approaches. **Methods:** Multiple RMS and ES cell lines were treated with IGF1R kinase inhibitors and assayed for up-regulation of various signaling pathways. Combination treatment with IGF1R inhibitors and inhibitors of additional signaling pathways were then tested in vitro and in vivo using standard techniques. For in vivo xenograft studies, treatments began 11 days following orthotopic injection of tumor cells. **Results:** We have identified repid up-regulation of Src family kinase (SFK) signaling within 4 hours of IGF1R blockade in both RMS and ES cell lines. Of note, combined treatment with IGF1R Ab plus IGF1R kinase inhibitors most potently upregulated SFK signaling. Based on these findings, we tested combined IGF1R blockade with SFK inhibition using the commercially available drug, dasatinib. We show that dual blockade of IGF1R and SFK pathways were synergistic in vitro. Furthermore, in xenograft models of RMS, the combination IGF1R and SFK inhibition led to long-term disease free status for at least 90 days in some mice, never seen in our hands previously using these models. **Conclusions:** This work identified that IGF-1R inhibition induced activation of Src kinase that may act as a by-pass pathway. Synergistic activity of IGF-1R and SFK kinase inhibitors was observed in vitro and in vivo. Dual IGFI and SFK kinase inhibition may lead to improved therapeutic outcomes.

10026 Poster Discussion Session (Board #36A), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

A phase I study of the anti-insulin like growth factor type 1 receptor (IGF-1R) antibody dalotuzumab in pediatric patients with advanced solid tumors.

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Background: Insulin-like growth factor signaling plays an important role in several pediatric cancers. Dalotuzumab is a highly specific, humanized IgG1 monoclonal antibody against IGF-1R. This multicenter phase 1 study explored the safety and pharmacokinetics (PK) of dalotuzumab in pediatric patients with advanced solid tumors. **Methods:** Dalotuzumab was administered intravenously every 3 weeks. Dose-escalation was performed according to a modified Toxicity Probability Interval (mTPI) design starting at 900 mg/m^2. The PK profile of dalotuzumab was evaluated with the primary goal of confirming that the Day 22 mean serum trough concentration exceeded 25 μg/mL. **Results:** 24 patients were enrolled and 20 treated (median age, 10.5 years; range, 3–17 years). Six patients had recurrent Ewing sarcoma. Patients received a median of 2 cycles (range, 1-10). No dose-limiting toxicity was observed in any of the three dose levels explored (900, 1200 and 1500 mg/m^2). Main treatment-related toxicities were Grade 3 elevated transaminases. PK data showed dose dependent increases in $AUC_{0-\infty}$ (105,000, 164,000 and 281,000 hr*mg/mL, for the 900, 1200 and 1500 mg/m^2 dose levels, respectively), C_{trough} (65.2, 71.6, 148 mg/mL) and C_{max} (559, 643, 888 mg/mL). The mean half-life was 247, 394 and 376 hours respectively. The C_{max} exhibited mild variability (4.8-35% Coefficient of Variation), whereas variability was moderate to high on the C_{trough} (39-200%), apparent $t_{1/2}$ (28-154%), $AUC_{0-\infty}$ (29-106%) and clearance (52-161%). Except for one patient at the 1200 mg/m^2 dose level, all patients met the PK target, a C_{trough} of 25 μg/mL, suggesting 900 mg/m^{2}as the recommended phase 2 dose (RP2D). One patient with Ewing sarcoma had a confirmed partial response; 2 patients with Ewing sarcoma and one with nephroblastoma had stable disease for at least 7, 5 and 6 months, respectively. **Conclusions:** Dalotuzumab is well tolerated in pediatric patients with advanced malignancies. The RP2D of 900 mg/m^2 was chosen based on tolerability and PK parameters. Preliminary data confirm prior reports suggesting activity in Ewing sarcoma. Clinical trial information: NCT01431547.

10027 Poster Discussion Session (Board #36B), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

A phase I study of ridaforolimus (MK-8669) in pediatric patients with advanced solid tumors.

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Background: Deregulation of the PI3K/AKT/mTOR signaling pathway occurs in many poor prognosis childhood malignancies and inhibition of this pathway is a promising novel therapeutic strategy. Ridaforolimus (MK-8669) is a highly selective orally bioavailable small molecule inhibitor of mTOR. This multi-centre, phase I dose escalation study of orally administered Ridaforolimus was designed to evaluate the maximum tolerated dose (MTD), safety profile, pharmacokinetic profile (PK), antitumor activity and pharmacodynamic (PD) biomarkers (phosphorylated Akt [pAkt] in platelet-rich plasma). **Methods:** Patients (pts) from 6 to <18 years (yrs) with advanced solid tumors were enrolled. Dose escalation was by a modified Toxicity Probability Intervals method (mTPI, Ji Y, et al. Clin Trials 2007) targeting a 30% dose limiting toxicity (DLT) ratio. Pts received 28 day cycles of Ridaforolimus (MK-8669), orally, five days out of seven. Dosing started at 22 mg/m^2, escalated to 28 and 33 mg/m^2, with an expansion cohort treated at the maximum administered dose. **Results:** 19 pts, age 8-17 (median 13.5 years), were enrolled and 18 treated from 6 international sites. Diagnoses included ependymoma (5), osteosarcoma (3), Ewings sarcoma (3) and other histologies (7). Four pts received dose level (DL) 1; 3 DL 2 and 11 DL 3. Pts received between 1-12+ courses. There was only one DLT (DL 2: grade 3 elevated alanine transaminase [ALT]) and no other grade 3-4 treatment-related toxicities. Preliminary analysis shows the most frequent drug-related adverse events were manageable grade 1-2 stomatitis (70.6%) and fatigue (52%). Dose escalation stopped at DL3 (33 mg/m2, 150% of the adult recommended phase 2 dose [RP2D]). There were no objective responses by RECIST1.1. Two pts remain on study, with continuing stable disease (pineoblastoma [12 courses], diffuse intrinsic pontine glioma [6 courses]). PK and PD analyses will be presented. **Conclusions:** Ridaforolimus is a safe and well tolerated, orally bioavailable mTOR inhibitor. The RP2D for Ridaforolimus in children is 33 mg/m^2. Prolonged disease stabilization was observed in two patients. PK/PD data will provide further data to support the RP2D. Further combination studies are warranted. Clinical trial information: NCT01431547.

10028 Poster Discussion Session (Board #36C), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Phase I/II study of brentuximab vedotin in pediatric patients (pts) with relapsed or refractory (RR) Hodgkin lymphoma (HL) or systemic anaplastic large-cell lymphoma (sALCL): Interim phase (ph) I safety data.

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Background: Brentuximab vedotin (ADCETRIS) is a novel antibody-drug conjugate that targets CD30, a cell surface antigen expressed by HL and sALCL. The ph 1 portion of this study evaluated safety, pharmacokinetics (PK), and recommended ph 2 dose (RP2D) of brentuximab vedotin in pediatric pts with RR CD30-expressing tumors. **Methods:** Ph 1/2, open-label, multicenter study in pts aged 2 to <18 years with RR HL or sALCL (5 to <18 years for HL). Pts received brentuximab vedotin by IV infusion once every 21 days (Q3wk). Ph 1 start dose was 1.4 mg/kg escalated to 1.8 mg/kg in a traditional 3+3 design. **Results:** 12 pts (median age 14.5 y; 10 HL; 2 sALCL) received brentuximab vedotin in the ph 1 portion (mg/kg/dose [n]: 1.4, [3]; 1.8 [9]). 1.8 mg/kg cohort was expanded from 6 to 9 pts to raise the ph 1 pediatric experience to 12 pts before the ph 2 portion. At data cut, pts had received a median of 3 cycles (range, 1–8). 11 pts (92%) had ≥1 treatment-emergent adverse event (TEAE): 2 at 1.4 mg/kg, 9 at 1.8 mg/kg. 6 pts (50%) had Gr ≥3 TEAE: 1 at 1.4 mg/kg, 5 at 1.8 mg/kg. The most frequent (≥15%) TEAE were nausea (50%), abdominal pain, diarrhea (25% each), upper abdominal pain, cough, fatigue, hypokalemia, leukopenia, decreased lymphocyte count, pain, paresthesia, vomiting, weight loss (17% each). 1 pt (8%) discontinued due to TEAE (Gr 3 hepatotoxicity). 7 serious AE (SAE) were reported in 4 pts at 1.8 mg/kg: Gr 2 supraventricular tachycardia unrelated to treatment in 1 pt; Gr 3 febrile neutropenia, Gr 3 hepatotoxicity and Gr 3 cardiac failure (not a cardiac event per later analysis) in 1 pt; Gr 3 bronchospasm and Gr 2 laryngeal edema in 1 pt; 1 cardiac arrest resulting in death, unrelated to treatment. 2 dose limiting toxicities were reported in 1 pt in the 1.8 mg/kg cohort (SAE: prolonged Gr 3 liver event, Gr 3 febrile neutropenia). PK data will be presented. **Conclusions:** Brentuximab vedotin is generally well tolerated in pediatric pts with RR CD30-positive HL or sALCL up to 1.8 mg/kg Q3wk. For the majority of pts, toxicities were generally mild to moderate and did not lead to discontinuation. 1.8 mg/kg is the RP2D for pediatric and adult pts. The ph 2 portion is ongoing. Clinical trial information: NCT01492088.

10029 Poster Discussion Session (Board #36D), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Weekly vinblastine in chemotherapy-naive children with unresectable or progressive low grade glioma: A Canadian cooperative study.

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Background: Vinblastine has shown promising activity in a phase II study in children with recurrent/refractory LGG. The aim of this study was to assess the activity of vinblastine in chemotherapy naïve children. **Methods:** Patients $<$ 18 years old with unresectable or progressive LGG were eligible if they had not received any previous treatment with chemotherapy or radiation. Vinblastine was administered weekly at a dose of 6 mg/m^{2}over a period of 70 weeks. Patients who showed progression on 2 consecutive imaging studies or evidence of clinical progression were removed from treatment. **Results:** 54 patients (23 female) were enrolled between 2007 and 2010. Median age at inclusion was 7 years, 13 patients were $<$ 3 years. 32 had chiasmatic/hypothalamic tumours, 6 had evidence of dissemination. 13 had neurofibromatosis type 1. Histology was pilocytic astrocytoma (25), pilomyxoid astrocytoma (4), low grade astrocytoma variant (8); 17 patients had no histological diagnosis. Treatment was well tolerated; however, only 14 patients received full dose for the duration of the study. Most common toxicity was haematological: 40 patients who experienced grade 3+ neutropenia. There were only 6 episodes of febrile neutropenia, 3 RBC transfusions and no toxic death. Best response to chemotherapy was assessed centrally by an independent radiologist: 1 CR, 10 PR, 3 MR, 28 SD, 12 PD, for a response rate of 24.5%. With a median follow-up of 2 years (9-48 months), progression-free survival at 2 years was 72.1% (95%CI: 58.1-82.2). One patient died of progression. **Conclusions:** Weekly vinblastine is well tolerated in paediatric LGG patients. Although the response rate appears inferior to other common LGG regimens, progression free survival at 2 years favourably compares to most currently used regimens. Supported by a grant from the Ontario Institute Cancer Research. Clinical trial information: 1000011227.

10030 Poster Discussion Session (Board #36E), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

A phase II trial of radiation and cetuximab followed by irinotecan/cetuximab for children with newly diagnosed diffuse pontine tumors and high-grade astrocytomas.

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Background: Diffuse intrinsic pontine gliomas (DIPG) and high-grade astrocytomas (HGA) have dismal prognoses. We previously demonstrated in a phase 1 study that cetuximab and irinotecan was a safe and tolerable regimen. Consequently, we initiated this 2-strata phase 2 trial to investigate the safety and efficacy of weekly cetuximab given with involved field external beam radiation therapy followed by 10 cycles of cetuximab and irinotecan for DIPG and HGA as determined by the 1-year progression-free survival. **Methods:** Eligible patients aged 3-21 years with newly diagnosed HGA or DIPG were enrolled to parallel strata. All patients received radiation therapy (5940 cGy) with concurrent cetuximab at 250mg/m^2 IV weekly for 6 weeks. Following radiation, patients received cetuximab (250mg/m^2 IV) weekly and irinotecan (16mg/m^2/day IV) daily x 5 for two weeks every 21 days for 30 weeks. Tumor, serum, and CSF samples were collected for correlative studies. Sera collected at the onset of rash were analyzed for inflammatory and immune-related cytokines. **Results:** Forty-eight patients (27 DIPG, 21 HGA) were enrolled and 45 were treated (median age 8 years; range: 3–19). Toxicities were manageable; the most common adverse events were fatigue, gastrointestinal complaints, neutropenia, rash, headache, electrolyte abnormalities, elevated ALT/AST, and fever. Grade 3-4 events in $\geq$10% of patients were hypokalemia and lymphopenia. 4 patients experienced cetuximab-related hypersensitivity reactions (2 grade 3 reactions). The median PFS was 9.5 months (95% CI: 7.0-12.2) for HGA and 7.8 months (7.0-8.6) for DIPG with a 1-year PFS$\pm$SE of 24$\pm$10% and 25%$\pm$10% respectively. The median OS for HGA was 17.7 months (95% CI: 14.1-18.0) and 11.5 months (8.8-14.2) for DIPG. Biological correlative studies will be presented. **Conclusions:** Cetuximab and radiation therapy followed by cetuximab and irinotecan is well tolerated in children. Based on the 1-year PFS, this regimen may deserve further investigation in patients with DIPG. Biological correlative studies will delineate the mechanisms of the rash and possible implications for EGFR-targeted therapeutics in such patients. Clinical trial information: NCT01012609.

10031 Poster Discussion Session (Board #36F), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Impact of gender on efficacy and acute toxicity in standard risk localized (SR) Ewing sarcomas (ES) in the Euro-Ewing99-R1 trial.

Hendrik Van Den Berg, Michael Paulussen, Nathalie Gaspar, Ian Lewis, Uta Dirksen, Bernadette Brennan, Gwenael Le Teuff, Jeremy Whelan, Andreas Ranft, Jean Marie Michon, Ruth Lydia Ladenstein, Perrine Marec-Berard, Lars Hjort, Keith Wheatley, Ian Robert Judson, Odile Oberlin, A. W Craft, Herbert Juergens, Marie-Cécile Le Deley, Euro-E.W.I.N.G. 99; Emma Children's Hospital/Academic Medical Center, Amsterdam, Netherlands; Kinderklinik Datteln, Dattlen, Germany; Institute Gustave Roussy, Villejuif, France; Alder Hey Children's NHS FT, Liverpool, United Kingdom; Department of Pediatric Hematology and Oncology, University Hospital, Muenster, Germany; Royal Manchester Children's Hospital, Manchester, United Kingdom; University College London Hospitals NHS Foundation Trust, London, United Kingdom; Institut Curie, Paris, France; St. Anna Children's Hospital and Research Institute, Vienna, Austria; Institut d'Hématologie et d'Oncologie Pédiatrie, Lyon, France; Lund University Hospital, Lund, Sweden; University of Birmingham, Birmingham, United Kingdom; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Institut Gustave Roussy, Villejuif, France; Sir James Spence Institute, Newcastle upon Tyne, United Kingdom; University Hospital of Muenster, Muenster, Germany

Background: The randomized Euro-EWING99-R1 trial assessed noninferiority of cyclophosphamide- vs ifosfamide-based consolidation regimens (VAC vs VAI) in SR localized ES patients. Overall, efficacy of VAC was deemed acceptable compared to VAI, with hazard ratio of event HR = 1.12 [0.89 - 1.41]. Based on its gender-stratified randomization, influence of gender on efficacy and acute toxicity were additionally explored. **Methods:** Impact of gender on EFS, acute toxicity by course, switches between treatment arms, and cumulative dose of alkylating agents was evaluated in multivariable models, including terms to test for heterogeneity of treatment effect by gender. Analysis was performed on the intention to treat population. **Results:** 856 patients (509 males, 347 females) were recruited between 2000 and 2010: 425 VAI and 431 VAC. EFS did not significantly differ between genders (p=0.33), but a marginal interaction was seen between treatment and gender (p=0.083): VAC was associated with poorer EFS in males than VAI, HR(VAC/VAI) = 1.34 [0.96 - 1.86], whereas, in females, VAC was slightly better than VAI, HR = 0.83 [0.54 - 1.28]. Similarly, males had a worse EFS than females with VAC, HR(M/F) = 1.42 [0.97 – 2.08], whereas results by gender were very similar with VAI, HR = 0.91 [0.62 – 1.33]. Severe hematological toxicity was more frequent with VAC than VAI whereas tubular renal impairment was more frequent with VAI. Severe toxicity was more frequent in females than in males, whatever the toxicity type, with no significant interaction between treatment and gender effect. 30 patients switched from VAI to VAC (21 F, 9 M) mostly due to renal toxicity, and 3 from VAC to VAI (1 F, 2 M). A reduction of alkylating agent cumulative dose >20% was more frequent in females (15% vs 9%, p=0.01), with no major difference between VAI and VAC (13% vs 10%, p=0.21). **Conclusions:** The marginal interaction between gender and type of alkylating agent on EFS has to be validated on external data. Differences of acute toxicity rate and compliance are not sufficient explanation. Effects of gender-dependant polymorphism/activity of metabolic enzymes (e.g. known for CYP2B6) of ifosfamide vs cyclophosphamide should be explored. Clinical trial information: NCT00020566.

10032 Poster Discussion Session (Board #36G), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Estimated long-term outcomes in children newly diagnosed with standard risk acute lymphoblastic leukemia (ALL) based on similarly treated members of the childhood cancer survivor study (CCSS) cohort.

Stefan Essig, Qiaozhi Li, Yan Chen, Johann Hitzler, Wendy M. Leisenring, Mark L. Greenberg, Charles A. Sklar, Melissa M. Hudson, Gregory T. Armstrong, Kevin R. Krull, Joseph Philip Neglia, Kevin C. Oeffinger, Leslie L. Robison, Yutaka Yasui, Paul C. Nathan; Institute of Social and Preventive Medicine, Bern, Switzerland; University of Alberta, Edmonton, AB, Canada; The Hospital for Sick Children, Toronto, ON, Canada; Fred Hutchinson Cancer Research Center, Seattle, WA; Memorial Sloan-Kettering Cancer Center, New York, NY; St. Jude Children's Research Hospital, Memphis, TN; University of Minnesota, Minneapolis, MN

Background: Therapy for ALL has evolved such that the risk for late effects in children treated in early eras is likely different from those that will occur in children treated today. In order to estimate future risks for late effects in newly diagnosed children with standard risk ALL, we examined the long-term outcomes in a cohort of patients enrolled in the CCSS who were treated in a manner analogous to contemporary ALL therapies. **Methods:** We assessed outcomes that occurred ≥5 years from diagnosis in survivors of ALL enrolled in the CCSS who were aged 1-9.9 years at diagnosis, treated with 0-120 mg/m^2 of anthracyclines and 0-1000 mg/m^2 of alkylating agents, and no radiotherapy. We compared their risks for death, second malignant neoplasms (SMN), chronic physical health conditions and decreased health status with the general population (death and SMN) and the CCSS sibling cohort (remaining outcomes). **Results:** 556 survivors were eligible. At last assessment, they were a median of 27.8 years old (range 9.1 to 45.7) and 23.4 years (range 5.0-38.0) from diagnosis. 29/556 (5.2%) died (standardized mortality ratio 3.6, 95% CI 2.4-5.2); 12 of these deaths were due to ALL recurrence. Compared to siblings, the rate ratio for ≥1 chronic condition was 1.4 (95% CI 1.3-1.6), and for a severe/life threatening chronic condition was 1.7 (95% CI 1.3-2.3). Four survivors (0.7%) developed a SMN (standardized incidence ratio 1.7, 95% CI 0.5-4.5), 114 were obese (odds ratio (OR) 1.2, 95% CI 1.0-1.5), and 2 (0.4%) reported a stroke. No survivors reported symptomatic congestive heart failure. The OR for reporting adverse general health was 1.2 (95% CI 0.8-1.8), poor mental health 1.3 (95% CI 1.0-1.8), decreased functional status 2.1 (95% CI 1.4-3.0), and activity limitations 1.4 (95% CI 1.1-1.8). **Conclusions:** Children treated for standard risk ALL on contemporary protocols are at increased risk for future chronic health conditions and decreased health status. Despite excellent survival after leukemia therapy, such survivors will likely benefit from life-long medical care focused on the long-term risks stemming from their therapy.

10033 Poster Discussion Session (Board #36H), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Investigating the pharmacokinetics and dosing of anticancer drugs in infants and young children.

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Background: Dosing regimens for anticancer drugs administered to infants and young children frequently differ between tumour types and protocols, with dosing based on body weight commonly implicated. We have recently highlighted a reduced exposure to 13-cis-retinoic acid in neuroblastoma patients <12kg dosed on body weight (*Clin Cancer Res*19:469-79,2013). Given the toxicity observed with many chemotherapeutics, it is appropriate to establish a pharmacological basis for dose adjustments implemented in younger patients. **Methods:** The pharmacokinetics of cyclophosphamide (CPA), actinomycin D (Act D), carboplatin and etoposide were investigated in children aged 0-6, 6-12 and 12-24 months. CPA was administered i.v. at a dose of 100-1,500 mg/m^2, with infusion times up to 1.5h, Act D as a bolus i.v. infusion of 0.4-1.5mg/m^2, carboplatin as an i.v. dose of 3.8-30mg/kg over 1-4h and etoposide as an i.v. dose of 3.5-14mg/kg over 1-6h. Eighty-six children were studied at 14 centres, with PK sampling carried out over 24h for CPA and Act D, 3h for carboplatin and up to 6h for etoposide. Plasma concentrations of CPA, Act D and etoposide were determined by LC-MS analysis, with carboplatin concentrations determined in plasma ultrafiltrate by AAS. PK parameters were calculated using WinNonlin or previously used PK models as appropriate. **Results:** Clearance values normalized to body weight ranged from 0.5-7.7 ml/min/kg for CPA, 1.7-17.4 for Act D, 1.6-10.5 for carboplatin and 0.2-1.7 for etoposide. No significant differences in normalized clearance were observed between the defined age cohorts of 0-6, 6-12 and 12-24 months and the data do not indicate clear differences in drug handling in infants and young children. However, when normalized clearance values were compared to data from older children, a greater degree of inter-patient variation was observed in patients <2 years than in children >2 years for all drugs. **Conclusions:** While normalized clearance values for the drugs studied do not support reduced dosing approaches, data suggest that individual drug clearance values may be more difficult to predict in younger patients. Further studies involving additional anticancer drugs may allow more rationale approaches to dosing. Clinical trial information: NCT00897871.

10034 Poster Discussion Session (Board #37A), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Computerized intervention for amelioration of cognitive late effects among childhood cancer survivors.

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Background: Children treated for cancer with CNS-directed therapy are at significant risk for attention and working memory (WM) problems. There is empirical support for pharmacotherapy and therapist-delivered cognitive rehabilitation; yet, the reach of these approaches is limited by medical contraindications, need for facility proximity and high resource utilization. A computer-based WM intervention has demonstrated efficacy for healthy individuals with attention disorders. We investigated this approach with childhood cancer survivors. **Methods:** Sixty-eight survivors of childhood acute lymphoblastic leukemia (ALL) or brain tumor (BT) with identified WM deficits were randomly assigned to a computerized WM intervention (18 males/16 females, 23 ALL/11 BT, age= 12.21±2.47) or a wait-list control group (18 males/16 females, 24 ALL/10 BT, age= 11.82±2.42). Participants in the intervention group were asked to complete 25 training sessions at home with weekly, phone-based coaching support. Cognitive assessments were completed pre- and post-intervention. **Results:** Among 34 participants randomized to intervention, 30 (88%) were adherent while 4 were removed from intervention because they failed to complete training in the allotted time. Survivors who completed the intervention demonstrated significantly greater improvements than controls on measures of attention (e.g., WISC-IV Spatial Span Forward 3.30±3.87 vs 1.33±2.20, p= .02, ES= .63), WM (e.g., WISC-IV Spatial Span Backward 3.13±3.19 vs 0.80±2.46, p= .002, ES= .82) and processing speed (e.g., Conners' CPT Hit Reaction Time -2.10±8.04 vs 2.36±6.68, p= .02, ES=.60), and showed greater reductions in parent reported executive dysfunction (e.g., Conners' Parent Rating Scale, III -6.73±8.25 vs .13±8.86, p= .003, ES= .80). No group differences in academic fluency were found (e.g., Woodcock Johnson III Math Fluency 0.90±4.59 vs 1.90±7.18, p= .52, ES= .17). **Conclusions:** Study results suggest computerized intervention is feasible and efficacious for childhood cancer survivors, with some evidence for generalized benefits. Computerized training may offer a safer, less time intensive and more portable alternative to existing interventions. Clinical trial information: NCT01217996.

10035 Poster Discussion Session (Board #37B), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Barriers to survivorship care in the Consortium for New England Childhood Cancer Survivors (CONNECCS).

Cindy L. Schwartz, Priay Hirway, Jeremy Ader, Heather Appleton Bradeen, Satkiran S. Grewal, Mary S Huang, Nina Kadan-Lottick, Naheed Usmani, Lisa Brazzamano Kenney; Hasbro Children's Hospital/Brown University, Providence, RI; Brown University School of Public Health, Providence, RI; Brown University, Providence, RI; University of Vermont, Burlington, VT; Baystate Medical Center, Springfield, MA; Massachusetts General Hospital, Boston, MA; Yale School of Medicine, New Haven, CT; University of Massachusetts Medical Center, Worcester, MA; Dana-Farber Cancer Institute, Boston, MA

Background: Although long-term adverse consequences of childhood cancer treatment may be mitigated by screening, prevention, and interventions, many survivors do not take advantage of survivorship care. We hypothesized that patients who are at risk for poor compliance with long-term follow-up are identifiable at diagnosis. **Methods:** To identify factors associated with poor follow-up compliance, 7 CONNECCS institutions evaluated a childhood acute lymphoblastic leukemia (ALL) survivor cohort diagnosed 1996-99. Data collected included: diagnosis year, age, race, ethnicity, gender, insurance, distance from center, CNS disease, and risk classification. Primary endpoints were compliance with 5 and 10-year follow-up. Differences in compliance were tested using chi-squared or t-tests. Logistic regression (including institution as a clustering variable) was used to calculate adjusted odds ratios (OR). **Results:** At diagnosis, the 358 ALL patients were: female (47%), age= 6.5 + 4.6 years, white/non-Hispanic (84%), black non-Hispanic (7%), high-risk (52%), CNS involvement (10%), privately insured (68%). Private insurance (OR 4.0; 95% CI 2.1-7.8) significantly increased the odds of 5-year compliance. Compliance with 10-year follow-up increased with private insurance (OR 3.3; 95% CI 1.4-8.1) but decreased with CNS disease (OR 0.36; 95% CI 0.31- 0.42) and with years of age (OR 0.93; 95% CI 0.88- 0.96). **Conclusions:** We evaluated predictors of long-term follow-up based on disease/demographic characteristics at diagnosis to identify cohorts in need of early interventions. In this regional cohort, patients from lower socioeconomic background (without private insurance) at diagnosis were less likely to participate in long-term follow-up care at 5 and 10 years from diagnosis. Older survivors and those with CNS disease were less likely to be in follow-up at 10 years. Future studies should investigate reasons why follow-up compliance is affected by 1) private insurance at diagnosis, 2) older age, and 3) CNS disease. Remediable causes might include: understanding of risk, adolescence/young adult transitions, and healthcare access.

10036 Poster Discussion Session (Board #37C), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Socioeconomic status and incidence of pediatric embryonal tumors in the United States.

Raquel Ataide Peres Silva, Tamara P. Pace-Emerson, Carlos Rodriguez-Galindo, A. Lindsay Frazier, Karina Braga Ribeiro; Faculdade de Ciencias Medicas da Santa Casa de Sao Paulo, Sao Paulo, Brazil; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute/Children's Hospital, Boston, MA

Background: Of the 13,000 children diagnosed with cancer each year in the United States (US), the embryonal solid tumors, neuroblastoma (NB), retinoblastoma (RB), Wilms tumors (WT), hepatoblastoma (HB), rhabdomyosarcomas (RMS) and germ cell tumors (GCT), account for over 30% of the cases. Social disparities in cancer are well studied for adults, but few studies have focused on children, mostly for leukemia. The aim of this study is to evaluate the differences in incidence of rare cancers according to socioeconomic status (SES). **Methods:** Cases aged 0-19 were identified from the Surveillance Epidemiology and End Results (SEER) cancer registries from 1992-2009. Using data from the US 2000 Census, the county of residence of the cases was categorized above or below the national average for SES measures including: % persons with< high school education, % persons below poverty, % persons unemployed and % households with > 1 person/room. Age standardized rates per million (ASR), rate ratios (RR) and 95% confidence intervals (CI) were obtained. The findings were validated using cases from the National Program of Cancer Registries (NPCR) from 1999-2009, analyzed with the same SES variables. **Results:** Among cases identified in SEER, rates of NB and WT are higher in counties with upper SES measures whereas RB and GCT occurred more frequently in counties with lower SES measures. No association was found between SES and rates of HB and RMS. The results were reproducible with NPCR cases. For instance, ASR of NB is lower (SEER: 5.86; NPCR: 7.48) in counties where >19.6% of the population had not completed high school and higher (SEER: 8.41; NPCR: 8.47) in counties where ≤19.6% had not achieved a high school degree. (SEER: RR=0.69; 95%CI=0.62-0.77; NPCR: RR=0.88; 95%CI=0.84-0.93). Analysis of NB rates according to poverty, unemployment and crowding showed consistent results, with higher rates in counties with higher SES. **Conclusions:** The findings are suggestive of a relation between SES and cancer susceptibility that may be connected to environment and lifestyle. Understanding the role of contributing causes demands further studies to evaluate why cancer rates vary across cultural and ethnic groups as well as the magnitude of specific SE aspects.

10037 Poster Discussion Session (Board #37D), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Outcome in congenital hepatoblastoma compared with previously reported data.

Angela D Trobaugh-Lotrario, Barbara H Chaiyachati, Rebecka Meyers, Beate Haberle, Gail Elizabeth Tomlinson, Howard M. Katzenstein, Marcio H. Malogolowkin, Dietrich von Schweinitz, Mark D. Krailo, James Henry Feusner; Sacred Heart Children's Hospital, Spokane, WA; University of Texas Southwestern, Dallas, TX; University of Utah, Salt Lake City, UT; Department of Pediatric Surgery, Munich, Germany; University of Texas Health Science Center at San Antonio, San Antonio, TX; Division of Pediatric Hematology/Oncology, Aflac Cancer Center, Children's Healthcare of Atlanta, Emory University, Atlanta, GA; Children's Hospital of Wisconsin, Milwaukee, WI; Children's Oncology Group, Arcadia, CA; Children's Hospital & Research Center at Oakland, Oakland, CA

Background: Congenital hepatoblastoma, defined as diagnosis in the first month of life (Ammann RA, Plaschkes JLeibundgut K. Congenital hepatoblastoma: A distinct entity? Med Pediatr Oncol 1999:32:466-468.), has been reported to have a poor prognosis; however, a comprehensive evaluation of this entity is lacking. **Methods:** We performed a retrospective review including three patients from the senior authors' personal series and 23 cases identified in the databases of several multicenter group studies (INT-0098, P9645, 881, P9346, HB 89, HB94 and HB 99). We then compared this series with the data of all cases of congenital hepatoblastoma previously published in the literature. **Results:** The overall 2-year survival in our case series was 86% (18/21) with a median followup of 85.5 months (range 44 to 230 months). Presentation and treatment were not substantially different from hepatoblastoma cohorts unselected for age. The infants in our study exhibited a comparable survival rate to the reported disease free survival for a similar cohort of hepatoblastoma patients unselected for age between 1986 and 2002 (82.5%) [Tiao GM, Bobey N, Allen S, et al. The current management of hepatoblastoma: A combination of chemotherapy, conventional resection, and liver transplantation. J Pediatr 2005:146:204-211.]. The overall 2-year survival rate of cases previously reported in the literature was 0% (0/11) for patients reported before 1992, and 47% (8/17) for those reported after 1992. The improved survival of our current series of patients, collected from the past 20 years of German and American multicenter trials and personal series, suggests that the outcome of HB at this young age is much better than has been historically reported. **Conclusions:** Congenital hepatoblastoma does not appear to confer a worse prognosis. The overall survival in our series does not appear to be worse than in older children; more rigorous analysis should be conducted in future multicenter trials. It is possible that congenital HB should be treated like all other patients with hepatoblastoma provided that the child is stable enough to proceed with surgery and chemotherapy and complete staging is performed.

10038 Poster Discussion Session (Board #37E), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Survival, surgical resectability, and late effects in the hepatoblastoma patients treated by cisplatin plus pirarubicin (CITA) chemotherapy.

Eiso Hiyama, Arata Kamimatsuse, Yoshiyuku Onitake, Yuka Ueda, Kenichiro Watanabe, Tomoro Hishiki, Tatsuro Tajiri, Kohmei Ida, Michihiro Yano, Satoshi Kondo, Takaharu Oue; Hiroshima University Hospital, Department of Pediatric Surgery, Hiroshima, Japan; Hiroshima University Hospital, Hiroshima, Japan; Japanese Study Group for Pediatric Liver Tumor, Hiroshima, Japan; Japanese Study Group for Pediatric Liver Tumor, Osaka, Japan

Background: The Japanese Study Group for Pediatric Liver Tumor(JPLT) is running cooperative treatment studies on hepatoblastoma (HB) since 1991. The main aim in JPLT-2 study was to evaluate the efficacy of cisplatin/pirarubicin. JPLT-2 protocol was launched in 1999 to evaluate the cure rate of risk-stratified HB: standard risk HB (a tumor involving three or fewer sectors of the liver), intermediate risk HB (a tumor involving all sectors of the liver or invasion into portal or hepatic vein) and high risk HB (a tumor involving all sectors of the liver or with metastasis). **Methods:** Until 2011, 313 children with hepatic tumors who were younger than 15 years of age were eligible for inclusion in the JPLT2 study. The cisplatin/pirarubicin regimen (CITA) is kept as the first line in 254 cases. In this study, we examined the outcome and late effects of the HB patients by the risk-stratified three groups (standard, intermediate and high risk groups). **Results:** Until 2011, 254 cases underwent the CITA protocol including 78 cases (18%) with metastatic tumors. The 3-year OS of the cases with standard risk HB were 94%, while that of the cases with Intermediate and high risk HB was 64% and 34%, respectively. Except for23 cases who underwent primary resection, complete resection of primary after CITA was performed 86% of standard risk, 66% of intermediate risk and 56% of high risk patients. And the late phase complications were 4 cases with maldevelopment, 15 with cardiac complications, 24 with ototoxicity and 5 with second malignancies. **Conclusions:** As compared with other regimens, CITA regimens achieved similar or superior rates of survival and resectability in standard risk patients. More promising strategies including adequate liver transplantation and new targeting drugs should be developed for intermediate and high risk HBs. Clinical trial information: UMIN000001116.

10039 Poster Discussion Session (Board #37F), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Comparison of Taqman low density array (TLDA) five-gene assay for tumor cells in bone marrow and blood with histologic bone marrow examination and imaging for disease assessment and outcome in patients with recurrent/refractory neuroblastoma (NBL): A new approaches to neuroblastoma therapy (NANT) study.

Araz Marachelian, Judith Villablanca, Shahab Asgharzadeh, Wei Yao Liu, Betty Liu, Sabrina Young, Brian D. Weiss, Howard M. Katzenstein, Susan Lerner Cohn, Sylvain Baruchel, Clare Twist, Meaghan Granger, Katherine K. Matthay, Jemily Malvar, Richard Sposto, Robert Seeger; The Neuro-oncology Program, Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles & Keck School of Medicine, University of Southern California, Los Angeles, CA; Children's Hospital Los Angeles, Los Angeles, CA; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Division of Pediatric Hematology/Oncology, Aflac Cancer Center, Children's Healthcare of Atlanta, Emory University, Atlanta, GA; The University of Chicago, Chicago, IL; The Hospital for Sick Children, Toronto, ON, Canada; Stanford University, Palo Alto, CA; Cook Children's Health Care System, Fort Worth, TX; University of California, San Francisco Children's Hospital, San Francisco, CA; Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, CA; Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles & Keck School of Medicine, University of Southern California, Los Angeles, CA

Background: Accurate quantification of tumor burden in NBL patients is needed to define homogenous populations for therapy and establish response criteria that predict outcome. The 5-gene TLDA assay was developed for quantification of NBL cells in bone marrow (BM) and blood (BLD). **Methods:** Expression of CHGA, DCX, DDC, PHOX2B, and TH (NBL genes) was quantified with TLDA and reported as the geometric mean cycle threshold for the 5 genes (DGS=detection gene score; inversely related to tumor content, 40=negative). Sixty-three patients with recurrent/refractory NBL had TLDA performed on 107 BM and 99 BLD samples (66 paired) at 140 time points. Based on central review of reports, tumor longest diameter (LD) on CT/MRI (n=118), and number of ^{123}I-MIBG avid sites (n=120) were recorded. Percentage of tumor cells in BM was from institutional reports of bilateral BM aspirates/biopsies (n=109). Overall response was assessed per NANT Response Criteria. Spearman rank correlation was performed. **Results:**TLDA detected tumor cells in 62/99(63%) BLD (average DGS=37.45) and 91/107(85%) BM samples (average DGS=33.42). 39/91(42%) with positive BM TLDA were negative by morphology. BLD and BM TLDA were correlated $r = 0.6540$, $p < 0.0001$ with stronger correlation with lower BM DGS scores. The BM and BLD DGS correlated with % BM involvement (BM $r = -0.63$, $p<0.0001$; BLD $r = -0.35$, $p=0.0023$) and number of MIBG sites (BM $r=-0.34$, $p=0.001$, BLD $r=-0.51$ $p<0.0001$) but not LD. Number of MIBG sites was also correlated with % BM involvement ($r = 0.45$, $p<0.001$) and LD ($r = 0.28$, $p=0.0039$). Analysis of 43 BM pairs demonstrated decreasing DGS correlated with overall progressive disease ($r = 0.39$, $p=0.01$). **Conclusions:** This TLDA assay detects NBL cells in both BM and BLD at high rates, and frequently detects tumor cells when BM morphology is negative. Quantification of tumor with DGS correlates with % BM involvement and number MIBG sites. TLDA may provide an additional parameter to delineate response in NBL. Clinical trial information: NCT01587300.

10040 Poster Discussion Session (Board #37G), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Integrated analysis of RNAi screens in pediatric rhabdomyosarcoma.

Fernanda Irene Arnaldez, Sirisha Chakka, Carly J Smith, Choh L Yeung, Natasha Caplen, Lee J. Helman; Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD; National Institutes of Health / National Cancer Institute / Genetics Branch, Gene Silencing Section, Bethesda, MD; Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; Gene Silencing Section, Genetics Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; Center for Cancer Research, National Cancer Institute, Bethesda, MD

Background: Rhabdomyosarcoma (RMS) is the most common pediatric soft tissue sarcoma. Embryonal RMS (ERMS) are characterized by 11p15 LOH, while alveolar RMS (ARMS) harbor a translocation between PAX3 or PAX7 and FOXO1. Relapsed or metastatic RMS has a poor prognosis with a 5-year survival rate of 25%. We hypothesized that a reduction in proliferation of ARMS cell lines as result of the loss of function (LOF) of a specific protein *via* RNAi likely point to novel targets that exhibit "synthetic lethality" with the *PAX3/7-FOXO1* translocation, and can be used to reveal unique ARMS vulnerabilities. **Methods:** We are using two complementary screening strategies to identify genes critical for RMS cell growth and survival. One RNAi screening strategy used an inducible LOF shRNA screen of 15,000 shRNA -5,000 genes- introduced into RH30 (ARMS) or RD (ERMS) cells. Data analysis after subtraction of targets related to common survival pathways revealed 40 genes with close association with RMS cell growth. Follow up analysis included further comparison of the effects of gene specific LOF in ARMS and ERMS cell lines and assessment in orthotopic xenografts. To increase the strength of our findings, we have also conducted parallel siRNA screens of the human kinome targeting 704 kinase genes (3 siRNAs per gene) in RH30 or RD cells. **Results:** Of the 40 genes identified by shRNA screening, 15 genes were identified as selectively needed for ARMS cell growth. Follow up analysis of one of these genes, TNK-2 (tyrosine kinase, non-receptor 2) in orthotopic xenografts, confirmed that LOF of TNK2 markedly decreases ARMS cell growth. The siRNA screen has identified a further putative 26 genes that selectively reduce ARMS cell growth. These screens have led us to focus on members of the ERK, PI3K and IGF1R pathways as potential targets for the treatment of ARMS. **Conclusions:** RNAi screening affords an unbiased method for the discovery and elucidation of gene function. Ongoing efforts are focused on the integration of results obtained to gain further insight into the signaling networks influencing alveolar rhabdomyosarcoma biology and thus identify a small group of druggable genes that could represent alveolar rhabdomyosarcoma specific vulnerabilities.

10041 Poster Discussion Session (Board #37H), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

The role of c-Met inhibition for neuroblastoma treatment.

Peter Zage, Kathy Scorsone, Linna Zhang; Baylor College of Medicine, Houston, TX

Background: Neuroblastoma is the most common extra-cranial solid tumor of childhood. Many children present with high-risk disease characterized by rapid tumor growth, resistance to chemotherapy, and widespread metastasis, and novel therapies are needed. Previous studies have identified a role for the HGF/c-Met pathway in the pathogenesis of neuroblastoma. We hypothesized that EMD1214063 would be effective against neuroblastoma tumor cells and tumors in preclinical models via inhibition of HGF/c-Met signaling. **Methods:** We determined the expression of c-Met in a panel of neuroblastoma tumor cells and neuroblastoma cell viability after treatment with EMD1214063 using MTT assays. Analyses were performed for changes in cell morphology, cell cycle progression, and cell death via apoptosis after EMD1214063 treatment. To investigate the efficacy of EMD1214063 against neuroblastoma tumors in vivo, neuroblastoma cells were injected orthotopically into immunocompromised mice, and the mice in which tumors developed were treated with oral EMD1214063. **Results:** All neuroblastoma cell lines were sensitive to EMD1214063, and IC50 values ranged from 2.4 - 8.5 mcM. EMD1214063 treatment inhibited HGF-mediated c-Met phosphorylation in neuroblastoma cells. EMD1214063 induced cell cycle arrest in neuroblastoma tumor cells with high c-Met expression, and induced apoptosis in all tested cell lines. In mice with neuroblastoma xenograft tumors, EMD1214063 inhibited tumor growth. **Conclusions:** Treatment of neuroblastoma tumor cells with EMD1214063 inhibits HGF-induced c-Met phosphorylation and results in cell death. Furthermore, EMD1214063 induces cell cycle arrrest prior to cell death in neuroblastoma tumor cells with high c-Met expression. EMD1214063 treatment is effective in reducing tumor growth *in vivo* in mice. Inhibition of c-Met represents a potential new therapeutic strategy for neuroblastoma, and further preclinical studies of EMD1214063 are warranted.

10042 Poster Discussion Session (Board #38A), Sat, 1:15 PM-5:00 PM and 4:45 PM-5:45 PM

Effect of a novel small molecule yk-4-279 on the ″undruggable″ target EWS-FLI1.

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Background: Chimeric transcription factors are ideal anti-cancer targets since they are only present in tumor cells, however they are often considered ‘undruggable’ proteins. The EWS-FLI1 fusion protein of Ewings sarcoma (ES) has been validated as an anticancer target both alone and as a partner of RNA Helicase A (RHA). Our prior work identified (S)-YK-4-279 as an enantiospecific inhibitor of EWS-FLI1 by blocking the interaction with RHA leading to apoptosis. **Methods:** Pharmacokinetic (PK) models of YK-4-279 for both IP and IV administration were developed in SD rats and BL6 mice using drug concentrations determined by a validated LC-MS/MS assay. Xenograft ES mice validated PK models with apoptosis measured by TUNEL. A novel nude rat ES orthotopic xenograft was created give (S)-YK-4-279 by continuous IV infusion. **Results:** SD rat and BL6 mouse PK modeling demonstrated an elimination half-life t1/2 of 30 minutes following IV administration; SCID/bg mice demonstrated 50% faster clearance. A survival curve showed maximal killing of ES cells between 1 and 3 microM YK-4-279 over a 40-hour time course. Clonogenic replating assays demonstrated 3 microM exposure for 72 hours would reduce replating efficiency of ES cells to less than 0.01%. SCID/bg ES xenografts treated with IP YK-4-279 BID for 6 doses showed a 25-35% enantiospecific tumor regression with an average 3.5-fold increase in apoptosis. A nude rat xenograft, with continuous infusion (S)-YK-4-279 maintained an average level of 4.9 microM in plasma for 26 days. The ES1 xenograft tumor responded in 4 of 5 animals, with complete regression in 2 of 5, without toxicity. **Conclusions:** A combination of PK modeling and cell culture studies confirmed that (S)-YK-4-279 is required to be present at low microM levels for optimal tumor response. These levels were achieved in a novel rat xenograft of ES in order to demonstrate an important proof of efficacy. These PK-driven xenograft therapy studies are useful for development of PK models to compare YK-4-279 levels with functional activity. Targeting ‘undruggable’ protein-protein interactions with small molecules is novel and the ES model shows that continuous IV infusion may be required for optimal clinical translation.

10043 **General Poster Session (Board #38B), Sat, 1:15 PM-5:00 PM**

Non-Hodgkin lymphoma in children: Is 1 g/m^2 methotrexate as effective as 5 g/m^2 in advanced-stage nonlymphoblastic non-Hodgkin lymphoma?

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Background: Survival rates in non-Hodgkin lymphoma (NHL) have increased significantly in the last decades. This study aims to assess the demographic data and treatment results of children with nonlymphoblastic NHL treated in a single institution. **Methods:** 106 children (74 male, 32 female), treated in Istanbul University, Oncology Institute, between 9/1989-12/2012 were evaluated retrospectively. Nonlymphoblastic NHL received COMP until 1991. After then, all received BFM protocols. They received BFM 90 protocol with 5 g/m2 methotrexate (MTX) until 1995 and modified BFM protocol with 1 g/m2 MTX thereafter. **Results**:The median age was 8(2-19) years. Histopathologic subtypes: 81 Burkitt, 25 large cell. The primary location was abdomen in 51, mediastinum 4, head/neck 31, 20 other (bone 8, breast 2, ovaries 2, skin 2, paravertebral 2, other 4). Bone marrow was involved in 10, CNS in 2. 40 patients had stage I+II, 44 stage III, and 22 stage IV disease. 23 patients died, 7 due to toxicity, 2 with second malignancies (AML,GBM). 10 year survival and EFS in the whole group was 76 and 76 % respectively. 10 year survival was 100, 94.3, 71.3 and 50% in stage I, II, III, and IV. In advanced stage nonlymphoblastic NHL patients, 10 year survival was significantly higher in patients receiving BFM regimen with 1 g/m2 MTX, than in ones receiving COMP or BFM protocol with 5 g/m2 MTX (10 year S, 81%, 46.7%, 44.4% respectively). These results were also compared with 47 advanced stage nonlymphoblastic NHL patients treated with 5 g/m2 BFM protocol in another center in the same university in the same time period (5 year S 78 %). **Conclusions:** Survival rates in the whole group are in parallel with advances attained in the world in NHL. The significantly higher survival rates achieved in patients with advanced stage non-lymphoblastic patients receiving modified BFM (1g/m2MTX) may be due to the decreased toxicity seen in this group and to the advances in supportive care in the last decade. In another major center in the same university that used the same protocol with 5 g/m2 MTX in the same time period, similar survival rates suggest that 1 g/m2 MTX which is cheaper and less toxic is also as effective as 5 gr/m2 in these patients.

10044 General Poster Session (Board #38C), Sat, 1:15 PM-5:00 PM

Outcome of risk-adapted therapy for pediatric acute lymphoblastic leukemia in Egypt.

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Background: With modern risk directed therapy, >80% of children with acute lymphoblastic leukemia (ALL) in western countries are cured. The 5-year event free survival (EFS) and relapse free survival (RFS) of pediatric ALL patients in Egypt were 65% and 75% respectively in a previous study using an intensive treatment protocol for all patients. Aim: To improve cure rates of Egyptian children with ALL using risk adapted therapy. **Methods:** From July 2007 to December 2010, 706 patients aged 1-18 years with newly diagnosed ALL were treated at Children Cancer Hospital Egypt with a risk directed ALL protocol adopted from St Jude Total Study XV. **Results:** B-precursor phenotype was encountered in 75.8% and T-cell in 24.2%. Based on initial presentation and response to therapy measured by minimal residual disease (MRD), 42.6%, 45.8% and 11.6% of the patients were classified as low, intermediate and high risk respectively. The 5-year RFS and EFS were 88.2 ± 1.5% and 76.5 ± 1.7% respectively. Adverse events included 4.4% induction deaths, 2.5% failure to achieve induction remission (1.4% remained refractory), 6.8% deaths in remission, 9.2% relapses (3.1% hematological, 1.8% combined hematological and CNS, 4% isolated CNS, 0.3% isolated testicular), 0.9% abandonment of therapy and one patient had secondary myeloid leukemia. The median follow up for patients alive in CR was 43months (range 24–65). The 5-year RFS of the low, intermediate and high risk groups were 92.2 ± 2.4%, 85.3 ± 2.2% and 82.7 ± 4.8% respectively ($p=0.001$), while the 5-year EFS were 87.6 ± 2.5%, 78.2 ± 2.5% and 57.9 ± 5.7% respectively ($p<0.001$). Prognostic factors that had statistically significant unfavorable impact on both EFS and RFS by univariate analysis were age ≥10 years, TLC $\geq 100 \times 10^9$/L, T-cell phenotype, risk groups, MRD d42 ≥1% and MRD W7 ≥0.1%, while MRD d15 ≥1% had statistically significant unfavorable outcome on EFS only. By multivariate analysis, TLC and MRD W7 had prognostic significance on EFS and RFS, MRD d42 on EFS, while MRD d15 had marginal significance on EFS ($p=0.055$). **Conclusions:** Risk adapted therapy was effective in improving ALL survival among patients at our institution compared with previous trials, although the outcome remains lower than that in high income countries.

10045 General Poster Session (Board #38D), Sat, 1:15 PM-5:00 PM

Comparison of standard immunohistochemistry and automated quantitative immunohistochemistry for quantification of signaling proteins in archival Ewing sarcoma samples.

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Background: Targeted therapies are increasingly being evaluated for patients with Ewing sarcoma (EWS). Optimal strategies for quantifying key signaling proteins from paraffin-embedded material remain unclear. We sought to quantify tumor expression of IGF-1R, EGFR, and PTEN in EWS using two different methodologies. **Methods:** Decalcified paraffin-embedded tissue was obtained from 40 patients with EWS. 28 samples were obtained at time of diagnosis, 6 after initial chemotherapy, and 6 at time of relapse. Tumor was evaluated for the expression of IGF-1R, PTEN, and EGFR using standard immunohistochemistry (IHC) and automated quantitative analysis (AQUA) immunohistochemistry. Standard IHC results were categorized as low, medium and high expression based on a pathologist's review. Expression by AQUA was measured as a continuous variable in arbitrary units. One sided ANOVA analysis was used to compare the mean AQUA expression for each analyte between categories of expression by IHC. **Results:** The mean age of patients was 15 years (range 1-49 yrs) at time of diagnosis. 68% were male and 66% had localized disease. Samples displayed a wide range of expression by AQUA: mean IGF-1R = 10702 (range 393 - 14424); EGFR = 2750 (range 672 – 9798); and PTEN = 2250 (range 251 – 6557). Mean IGF-1R expression by AQUA did not differ significantly between standard IHC expression categories (mean IGF-1R expression by AQUA for low IHC = 11255, medium IHC = 11070, high IHC = 11023; p = 0.98). Mean PTEN expression by AQUA was higher in the medium and high IHC categories (mean PTEN expression by AQUA for low IHC = 1229, medium IHC = 2715, high IHC = 2940; p = 0.064). Only two samples expressed EGFR by standard IHC. These samples qualitatively had higher AQUA expression levels, but there were too few samples for a reliable determination of statistical significance. **Conclusions:** AQUA provides a more dynamic range for each marker, though there was poor correlation with standard IHC results. Larger sample sets are needed to determine the optimal approach for quantifying signaling proteins in Ewing sarcoma.

10046 General Poster Session (Board #38E), Sat, 1:15 PM-5:00 PM

Characterization of neuroblastic tumors as developmental cancers with survival determined by histology, age, and location.

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Background: Mortality associated with peripheral neuroblastic tumors (pNT), comprising neuroblastoma (NB) and ganglioneuroblastoma (GNB), varies with some tumors spontaneously regressing and others showing poor response to therapy, indicating different biologic mechanisms. We aimed to determine how epidemiologic constructs inform the underlying biology of pNT. **Methods:** Using the Surveillance Epidemiology and End Results (SEER 18) population-based registry, we identified 3,540 pNT (3,003 NB and 537 GNB) in patients from 1973-2009. Differences in histology (NB vs. GNB), gender, age ($<$18 months, 18 months-4 years, 5-14 years, or $\geq$15 years), race (white, black, or other), location of primary tumor (adrenal, abdominal, chest, head/neck, pelvic, or other), and stage (locoregional vs. metastatic) were evaluated with chi-squared tests using SAS 9.3. Kaplan Meier curves with log-rank tests as well as univariate and multivariate Cox proportional hazard regression methods were employed to determine the influence of these factors on survival. **Results:** NB occurred more frequently in infants (50%), arose in the adrenals (45%), and were metastatic at diagnosis (57%), while GNB more often affected children 18 months-4 years (48%, $p < 0.001$), occurred in the chest (31%, $p < 0.001$), and were locoregional (78%, $p < 0.001$). The 5-year overall survival (OS) rate in NB was 59% compared to 80% in GNB ($p < 0.001$). In NB, the 5-year OS rate was 81% in infants $<$18 months and 21-39% in the older groups ($p < 0.001$); however, in GNB, the 5-year OS was 40% in subjects $>$15 years and 81-93% in the younger groups ($p < 0.001$). In multivariate analysis of pNT, neuroblastoma, age $>$18 months, adrenal site of primary tumor, and metastatic disease were independent poor prognostic factors. Chest (HR 0.27 [0.21-0.35]), head/neck (HR 0.34 [0.20-0.52]), and pelvic (HR 0.35 [0.24-0.52]) tumors had the most improved survival compared to adrenal primaries. **Conclusions:** Although pNT are often evaluated together, NB and GNB represent two significantly distinct diseases. For each, survival is strongly determined by age, primary tumor location, and stage. These differences may stem from unique developmental mechanisms underlying tumorigenesis.

10047 General Poster Session (Board #38F), Sat, 1:15 PM-5:00 PM

A phase I dose-escalation study of intratumoral herpes simplex virus-1 mutant HSV1716 in pediatric/young adult patients with refractory non-central nervous system solid tumors.

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Background: HSV1716 is a mutant herpes simplex virus type 1 deleted in the RL1 gene which encodes the protein ICP34.5, a specific determinant of virulence. Mutants lacking the RL1 gene are capable of replication in actively dividing cells but not in terminally differentiated cells – a phenotype exploited to selectively kill tumor cells. Studies in adult patients with high grade glioma, melanoma and squamous cell carcinoma report that HSV1716 is safe when administered by intra-tumoral injection. This is the first study of HSV1716 in pediatric/young adult patients. **Methods:** The primary endpoint of the study is to assess safety of intratumoral HSV1716 in pediatric/young adult patients, and to determine any dose-limiting toxicities (DLT) at the doses given. Patients undergo long-term follow up in accordance with FDA guidelines for viral vectors. The secondary endpoints of the study are to measure: (i) antiviral immune response; (ii) systemic viremia and viral shedding and (iii) the antitumor activity of HSV1716 by radiological response within the confines of a Phase I study. Patients aged 7 to 30 with solid non-CNS tumors refractory to standard therapy (or for which no therapy exists) are eligible for the study provided the target lesion is accessible to image-guided injection. Eligible patients receive a single dose of HSV1716 (Virttu Biologics Limited) at either 10^5 or $2x10^6$ plaque forming units (pfu) HSV1716 administered directly into the tumor via ultrasound or CT-guided injection by an interventional radiologist. Tumor response between baseline and day 28 is assessed by modified RECIST criteria. Patients showing at least stable disease may receive up to a 3 additional doses of HSV1716. **Results:** Recruitment of the first cohort of 3 patients has been completed without DLT or procedure related severe adverse events. In the second cohort, 2 patients have been treated without DLT or procedure related SAE. **Conclusions:** The trial is in progress and the study is open to recruitment. Clinical trial information: NCT00931931.

10048 General Poster Session (Board #38G), Sat, 1:15 PM-5:00 PM

Targeting apoptosis and autophagy by a novel bcl-2 inhibitor, GX15-070, in neuroblastoma.

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Background: Neuroblastoma (NB) is a frequent pediatric tumor with poor prognosis. The disregulation of the anti-apoptotic protein Bcl-2 is crucial for the tumoral development and chemoresistance. Autophagy is also implicated in tumor cell survival and chemoresistance. The aim of our study was to demonstrate the *in vitro* and *in vivo* therapeutic efficiency of GX 15-070, a Bcl-2 inhibitor, used alone and in combination with conventional drugs used in the treatment of NB and hydroxychloroquine (HCQ), a known autophagy inhibitor. **Methods:** Using 6 NB cell lines, cell viability (MTT) assays were done at progressively increased concentrations of GX 15-070 alone or in combination with cisplatin or with Z-VAD-FMK, a broad-spectrum caspase inhibitor. Apoptosis was tested by evaluating the cleavage of caspase 3 by western blots (WB) and the Annexin V/7-AAD staining studied by FACS. To assess if autophagy was modified by GX 15-070, the cleavage of LC3 protein was tested by WB and cell survival were tested with combination of GX 15-070 and HCQ. To verify the anti-tumor activity *in vivo* of GX 15-070, orthotopic injections were made on NSG mice treated with GX 15-070 alone and in combination with HCQ. **Results:** It was observed a high sensitivity of the NB cells to GX 15-070 with increase of cell death and a potential synergistic of this molecule when it's combined with cisplatin or HCQ. This cell death was due to apoptosis and may also be inhibited by Z-VAD-FMK. GX 15-070 alone or associated to cisplatin increased the autophagy. The *in vivo* study showed that GX 15-070 treatment used alone or in combination with HCQ significantly decreased the size of the tumor. **Conclusions:** Our results support the interest of GX 15-070 in the treatment of NB alone or in combination with classical drugs. Our studies also support that activation of apoptosis associated with inhibition of autophagy have a synergistic potential against tumoral progression and must have to be considered in further mechanistic studies for the optimization of more efficient combined therapies in the treatment of NB.

10049 **General Poster Session (Board #38H), Sat, 1:15 PM-5:00 PM**

Are adult and pediatric neuroblastoma clinically different entities?

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Background: It is unknown if the presentation, treatment, and outcomes differ between adults and pediatric patients with neuroblastoma. **Methods:** Medical records of 118 adults (patients >17 years old) and 112 pediatric patients (ages 2-17), who were treated for neuroblastoma at the University of Texas M.D. Anderson Cancer Center from 1994 to September 2012, were reviewed. International Neuroblastoma Risk Group (INRG) variables were abstracted. These include age, stage, tumor histology, and molecular and cytogenetic characteristics. The primary outcome of interest was overall survival (OS). **Results:** Median age of pediatric patients was 5 years (range 3-16) and 47 years (range 18-82) for adult patients. Beyond age and stage, other components of the INRG classification were not available for any adult patient. Cytogenetic and molecular studies were performed in 32 (26%) of pediatric patients. Adults with L1 disease experienced an actuarial OS of 94%, 90%, and 69% at years 3, 5, and 10, respectively. The cohort who presented with L2 disease had an estimated OS of 83% at 3 year, 73% at 5 years, and 41% at 10 years. Adults with M disease experienced an actuarial OS of 68%, 33%, and 13% at years 1, 2 and 5, respectively. In the adult cohort, the INRG stage was prognostic in univariate analysis ($p<0.001$). For all stage-matched risk categories, adults did not have a statistically different prognosis than children (L1-$p=0.40$, L2-$p=0.54$, M-$p=0.73$). **Conclusions:** Adult and pediatric patients with neuroblastoma achieve similar survival outcomes, with good prognosis for early-stage patients. Future work should focus on developing predictive markers for determining which patients benefit from more aggressive therapy.

Treatment variable	Adult (%)	Pediatric (%)	P value
L1 patients	57 (58)	24 (21)	
Surgery	56 (99)	22 (92)	0.19
Radiation	31 (54)	9 (38)	0.17
Chemotherapy	3 (5)	8 (33)	0.003
Auto-SCT	2 (4)	5 (21)	0.02
L2 patients	44 (37)	12 (11)	
Surgery	37 (81)	10 (83)	0.95
Radiation	32 (73)	5 (42)	0.05
Chemotherapy	21 (48)	8 (67)	0.25
Auto-SCT	1 (2)	1 (8)	0.35
M patients	17 (14)	76 (68)	
Surgery	12 (71)	58 (76)	0.62
Radiation	6 (35)	54 (71)	0.008
Chemotherapy	15 (88)	73 (96)	0.22
Auto-SCT	3 (18)	4 (5)	0.34

10050 General Poster Session (Board #39A), Sat, 1:15 PM-5:00 PM

Multicenter phase I/II trial of topotecan (T) and ifosfamide (I) combination as second-line therapy for pediatric solid cancer: Phase II results.

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Background: Both of T and I are key drugs for recurrent pediatric solid malignancies but rarely used in combination. Results of the phase I portion of the combination of T and I chemotherapy (TI) which is dose-finding study by CRM method in ASCO 2010. We hereby report the results of efficacy and safety screening of TI conducted as a phase II portion. **Methods:** Recurrent pediatric solid malignancies with history of chemotherapy no more than 20 cycles (Cs) are eligible. Combination of I (1.2g/m^2/day) and T (0.6 mg/m^2/day) were administered day 1 through 5 up to six Cs. In the phase II portion, a Simon optimal two-stage design was adopted using treatment compliance with 4 Cs of TI as primary endpoint. Unacceptable compliance was set at 20% and promising one at 40%. If more than two patients (pts) among initial 13-15 pts successfully complete 4 Cs, patients' enrollment is allowed to continue until a total of 33 pts in the phase II portion. Complete or Partial Response (CR+PR) was evaluated according to RECIST 1.0 criteria and toxicity, CTCAE v3.0. **Results:** 35 pts, median age 12 years (range 1-28) has been registered in both phase I and II between March 2008 and January 2013 in 8 centers: 7 neuroblastoma (NB), 8 rhabdomyosarcoma (RMS), 8 osteosarcoma (OS), 6 Ewing's sarcoma (ES), 2 hepatoblastoma (HB), and 4 others. 13 pts out of total 34 pts (38%) completed 6 Cs. 13 pts out of 28 pts (36%, the phaseII portion) received more than 4 Cs without meeting stopping criteria of protocol treatment. This has reached the predefined efficient level. No Grade 4 non-hematological toxicity occurred. Grade 2-4 fatigue, anorexia, and nausea were 20% or less. Grade 3 or 4 neutropenia was frequent (105/127 Cs, 83%), though only 9 % (12 Cs) developed febrile neutropenia. 2 CR (HB, ES) and 2 PR (RMS, OS) were observed at best response among 22 pts with measurable disease, leading to an estimated OR rate of 18% (95%CI 5-40%). 14 patients had disease stabilization. One year progression-free survival rate and overall survival rate are 21% and 64%. **Conclusions:** TI achieved very good compliance and favorable toxicity as well as good tumor control rate. This combination is a new promising 2nd line therapy for pediatric solid malignancies. Clinical trial information: UMIN000001037.

10051 General Poster Session (Board #39B), Sat, 1:15 PM-5:00 PM

Association of genetic polymorphisms in the folate pathway with efficacy and toxicity of methotrexate in pediatric osteosarcoma.

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Background: Osteosarcoma is the most common childhood malignant bone tumor. Methotrexate (MTX), one of the main drugs used for osteosarcoma, is a representative folic acid antagonist. Genetic polymorphisms in folate pathway genes are expected to influence the response and toxicity of high-dose MTX therapy. However, there are scarce data available regarding associations between genetic polymorphisms and pediatric osteosarcoma. This study evaluated the effect of common genetic polymorphisms in the folate metabolic pathway on overall survival, event-free survival and histological response to neoadjuvant chemotherapy including high-dose MTX. In addition, whether these genetic polymorphisms affect the concentrations of MTX and toxicity after high-dose MTX therapy for osteosarcoma was investigated. **Methods:** Blood and tissue samples from 48 osteosarcoma patients who had completed chemotherapy were obtained, and the following polymorphisms were analyzed; RFC1 80G>A, DHFR 829C>T, MTHFR 677C>T, MTHFR 1298A>C, AMPD1 34C>T, ATIC 347C>G, and ITPA 94C>A. Associations between candidate polymorphisms and survival, histological response (tumor necrosis rate) and MTX level and toxicity after high-dose MTX therapy were analyzed. **Results:** Event-free survival significantly decreased in DHFR 829 CC homozygote ($P=0.045$). Variant carriers of MTHFR 677C>T had tendency towards poor histological response ($P=0.078$). MTX concentration was significantly associated with RFC1 80G>A polymorphism ($P=0.027$). Liver toxicity after high-dose MTX was associated with ATIC 347C>G ($P=0.043$) and tended to increase in carriers of MTHFR 677C>T ($P=0.069$). Severe stomatitis was associated with RFC1 80G>A ($P=0.012$). **Conclusions:** This study has demonstrated that several genetic polymorphisms in folate pathway can significantly influence therapeutic response, clinical outcome and MTX level and toxicity after high-dose MTX therapy in osteosarcoma patients. If these associations are independently validated, these variants could be used as genetic predictors of clinical outcome in the treatment of patients with osteosarcoma, aiding the development of tailored therapeutic approaches.

10052 General Poster Session (Board #39C), Sat, 1:15 PM-5:00 PM

Clinical prognostic factors in pediatric Ewing sarcoma.

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Background: Treatment of Ewing sarcoma necessitates coordinated multi-disciplinary care that includes chemotherapy, surgery, and/or radiation. In developed countries, patients with localized disease have an overall survival of 70-80%, compared to 20-30% for those with metastases. The outcome of children with Ewing sarcoma in less developed countries has not been adequately described. We analyzed prognostic factors for Ewing sarcoma patients treated at a single institution in Lebanon, a developing country with available multidisciplinary treatment modalities. **Methods:** We reviewed characteristics and outcome of 42 pediatric patients treated at a multidisciplinary cancer center in Lebanon, between January 1999 and October 2012. Kaplan Meier curves were generated to estimate survival. **Results:** Median age at presentation was 10 years (range 1-18), and median follow-up was 41 months (range 8-110). Commonly affected primary sites included the extremity (36%, n=15), chest wall (19%, n=8), and pelvis (14%, n=6). Tumor size was $\geq$ 8cm in twenty (47.6%) patients. Thirty-two patients (76%) had localized disease, and ten (24%) had metastatic disease. All patients received 14 cycles of chemotherapy, with VDC alternating with IE. Local control was surgery alone (29%, n=12), radiotherapy alone (33%, n=14), or combination (38%, n=16). For patients with localized disease, the 5-year OS and DFS rates were 68% and 55% respectively, while for metastatic disease they were 28% and 25%. Tumor recurrence was local in 8 patients, distant in 8, and combined in 2. Factors associated with improved outcome included localized disease, extremity site, surgery, and timely local control. In multivariate analysis, timing of local control and metastatic disease were prognostically significant determinants of outcome. **Conclusions:** Treatment of childhood Ewing sarcoma in a multidisciplinary cancer center in Lebanon results in similar survival to that in developed countries when similar protocols are applied. Strong prognostic factors included stage (localized vs. metastatic), and timing of local control. Patients who had a local control time delay of more than 3 weeks fared worse, strongly suggesting that delays in local control should be actively minimized in Ewing sarcoma.

10053 General Poster Session (Board #39D), Sat, 1:15 PM-5:00 PM

The Children's Oncology Group and QuadW Foundation osteosarcoma banking experience.

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Background: Survival rates of osteosarcoma patients have remained stagnant over the last twenty years. Predictive biomarkers of response to treatment and likelihood of recurrence are yet to be developed. In order to develop new therapeutics and better risk-stratified regimens, a greater understanding of osteosarcoma biology is needed. The Children's Oncology Group (COG) addressed this need by banking more than 10,000 tumor and tissue samples from over 1500 patients with osteosarcoma, but many samples lacked clinically relevant data. **Methods:** 1105 eligible patients enrolled on the COG osteosarcoma biology study P9851. Of those, 510 patients were not enrolled on a concurrent therapeutic trial, which limited the clinical annotation of those samples. 589 patients have enrolled on the successor study AOST06B1. The lack of clinical annotation of the P9851 specimens limited their value, and the lack of statistical support slowed the analysis of several biology studies. The QuadW Foundation, CureSearch, and the COG formed the Childhood Sarcoma Biostatistics and Annotation Office (CSBAO) in 2008 to link clinically annotated patient data to the samples and to provide statistical support. **Results:** In 2008, only 5.3% of samples from the 510 P9851 patients not enrolled on a therapeutic study had full clinical annotation. The efforts of the CSBAO have linked clinical annotation to 90.8% of those specimens and provided statistical analyses. As a result, 18 biology studies in osteosarcoma are completed, with 11 published in peer-reviewed journals. Samples were provided to the TARGET program (for gene expression arrays, copy number analysis, and sequencing data); the resulting data will be available to the scientific community for *in silico* studies. **Conclusions:** The efforts of the CSBAO have led to a substantial increase in the value of a large osteosarcoma biospecimen repository by clinically annotating the specimens and providing statistical resources for analyses of planned and completed studies. These samples with annotated patient information are available by request to the research community for basic and translational science projects to improve the biological understanding of, and the treatment of patients with osteosarcoma. Clinical trial information: NCT00899275.

10054 General Poster Session (Board #39E), Sat, 1:15 PM-5:00 PM

Evaluation of the necessity of bilateral bone marrow aspirates and biopsies for the diagnosis of metastatic disease in pediatric patients with solid tumors.

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Background: Standard practice for staging solid tumors has been to perform bilateral bone marrow aspirates (BMA) and biopsies (BMB). However, the diagnostic yield of performing all 4 tests has not been thoroughly evaluated. This study evaluated the concordance between test types (aspirate and biopsy) and sites (right and left) to evaluate whether one type or one side would be sufficient. **Methods:** All patients with solid tumors who underwent a diagnostic bilateral bone marrow biopsy and aspirate performed between 2006 and 2011 at Children's Hospital Boston were identifed in a search of hematopathology records.. Kappa coeffcients were estimated. **Results:** A search of the hematopathology data records revealed a total of 112 patients who had had a diagnostic bilateral BMA and BMB including patients with neuroblastoma (n=70), Ewing's Sarcoma (n=11), rhabdomyosarcoma (n=25), retinoblastoma (n=5), and undifferentiated sarcoma (n=1). 73% (n=82) of the patients were negative for all tests; 27% (n=30) had at least one positive test. The results between right and left and aspirate and biopsy were highly correlated.(Kappa statistics: BMA and BMB (0.85); BMA-left and BMB-left (0.82); BMA-right and BMB-right (0.84); BMA-left and BMA-right (0.77); BMB-left and BMB-right (0.95). All 4 tests were positive in 63%, 3 tests positive in 10%, 2 tests positive in 13% and one test positive in 13%. The distribution of positive results did not differ by disease. Among 11 patients with less than 4 positive tests, 10 would have been diagnosed correctly with bilateral aspirates; only one patient (neuroblastoma) had positive results on biopsy only. In this patient, neither aspirate had spicules and was therefore likely an inadequate specimen. **Conclusions:** Bone marrow biopsy may not be essential for accurate diagnosis of metastatic disease in pediatric solid tumor patients. Further confirmation of these findings in a larger sample is warranted.

10055 General Poster Session (Board #39F), Sat, 1:15 PM-5:00 PM

Prognostic impact and detection of minimal residual disease (MRD) in neuroblastoma patients.

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Background: Bone marrow (BM) involvement and MRD detection in neuroblastoma (NB) seems to be useful tool for patients' prognosis, stratification and risk-adapted treatment. Real-time PCR (RQ-PCR) of tumor-specific gene transcripts and flow cytometry (FC) are commonly applied for this purpose. Aim. RQ-PCR MRD marker definition, its qualitative concordance with FC and prognostic impact in NB patients. **Methods:** We analyzed 331 BM samples from 57 NB patients and 26 'normal' BM samples from 20 patients without malignancies for *PHOX2B*, *TH*, *ELAVL4* and *GD2* genes expression. BM samples were defined as positive either in case of positivity for *PHOX2B* or in case of NB cells presence in BM. 326 BM samples from 52 NB patients were analyzed by RQ-PCR and FC together. **Results:** *PHOX2B* and *TH* were not detecting in normal BM samples. Out of 224 negative BM samples *TH* was identified in 5 only, while *ELAVL4* and *GD2* expression was detected in the majority of normal and negative BM samples: 20 and 15 from 26 normal; 209 and 197 out of 224 negative samples correspondingly. *TH*, *ELAVL4* and *GD2* expression in positive BM samples was significantly higher comparing to negative and normal BM samples.Threshold levels of each gene expression were established by ROC-analysis and subsequently applied for overall correct prediction (OCP) calculation. OCP for *PHOX2B* and *TH* achieved 0.994 and 0.952, while OCP for *ELAVL4* and *GD2* were significantly lower: 0.828 and 0.767 respectively. Analytical sensitivity of RQ-PCR for *PHOX2B* achieved 1E-06, while sensitivity of FC ranged from 1E-03 to 1E-05. In 193(59.2%) out of 326 evaluated samples BM was negative by both methods. 38(11.7%) samples were negative by FC but positive by RQ-PCR for *PHOX2B* expression. 31(9.5%) samples were positive by FC but negative by RQ-PCR. 64(19.6%) samples were positive by both techniques. Thus qualitative concordance between RQ-PCR and FC achieved 78.8%. **Conclusions:** Patients with detectable *PHOX2B* expression have lower event-free survival comparing to patients with *PHOX2B* negative BM: 0.30 ± 0.10 and 0.77 ± 0.27 respectively, $p=0.002$ and overall survival is 0.51 ± 0.11 and 0.79 ± 0.07 correspondingly, $p=0.083$. Median of follow up in our NB patients series is 42 months, ranged from 1 to 156.

10056 General Poster Session (Board #39G), Sat, 1:15 PM-5:00 PM

Is magnetic resonance useful predicting neoadjuvant response in children with osteosarcoma?

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Background: Few prognostic factors had been described for pediatric high-grade osteosarcoma (HGO). Primary tumor necrosis percentage after neoadjuvant chemotherapy, analyzed by pathologists, remains as an important prognostic factor. Magnetic resonance imaging (MRI) has been postulated to predict necrosis in adults. Our aim was therefore to calculate the diagnostic utility of MRI in children. **Methods:** Prospective, longitudinal and clinical study was performed from September 2011 to January 2012. Twenty two patients ($<$ 18 years), with extremity HGO and no prior chemotherapy treatment were included. All had MRI from diagnosis and just before surgery. We performed a sensibility-specificity analysis comparing percentage of necrosis by MRI vs histological Rosen grades (grades I and II were classified as bad responders; III and IV as good responders). Cut off value for MRI was 90%. Agreement between radiologists was calculated by Cohen´s Kappa coefficient. **Results:** Average age was 11.7 $\pm$ 3.04 (SD), 54.5% were women. All patients received neoadyuvant chemotherapy (cisplatin 120mg/m^2 and adriamicin 75mg/m^2). Nine patients had limb-sparing surgery, 8 limb disarticulation and 5 amputations; 72.8% were classified as bad responders by histology. MRI sensibility was 25%, specificity 86.6%, positive predictive value 50% and negative predictive value 68.4%. Kappa correlation coefficient between radiologists was 0,229. **Conclusions:** Diagnostic utility values in this study were lower than those reported previously. Torricelli, Dyke and Guo reported MRI sensibility of over 70% and specificity ranging from 37% to 87% (similar number of patients). Predictive values were also higher ($>$ 80%). Differences are likely explained by the lack of correlation between radiologists. Our results support the need to establish systematized criteria to measure necrosis by MRI. In order to predict clinical response to chemotherapy in HGO, it is necessary to establish areas and cut off percentages of necrosis for appropriate clinical decision making.

10057 General Poster Session (Board #39H), Sat, 1:15 PM-5:00 PM

Double akylating agents treatment with ifosfamide (IFOS) and cyclophosphamide (CYCLO) for relapsed pediatric solid tumors.

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Background: CYCLO and IFOS are two of the most active agents in childhood cancer. There is non-cross resistance between CYCLO and IFOS and they have dissimilar toxic side effects. In vitro, tumor model systems document that alkylator resistance may be overcome by several fold increases in drug concentration. We developed a strategy in attempt to limit side effects and increase anticancer activity of high doses oxazaphosphorines therapy: an association of IFOS plus CYCLO, giving an equivalent to 20g/m^2 of IFOS or 5g/m^2 of CYCLO. The schedule is the association of these two drugs: CYCLO 2,5g/m^2 (corresponding to 10g/m^2 of IFOS) plus IFOS 10g/m^2. **Methods:** Eligibility included recurrent/refractory measurable disease, life expectancy $>$ 6 weeks, adequate renal, hepatic and bone marrow function. CYCLO (2,5g/m^2) and IFOS (10g/m^2) with Mesna, with interval of 21 days. Responses were evaluated after 2 cycles.So far**,** 13 patients were enrolled: median age 17 years (5-26), 9M:4F,6 osteosarcoma, 1 hemangioperycitoma, 2 medulloblastoma, 1 nasopharyngeal carcinoma, 1 Wilms tumor,1 synoviosarcoma, 1 retinoblastoma. Six patients received IFOS previously (Total= 38 - 63 g/m^2) and 5 CYCLO. **Results:** Thirty four cycles were evaluated. Toxicity was tolerable with no death. Main adverse event was neutropenia grade (GR) 4 in all cycles, median duration of seven days (3-15), GCS-F was used in all cycles; anemia GR 3 and 4 and thrombocytopenia GR 4 in 14 cycles; infection GR 3 and 4 in 15 cycles; hemorrhage cystitis GR 1 in 2 cycles and neurologic toxicity GR 2 in 6 cycles. No acute renal toxicity was observed. Responses were 2 complete response (CR), 5 partial responses (PR), 3 stable disease, and 3 progress disease. **Conclusions:** This schedule is feasible with high response rate (CR+PR=54%). Due to lack of new agents, innovative approaches for high risk patients can have a potential benefit. More patients are warranted.

10058 **General Poster Session (Board #40A), Sat, 1:15 PM-5:00 PM**

Results with the intensive chemotherapy Mexican regimen in the treatment of pediatric high-grade osteosarcoma: Experience at the Instituto Nacional de Pediatria.

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Background: In Mexico, pediatric high-grade osteosarcoma (HGO) occupies the fifth place of all pediatrics cancers, representing the 4.4%. It presents with a high incidence of metastatic pulmonary disease and large primary tumor volume at diagnosis, resulting in poor survival. The results of the named *2005 Chemotherapy Regimen* are very promising. **Methods:** A retrospective, longitudinal, clinical study was performed from January 2005 to January 2012, including 55 patients (<18 years old) with extremity HGO and no prior chemotherapy treatment. All patients received a 10-week neoadjuvant-chemotherapy regimen (6 curses), with cisplatino 120mg/m^2 plus doxorrubicina 75mg/m^2 and a 15-week adjuvant-treatment (5 curses) with ciclofosfamide 1800 mg/m^2 plus etoposide 900 mg/m^2. **Results:** Median age was 12 years, 51% boys and 49% girls. There were 51% distal femur, 11% proximal humerus, 18.2% proximal tibia, 7.3% distal tibia, 5.4% fibula and 5.5% proximal femur. Thirty-two patients (58.2%) had pulmonary metastases at diagnosis. There were 76.4% osteoblastic tumors, 16% chondroblastic and 7.3% telangiectatic. Twenty patients (36.4%) had an amputation procedure and 15 (27%) a limb desarticulation, 18 by a great tumor volume at diagnosis and two by eventual local relapse. Twelve patients (22%) had limb-sparing surgery. There were 10 (18.2%) good-responder patients and 38 (69%) bad-responders to neoadjuvant-chemotherapy. The overall survival (OS) for non-metastatic patients was 70% and 35% for metastatic patients (p 0.016). The event-free survival for non-metastatic patients was 65% and 30% for metastatic patients (p 0.032). OS for good-responders was 80% and 50% for bad-responders (p 0.009). No important toxicity and no second malignancies were reported. **Conclusions:** In spite of the presence of significant unfavorable prognostic factors in our patients, this intensive chemotherapy regimen showed improved results in overall survival as compared to other standard regimens, being short, inexpensive and with relatively few adverse events. This regimen can be useful in other developing countries.

10059 **General Poster Session (Board #40B), Sat, 1:15 PM-5:00 PM**

Treatment results of children with neuroblastoma in Hospital Infantil de Mexico Federico Gomez.

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Background: Neuroblastoma (NB) is the main extracraneal cancer in children. Progress in survival has not been the same as in other neoplasms despite molecular markers research and new drugs. Our aim was to describe low and high risk patients at Hospital Infantil de México Federico Gómez (HIMFG) and their results. **Methods:** We included children from 0 to 18 years con NB diagnosed at HIMFG between january, 2002 and december 2011. We perform a retrospective, retrolective and descriptive study analyzing demographic variables and survival with Kaplan Meier. **Results:** 64 consecutive patients were included. 73.4% had metastasis at diagnosis (bone marrow 23.4%, liver 18.8%, bone 17.2%, 4.7% central nervous system, 9.4% other). 87.5% of patients received neoadyuvant chemotherapy. Patients were treated with POG 8104 y 8441. Global survival of patients with E4 stage was 50% at 120 months, with E3 of 76.5% at 110 months; stage 1, 2 patient´s survival was 4S 100% at120 months. **Conclusions:** At HIMFG, in Mexico City, 75% of patients with NB arrive with metastatic disease. Clinical prognosis factors are still current in development countries. Our results are similar as in developed countries suggesting that with low resources, we can obtain satisfactory results only with clinical evaluation.

10060 General Poster Session (Board #40C), Sat, 1:15 PM-5:00 PM

Biomarkers of radiation exposure in children with neuroblastoma treated with ^{131}I-mIBG.

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Background: Neuroblastoma (NB) is the most common solid extra-cranial tumor of childhood. ^{131}I-mIBG is a targeted radiopharmaceutical for patients with advanced NB and is one of the most active agents in this treatment resistant population. To date, no clinically relevant biomarkers of response or toxicity have been reported in patients treated with ^{131}I-mIBG. **Methods:** Patients with relapsed or refractory NB who received ^{131}I-mIBG at UCSF were eligible to participate in this prospective correlative study. Blood samples were obtained at baseline and 72 hours after ^{131}I-mIBG infusion. We quantified a panel of biomarkers shown to be effected in patients receiving other forms of radiation, including: serum amylase; plasma Flt-3 ligand; plasma monocyte colony stimulating factor (MCSF); and *CDKN1A* mRNA in mononuclear cells. Extent of modulation of each marker was evaluated using paired t-tests at hour 0 and 72. We assessed potential differential modulation between groups based on response (PR/CR vs SD/PD), toxicity (grade 3 non-hematologic toxicity; grade 4 neutropenia or thrombocytopenia) or administration of combination therapy (^{131}I-mIBG alone vs in combination with vincristine/irinotecan or vorinostat) using unpaired t-tests. **Results:** 26 patients (21 male; median age 7 years) participated and received a median ^{131}I-mIBG dose of 18 mCi/kg. 16 patients received ^{131}I-mIBG in combination. We observed robust modulation of amylase (median fold increase from baseline 3.1; $p < 0.0001$), Flt-3 ligand (median fold increase from baseline 3.6; $p = 0.0005$), and *CDKN1A* mRNA (median fold decrease from baseline 4.3, $p = 0.0002$). No differences were noted in MCSF ($p = 0.80$). Patients receiving combination ^{131}I-mIBG had more robust modulation of Flt-3 ligand (mean difference 296 pg/mL; $p = 0.02$) compared to single agent ^{131}I-mIBG. No correlations with clinical response or toxicity were found. **Conclusions:** Amylase, Flt-3 ligand, and *CDKN1A* mRNA all show robust modulation after ^{131}I-mIBG treatment. Patients receiving ^{131}I-mIBG in combination demonstrated the largest changes in plasma Flt-3 ligand. In this initial analysis, no associations were found between response or toxicity and the proposed biomarkers.

10061 General Poster Session (Board #40D), Sat, 1:15 PM-5:00 PM

Birth and maternal characteristics, and childhood cancer in the United States: An ecological study.

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Background: Childhood cancer is rare, yet it represents a major cause of mortality in this age group. Its etiology is largely unknown. The aim of this study was to identify associations between pre- and perinatal characteristics and cancer development in children below age 5. **Methods:** We developed an ecological study correlating birth information and childhood cancer incidence in 0-4 year old at the State level. The following variables were analyzed: birth weight (BW), preterm birth, maternal age, plurality, maternal smoking, chronic hypertension (CH), diabetes mellitus (DM), pregnancy associated hypertension (PH) and eclampsia. Birth characteristics were obtained from Centers for Disease Control and Prevention (CDC) database (1995-2009), and childhood cancer incidence data from the National Program of Cancer Registries (NPCR) and the Surveillance, Epidemiology and End Results (SEER) program (1999-2009). Spearman correlation coefficients were calculated with SAS 9.2 (Cary, NC). Bonferroni correction was applied for multiple comparisons, ie, only results with p£0.01 were considered significant. **Results:** Acute lymphoid leukemia (ALL) ($r=0.47$, $p<0.001$), astrocytoma (AST) ($r=0.59$, $p<0.001$), neuroblastoma (NB) ($r=0.48$, $p<0.001$) and rhabdomyosarcoma (RMS) ($r=0.51$, $p=0.003$) were positively correlated with high BW (>4000g). ALL ($r=0.46$, $p<0.001$) was also positively correlated with advanced maternal age (40+ years). Moreover, a positive correlation was found between plurality and NB ($r=0.50$, $p<0.001$). Regarding maternal conditions, the following positive correlations were identified: DM with AST ($r=0.40$, $p=0.009$), NB ($r=0.38$, $p=0.01$) and WT ($r=0.38$, $p=0.01$). **Conclusions:** Well established correlations were replicated and new associations were suggested (e.g., AST and DM). In spite of the limitation of an ecological approach, this study provided new hypotheses to be explored in further analytical studies based on individual data.

10062 General Poster Session (Board #40E), Sat, 1:15 PM-5:00 PM

Predictors of declining levels of physical activity among adult survivors of childhood cancer.

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Background: Childhood cancer survivors are at increased risk of developing obesity-related diseases, yet many survivors do not meet established guidelines for physical activity. We aimed to identify demographic and health-related predictors of declining physical activity among participants in the Childhood Cancer Survivor Study (CCSS). **Methods:** Analyses included 6617 >5 year childhood cancer survivors diagnosed between 1970-86 who completed the CCSS 2003 and 2007 follow-up questionnaires, and1992 siblings. Participants were classified as active if they reported engaging in any physical activity other than their regular job duties in the prior month. Generalized linear models using a log-link and Poisson distribution were used to compare participants whose physical activity levels fell from active to inactive over the study interval to those who remained active or whose activity levels improved. In addition to analyses comparing survivors to siblings, selected demographic factors and chronic conditions (CTCAE v4.0 Grade 3 and 4) were evaluated as risk factors in an analysis among survivors alone. Risk ratios (RR) with 95% confidence intervals (CI) are reported. **Results:** The median age at last follow-up among survivors and siblings was 36 (range: 21-58) and 38 (range: 21-62) years, respectively. Approximately 14% of survivors and 9% of siblings reported declines in physical activity across the study interval ($p<0.01$). Factors that predicted declining levels of physical activity included BMI$\geq$30kg/m^2 (RR=1.4, 95% CI=1.3-1.7, $p<0.01$), BMI$<$18.5kg/m^2 (RR=1.4, 95% CI=1.0-1.8, $p=0.03$), not completing high school (RR=1.7, 95% CI=1.2-2.2, $p<0.01$), and black race (RR=1.6, 95% CI=1.2-2.1, $p<0.01$). In a model limited to survivors, declining levels of physical activity were more likely among survivors who reported the presence of Grade 3 or 4 neurological (RR=1.5, 95% CI=1.2-1.8, $p<0.01$) or cardiac conditions (RR=1.5, 95% CI=1.3-1.9, $p<0.01$). **Conclusions:** Childhood cancer survivors are at increased risk of becoming inactive over time compared to siblings. Interventions targeting survivors at highest risk of decline are required to reduce the risk of chronic diseases associated with an inactive lifestyle.

10063 General Poster Session (Board #40F), Sat, 1:15 PM-5:00 PM

Health practices and behaviors of childhood cancer survivors not attending a comprehensive survivor clinic.

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Background: Little is known regarding the health practices and behaviors of childhood cancer patients who have not received recommended survivorship care, a group that represents the majority of survivors. **Methods:** Using the Yale Tumor Registry, consisting of patients from Southern Connecticut, we identified patients who were diagnosed from 2000-2011 with an invasive cancer at age ≤18 years, are currently alive and cancer-free at least one year after therapy, live within 100 miles of Yale HEROS Childhood Cancer Survivor Clinic, never previously attended a survivor clinic, and consented to a research study to investigate survivor care. Participants completed postal or on-line surveys regarding health communication preferences, utilization of services, and behaviors. **Results:** The 68 participants had a mean age of 16.8 (range 6-27) years at evaluation and 6.7 years since diagnosis with 53% female and 50% currently >18 years. Overall, 100% had seen a primary care physician and 71% their pediatric oncologist in the past year. Forty-six percent had also seen a subspecialist with orthopedics (10%), dermatology (9%), endocrinology (6%), and OB/GYN (6%) as the most common specialties; 16% reported two or more subspecialists. Most (83%) had commercial insurance, while 17% had federal insurance. For communication preferences with their providers, willingness to communicate by cell phone, text messages, and email were 59%, 56%, and 87%, respectively. For health behaviors, only 16% of participants met CDC guidelines for fruit and 19.1% for vegetable intake. Among adults, 12% were active smokers. Only 6% of children and 33% of adults met age-specific CDC recommendations for moderate weekly physical activity. **Conclusions:** Survivors of childhood cancer were overall highly connected to primary care and other health services, despite not participating in survivorship care. However, inadequate diet and physical activity results suggest patients could benefit from behavioral interventions.

10064 **General Poster Session (Board #40G), Sat, 1:15 PM-5:00 PM**

Depression and anxiety (DA) in children within one year of a cancer diagnosis.

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Background: While 10% of children were treated with anti-depressants within 1 year of a cancer diagnosis in a previous study, neither the prevalence nor time course of DA were studied. The American Association of Pediatrics advocates for the use of screening for DA, yet data are lacking regarding timing, frequency, or predictive success of screening in children concurrently receiving therapy for cancer. **Methods:** We evaluated 87 prospectively diagnosed children at a single institution for DA at 5 time points during the first year of a cancer diagnosis. 55 children completed all screening, 70 missed at most one visit. Starting within 1 month of cancer diagnosis, patients completed the Childhood Depression Inventory (CDI) and the Speilberger State/Trait Anxiety Inventory (STAI) and again at 3, 6, 9, and 12 months. Those patients who scored $\geq$ 11 on the CDI or $\geq$ one standard deviation above the mean for age on the STAI were referred for psychiatric consultation the same day. **Results:** Overall 33 patients (39%) indicated symptoms suggestive of either depression or anxiety during their first year of cancer therapy; n=29 (35%) depression, n=17 (20%) state and n=10 (12%) trait anxiety. Fifty-six consultations resulted in 33 psychiatry diagnoses confirmed in 21 patients (23 depression, 3 anxiety and 7 other). Half of the patients received a diagnosis of DA at least twice over the course of the study, suggesting persistent, significant symptoms. **Conclusions:** We conclude that screening for DA is effective in children with cancer and that prevalence for symptoms is high. The highest risk for symptoms of DA is within 1 month of diagnosis but during the 1st year of therapy children continue to suffer symptoms of DA highlighting the importance of continued screening.

	0	3	6	9	12
# Patients screened	80	71	73	70	67
CDI $\geq$ 11	19 (24%)	5 (7%)	6 (8%)	5 (7%)	3 (5%)
STAI state $\geq$ 1 SD above mean	9 (11%)	3 (4%)	4 (6%)	3 (4%)	2 (3%)
STAI trait $\geq$ 1 SD above mean	3 (4%)	2 (3%)	2 (3%)	2 (3%)	2 (3%)
# Psychiatry consults	25	8	11	8	4
# Psychiatry diagnoses	11	4	9	6	3
# Patients diagnosed	11	3	4	3	-

10065 General Poster Session (Board #40H), Sat, 1:15 PM-5:00 PM

First results of prophylaxis for bacterial and fungal infections in pediatric patients with high-risk acute lymphocytic leukemia (ALL).

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Background: Bacterial and invasive fungal infections remain a major contributor to treatment related morbidity and mortality in cancer patients. It has been published data of potential prevention; in immunocompromised hosts derive primarily from adult studies. However, children differ from adults in terms of the infections types as they develop or manifest, as well as their metabolism of treatment agents. From April 2010 to January 2011, 6 ALL patients received 35 intensive chemotherapy cycles during the first 6 months after diagnosis, 2 died due to infection. **Methods:** From April 2011 to January 2012, a prospective analysis in 8 high risk ALL patients (BFM criteria) after 31 cycles of intensive chemotherapy were performed during the first 6 months of treatment followed by antibacterial and antifungal prophylaxis. Drugs are: ciprophloxacin 1000mg per day when weight highest than 30 kg and 500mg per day when lower weigh and fluconazole 100mg per day for the lower weigh and 150mg for the higher. All patient received granulocyte colony-stimulating factor after each cycles until complete neutrophils recovery. **Results:** In 20/31 cycles, hospitalization was needed, due to febrile neutropenia. Diarrhea, sepsis and renal failure were other reasons for hospitalization. Platelet transfusions and blood transfusions were performed in 12 and 9 hospitalization respectively. The majority of proven infections (n=7) were bacterial, Gram negative (Pseudomonas aeruginosa and Klebsiella spp), Gram positive, Candida (1 cycle). Hospitalization time was between 2 and 25 days (median time 10 days). In 4 cycles, intensive care unit was needed. No death occurred. **Conclusions:** Bacterial and fungal infections continue to be a leading cause of morbidity and mortality in children receiving intensive therapy. Pharmacologic prophylaxis can contribute to decrease mortality due to infection in this population.

10066 General Poster Session (Board #41A), Sat, 1:15 PM-5:00 PM

Attitudes to the return of incidental and targeted genomic findings obtained in a high-risk pediatric cancer versus an inherited genetic condition research setting.

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Background: The disclosure of clinically significant, validated incidental and target findings to participants in genomic research is often recommended. There have been no reports on whether attitudes of parents differ if these findings emerge from an acquired pediatric cancer versus an inherited genetic condition setting. **Methods:** Parents in 3 large-scale projects [Canadian Pediatric Cancer Genome Consortium (CPCGC), the Finding of Rare Genes Canada Consortium (FORGE) and the Orphan Diseases: identifying Genes and Novel Therapeutics to Enhance Treatment Project (IGNITE)] were surveyed using a mailed, validated 29-item questionnaire. Two reminders were sent. Analysis was by descriptive and Chi-square statistics. **Results:** Response rate: 64% (n=307/480). 40% were > 50 yrs age; more than half had a grade 12 education. 86 were parents of poor risk pediatric cancer patients and 221 were parents or individuals with rare inherited conditions. Most stated a very strong or strong right to genomic research results, irrespective if from the target condition (97%) or incidental (86%). 70% wish genetic counselling pre- and post-research testing; an additional 20% were uncertain what this entails. Almost all indicated that genomic research for childhood onset conditions should occur, regardless of whether therapy existed (99%) or not (91%). A few indicated that they would not want incidental results showing an untreatable fatal condition (17%). Most want results, even if these suggest susceptibility to multiple conditions (87%) or are of uncertain health impact (84%). Most felt a right to genomic research that showed a serious condition in siblings, whether treatable (94%) or not (89%). 74% strongly support that results discovered after death of the proband be shared with family. **Conclusions:** Parents of children in both cancer and inherited rare conditions genomic research do not differ in indicating a strong right and desire to receive research results, even if they are of uncertain impact, of childhood onset, or after death of the proband. Clear delineation of what will or will not be offered from genomic research should be established at the time of consent.

10067 **General Poster Session (Board #41B), Sat, 1:15 PM-5:00 PM**

Turkish National Pediatric Cancer Registry 2002-2008 (Turkish Pediatric Oncology Group and Turkish Pediatric Hematology Society).

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Background: In childhood cancers cure rates increased up to 80% in the developed countries. On the other hand cure rates goes down 10-20% percent in countries with low resource settings. Reliable pediatric cancer data is essential for all countries. We established a nationwide pediatric cancer registry. **Methods:** Turkish Pediatric Oncology & Pediatric Hematology Society established a web-based database for the registry of all pediatric cancers. 11898 cases were registered between 2002-2008 from 65 centers. Various demographic data & survival endpoints were recorded & analyzed. Diseases were grouped according to the International Classification of Childhood Cancer. **Results:** In all 11898 cases, median age was 6 years (M/F= 6786/5112=1.32). Distribution in age groups were: 0-4 years, 42.5%; 5-9 years, 27.2%; 10-14 years, 23.4%; 15-19 years, 6.8%; >19 years, 0.1%. Only 3.8% of cases were diagnosed with clinical+radiological, the rest with histopathological data Distribution of cases in disease groups were [median age in yrs, M/F]: Leukemias (n=3777) 31.7% [5.5, 2137/1640=.31]; Lymphomas (n=2040) 17.1% [8.3, 1405/635=2.21]; CNS tumors (n=1588) 13.3% [6.9, 913/675=1.3]; Sympathetic tumors (n=889) 7.5% [2.1, 453/436=1.03]; Retinoblastoma (n=371) 3.1% [2, 181/190=0.95]; Renal tumors (n=655) 5.5% [3, 333/322=1.03]; Hepatic (n=166) 1.4% [1.8, 101/65=1.5]; Bone tumors (n=717) 6% [12.2, 407/310=1.3]; Soft tissue tumors (n=773) 6.5% [6.5, 442/331=1.3]; Germ cell tumors (n=531) 4.5% [5, 210/321=0.6]; Carcinomas and other malignant epithelial tumors (n=323) 2.7% [12, 164/159=1.03]; Others/unspecified malignant tumors (n=68) 0.6% [4.5, 40/28=1.4]. Five-year overall survival in all cases was 65%. **Conclusions:** This registry provides a critical information about the distribution of childhood cancer since this is the only nationwide pediatric cancer registry in Turkey. With the recent trends in non-communicable diseases at global level, registry data will be very helpful for national cancer control plans, which will also be used to compare at national and international level. This will also be a good example for many other countries with similar resources to do such projects.

10068 General Poster Session (Board #41C), Sat, 1:15 PM-5:00 PM

Risk factors for underlying vitamin D deficiency in children with cancer at their diagnosis for cancer.

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Background: There is increasing interest in the possible association between cancer incidence and vitamin D. Our recent study showed a prominent Vit D deficiency in our pediatric cancer patients during their admition. **Methods:** Seventy newly diagnosed Pediatric cancer patients that have been defined as Vit D deficiency at our clinic, enrolled the study between 2010-2013. A questionare with 32 questiones has been performed to each patient's family. Questiones are designed to determine risk factors for Vit D deficiency like; daily sun light exposure, consumption of food that known as source of the Vit D, suplementation during pregnancy, lactation and during infancy,etc.SPSS 11.5 program used for istatistical analyses **Results:** This study has been designed as a questionare based research to find out possible risk factors for Vit D deficiency in our patients. Seventy patients with leukemias , lymphomas and solid tumors were included in the study. Fourtysix boys (66%) and 24 girls (34%) were between 2 months to 18 years old (median: 9 years). Almost 60 % of the patients have been borned during autumn or winter. Education level : 8 % of the fathers and 19 % of the mothers were not received any education at school. During pregnancy 64% and during lactation 83% of the mothers have not been supplemented with Vit D. Seventy four percent of the mothers did not have any knowledge about importance of the Vit D. Supplementation of the Vit D during infancy was not avaliable for 58% of the patients. Daily exposure to the sun light was between 0 to 6 hours (median:2.2 hours/day). Monthly consumption of fish and egg was between 0 to 5 times (median: 1.3 time/month) for fish and between 0 to 45 eggs (median 13.9 eggs/ month) respectively. Daily consumption of the milk was between 0 to 2 glases (median: 1 glass/day) . **Conclusions:** Famillies are not aware of the importance of Vit D**.** Consumption of Vit D containing foods are much lover than recomended nutrition facts.A special attention has to be given for education of parents for vit D supplementation during pregnancy, lactation and infancy. Besides, it should be started to educate peopele beginning from their childhood to have enough daily sun light exposure and Vit D containing foods as a part of their healthy life style.

10069 General Poster Session (Board #41D), Sat, 1:15 PM-5:00 PM

Surveillance and follow up of pediatric cancer from a developing country.

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Background: Childhood cancers, a leading cause of childhood deaths, affect more than 200,000 children worldwide, of which >80% are from developing nations. This demands for proper measurement of the incidence of various childhood cancers which led to a novel study in assessing the burden of childhood cancers in eastern India through analysis of hospital-based cancer registry data from our institute in between January 2001- December 2011. **Methods:** 3,200pediatriccancer patients between 0-15 yearsdiagnosed by means of histological and cytological examinations were included in this study. Based on histopathological classification, cancer cases were distributed into 3 different age groups. Their respective family functioning, mental health, self-esteem and social competence were examined. Details of disease, tobacco usage along with socio demographic data were collected through standard questionnaires. Comparative measures of disease incidence were also calculated. For measuring the tolerance, different drugs were administered to patients. **Results:** The incidence of different malignancies was recorded which were Leukemia (34.9%), Lymphoma (24.1%), Hodgkin's disease (18.1%), NHL (6.0%), Ewing's sarcoma (4.9%), Rhabdomyosarcoma (3.6%), Neuroblastoma (2.0%), Brain tumour (9.9%), Wilm's tumour (6.0%), Lymphoid Leukemia (26.9%), Myeloid Leukemia (7.9%), Germ cell tumour (4.2%), Osteosarcoma (4.0%), Retinoblastoma (2.0%) and Soft tissue sarcoma (2.3%)**.** The disease free survival (DFS) for ALL was 76%, NHL (84%), Soft tissue sarcoma (78%), CML (98%), AML (48%) and germ cell tumour (95%). Finally, 53.33% patients were subjected to post-therapy assessment, of which 98% showed no after effect of therapy on growth chart, heart and endocrine function. The toxicity of grade III and IV chemotherapy ranges from 10-20%. **Conclusions:** Based on our study, the most happening cancer was Leukemia (34.9%) followed by Lymphoma (24.1%) and soft tissue sarcoma (18%). The overall disease free survival for pediatric patients was 72% with acceptable toxicity. Our results are comparable with the studies of other developed countries.

10070 General Poster Session (Board #41E), Sat, 1:15 PM-5:00 PM

Access to cancer chemotherapy and predictors of early mortality for childhood cancers in Uganda.

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Background: Although many childhood cancers respond well to chemotherapy, survival among children with cancer in sub-Saharan Africa is poor. Little is known about children's access to specialized cancer care in SSA or factors contributing to poor early outcomes. We aimed: 1) To estimate the proportion of childhood cancer patients without access to chemotherapy in Uganda; 2) To describe 30-day survival rates and predictors of mortality post diagnosis among children with lymphoma or Kaposi sarcoma (KS), the two most common pediatric cancers in Uganda. **Methods:** A retrospective study of incident childhood (age< 20 years) cancers diagnosed in Kyandondo County, Uganda from 2006-2009. We compared records of the population-based Kampala Cancer Registry (KCR) and patient records at the Uganda Cancer Institute (UCI), Uganda's sole dedicated cancer treatment center. Patient characteristics were compared using Mann-Whitney and Pearson's chi-square tests. Kaplan-Meier method and Cox regression models were used to describe mortality. **Results:** Of the 658 pediatric cases recorded in the KCR, only 238 (36%) presented to UCI. Patients identified in the KCR who did not present for care were more likely to be female, diagnosed in earlier years of the study, and to have a cancer other than KS or lymphoma. Of the 177 lymphoma and KS cases at UCI, 43.7% were Burkitt lymphoma (BL), 32.5% KS, and 23.8% other lymphomas. The post diagnosis 30-day overall survival rate was 77%. In multivariate analysis, age, gender, HIV status, platelets, and stage of cancer did not impact mortality. An increased risk of death at 30 days was predicted by presence of B-symptoms (HR=10.3, p=0.05), a diagnosis of BL compared to other lymphomas (HR=14.8, p=0.007), poor performance status (Karnofsky score <70, HR=14.7, p<0.001), and anemia (HR 1.5-fold per 1g/dL decrease in hemoglobin, p=0.002). **Conclusions:** Childhood cancer patients in Uganda have limited access to comprehensive care. Among those presenting to the UCI, a significant proportion die before they can benefit from chemotherapy. BL diagnosis, B-symptoms, performance status and hemoglobin level may be important predictors of early mortality among childhood cancer patients in sub-Saharan Africa.

10071 General Poster Session (Board #41F), Sat, 1:15 PM-5:00 PM

Screening with whole-body MRI (WB-MRI) in pediatric patients with Li Fraumeni syndrome (LFS).

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Background: LFS is a rare hereditary cancer syndrome characterized by a high risk of developing a wide range of malignancies. Germline mutations in the tp53 gene confer approximately a 12-fold risk of developing cancer by age 20. Given the potential for diverse malignancies, cancer surveillance in LFS patients is challenging. We piloted the use of WB-MRI for pediatric LFS patients as a cancer screening tool. **Methods:** Eligibility included: documented tp53 mutation, or obligate carrier status based upon family history/genetic testing, and no recent cancer diagnosis. WB-MRI was performed as a research test, in conjunction with recommended clinical screening based upon family history and clinician recommendation. Our primary aim was to determine the feasibility (defined as 87% completion rate) of obtaining two planned annual MRI scans in 15 pediatric LFS patients. Our secondary aim was to calculate the incidence and describe the characteristics of primary cancers detected. **Results:** Nine pediatric patients from 5 families have been enrolled and all have successfully completed one WB-MRI. Seven patients were known carriers, and 2 underwent genetic testing in order to enroll in the study. Median age was 12 years, range 6 to 15. Scan time was 60-90 minutes and 2 patients required anesthesia with propofol. There were no acute scan complications. Six of the 9 (67%) scans demonstrated incidental findings (T2 cerebral cortex abnormality, L5-S1 synovial cyst, thoracic syrinx, T12 hemangioma, 2 ovarian cysts, and degenerative disc disease). Only one patient underwent a dedicated follow-up imaging study for an abnormality on WB-MRI. None of the patients required biopsy. All patients had normal screening laboratory work. These results are being presented early to foster collaboration. **Conclusions:** All patients enrolled on our study tolerated WB-MRI; none were diagnosed with a new malignancy. Although preliminary, our results to date are in contrast to previous reports documenting a high incidence of cancers detected during screening of LFS patients. WB-MRI may be a promising approach to screening; a large multi-center trial will be needed to determine its efficacy in detecting incident cancers and true test characteristics.

TPS10072 **General Poster Session (Board #41G), Sat, 1:15 PM-5:00 PM**

Pilot study of redirected autologous T cells engineered to contain anti-CD19 attached to TCRζ and 4-1BB signaling domains in patients with chemotherapy-resistant or -refractory CD19+ leukemia and lymphoma.

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Background: Outcomes remain poor for patients (pts) with relapsed or refractory (r/r) B-cell malignancies such as acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). CD19 is an attractive therapeutic target because it is widely expressed on normal and malignant B cells throughout B-cell maturation but not on pluripotent stem cells or non–B-cell tissues. We have developed chimeric antigen receptor T cells to target CD19+ cells (CART-19 or CTL019). This approach involves patient-derived T cells that are genetically modified via lentiviral transduction to express a CD19 antigen recognition domain attached to intracellular signaling domains (TCRζ and 4-1BB) that mediate T-cell activation. A recent study in CLL showed that CART-19 therapy had potent activity with responses in 5/8 evaluable pts (3 CR, 2 PR). Pts achieving CR (two > 24 months and one > 5 months) remain in CR with detectable CART-19 cells (Porter et al. ASH 2012). Here we describe a study of CART-19 therapy in pediatric pts with r/r leukemia and lymphoma (NCT01626495). **Methods:** Pts eligible for this single-arm, open-label study are aged 1 to 24 years with r/r CD19+ B-cell malignancies, without a transplant option or having relapsed after allogeneic stem cell transplantation (ASCT). Pts will undergo leukapheresis to obtain T cells, which will be stimulated, expanded, and transduced ex vivo to express the chimeric antigen receptor. Pts may receive lymphodepleting chemotherapy prior to CART-19 infusion. Study objectives: determine the safety and feasibility of administering CART-19 therapy to pediatric pts, assess duration of in vivo survival of CART-19 cells, and measure antitumor response. There are 2 cohorts in the study: Cohort 1 includes pts who have not undergone ASCT and are not currently eligible for a transplant, and cohort 2 includes pts who relapsed after ASCT. Cells are collected from the recipient, not the donor, which allows for this approach to be used in pts s/p cord blood transplant, and which we hypothesize will reduce the risk of GVHD as a result of toleration of the T cells in the recipient. To date, 7 pts have been enrolled. Clinical trial information: NCT01626495.

TPS10073 **General Poster Session (Board #41H), Sat, 1:15 PM-5:00 PM**

Trial of zoledronic acid and interleukin-2 to expand tumoricidal γδ T cells in vivo in patients with refractory neuroblastoma.

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Background: CD3+ γδ+ T cells comprise 2 to 5% of the circulating T cells. Vγ9Vδ2+ cells are the dominant circulating γδ T cell and recognize non-peptide phosphoantigens and stress-associated NKG2D ligands expressed on malignant cells. Strategies that incorporate the tumoricidal properties of γδ T cells represent a promising means of harnessing the innate immune system to treat malignancies including neuroblastoma (NB). Indeed, γδ T cells from both healthy volunteers and NB patients exert a potent cytotoxic effect on NB cell lines and autologous NB *in vitro* following expansion and activation in culture. Vγ9Vδ2+ cells can also be induced to proliferate *in vivo*. By blocking farnesyl pyrophosphate synthase in the mevalonate pathway of isoprenoid synthesis in monocytes, the aminobisphosphonate zoledronic acid (ZOL) promotes the accumulation of isopentenyl pyrophosphate which is sensed by γδ T cells. IL-2 is also required for robust expansion γδ T cells. **Methods:** The trial is a prospective, non-randomized trial that assesses two dose levels of recombinant IL-2 (aldesleukin) in combination with ZOL. To be eligible for the study patients must be 2 to 21 years of age with refractory neuroblastoma with no known curative therapeutic options. Patients must also have adequate organ function and performance status. ZOL is given intravenously on day 1, and aldesleukin is given subcutaneously on days 1 to 5 and 15 to 19 of every 28 day cycle. The single-institution study is being conducted at the University of Alabama at Birmingham. Correlative studies include evaluating the absolute count, phenotype, activation, and effector/memory progression of γδ T cells by flow cytometry and the biological function of autologous expanded/activated γδ T cells by *in vitro* cytotoxicity assays employing established human NB cell lines. In order to determine the ability of *in vivo* expanded/activated γδ T cells to infiltrate NB tissue, bone marrow core biopsies obtained before and after the first course of therapy from patients with bone marrow metastasis are assayed for T cell infiltration by immunohistochemistry. The study has currently enrolled 1 of the planned 6 patients. Clinical trial information: NCT01404702.