Matthias Guckenberger[6], Volker Budach[7], Jutta Welzel[8], Christoph Pöttgen[9], Heinz Schmidberger[10], Frank Heinzelmann[11], Frank Paulsen[11], Montserrat Pazos[12], Rudolf Schwarz[13], Dagmar Hornung[13], Carmen Martini[14], Anca Ligia Grosu[14], Frank Michael Meyer[15], Karolina Jablonska[16], Juergen Dunst[17], Karin S. Kapp[18], Karin Dieckmann[19], Beate Timmermann[20], Torsten Pietsch[21], Monika Warmuth-Metz[22], Robert Kwiecien[23], Martin Benesch[24], Nicolas U. Gerber[25], Stefan M. Pfister[26], Steven C. Clifford[27], Katja von Hoff[28], Sabine Klagges[1], Stefan Rutkowski[29], Rolf-Dieter Kortmann[1], and Martin Mynarek[29]; [1]Department for Radiation Oncology, University of Leipzig Medical Center, Leipzig, Germany, [2]Department of Radiation Oncology, Chemnitz Municipal Hospital, Chemnitz, Germany, [3]Department of Pediatric Hematology and Oncology, University Hospital Geneva, Geneva, Switzerland, [4]Department of Radiation Oncology, Medical Faculty, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany, [5]Radiation Oncology, Munich-Schwabing Municipal Hospital, Munich, Germany, [6]Department of Radiation Oncology, University of Zurich Medical Center, Zurich, Germany, [7]Department for Radiation Oncology, Charité School of Medicine and University Hospital Berlin, Berlin, Germany, [8]Department of Radiation Oncology, Pius Hospital Oldenburg, Oldenburg, Germany, [9]Department of Radiotherapy, West German Cancer Center, University of Duisburg-Essen, Essen, Germany, [10]Department for Radiation Oncology, University of Mainz Medical Center, Mainz, Germany, [11]Department for Radiation Oncology, University of Tuebingen Medical Center, Tuebingen, Germany, [12]Department of Radiotherapy and Radiation Oncology, Ludwig Maximilian University Munich, Munich, Germany, [13]Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany, [14]Department of Radiation Oncology, University Medical Center Freiburg, Freiburg, Germany, [15]Radiation Oncology, MVZ medical care center, Hospital Augsburg, Augsburg, Germany, [16]Department of Radiation Oncology, University Medical Center Cologne, Cologne, Germany, [17]Department of Radiation Oncology, University Hospital Schleswig-Holstein, Kiel, Germany, [18]Department of Therapeutic Radiology and Oncology, Medical University of Graz, Graz, Austria, [19]Department of Radiotherapy, Medical University of Vienna, Vienna, Austria, [20]Clinic for Particle Therapy, West German Proton Therapy Centre, University of Essen, Essen, Germany, [21]Department of Neuropathology, University of Bonn, Bonn, Germany, [22]Department of Neuroradiology, University of Wuerzburg, Wuerzburg, Germany, [23]Institute of Biometry and Clinical Research, University of Muenster, Muenster, Germany, [24]Division of Pediatric Hematology/Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria, [25]Children´s Hospital, University of Zurich, Zurich, Switzerland, [26]Hopp Children´s Cancer Center Heidelberg (KiTZ), Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Department of Pediatric Oncology, Hematology and Immunology, Heidelberg University Hospital, Heidelberg, Germany, [27]Wolfson Childhood Cancer Research Centre, Newcastle University Centre for Cancer, Newcastle upon Tyne, United Kingdom, [28]Department of Paediatric Oncology and Hematology, Charité University Medicine Berlin, Berlin, Germany, [29]Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

PURPOSE: To evaluate prognostic factors and impact of participation in a randomized trial in non-metastatic medulloblastoma. METHODS AND PATIENTS: 382 patients with non-metastatic medulloblastoma aged 4–21 years with primary neurosurgical resections between 2001 and 2011 were enrolled into the HIT 2000 trial and centrally reviewed. Between 2001 and 2006, 176 of these patients participated in the randomized trial HIT-SIOP PNET 4. Three different radiotherapy protocols were applied. Molecular subgroup was available for 157 patients. RESULTS: Median follow-up was 6.35 [0.09–13.86] years. The 5-year progression-free (PFS) and overall survival (OS) rates were 80.3 % ± 2.1 % and 86.5 % ± 1.8 %, respectively. On univariate analysis, there was no difference in PFS and OS according to radiotherapy protocols or in patients who participated in the HIT-SIOP PNET 4 trial or not, while histology, molecular subgroup and postoperative residual tumor influenced PFS significantly. Time interval between surgery and irradiation (≤48 days vs. ≥49 days) failed the significance level (p=0.052). On multivariate analyses, molecular subgroup (WNT activated vs. Group3 HR 5.49; p=0.014) and time interval between surgery and irradiation (HR 2.2; p=0.018) were confirmed as independent risk factors. CONCLUSION: Using a centralized review system, multiprofessional and multiinstitutional collaboration as established for pediatric brain tumor patients in Germany, and risk-stratified therapy, outcome for non-metastatic medulloblastoma treated within HIT-SIOP PNET4 could be maintained outside the randomized trial. Prolonged time to radiotherapy negatively influenced survival.

## MBCL-12. MOLECULAR SIGNATURES AND TUMOR INFILTRATING IMMUNOLOGICAL CELLS ASSOCIATED WITH ASIAN MEDULLOBLASTOMA PATIENT SURVIVAL

Kung-Hao Liang[1], Kuo-Sheng Wu[2], Yi-Yen Lee[1], Muh-Lii Liang[1], Jun-Jeng Fen[1], and Tai-Tong Wong[3]; [1]Taipei Veterans General Hospital, Taipei, Taiwan, [2]Taipei Medical University, Taipei, Taiwan, [3]Taipei Medical University Hospital, Taipei, Taiwan

BACKGROUND: Medulloblastoma is an aggressive pediatric brain tumor with surgery and post-resection radiotherapy plus chemotherapy as the major type of treatment currently. METHODS: A cohort of 52 medulloblastoma patients were treated in Taipei Medical University Hospital and Taipei Veterans General Hospital. Among them, 28 (53.85%) are male. The average age at presentation is 7.21 ± 4.15. Genome-wide RNA profiling were performed on fresh-frozen surgical samples. Tumor infiltrating immune cell percentages were inferred by the cibersort immune deconvolution algorithm. RESULTS: A total of 13 leading genes, including DLL1, ASIC2, SLC22A17, TRPM3, RPS2P5 and KCNC3, were found to be significantly associated with overall survival (All P < 0.001). A risk score was constructed, which is indicative of overall survival (Hazard Ratio [HR] = 2.720, 95% confidence interval [CI] = 1.798 ~ 4.112, P < 0.001) and recurrence-free survival (HR = 1.645, CI = 1.337 ~ 2.025, P < 0.001). After adjustment of clinical factors, the score remained significantly associated with overall survival (HR = 2.781, CI = 1.762 ~ 4.390, P < 0.001) and recurrence-free survival (HR = 1.604, CI = 1.292 ~ 1.992, P < 0.001). The percentage of Natural Killer and T follicular helper (Tfh) cells were higher in patients with better overall survival (P = 0.046 and 0.001, respectively). Furthermore, the Tfh percentage is also positively associated with mutation burdens in the expressed exonic regions (P < 0.001). CONCLUSION: Higher mutation burdens are correlated with higher levels of tumor infiltrating Tfh cells, which is indicative of better post-surgery prognosis.

## MBCL-13. CORRELATION OF HISTOPATHOLOGY, CHROMOSOMAL MICROARRAY, AND NANOSTRING BASED 22-GENE ASSAY FOR MEDULLOBLASTOMA SUBGROUP ASSIGNMENT ON "HEAD START" 4 CLINICAL TRIAL

Girish Dhall[1], Parth Patel[2], Megan Blue[2], Jaclyn Biegel[3], Isabel Almiraz-Suarez[4], Eugene Hwang[4], Christopher Pierson[2], Daniel Boue[2], and Jonathan Finlay[2]; [1]University of Alabama at Birmingham, Birmingham, AL, USA, [2]Nationwide Children's Hospital, Columbus, OH, USA, [3]Children's Hospital Los Angeles, Los Angeles, CA, USA, [4]Children's National Medical Center, Washington DC, USA

"Head Start" 4 (HS 4) is a prospective randomized clinical trial that tailors treatment based on medulloblastoma molecular subgroups and response to induction chemotherapy to compare efficacy of one versus three (tandem) cycles of myeloablative chemotherapy. Advances in RNA and DNA profiling have identified four molecular subgroups of medulloblastoma with prognostic significance: Sonic Hedgehog (SHH) subtype, WNT subtype, Group 3, and Group 4. In HS 4 trial, we utilize a combination of histopathology and immunohistochemistry (pathology/IHC), as well as chromosomal microarray analysis (CMA) utilizing OncoScan™ (Thermo Fisher) to classify medulloblastoma samples into either SHH, WNT, or non-WNT/non-SHH (Group 3/4) subgroups at the time of diagnosis. NanoString based 22-gene assay is performed retrospectively to test concordance. We have pathology/IHC, CMA, and NanoString data on 26 infants and young children with medulloblastoma enrolled on HS 4. Pathology/IHC was able to assign samples to SHH, WNT, and non-WNT/non-SHH subgroups in all but two cases: one case was classified as Group 3, and the second as SHH by both CMA and NanoString. CMA was indeterminate in six cases, of which, pathology/IHC was able to assign all six samples aforementioned three subgroups. NanoString was indeterminate in two cases: one case was classified as SHH by CMA and pathology/IHC, and the second case was indeterminate by CMA but was assigned as non-WNT/non-SHH on pathology/IHC. There is excellent correlation between NanoString and combination of histopathology and CMA for core medulloblastoma subgrouping on HS 4. Methylation studies are ongoing.

## MBCL-14. A STUDY OF LOW-DOSE CRANIOSPINAL RADIATION THERAPY IN PATIENTS WITH NEWLY DIAGNOSED AVERAGE-RISK MEDULLOBLASTOMA

Aaron Mochizuki[1], Anna Janss[2], Sonia Partap[1], Paul Fisher[1], Yimei Li[3], Michael Fisher[3], and Jane Minturn[3]; [1]Lucile Packard Children's Hospital at Stanford University, Palo Alto, CA, USA, [2]Children's Healthcare of Atlanta, Atlanta, GA, USA, [3]Children's Hospital of Philadelphia, Philadelphia, PA, USA

INTRODUCTION: Medulloblastoma is one of the most common malignant brain tumors in children. To date, the treatment of average-risk (non-metastatic, completely resected) medulloblastoma includes craniospinal radiation therapy and adjuvant chemotherapy. Modern treatment modalities and now risk stratification of subgroups have extended the survival of these patients, exposing the long-term morbidities associated with radiation therapy. METHODS: We performed a single-arm, multi-institution study, seeking to reduce the late effects of treatment in patients with average-risk medulloblastoma prior to advances in molecular subgrouping. To do so, we

reduced the dose of craniospinal irradiation by 25% to 18 gray with the goal of maintaining the therapeutic efficacy as described in CCG 9892 with maintenance chemotherapy. RESULTS: 28 patients aged 3–30 years were enrolled across three institutions between April 2001 and December 2010. Median age at enrollment was 9 years with a median follow-up time of 11.7 years. The 3-year relapse-free (RFS) and overall survival (OS) were 78.6% (95% CI 58.4% to 89.8%) and 92.9% (95% CI 74.4% to 98.2%), respectively. The 5-year RFS and OS were 71.4% (95% CI 50.1% to 84.6%) and 85.7% (95% CI 66.3% to 94.4%), respectively. Toxicities were similar to those seen in other studies; there were no grade 5 toxicities. CONCLUSIONS: Given the known neurocognitive adverse effects associated with cranial radiation therapy, studies to evaluate the feasibility of dose reduction are needed. In this study, we demonstrate that select patients with average-risk medulloblastoma may benefit from reduced craniospinal radiation dose of 18 gray without impacting relapse-free or overall survival.

### MBCL-15. IMPACT OF MOLECULAR SUBGROUPS ON OUTCOMES FOLLOWING RADIATION TREATMENT RANDOMIZATIONS FOR AVERAGE RISK MEDULLOBLASTOMA: A PLANNED ANALYSIS OF CHILDREN'S ONCOLOGY GROUP (COG) ACNS0331

Jeff Michalski[1], Paul Northcott[2], Yimei Li[2], Catherine Billups[2], Kyle Smith[2], Peter Burger[3], Thomas Merchant[2], Amar Gajjar[2], TJ Fitzgerald[4], Gilbert Vezina[5], Maryam Fouladi[6], Roger Packer[5], Nancy Tarbell[7], and Anna Janss[8]; [1]Washington University School of Medicine, St. Louis, MO, USA, [2]St. Jude's Research Hospital, Memphis, TN, USA, [3]Johns Hopkins Hospital, Baltimore, MD, USA, [4]UMass Memorial Medical Center, Worcester, MA, USA, [5]Children's National Medical Center, Washington, DC, USA, [6]Cincinnati Children's Medical Center, Cincinnati, OH, USA, [7]Massachusetts General Hospital, Boston, MA, USA, [8]Children's Healthcare of Atlanta, Atlanta, GA, USA

The COG conducted a randomized trial for average-risk medulloblastoma (AR-MB). Patients age 3–21 years were randomized to a radiation boost to the whole posterior fossa (PFRT) or an involved field volume (IFRT) after receiving CSI. Patients age 3–7 years were also randomized to standard dose CSI (23.4Gy, SDCSI) or low dose CSI (18Gy, LDCSI). 464 evaluable patients were available to compare PFRT vs. IFRT and 226 for SDCSI vs. LDCSI. 380 cases had sufficient tissue for DNA methylation-based molecular classification: 362 confirmed medulloblastoma; 6 non-medulloblastoma; 12 inconclusive. Molecular subgrouping confirmed the following representation amongst the evaluable cohort: 156 Group 4 (43.1%), 76 Group 3 (21.0%), 66 SHH (18.2%), 64 WNT (17.7%). Five-year event-free survival (EFS) estimates were 82.5±2.7% and 80.5±2.7% for IFRT and PFRT, respectively (p=0.44). Five-year EFS estimates were 71.4±4.4% and 82.9±3.7% for LDCSI and SDCSI, respectively (p=0.028). EFS distributions differed significantly by subgroup (p<0.0001). Group 3 had the worst outcome, while WNT had the best outcome. There was a significant difference in EFS by RT group among SHH patients; SHH patients receiving IFRT arm had better EFS compared to PFRT (p=0.018). There was a significant difference in EFS distributions by CSI group in Group 4 patients; young Group 4 patients treated with SDCSI had better EFS compared to LDCSI (p=0.047). As previously reported, IFRT is noninferior to PFRT in all patients with AR-MB but LDCSI is worse than SDCSI in younger children. Significant differences in outcome by study randomization and molecular subgroup are observed.

### MBCL-16. EFFICACY OF CARBOPLATIN GIVEN CONCOMITANTLY WITH RADIATION AND ISOTRETINOIN AS A PRO-APOPTOTIC AGENT IN MAINTENANCE THERAPY IN HIGH-RISK MEDULLOBLASTOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

Sarah Leary[1,2], Roger Packer[3], Alok Jaju[4], Linda Heier[5], Peter Burger[6,7], Kyle Smith[8], Jeff Michalski[9], Yimei Li[8], Catherine Billups[8], Eugene Hwang[3], Amar Gajjar[8], Ian Pollack[10], Maryam Fouladi[11], Paul Northcott[8], and James Olson[12,1]; [1]Seattle Children's, Seattle, WA, USA, [2]University of Washington, Seattle, WA, USA, [3]Children's National Medical Center, Washington, DC, USA, [4]Ann and Robert H Lurie Children's Hospital, Chicago, IL, USA, [5]NYP/Weill Cornell Medical Center, New York, NY, USA, [6]Johns Hopkins University, Baltimore, MD, USA, [7]Sidney Kimmel Cancer Center, Baltimore, MD, USA, [8]St. Jude Children's Research Hospital, Memphis, TN, USA, [9]Washington University School of Medicine, St. Louis, MO, USA, [10]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA, [11]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [12]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

BACKGROUND: Metastasis, residual disease, and diffuse anaplasia are high-risk features in medulloblastoma. METHODS: This was a randomized phase 3 study. Patients age 3–21 years with high-risk medulloblastoma received (+/-) daily carboplatin with 36Gy craniospinal radiation and weekly Vincristine followed by six cycles of maintenance chemotherapy with Cisplatin, Cyclophosphamide and Vincristine (+/) 12 cycles of isotretinoin during and following maintenance. The primary endpoint was event-free survival, with exact log-rank test to compare arms. Retrospective molecular analysis included DNA methylation and exome sequencing. RESULTS: Of 294 medulloblastoma patients enrolled, 261 were eligible by central review of radiology and pathology, median age 8.6 years (range 3.3–21.2), 70% male, 189 (72%) with metastatic disease, 58 (22%) with diffuse anaplasia, 14 (5%) with >1.5cm2 residual disease. The 5-year EFS and OS for all subjects was 63%+4 and 73%+3, respectively. Isotretinoin randomization was closed due to futility. 5-year EFS was 66 + 5 with carboplatin versus 59 + 5 without (p=0.11), with effect exclusively observed in Group 3 subtype: 73%+8 with carboplatin versus 54%+9 without (p<0.05). Overall survival differed by molecular subgroup (p=0.006): WNT 100%, SHH 54%+11, Group 3 74%+6, Group 4 77%+5 at 5 years. *MYC* amplification or isochromosome 17 were unfavorable in Group 3 (p=0.029). Chromosome 11 loss or chromosome 17 gain were favorable in group 4 (p<0.001). No survival difference was observed with *TP53* mutation in SHH subtype in this high-risk cohort. CONCLUSIONS: Therapy intensification with carboplatin improved survival for high-risk group 3 medulloblastoma. These findings further support an integrated clinical and molecular risk stratification for medulloblastoma.

### MBCL-17. METASTATIC MEDULLOBLASTOMA CAN BE CURED WITHOUT EXCISION OF THE PRIMARY TUMOR: A SINGLE CENTER EXPERIENCE

Rina Dvir[1,2], Shlomi Constantini[3,4], Jonathan Roth[3,4], Hila Rosenfeld-Keidar[1], Inna Ospovat[5], and Ronit Elhasid[1,2]; [1]Pediatric Hemato-Oncology Department, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel, [2]Sackler Medical School, Tel-Aviv University, Tel-Aviv, Israel, [3]Pediatric Neurosurgery Department, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel, [4]Sackler Medical School, Tel-Aviv University, Tel-Aviv, Israel, [5]Radiotherapy Department, Tel-Aviv Sourasky Medical Center, Tel-aviv, Israel

INTRODUCTION: Metastatic medulloblastoma is a challenging disease The current clinical approach advocates removal of the primary tumor in the posterior fossa despite evidence of metastatic disease and administer oncologic treatment within several weeks: Infants of 3–4 years are treated by tandem high dose chemotherapy with stem cell support (ACNS0334 protocol), while older children are given radiotherapy and tandem high dose chemotherapy with stem cell support (SJMB03 protocol). We postulate that a resection of the primary tumor is not obligatory, and a biopsy may suffice in order to enable prompt oncological treatment without affecting the long-term survival. PATIENTS AND METHODS: Between 2010-2019 7 patients with metastatic medulloblastoma (median age 4.5, age 1–10) were treated with biopsy only, five spinal and two from the primary tumor. Six children had a concurrent VP shunt. Four presented with cord compression, and two with neurological deterioration. Four needed emergency radiotherapy. Two infants received protocol ACNS0334, five patients received protocol SJMB03. RESULTS: Six patients (85%) survived; .3 patients are long term survivors (> 5 years), 2 patients are in remission for 2–3 years, one patient is on active therapy. Only 1 patient died after a late (4 years) metastatic relapse not in the posterior fossa. CONCLUSIONS: Metastatic medulloblastoma can be cured without excision of the primary tumor and without mutilating surgery. Long term prognosis is probably more attributable to disease subtype and prompt oncologic treatment. This approach merits further studies and may have implications on treatment of non-metastatic tumors.

### MBCL-18. ANALYSIS OF DNA METHYLATION PROFILES OF PEDIATRIC MEDULLOBLASTOMAS: EXPERIENCE AT THE BAMBINO GESÙ CHILDREN'S HOSPITAL

Evelina Miele, Giuseppe Petruzzellis, Lucia Pedace, Antonella Cacchione, Andrea Carai, Giovanna Stefania Colafati, Francesca Diomedi Camassei, Sabrina Rossi, Franco Locatelli, and Angela Mastronuzzi; Bambino Gesù Children's Hospital, Rome, Italy

BACKGROUND: Medulloblastoma is the most frequent malignant brain tumor in children, still resulting fatal in about one third of affected patients. An accurate diagnosis is essential for correct therapeutic stratification. The DNA methylation profile (DMP) is a combination of changes in DNA methylation and genetic features that reflect the cell of tumor origin. DMP contributed to classify Medulloblastoma into four subgroups: WNT, SHH, Group 3/4 (the latter recently further subdivided into 8 subclasses). Each Methylation is associated with different genetic, demographic and clinical characteristics. We report our experience on Medulloblastoma molecular classification based on DMP. MATERIALS AND METHODS: 54 Medulloblastoma patients (28 males, 26 females) were selected. The DMP analysis was carried out via IlluminaEPICarrays. The results were obtained using the brain tumor classifier (Capper, 2018). RESULTS: In all cases the DMP allowed to classify the neoplasm, with an optimal score, in a defined methylation class. 10 WNTs, 15 SHHs, 10 Group 3, 19 Group 4 were found. Groups 3/4 were further re-