and 5 without adequate details of treatment or outcomes) were excluded from the survival analysis which was restricted to 54 patients. At a median follow-up of 66 months, Kaplan-Meier estimates of 5-year progression-free survival and overall survival were 87.9% and 92.8% respectively. Traditional high-risk features such as age, residual tumor (>1.5cm^2) and leptomeningeal metastases (M+) did not emerge as significant prognostic factors for survival in this molecularly-characterized WNT-MB cohort. CONCLUSION: WNT-MB patients have excellent survival outcomes irrespective of traditional high-risk features suggesting the need for more tailored and refined risk-stratification with potential de-intensification of therapy. ACKNOWLEDGEMENTS: Brain Tumor Foundation (BTF) of India

MEDB-28. CDK9 IS A DRUGGABLE MEDIATOR SUSTAINING MYC-DRIVEN CIRCUITRY IN MEDULLOBLASTOMA

Krishna Madhavan, Faye Walker, Dong Wang, Lays Martin Sobral, Ilango Balakrishnan, Angela Pierce, Natalie Serkova, Nicholas Foreman, Sujatha Venkataraman, Rajeev Vibhakar, Nathan Dahl; University of Colorado, Aurora, CO, USA

BACKGROUND: Though long recognized as a master regulator of cell proliferation across a wide range of cancers, Myc has proven elusive to direct therapeutic targeting. The CDK9-containing PTEFb, complexed with either BRD4 or SEC, facilitates Myc-driven transcriptional programs and is necessary for sustaining expression of Myc itself. Advances in development of clinical-grade CDK9 inhibitors creates an opportunity to examine this as a rational therapy for Myc-driven medulloblastoma. METHODS: We used both RNAi depletion and a panel of pharmacologic agents to characterize the mechanistic and functional consequences of CDK9 inhibition in Myc-driven medulloblastoma. We used a combination of clonogenic assays and live cell imaging to assess the cytotoxic effects of CDK9 activity loss. We then performed a combination of CUT&RUN and RNA-seq to evaluate alterations to Myc binding and downstream Myc-driven transcriptional programs. Finally, we employed orthotopic xenograft models of medulloblastoma to assess CNS penetration, tolerability, and anti-tumor efficacy of lead CDK9i candidate compounds. RESULTS: Genetic or pharmacologic inhibition of CDK9 leads to a loss of Myc expression and downregulation of hallmark Myc-driven transcriptional programs. This corresponds to a loss of cell fitness, as measured by decreased proliferation and clonogenic potential. Clinically relevant CDK9 inhibitors show variable efficacy in vivo, but the CNS-penetrant zotiraciclib achieved a significant prolongation in xenograft survival. CONCLUSION: CDK9 catalytic activity represents a druggable vulnerability underpinning Myc-driven transcriptional programs. The development of CNS-penetrant CDK9 inhibitors may open new avenues for rational therapy in these high-risk medulloblastomas.

MEDB-29. APPLICATION OF ROTTERDAM POST-OPERATIVE CEREBELLAR MUTISM SYNDROME PREDICTION MODEL TO PATIENTS OPERATED FOR MEDULLOBLASTOMA IN A SINGLE INSTITUTION

Raja Khan[1], Bush Savannah[2], Frederick Boop[1], Amar Gajjar[1], Zoltan Patay[1], Giles Robinson[1], Paul Klimo[1]; [1]St. Jude Children's Research Hospital, Memphis, Tennessee, USA. [2]School of Medicine, University of Tennessee, Memphis, Tennessee, USA

BACKGROUND: Post-operative cerebellar mutism syndrome (CMS) develops in up to 30% of children. The Rotterdam model (RM) predicts a 66% risk of CMS in patients with a score ≥100. However, our findings suggested that surgical experience contributes to CMS risk. The aim of this study was to retrospectively apply the RM and report incidence of CMS in high-risk patients from our institution. METHODS: Participants had to have first tumor resection at our institution and be enrolled on SJMB12 protocol (NCT01878617). All participants got structured serial neurologic evaluations. CMS, when present, was categorized into type 1 (complete mutism) and type 2 (paucity of speech with an inability to string 3-word sentence). Rotterdam score is calculated based on pre-operative imaging parameters and study neurologist (RBK) obtained it while blinded to CMS status. RESULTS: Of the 40 (14 female, 26 male) study participants, 4 (10%) had CMS (3 CMS1, 1 CMS2). Median age at tumor resection was 11.7 years (range 3.5-17.8). Tumor location was midline in 30 (75%), right lateral 6 (15%) and left lateral 4 (10%). Median Evans index was 0.3 (0.2-0.4) and 34 (85%) were ≥0.3 (indicative of hydrocephalus); 5 participants needed ventricular shunt. Median tumor volume was 50 cm3 (2-180.6). Gross total resection was achieved in 35 (87.5%), near total in 4 (10%) and subtotal in 1. Twelve tumors were SHH, 7 WNT, and 29 NWNS. Median RM score was 90 (25 – 145). Eighteen participants had a score of ≥100 and 16.7% of these (n=3) had CMS. Scores for the 4 with CMS were 85, 125, 145 and 145. CONCLUSION: At our institution, the incidence of CMS in those that had RM of ≥100 was much lower than reported risk of 66%. This data supports our hypothesis that neurosurgical experience remains a significant risk factor in the development of CMS.

MEDB-30. SUBCLASSIFICATION OF GROUP 3/4 MEDULLOBLASTOMA AS A POTENTIAL PROGNOSTIC BIOMARKER TO REDUCE THE DOSE OF CRANIOSPINAL IRRADIATION IN PATIENTS WITH METASTATIC TUMORS: A JAPANESE PEDIATRIC MOLECULAR NEURO-ONCOLOGY GROUP STUDY

Kohei Fukuoka[1], Jun Kurihara[2], Makiko Mori[1], Yuki Arakawa[1], Ema Yoshioka[3], Tomoko Shofuda[3], Yuko Matsushita[4,5], Yuko Hibiya[4,5], Satoko Honda[6], Atsuko Nakazawa[6], Chikako Kiyotani[7], Naoki Kagawa[8], Kai Yamasaki[9], Ryo Ando[10], Dai Keino[11], Yosuke Miyairi[12], Takuya Akai[13], Masayuki Kanamori[14], Joji Ishida[15], Young-Soo Park[16], Atsufumi Kawamura[17], Atsushi Sasaki[18], Ryo Nishikawa[19], Isao Date[15], Motoo Nagane[20], Katsuyoshi Koh[1], Koichi Ichimura[4,5], Yonehiro Kanemura[3]; [1]Department of Hematology/Oncology, Saitama Children's Medical Center, Saitama, Japan. [2]Department of Neurosurgery, Saitama Children's Medical Center, Saitama, Japan. [3]Department of Biomedical Research and Innovation, Institute for Clinical Research, Osaka National Hospital, National Hospital Organization, Osaka, Japan. [4]Division of Brain Tumor Translational Research, National Cancer Center Research Institute, Tokyo, Japan. [5]Department of Brain Disease Translational Research, Juntendo University Faculty of Medicine, Tokyo, Japan. [6]Department of Clinical Research, Saitama Children's Medical Center, Saitama, Japan. [7]Children's Cancer Center, National Center for Child Health and Development, Tokyo, Japan. [8]Department of Neurosurgery, Osaka University Graduate School of Medicine, Osaka, Japan. [9]Department of Pediatric Hematology and Oncology, Osaka City General Hospital, Osaka, Japan. [10]Department of Neurosurgery, Chiba Children's Hospital, Chiba, Japan. [11]Division of Hematology/Oncology, Kanagawa Children's Medical Center, Yokohama, Japan. [12]Department of Neurosurgery, Nagano Children's Hospital, Nagano, Japan. [13]Departments of Neurosurgery, Graduate School of Medicine and Pharmaceutical Science, University of Toyama, Toyama, Japan. [14]Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Japan. [15]Department of Neurological Surgery, Okayama University Graduate School, Okayama, Japan. [16]Department of Neurosurgery Nara Medical University, Nara, Japan. [17]Department of Neurosurgery, Hyogo Prefectural Kobe Children's Hospital, Kobe, Japan. [18]Department of Pathology, Saitama Medical University, Moroyama, Japan. [19]Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, Hidaka, Japan. [20]Department of Neurosurgery, Kyorin University Faculty of Medicine, Mitaka, Japan

BACKGROUND: In patients with medulloblastoma, one of the most significant challenges is to reduce the dose of craniospinal irradiation (CSI) to minimize neurological sequelae in survivors. Molecular characterization of patients treated using lower-dose CSI rather than standard therapy is important for further reducing the treatment burden. METHODS: We conducted DNA methylation analysis using an Illumina Methylation EPIC array to investigate molecular prognostic markers in 38 patients with medulloblastoma who were registered in the Japan Pediatric Molecular Neuro-Oncology Group and were treated using lower-dose CSI rather than standard-dose radiation therapy. RESULTS: Among the patients, 23 were classified as having a "standard-risk" and 15 as having a "high-risk" according to the classic classification based on tumor resection rate and presence of metastasis, respectively. The median follow-up period was 71.5 months. The median CSI dose was 18 Gy in both groups, and 10 patients in the "high-risk" group received a CSI dose of 23.4 Gy or 24 Gy. Molecular subgrouping revealed the "standard-risk" cohort included 5 WNT, 2 SHH, and 16 Group 3/4 cases; all 15 patients in the "high-risk" cohort had Group 3/4 medulloblastoma. Among the patients with Group 3/4 medulloblastoma, 13 of the 16 "standard-risk" patients were subclassified as subtypes I, IV, VI, and VII, which were associated with a good prognosis according to the novel sub-subclassification among Group 3/4 medulloblastomas. However, only 6 of the 15 "high-risk" patients were included in the subtypes. The good prognostic subtype cases among "high-risk" cohort were all survived without recurrence, in contrast to a worse prognosis (5-year progression free survival=33.3%; p=0.01) of the other cases. CONCLUSION: Although these findings require validation in a larger cohort, the present findings suggest that the novel sub-subclassification of Group 3/4 medulloblastoma may be a promising prognostic biomarker for reducing the dose of CSI in patients with metastatic medulloblastoma.

MEDB-31. THE CLINICAL SIGNIFICANCE OF EXTENT OF RESECTION IN MEDULLOBLASTOMA

Claire Keeling, Simon Davies, Debbie Hicks, Steven Clifford; Wolfson Childhood Cancer Research Centre, Newcastle University Centre for Cancer, Newcastle-upon-Tyne, Tyne and Wear, United Kingdom

Medulloblastoma (MB) patients determined to have a sub-total resection (STR), defined by >1.5cm^2 post-surgical tumour residuum, receive intensified treatment regimes, but recently the designation of STR as a high risk feature is being questioned. We aimed to assess the clinical correlates of ex-

tent of resection (EOR) and its impact on survival, with particular consideration of EOR in relation to the four MB consensus molecular subgroups (WNT, SHH, Group 3, Group 4). We collected data from 1113 patients (n=419, UK CCLG institutions; n=694, published data) representing the largest ever combined cohort constructed to assess the impact of EOR in medulloblastoma. We performed association analyses and univariate/multivariate survival analysis using Kaplan-Meier, log-rank and Cox proportional hazard modelling, analysing overall survival (OS) cohort-wide and with reference to molecular subgroups and clinical features. Association analysis of the combined cohort evidenced that infant patients were more likely to have STR (p=0.02). In this whole-cohort analysis, EOR was significantly associated with survival in univariate analysis (HR 1.64, 95% CI 1.30-2.07, p=<0.001) but not in multivariate analysis. STR was variably prognostic in sub-cohort analyses of specific demographics and molecular subgroup; worse outcomes were observed in patients <5 years in SHH (p=0.044) and Group 4 (p=0.044). This was true for WNT patients >5 years old at diagnosis (p=0.034) although numbers were small and require validation in even larger cohorts. In this cohort of >1100 MBs, STR was significantly associated with a lower OS in univariate analysis, but this was driven by specific disease contexts (SHH and Group 4 patients <5 years old). STR was not independently prognostic overall or in any setting. We recommended that surgeons should continue to pursue maximal *safe* resection for all MB patients but suggest that consideration of STR as a high-risk feature should be disease context specific.

MEDB-32. REDUCING TREATMENT-RELATED TOXICITY FOR CHILDREN WITH WNT-ACTIVATED MEDULLOBLASTOMA

Jessica Taylor, Joseph Toker, Katherine Masih, Erica Nathan, Sabrina Terranova, Richard Gilbertson; CRUK Cambridge Institute, Cambridge, United Kingdom

WNT-medulloblastoma has an excellent prognosis, with an overall survival rate of 90% among children receiving standard-of-care (SOC) surgical resection, radiotherapy, and chemotherapy. Unfortunately, while curative, this treatment is associated with major, long-term, debilitating motor, developmental, and neuroendocrine side effects. Therefore, it is crucial we develop effective, less toxic therapies for these children. Similarities have been demonstrated between cancer cell lysosomes and those of patients with Niemann-Pick, a lysosomal storage disease characterised by lysosomal fragility and sphingomyelin accumulation. A class of drugs known as Functional Inhibitors of Acid Sphingomyelinase (FIASMAs), increase lysosomal sphingomyelin and destabilise the cancer cell's more fragile lysosomal membrane which leads to the induction of cell-death pathways via lysosomal membrane permeabilisation. Loratadine, an antihistamine with high FIASMA activity, consistently induced lysosomal membrane permeabilisation, leading to increased cell-death, in our panel of mouse and human WNT-medulloblastoma lines. Loratadine exhibited no detrimental effect on normal mouse embryonic stem cells from the lower rhombic lip – the putative cell of origin in WNT-medulloblastoma. Luciferase-expressing mouse WNT-medulloblastoma cells were orthotopically implanted into CD1-nude mice and monitored for tumour development via bioluminescent imaging. Upon tumour engraftment, mice were subjected to reduced SOC (radiotherapy and adjuvant vincristine) plus a clinically relevant dose of loratadine. Response and survival were compared to mice treated with full SOC (radiotherapy, vincristine, cisplatin, and etoposide). Mice treated with 2mg/kg/day of loratadine following reduced SOC demonstrated increased survival when compared to those treated with full SOC (p=0.02) along with a significant reduction in weight loss during treatment (p=<0.0001). This work suggests that loratadine, or other FIASMA compounds, may be good alternative adjuvant therapies for WNT-medulloblastoma. Using less toxic adjuvants could improve long-term outcomes through reducing therapeutic related toxicities for children with this devastating disease.

MEDB-33. THE LANDSCAPE OF ECDNA IN MEDULLOBLASTOMA

Owen Chapman[1], Sunita Sridhar[1,2], Shanqing Wang[1], Jon Larson[3], Robert Wechsler-Reya[3], Jill Mesirov[1], Lukas Chavez[1]; [1]UC San Diego, La Jolla, CA, USA. [2]Rady Children's Hospital, San Diego, CA, USA. [3]Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA

Extrachromosomal circular DNA (ecDNA) is an important driver of aggressive cancers, including medulloblastoma (MB), the most common malignant pediatric brain tumor. To assess the clinical importance of ecDNA in MB, we applied computational methods to detect ecDNA in the genomes of a cohort of 468 MB patients and 31 MB model systems. Among patients, ecDNA was detected in 18% of tumors and carried a threefold greater risk of mortality. Affected genomic loci harbor up to hundredfold amplification of oncogenes including MYC, MYCN, TERT, and other novel putative oncogenes. Between sequential patient biopsies at initial diagnosis and subsequent relapse, we observed structural variation at ecDNA loci and generation of new ecDNA sequences. Among model systems, ecDNA was found in 19 of 31 genomes (61%). Although ecDNA was far more prevalent among MB models than patients, the ecDNA genomic sequences were conserved between most patient-derived xenograft (PDX) models and the human tumors from which they were made. To elucidate the functional regulatory landscapes of ecDNAs in MB, we generated transcriptional (RNA-seq), accessible chromatin (ATAC-seq), and chromatin interaction (Hi-C) profiles of 6 MB tumor samples. In each case, we identified regulatory interactions that cross fusion breakpoints on the ecDNA, representing potential "enhancer rewiring" events which may contribute to transcriptional activation of co-amplified oncogenes. To test this hypothesis, we are currently conducting in vitro CRISPRi screens targeting regulatory regions on the ecDNA of a MB cell line to determine whether these enhancers promote proliferation. Using single-cell sequencing, we have also begun exploring intratumoral heterogeneity of ecDNA in a p53-mutant SHH MB patient tumor and its corresponding PDX model. In summary, our study analyzes the frequency, diversity, and functional relevance of ecDNA across MB subgroups and provides strong justification for continued mechanistic studies of ecDNA in MB with the potential to uncover new therapeutic approaches.

MEDB-34. A VERY RARE CASE: MEDULLOBLASTOMA RELAPSE WITH BONE MARROW INFILTRATION IN A TODDLER

Claudia Zinke[1], Gudrun Fleischhack[2], Julia Hauer[1], Björn Sönke Lange[1], Jenny Dörnemann[1], Gabriele Hahn[3], Gabriele Schackert[4], Kristin Gurtner[5], Matthias Meinhardt[6], Korinna Jöhrens[6], Ralf Knöfler[1]; [1]University Hospital Carl Gustav Carus, Department of Pediatrics, Pediatric Hematology and Oncology, Dresden, Germany. [2]University Hospital of Essen; Department of Pediatrics, Pediatric Hematology and Oncology, Pediatrics III, Essen, Germany. [3]University Hospital Carl Gustav Carus, Department of Diagnostic and Interventional Radiology, Dresden, Germany. [4]University Hospital Carl Gustav Carus, Department of Neurosurgery, Dresden, Germany. [5]University Hospital Carl Gustav Carus, Department of Radiation Therapy and Radiation Oncology, Dresden, Germany. [6]University Hospital Carl Gustav Carus, Department of Pathology, Dresden, Germany

We report about a female toddler congenitally deaf and diagnosed with a non-metastatic desmoplastic medulloblastoma (SHH activated, *TP53*-wt, variant in *LDB1* gene). No tumor predisposition syndrome was found. After complete tumor resection the patient was treated according to I-HIT-MED-Guidance protocol. Five months later an asymptomatic localised relapse (same histology, *PTEN* frameshift deletion, *TERT* mutation, *LDB1* mutation) detected by routine MRI was treated by complete resection, craniospinal irradiation and an antiangiogenic regimen adapted from the MEMMAT scheme including fenofibrate, thalidomide, celecoxib, topotecan, temozolomide, bevacizumab and intraventricular cytarabine. Before start of systemic treatment blood cell counts were normal. In the second cycle we had to interrupt chemotherapy due to a leukopenia while continuing the antiangiogenic treatment. In order to avoid relevant bone marrow toxicity chemotherapy doses were reduced. Nevertheless we had to stop the fourth cycle because of a severe pancytopenia. Same time the girl presented with fever, neck and leg pain. A full blood count showed: hemoglobin 6.92 g/dl, leukocytes 640/µl, platelets 8,000/µl. Suspecting an infection supported by the presence of a high CrP value of 230 mg/l the patient was treated with i.v. antibiotics. MRI showed an unspecific retropharyngeal soft tissue augmentation, a pleural effusion and high T2 signals in multiple vertebral bodies but no central tumor relapse. The bone marrow diagnostics revealed a diffuse medulloblastoma cell infiltration with the known *PTEN* frameshift deletion and *LDB1* mutation. The liquor was tumor-cell free. We report on an extremely rare case of an early local relapse of desmoplastic medulloblastoma progressing to a diffuse bone marrow infiltration in a toddler. The girl died due to therapy resistance 9 weeks after bone marrow relapse. It remains unclear whether the fatal course was related to the hereditary deafness syndrome and the molecular alterations of the tumor.

MEDB-35. RELATIONSHIP BETWEEN GENETIC PROFILE, HISTOLOGY, CLINICAL FEATURES AND LONG-TERM OUTCOME IN YOUNG CHILDREN MEDULLOBLASTOMA (YCMB) TREATED WITH UPFRONT HIGH DOSE CHEMOTHERAPY (HDCT) IN ITALY

Maria Luisa Garrè[1], Maura Massimino[2], Francesca Romana Buttarelli[3], Lorenza Gandola[4], Salvina Barra[5], Felice Giangaspero[3,6], Tobias Goschzik[7], Veronica Biassoni[2], Lorenza Pastorino[8], Angela Pistorio[9], Torsten Pietsch[7]; [1]Neuroncology Unit, IRCCS- Istituto Giannina Gaslini, Genoa, Italy. [2]Pediatric Oncology Unit, Fondazione IRCCS-Istituto Nazionale dei Tumori, Milan, Italy. [3]Department of Radiologic,Oncologic and Anatomopathological Sciences, University La Sapienza, Rome, Italy. [4]Department of Radiation Oncology, Fondazione IRCCS-Istituto Nazionale dei Tumori, Milan, Italy. [5]Radiotherapypy Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy. [6]IRCCS Neuromed, Pozzilli, Isernia, Italy. [7]Department of Neuropathology, University of Bonn Medical Center, Bonn, Germany. [8]Genetics of rare cancers, IRCCS Ospedale Policlinico