the course of LE, and to investigate its impact on long-term neurocognitive and behavioural outcome. METHODS: A French retrospective, multicenter study including 35 children under 5 years of age, treated between 2009 and 2017, with a median follow up of 72 months. All follow-up MRIs including assessment of the severity of the LE (Fazekas and CTCAE grading) and all NP evaluations were centrally rewieved. RESULTS: 25/34 evaluable patients presented a LE during follow up, in a median delay of 2 months (1 - 17 months) after the start of chemotherapy. Grade 2 and 3 abnormalities were correlated with higher cumulative dose of ITV -MTX (p=0,01). Full Scale IQ (FSIQ) and Wechsler indexes were in the average or low average of the reference population. FSIQ was deficient in 7/20 evaluable patients. Processing speed (PSI) was the most frequently impaired neurocognitive domain: 9/20 patients with borderline or very low score, all having received a significantly higher cumulative dose of ITV-MTX (p=0,04). A decrease in overall NP scores was observed in patients for whom grade 2 or 3 LE persisted at the end of follow-up with an average FSIQ estimated at 82.1 (SD 16.9) versus 94.2 (SD 20.6). This decrease was significant for PSI (p=0,049). LE and neurocognitive impairments were not correlated with a younger age at diagnosis. CONCLUSION: This study confirmed the responsibility of MTX, and in particular ITV-MTX therapy in the onset and, most often, persistence of LE and its association with neurocognitive disorders.

MEDB-14. CLINICAL OUTCOME OF PEDIATRIC MEDULLOBLASTOMA PATIENTS WITH LI-FRAUMENI SYNDROME

Anna Kolodziejczak[1,2], Lea Guerrini-Rousseau[3], Julien Masliah Planchon[4], Jonas Ecker[1,5], Florian Selt[1,5], Martin Mynarek[6,7], Denise Obrecht[6], Martin Sill[1,8], Steffen Hirsch[1,9], Dominik Sturm[1,5], Sebastian M. Waszak[10,11], Vijay Ramaswamy[12,13], Virve Pentikainen[14], Haci Ahmet Demir[15], Steven C. Clifford[16], Ed Schwalbe[16,17], Luca Massimi[18], Matija Snuderl[19], Kristyn Galbraith[19], Matthias A. Karajannis[20], Katie Hill[20], Bryan Li[20], Christine L. White[21], Shelagh Redmond[22], Loizou Loizos[23], Marcus Jakob[24], Uwe Kordes[6], Irene Schmid[25], Julia Hauer[26], Claudia Blattmann[27], Maria Filippidou[28], Wolfram Scheurlen[29], Udo Kontny[30], Kerstin Grund[9], Christian Sutter[9], Torsten Pietsch[31], Cornelis M. van Tilburg[1,32], Stephan Frank[33], Denis M. Schewe[34], David Malkin[35], Michael D. Taylor[12], Uri Tabori[13], Eric Bouffet[36], Marcel Kool[1,8], Felix Sahm[1,37], Andreas von Deimling[2,37], Andrey Korshunov[2,37], Katja Von Hoff[38], Christian Kratz[39], David T.W. Jones[1,40], Stefan Rutkowski[6], Olaf Witt[1,5], Gaelle Bougeard[41], Kristian W. Pajtler[1,5], Stefan M. Pfister[1,5], Franck Bourdeaut[4], Till Milde[1,5]; [1]Hopp Children's Cancer Center (KiTZ), Heidelberg, Germany. [2]CCU Pediatric Oncology, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany. [3]Gustave Roussy Institute, Paris, France. [4]SIREDO Pediatric Oncology Center, Curie Institute, Paris-Science Lettres University, Paris, France. [5]Pediatric Oncology, Hematology, and Immunology, Center for Child and Adolescent Medicine, Heidelberg University Hospital, Heidelberg, Germany. [6]Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [7]Mildred Scheel Cancer Career Center HaTriCS[4], University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [8]Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany. [9]Institute of Human Genetics, University Hospital Heidelberg, Heidelberg, Germany. [10]Centre for Molecular Medicine Norway (NCMM), Nordic EMBL Partnership, University of Oslo and Oslo University Hospital, Oslo, Norway. [11]Department of Neurology, University of California, San Francisco, CA, USA. [12]Division of Neurosurgery, Program in Developmental and Stem Cell Biology, Arthur and Sonia Labatt Brain Tumour Research Centre, Hospital for Sick Children, Toronto, Ontario, Canada. [13]Division of Hematology and Oncology, Hospital for Sick Children, Toronto, Ontario, Canada. [14]Division of Hematology-Oncology and Stem Cell Transplantation, Children's Hospital, Helsinki University Hospital, Helsinki, Finland. [15]Department of Pediatric Hematology-Oncology, Private Memorial Ankara Hospital, Ankara, Turkey. [16]Wolfson Childhood Cancer Research Centre, Newcastle University Centre for Cancer, Newcastle, United Kingdom. [17]Applied Sciences, Northumbria University, Newcastle, United Kingdom. [18]Department of Pediatric Neurosurgery, Catholic University Medical School, Rome, Italy. [19]Department of Pathology, New York University Langone Health, New York City, NY, USA. [20]Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York City, NY, USA. [21]Victorian Clinical Genetics Services, Parkville, Australia. [22]Swiss Childhood Cancer Registry, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [23]Pediatric Oncology/Hematology/Immunology at the Medical School of the University of Nicosia, Nicosia, Cyprus. [24]Department of Paediatric Haematology, Oncology and Stem-Cell Transplantation, University Hospital Regensburg, Regensburg, Germany. [25]Paediatric Haematology and Oncology, Dr. von Hauner Children's Hospital, Ludwig Maximilian University, Munich, Germany. [26]Pediatric Haematology and Oncology, University Hospital Carl Gustav Carus, Dresden, Germany. [27]Paediatric Haematology, Oncology and Immunology, Olgahospital, Stuttgart, Germany. [28]Division of Pediatric Hematology-Oncology, First Department of Pediatrics, National and Kapodistrian University of Athens, "Aghia Sophia" Children's Hospital, Athens, Greece. [29]Paediatric Haematology and Oncology, Cnopfsche Paediatric Clinic, Nurnberg, Germany. [30]Department of Paediatric Haematology, Oncology and Stem-Cell Transplantation, Paediatric Clinic, University Hospital Aachen, Aachen, Germany. [31]Neuropathology Institute, DGNN Brain Tumor Reference Center, University of Bonn Medical Center, Bonn, Germany. [32]Department of Pediatric Oncology, Hematology, Immunology and Pulmonology, Heidelberg University Hospital, Heidelberg, Germany. [33]Division of Neuropathology, Institute of Pathology, Basel University Hospital, Basel, Switzerland. [34]Department of Pediatrics, Otto-von-Guericke University Magdeburg, Magdeburg, Germany. [35]Genetics and Genome Biology Program, The Hospital for Sick Children, Toronto, Ontario, Canada. [36]The Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, Toronto, ON M^5G $^1X^8$, Canada; Division of Haematology / Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada. [37]Neuropathology, Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany. [38]Department of Pediatric Oncology and Hematology, Charité – Universitätsmedizin Berlin, Berlin, Germany. [39]Pediatric Haematology and Oncology, Hannover Medical School, Hannover, Germany. [40]Pediatric Glioma Research, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany. [41]Inserm U^{1245} Cancer and Brain Genomics, UNIROUEN, Normandie Univ, and Department of Genetics, Rouen University Hospital, Rouen, France

PURPOSE: The prognosis for SHH-medulloblastoma (MB) patients with Li-Fraumeni syndrome (LFS) is poor. Due to lack of comprehensive data for these patients, it is challenging to establish effective therapeutic recommendations. We here describe the largest retrospective cohort of pediatric LFS SHH-MB patients to date and their clinical outcomes. PATIENTS AND METHODS: N=31 patients with LFS SHH-MB were included in this retrospective multicenter study. *TP53* variant type, clinical parameters including treatment modalities, event-free survival (EFS) and overall survival (OS), as well as recurrence patterns and incidence of secondary neoplasms, were evaluated. RESULTS: All LFS-MBs were classified as SHH subgroup, in 30/31 cases based on DNA methylation analysis. The majority of constitutional *TP53* variants (72%) represented missense variants, and all except two truncating variants were located within the DNA-binding domain. 54% were large cell anaplastic, 69% gross totally resected and 81% had M0 status. The 2-(y)ear and 5-(y)ear EFS were 26% and 8,8%, respectively, and 2y- and 5y-OS 40% and 12%. Patients who received post-operative radiotherapy (RT) followed by chemotherapy (CT) showed significantly better outcomes (2y-EFS:43%) compared to patients who received CT before RT (30%) ($p<0.05$). The 2y-EFS and 2y-OS were similar when treated with protocols including high-dose chemotherapy (EFS:22%, OS:44%) compared to patients treated with maintenance-type chemotherapy (EFS:31%, OS:45%). Recurrence occurred in 73.3% of cases independent of resection or M-status, typically within the radiation field (75% of RT-treated patients). Secondary malignancies developed in 12.5% and were cause of death in all affected patients. CONCLUSIONS: Patients with LFS-MBs have a dismal prognosis. This retrospective study suggests that upfront RT may increase EFS, while intensive therapeutic approaches including high-dose chemotherapy did not translate into increased survival of this patient group. To improve outcomes of LFS-MB patients, prospective collection of clinical data and development of treatment guidelines are required.

MEDB-15. DYNAMIC CHROMATIN ALTERATION INDUCES ONCOGENIC HIJACKING BY ESSENTIAL TRANSCRIPTIONAL FACTORS DURING SHH MEDULLOBLASTOMA TUMORIGENESIS

Ryo Shiraishi[1], Gabriele Cancila[2], Kohei Kumegawa[3], Patricia da Silva[4], Owen Chapman[5], Wang Wanchen[1], Maki Jami[1], Mikio Hoshino[1], Stefan Pfister[4], Lukas Chavez[5], Reo Maruyama[3], Olivier Ayrault[2], Daisuke Kawauchi[1]; [11]. National Center of Neurology and Psychiatry, Tokyo, Japan. [22]. Institut Curie, Paris, France. [33]. Japanese Foundation for Cancer Research, Tokyo, Japan. [44]. Hopp Children´s Cancer Center Heidelberg (KiTZ), German Cancer Research Center (DKFZ) and Heidelberg University Hospital, Heidelberg, Germany. [55]. University of California San Diego, San Diego, USA

Medulloblastoma is a malignant brain tumor that occurs in the cerebellum, most frequently in children. Medulloblastoma is molecularly classified into four major groups, and therapies are now being developed according to the nature of these groups and subgroups. However, there are currently no effective molecularly targeted drugs for most of these groups. In recent years, we have been analyzing the genomes of medulloblastomas to identify genetic mutations involved in tumorigen-

esis. Among them, mutations in chromatin modifiers are frequently detected in medulloblastoma, suggesting the importance of alterations in the epigenome in tumor development. However, it remains unclear how epigenomic changes are involved in tumorigenesis. Here, we have used the SHH-group medulloblastoma (MB-SHH) mouse model to understand the epigenomic changes during tumor development and identify new therapeutic targets for medulloblastoma. To this end, we utilized an Atoh1-EGFP:Ptch1+/- mice that specifically label cerebellar granule cell progenitors (GNPs) that are known to be the cellular origin of MB-SHH, preneoplastic (PNCs) and tumor cells with EGFP during MB-SHH formation. Following FACS-based collection of EGFP-positive cells, comparative ATAC-seq analysis revealed that the open chromatin regions dynamically changed during transformation of GNPs into PNCs with enrichment of nuclear factor I (NFI) binding motifs. Cut & Tag analysis on these cells showed that NFI proteins bound chromatin regions that become more accessible during tumorigenesis, suggesting that NFI could play an important role in tumorigenesis after the epigenomic changes. Indeed, CRISPR-engineered in vivo somatic deletion of Nfia and/or Nfib prevented hyperplasia formation, confirming their essential role in tumor initiation. Knockdown of either NFIA or NFIB in patient-derived xenograft models also attenuated tumor growth. Thus, our study has uncovered a novel oncogenic mechanism that contributes to the development of MB-SHH tumors via alterations of accessible chromatin and aberrant DNA binding of NFI transcription factors.

MEDB-16. PERSISTENT RADIOLOGICAL LESIONS AT THE END OF PRIMARY THERAPY IN CHILDHOOD MEDULLOBLASTOMA: RESIDUAL LESION OR ACTIVE RESIDUAL TUMOR?

Lena Schömig[1], Denise Obrecht[1], Martin Mynarek[1,2], Brigitte Bison[3], Rudolf Schwarz[4], Torsten Pietsch[5,6], Stefan Rutkowski[1], Martin Benesch[7]; [1]Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [2]Mildred Scheel Cancer Career Center HaTriCS[4], University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [3]Department of Neuroradiology, University Hospital Augsburg, Augsburg, Germany. [4]Department for Radiotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [5]Institute of Neuropathology, Brain Tumor Reference Center of the German Society for Neuropathology and Neuroanatomy (DGNN), Bonn, Germany. [6]DZNE German Center for Neurodegenerative Diseases, Bonn, Germany. [7]Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

BACKGROUND: Magnetic resonance imaging (MRI) of patients with medulloblastoma (MB) often shows persistent residual findings after primary treatment. Criteria for characterizing these lesions and consensus on further therapeutic approaches are not established. MATERIAL AND METHODS: Eighty-four patients ≥4 years with centrally reviewed residual lesions on MRI at the end of primary therapy with initial surgery between 2000 and 2018 were identified. Data were extracted from the German HIT-MED database. RESULTS: Median age at initial diagnosis was 9.3 (4.0-20.8) years. 91.7% were histologically classified as CMB, 7.1% as LC/AMB and 1.2% as DMB. The majority (65.5%) of the evaluated cohort was assigned to molecular subgroup 4, 24.1% to group 3, 6.8% to WNT, 3.4% to SHH. Median follow-up for survivors was 5.96 (1.41-16.67) years. Univariate analysis revealed that patients showing an overall partial response (PR) to primary therapy have a significantly lower risk of progression of residual lesions compared to patients with stable disease (SD) (5-year PFS [PR]: 62.5±7,0; 5-year PFS [SD]: 35.9±12.8; 5-year OS [PR]: 85.6±5.1; 5-year OS [SD]: 54.1±13.7; p=0.02 [PFS], p=0.04 [OS]). Additionally, patients with multiple residual lesions (M+ and R+) were at higher risk of progression (5-year PFS [R+ only]: 72.4±12.0, 5-year PFS [R+/M+]: 22.9±17.9; p=0.02 [PFS]). Further procedures after the end of primary therapy (additional resections, chemotherapy, radiotherapy) did not impact on PFS and OS. These results were confirmed by multivariate Cox regression. For molecular or histological type no significant effect was found, presumably due to small cohort. CONCLUSION: PFS in patients with residual lesions at the end of primary treatment depends on the overall response to primary therapy. Additional procedures do not seem to be superior compared to watch-and-wait strategies. Decisions regarding further therapies should be scrutinized on a case-by-case basis. Further identification of biomarkers is warranted.

MEDB-17. RE-IRRADIATION FOR RECURRENT MEDULLOBLASTOMA IN A MATCHED COHORT: ADVANTAGEOUS ESPECIALLY IN PATIENTS WITHOUT RESECTION

Jonas E. Adolph[1], Stephan Tippelt[1], Sebastian Tschirner[1], Christine Gaab[1], Ruth Mikasch[1], Martin Mynarek[2,3], Stefan Rutkowski[2], Monika Warmuth-Metz[4], Brigitte Bison[5], Stefan M. Pfister[6,7], Olaf Witt[6,7], Torsten Pietsch[8], Rolf-Dieter Kortmann[9], Stefan Dietzsch[10,11], Beate Timmermann[11], Gudrun Fleischhack[12]; [1]Department of Pediatrics III, Center for Translational Neuro- and Behavioral Sciences (CTNBS), University Hospital of Essen, Essen, Germany. [2]University Medical Center Hamburg-Eppendorf, Dept. of Pediatric Hematology and Oncology, Hamburg, Germany. [3]Mildred Scheel Cancer Career Center HaTriCS [4], University Medical Center HamburgEppendorf, Hamburg, Germany. [4]Diagnostic and Interventional Neuroradiology, University Hospital Wuerzburg, Wuerzburg, Germany. [5]Department of Neuroradiology, University Hospital Augsburg, Augsburg, Germany. [6]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany. [7]German Cancer Research Center (DKFZ)) and German Cancer Consortium (DKTK), Heidelberg, Germany. [8]University Hospital of Bonn, Institute of Neuropathology, DGNN Brain Tumor Reference Center, Bonn, Germany. [9]University Leipzig, Department of Radio-Oncology, Leipzig, Germany. [10]rolf-dieter.kortmann@medizin.uni-leipzig.de, Leipzig, Germany. [11]University Hospital of Essen, West German Proton Therapy Centre Essen, Essen, Germany. [12]Department of Pediatrics III, Center for Translational Neuro- and Behavioral Sciences (CTNBS), University Hospital of Essen, Essen, Ghana

INTRODUCTION: Radiotherapy with craniospinal irradiation (CSI) is an important part of initial treatment for medulloblastoma in most children. Radiotherapy after recurrence is currently not widely used. This analysis aims to evaluate whether re-irradiation (RT2) may show survival benefits. METHODS: Data for patients with recurrent medulloblastomas from the German HIT-REZ studies was gathered. Patients with RT2 at 1st recurrence were matched by propensity score to an equal number of patients without radiotherapy. Matching variables were sex, initial therapy, time to recurrence, metastatic stage and therapy at 1st recurrence and radiotherapy at subsequent recurrences. The matched cohort was analysed regarding PFS and OS after 1st recurrence. RESULTS: From a cohort of 240 pre-irradiated patients, 106 patients were matched. Patients with RT2 showed improved median PFS [21.0 months (95%-CI: 17.5 – 27.6)] and OS [37.5 months (CI: 30.0 – 59.4)] compared to control patients [(PFS: 12.0 months (CI: 8.1 – 17.7) / OS: 20.1 months (CI: 14.5 – 44.8)]. When stratifying by resection at recurrence (36.8% resected), a survival advantage for RT2 was found in patients without resection in PFS [19.6 (CI: 14.9 – 31.5) vs. 8.0 months (CI: 5.4 – 14.4)] and OS [41.9 (CI: 30.0 – 59.4) vs. 13.3 months (CI: 8.1 – 36.7)]. However, no advantage was found after resection [PFS: 22.5 (CI: 17.5 – 50.4) vs. 19.1 months (CI: 14.1 – 34.3) / OS: 32.3 (CI: 27.6 – NA) vs. 48 months (CI: 23.4 – NA)]. CSI was used in 6 patients without differences in survival to focal RT2. Median PFS after first irradiation was 32.5 months, after RT2 20.9 months. No patients with RT2 were alive past 10 years after 1st recurrence.**CONCLUSION**: Patients with recurrent medulloblastoma show benefits from RT2 in median PFS and OS. However, no advantage for RT2 was found when resection was also applied at recurrence. Cure after treatment with RT2 was not found in our cohort.

MEDB-18. ELONGATION CONTROL OF MRNA TRANSLATION SUPPORTS GROUP 3 MEDULLOBLASTOMA ADAPTATION TO NUTRIENT DEPRIVATION

Alberto Delaidelli[1,2], Betty Yao[2], Que Xi Wang[2], Yue Zhou Huang[2], Gian Luca Negri[3], Christopher Hughes[2], Haifeng Zhang[2], Gabriel Leprivier[4], Poul Sorensen[1]; [1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada. [2]Department of Molecular Oncology, British Columbia Cancer Research Centre, Vancouver, Canada. [3]Canada's Michael Smith Genome Sciences Centre, BC Cancer, Vancouver, Canada. [4]Institute of Neuropathology, University Hospital Düsseldorf, Düsseldorf, Germany

Group 3 affiliation and *MYC* genetic amplification are associated with poor life expectancy and substantial morbidity in children suffering from medulloblastoma (MB). However, the high metabolic demand induced by MYC-driven transformation sensitizes MYC-overexpressing MB to cell death under conditions of nutrient deprivation (ND). Additionally, MYC-driven transformation is known to promote mitochondrial oxidative phosphorylation (OXPHOS). We previously reported that eukaryotic Elongation Factor Kinase 2 (eEF2K), the master regulator of mRNA translation elongation, promotes survival of MYC-overexpressing tumors under ND. Interestingly, eEF2K is overexpressed in MYC-driven MB and our preliminary proteomics data highlight large-scale alterations in OXPHOS components affecting eEF2K deficient MB cells. We therefore hypothesized that eEF2K activity is required for the selective translation of mRNAs needed for efficient OXPHOS, and for the progression of MYC-driven MB. We peformed Multiplexed enhanced Protein Dynamic Mass Spectrometry in eEF2K knockdown MYC-overexpressing D425 MB cells to identify mRNAs selectively translated upon eEF2K activation. Messenger RNAs encoding multiple (9 out of 10 detected) components of the mitochondrial OXPHOS pathway are selectively translated upon eEF2K activation. Inactivation of eEF2K by genetic KO leads to the disassembly of electron transport chain (ETC) complexes I-IV without affecting mRNA levels of their respective components. Consistently, *eEF2K* KO MB cells display decreased mitochondrial membrane potential and 20%