membrane potential and decreasing oxygen consumption rate along with extracellular acidification rate after abemaciclib/SpyADI monotherapy or its combination regimens. TEM confirmed damaged mitochondria and endoplasmic reticulum together with increased vacuolization under CDKi mono- and SEQ- CDKi/SpyADI combination therapy. SEQ-abemaciclib/SpyADI treatment suppressed the DSB repair system via NHEJ and HR, whereas SEQ-dinaciclib/SpyADI treatment increased γ-H2AX accumulation and induced Rad51/Ku80. The latter combination also activated the stress sensor GADD45 and β-catenin antagonist AXIN2. CONCLUSION: This study highlights the antitumoral potential of a combined SpyADI/CDKi approach. We show that sequential application of these substances has complex effects on mitochondrial dysfunction, invasiveness, and DNA-damage response. This provides a good starting point for further proof-of-concept studies to move forward with this strategy.

HGG-14. MOLECULAR CHARACTERIZATION OF UNIQUE BIOLOGICAL SUBGROUPS AMONG H3 WILD TYPE HIGH-GRADE GLIOMAS

Katerina Vanova[1,2], Lenka Krskova[1,3], Ales Vicha[1,2], David Sumerauer[1,2], Josef Zamecnik[1,3], Miroslav Koblizek[1,3], Petr Libý[4], Vladimir Benes[4], Bela Malinova[5], Michal Zapotocky[1,2]; [1]Prague Brain Tumor Research Group, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic. [2]Department of Pediatric Haematology and Oncology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic. [3]Department of Pathology and Molecular Medicine, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic. [4]Department of Neurosurgery, Second Faculty of Medicine, Charles University and University Hospital Motol, prague, Czech Republic. [5]Department of Oncology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

INTRODUCTION: Paediatric high-grade gliomas (HGG) are characterised by the aggressive biological behaviour with dismal prognosis of long-term survival 10-15%. Current molecular-biological diagnostic approaches allow for more precise characterization and determination of new unique subgroups of HGG. Our aim was to identify novel and rare HGG subgroups within our institution cohort. PATIENTS AND METHODS: Our reference centre patients´ cohort consisted of 97 clinically annotated patients with HGG diagnosed between 2000 and 2021. Sanger sequencing was used for screening of the most common HGG-related oncogenic drivers; furthermore we employed whole genome methylation array (Illumina Infinium MethylationEPIC BeadChip) and for selected samples RNA sequencing and expression profiling. RESULTS: Based on H3 status and previous radiotherapy we separated our HGG cases into the RIG, H3mut and H3wt groups. In contrast to H3mut(n=35) and RIG(n=11) that were uniformly fatal, H3wt group contained a proportion of long-term survivors. In the H3wt group we found patients carrying driver mutations in IDH1/2 (n=2) and BRAFV600E (7). Five young patients (under 3) consisted of 3 infant hemispheric gliomas (with NTRK and ROS1 fusions), one gliomatosis cerebri and one brainstem anaplastic astrocytoma with MYB/QKI fusion. We also identified a rare EWSR1-PATZ1 gene fusion in one patient. Importantly, long-term survivors recruited from these subgroups. On the contrary, four cases of MYCN GBM with poor prognosis presented in various locations: one disseminated, one gliomatosis cerebri and two with hemispheric tumour. We identified one patient with "hypermutated" glioblastoma and used targeted therapy with Nivolumab. In three samples of our patients with thalamic glioblastomas, we detected "loss of H3K27-trimethylation" caused by EZHIP overexpression. These tumours proved to be very aggressive with early metastatic recurrence and dismal prognosis. SUMMARY: Detailed characterization of H3 wild-type HGG is very important for further understanding of their biological behaviour, diagnostics, prognostication and identification of therapeutic targets.

HGG-15. GENERATION OF A NOVEL MOUSE MODEL FOR BRAIN TUMORS OF THE DNA METHYLATION CLASS "GBM MYCN"

Melanie Schoof[1,2], Shweta Godbole[3], Carolin Walter[4,5], Matthias Dottermusch[3,6], Thomas Albert[5], Annika Ballast[5], Carolin Göbel[1,2], Sina Neyazi[1,2], Dörthe Holdhof[1,2], Catena Kresbach[1,6], Mirjam Blattner-Johnson[7,8], Franziska Modemann[9], Ann-Kristin Afflerbach[1,2], Alicia Eckhardt[1,2], Nina Struve[10,11], David Jones[7,8], Kornelius Kerl[5], Julia E. Neumann[3,6], Ulrich Schüller[2,6]; [1]Research Institute Children's Cancer Center, Hamburg, Germany. [2]Department of Pediatric Hematology and Oncology, University Medical Center, Hamburg-Eppendorf, Hamburg, Germany. [3]Center for Molecular Neurobiology, Hamburg, Germany. [4]Institute of Medical Informatics, University of Münster, [48149] Münster, Germany, and Institute of Molecular Tumorbiology, University of Münster, Muenster, Germany. [5]Pediatric Hematology and Oncology, University Children's Hospital Muenster, Muenster, Germany. [6]Institute of Neuropathology, University Medical Center, Hamburg-Eppendorf, Hamburg, Germany. [7]Hopp Children's Cancer Center (KiTZ), Heidelberg, Germany. [8]Pediatric Glioma Research Group, German Cancer Research Center (DKFZ), Heidelberg, Germany. [9]Center for Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [10]Mildred Scheel Cancer Career Center HaTriCS[4] University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [11]Laboratory of Radiobiology & Experimental Radiation Oncology, Hubertus Wald Tumorzentrum - University Cancer Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Multiple recent publications have described a highly aggressive subgroup of pediatric glioblastoma, which is clearly separable from other pediatric and adult glioblastoma based on its DNA methylation profile (GBM MYCN). These tumors almost exclusively occur in children and have a median overall survival of only 14 months. Many tumors in this group are driven by MYCN amplifications and harbor TP53 mutations. Otherwise, information about these tumors are still sparse and treatment is ineffective and causes severe side effects in many cases. In order to further investigate the biology and treatment options of these tumors, preclinical models are urgently needed. Here, we describe the generation of *hGFAP-cre::TP53Fl/Fl::lsl-MYCN* mice, which carry a loss of TP53 and show aberrant MYCN expression in neural precursors of the central nervous system. These animals develop large forebrain tumors within the first 80 days of life with 100 % penetrance. These tumors resemble human GBM MYCN tumors by histology, global gene expression, and DNA methylation. In order to understand the developmental biology and intratumoral heterogeneity, we employed single cell RNA sequencing (scRNAseq) to the murine tumors with first results indicating a resemblance of tumor cells to committed oligodendrocyte precursors. We further show that both murine and human tumor cells are sensitive to AURKA inhibition in vitro, suggesting a potential new therapeutic option for improved patient care. We believe that further characterization and utilization of the model will pave the way to improved treatment strategies for patients with these highly aggressive tumors.

HGG-16. FINAL ANALYSIS OF THE HIT-HGG-2007 TRIAL (ISRCTN19852453): SIGNIFICANT SURVIVAL BENEFIT FOR PONTINE AND NON-PONTINE PEDIATRIC HIGH-GRADE GLIOMAS IN COMPARISON TO PREVIOUS HIT-GBM-C/-D TRIALS.

Andrè O. von Bueren[1], Robert Kwiecien[2], Gerrit H. Gielen[3], Martin Benesch[4], Thomas Perwein[4], Gunther Nussbaumer[4], Dominik Sturm[5,6], David T.W. Jones[5,6], Stefan M. Pfister[5,7], Matthias Eyrich[8], Stefan Rutkowski[9], Gudrun Fleischhack[10], Miriam von Buiren[11], Michael Karremann[12], Rolf-Dieter Kortmann[13], Christian Hagel[14], Gabriele Calaminus[15], Andreas Faldum[2], Brigitte Bison[16], Torsten Pietsch[3], Marion Hoffmann[17], Christof M. Kramm[17]; [1]Division of Pediatric Oncology and Hematology, Department of Women, Child and Adolescent, University Hospital of Geneva, Geneva, Switzerland. [2]Institute of Biostatistics and Clinical Research, Faculty of Medicine, University of Münster, Münster, Germany. [3]Institute of Neuropathology, DGNN Brain Tumor Reference Center, University of Bonn Medical Center, Bonn, Germany. [4]Division of Pediatric Hematology-Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria. [5]Hopp Children's Cancer Center (KiTZ), Heidelberg, Germany. [6]Division Pediatric Glioma Research, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany. [7]Division Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany. [8]Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, University Children's Hospital, University Medical Center, University of Würzburg, Würzburg, Germany. [9]Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [10]Pediatrics III, Center for Translational Neuro- and Behavioral Sciences (CTNBS), University Hospital of Essen, Essen, Germany. [11]Department of Pediatric Hematology and Oncology, Center for Pediatrics, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany. [12]Department of Pediatric and Adolescent Medicine, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. [13]Department of Radiotherapy and Radiation Oncology, University Hospital Leipzig, Leipzig, Germany. [14]Institute of Neuropathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [15]Department of Pediatric Hematology and Oncology, University Hospital Bonn, Bonn, Germany. [16]Department of Neuroradiology, University Hospital of Augsburg, Augsburg, Germany. [17]Division of Pediatric Hematology and Oncology, University Medical Center Göttingen, Göttingen, Germany

The aim of the HIT-HGG-2007 trial (ISRCTN19852453) was to demonstrate therapeutic non-inferiority of temozolomide radiochemotherapy for pediatric patients (3-18 years) with high-grade gliomas (pedHGG) in comparison to the cisplatinum-based radiochemotherapy of the two previous clinical trials HIT-GBM-C/-D. Between 06/2009 and 12/2016, 456 patients were enrolled at 79 centers in Germany, Austria, and Switzerland (n=18 dropouts, remaining