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**BACKGROUND:** TRK fusions are detected in less than 3% of CNS tumors. Given their rarity, there are limited data on the clinical course of these patients. **METHODS:** We contacted 166 oncology centers worldwide to retrieve data on patients with TRK fusion-driven CNS tumors. Data extracted included demographics, histopathology, NTRK gene fusion, treatment modalities and outcomes. Patients less than 18 years of age at diagnosis were included in this analysis. **RESULTS:** Seventy-three pediatric patients with TRK fusion-driven primary CNS tumors were identified. Median age at diagnosis was 2.4 years (range 0.0–17.8) and 60.2% were male. NTRK2 gene fusions were found in 37 patients (50.7%), NTRK1 and NTRK3 aberrations were detected in 19 (26.0%) and 17 (23.3%), respectively. Tumor types included 38 high-grade gliomas (HGG; 52.1%), 20 low-grade gliomas (LGG; 27.4%), 4 embryonal tumors (5.5%) and 11 others (15.1%). Median follow-up was 46.5 months (range 3–226). During the course of their disease, a total of 62 (84.9%) patients underwent surgery with a treatment intent, 50 (68.5%) patients received chemotherapy, 35 (47.9%) patients received radiation therapy, while 34 (46.6%) patients received NTRK inhibitors (3 as first line treatment). Twenty-four (32.9%) had no progression including 9 LGG (45%) and 9 HGG (23.6%). At last follow-up, only one (5.6%–18 evaluable) patient with LGG died compared to 11 with HGG (35.5%–31 evaluable). For LGG the median progression-free survival (PFS) after the first line of treatment was 17 months (95% CI: 0.0–35.5)

and median overall survival (OS) was not reached. For patients with HGG the median PFS was 30 months (95% CI: 11.9–48.1) and median OS was 182 months (95% CI 20.2–343.8). **CONCLUSIONS:** We report the largest cohort of pediatric patients with TRK fusion-driven primary CNS tumors. These results will help us to better understand clinical evolution and compare outcomes with ongoing clinical trials.

#### HGG-12. RAPID PTEFB-DEPENDENT TRANSCRIPTIONAL REORGANIZATION UNDERPINS THE GLIOMA ADAPTIVE RESPONSE TO RADIOTHERAPY

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**BACKGROUND:** Dynamic regulation of gene expression is fundamental for cellular adaptation to exogenous stressors. PTEFb-mediated promoter proximal pause-release of Pol II is a conserved regulatory mechanism for synchronous transcriptional induction best described in response to heat shock, but this pro-survival role has not been examined in the applied context of cancer therapy. **DESIGN/METHOD:** In order to examine the dynamics of chromatin reorganization following radiotherapy, we performed a combination of ChIP-, ATAC-, and RNA-seq in model systems of diffuse intrinsic pontine glioma (DIPG) and other pediatric high-grade gliomas (pHGG) following IR exposure. We interrogated IR-induced gene expression in the presence or absence of PTEFb blockade, including both mechanistic and functional consequences of concurrent inhibition or genetic depletion. We utilized culture models with live cell imaging to assess the therapeutic synergy of PTEFb inhibition with IR, as well as the therapeutic index of this intervention relative to normal controls. Finally, we employed orthotopic models of pHGG treated with conformal radiotherapy and CNS-penetrant PTEFb inhibitors in order to assess tolerability and anti-tumor effect in vivo. **RESULTS:** Rapid genome-wide redistribution of active chromatin features and PTEFb facilitates Pol II pause-release to drive nascent transcriptional induction within hours of exposure to therapeutic ionizing radiation. Concurrent inhibition of PTEFb imparts a transcription elongation defect, abrogating canonical adaptive programs such as DNA damage repair and cell cycle regulation. This combination demonstrates a potent, synergistic therapeutic potential agnostic of glioma subtype, leading to a marked induction of tumor cell apoptosis and prolongation of xenograft survival. **CONCLUSION:** These studies reveal a central role for PTEFb underpinning the early adaptive response to radiotherapy, opening new avenues for combinatorial treatment in these lethal malignancies.

#### HGG-13. COMBINED CDK INHIBITION AND ARGININE-DEPRIVATION AS TARGETED THERAPY FOR ARGININE-AUXOTROPHIC GLIOBLASTOMA MULTIFORME CELLS

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**INTRODUCTION/BACKGROUND:** Glioblastoma multiforme show constitutive activation of cyclin-dependent kinases (CDKs) or arginine auxotrophy. This renders tumor cells vulnerable towards arginine-depleting substances, such as arginine deiminase from *Streptococcus pyogenes* (SpyADI). Previously, we confirmed the susceptibility of patient-derived GBM cells towards administration of SpyADI as well as CDK inhibitors (CDKis). To improve effects, we applied a sequential (SEQ) CDKi/SpyADI approach to examine mechanistic insights and drug susceptibility. **MATERIALS AND METHODS:** Three arginine-auxotrophic patient-derived GBM lines with different molecular characteristics were cultured in 2D and 3D (spheres and glioma stem-like cells (GSC)) and effects of this combined CDKi/SpyADI approach were analyzed. This included viability staining via Calcein AM in 2D and 3D-Glo in 3D culture and cell death analysis via flow cytometry. Therapy-induced morphological changes were identified with transmission electron microscopy (TEM). Besides, 3D-invasiveness, cellular stress, and DNA damage responses were measured. **RESULTS:** All SEQ-CDKi/SpyADI combinations yielded synergistic antitumor effects, characterized by impaired cell proliferation, invasiveness, and viability. Notably, this SEQ-CDKi/SpyADI approach was most effective in 3D models. Mitochondrial impairment was demonstrated by increasing mitochondrial

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  $\gamma$ -H2AX accumulation and induced Rad51/Ku80. The latter combination also activated the stress sensor GADD45 and  $\beta$ -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

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**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"

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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::Isl-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.

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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 cisplatin-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