patients for confirmatory analysis: n=438). 438 patients from HIT-GBM-C/-D served as historical control. All pedHGG diagnoses had been confirmed by central neuroradiological and neuropathological review. Primary objective was achieved since non-inferiority of HIT-HGG-2007 in comparison to HIT-GBM-C/-D as indicated by 6 months event-free survival (EFS) was statistically confirmed (p=0.0125). Statistical survival analyses even revealed a better overall survival (OS) and EFS for HIT-HGG-2007 patients in comparison to their HIT-GBM-C/-D counterparts (EFS: p<0.0001; OS: p=0.0328). While EFS subgroup analyses for pontine and non-pontine pedHGG also showed a better survival of HIT-HGG-2007 patients (median EFS pontine pedHGG: 8.2 (n=152; confidence interval (CI): 7.6-9.4) versus 6.2 (n=170; CI: 5.5-6.9) months, p=0.0079; median EFS non-pontine pedHGG: 10.7 (n=276; CI: 9.6-12.4) versus 7.4 (n=267; CI: 6.4-9.2) months, p<0.0001), OS was only improved in HIT-HGG-2007 patients with non-pontine pedHGG (median OS non-pontine pedHGG: 19.3 (CI: 16.8-23.3) versus 16.2 (CI: 14.2-19.1) months; p=0.0181) but not with pontine pedHGG (median OS pontine pedHGG: 11.4 months versus 11.3 months, p=0.4021) Toxicity profile of HIT-HGG-2007 seemed very favorable with most CTCAE (common toxicity criteria adverse event) ≥ grade 3 as hematological toxicity, hepatotoxicity, and neurotoxicity. Less toxicity was observed during concomitant radiochemotherapy in comparison to HIT-GBM-C/-D. Further subgroup survival analyses as well as the assessment of the impact of MGMT promoter methylation are ongoing. In conclusion, our data show non-inferiority of the HIT-HGG-2007 trial with increased survival and less toxicity when compared with previous trials HIT-GBM-C/-D.

HGG-17. NOVEL FUSION IN CONGENITAL BRAINSTEM DIFFUSE HIGH-GRADE GLIOMA

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BACKGROUND: Infant-type hemispheric glioma, previously termed infantile glioblastoma multiforme, is a rare infantile neoplasm with improved survival and distinct molecular features when compared to other pediatric and adult-type high-grade glioma. Infant-type high-grade gliomas are typically located in the cerebral hemispheres and are characterized by ALK, ROS1, MET, and NTRK fusions. Typical brainstem gliomas (diffuse midline glioma, H3 K27-altered or diffuse intrinsic pontine glioma) are comparatively rare in this age group. As a result, the biology of brainstem congenital high-grade gliomas is poorly described. RESULTS: A 3 month old female who initially presented with failure to thrive had an apneic event and was found to have an infiltrative mass in the medulla with expansion into the pons and cervical spine on magnetic resonance imaging. She underwent surgical biopsy with pathology revealing diffuse high-grade glioma, WHO grade 4. Next generation sequencing showed no alterations to H3F3A, IDH, or fusions involving BRAF, ALK, ROS1, MET, or NTRK. Whole-transcriptome sequencing revealed a novel fusion of PDGFRB:APOBEC3C. She received chemotherapy with 2 cycles of carboplatin/etoposide and 2 cycles of carboplatin/etoposide/imatinib before having disease progression. She then underwent palliative radiation (35 Gy in 10 fractions) with near complete regression of her disease. Surprisingly, our patient has not had any progression of disease or new lesions now two years from her last therapy. CONCLUSION: Congenital high-grade glioma is a rare, unique entity that greatly differs from its adult and childhood counterparts. Here, we discuss a previously-unreported fusion of PDGFB:APOBEC3C in a patient with congenital brainstem diffuse high-grade glioma with a favorable clinical course. This highlights the importance of routine molecular characterization, both to better understand the complex biology of this rare disease and to guide prognosis and clinical decision making for individual patients and families.

HGG-18. LONG-TERM EFFICACY AND SAFETY OF LAROTRECTINIB IN PAEDIATRIC PATIENTS WITH TROPOMYOSIN RECEPTOR KINASE (TRK) FUSION-POSITIVE PRIMARY CENTRAL NERVOUS SYSTEM (CNS) TUMOURS

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INTRODUCTION: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in various tumours. Larotrectinib, a highly selective TRK inhibitor, demonstrated an objective response rate (ORR) of 75% across 206 evaluable patients with various non-primary CNS cancers (Hong et al, ASCO 2021). We report long-term data on larotrectinib-treated paediatric patients with TRK fusion-positive primary CNS tumours. METHODS: Patients aged <18 years with TRK fusion-positive primary CNS tumours enrolled in two clinical trials (NCT02637687, NCT02576431) were included. Larotrectinib was administered at 100 mg/m^2 (maximum: 100 mg) twice-daily. Response was investigator-assessed per RECIST v1.1 and RANO. RESULTS: As of July 2021, 28 patients with TRK fusion-positive primary CNS tumours were enrolled, including 14 high-grade and eight low-grade gliomas. Median age at enrolment was 7.0 years (range 1.0–17.0). Twenty-three patients (82%) received prior systemic therapy and 12 (43%) received prior radiotherapy. The ORR was 39% (95% confidence interval [CI] 22–59): three complete responses, eight partial responses, 15 stable disease and two progressive disease. The 24-week disease control rate was 82% (95% CI 63–94). Median duration of response (DoR) was not reached; median follow-up was 25.6 months. Median progression-free survival was 21.9 months (95% CI 9.2–not estimable). Median overall survival (OS) was not reached; median follow-up was 27.6 months. DoR and OS 24-month rates were 53% and 71%, respectively. Treatment duration ranged from 1.0 to 39.0+ months. Treatment-related adverse events (TRAEs) were mostly Grade 1–2. Grade 3–4 events occurred in three patients (increased gamma-glutamyltransferase, hyperglycaemia, hypernatraemia, hyponatraemia and neutropaenia). No patients discontinued treatment due to TRAEs. Fourteen patients progressed on treatment; four continued treatment post-progression for ≥4 weeks. CONCLUSION: Larotrectinib demonstrated high disease control rate, durable responses and a manageable safety profile. These results support testing for *NTRK* gene fusions in paediatric patients with primary CNS tumours.

HGG-19. CO-OCCURRENCES OF A HIGH-GRADE GLIOMA WITH CAVERNOUS MALFORMATIONS AND PATHOGENIC VARIANTS IN *PDCD10* AND *SMARCA4*

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INTRODUCTION: The co-occurrence of multiple disease processes can make for more challenging diagnoses. Here we report an unusual case of a patient found to have an *IDH1*-mutant high-grade glioma along with multiple cerebral cavernous malformations and pathogenic germline variants in *PDCD10* and *SMARCA4*. CASE DESCRIPTION: A 17-year-old female presented with left arm paresthesia and weakness along with persistent headaches within the frontal and occipital regions that progressed in intensity to include nausea and emesis. A fast sequence magnetic resonance imaging (MRI) of her head was obtained that revealed the presence of multiple bilateral cystic lesions suspicious for cavernomas, with the most notable lesion in the right parietal lobe. Ophthalmology consultation revealed grade III papilledema bilaterally. A full brain MRI with and without contrast was obtained and demonstrated a right anterior parietal lobe lesion with associated mass effect, as well as multiple bilateral supratentorial and left cerebellar cavernous malformations. The patient underwent tumor debulking of her dominant lesion. Pathology revealed an *IDH1*-mutant diffuse astrocytoma, WHO grade III. Tumor genetic testing was done and identified a *SMARCA4* and two *TP53* variants. Germline genetic testing was then pursued which revealed a *PDCD10* pathogenic variant consistent with familial cerebral cavernous malformation syndrome and a likely pathogenic variant in *SMARCA4*. Treatment of her high-grade-glioma included radiation therapy followed by maintenance oral temozolomide. DISCUSSION: This case illustrates the unusual co-occurrences of a high-grade glioma with familial cavernous malformation syndrome and germline pathogenic variants in PDCD10 and *SMARCA4*. Our patient continues to do well clinically, but because of her risk of developing small cell carcinoma of the ovary she has elected to undergo a prophylactic bilateral salpingo-oophorectomy. Recognition of abnormal genetic results is critical in the setting of multiple disease processes and can play a crucial role in the on-going care for a patient.

HGG-20. PRMT5 PROMOTES THE FORMATION AND GROWTH OF PEDIATRIC HIGH-GRADE GLIOMA BY MAINTAINING TUMOR STEM CELL POPULATIONS

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BACKGROUND: Pediatric high-grade gliomas (PHGG) are aggressive, undifferentiated CNS tumors comprising two broad subtypes: diffuse mid-

line glioma with H3K27M mutations (DMG) and cortical high-grade glioma (H3K27-wild-type (wt) PHGG). During normal development, PRMT5 promotes stem cell self-renewal through methylation of arginine residues in histone tails. We hypothesized that PRMT5 controls self-renewal essential to the proliferation of PHGG tumor initiating cells (TICs). METHODS: We identified PRMT5 as potentially oncogenic in PHGG through a screen of 4,139 shRNAs targeting 406 genes with epigenetic activity. To elucidate PRMT5's activity, we used lentiviral shRNA delivery to knock down (KD) PRMT5 expression in four DMG and one H3K27-wt PHGG cell lines. We performed in vitro growth, cell cycle, apoptosis, limiting dilution and bulk RNA-Seq assays to determine the phenotypic effects of PRMT5 KD. To identify PRMT5's gene targets, we performed cleavage under targets & release using nuclease (CUT&RUN) followed by qPCR and are currently performing CUT&RUN-Seq. We orthotopically implanted PRMT5 KD PHGG cells into mice and tracked survival, tumor growth and tumor histological characteristics. RESULTS: In vitro, PRMT5 KD reduced cell growth ($p<0.001$), slowed cell cycle progression and increased apoptosis. PRMT KD also slowed neurosphere formation, demonstrating reduced self-renewal ($p<7E-9$). Geneset expression analysis showed PRMT5 KD reduced expression of self-renewal genes and increased expression of differentiation genes (FDR<0.0001). In vivo, PRMT5 KD reduced tumor growth, as monitored by bioluminescence and MRI, and aggressiveness, based on Ki-67 staining ($p<0.05$), leading to increased survival ($p<0.001$). CUT&RUN-qPCR results showed PRMT5 KD led to decreased expression and H3K4me3 promoter occupancy at PAX3, and decreased expression and increased H3K27me3 occupancy at S100A6. PAX3 and S100A6 are oncogenes that preserve TIC self-renewal. CONCLUSION. In vitro experiments show that PRMT5 KD epigenetically reduces TIC self-renewal. In vitro and in vivo, PRMT5 KD reduced PHGG tumor cell growth and aggressiveness.

HGG-21. ONCOGENIC TYROSINE KINASE GENE FUSIONS IN INFANT-TYPE HEMISPHERIC GLIOMAS - COMPARISON OF RNA- AND DNA-BASED METHODS FOR THEIR RELIABLE DETECTION

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High-grade diffuse gliomas (HGG) in early childhood are characterized by a more favorable outcome compared to older children. We demonstrated in previous studies that these tumors have stable genomes. Activating tyrosine kinase gene fusions in infant-type hemispheric gliomas represent therapeutic targets. 50 supratentorial HGG occurring in children younger than four years were retrieved from the archives of the Brain Tumor Reference Center, Institute of Neuropathology, Bonn University. DNA and RNA were extracted from FFPE tumor samples. Gene fusions were identified on the DNA level by FISH using break-apart probes for *ALK, NTRK1, -2, -3, ROS1* and *MET* and Molecular Inversion Probe (MIP) methodology. On the RNA level, fusion transcripts were detected by targeted RNA sequencing as well as Nanostring assay with fusion-specific probes. 37 supratentorial HGG occurred in the first year of life, 13 HGG between one and four years. 18 cases showed fusions of *ALK* to different partners; all occurred in the first year of life (18/37, 48.6%). Fusions of *ROS1* were found in 5, *MET* in 3, *NTRK1, -2, -3* in 10 cases. 12 cases showed no and two cases novel fusions. The different methods led to comparable results. Only recurrent fusions with known fusion partners were detectable with fusion sequence-specific Nanostring probes and library construction for targeted RNA sequencing failed in a fraction of cases. Break-apart FISH led to reliable results on the next day, and MIP technology represented the most sensitive method for analysis of FFPE samples. Gene fusions involving the tyrosine kinase genes *ALK, MET, ROS1* and *NTRK1, -2, -3* occurred in 72% of HGG of young children; most frequent were ALK fusions occurring in tumors of infants. DNA-based MIP technology represented the most robust and sensitive assay. A combination of RNA- and DNA-based methods to detect these fusions with high reliability is recommended.

HGG-22. UPTAKE OF INVESTIGATIONAL THERAPY IN CHILDREN WITH HIGH GRADE GLIOMA

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High grade gliomas (HGG) in children carry a dismal prognosis. Standard therapy includes resection when possible, radiotherapy and sometimes the addition of temozolomide. There is no standard treatment for progression or relapse. Since November 2018 we have offered upfront molecular testing to all children with HGG who had biopsy/ resection. Testing was mainly done by next generation sequencing panel, and some had research based methylation profiling and RNA seq. We aimed to see whether families chose to receive additional investigational treatment as a result of the molecular testing results and whether the treatment involved participation in a clinical study, or whether treatment was compassionate. A total of 22 patients aged 2.8-16.8 years with HGG had a biopsy/resection over this three year period. Thirteen had diffuse midline glioma (DMG) of which 11 had the H3K27 mutation, and 9 were cortical. Six children had underlying predisposition syndromes: mismatch repair deficiency (n=3 proven + 1 highly suspected), neurofibromatosis1 (n=1), Li-Fraumeni (n=1). All the cortical gliomas had potential treatment options based on their molecular testing. 10/22 (45%) children received investigational therapy of which only three participated in a clinical study while the rest received compassionate therapy. Compassionate treatments included BRAF/MEK inhibitors (n=4), Larotrectinib (n=1), and immune checkpoint inhibitors (n=2). Of the 12 who did not receive investigational therapy, four, all cortical, have potential therapy options but are currently in remission. Of the remaining eight, two had very rapid clinical deterioration and died, and six (all DMG) did not wish/ were unable to travel abroad and no relevant clinical study was available locally. We conclude that the families of children with HGG are highly motivated to receive investigational therapy. Upfront molecular testing of these tumors, especially for cortical HGG, is imperative and there is a growing need for accessible clinical studies.

HGG-23. THE PRESENCE OF *ROS1* FUSIONS ARE NOT LIMITED ONLY TO INFANTILE HEMISPHERIC GLIOMA.

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INTRODUCTION: Diffuse pediatric-type high-grade gliomas are diffuse gliomas with histological features of malignancy, typically occurring in children, and infants. For these tumors, precise classification, identification of prognostic and predictive factors requires molecular analysis. The ROS proto-oncogene 1 (*ROS1*) gene encodes a receptor tyrosine kinase that is involved in chromosomal rearrangements in numerous malignancies, and may be an attractive therapeutic target, since specific inhibitors have been approved for several neoplasms. Molecular evaluation including detection of *ROS1* fusions in pediatric gliomas are not included in standard diagnostic tests so far, therefore data on its significance is still limited. We present two cases of pediatric *ROS1* fusion-positive brain tumors. METHODS AND RESULTS: The patient no.1 was 1 year old boy with disseminated brain lesions. Histopathological examination displayed the presence of a neoplasm, which was composed of round and spindle-shaped cells with palisading necrosis, mitotic activity, and microvascular proliferation. The patient no.2 is 9 years old girl with tumor located in left frontal lobe. Microscopically, the neoplasm revealed the presence of oligodenroglial-like component with microvascular proliferation, and high mitotic activity. Targeted gene sequencing panel - Ampliseq Childhood Cancer Panel for Illumina was used to detect diagnostic and targetable gene fusions. In both of patients *ROS1:GOPC* gene fusions were detect. Identified fusions allowed to established diagnosis - infant-type hemispheric glioma with *ROS1* fusion (patient no 1) and - diffuse pediatric-type high grade glioma with *ROS1* fusion (patient no 2). CONCLUSIONS: Our results indicate, that the presence of *ROS1* fusions are not limited to the infant-type hemispheric gliomas only and may play a role in other glioma entities. It may be worth to include this biomarker in the diagnostic panel of pediatric brain tumors to establish a more precise diagnosis and a potential therapeutic target. Funded by National Science Centre, Poland (2016/23/B/NZ2/03064).

HGG-24. NTRK-REARRANGED INFANTILE GLIOMAS OF SUPRASELLAR/ OPTIC PATHWAY ORIGIN

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BACKGROUND: Oncogenic fusions involving neurotrophic tyrosine receptor kinase (NTRK) have been identified across cancer types and represent potential therapeutic targets given availability of TRK inhibitors. Gliomas harboring NTRK fusions have been described most commonly in infants with high-grade histology and hemispheric tumor location, though there is emerging evidence suggesting clinical, histopathologic, and molecular heterogeneity. Herein, we present two cases of NTRK-rearranged suprasellar/ optic pathway gliomas. CASE DESCRIPTIONS: The first patient was diagnosed at 6 months old with an extensive suprasellar/ optic pathway tumor, treated with carboplatin/ vincristine, which initially re-