sponded but subsequently progressed. A biopsy was then performed, with pathology consistent with infiltrating piloid astrocytoma with anaplastic features (elevated mitoses and Ki-67 index); a BCAN-NTRK1 fusion was identified by RT-PCR and confirmed by Sanger sequencing. After further disease progression on vinblastine monotherapy, this patient began treatment with entrectinib (NCT02650401), with favorable clinical and radiographic responses thus far. The second patient was diagnosed with a large suprasellar/ optic pathway tumor at 3 years old, and underwent upfront partial resection, revealing similar infiltrating piloid/pilocytic astrocytoma with anaplastic features (elevated mitoses and Ki-67 index). A diagnosis of "midline" infantile high-grade glioma (HGG) was also considered, as with the former case. Sequencing demonstrated a SOX10-NTRK3 rearrangement, resulting in an integrated diagnosis of NTRK-fused infantile HGG, for which the patient recently started treatment with larotrectinib (NCT04655404). Both patients' fusions retain the entire kinase domain of respective NTRK partners, supporting oncogenicity, and neither tumor harbored additional somatic pathogenic variants (both lacked BRAF alterations). Methylation profiling did not confidently classify either tumor. CONCLUSIONS: NTRK-rearranged gliomas may present with primary suprasellar/ optic pathway involvement in infants. Given the potential to offer targeted therapy, testing for the presence of NTRK fusions should be strongly considered for infantile gliomas in any location, including midline, and across the histologic spectrum.

HGG-25. TARGETING KLF5 REDUCES TUMORIGENIC PHENOTYPE IN A MURINE GLIOBLASTOMA (GBM) MODEL

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Sex differences are evident in the incidence, therapeutic response and survival of patients with various cancers including the most common, aggressive and incurable GBM. We generated a murine GBM model of male and female astrocytes with dual loss of NF1 and P53 that yielded a sex-biased transformation of the astrocytes with male cells being significantly more tumorigenic and therapeutically resistant compared to female cells. In our current work, we aimed to delineate the molecular mechanisms driving this sex-biased tumorigenic phenotype in order to deliver therapies that are more effective to patients with GBM. We examined the inhibition of KLF5 on tumorigenic phenotypes using cellular bio-functional assays. We used barcoded transposon calling cards to determine the genomic localization of KLF5 and the differentially induced gene expression in male versus female GBM cells. Chemical inhibition or shRNA knock-down of KLF5 significantly reduced proliferation, migration, clonogenic stem-cell frequency and survival, but increase apoptosis in male and female GBM cells. Interestingly, male, but not female, GBM cells exhibited an increased migratory phenotype after radiation that inhibition of KLF5 significantly reduced. Moreover, KLF5 inhibition significantly reduced the protein expression of tumorigenic PDGFRB, AKT, ERK and the stem marker Sox-2. Transposon calling cards mapped unique KLF5 genomic localization in male versus female GBM cells with significantly differential gene expression profiles between the two. The top genes induced by KLF5 in male cells were primarily affiliated with poorer prognosis and reduced survival, whereas in female cells they were affiliated with better prognosis and improved survival in patients with cancer. Our findings provide a promising exploratory avenue for KLF5 as a therapeutic target in GBM and warrants further investigation in order to delineate the precise molecular mechanisms driving this antitumor response so that targeted therapy would be more effective taking into consideration the sex-differences in patients with GBM.

HGG-26. COMPREHENSIVE GENOMIC PROFILING OF PEDIATRIC AND AYA HIGH-GRADE GLIOMAS REVEALS A HIGH PREVALENCE OF ATRX AND HOMOLOGOUS RECOMBINATION REPAIR (HRR) MUTATIONS

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BACKGROUND: Pediatric high-grade glioma (HGG) is a devastating heterogenous disease with a clear need for more effective treatment options. Advances in high-throughput molecular sequencing have advanced our understanding of these tumors and yet outcomes remain poor as only a very small subset of patients have demonstrated benefit from targeted therapy approaches. METHODS: We compiled genomic data from 980 pediatric (N=400) and AYA (18 to 30 yrs, N=580) HGG cases that underwent targeted, panel-based comprehensive genomic profiling (FoundationOne® CDx). RESULTS: Among pediatric patients, mutations in ATRX or HRR-related genes were among the most prevalent at 24.25% and 19.5%, respectively. Other commonly occurring mutations were seen in TP53 (58.25%), H3F3A (43%), and PIK3CA/PIK3R1 (22%). Among AYA patients, mutations in ATRX and HRR-related genes were seen in 51.72% and 17.24% of cases, respectively. The most common mutations seen in this older population were in TP53 (76.38%), IDH1/2 (50.86%), PI3KCA/PIK3R1 (20.52%), and H3F3A (18.28%). Among patients with diffuse midline glioma (harboring H3K27M mutations), ATRX and HRR mutations were reported in 21.27% and 13.57% of cases, respectively. Among pediatric patients with histone wild type HGG, mutations in ATRX and HRR-related genes occurred in 20.61% and 21.05% of cases, respectively. CONCLUSION: Alterations in ATRX and HRR-related genes are among the most prevalent mutations in pediatric and AYA HGG. Consideration should be made towards the development of subtype-specific treatment protocols using PARP and/or ATR inhibitors aimed at this subgroup of patients.

HGG-27. UNDERSTANDING THE ROLE OF PLAG FAMILY TRANSCRIPTION FACTORS IN CORTEX DEVELOPMENT AND TUMORIGENESIS

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Gliomas are the most common type of central nervous system (CNS) tumors in children. Therapy and outcome often reflect the grade of the tumor, with high grade glioma (HGG) leading to a significantly worse survival prognosis than low grade glioma. However, HGG are highly diverse regarding their molecular entities and clinical associations. In some pediatric-type histone 3 K27M mutated HGG, the zinc-finger transcription factor PLAG1 was previously found to be overexpressed, which is also confirmed by patient data from the INFORM program. Further, in a novel type of embryonic CNS tumors without histone mutations, the PLAG1-related genes PLAGL1/PLAGL2 are amplified. However, the consequences of aberrant PLAG gene expression on CNS tumor formation during development are unknown. Especially the understanding of downstream signaling pathways that are commonly altered by this transcription factor family could provide necessary starting points for more specific therapy. We use transgenic mouse models with targeted PLAG1 overexpression in neural stem and progenitor cells to investigate the function of PLAG1 in cerebral cortex development and tumorigenesis. We found that PLAG1 overexpression together with heterozygous loss of p53 activity causes neurological defects and impaired cortex development. Next, to understand how PLAG gene overexpression affects neural specification, we will overexpress the PLAG genes in embryonic neural stem and progenitor cells using *in utero* electroporation. After FACS isolation of electroporated cells and single nucleus RNA sequencing, we will assess how the overexpression changes the transcriptional trajectories of neural development in mouse cortex stem and progenitor cells. We hypothesize that an early event leads to the constitutive upregulation of PLAG genes, which are usually tightly regulated during development, in patients with pediatric brain tumors harboring aberrant PLAG gene expression. Deciphering the transcriptional downstream pathways of this aberrant expression in neural stem and progenitor cells seems promising to find new potential therapeutic targets.

HGG-28. CLIC1 AND CLIC4 ION CHANNEL DEFICIENCY CONFERS INCREASED SENSITIVITY TO TUMOUR TREATING FIELDS AND IMPROVED SURVIVAL IN PAEDIATRIC GLIOBLASTOMA

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Paediatric Glioblastoma Multiforme (pGBM) is a lethal brain cancer with an average survival of 14 months. Due to the scarcity of effective treatment, pGBM forms the leading cause of CNS cancer death in children. Optune™ is a non-invasive therapy that uses alternating electric fields – coined TT fields - to disrupt cancer cell division, however it is not currently approved in children. Evidence shows that ion channels not only regulate electrical signalling of excitable cells, but also play a crucial role in the development and progression of brain tumours, essential in cell cycle control and therefore presenting as valuable therapeutic targets. Candidate ion channel genes (ICG) associated with the malignant status of high-grade glioma (HGG) were identified via multivariate analysis of in-house and publicly available data sets. RNA sequencing of in-house patient tissues revealed an increased expression of CLIC1 and CLIC4, with pHGG exhibiting increased expression at protein and RNA levels in both the Paugh data set and in-house primary cell lines and TMAs. Clinical correlation determined that CLIC4 and CLIC1 deficiency was associated with increased overall survival (p=<0.03). siRNA depletion of CLIC1 and CLIC4 propagated a reduction in the prolif-