have furthermore identified alterations in more than 100 lncRNAs in DIPG. METHODS: To identify lncRNAs required for proliferation of patient-derived DIPG cancer cells, we designed two custom genome-scale lncRNA libraries. We generated a genome-scale lncRNA CRISPR-Cas9 knockout pooled library, consisting of 45,766 single guide RNAs (sgRNAs). Additionally, we generated a genome-wide CRISPR interference pooled library consisting of 45,608 sgRNAs, targeting lncRNA transcription start sites (TSS). RESULTS: We utilized in vitro histone-mutant pHGG models as well as edited clones of these models with the K27M mutant corrected in order to compare lncRNA dependencies in these two contexts. We have successfully performed genome-scale CRISPR-Cas9 knockout and CRISPR interference screens targeting lncRNAs in these cell lines, revealing lncRNA dependencies. Candidate dependencies in our CRISPR-Cas9 knockout screen include LOC100507412, LOC105379524, and LINC02193. **CONCLUSION:** Genome-wide lncRNA CRISPR knock-out and CRISPR interference screens are a novel approach for the unbiased identification of lncRNAs that are required for pediatric high-grade glioma proliferation. Further validation of specific lncRNAs is required, and these lncRNA dependencies represent potential novel therapeutic targets.

HGG-37. A CASE OF *ETV6-NTRK3* FUSION DRIVEN INFANTILE HEMISPHERIC GLIOMA (IHG) WITH ACQUIRED DRUG RESISTANCE AGAINST FIRST- AND SECOND-GENERATION NTRK-INHIBITORS

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A 3-month-old girl had left cerebral infantile hemispheric glioma (IHG), H3 wild type (wt), Grade IV (WHO2020) with diffuse leptomeningeal and spinal metastasis. Craniotomies were performed twice which achieved partial resection. Histopathology revealed high grade glioma, Ki67 30-40%, mitosis and widespread necrosis. IHC showed H3wt, IDH-, and retained INI-1. RNAseq found *ETV6-NTRK3* fusion. She was treated per Baby POG-9233, however after 3 cycles, there was mixed response (static for primary, partial response for metastasis). She had severe developmental delay, right hemiparesis and dysphagia. Aiming for better disease control and potential resectability, we switched to first-generation NTRK-inhibitor, Larotrectinib. MRI at 3 months showed significant interval reduction in tumour size, then became static at 6 months. She was stable with gradual neurological improvement until 10 months after Larotrectinib, there was worsening neurology and imaging confirmed tumour progression with haemorrhage. Craniotomy was performed for haemostasis and tumour debulking. Histopathology showed same IHG with *ETV6-NTRK3* fusion. Targeted panel sequencing found *NTRK3 p.Gly623Arg* mutation, a solvent-front substitution responsible for acquired resistance to first-generation TRK-inhibitors. *BRAFV600E* and *MET* amplification were not detected. Larotrectinib was switched to second-generation NTRK-inhibitor, Selitrectinib. MRI at 1 month showed post-operative changes, but disease progressed at 3 months and in an accelerated manner over the course of 10 days while on therapy. Choice of conventional chemotherapy and radiotherapy were discussed, but the girl deteriorated rapidly and deceased (3 months from start of Selitrectinib, 19 months from diagnosis). CONCLUSION: IHG is aggressive with challenging surgery and medical treatment. The use of small molecular inhibitor requires careful consideration, i.e. treatment effect, toxicity and potential acquired drug resistance as showed in this case. For unresectable tumour, it may be inevitable as we also reported a similar case with *ROS1* fusion. Access to newer novel agents is difficult while therapeutic effect is uncertain.

HGG-38. GLIOMATOSIS CEREBRI/GLIOBLASTOMA WITH DISCORDANT HISTOLOGICAL AND MOLECULAR PROFILES - TREATMENT AND OUTCOME OF A PEDIATRIC PATIENT

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Gliomatosis cerebri is no longer recognized as a distinctive pathological diagnosis, but a manifestation of diffuse glioma involving at least three cerebral lobes. Lack of understanding in this manifestation of CNS neoplasms limits treatment for this aggressive disease. Here we present a case of stabilization of disease in a pediatric patient with unusual molecular profiles normally associated with aggressive tumor behavior. A nine-year-old male presented with acute onset of right-sided vision changes, headache and numbness of the left arm and leg for one day. He also had a three-month history of an asymptomatic bump on the right temporal skull bone. MRI of the brain was significant for diffuse thickening of the cortex of the entire right hemisphere (temporal>frontal>parietal lobes). No specific enhancing lesion or restricted diffusion was noted. Histologically, the tissue had findings of diffuse low-grade astrocytoma. Molecular genetic testing was notable for TERT and EGFR mutations which are more consistent with adult type high-grade astrocytic tumors. MGMT promoter methylation array was negative. Final diagnosis was glioblastoma, IDH and H3 wildtype. All the molecular features of this tumor were high-grade with an average progression free survival of less than 12 months. Despite the lack of methylation, we opted to include alkylating agents in a maintenance chemotherapy treatment plan following radiation therapy with concurrent temozolomide. Despite poor prognostic factors, the patient is alive without signs of progression 2.5 years post-diagnosis. Targeted agents were not used in upfront treatment for this patient. This is a rare case of stabilization of disease with conventional treatment in a very aggressive tumor. This case is a rare constellation of an 'adult-type' molecular profile in a pediatric patient with a low grade, less aggressive behavior profile, and highlights the need to better understand this rare subtype of tumors in children.

HGG-39. INTEGRATIVE ANALYSES OF BRAFP.V600E MUTATED GLIOMAS: FROM EPIGENETIC TO METABOLIC CHARACTERISTICS

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BRAF p.v600e mutation is encountered in brain tumors, mostly low grade pediatric diffuse gliomas (LGG) and epileptogenic glioneuronal tumors such as gangliogliomas (GG) or pleomorphic xanthoastrocytomas (PXA). Less frequently this mutation is present in high grade glial or glioneuronal tumors such as pleomorphic xanthoastrocytomas with anaplasia, anaplastic ganglioglioma, anaplastic diffuse astrocytomas or glioblastomas. Recently, few publications were highlighting differently the impact of BRAF mutation and CDKN2A deletion, as independent prognostic factors linked to a worst outcome in low grade forms. We studied retrospectively a monocentric cohort of 17 LGGs (14 GG and 3 pilocytic astrocytomas) and 7 BRAF pv600e HGG. The patients were aged below 20 years. We focused on extended tumors' biology assessment (MethylEpic 850K, Next-Generation sequencing, RNA sequencing and metabolomics), as well as tumor immune microenvironment by immunohistochemistry. Among the LGGs, only one had a CDKN2A deletion and one a gain on chromosome 5. All except two LGGs had a complete surgical resection. Four of them were treated by chemotherapies but underwent relapses. All HGGs had a surgical resection followed by a first line chemotherapy (mainly Stupp protocol) and radiotherapy. Five patients relapsed rapidly, benefiting from targeted therapy with vemurafenib and/or biotherapy associating dabrafenib plus trametinib. Among those HGGs, we had both subgroups: "de novo" tumors and patients with a history of LGG tumors. Both were responding well to targeted treatments. The biology uncovers in all HGGs a loss of CDKN2A gene and/or protein. Additionally to this gene abnormality, specific transcriptomic expressions were associated to therapeutic response and immune microenvironment. Epigenetic modulation was linked to specific metabolic switches when BRAF p.v600e gliomas were getting higher grade features (e.g., glutaminolysis, serinolysis and phospholipidic metabolism). Those characteristics seem to be able to predict in LGG p.v600e potential evolution.

HGG-40. NF1 MOSAICISM IN A CMMRD-PATIENT WITH A GLIOBLASTOMA

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Constitutional Mismatch Repair Deficiency (CMMRD) and Neurofibromatosis type 1 (NF1) are brain tumor predisposing syndromes associated with café-au-lait macules (CALM). Due to this overlap, establishing the differential diagnosis can be difficult, but remains crucial as treatments and surveillance protocols clearly differ for affected patient according to the