RAF inhibitors target this pathway and are efficacious in early phase trials in recurrent pLGGs. However, not all patients respond to monotherapy, and many experience progression after completion of therapy. Evaluating combination therapies that may enhance efficacy or prolong disease stabilization is warranted. Lenalidomide is an immunomodulatory agent with an anti-tumor effect demonstrated in phase 1 trials in recurrent pediatric central nervous system (CNS) tumors. OBJECTIVE: To describe our institutional experience using concurrent trametinib and lenalidomide in the treatment of primary pediatric central and peripheral nervous system (PNS) tumors. METHODS: Retrospective review of patients' medical records. RESULTS: Four patients with locally recurrent primary CNS or PNS tumors, three with WHO grade II pilomyxoid astrocytomas and one with a plexiform neurofibroma, were treated with trametinib and lenalidomide concurrently. Two patients developed severe thromboembolic events. One patient was treated with combination therapy for seven months until trametinib and lenalidomide were held after urgent ventriculoperitoneal shunt revision. Shortly following shunt revision, he experienced near-complete vision loss. MRI of the brain demonstrated a left posterior watershed territory hypoxic-ischemic injury. In a second patient, after four months of combination therapy, surveillance echocardiogram showed an incidental finding of severe biventricular dysfunction with a left ventricular ejection fraction (LVEF) of 17.7% and two mural thrombi in the left ventricular apex. She started losartan and enoxaparin and discontinued trametinib and lenalidomide. Her LVEF normalized four months later, and the mural thrombi resolved. CONCLUSIONS: Given the severe thromboembolic events experienced by these patients treated with concomitant trametinib and lenalidomide, this combination requires further investigation, and we urge caution if used concurrently.

LGG-43. REDUCTION IN THE CEREBROSPINAL FLUID PROTEIN LEVEL AFTER BEVACIZUMAB TREATMENT IN PATIENTS WITH OPTIC PATHWAY LOW-GRADE GLIOMAS

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Cases Presentations: Case 1: A 1-year-old boy with suprasellar pilocytic astrocytoma with previous history of shunting disfunction, treatment according vinblastine protocol due to anaphylactic reaction with carboplatin presented with ascites and necessity of ventricular-atrial shunt. Due to high protein cerebrospinal fluid (CSF) level (551mg/dl) he was submitted to external ventricular drainage and bevacizumab 10mg/kg was associated to his oncology treatment. After three cycles of bevacizumab, the patients' CSF protein levels decreased dramatically 178 mg/dL, allowing the shunt procedure without complications and shorter hospital stay. Case 2: A ten-year-old boy with suprasellar pilocytic astrocytoma treated with three lines of chemotherapy showed tumor progression one year after the end of carboplatin-vincristine protocol and shunting disfunction. External ventricular drainage was performed, and the CSF showed 590mg/dl protein level. He was treated with vinblastine 6mg/m2 weekly and bevacizumab 10mg/kg each 14 days. After two cycles of bevacizumab, the protein level was 191mg/dl allowing another V-P shunt procedure. Discussion: Optic pathway gliomas frequently cause elevated cerebrospinal fluid protein concentrations leading to shunts occlusions and failures, necessity of external ventricular drainage and longtime hospitalization, implicating risk of serious infections. Bevacizumab is a monoclonal antibody with immunomodulatory and anti-vascular endothelial growth factor (VEGF) activities that has been used in combination with other chemotherapeutic agents such as irinotecan and vinblastine to treat low-grade gliomas and has been reported to decrease the CSF protein concentration.Final Comments: Bevacizumab treatment in patients with gliomas and high CSF protein levels seems effective in decreasing protein leakage from the vessels to the ventricles, thereby improving the scope for successful shunt placement.

LGG-44. MULTI-OMIC ANALYSIS REVEALS INTEGRATED SIGNALLING NETWORKS IN PAEDIATRIC LOW-GRADE GLIOMA

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Paediatric low-grade gliomas (pLGGs) are the most common type of childhood CNS tumours. Our study included pilocytic astrocytomas (PAs; KIAA1549:BRAF), glioneuronal tumours (GNTs; BRAFV600E) and location-matched controls. We initially performed kinase substrate enrichment analysis (KSEA) to infer differential kinase activity, which allowed us to identify altered signalling networks in the two tumour types. Here we report the integration of these kinase signalling networks together with total proteomics, transcription factor enrichment analysis (TFEA) and transcriptomics (coding and non-coding). Total proteomic profiling confirmed an increase in proteins involved in cell cycle, inflammatory response and signal transduction in PAs, whilst there was an increase in proteins promoting cell growth, immune response and inflammation in GNTs. TFEA was performed using the DoRothEA database to identify master transcriptional regulators. We observed significant activation of transcription factors (TFs) that are direct targets of MAPK signalling in both tumour types. Notable differences include the higher activation of NF-kB/STAT TFs in PAs and the increased activation of RFX1/2 in GNTs. Next, we constructed kinase-TF networks and identified multiple kinases targeting STAT3 in PAs and STAT1/3 in GNTs. Pathway analysis of RNA-Sequencing data showed enrichment of NF-kB in both tumours and repression of E2F target genes (PA) and reduced expression of MYC target genes (GNT). We developed a BRAF-OIS signature and found 23 genes commonly enriched in both tumour types, highlighting shared senescence-associated targets. MicroRNA profiling identified upregulation of microRNAs that target MAPK and NF-kB signalling networks, and many down-regulated microRNAs with tumour suppressive roles. Finally, we identified several lncRNAs known to be differentially expressed in glioma and, whilst their mechanism(s) of action are varied, they are thought to act with other well-established regulators to fine-tune cellular processes. Taken together, we present a comprehensive signalling network as a framework for studying pLGGs.

LGG-45. GENETIC DEPENDENCIES IN *MYB/MYBL1*-DRIVEN PEDIATRIC LOW-GRADE GLIOMA MODELS

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AIM: Pediatric low-grade gliomas (pLGGs) are a heterogenous group of tumors, diverse in their localization, histology, mutational landscape, clinical behavior, and treatment response. Genomic alterations impacting the MYB family of transcription factors were identified in two distinct pLGG subtypes: Angiocentric Gliomas (AG) and Diffuse Astrocytomas (DA). The molecular profiles and therapeutic vulnerabilities associated with these genomic alterations remain unexplored. In this study we highlight the use of genome-wide CRISPR/Cas9 knock-out screens for an unbiased identification of translatable therapeutic targets. **METHODOLOGY**: Given the lack of patient-derived pLGG cell lines, we engineered *in vitro* pLGG mouse and human neural stem cell (NSC) models to harbor pLGG-relevant genomic alterations. We performed single cell RNA sequencing to investigate the transcriptional profiles driven by these mutations and to dissect the central regulatory networks enabling tumorigenesis. Specific genetic dependencies associated with *MYB/MYBL1* mutations were screened using the Brie genome-wide mouse CRISPR lentiviral knock-out pooled library, consisting of 78,637 single guide RNAs (sgRNAs) targeting 19,674 mouse genes. RESULTS: We have successfully generated *in vitro* NSC-based pLGG models crucial to deepening our knowledge on pLGG biology and the identification of translatable therapeutic targets. Genome-scale CRISPR/Cas9 knock-out screens in isogenic NSCs models, expressing distinct *MYB/MYBL1* alterations or a control transgene, revealed several differential genetic dependencies. Among the top identified dependencies are regulators of cell-stress response, cell-cycle progression, and modulators of the ubiquitin-proteasome degradation pathway. **CONCLUSION**: Genome-wide CRISPR knock-out screens are a powerful tool for the unbiased identification of mutation-specific genetic dependencies that can be explored as candidates for precision medicine approaches.

LGG-46. SURVIVAL OF THE FITTEST? A PROGNOSTIC EVALUATION OF PAEDIATRIC LOW-GRADE GLIOMA (PLGG) SURVIVOR FUNCTIONAL OUTCOMES

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