geted agents are increasingly being utilized to treat LGG, but the effect of these agents on accompanying neurologic complications are poorly understood. CASE: An 8-years old male with Neurofibromatosis Type 1 (NF1), medically refractory epilepsy and deep extensive glioma (extending from the optic pathway and involving the basal ganglia and corpus collosum) began selumetinib therapy due to radiographic and symptomatic tumor progression. Radiographic response (resolution of enhancement) was observed at 12 weeks of therapy, accompanied by improvement in seizure frequency, hemiparesis, and academic performance. Due to cardiotoxicity observed at that time (asymptomatic decreased ejection fraction and shortening fraction on echocardiogram), selumetinib was reduced to 50% dosing. On this reduced dose of selumetinib, seizures increased in frequency with subsequent worsening hemiparesis and recurrence of learning difficulties. One month later, dosing was escalated back to 100% due to interval resolution of cardiotoxicity, resulting in resolution of seizures and improvement in focal neurologic deficits and cognition. DISCUSSION: Dose-dependent response to MEK inhibition was observed without concurrent changes in anti-epileptic medications. The tumor was stable in size despite improved enhancement with treatment, suggesting that objective response by RANO criteria is not necessary for improved seizure control in LGG. Recent work has implicated the RAS/MEK/ERK pathway in neuronal precursor cells as a cause for epilepsy, suggesting that MEK inhibition of NF1-heterozygous neurons could be contributing to treatment response in this patient. Improvements in weakness and academic performance may have been due to improved seizure control or a direct effect of MEK inhibition on NF1-heterozygous neurons. CONCLUSION: MEK inhibition may have a clinically relevant anti-seizure effect for patients with pediatric LGG or NF1.

LGG-39. ASCITES IN A MEDULLARY AND LEPTOMENINGEAL GANGLIOGLIOMA PATIENT FOLLOWING CISPLATIN TREATMENT NECESSITATING CESSATION OF THERAPY AND CONVERSION TO VA SHUNT

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INTRODUCTION: Ganglioglioma is a low grade neoplasm consisting of dysplastic neuronal and neoplastic glial cells and accounts for 5% of pediatric CNS tumors. Management often includes CNS diversion. There have been case reports in which platinum containing chemotherapy has been thought to contribute to CSF malabsorption leading to ascites. CASE: A 13 month old male developed progressive macrocephaly, developmental delay, chronic emesis, and intermittent bilateral cranial nerve VI palsy over the 5 months prior to presentation. MRI brain/spine was significant for an enhancing nodule in the left posterior lateral medulla, nodular thickening and enhancement along the brainstem down to the conus medullaris and in the tentorium, with associated hydrocephalus. Biopsy of the medullary nodule and of the enhancement were consistent with ganglioglioma with BRAF-KIAA1549 fusion, equivocal MYCN amplification, and no BRAF V600E mutation. A ventriculo-peritoneal shunt was placed at the time of biopsy. Therapy was initiated with vincristine (1.5 mg/m2) and carboplatin (175 mg/m2.) Following the 12 week induction phase of therapy, he developed increasing diarrhea, emesis, and abdominal ascites. Peritoneal fluid analysis had no malignant cells and low protein compared to CSF. Ascites was responsive to drainage but would rapidly re-accumulate. Ultimately the patient's chemotherapy was discontinued after 2 maintenance cycles due to continued symptoms. Acetazolamide was trialed but discontinued due to side effects, so its efficacy could not be determined. He underwent shunt externalization followed by venticulo-atrial (VA) shunt re-internalization. He has not had ascites since that time, at 4 months from surgery. His CNS disease burden has been stable at 6 months off therapy. DISCUSSION: Ascites was most likely due to CSF malabsorption in the abdomen with a possible contribution from platinum containing chemotherapy and less likely secondary to malignant peritoneal cells. Resolution since VA shunt internalization makes alternate explanations less likely.

LGG-40. GROWTH HORMONE REPLACEMENT IN CHILDREN ON THERAPY WITH VEMURAFENIB FOR LOW GRADE GLIOMA

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BRAF inhibitors (iBRAF) are a therapeutical option for pediatric Low-Grade-Gliomas (pLGG), but their chronic use may be needed to prevent tumor regrowth. Growth hormone (GH) replacement in children with GH deficiency (GHD) and on oncological treatment is under debate. We report on our experience of recombinant human GH (rhGH) replacement in two children (1 Female, 1 Male) which started Vemurafenib therapy, at 5 (F) and 9,25 (M) years of age, for recurrent/progressive chiasmatic-hypothalamic pLGG, with partial response (RANO criteria) and subsequent stable disease. A diagnosis of GHD was established at 9,2 (F) and 11,2 (M) years of age (GH peaks to stimulation tests <3mcg/L), 4,2 (F) and 1,9 (M) years after Vemurafenib start. Both patients were treated with GnRH analogues for precocious puberty. rhGH dose was titrated to 0.020 mg/kg/day during follow-up based on IGF-1 levels < +2 SDS. Height remained stable in both (F: -3,4SDS; M: 0SDS), with a mean growth velocity after 2 years around 6 cm/yr. BMI increased in the F (1,59 to 1,78 SDS) and decreased in the M (2,66 to 2,56 SDS); Dual-X-ray absorbiometry confirmed high fat mass at T0 (F:54,6%; M:48%) and at T24 (F:49,2%; M:48,1%). Lipid profile improved in both patients (F: Triglycerides 175 to 152 mg/dl, LDL 195 to 155 mg/dl; M: Triglycerides 138 to 118 mg/dl, LDL 147 to 147 mg/dl, at T0 and T24, respectively), while baseline blood glucose increased (F: 83 to 96 mg/dl; M 82 to 91 mg/dl). Residual tumor was stable in both patients. CONCLUSIONS: In 2 GHD patients due to pLGG and treated with Vemurafenib, two-years of low-dose rhGH showed beneficial effects on height stabilization and on lipid profile, and a different impact on body composition parameters; rhGH was safe and not associated with residual tumor growth.

LGG-41. THE CLINICAL AND MOLECULAR LANDSCAPE OF GLIOMAS IN ADOLESCENTS AND YOUNG ADULTS

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OBJECTIVE: Gliomas in adolescents and young adults (AYA) are commonly treated with a standard chemo-radiation approach based on data from adults. The clinical impact of paediatric-type alterations in these tumours is unknown. METHODS: We compiled a multi-institutional cohort of patients diagnosed with glioma between 15-39.9 years over 20 years. Complete molecular analysis, therapeutic data and outcome was collected. For specific alterations, analysis included patients aged 0-39.9 years. RESULTS: A total of 1900 patients with 876 AYA gliomas were included. Ongoing analysis reveals genetic alterations in 95% of available tumours. IDH-mutant tumours account for only 53%, while paediatric-type mutations were found in 35% of AYA tumours with IDH-WT GBM accounting for the remaining 12%. The most common paediatric alterations in AYAs included BRAF p.V600E (11%) and FGFR alterations (6%) while BRAF fusions, H3 p.K27M and H3.3 p.G34R were rarely observed (4%, 4% and 1% respectively). BRAF fused tumours with non-canonical binding partners were enriched in AYAs. Analysis of BRAF-V600E gliomas between ages 0-40 revealed increased tendency for malignant tumours in patients >20 years suggesting malignant transformation possibly due to higher rate of secondary hits including TP53, CDKN2A and ATRX mutations. This resulted in worse overall-survival for AYA patients with BRAF-V600E glioma when compared to children under 20 years (p=0.0032). Ten-year OS of 100%, 90% and 95% was seen for BRAF fused, BRAF-V600E and FGFR-altered AYA low grade glioma respectively, compared to 14% and 25% for BRAF-V600E and FGFR-altered high grade glioma. In contrast, continuous decline was observed in the IDH-mutant gliomas with 10-year OS of 50% which declined to 29% at 15 years. CONCLUSIONS: Gliomas in AYA are enriched for paediatric-type alterations with distinct molecularly-based outcomes. As these tumours carry different outcomes than childhood glioma and may respond to targeted inhibitors, AYA gliomas would benefit from comprehensive diagnostic and therapeutic approaches.

LGG-42. THROMBOEMBOLIC TOXICITY OBSERVED WITH CONCURRENT TRAMETINIB AND LENALIDOMIDE THERAPY

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INTRODUCTION: Event-free survival of pediatric low-grade glioma (pLGG) is poor, and patients often require multiple treatment strategies. The hallmark of pLGGs are genetic aberrations of the mitogen-activated protein kinase pathway, which lead to constitutive pathway activation. MEK and

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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