

Cells in both states were treated with different BH3-mimetics. Inhibition of metabolic activity was measured after 72 hours. Target expression was assessed by RT-qPCR and Western blot. On-target activity of BH3-mimetics was determined by immunoprecipitation (IP) of Bcl-xL/BAK. Results: BH3-mimetics with strong binding affinity for Bcl-xL (Navitoclax, A-1131852, A-1155463) showed selectivity for senescent cells in 2/3 models (DKFZ-BT66 and DKFZ-BT314) and acted in nanomolar ranges. IC<sub>50</sub>s for Navitoclax (C<sub>max</sub> 6600nM in patients) were 40nM (OIS) vs. 200nM (proliferation) and 170nM (OIS) vs. 3700nM (proliferation) in DKFZ-BT66 and DKFZ-BT314, respectively. Target engagement was evident in the Bcl-xL/BAK-IP, and target expression of Bcl-xL was similar in all models studied. The relative resistance of senescent DKFZ-BT308 despite on-target activity is currently being investigated. Conclusion: Senolytic treatment of PA with BH3-mimetics targeting Bcl-xL is a promising new strategy directly targeting the major senescent part of the tumor in clinically archivable concentrations. However, our data suggests that not all PAs may respond to treatment. The analysis of comparative gene expression analysis and BH3-profiling is ongoing to define predictive biomarkers.

#### LGG-12. SAFETY AND EFFICACY OF DUAL THERAPY WITH DABRAFENIB AND TRAMETINIB IN AN INFANT WITH BRAF V600E MUTANT INOPERABLE LOW GRADE GLIOMA

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Objective: To describe safety and efficacy of dual targeted therapy with dabrafenib (BRAFi) and trametinib (MEKi) in an infant with inoperable low grade glioma with BRAF V600E mutation. Introduction: Safety and efficacy of dual targeted therapy with BRAFi and MEKi for pediatric low grade glioma (pLGG) is currently being evaluated, however, infants are usually not included in these clinical trials. Case: We report a case of a 2-month-old male infant who presented with involuntary movements and gaze deviation concerning for seizures. MRI brain revealed a tumor involving the medulla, T2/FLAIR dimensions: 2.5 x 2.2 x 2.7 cm and drop metastases to the cauda equina. An EEG ruled out seizure activity. Tumor biopsy was performed revealing Ganglioglioma, WHO grade I. IHC and somatic next generation sequencing revealed BRAF V600E point mutation. Germline testing was negative. Due to tumor progression on traditional chemotherapy, compassionate use of dual targeted therapy with dabrafenib (5.25mg/kg/day divided twice daily) and trametinib (0.032mg/kg daily) was initiated at 4.5 months of age. The patient has tolerated dual therapy for nearly 1 year without significant toxicity with exception of grade I skin rash. In terms of functional outcomes, previously noticed vocal cord paresis has resolved and our patient with global developmental delay continues to make developmental gains, albeit slowly. On recent neuroimaging, pLGG has continued to grow T2/FLAIR dimensions: 3.5 x 3.5 x 3.7 cm, however, combination therapy has halted the rate of growth of this tumor. Conclusion: To our knowledge, our patient is the youngest to receive combination of BRAFi and MEKi. Tumor targeted therapy could be an important treatment option for infants with inoperable pLGG where aggressive surgery and radiation therapy are associated with significant morbidity. Multi-institutional clinical trials that include infants are needed to further comment on safety and efficacy of these agents.

#### LGG-13. PILOCYTIC ASTROCYTOMAS WITH NOVEL BRAF FUSIONS DEMONSTRATE MAPK PATHWAY ACTIVATION

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Background: Pilocytic astrocytomas (PAs) are the most common pediatric low-grade glioma subtype. Oftentimes, PAs demonstrate somatic genetic alterations, the most common being the *BRAF-KIAA1549* fusion, which results in constitutive activation of the MAPK pathway. Better understanding of the effects of other RAF fusions is necessary to determine the potential utility of MAPK-targeting therapies. Methods: Three patients presented to Children's Hospital Colorado and were ultimately diagnosed with PAs harboring previously unreported gene fusions identified as *FYCO-RAF1*, *CCTNNBP2-BRAF*, and *SLC44A1-BRAF*. Utilizing immunohistochemistry, we stained novel samples and controls for ERK and pERK (phosphorylated ERK) to assess the activation of the MAPK pathway. PAs with known *BRAF-KIAA1549* fusions (4 samples) and normal brain tissue (5 samples) were used as positive and negative controls, respectively. We additionally performed RNA sequencing to better understand expression changes associated with these fusions, utilizing Metascape and GSEA (Gene Set Enrichment Analysis) for analysis. Results: Immunohistochemistry of negative control samples demonstrated less p-ERK than ERK (ratios of 0.6–0.9, mean 0.8). All samples with novel fusions demonstrated statistically significantly higher

p-ERK expression compared to negative controls (ratios of 1.3–1.7, mean 1.4). These experimental samples also all fell within the p-ERK to ERK expression range of the positive control samples, which demonstrated the widest range of expression (ratios of 1.1–4.5, mean 2.2). Our molecular analysis further confirmed these results, with GSEA demonstrating positively upregulated MAPK and ERK pathways in 2 positive controls and 1 novel fusion sample. Metascape analysis emphasized overall similar gene expression between these samples, demonstrating many shared genes and functional pathways. Conclusions: We identified 3 previously unreported RAF fusions in PA that demonstrate activation of the MAPK pathway, although not as extensively as seen in some positive control samples with *BRAF-KIAA1549* fusions. MEK inhibition may be a useful therapeutic strategy in these tumors if targeted therapy is indicated.

#### LGG-14. PRESENTATION CHARACTERISTICS AND TREATMENT OUTCOMES FOR PEDIATRIC OPTIC PATHWAY GLIOMAS IN QATAR

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Objectives: To review the presentation characteristics and treatment outcomes for pediatric optic pathway gliomas (OPG) in Qatar. Methods: Retrospective review of data for children with OPG from January 2009 to February 2021. Presenting features, diagnostic imaging and indications for treatment were reviewed. Progression free survival (PFS) and overall survival (OS) were computed using standard statistical methods. Medical notes were also reviewed for visual outcomes. Results: Nineteen patients were diagnosed with OPG during the study period. There were 10 (52%) females. Median age was 29 months (range 6–186) months. Eleven (57%) tumors were related to neurofibromatosis Type 1 (NF-1). Nine (47%) of OPG were located in optic nerves, 5 (26%) were chiasmatic/suprasellar, while the remaining 5 (26%) involved a combination of structures. Seven (36%) children presented with oculo-visual symptoms. Another 7 were diagnosed on screening imaging for NF-1. Seven (36%) children had debulking surgery/biopsy, while the remaining patients were diagnosed on neuro-imaging alone. Thirteen (68%) patients were treated with chemotherapy and 2 received additional radiotherapy. Indications for non-surgical treatment included visual impairment (46%) and large/progressive tumor (54%). Carboplatin based regimens were used as first line chemotherapy for 76 % of patients. Five (38%) patients required more than one lines of treatment. OS and PFS at 36 months were 100% and 48%. Baseline visual assessment showed 5 children each (26%) had unilateral and bilateral visual impairment, while 9 (48%) had normal vision. Of the 6 children receiving chemotherapy for visual impairment, 2 (33%) showed improvement. Of the 7 children treated for large/progressive tumors, 3 (42%) showed partial response, 2 (28%) had progressive disease and 1 had stable disease after the first line therapy. Conclusions: Our results are in-keeping with international data for optic pathway gliomas. Early referral and diagnosis may improve visual outcomes for this group of tumors.

#### LGG-15. COMPREHENSIVE ANALYSIS OF MYB/MYB1-ALTERED GLIOMAS: A MULTI-INSTITUTIONAL EXPERIENCE OF 33 GLIOMAS

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Background: Pediatric diffuse gliomas harbor recurrent genetic alterations, including those in *MYB* and *MYBL1*. Regardless of histopathologic classification, low-grade diffuse gliomas with *MYB/MYBL1* alterations represent a single disease entity. Additional insight is needed to define optimal therapeutic strategies for these tumors. Methods: We retrospectively reviewed gliomas with *MYB* or *MYBL1* alterations treated or referred for pathologic review at St. Jude Children's Research Hospital (St. Jude). Tumor specimens were centrally reviewed. Molecular characterization and clinical data were collated from St. Jude and referring institutions. Results: Thirty-three patients were identified. Two tumors had *MYBL1* alterations, while 31 had *MYB* alterations. *MYB-QKI* fusion was the most common alteration. Eighteen (55%) were male. The median age at diagnosis was 5 years (range, 0–40 years). Most tumors were in the cerebral cortex (22/33), and the most common presentation was seizures (16/33). Three patients (9%) presented with hydrocephalus and required cerebrospinal fluid diversion. Two patients (6%) presented with metastatic disease. Gross-total resection was achieved in 15 patients (45%).