Therapy poses challenges as it is unclear if the biology and prognosis of pediatric *IDH*-mutant gliomas are identical to adults. METHODS: We performed an IRB approved, systematic retrospective search for *IDH*-mutant gliomas in the Dana-Farber Cancer Institute/Boston Children's Hospital database between 2009–2018, analyzing incidence, demographics, histology, co-occurring genetic alterations and outcome. RESULTS: We identified 575 patients with glioma, ages 0–21 years. Of these, 394 underwent biopsy/resection (0–9 years:n=204; 10–21 years:n=190), with 294 genetic testing. Fifteen of 294 tumors (5%) were *IDH1*-mutant. Among patients 0–9 years and 10–21 years, 1/156 (0.6%) and 14/138 (10%) had *IDH1*-mutant tumors, respectively. Among patients 10–21 year old, 13/115 low-grade gliomas were *IDH1*-mutant (11%). High-grade gliomas accounted for the remaining 23, with one *IDH1*-mutant glioma (4%). Most common co-occurring genetic alterations for diffuse astrocytoma (n=12) were *TP53* (n=9) and *ATRX* (n=2). Three patients with *IDH1*-mutant oligodendrogliomas had 1p/19q deletion. Eleven *IDH1*-mutant patients were evaluable for outcomes with median follow-up of five years. Five-year radiation-free, progression-free and overall survival for patients with low-grade histology were 76% and 100%, respectively. One patient with high-grade glioma recurred 1.2 years after upfront chemo-radiation and died soon after recurrence. CONCLUSION: *IDH*-mutant gliomas comprise a small proportion of pediatric gliomas. Incidence rate is higher in the second decade of life. Comparative analyses between pediatric *IDH*-mutant gliomas and adult historical cohorts are currently underway, evaluating outcomes, radiation therapy and frequency of malignant transformation.

LGG-04. A PHASE II RE-TREATMENT STUDY OF SELUMETINIB FOR RECURRENT OR PROGRESSIVE PEDIATRIC LOW-GRADE GLIOMA (PLGG): A PEDIATRIC BRAIN TUMOR CONSORTIUM (PBTC) STUDY

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The PBTC conducted a re-treatment study (NCT01089101) evaluating selumetinib (AZD6244, ARRY-142886), a MEK I/II inhibitor, in children with recurrent/progressive pLGG. Eligible patients must have previously enrolled on PBTC-029 or PBTC-029B and progressed after coming off treatment with selumetinib. Patients must have maintained stable disease (SD) for ≥12 courses or had a sustained radiographic response (partial or complete) during their first exposure to selumetinib. Thirty-five eligible patients (median age: 13.11 years [range 7.96–25.33]) were enrolled, 57% of whom had optic pathway or hypothalamic target lesions. At the time of submission, median duration of treatment was 18 courses (range 2–48) and 21 subjects remained on therapy. Best responses reported to date are 6/35 (17%) partial response, 22/35 (63%) SD and 7/35 (20%) progressive disease with a 2-year progression-free survival of 75.7 + 8.3%, which met the design parameters for success. The most common attributable toxicities were grade 1 diarrhea, elevated AST, hypoalbuminemia, elevated CPK, maculo-papular rash, fatigue, paronychia, ALT elevation, acneiform rash and grade 2 CPK elevation. Rare grade 3 toxicities included CPK elevation (3), lymphopenia (2), paronychia (2) and ALT elevation (2). There was only one grade 4 CPK elevation. Five patients (14%) required dose reductions due to toxicity. There does not appear to be a notable difference in toxicities observed during initial selumetinib therapy versus re-treatment. In pLGG that has recurred/progressed following treatment with selumetinib, re-treatment with selumetinib appears to be effective with 80% of patients again achieving response or prolonged stable disease. Long-term follow-up is ongoing.

LGG-05. MOLECULAR GUIDED THERAPY FOR A PEDIATRIC LOW GRADE GLIOMA: A CASE REPORT

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Low grade gliomas are the most common type of central nervous system tumors among children. Despite the fact that they are not typically life threatening, low grade gliomas remain a significant clinical challenge. Case Study: Patient is a 4-year-old male who presented at 20 months of age with several weeks of ataxia, emesis, and head tilt. Imaging revealed a right temporal lobe lesion; he was subsequently taken to surgery, where a gross total resection was achieved. Imaging 9 months post resection revealed recurrent disease within the right temporal region with leptomeningeal involvement. Four months later imaging revealed progression of multifocal disease and new growth within the sella. At this time the patient started standard treatment, Carboplatin and Vincristine, per CCG 9952A. Persistent slow progression was observed despite receiving standard therapy. The patient developed a grade 3 reaction to carboplatin, worsening with each subsequent dose. At this time, he was referred to our Precision Genomics Neuro Oncology program for tumor molecular characterization. Somatic tumor testing revealed an ETV6-NTRK3 fusion, at which time standard treatment was stopped, and patient began targeted therapy, Larotrectinib. Imaging was preformed 2 months post start of targeted therapy and revealed interval decrease in size of previously enhancing nodular lesions; findings consistent with treatment response. Disease burden continues to decrease with therapy. This case illustrates a clear benefit of using molecular guided therapy in low grade gliomas.

LGG-06. LONG-TERM OUTCOME OF NEWLY DIAGNOSED LOW GRADE GLIOMA

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INTRODUCTION: Low grade glioma (LGG) is the most common central nervous system (CNS) tumor in children accounted for 30–50%. Regarding benign characteristic of disease, surgical management remains the mainstay of treatment. However, surgical approach is limited in some conditions such as location at brainstem or infiltrative tumor. Chemotherapy and radiation treatments have been included in order to control tumor progression. The 5-years survival rate is approach 90% especially in patients who receive complete resection. However, the outcome of children with LGG in low to middle income is limited. Therefore, the aim of the study was to determine long-term outcome of children with newly diagnosed LGG. METHODS: A retrospective study enrolled children aged <18 years who were newly diagnosed LGG during January 2006- December 2019. Diagnosis of LGG was confirmed by histological findings of grade I and II according to WHO criteria. RESULTS: A total of 40 patients, female to male ratio was 1:1.35 and mean (SD) for age was 6.7 (4.0) years. The most common location was optic chiasmatic pathway (42.5%), followed by suprasellar region (25.0%). Sixty percent of patients received at least partial tumor removal. Chemotherapy and radiation had been used in 70% and 10.0% respectively. The 10-year progression free survival was 74.1±11.4% and overall survival was 96.2±3.8%. SUMMARY: Treatment of Pediatric LGG mainly required surgical management, however, chemotherapy and radiation had been used in progressive disease. The outcome was excellent.

LGG-09. CORRELATING GENETIC SIGNATURE OF PILOMYXOID ASTROCYTOMAS AND PILOCYTIC ASTROCYTOMAS WITH QUALITATIVE AND QUANTITATIVE MR IMAGING CHARACTERISTICS

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PURPOSE: Pilomyxoid astrocytomas are predominantly located in supra-chiasmatic region and are more clinically aggressive than pilocytic astrocytomas, although recent WHO 2016 classification placed them into the grade I/II category. In our study, we describe imaging correlation of PMA to their genetic signature. MATERIALS AND METHODS: We identified 12 pediatric patients with pathologically proven PMA, PA, and PA with myxoid features in an IRB approved study. Three of the tumors had whole exome somatic and germline sequencing. Qualitative MRI characteristics of location, size, enhancement, edema, T2 and T1 intensity, and multifocality were assessed. RESULTS: Among the PMA, 3 cases were found to have *KIAA1549-BRAF* fusion, 1 case *BRAF* V600E mutation, and 2 cases had wildtype *BRAF*. The *BRAF* wildtype tumors had atypical imaging features with intraventricular extension of tumor, involvement of frontal lobe parenchyma and one tumor demonstrating increase in size and development of enhancement at 5 years. Whole exome sequencing of *BRAF* wildtype tumors identified somatic truncation mutations in *NF1* R1534X and R1513X with wildtype germline *NF1* and missense mutations in KMT2C and GLTSCR1. Among PAM, one was *BRAF* wildtype with mutations i *PTCH1* M956V and *PTPN1* (A72V) and demonstrated atypical features of intratumoral hemorrhage on presentation. Among PA, one was positive for *KIAA1549-BRAF*, one was *BRAF* wildtype. CONCLUSIONS: *BRAF* wildtype PMA and PA demonstrate atypical tumor localization and are associated with atypical genetic mutations on whole exome sequencing. On the contrary, presence

of *KIAA1549-BRAF* fusion or *BRAF* V600E mutation within PMA and PA correlates with classic qualitative imaging characteristics.

LGG-11. INSTITUTIONAL EXPERIENCE OF BRAF TARGETING THERAPY

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BACKGROUND: The use of BRAF inhibitors is widely accepted in adult oncology as treatment for BRAF mutated cancers. BRAF alterations are frequently found in both pediatric low grade and high-grade gliomas, which has opened a new door to targeted therapies for pediatric gliomas. Targeted therapy drugs are associated with predictable patterns of adverse events. However treating in children may potentiate unique challenges. We present our institutional experience of targeted therapy with a focus on adverse events. METHODS: We conducted a retrospective chart review of patients treated with BRAF and/or MEK inhibitors between 2015–2019. RESULTS: There are nine patients treated with either MEK inhibitor(n=) or the combination therapy(n=). The most common diagnosis was Pilocytic astrocytoma. Targeted therapy was chosen as salvage therapy in all patients. The most common side effect was a pruritic erythematous rash, observed in 8 out of 9 patients. Cardiac toxicity (Grade 2, n=1) and GI toxicity (Grade 3, n=1) were found in patients treated with MEK inhibitor. Both cases resulted in cessation of therapy or significant decreased dose respectively. While two patients died due to progression of disease and two other continued to progress, 5 patients have demonstrated stable disease while on therapy. CONCLUSIONS: Our study revealed the incidence of severe adverse events in two patients with BRAF targeted therapy. Due to the potential life-long use of targeted therapy, it is important to follow guidelines of adverse event monitoring and to develop a prevention and management strategy for severe adverse events.

LGG-12. TRAMETINIB FOR PEDIATRIC LOW GRADE GLIOMAS: A SINGLE INSTITUTION EXPERIENCE

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INTRODUCTION: Low grade gliomas (LGG) are the most common pediatric brain tumors. Tumors not amenable to resection can recur or progress despite treatment with chemotherapy and/or radiation. Recent discovery of the activation of the mitogen-activated-protein-kinase (MAPK) pathway as the primary oncogenic driver for this group of tumors has led to a shift towards the use of BRAF and MEK inhibitors. METHODS: Herein we performed a chart review of seven pediatric LGG treated with trametinib, a MEK inhibitor. While most were treated in the relapse setting, one patient was treated for de novo LGG as a result of experiencing multiple severe adverse effects to conventional agents. RESULTS: Median age was 14 years old (range: 5 to 17 years). Six of seven patients had tissue for molecular characterization. The 2 patients with Neurofibromatosis Type 1 (NF-1) carried no other molecular aberrations. Two had the BRAF V600e mutation (1 had a concurrent PTPN11 mutation) and 2 were positive for the KIAA1549-BRAF fusion. Average duration on treatment was 8 months (range: 3 to 31 months). Disease control was achieved in 6 of 7 subjects, with one PR as best response. One patient with concurrent BRAF V600e and PTPN11 mutations progressed on trametinib and was switched to dual BRAF and MEK inhibitor therapy. Most common toxicities were acne (57.1%), oral mucositis (42.9%), skin rash, and paronychia (both 28.6%). Three patients required dose reduction and/or intermittent dose interruption. CONCLUSION: Our data supports the use of trametinib for both upfront and relapsed/refractory pediatric LGG.

LGG-13. THE CLINICAL AND MOLECULAR LANDSCAPE OF GLIOMAS IN ADOLESCENTS AND YOUNG ADULTS

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OBJECTIVE: Pediatric low grade gliomas are typically driven by MAPK upregulation with excellent long-term survival. In contrast, adult lower grade gliomas commonly harbor IDH-1 mutations and undergo malignant transformation. Gliomas in adolescents and young adults (AYA) are an orphan group of tumors that have been poorly described. We aim to determine the clinical and molecular landscape of AYA gliomas. METHODS: A multi-institutional population based cohort of 839 patients diagnosed with glioma between 15–40 years has been identified. Complete molecular analysis, long term outcome and therapeutic data are being collected. RESULTS: Of 364 AYA gliomas analyzed, the prevalence of WHO grade I tumors was highest in those <21 years (54%), while the prevalence of higher grade tumors increased with age. Interestingly, only 38% harbor IDH-1 mutations while 23% harbor pediatric mutations, including 8% with BRAF p.V600E, and 4% with *KIAA1549:BRAF* fusion. The median age for IDH-1 mutation is 32 years, with highest frequency in WHO grade II and III tumors. In contrast, BRAF alterations were most frequently observed in WHO grade I and II tumors and enriched in those less than 20 years. Five-year progression-free survival for BRAF fusion, p.V600E and IDH-1 p.R132H were 81%, 78% and 26% respectively. No survivors were observed in H3 p.K27M and p.G34R gliomas (p<0.0001). CONCLUSIONS: Gliomas in AYA overlap pediatric and adult classification and exhibit enrichment for pediatric alterations. As the latter are associated with improved PFS and are amenable to targeted therapies, this should be considered in the work up of these tumors.

LGG-14. MULTI-OMIC ANALYSIS OF MAPK ACTIVATION IN PEDIATRIC PILOCYTIC ASTROCYTOMA

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Pilocytic astrocytomas (PA) are low-grade gliomas (pLGG) and are the most frequent childhood brain tumors. They are characterized by oncogene-induced senescence (OIS) initiated and sustained by senescence-associated secretory phenotype (SASP) factors. OIS and SASP in PA are thought to be driven by aberrations of the mitogen-activated protein kinase (MAPK) pathway (e.g. KIAA1549:BRAF fusion, $BRAF^{V600E}$ mutation, for the most common MAPK alterations occuring in PA), leading to its sustained activation. The MAPK pathway cascade is activated in a sequential manner: 1) ERK activation, which phosphorylates downstream partners in both cytoplasm and nucleus. 2) ERK-mediated induction of immediate early genes encoding transcription factors. 3) Induction of MAPK target genes expression. 4) Activation of downstream pathways. Our aim is to unravel the molecular partners involved at each level of the sustained MAPK pathway activation in pLGG with different genetic backgrounds (KIAA1549:BRAF fusion and $BRAF^{V600E}$ mutation), and leading to the induction of OIS and SASP factors expression. pLGG cell lines DKFZ-BT66 (KIAA1549:BRAF) and BT-40 ($BRAF^{V600E}$) were treated with the MEK inhibitor trametinib at key time points, and gene expression profile analysis was performed, allowing transcriptome analysis at each step of the MAPK cascade. This will be combined with a whole proteomic and phospho-proteomic analysis. Combination of the transcriptome and proteome data layers will allow the identification of a) downstream targetable partners activated by the MAPK pathway involved in PA senescence, b) new putative targets that might bring benefit in combination with MAPK inhibitors.

LGG-15. PEDIATRIC LOW-GRADE GLIOMAS IN SAUDI ARABIA: RETROSPECTIVE ANALYSIS OF CHILDREN WITH LOW-GRADE GLIOMAS TREATED IN KING FAHAD MEDICAL CITY KFMC-SINGLE INSTITUTIONAL EXPERIENCE

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