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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Pediatric Low-grade gliomas (PLGGs) are extremely heterogeneous tumors and account for approximately 35% of childhood brain tumors. This retrospective study on 55 newly diagnosed children (<14 ys) with pathologically confirmed LGG from 2006 to 2016 aimed to review demographic data, clinical and therapeutic aspects and treatment outcome of PLGGs in children in Saudi Arabia. RESULTS: 33 (60.0%) males,22 (40.0%) females, median age at diagnosis 68 months. Pilocytic astrocytoma was the most common pathological diagnosis 42 (76.4%) location of tumor was Infratentorial in 30 patients (54.0%) and Supratentorial in 24 patients (43.2%), 19 patients (34.6%) had total surgical excision, 10 (18.2%) subtotal resection, 20 (36.4%) partial excision and 6 (10.9%) had biopsy only; After initial Surgery 30 patients (54.5%) required adjuvant chemotherapy of whom 14 patients (46.7%) experienced a treatment failure event, 25 patients (45.5%) who were initially observed post surgery 6 patients (24%) of them had relapse /progression and required further therapy. Only 2 patients (3.6%) received radiotherapy due to uncontrolled progression first line chemotherapy carboplatin and vincristine (CV) regimen was tolerated, Carboplatin allergic reactions developed in 21.1% of patients. Median follow-up of 6.49 years, the median time of relapse/ progression was 2.85 years The 5-year overall survival (OS) rates and progression free survival for all patients were 92.2 %, and 63.3% respectively. This study was to document the outcome of pediatric LGG in Saudi Arabia and to serve as a guideline for the future management with incorporation of molecular studies on pediatric LGGs which may help improve the outcome for Saudi children with LGG.

LGG-16. PILOMYXOID ASTROCYTOMA OF THE CERVICAL SPINAL CORD IN A 7-YEAR-OLD ARMENIAN BOY: A CASE REPORT

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BACKGROUND: Pilomyxoid astrocytoma (PMA) is a glial tumor that occurs predominantly in the hypothalamic-chiasmatic region and rarely in spinal cord. It has similar features as pilocytic astrocytomas, with some distinct histological characteristics and worse prognosis. The 2007 WHO recognized PMA as a Grade II glioma due to its aggressive behavior and dissemination tendency, but according to 2016 version grading of the pilomyxoid variant is under research. Here we report a case with a rare location, aggressive behavior and rapid progression. CASE PRESENTATION: A 7-year-old boy presented with headache, nausea, vomiting. Imaging revealed an intramedullary tumor extending from C2 to C6 with hydrocephalus. A ventriculo-peritoneal shunt and complete surgical resection were performed with significant improvement in the patient's condition. Histopathological findings were consistent with pilomyxoid variant of pilocytic astrocytoma, with negative BRAF V600E and MGMT. Three months later, the follow-up imaging revealed disease recurrence with leptomeningeal metastases, for which the patient received standard-dose craniospinal irradiation 35.2 Gy with boosts to tumor bed and metastatic sites 49.6 Gy and 54 Gy respectively. 11 months later tumor progression was revealed with new metastatic lesions in the bones. Patient received 6 cycles of chemotherapy with TMZ and Avastin, but continued to suffer disease progression on therapy and he succumbed to his disease at 24 months from diagnosis. CONCLUSION: Given the rarity of documented patients with spinal pilomyxoid astrocytoma with rapid progression, as well as the lack of certain WHO classification and treatment guidelines, this case report might be useful for development of more efficient treatment strategies.

LGG-17. SYNERGISTIC ACTIVITY OF MAPK INHIBITOR CLASSES REVEALED BY A NOVEL CELL-BASED MAPK ACTIVITY PEDIATRIC LOW-GRADE GLIOMA ASSAY

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Pilocytic astrocytomas (PAs) and other pediatric low-grade gliomas (pLGGs) exhibit aberrant activation of the MAPK signaling pathway caused by genetic alterations, most commonly KIAA1549:BRAF fusions, BRAF V600E and NF1 mutations. In such a single-pathway disease, novel drugs targeting the MAPK pathway (MAPKi) are prime candidates for treatment. We developed an assay suitable for pre-clinical testing of MAPKi in pLGGs, aiming at the identification of novel MAPK pathway suppressing synergistic drug combinations. We generated a reporter plasmid (pDIPZ) expressing destabilized firefly luciferase driven by a MAPK-responsive ELK-1-binding element, packaged in a lentiviral vector system. We stably transfected pediatric glioma cell lines with a BRAF fusion (DKFZ-BT66) and a BRAFV600E mutation (BT-40) background, respectively. Measurement of MAPK pathway activity was performed using the luciferase reporter. pERK protein levels were detected for validation. We performed a screen of a MAPKi library and calculated Combination Indices of selected combinations. The MAPKi library screen revealed MEK inhibitors as the class inhibiting the pathway with the lowest IC50s, followed by ERK and second generation RAF inhibitors. Synergistic effects in both BRAF-fusion and BRAFV600E mutation backgrounds were observed following combination treatments with different MAPKi classes (RAFi/MEKi, > RAFi/ERKi > MEKi/ERKi). We have generated a novel reporter assay for medium- to high-throughput pre-clinical drug testing of MAPKi in pLGG cell lines. MEK, ERK and next-generation RAF inhibitors were confirmed as potential treatment approaches for KIAA1549:BRAF and BRAFV600E mutated pLGGs. Synergistic suppression of MAPK pathway activity upon combination treatments was revealed using our assay in addition.

LGG-18. EVEROLIMUS TREATMENT IN PEDIATRIC PATIENTS AFFECTED BY LOW-GRADE GLIOMAS (PLGG) NON-TSC, BRAF V600-WT

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BACKGROUND: MAPK pathway is the hallmark of pediatric low grade gliomas (pLGGs); hyperactivation of mTOR (mammalian target of rapamycin) might be a suitable biomarker for therapeutic response. We investigated the feasibility of Everolimus, mTOR inhibitor, in patients affected by pLGGs. METHODS: Patients 1 to 18 years old, diagnosed with pLGG, with a positive tumor biopsy for mTOR/phospho-mTOR and radiological and / or clinical disease progression, treated at Bambino Gesù Children's Hospital in Rome were evaluated. Tumor DNA methylation analysis was performed in 10 cases. Exclusion criteria included: Tuberous Sclerosis patients, Sub Ependymal Giant Astrocytoma. Everolimus was administered orally at a dose of 2.5 mg or 5 mg daily based on body weight. Patients were evaluated with brain MRI every 4, 8 and 12 months after treatment start and every six months thereafter. RESULTS: 16 patients were enrolled from September 2014 and 2019. The median age was 7.5 years old. All patients had at least one adverse event. Events rated as severe (grade 3/4) were reported in 6 patients. Stomatitis was the most frequent adverse event. One patient discontinued treatment due to grade 4 toxicity (ulcerative stomatitis and fatigue). The median duration of treatment was 21 months (4–57 months). Brain MRI evaluations have showed disease stability in 11 patients, partial response in 2 patients and disease progression in 3 patients. CONCLUSIONS: Everolimus has proven to be well tolerated and effective treatment in terms of disease stability in patients with pLGGs. It's also an excellent example of chemo-free personalized approach.

LGG-19. SPINAL LOW-GRADE GLIOMAS IN CANADIAN CHILDREN: A MULTI-CENTRE RETROSPECTIVE REVIEW

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