LGG-46. MOLECULAR CHARACTERIZATION OF HEMISPHERIC LOW-GRADE GLIOMAS IN CHILDREN

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BACKGROUND: Heterogeneous pathology in hemispheric low-grade gliomas (hemLGG) stress the importance of molecular testing in terms of prognosis prediction and targeted therapy options. METHODS: Demographic data was collected and targeted genomic approach was employed in the single institutional study. RT-PCR was used to screen for KIAA1549-BRAF fusion and FGFR1 tyrosine-kinase domain duplication (FGFR1-ITD). Direct sequencing evaluated point mutations (BRAF ex15 and ex11, FGFR1 ex12 and ex14). Samples with no detected alteration were subjected to panel RNA-sequencing (FusionPlex Archer Diagnostics). RESULTS: Within 2000–2019 were diagnosed 76 patients with hemLGG (median age 11.1y, range 0.0y–18.5y) comprising predominantly of ganglioglioma, dysembryoplastic neuroepithelial tumors, and diffuse astrocytoma. 40 % of hemLGG were characterized by BRAF alterations with over 2/3 of those cases harboring BRAF point mutations (two BRAFex11, 12 BRAFV600E). Notably, BRAF fusions were uncommon and detected only in six patients (two KIAA-BRAF fusion, two minor oncogenic BRAF variants, two non-KIAA BRAF fusion). 25 % of alterations were found in genes for receptor tyrosine kinases, consisting of seven patients with FGFR1-ITD, three FGFR2/3 fusions, two FGFR1 mutations, two ALK fusions, and one ROS fusion. Out of MAP kinase pathway, the most frequent alteration was IDH1 mutations (n=9). Two angiocentric gliomas were characterized by MYB-QKI fusion. CONCLUSION: Targeted sequencing combined with RNA-sequencing is feasible to establish molecular diagnosis in majority of cases and reveal new and rare alterations. Significant prevalence of non-BRAF alterations explains heterogeneity among hemLGG.

LGG-47. SYSTEMIC THERAPY OF ROSETTE-FORMING GLIONEURONAL TUMOR OF THE FOURTH VENTRICLE INAN ADOLESCENT

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An 11 y.o. female presented to a GI specialist with complaints of morning vomiting and periumbilical abdominal pain for several months. Had progressing symptoms with GI work-up for ~1 year. She developed diplopia and worsening headaches. Imaging revealed a T2/FLAIR hyperintense mass in the 4th ventricle with heterogeneous enhancement and obstructive hydrocephalus. Three T2 bright, non-enhancing, subcentimeter masses identified in the right cerebellum. Due to poor differentiation between tumor and normal tissue at brainstem, only partial resection (PR) was feasible. Pathology initially called pilocytic astrocytoma (PA). All symptoms resolved after PR. Slow progression in the tumor and "satellite" lesions noted over two years. Second opinion and molecular typing reclassified the tumor as rosette-forming glioneuronal tumor (RFGNT) with a mutation in *PIK3CA*. Therapy started with vinblastine and carboplatin with stable disease x 7 months, discontinued due to allergic reaction to carboplatin. Initiated therapy with everolimus, an mTOR inhibitor. The tumor's characteristics on imaging changed with initial growth and increase in peripheral enhancement in one satellite and the primary tumor. Nevertheless, we persevered. When comparing pre-treatment MRI to most recent 7 months later, there has been an overall decrease in volume of expansile heterogenous tumor along the margins of the fourth ventricle. The degree of peripheral enhancement associated with the mass has increased. RFGNT is a rare tumor included in WHO classification since 2007. Ellezam et al identified recurrent *PIK3CA* mutations. To our knowledge, this is the only report of treatment targeting the mutation. We report a radiographic response despite initial growth.

LGG-48. PROLIFIC GROWTH OF BRAF V600E MUTANT PILOCYTIC ASTROCYTOMA WHILE ON KETOGENIC DIET: CASE REPORT

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Epilepsy is a common diagnosis among pediatric patients with supratentorial tumors, particularly infiltrating gliomas. The ketogenic diet can be a successful antiepileptic therapy for patients with medically intractable epilepsy. Acetoacetate, a main ketone released during ketosis, has been shown to increase $BRAF^{V600E}$ binding to MEK1 and MEK1 phosphorylation in $BRAF^{V600E}$ mutant melanoma cells, thereby promoting proliferation and tumor growth (Kang et al, 2015, Xia et al, 2017). $BRAF^{V600E}$ mutation is common in pediatric low-grade gliomas. Therefore, use of a ketogenic diet to manage coincident epilepsy could, in theory, promote tumor growth. However, this has not been previously reported in a human patient. We present a 3 year-old male with a non-NF1 optic pathway $BRAF^{V600E}$ mutant pilocytic astrocytoma and medically intractable epilepsy. He was treated with carboplatin and bevacizumab for 1 year, with good tumor response and vision recovery. He showed stable, non-progressive disease for several months. He was placed on a ketogenic diet 9 months into treatment and became seizure free. Tumor recurrence occurred at 8 months off therapy, at which time a biopsy demonstrated $BRAF^{V600E}$ mutation. The tumor progressed rapidly despite treatment with Trametinib and Dabrafenib, leading to salvage therapy with carboplatin, vinblastine, bevacizumab, and XRT, without tumor control. We discuss the potential effect of the ketogenic diet on this patient's outcome.

LGG-49. SAFETY AND EFFICACY OF TRAMETINIB (T) MONOTHERAPY AND DABRAFENIB + TRAMETINIB (D+T) COMBINATION THERAPY IN PEDIATRIC PATIENTS WITH *BRAF* V600-MUTANT LOW-GRADE GLIOMA (LGG)

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BACKGROUND: Children with *BRAF* V600-mutant LGG have suboptimal response to standard chemotherapy. Previously, D (*BRAF* V600 inhibitor) monotherapy has demonstrated clinical benefit in this population. We report interim analysis results of pediatric patients with recurrent/refractory *BRAF* V600-mutant LGG treated with either T (MEK1/2 inhibitor) monotherapy or D+T combination therapy. METHODS: This is a 4-part, open-label, multicenter, phase I/II study (NCT02124772) in pediatric patients (<18 y) with refractory/recurrent tumors. The dose-finding phase, including dose confirmation stratified by age, was followed by disease-specific cohorts at recommended dose levels. Efficacy was determined by both investigator and independent review using RANO criteria. Adverse events (AEs) were assessed per NCI-CTCAE v4.03. RESULTS: Of 49 pediatric patients with *BRAF* V600-mutant LGG (T, n=13; D+T, n=36) enrolled, pooled efficacy data was available for both treatments while safety data was available for 30 patients (T, n=10; D+T, n=20). Most patients (n=8/10) receiving T monotherapy withdrew/discontinued the treatment in contrast to 3/20 in the D+T group. Pyrexia occurred in 50% of patients (n=5/10) in the monotherapy group and was a frequent AE in the combination group (75%; n=15/20). Objective response rate per independent review was 15% (95% CI, 2%–45%) with T monotherapy and 25% (95% CI, 12%–42%) with D+T combination therapy. Seven patients (54%) on monotherapy and 33 patients (92%) on combination therapy had stable disease or better. CONCLUSION: In pediatric patients with previously treated *BRAF* V600-mutant LGG, T monotherapy and D+T combination therapy demonstrated clinical activity, with pyrexia being a common AE.

LGG-50. INTEGRATED MOLECULAR AND CLINICAL ANALYSIS OF 1,000 PEDIATRIC LOW-GRADE GLIOMAS UNCOVERS NOVEL SUBGROUPS FOR CLINICAL RISK STRATIFICATION

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Pediatric low-grade gliomas (pLGG) are primarily driven by genetic alterations in the RAS/MAPK pathway, most commonly involving BRAF of NF1. Despite their molecular convergence, pLGG often show unexplained variability in their clinical outcome. To address this, we molecularly characterized a cohort of >1,000 clinically annotated pLGG. 84% of cases harbored a detectable driver mutation. The remaining 16% of patients nonetheless showed RAS/MAPK pathway up-regulation at the RNA level. The clinical presentation and outcome of pLGG appeared highly variable and linked to the alteration type: re-arrangement or SNV. Re-arrangement-driven tumors were diagnosed at a younger age (6.6 versus 10.9 years, p<0.0001),