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Pediatric low-grade glioma (pLGG), the most common brain tumors in children, are driven by alterations in the MAPK pathway. Several clinical trials have shown the potential for MAPK inhibitor (MAPKi) treatment in pLGG. However, the range of response to MAPKi is heterogeneous, even between tumors sharing the same driving MAPK alteration. A predictive stratification tool is needed to identify tumors that will be sensitive to MAPK inhibition. We generated sensitivity gene signatures for each MAPKi class (BRAFi, MEKi, ERKi), based on MAPK-related genes differentially regulated between MAPKi sensitive and non-sensitive cell lines from the Genomics of Drug Sensitivity in Cancer (GDSC) dataset. Single sample Gene Set Enrichment Analysis was used to measure and validate the MAPKi predictive sensitivity scores in the GDSC dataset and an independent patient-derived xenograft (PDX) dataset (XevaDB). The validated signatures were tested in a pLGG-specific background, using gene expression data from pLGG cell lines and primary pLGG samples. Our MAPKi sensitivity signatures discriminated MAPKi sensitive and non-sensitive cells in the GDSC dataset, and significantly correlated with MAPKi response in the PDX dataset. The sensitivity scores discerned gliomas with varying MAPK alterations from those without MAPK alterations, and showed higher scores in pLGG compared to high-grade gliomas and normal brain tissue. MAPKi-predicted sensitivity was heterogeneous within pLGG groups with a common MAPK alteration, as observed in MAPKi clinical trials. Intriguingly, we observed a strong positive correlation between our MAPKi sensitivity signature scores and the predicted immune cell infiltration rate as determined by the ESTIMATE score. These data demonstrate the potential relevance of gene-expression signatures to predict response to MAPKi treatment in pLGG patients, worth of further investigation in a prospective manner in upcoming clinical trials. In addition, our data could support a role of immune cell infiltration in the response to MAPKi in pLGG, warranting further validation.

LGG-27. MOLECULAR IMPLICATIONS OF MITOGEN-ACTIVATED PROTEIN KINASE PATHWAY INHIBITION BY THE MEK INHIBITOR TRAMETINIB IN BRAF-FUSION-DRIVEN PEDIATRIC PILOCYTIC ASTROCYTOMA

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Pilocytic astrocytomas (PA) are the most common pediatric brain tumors. They are characterized by driving alterations in the mitogen-activated protein kinase (MAPK) pathway, leading to its constitutive activation and modulating the balance between cell proliferation and oncogene-induced senescence (OIS) sustained by senescence-associated secretory phenotype (SASP) factors. This makes PA susceptible to MAPK inhibitor (MAPKi) therapies, which show encouraging results in phase 1/2 clinical trials. However, little is known about the molecular implications of MAPK inhibition in PA. The DKFZ-BT66 cell line, derived from a primary KIAA:BRAF-fusion positive PA, was used as a model system. DKFZ-BT66 were treated with the MEKi trametinib for different durations in both proliferative and senescent states. Gene expression was analyzed by gene expression profiling and protein expression/phosphoregulation by data-dependent mass spectrometry followed by label-free quantitative analysis. A time course analysis based on differentially expressed genes and phosphorylated proteins was performed, followed by a single-sample gene set enrichment analysis (ssGSEA) and kinase substrate enrichment analysis, respectively. Differential gene expression analysis revealed that MEK inhibition led to the inhibition of the OIS/SASP gene programs in senescent DKFZ-BT66, with downregulation of key OIS/SASP partners such as IL1B on the protein level. This functionally translated into a de-sensitization of these cells towards the senolytic agent navitoclax. ssGSEA showed that most MAPK-related signatures were downregulated upon MEKi treatment, while pathways related to upstream MAPK activators (including FGFR, NTRK and TGFB pathways) were upregulated, in both proliferating and senescent DKFZ-BT66. This data indicates that MAPKi reverses OIS in senescent PA cells, while inducing the activation of MAPK upstream regulators in proliferating and senescent PA cells, identifying putative co-targets that could help increase treatment's efficacy. Validation of these targets by post-translational modification enrichment analysis of the phosphoproteomics dataset is ongoing.

LGG-28. RAPID SYMPTOMATIC IMPROVEMENT FOR A PATIENT TREATED WITH BRAF INHIBITION FOR BRAFV600E MUTATED GANGLIOGLIOMA

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BACKGROUND: Biologically targeted agents such as the BRAF inhibitor dabrafenib are now used to treat progressive low-grade glioma (LGG), but the effect of these agents on the neurologic symptoms that accompany LGGs is poorly understood. CASE: A 21-year-old male was diagnosed with medullary ganglioglioma (GG) after presenting with persistent vertigo and positional headaches. Immunohistochemistry was consistent with BRAF V600E mutation and dabrafenib was started. The patient had resolution of his neurologic symptoms within 3 weeks of treatment initiation; surveillance MRI several months later demonstrated interval decrease in tumor size. The patient remained on therapy for 2 years. Several days after planned drug discontinuation the patient had re-emergence of persistent vertigo that impaired his ability to work. Repeat imaging two months later demonstrated an increase in tumor size and solid enhancement along tumor margins. He was restarted on dabrafenib. Within one week, he again had complete resolution of his vertigo. DISCUSSION: Gangliogliomas are comprised of mixed neuronal and glial components and associated with epilepsy, headache and other localizing neurologic symptoms. In this report, we describe clinical and radiographic response from single-therapy dabrafenib in a patient with BRAF V600E+ GG, along with a very rapid resolution of neurologic symptoms upon initiation of the drug and recrudescence shortly following cessation of therapy. The symptoms subsided within a week of restarting dabrafenib, suggesting a separate, more rapid mechanism of symptom reversal than decline in tumor size. BRAF mutations have been identified in both the neuronal and glial components of ganglioglioma, suggesting that dabrafenib may provide symptomatic relief via inhibition of abberant neuronal processes. CONCLUSION: BRAF inhibitors can rapidly improve neurological symptoms via a rapid, not yet fully elucidated mechanism. Kinetics of this response suggest it is independent of effects on tumor volume and the degree of compression to tissue surrounding the tumor.