ABSTRACT CITATION ID: NOAE064.402
LGG-08. EXPANDING THE SPECTRUM OF MANS-ASSOCIATED NEOPLASM POSSIBLE MBD4-ASSOCIATED NEOPLASIA SYNDROME (MANS)-RELATED NEOPLASMS
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Patients with pediatric low-grade gliomas (pLGG), the most common primary brain tumor in children, can often benefit from MAPK inhibitor (MAPKi) treatment. However, rapid tumor regrowth, also referred to as rebound growth, may occur once treatment is stopped, constituting a significant clinical challenge. Four patient-derived pLGG models were investigated to model rebound growth in vitro based on viable cell counts in response to MAPKi treatment and withdrawal. A multi-omics dataset of the rebound model encompassing different MAPKi withdrawal timepoints was generated using RNA sequencing and LC-MS/MS based phospho-proteomics to investigate possible driving mechanisms of rebound growth. Following in vitro validation, putative rebound driving mechanisms were validated in vivo using the BT-40 orthotopic xenograft model. Of the tested models, BT-40 (BRAFV600E, CDKN2A/Bdel) showed rebound growth upon MAPKi withdrawal, characterized by faster cell growth after MAPKi withdrawal compared to standard-of-care chemotherapy. Using this model, we observed MAPK pathway reactivation within hours after withdrawal, associated with a transient overactivation of key MAPK molecules at transcriptional (e.g. FOS) and phosphorylation (e.g. pMEK) levels. Additionally, we observed increased expression and secretion of cytokines (in particular CCL2, CX3CL1, CXCL10 and CCL7) upon MAPKi treatment, maintained during early withdrawal (at least until 24 h). While increased cytokine expression did not affect response to MAPKi or rebound growth upon withdrawal in an autocrine manner, increased attraction of microglia cells mediated by these cytokines was observed. MAPK pathway reactivation during rebound growth and increased expression of CX3CL1 and CXCL10 induced by MAPKi treatment could further be confirmed in vivo. Taken together, these data indicate a rapid MAPK reactivation upon MAPKi withdrawal as a tumor cell intrinsic rebound driving mechanism. Furthermore, increased microglia recruitment during MAPKi treatment and withdrawal, mediated by cytokines, may play a role in response to MAPKi treatment and rebound growth upon withdrawal, warranting further evaluation.