Abstracts

BACKGROUND: SJDAWN (NCT03434262) is a St. Jude Children’s Research Hospital phase 1 trial that assessed the safety and benefit of CDK4/6 inhibitor-based therapy in patients with relapsed CNS tumors. To capture tumor evolution dynamics and arising resistance mechanisms in response to treatment, 143 longitudinal CSF samples were collected from 34/68 (50%) patients for cell-free DNA (cfDNA) analysis. METHODS: cfDNA was extracted from CSF liquid biopsies and analyzed using a novel methylation-based platform that integrates copy number, tumor classification, and deconvolution of methylation signatures into normal vs. disease fractions. Samples with measurable residual disease (MRD) were further characterized by deep whole-genome sequencing to discover mutation-driven resistance mechanisms. When available, pre- and post-SJDAWN tumor tissues were processed for single-nucleus multi-omics to track tumor evolution at single-cell resolution. RESULTS: In the context of CDK4/6 inhibitor-based therapy, longitudinal cfDNA assessment revealed treatment-induced selection for subclones with focal amplification of positive cell cycle regulators CDK6, CCND2, and MYCN. Emergence of these resistance mechanisms notably preceded disease progression on MRI and CSF cytology by up to 6 months. Of the 68 patients enrolled on SJDAWN, 4 patients (3 Group 3/4, subtype III medulloblastomas and 1 anaplastic ependymoma) achieved >2-year progression-free survival. Interestingly, serial cfDNA profiling of 1 long-term survivor (Group 3/4, subtype III medulloblastoma) exhibited undetectable MRD status for >1.3 years prior to reemergence, suggesting tumor senescence by CDK4/6 inhibition may impede circulating tumor DNA (ctDNA) release kinetics. CSF liquid biopsies were further evaluated in comparison to matched tumor tissues, and changes in CSF-specific subclones were observed in response to treatment. CONCLUSIONS: In addition to early MRD detection, liquid biopsies capture tumor evolution dynamics and can inform developing resistance mechanisms. Focal amplification of CDK6, CCND2, and MYCN facilitates CDK4/6 inhibitor resistance. In responders, treatment-induced senescence may inhibit ctDNA release kinetics.

ABSTRACT CITATION ID: NOAE064.022
BIOM-02. DISSECTING CDK4/6 INHIBITOR RESISTANCE MECHANISMS IN RECURRENT PEDIATRIC BRAIN TUMORS WITH LONGITUDINAL CSF LIQUID BIOPSIES FROM THE SJDAWN CLINICAL TRIAL
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