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Abstracts

PL-03. FEASIBILITY OF GENOMICS-ENABLED THERAPY FOR PEDIATRIC HIGH-GRADE GLIOMAS AND DIFFUSE PONTINE GLIOMAS

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Children with pediatric high-grade gliomas (pHGG) including diffuse intrinsic pontine gliomas (DIPG) continue to have a dismal prognosis and, as a result, novel therapeutic approaches are needed. We evaluated whether genomic profiling, defined as sequencing of tumor and germline exomes and tumor RNA, can be used to identify distinct, actionable events that may guide treatment of children with pHGG. Tumor from eight archival cases

were assessed to confirm high tumor cellularity of samples (>60%) and were evaluated by genomic profiling. Successfully sequenced tumor specimens originated from DIPG (n = 2), astrocytoma grade II (n = 1), astrocytoma grade III (n = 1), glioblastoma (n = 4). We generated average mapped coverages of >145X across all exomes and generated >190M reads for each tumor RNA. Identified alterations were matched to potential therapeutic options using a custom drug-matching pipeline utilizing a pharmacopeia that includes FDA-approved drugs, potential repositioned agents, and investigational compounds. Alterations in genes previously implicated in pediatric glioma were identified, including mutations in histone H3 (H3F3A), PDGFRA, TP53, and ATRX and copy number loss of CDKN2A. Alterations associated with potential sensitivity to FDA-approved oncology agents included frameshift and splice-site mutations in TSC2 and extracellular mutations in PDGFRA (E229K, C235Y mutations; previously reported in pHGG), with predicted sensitivity to mTOR inhibitors and PDGFRA inhibitors, respectively. Inclusion of repositioned therapies and agents in clinical development expanded the actionable roster to include: CDKN2A deletion, BRD4 gain, PRKCI gain, ATM mutation, and overexpression of EZH2, KIF11, MELK, PLK4, and WEE1, several of which are direct targets of investigational agents currently in clinical trials. In conclusion, potentially actionable alterations were uncovered by applying integrative sequencing strategies to pHGG patients. Future efforts will apply this strategy in children with DIPG utilizing pre-treatment biopsies to inform treatment options following initial radiotherapy.