ABSTRACT

Neuro Oncol. 2022 Apr 9:noac096. doi: 10.1093/neuonc/noac096. Online ahead of print.

Upfront Molecular Targeted Therapy for the Treatment of BRAF-Mutant Pediatric High-Grade Glioma.

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BACKGROUND: The prognosis for patients with pediatric high-grade glioma (pHGG) is poor despite aggressive multi-modal therapy. Objective responses to targeted therapy with BRAF inhibitors have been reported in some patients with recurrent BRAF-mutant pHGG but are rarely sustained.

METHODS: We performed a retrospective, multi-institutional review of patients with BRAF-mutant pHGG treated with off-label BRAF +/- MEK inhibitors as part of their initial therapy.

RESULTS: Nineteen patients were identified, with a median age of 11.7 years (range, 2.3-21.4). Histologic diagnoses included HGG (n=6), glioblastoma (n=3), anaplastic ganglioglioma (n=4), diffuse midline glioma (n=3), high-grade neuroepithelial tumor (n=1), anaplastic astrocytoma (n=1), and anaplastic astroblastoma (n=1). Recurrent concomitant oncogenic alterations included CDKN2A/B loss, H3 K27M, as well as mutations in ATRX, EGFR and TERT. Eight patients received BRAF inhibitor monotherapy. Eleven patients received combination therapy with BRAF and MEK inhibitors. Most patients tolerated long-term treatment well with no grade 4-5 toxicities. Objective and durable imaging responses were seen in the majority of patients with measurable disease. At a median follow-up of 2.3 years (range, 0.3-6.5), three-year progression-free and overall survival for the cohort were 65% and 82%, respectively, and superior

to a historical control cohort of BRAF-mutant pHGG patients treated with conventional therapies.

CONCLUSIONS: Upfront targeted therapy for patients with BRAF-mutant pHGG is feasible and effective, with superior clinical outcomes compared to historical data. This promising treatment paradigm is currently being evaluated prospectively in the Children's Oncology Group ACNS1723 clinical trial.

DOI: 10.1093/neuonc/noac096
PMID: 35397478