TITLE: First-in-children phase 1 trial of indoximod-based chemo-immunotherapy for patients with pediatric brain tumors: analysis of safety, tolerability, and 5-year outcome

BACKGROUND: Recurrent brain tumors are the leading cause of cancer death in children. We conducted a first-in-children, two-institution, Phase 1 open-label dose-confirmation study using a 3+3 design, with expansion cohorts, to determine the recommended pediatric dose of the IDO pathway-inhibitor indoximod (NCT02502708). DESIGN/METHODS: Eligible patients were 3-22 years old with either recurrent malignant brain tumor or newly-diagnosed diffuse intrinsic pontine glioma (DIPG). Palliative radiation, surgery or dexamethasone were allowed as needed for patient management. Separate dose-finding arms were performed for indoximod plus temozolomide (200 mg/m2/day orally for 5 days of each 28-day cycle) and for indoximod plus conformal radiation (in patients for whom re-irradiation was planned as standard-of-care). At progression, patients who were otherwise clinically stable were offered crossover to indoximod plus a second-line chemotherapy regimen (cyclophosphamide 2.5 mg/kg/day orally and etoposide 50 mg/m2/day orally for 21 days of each 28-day cycle). RESULTS: Between December 2015 and January 2019, the study enrolled 81 brain tumor patients, including newly-diagnosed DIPG (n= 13) or recurrent ependymoma (n= 27), glioblastoma/high-grade glioma (n= 19), medulloblastoma (n= 13), or other CNS tumors (n= 9). Median follow-up was 52 months (range 39-77 months). No dose-limiting toxicities were observed, and the pediatric indoximod dose was determined (19.2 mg/kg/dose, given twice daily). Indoximod was well tolerated and did not affect the ability to deliver chemotherapy or radiation as planned. Median overall survival was 13.6 months (n= 81). Median overall survival was 34.7 months for the subset of patients who continued indoximod with second-line chemotherapy after progression on indoximod plus temozolomide (n= 18). CONCLUSIONS: Indoximod was well tolerated and could be combined with a variety of standard treatments for pediatric brain tumors. Preliminary anti-tumor activity and overall survival suggest that indoximod with standard therapy should be further evaluated in pediatric brain tumors, and potentially other pediatric solid tumors.

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