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A Phase I Trial of Panobinostat in Children with Diffuse Intrinsic Pontine Glioma: A Report from the Pediatric Brain Tumor Consortium (PBTC-047)

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Abstract

Study objectives: Diffuse intrinsic pontine glioma (DIPG) is a lethal childhood cancer with median survival of less than 1 year. Panobinostat is an oral multi-histone deacetylase inhibitor with preclinical activity in DIPG models. Study objectives were to determine safety, tolerability, maximum tolerated dose (MTD), toxicity profile and pharmacokinetics of panobinostat in children with DIPG.

Patients and methods: In stratum 1, panobinostat was administered three days per week for three weeks on, one week off to children with progressive DIPG, with dose escalation following a two-stage continual reassessment method. After this MTD was determined, the study was amended to evaluate the MTD in children with non-progressive DIPG/Diffuse midline glioma (DMG) (stratum 2) on an alternate schedule, three days a week every other week in an effort to escalate the dose.

Results: For stratum 1, 19 subjects enrolled with 17/19 evaluable for dose-finding. The MTD was 10 mg/m 2/dose. Dose-limiting toxicities included thrombocytopenia and neutropenia. Posterior reversible encephalopathy syndrome was reported in one patient. For stratum 2, 34 eligible subjects enrolled with 29/34 evaluable for dose-finding. The MTD on this schedule was 22 mg/m 2/dose. DLTs included thrombocytopenia, neutropenia, neutropenia with grade 4 thrombocytopenia, prolonged intolerable nausea, and increased ALT.

Conclusions: The MTD of panobinostat is 10 mg/m 2/dose administered 3 times per week for 3 weeks on/1 week off in children with progressive DIPG/DMG and 22 mg/m 2/dose administered 3 times per week for 1 week on/1 week off when administered in a similar population pre-progression. The most common toxicity for both schedules was myelosuppression.

Keywords: DIPG; HDAC inhibitors; brainstem glioma; epigenetics; midline glioma.