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Phase 1 trial of selinexor in pediatric recurrent/refractory solid and CNS tumors (ADVL1414): A Children's Oncology Group Phase 1 Consortium Trial

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Abstract

Background: Selinexor is a first-in-class, central nervous system (CNS)-penetrant, oral inhibitor of exportin 1 (XPO1), the main nuclear exporter of many key tumor suppressors. We report a phase 1 trial of selinexor in children and adolescents with recurrent CNS and solid tumors (NCT02323880).

Methods: A rolling-six design was used to evaluate the maximum tolerated dose (MTD) and first dose pharmacokinetics (PK) of selinexor administered once (QW, 35-45 mg/m2) or twice (BIW, 20-35 mg/m2) weekly during a 28-day cycle (Part A). Ten additional patients with high-grade glioma (HGG) were treated at the QW MTD (Part B).

Results: In Part A, 49 patients were enrolled. Continuous BIW dosing was limited by extended hematologic toxicity. The MTD on a BIW schedule for three weeks on/one-week off (BIW 3/1) was 20 mg/m2/dose. Dose-limiting toxicities (DLTs) on this schedule included fatigue, acute reversible neurologic changes, neutropenia, thrombocytopenia, and AST/ALT increase. On a continuous QW schedule, the MTD was 35 mg/m2/dose, DLTs included seizure and thrombocytopenia. In Part B (HGG expansion), there were no additional DLTs observed. Non-dose-limiting toxicity included lymphopenia, leukopenia, neutropenia, thrombocytopenia, anorexia, fatigue, hypophosphatemia, nausea, and vomiting. There were no objective responses. The median number of cycles received was 1 (range 1-9); Eight of 59 patients (13.5%) received 5-9 cycles, five of whom had HGG.

Conclusions: Selinexor-related toxicities were primarily hematologic and neurologic requiring dose or dose-frequency reduction. The MTD and recommended initial phase 2 dose of selinexor in children and adolescents with recurrent solid and CNS tumors is 35 mg/m2/dose QW.