Phase 1 trial of p28 (NSC745104), a non-HDM2-mediated peptide inhibitor of p53 ubiquitination in pediatric patients with recurrent or progressive central nervous system tumors: A Pediatric Brain Tumor Consortium Study.


Abstract

BACKGROUND: p53 is a promising target in human cancer. p28 is a cell-penetrating peptide that preferentially enters cancer cells and binds to both wild-type and mutant p53 protein, inhibiting COP1-mediated ubiquitination and proteasomal degradation. This results in increased levels of p53, which induces cell cycle arrest at G2/M. We conducted a phase 1 study to determine the maximum-tolerated dose (MTD) and describe the dose-limiting toxicities (DLTs) and pharmacokinetics (PKs) of p28 in children.

METHODS: Children aged 3-21 years with recurrent or progressive central nervous system tumors were eligible. Intravenous p28 was administered 3 times weekly for 4 consecutive weeks of a 6-week cycle at 4.16 mg/kg/dose (the adult recommended phase 2 dose) using a rolling-6 study design. Expression status of p53 was characterized by immunohistochemistry, and serum PK parameters were established on the second dose.

RESULTS: Of the 18 eligible patients enrolled in the study, 12 completed the DLT monitoring period and were evaluable for toxicity. p28 was well-tolerated; 7 participants received ≥2 courses, and the most common adverse event attributed to the drug was transient grade 1 infusion-related reaction. PK analysis revealed a profile similar to adults; however, an increased area under the curve was observed in pediatric patients. High p53 expression in tumor cell nuclei was observed in 6 of 12 available tissue samples. There were no objective responses; 2 participants remained stable on the study for >4 cycles.

CONCLUSIONS: This phase 1 study demonstrated that p28 is well-tolerated in children with recurrent CNS malignancies at the adult recommended phase 2 dose.

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KEYWORDS: azurin; central nervous system tumors; p28; pediatric; phase 1

PMID: 27022131 [PubMed - as supplied by publisher]