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Phase II Study of Ulixertinib in Children and Young Adults With Tumors Harboring Activating Mitogen-Activated Protein Kinase Pathway Alterations: APEC1621J of the National Cancer Institute-Children's Oncology Group Pediatric MATCH Trial

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Abstract

Purpose: The National Cancer Institute-Children's Oncology Group (NCI-COG) Pediatric MATCH trial assigns patients age 1-21 years with refractory malignancies to phase II treatment arms of molecularly targeted therapies on the basis of genetic alterations detected in their tumor. Patients with activating alterations in the mitogen-activated protein kinase pathway were treated with ulixertinib, an extracellular signal-regulated kinase (ERK)1/2 inhibitor.

Methods: As there were no previous pediatric data, ulixertinib was initially tested in a dose escalation cohort to establish the recommended phase II dose (RP2D) before proceeding to the phase II cohort. Ulixertinib was administered at 260 mg/m^2/dose orally twice a day (dose level 1 [DL1], n = 15) or 350 mg/m^2/dose orally twice a day (DL2, n = 5). The primary end point was objective response rate; secondary end points included safety/tolerability and progression-free survival (PFS).

Results: Twenty patients (median 12 years; range, 5-20) were treated, all evaluable for response. CNS tumors comprised 55% (11/20) of diagnoses, with high-grade glioma and low-grade glioma most common (n = 5 each). All CNS tumors except one harbored *BRAF* fusions or V600E mutations. Rhabdomyosarcoma (n = 5) was the most frequent non-CNS diagnosis. DL1 was declared the RP2D in the dose escalation cohort after dose-limiting toxicities in Cycle 1 occurred in 1/6 patients at DL1 and 2/5 patients at DL2, including fatigue, anorexia, rash, nausea, vomiting, diarrhea, dehydration, hypoalbuminemia, and hypernatremia. No objective responses were observed. Six-month PFS was 37% (95% CI, 17 to 58). Three patients with *BRAF*-altered CNS tumors achieved stable disease >6 months.

Conclusion: Ulixertinib, a novel targeted agent with no previous pediatric data, was successfully evaluated in a national precision medicine basket trial. The pediatric RP2D of ulixertinib is 260 mg/m^2/dose orally twice a day. Limited single-agent efficacy was observed in a biomarker-selected cohort of refractory pediatric tumors.