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Phase II Study of Defactinib (VS6063) in Patients With Tumors With *NF2* Loss: Results From the NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol U

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Abstract

Purpose: The NCI-MATCH trial assigned patients with solid tumors, lymphomas, or multiple myeloma to targeted therapies on the basis of identified genetic alterations from tumor biopsies. In preclinical models, *neurofibromatosis 2* (*NF2*)-inactivated tumors display sensitivity to focal adhesion kinase (FAK) inhibition. The EAY131-U subprotocol evaluated the efficacy of defactinib, a FAK inhibitor, in patients with *NF2*-altered tumors.

Methods: Patients whose tumors harbored an inactivating *NF2* mutation on next-generation sequencing were assigned to subprotocol U. Defactinib 400 mg was given orally twice a day until progression or intolerable toxicity. The primary end point was objective response rate (ORR), secondary end points included toxicity, progression-free survival (PFS), and 6-month PFS.

Results: Of 5,548 patients with sufficient tissue for genomic analysis, 57 patients were found to have *NF2* alterations. Thirty-five patients ultimately enrolled and 33 were treated, with one not having central confirmation and two ineligible for outcome analysis. All patients had received previous treatment, with 52% having received three or more previous lines of therapy. The most common treatment-related toxicities were fatigue (36%), nausea (33%), and hyperbilirubinemia (27%), with 27% of patients having grade 3 toxicities. Median follow-up was 35.9 months with an ORR of 3% from one partial response in a patient with choroid meningioma. Among the 12 patients (40%) with a best response of stable disease, eight demonstrated some tumor shrinkage. Median PFS was 1.9 months, and six patients achieved a PFS >5.5 months. No correlation was identified between clinical outcomes and tumor histology or specific *NF2* genotype.

Conclusion: This protocol did not meet its prespecified primary end point. Defactinib monotherapy had limited clinical activity in this cohort of previously treated patients with solid tumors exhibiting *NF2* loss.