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Phase II Study of Vismodegib in Patients With *SMO*- or *PTCH1*-Mutated Tumors: Results From the National Cancer Institute Molecular Analysis for Therapy Choice Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Trial (EAY131) Subprotocol T

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Abstract

Purpose: The National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) (EAY131, ClinicalTrials.gov identifier: NCT02465060) trial pairs patients with targeted therapies on the basis of tumor genomic alterations. Subprotocol T assessed vismodegib, a hedgehog pathway inhibitor, in patients with Patched-1 (*PTCH1*) and Smoothened (*SMO*) alterations (excluding basal cell carcinoma).

Methods: Eligible patients received oral vismodegib (150 mg daily) until progression or toxicity. The primary end point was objective response rate, with secondary end points including 6-month progression-free survival (PFS), survival, and predictive biomarkers. Optional plasma for cell-free DNA analysis was collected at enrollment, on treatment, and at progression.

Results: From June 2016 to September 2020, 34 patients enrolled; 31 eligible patients (nine *SMO*, 22 *PTCH1*) received treatment, with 25 confirmed by the central NCI-MATCH assay (primary analysis cohort). Median age of the 31 eligible patients was 64 years, with 48.4% being women. Sixty-one percent received ≥3 previous therapies and 74% had multiple co-occurring mutations. Objective response rate was 8% (2/25 [90% CI, 1.4 to 23.1]) in the primary analysis cohort and 6.5% (2/31 [90% CI, 1.2 to 19]) overall. Partial responses occurred in soft tissue sarcoma (*PTCH1*) and meningioma (*SMO*), with response durations of 19 and 9.23 months, respectively. Six-month PFS rates were similar (24%, 23.2%), with an identical median PFS of 1.8 months and median overall survival of 7.3 months for the analyzable and primary analysis patient cohorts. Four patients (12.9%) discontinued therapy because of adverse events. Common toxicities included grade 1-2 fatigue, anorexia, weight loss, alopecia, and dysgeusia. Four on-study deaths occurred, none treatment-related.

Conclusion: Vismodegib was well tolerated with mainly grade 1-2 toxicities, but it did not meet the primary end point. Select patients with specific *SMO* and *PTCH1* alterations had notable responses, warranting further comprehensive molecular analyses to elucidate resistance mechanisms.

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