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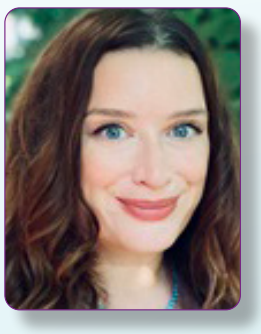

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nature communications

Binimetinib and encorafenib for the treatment of advanced solid tumors with non-V600E BRAF mutations: results from the Phase II BEAVER trial

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Class 2 and 3 non-V600E BRAF mutations are oncogenic drivers in many cancer types. Currently, there are no established targeted therapies with proven efficacy for cancers with non-V600E BRAF mutations.

The BEAVER trial (NCT03839342) was an investigator-initiated, Phase II clinical trial designed to evaluate the efficacy of BRAF and MEK inhibitors in patients with non-V600E BRAF mutations. The primary outcome was objective response rate (ORR). The best ORR was 14% (3/21), the primary endpoint was not met.

By analyzing genomic data from patient tumors, circulating tumor DNA (ctDNA), patient-derived xenograft (PDX) models generated from enrolled patients, and Class 2 & 3 BRAF mutant cell lines, we discovered MAPK-dependent and independent mechanisms of resistance to BRAF/MEK inhibition. These mechanisms include the acquisition of new mutations in NRAS, MAP2K1, RAF1, and RB in ctDNA at the time of disease progression. CDK4/6 and SHP2 emerge as mediators of intrinsic resistance to BRAF/MEK inhibition in Class 2 & 3 BRAF mutant tumors.

Therapeutic strategies combining CDK4/6 or SHP2 inhibitors with BRAF/MEK inhibitors in preclinical models show greater efficacy than BRAF/MEK inhibitors alone in these cancers.

https://www.nature.com/articles/s41467-025-68076-7