BEACON CRC: Safety Lead-In (SLI) for the Combination of Binimetinib (BNI), Encorafenib (ENCO), and Cetuximab in Patients with BRAFV600E Metastatic Colorectal Cancer (mCRC)


Background: Objective response rates (ORR) of 16%-22% are generally expected when BRAFV600E inhibitor monotherapy are used in patients with BRAFV600E mCRC. Recent data suggest that combination therapies have the potential to improve clinical benefit in patients with BRAFV600E mCRC. The current phase 1 study assessed the safety of Binimetinib, Encorafenib, and Cetuximab (BEN) in patients with BRAFV600E mCRC.

Methods: The 1:1:3 phase 1 study (NCT02758600) was conducted in 3 cohorts: 1) Binimetinib 100 mg / Encorafenib 150 mg QD (B150), 2) Binimetinib 100 mg / Encorafenib 150 mg / Cetuximab (B150C), 3) Binimetinib 100 mg / Encorafenib 300 mg / Cetuximab (B300C). The lead-in dose of B150 was escalated to 150 mg / day in the B150C cohort and then 250 mg / QW in the B300C cohort. A maximum of 215 patients across all 3 arms). Treatment was continued until objective progression or unacceptable toxicity. The primary endpoint was the occurrence of DLTs. The study was conducted at 28 sites across 5 countries. Of 171 patients with a BRAFV600E mutation, 171 were evaluable for efficacy. Safety and tolerability data were reported separately. 

Results: A total of 171 patients were treated with a median 1.2 cycles of BEN in 16 arms. The most common AEs were grade 1-2 arthralgias, nausea, vomiting, and diarrhea. Grade 3 AEs occurred in 15% of patients, with the most common skin AE (in 12% of patients) being grade 1-2 rash. Most serious AEs were grade 3 (n=14) and included skin disorders (n=8), infection (n=2), gastrointestinal disorders (n=1), and myelosuppression (n=1). At least 1 patient discontinued due to AEs. 6 patients experienced DLTs: 2 patients (10%) each had grade 3 increased AST, 2 patients had grade 3 cutaneous toxicity, 1 patient had grade 3 vomiting, and 1 patient had grade 3 diarrhea. The maximum tolerated dose was BEN 250 mg / QW. Histological confirmation of BRAFV600E mCRC was obtained in 155 (91%) patients. The estimated ORR was 4% and PFS was 2 months.

Conclusions: Single-agent BEN, and the combination of BEN plus cetuximab, have been shown to be safe and well tolerated compared with other BRAFV600E inhibitor combinations. The addition of cetuximab to BEN was associated with increased toxicities, particularly cutaneous toxicities. BEN had some activity in BRAFV600E mCRC with an ORR of 4% and an estimated PFS of 2 months. Future studies with RAD001 or COMBO-2 will focus on improving benefit with additional combinations.

References