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BREAKWATER: an open-label, multicenter, randomized, phase 3 study, with a safety lead-in (SLI), of first-line (1L) encorafenib (E) + cetuximab (C) ± chemotherapy (CT) vs standard-of-care (SOC) CT for BRAF V600E-mutant metastatic colorectal cancer (mCRC)

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Objective

- This phase 3 trial evaluates the efficacy and safety of EC + CT vs SOC CT for BRAF V600E-mutant mCRC
- An SLI was used to determine the recommended phase 3 regimen

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Background

- Globally, 8%-12% of patients with mCRC have *BRAF* V600E mutations, which confer poor prognosis[1]
- EC was approved for the treatment of previously treated patients with BRAF V600E-mutant mCRC based on the phase 3 BEACON trial[2]
- 1L treatment options remain an unmet need for patients with BRAF V600E-mutant mCRC[3]
- BREAKWATER (NCT04607421) is evaluating EC ± CT vs SOC CT in patients with previously untreated BRAF V600E-mutant mCRC
- The BREAKWATER SLI (N=57) evaluated patients who had received ≤1 prior treatment for mCRC[4]
  - EC + CT showed encouraging antitumor activity (**Table 1**)
- Based on the results of the SLI, EC + mFOLFOX6 was selected as the recommended phase 3 regimen

Table 1. BREAKWATER SLI Antitumor Activity Overview[4]

	1L		2L	
	EC + mFOLFOX6	EC + FOLFIRI	EC + mFOLFOX6	EC + FOLFIRI
	n=19	n=12	n=8	n=18
Confirmed best overall response by BICR, n (%)				
ORR (95% CI), %	68.4 (46.0, 84.6)	75.0 (46.8, 91.1)	37.5 (13.7, 69.4)	44.4 (24.6, 66.3)
CR	1 (5.3)	2 (16.7)	0	1 (5.6)[a]
PR	12 (63.2)	7 (58.3)	3 (37.5)	7 (38.9)
SD	4 (21.1)	2 (16.7)	5 (62.5)	7 (38.9)
PD	1 (5.3)	0	0	0
Non-CR/non-PD[b]	0	1 (8.3)	0	2 (11.1)
Not evaluable[c]	1 (5.3)	0	0	1 (5.6)
mPFS by BICR, months (95% CI)	11.1 (8.5, NE)	NE (13.8, NE)	10.8 (4.3, NE)	12.6 (6.9, NE)
Responders	n=13	n=9	n=3	n=8
mTTR (range), weeks	6.9 (5.9-30.0)	7.0 (6.1-42.7)	6.9 (6.4-23.1)	13.0 (6.1-47.3)
mDOR (95% CI), months	9.8 (6.9, NE)	12.4 (6.9, NE)	NE (5.6, NE)	9.9 (5.5, NE)
≥6 months, n (%)	7 (53.8)	6 (66.7)	1 (33.3)	4 (50.0)

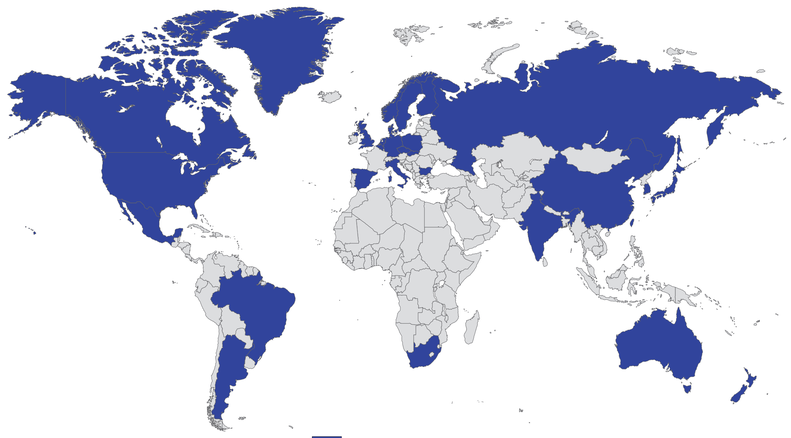
Data cutoff: September 5, 2022.

[a] This participant with CR only had nontarget lesions at baseline. [b] Participants with only nontarget lesions at baseline. [c] Reasons included SD <6 weeks after treatment start date (1 patient in the EC + mFOLFOX6 cohort in the 1L setting) and early death (1 patient in the EC + FOLFIRI cohort in the 2L setting).
1L, first line; 2L, second line; BICR, blinded independent central review; CR, complete response; mDOR, median duration of response; EC, encorafenib plus cetuximab; FOLFIRI, fluorouracil/leucovorin/irinotecan; mFOLFOX, modified fluorouracil/leucovorin/oxaliplatin; mPFS, median progression-free survival; mTTR, median time to response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Enrollment status

- Approximately 620 patients will be enrolled in the phase 3 portion and an additional 135 patients will be enrolled in cohort 3 (**Figure 1**)
- Phase 3 enrollment began in November 2021 across approximately 240 sites (**Figure 2**)
  - 433 patients have been enrolled as of April 21, 2023

Figure 2. BREAKWATER Study Sites

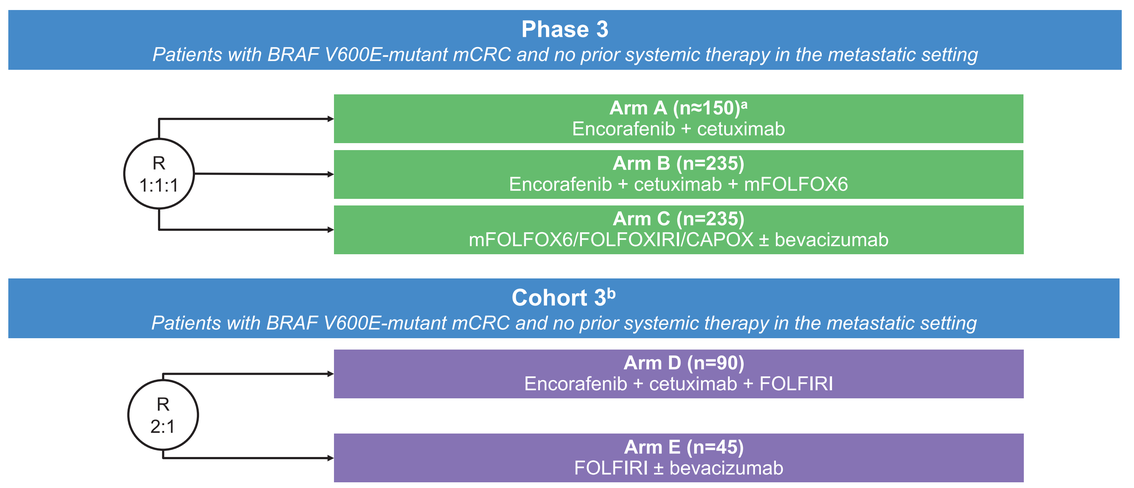


Methods

Study design

- BREAKWATER is an ongoing, open-label, multicenter, randomized, phase 3 study evaluating 1L EC ± CT vs SOC CT alone in patients with BRAF V600E-mutant mCRC (**Figure 1**, **Table 2**)

Figure 1. BREAKWATER Phase 3 and Cohort 3 Trial Design



Stratification factors

- Phase 3: regions (US/Canada vs Europe vs Rest of World) and ECOG PS (0 vs 1)
- Cohort 3: ECOG PS (0 vs 1)

Inclusion criteria

- Age ≥16 years (or ≥18 years based on country)
- No prior systemic treatment for metastatic disease
- Measurable disease (RECIST 1.1)
- BRAF V600E-mutant mCRC (based on blood or tumor tissue)
- ECOG PS 0 or 1
- Adequate bone marrow, hepatic, and renal function

Exclusion criteria

- Prior BRAF or EGFR inhibitors
- Symptomatic brain metastases (unless stable for ≥4 weeks prior to randomization)
- MSI-H/dMMR tumors (unless ineligible to receive immune checkpoint inhibitors due to a pre-existing medical condition)

[a] In the phase 3 portion of the study, randomization to Arm A will cease upon site institutional review board/ethics committee and competent authority approval of protocol amendment 5. Following this protocol amendment, randomization is 1:1 into Arms B and C. [b] Cohort 3 will begin after phase 3 enrollment is complete.
CAPOX, capecitabine/oxaliplatin; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil/leucovorin/irinotecan; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; FOLFOXIRI, fluorouracil/leucovorin/oxaliplatin/irinotecan; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2. BREAKWATER Study Endpoints

Endpoints	Phase 3	Cohort 3
Primary	PFS[a] and ORR[a] (Arm B vs C)	ORR[a] (Arm D vs E)
Key secondary	OS (Arm B vs C)	PFS[a] (Arm D vs E)
Other secondary	ORR[b] (Arm A vs B, A vs C), DOR,[b] PFS[b] (Arm A vs B, A vs C), OS (Arm A vs B, A vs C), TTR,[b] PFS2, AEs,[c] PRO scores,[d] trough plasma concentrations of encorafenib and its metabolite LHY746 (Arms A and B), PK parameters of encorafenib and its metabolite LHY746, MSI status,[e] *BRAF* V600E VAF, and/or overall mean VAF	ORR, DOR,[b] PFS, OS, TTR,[b] AEs,[c] PRO scores,[d] trough plasma concentrations of encorafenib and its metabolite LHY746, MSI status,[e] *BRAF* V600E VAF, and/or overall mean VAF

[a] By BICR. [b] By BICR and investigator. [c] Graded according to NCI CTCAE v4.03. [d] As measured by the EORTC QLQ-C30, EQ-5D-5L, and anchoring instruments PGI-S and PGI-C. [e] Determined by retrospective central testing of baseline tumor tissue.
AE, adverse event; BICR, blinded independent central review; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire: 30-item core questionnaire; EQ-5D-5L, EuroQol 5-dimension 5-level; MSI, microsatellite instability; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetics; PRO, patient-reported outcome; TTR, time to response; VAF, variant allele frequency.

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