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Subsequent therapies in the phase 3 BREAKWATER study of first-line encorafenib + cetuximab + mFOLFOX6 in patients with BRAF V600E-mutant metastatic colorectal cancer

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Objectives

- We present data on subsequent therapies received by patients enrolled in the phase 3 BREAKWATER study of 1L EC ± mFOLFOX6 vs control in BRAF V600E-mutant mCRC

Conclusions

- The majority of patients who discontinued study treatment in BREAKWATER received subsequent systemic anticancer therapy
- Of the patients in the control arm who received subsequent therapies, the majority received BRAF inhibitor–based targeted therapies, most frequently in the 2L
- This treatment pattern corresponds to current real-world clinical practice and supports that the improved outcomes observed with EC+mFOLFOX6 in the 1L are based on evaluation against valid current treatments
- PFS after subsequent therapy (PFS2) was longer in the EC+mFOLFOX6 arm than in patients in the control arm who received EC-based treatment in the 2L, suggesting a long-term clinical benefit of upfront treatment with EC+mFOLFOX6 vs sequential use of 1L chemotherapy and 2L EC
- Together with the statistically significant and clinically meaningful improvement in OS with EC+mFOLFOX6 vs control, these results further support EC+mFOLFOX6 as a current 1L standard of care for BRAF V600E-mutant mCRC

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Abbreviations: 1L, first line; 2L, second line; 3L, third line; 4L, fourth line; 5L, fifth line; 6L, sixth line; 7L, seventh line; ATP, adenosine triphosphate; BICR, blinded independent central review; CAPOX, capecitabine/oxaliplatin; DCR, duration of response; dMMR, deficient mismatch repair; EC, encorafenib+cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; FOLFOXIRI, fluorouracil/leucovorin/oxaliplatin/irinotecan; HR, hazard ratio; mCRC, metastatic colorectal cancer; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; MSI-H, microsatellite instability-high; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; PRO, patient reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

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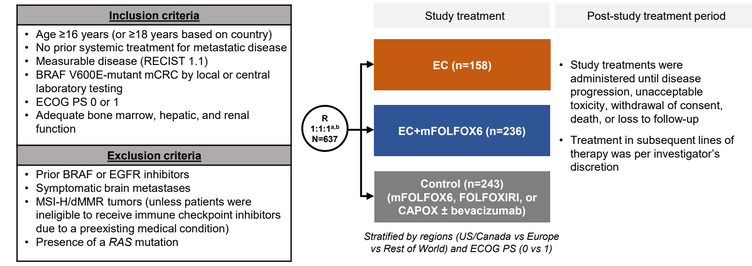
Background

- *BRAF* V600E mutations are present in 8% to 12% of patients with mCRC and are associated with poorer prognosis and reduced efficacy of standard chemotherapy compared with *BRAF* wild-type disease[1,2]
- Encorafenib is a highly selective, ATP-competitive BRAF inhibitor with longer pharmacodynamic activity than other approved BRAF inhibitors[3,4]
- Encorafenib in combination with the anti-EGFR monoclonal antibody cetuximab is established as standard care for previously treated BRAF V600E-mutated mCRC[5]
- In the 1L setting, treatment for BRAF V600E-mutated mCRC has historically consisted of chemotherapy with or without a biologic agent (eg, bevacizumab); however, efficacy is limited[6,7]
- The ongoing phase 3 BREAKWATER study (NCT04607421) is evaluating EC±mFOLFOX6 for 1L treatment of BRAF V600E-mutant mCRC[8,9]
- EC+mFOLFOX6 demonstrated statistically significant and clinically meaningful improvements in ORR, PFS, and OS vs chemotherapy with or without bevacizumab as control in BREAKWATER[8,9]
  - ORR was 60.9% vs 40.0% (odds ratio 2.443; *P*=0.0008),[8] median PFS was 12.8 vs 7.1 months (HR 0.53; *P*<0.001), and median OS was 30.3 vs 15.1 months (HR 0.49; *P*<0.001)
- EC+mFOLFOX6 was granted accelerated approval by the US FDA as part of Project FrontRunner for patients with BRAF V600E-mutant mCRC, including in the 1L setting[10]; this was followed by several recent full approvals in countries in Latin America and conditional approval in Canada
- EC+mFOLFOX6 is a new standard of care for 1L treatment of BRAF V600E-mutant mCRC

Methods

- BREAKWATER is an open-label, global, randomized, phase 3 study in patients with previously untreated BRAF V600E-mutant mCRC[8,9] (**Figure 1**)
- Patients were randomized 1:1:1 to receive EC, EC+mFOLFOX6, or control (investigator's choice of chemotherapy with or without bevacizumab)
- Subsequent anticancer therapies after discontinuing study treatment were per investigator discretion
- PFS2 was defined as the time from randomization to second objective disease progression (progressive disease after the start of subsequent anticancer therapy) per RECIST 1.1 (by investigator assessment), discontinuation of next-line treatment after first objective disease progression (by investigator assessment), or death from any cause, whichever occurs first

Figure 1. BREAKWATER Study Design



Dual primary endpoints: ORR[c] by BICR, PFS by BICR (for EC+mFOLFOX6 vs control)
Key secondary endpoint: OS (for EC+mFOLFOX6 vs control)
Other secondary endpoints: TTR, DOR, PFS2, PROs, safety

[a]Following a protocol amendment, enrollment to the EC arm was stopped and patients were randomized 1:1 to the EC+mFOLFOX6 or control arms. [b]Patients were enrolled between November 16, 2021, and December 22, 2023. [c]In the first 110 patients in each of the EC+mFOLFOX6 and control arms.

Results

- The BREAKWATER EC, EC+mFOLFOX6, and control arms included 158, 236, and 243 patients, respectively, for the full analysis set and 153, 232, and 229 patients, respectively, for the safety analysis set, which consisted of all patients who received ≥1 dose of study treatment
- Baseline demographic and disease characteristics for the full analysis set were generally balanced between treatment groups[9]

Surgical conversion rate

- The number of patients who had cancer surgery with curative intent is shown in **Table 1:**

Table 1. Surgical Conversion Rate[a] (Safety Analysis Set)

n (%)	EC n=153	EC+mFOLFOX6 n=232	Control n=229
Patients with cancer surgery with curative intent	4 (2.6)	12 (5.2)	12 (5.2)
Patients with complete resection	3 (2.0)	7 (3.0)	8 (3.5)

[a]The percentage of patients who become eligible for surgery and undergo surgery with curative intent as a result of receiving study treatment.

Subsequent systemic anticancer therapies

- At the data cutoff of January 6, 2025, the majority of patients had discontinued study treatment. Of these patients, 73.3% in the EC arm, 63.9% in the EC+mFOLFOX6 arm, and 61.2% in the control arm received ≥1 subsequent systemic anticancer treatment (**Table 2**)
- Of the patients treated with subsequent systemic anticancer therapy, 19.6% (21/107), 17.6% (19/108), and 71.9% (100/139) in the EC, EC+mFOLFOX6, and control arms, respectively, received subsequent BRAF inhibitor-based therapies (**Table 2**)
  - The majority of patients in the EC and the EC+mFOLFOX6 arms received subsequent chemotherapies, with FOLFOX- and FOLFIRI-based regimens being the most commonly used in the EC arm and FOLFIRI-based regimens being the most commonly used in the EC+mFOLFOX6 arm
- Among patients who received a subsequent BRAF-inhibitor-based therapy in the control arm (n=100), most were treated with EC-based regimens (n=77) (**Table 2**)

Table 2. Subsequent Systemic Anticancer Therapies

Patients, n/N (%)	EC n=158	EC+mFOLFOX6 n=236	Control n=243
Discontinued study treatment	146/158 (92.4)	169/236 (71.6)	227/243 (93.4)
Any subsequent systemic anticancer treatment	107/146 (73.3)	108/169 (63.9)	139/227 (61.2)
Any BRAF inhibitor ± combination[a]	21/107 (19.6)	19/108 (17.6)	100/139 (71.9)
EC ± combination[a]	14/107 (13.1)	15/108 (13.9)	77/139 (55.4)
EC	4/107 (3.7)	9/108 (8.3)	62/139 (44.6)
Encorafenib + panitumumab ± combination[a]	0	1/108 (0.9)	4/139 (2.9)
Encorafenib + panitumumab	0	0	4/139 (2.9)

[a]Treatment ± combination denotes the indicated treatment given with or without any additional anticancer agents.

- In the control arm, subsequent BRAF inhibitor–based therapies predominated in the 2L, with 59.7% of patients (83/139) receiving BRAF inhibitor–based regimens vs 35.3% of patients (49/139) receiving chemotherapy–based regimens (**Table 3**)
  - Of the 83 patients who received a subsequent BRAF inhibitor–based therapy in the 2L, 53 patients received EC
- Most of the patients treated with BRAF inhibitor–based therapies in the control arm received these in the 2L (83%, 83/100) and/or 3L (18%, 18/100) of therapy (**Table 3**)

Table 3. Subsequent Systemic Anticancer Treatment by Line of Therapy

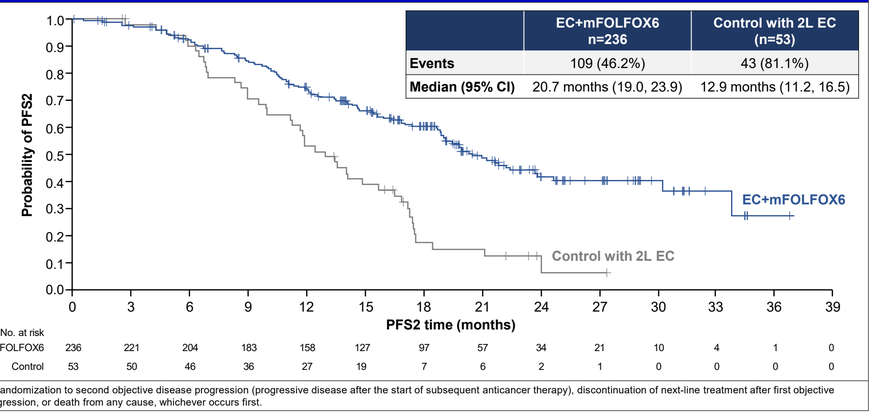
Patients receiving subsequent systemic anticancer treatment , n/N (%)	EC n=158	EC+mFOLFOX6 n=236	Control n=243
Patients who discontinued treatment	146/158 (92.4)	169/236 (71.6)	227/243 (93.4)
2L	107/146 (73.3)	108/169 (63.9)	139/227 (61.2)
BRAF inhibitor ± combination[a]	8/107 (7.5)	10/108 (9.3)	83/139 (59.7)
Chemotherapy-based[b]	99/107 (92.5)	91/108 (84.3)	49/139 (35.3)
Fruquintinib, regorafenib, or trifluridine/tipiracil ± VEGF inhibitor	0	2/108 (1.9)	2/139 (1.4)
Immunotherapy or other	0	5/108 (4.6)	5/139 (3.6)
3L	48/146 (32.9)	30/169 (17.8)	53/227 (23.3)
BRAF inhibitor ± combination[a]	8/48 (16.7)	10/30 (33.3)	18/53 (34.0)
Chemotherapy-based[b]	34/48 (70.8)	8/30 (26.7)	27/53 (50.9)
Fruquintinib, regorafenib, or trifluridine/tipiracil ± VEGF inhibitor	5/48 (10.4)	9/30 (30.0)	5/53 (9.4)
Immunotherapy or other	1/48 (2.1)	3/30 (10.0)	3/53 (5.7)
4L	21/146 (14.4)	7/169 (4.1)	18/227 (7.9)
BRAF inhibitor ± combination[a]	6/21 (28.6)	1/7 (14.3)	5/18 (27.8)
Chemotherapy-based[b]	7/21 (33.3)	3/7 (42.9)	7/18 (38.9)
Fruquintinib, regorafenib, or trifluridine/tipiracil ± VEGF inhibitor	7/21 (33.3)	2/7 (28.6)	6/18 (33.3)
Immunotherapy or other	1/21 (4.8)	1/7 (14.3)	0
5L	9/146 (6.2)	3/169 (1.8)	10/227 (4.4)
BRAF inhibitor ± combination[a]	1/9 (11.1)	2/3 (66.7)	1/10 (10.0)
Chemotherapy-based[b]	5/9 (55.6)	0	3/10 (30.0)
Fruquintinib, regorafenib, or trifluridine/tipiracil ± VEGF inhibitor	3/9 (33.3)	1/3 (33.3)	5/10 (50.0)
Immunotherapy or other	0	0	1/10 (10.0)
6L	6/146 (4.1)	0	4/227 (1.8)
BRAF inhibitor ± combination[a]	1/6 (16.7)	0	0
Chemotherapy-based[b]	2/6 (33.3)	0	1/4 (25.0)
Fruquintinib, regorafenib, or trifluridine/tipiracil ± VEGF inhibitor	3/6 (50.0)	0	3/4 (75.0)
7L	2/146 (1.4)	0	1/227 (0.4)
BRAF inhibitor ± combination[a]	0	0	0
Chemotherapy-based[b]	2/2 (100)	0	0
Immunotherapy or other	0	0	1/1 (100.0)
BRAF inhibitor ± combination[a] in any line	21/107 (19.6)	19/108 (17.6)	100/139 (71.9)
BRAF inhibitor ± combination[a] in >1 subsequent line	3/107 (2.8)	3/108 (2.8)	6/139 (4.3)

[a]Treatment ± combination denotes the indicated treatment given with or without any additional anticancer agents.
[b]CAPIRI ± combination, CAPOX ± combination, FOLFIRI ± combination, FOLFOX ± combination, FOLFOXIRI ± combination, or single-agent chemotherapy.

PFS2

- Median time from randomization to second progression, discontinuation of next-line treatment, or death was 20.7 months for patients in the EC+mFOLFOX6 arm compared with 12.9 months for patients in the control arm who received EC as their first subsequent treatment (**Figure 2**)

Figure 2. PFS2[a]



	EC+mFOLFOX6 n=236	Control with 2L EC (n=53)
Events	109 (46.2%)	43 (81.1%)
Median (95% CI)	20.7 months (19.0, 23.9)	12.9 months (11.2, 16.5)

[a]Time from randomization to second objective disease progression (progressive disease after the start of subsequent anticancer therapy), discontinuation of next-line treatment after first objective disease progression, or death from any cause, whichever occurs first.