

## ORIGINAL ARTICLE

# Encorafenib, Cetuximab, and mFOLFOX6 in BRAF-Mutated Colorectal Cancer

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## ABSTRACT

**BACKGROUND**

First-line treatment with encorafenib plus cetuximab (EC) with or without chemotherapy (oxaliplatin, leucovorin, and fluorouracil [mFOLFOX6]) for BRAF V600E–mutated metastatic colorectal cancer, an aggressive subtype with a poor prognosis, was compared with standard care (chemotherapy with or without bevacizumab) in an open-label, phase 3 trial, which showed significance regarding one of the two primary end points, objective response according to blinded independent central review (odds ratio for EC+mFOLFOX6 vs. standard care, 2.44; one-sided  $P < 0.001$ ). This result led to accelerated Food and Drug Administration approval of this investigational combination therapy for BRAF V600E–mutated metastatic colorectal cancer, including as first-line therapy. Data on progression-free survival (the second primary end point) and an updated interim analysis of overall survival are now available.

**METHODS**

We randomly assigned patients with untreated BRAF V600E–mutated metastatic colorectal cancer to receive EC, EC+mFOLFOX6, or standard care. The two primary end points were objective response (reported previously) and progression-free survival according to blinded independent central review in the EC+mFOLFOX6 group and the standard-care group. The key secondary end point was overall survival.

**RESULTS**

Significantly longer progression-free survival was seen with EC+mFOLFOX6 than with standard care (median, 12.8 vs. 7.1 months; hazard ratio for progression or death, 0.53; 95% confidence interval [CI], 0.41 to 0.68;  $P < 0.001$ ). In an interim analysis, overall survival was significantly longer with EC+mFOLFOX6 than with standard care (median, 30.3 vs. 15.1 months; hazard ratio for death, 0.49; 95% CI, 0.38 to 0.63;  $P < 0.001$ ). The incidence of serious adverse events during treatment was 46.1% with EC+mFOLFOX6 and 38.9% with standard care. Safety profiles were consistent with those known for each agent.

**CONCLUSIONS**

This trial showed significantly longer progression-free survival and overall survival with first-line treatment with EC+mFOLFOX6 than with standard care among patients with BRAF V600E–mutated metastatic colorectal cancer. (Funded by Pfizer and others; BREAKWATER ClinicalTrials.gov number, NCT04607421.)

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\*A list of the investigators in the BREAKWATER trial is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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This article was published on May 30, 2025, at [NEJM.org](http://NEJM.org).

DOI: 10.1056/NEJMoa2501912

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APPROXIMATELY 8 TO 12% OF METASTATIC colorectal cancers harbor *BRAF* V600E mutations.<sup>1,2</sup> *BRAF* V600E–mutated metastatic colorectal cancer has emerged as a distinct subtype of this disease and is characterized by a poorer prognosis and lower responses to chemotherapy than is seen in *BRAF* wild-type disease.<sup>1,2</sup> Encorafenib is a highly selective, ATP-competitive, small-molecule *BRAF* inhibitor with antiproliferative and apoptotic activity in tumor cells expressing *BRAF* V600E mutations and has longer pharmacodynamic activity than other approved *BRAF* inhibitors.<sup>3,4</sup> In colorectal cancer, *BRAF* inhibition alone can cause the *BRAF* pathway to be reactivated by epidermal growth factor receptor (EGFR) owing to feedback loops within the signaling network (also known as rapid pathway feedback reactivation), which attenuates the activity of *BRAF* inhibitors.<sup>5,6</sup> The value of targeting *BRAF* simultaneously with EGFR inhibition to overcome reactivation has been shown previously.<sup>6–9</sup>

On the basis of the results of the BEACON CRC (Binimetinib, Encorafenib, and Cetuximab Combined to Treat *BRAF*-Mutant Colorectal Cancer) trial,<sup>10</sup> encorafenib plus cetuximab, an anti-EGFR monoclonal antibody, was established as the standard care for previously treated *BRAF* V600E–mutated metastatic colorectal cancer.<sup>11</sup> In the context of first-line therapy, chemotherapy with or without a biologic agent (e.g., bevacizumab) was the standard care for *BRAF* V600E–mutated metastatic colorectal cancer and was associated with poorer outcomes than were seen in patients with *BRAF* wild-type metastatic colorectal cancer (median progression-free survival, 5.8 vs. 9.2 months; median overall survival, 11.1 vs. 23.7 months).<sup>12,13</sup> Data have been limited with respect to first-line treatment targeting the activation pathway that can show improved efficacy in *BRAF* V600E–mutated metastatic colorectal cancer.

We conducted a phase 3 trial (BREAKWATER) to evaluate encorafenib plus cetuximab (EC) with or without chemotherapy (oxaliplatin, leucovorin, and fluorouracil [mFOLFOX6]) as compared with standard care, defined as the investigator's choice of chemotherapy (mFOLFOX6; irinotecan, oxaliplatin, leucovorin, and fluorouracil [FOLFOXIRI]; or oxaliplatin and capecitabine [CAPOX]) with or without bevacizumab, for the first-line treatment of *BRAF* V600E–mutated metastatic colorectal cancer.<sup>14</sup> Results from the safety lead-in portion

of the trial showed encouraging responses and progression-free survival with EC+mFOLFOX6 and with EC plus irinotecan, leucovorin, and fluorouracil (FOLFIRI).<sup>15,16</sup>

Our trial previously showed significance regarding one of the two primary end points, objective response according to blinded independent central review in the objective response analysis set (which included 220 patients). A significantly higher percentage of patients had a confirmed objective response with EC+mFOLFOX6 than with standard care (60.9% vs. 40.0%; odds ratio, 2.44; one-sided  $P < 0.001$ ) at the data-cutoff date (December 22, 2023). Responses were rapid and durable.<sup>14</sup> On the basis of these results, this investigational combination therapy was granted accelerated approval by the Food and Drug Administration as part of Project FrontRunner. EC+mFOLFOX6 is currently the first-line activation pathway–targeted treatment indicated in *BRAF* V600E–mutated metastatic colorectal cancer. Here, we report the primary analysis of progression-free survival according to blinded independent central review (the second of the two primary end points), as well as an updated interim analysis of overall survival, safety, and descriptive analyses of other secondary end points.

## METHODS

### TRIAL OVERSIGHT

In this ongoing open-label, randomized, phase 3 trial, we enrolled patients in 28 countries. The trial was designed and overseen by the sponsor (Pfizer) and a steering committee. An independent data and safety monitoring committee oversaw the trial for unblinded safety monitoring. The protocol, including amendments, was approved by the relevant ethics committee or institutional review board at each trial site and is available with the full text of this article at NEJM.org. The trial was performed in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable Good Clinical Practice guidelines of the International Conference on Harmonisation, and applicable laws and regulations, including applicable privacy laws. Data collection and analyses were performed by the sponsor in collaboration with the authors. The authors

had access to the trial data. The first draft of the manuscript was developed with the use of third-party medical writing assistance, funded by the sponsor, in collaboration with the authors. All the authors, including those who are employees of the sponsor, made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

#### TRIAL DESIGN, PATIENTS, AND TREATMENT

Eligible patients were at least 16 years of age (where permitted locally; otherwise,  $\geq 18$  years of age) and had histologically or cytologically confirmed colorectal adenocarcinoma with evidence of stage IV metastatic disease, measurable disease (according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1),<sup>17</sup> and a BRAF V600E mutation as assessed by local testing (with the use of either tissue or blood) or central laboratory testing at enrollment. Key exclusion criteria were the previous receipt of systemic treatment for metastatic disease; previous receipt of a BRAF or EGFR inhibitor; symptomatic brain metastases; microsatellite-instability–high, mismatch-repair–deficient (MSI-H–dMMR) tumors (unless the patient was ineligible to receive immune checkpoint inhibitors); and a RAS mutation. Additional details are provided in the protocol. Written informed consent was obtained from all the patients before enrollment.

Patients were randomly assigned in a 1:1:1 ratio to receive EC, EC+mFOLFOX6, or standard care. Patients in the EC group received encorafenib (300 mg, orally once daily) and cetuximab (500 mg per square meter of body-surface area, intravenously once every 2 weeks). Patients in the EC+mFOLFOX6 group received encorafenib (300 mg, orally once daily) and cetuximab (500 mg per square meter, intravenously once every 2 weeks) plus all the components of mFOLFOX6 administered once every 2 weeks in a 28-day cycle: oxaliplatin (85 mg per square meter, intravenously), leucovorin (400 mg per square meter, intravenously), and fluorouracil (400 mg per square meter as an intravenous bolus and then 2400 mg per square meter as a continuous intravenous infusion over a period of 46 to 48 hours). Patients in the standard-care group received the investigator's choice of chemotherapy (mFOLFOX6 with or without bevacizumab, FOLFOXIRI with or without bevacizumab, or CAPOX with or without

bevacizumab; doses have been reported previously<sup>14</sup>).

All the assigned trial treatments were administered until discontinuation criteria (i.e., disease progression, unacceptable toxic effects, withdrawal of consent, death, or loss to follow-up) were met. After a protocol amendment, enrollment in the EC group was stopped, and subsequently enrolled patients were randomly assigned in a 1:1 ratio to receive either EC+mFOLFOX6 or standard care.

Stratification factors at randomization were the Eastern Cooperative Oncology Group performance-status score (0 vs. 1; on a 5-point scale, with higher scores indicating greater disability) and geographic region (United States or Canada vs. Europe vs. the rest of the world). Randomization was implemented by means of interactive response technology (see the protocol).

#### END POINTS

The two primary end points were objective response (assessed in the objective response analysis set, defined as the first 110 patients who were randomly assigned to each of the EC+mFOLFOX6 and standard-care groups) and progression-free survival, both of which were assessed by means of blinded independent central review and compared between the EC+mFOLFOX6 group and the standard-care group. The primary analysis of objective response was reported previously, along with an interim analysis of overall survival, as part of an accelerated approval pathway.<sup>14</sup> Progression-free survival was defined as the time from randomization to the earliest documented disease progression as assessed according to RECIST, version 1.1,<sup>17</sup> or death from any cause, whichever occurred first. Subgroup analyses of the two primary end points (objective response and progression-free survival) were prespecified.

The key secondary end point was overall survival, which was defined as the time from randomization to death from any cause and was compared between the EC+mFOLFOX6 group and the standard-care group. Subgroup analyses of overall survival were prespecified. Other secondary end points included the time to response, duration of response, disease progression after the next line of therapy, patient-reported outcomes, pharmacokinetics, safety, and biomarker end points. Progression-free survival after the next line of therapy (second progression-free survival)

was defined as the time from randomization to the date of discontinuation of next-line treatment after the first documentation of objective disease progression (according to the investigator's assessment), to the occurrence of second documentation of objective disease progression, or to death from any cause, whichever occurred first.

Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 27.1.<sup>18</sup> The severity of adverse events was graded with the use of the Common Terminology Criteria for Adverse Events, version 4.03, of the National Cancer Institute.<sup>19</sup>

#### STATISTICAL ANALYSIS

The primary end point of progression-free survival according to blinded independent central review was analyzed, with the use of a one-sided alpha of 0.023, in all the patients who had undergone randomization. A one-sided alpha of 0.001 was used for the primary analysis of the other primary end point, objective response (Table S2 in the Supplementary Appendix, available at NEJM.org).<sup>14</sup> The primary analysis of progression-free survival was prespecified to take place after at least 230 total events of disease progression or death had occurred in the EC+mFOLFOX6 group and the standard-care group and at least 12 months after the completion of enrollment of the phase 3 portion of the trial. We calculated that this number of events would be necessary for the trial to have at least 85% power to detect a hazard ratio for progression or death of 0.67 with the use of a one-sided stratified log-rank test at a significance level of 0.023. The sample size (235 patients per group) was determined on the basis of the assumption of a hazard ratio of 0.67 under the exponential model assumptions with a median progression-free survival of 7.0 months in the standard-care group and 10.4 months in the EC+mFOLFOX6 group.

The treatment effect in the analysis of progression-free survival was evaluated with the use of a Cox proportional-hazards model, with stratification according to baseline stratification factors. The hazard ratio for disease progression or death and its corresponding 95% confidence interval were reported. The Kaplan–Meier approach was used to estimate the median progression-free survival in each group; the 95% confidence intervals were calculated by means of the Brookmeyer–Crowley method.

After we used a prespecified hierarchical testing procedure to control the familywise type I error,<sup>20</sup> an interim analysis of the key secondary end point (overall survival) in all the patients who had undergone randomization could be conducted with the use of a portion of the one-sided alpha of 0.023 if the results of the primary analysis of progression-free survival were significant or with the use of a portion of the one-sided alpha of 0.001 if the results of the progression-free survival analysis were not significant. The treatment effect in the analysis of overall survival was evaluated with the use of a Cox proportional-hazards model, with stratification according to baseline stratification factors.

Analyses of objective response, time to response, and duration of response were updated and included data from all the patients who had undergone randomization. All these analyses are descriptive. Although the hypothesis testing was one-sided, we report two-sided P values and two-sided 95% confidence intervals here, in accordance with conventional reporting practices. The safety analysis set included all the patients who received at least one dose of trial drug.

## RESULTS

#### PATIENTS

Patients were enrolled in the phase 3 portion of this trial between November 16, 2021, and December 22, 2023.<sup>14</sup> A total of 158 patients were assigned to the EC group, 236 to the EC+mFOLFOX6 group, and 243 to the standard-care group (Fig. S1). In the standard-care group, 197 patients (81.1%) received bevacizumab with chemotherapy. The demographic and disease characteristics of the patients at baseline are reported in Table 1.<sup>14</sup> The representativeness of the trial population is discussed in Table S1.

#### EFFICACY

The data-cutoff date for the analyses was January 6, 2025. The median follow-up for progression-free survival was 16.8 months (95% CI, 15.1 to 18.4) in the EC+mFOLFOX6 group and 9.8 months (95% CI, 8.5 to 13.0) in the standard-care group. The median progression-free survival was 12.8 months (95% CI, 11.2 to 15.9) in the EC+mFOLFOX6 group, as compared with 7.1 months (95% CI, 6.8 to 8.5) in the standard-care group (hazard ratio for disease progression or death, 0.53; 95% CI,



0.41 to 0.68;  $P < 0.001$ ) (Fig. 1A and Fig. S2). The results of the prespecified subgroup analyses of progression-free survival were consistent with the results observed in the overall population (Fig. 1B). Progression-free survival according to the investigator's assessment also showed consistent treatment effects (Table S3). In the EC group, the median progression-free survival was 6.8 months (95% CI, 5.7 to 8.3) (Fig. 1A), with a median follow-up of 18.0 months (95% CI, 10.9 to 25.2).

Given that the primary analysis of progression-free survival was significant, a prespecified updated interim analysis of overall survival (key secondary end point) was performed, which met the specified significance threshold for superiority. As of the data-cutoff date, 242 deaths (81.5% of the 297 deaths expected for the final analysis) had occurred. A total of 94 patients (39.8%) in the EC+mFOLFOX6 group and 148 (60.9%) in the standard-care group died. The median follow-up in the analysis of overall survival was 21.8 months (95% CI, 20.4 to 23.4) in the EC+mFOLFOX6 group and 22.2 months (95% CI, 18.9 to 23.5) in the standard-care group. The median overall survival was 30.3 months (95% CI, 21.7 to could not be estimated) in the EC+mFOLFOX6 group, as compared with 15.1 months (95% CI, 13.7 to 17.7) in the standard-care group (hazard ratio for death, 0.49; 95% CI, 0.38 to 0.63;  $P < 0.001$ ) (Fig. 2A and Fig. S3). The estimated overall survival was 80.1% in the EC+mFOLFOX6 group and 66.0% in the standard-care group at 12 months and was 52.0% and 29.0%, respectively, at 24 months. The results of the prespecified subgroup analyses of overall survival were consistent with the results observed in the overall population (Fig. 2B). In the EC group, the median overall survival was 19.5 months (95% CI, 17.6 to 22.5) (Fig. 2A), with a median follow-up of 26.3 months (95% CI, 25.3 to 29.2).

A confirmed objective response occurred in 65.7% of the patients (95% CI, 59.4 to 71.4) in the EC+mFOLFOX6 group and in 37.4% of the patients (95% CI, 31.6 to 43.7) in the standard-care group. The median time to response was 7.0 weeks (range, 5.1 to 103.6) in the EC+mFOLFOX6 group and 7.3 weeks (range, 5.4 to 48.0) in the standard-care group, and the median duration of response was 13.9 months (95% CI, 10.9 to 18.5) and 10.8 months (95% CI, 7.6 to 13.4), respectively (Table S4). In the EC group, 45.6% of the

patients (95% CI, 38.0 to 53.3) had a confirmed objective response, the median time to response was 6.6 weeks (range, 4.3 to 86.4), and the median duration of response was 7.0 months (95% CI, 4.2 to 11.6).

#### SUBSEQUENT SYSTEMIC ANTICANCER TREATMENTS AND SECOND PROGRESSION-FREE SURVIVAL

A total of 12 of 158 patients (7.6%) in the EC+ group, 67 of 236 (28.4%) in the EC+mFOLFOX6 group, and 16 of 243 (6.6%) in the standard-care group were still receiving trial treatment as of the data-cutoff date. Among the patients who had discontinued treatment, 108 of 169 patients (63.9%) in the EC+mFOLFOX6 group and 139 of 227 (61.2%) in the standard-care group received subsequent systemic anticancer treatment; 107 of 146 patients (73.3%) in the EC group received subsequent systemic anticancer treatment (Table S5). The majority of patients in the EC group and the EC+mFOLFOX6 group received subsequent chemotherapies. Of the 139 patients in the standard-care group who received any subsequent systemic anticancer treatment, 100 (71.9%) received BRAF inhibitor-based subsequent therapies. In the analysis of second progression-free survival, the median time to second progression or death was 20.7 months (95% CI, 19.0 to 23.9) in the EC+mFOLFOX6 group, 12.7 months (95% CI, 11.2 to 13.7) in the standard-care group, and 14.3 months (95% CI, 12.7 to 16.6) in the EC group (Table S6).

#### SAFETY

The median duration of treatment was 27.0 weeks (range, 2.0 to 153.6) in the EC group, 49.8 weeks (range, 1.3 to 161.9) in the EC+mFOLFOX6 group, and 25.9 weeks (range, 2.0 to 150.0) in the standard-care group (Table S7). The safety analysis set included 153 patients in the EC group, 232 in the EC+mFOLFOX6 group, and 229 in the standard-care group. A safety summary is provided in Table S8. Adverse events during treatment occurred in 97.4% of the patients who received EC, in 100% of those who received EC+mFOLFOX6, and in 99.1% of those who received standard care. The most frequent adverse events during treatment (occurring in  $\geq 30\%$  of the patients in any group) were arthralgia (in 34.6% of the patients) in the EC group; nausea (in 53.9%), anemia (in 46.1%), diarrhea (in 41.8%), decreased appetite (in 37.5%), vomiting (in 36.2%), decreased

**Table 1. Characteristics of the Patients at Baseline.\***

Characteristic	EC (N=158)	EC+mFOLFOX6 (N=236)	Standard Care (N=243)
Median age (range) — yr	59 (26–84)	60 (24–81)	62 (28–84)
Female sex — no. (%)	79 (50.0)	113 (47.9)	124 (51.0)
Race or ethnic group — no. (%)†			
White	88 (55.7)	141 (59.7)	144 (59.3)
Asian	64 (40.5)	88 (37.3)	91 (37.4)
Multiple	0	0	2 (0.8)
Black	1 (0.6)	0	1 (0.4)
American Indian or Alaska Native	1 (0.6)	0	0
Not reported	4 (2.5)	7 (3.0)	5 (2.1)
Location of tumor — no. (%)			
Left side of colon	69 (43.7)	90 (38.1)	98 (40.3)
Right side of colon	89 (56.3)	146 (61.9)	145 (59.7)
Disease stage at initial diagnosis — no. (%)			
I	4 (2.5)	3 (1.3)	2 (0.8)
II	7 (4.4)	13 (5.5)	10 (4.1)
III	24 (15.2)	38 (16.1)	45 (18.5)
IV	123 (77.8)	182 (77.1)	186 (76.5)
Primary tumor resection — no. (%)			
Complete	81 (51.3)	116 (49.2)	110 (45.3)
Partial	9 (5.7)	14 (5.9)	11 (4.5)
None	68 (43.0)	106 (44.9)	122 (50.2)
No. of organs involved — no. (%)‡			
≤2	86 (54.4)	119 (50.4)	127 (52.3)
≥3	72 (45.6)	117 (49.6)	116 (47.7)
Liver metastases — no. (%)‡			
Yes	94 (59.5)	147 (62.3)	160 (65.8)
No	64 (40.5)	89 (37.7)	83 (34.2)
ECOG performance-status score — no. (%)			
0	79 (50.0)	128 (54.2)	131 (53.9)
1	74 (46.8)	104 (44.1)	98 (40.3)
Missing data	5 (3.2)	4 (1.7)	14 (5.8)
BRAF V600E status in tumor tissue according to central laboratory — no. (%)§			
Detected	150 (94.9)	226 (95.8)	224 (92.2)
Indeterminate	1 (0.6)	0	1 (0.4)
Not detected	0	4 (1.7)	2 (0.8)
Data not available	7 (4.4)	6 (2.5)	16 (6.6)
Local microsatellite-instability, mismatch-repair-deficiency status — no. (%)¶			
High microsatellite instability, mismatch-repair deficient	0	1 (0.4)	0

**Table 1. (Continued.)**

Characteristic	EC (N=158)	EC+mFOLFOX6 (N=236)	Standard Care (N=243)
Microsatellite-stable, mismatch-repair proficient	152 (96.2)	229 (97.0)	227 (93.4)
Data not available	6 (3.8)	6 (2.5)	16 (6.6)
Carcinoembryonic antigen — no. (%)			
≤5 µg/liter	50 (31.6)	64 (27.1)	63 (25.9)
>5 µg/liter	102 (64.6)	167 (70.8)	163 (67.1)
Missing data	6 (3.8)	5 (2.1)	17 (7.0)
C-reactive protein — no. (%)			
≤10 mg/liter	91 (57.6)	125 (53.0)	118 (48.6)
>10 mg/liter	61 (38.6)	105 (44.5)	108 (44.4)
Missing data	6 (3.8)	6 (2.5)	17 (7.0)

\* Patients were assigned to receive encorafenib plus cetuximab (EC), EC plus chemotherapy (oxaliplatin, leucovorin, and fluorouracil [mFOLFOX6]), or standard-care group (investigator's choice of chemotherapy). The last assessment before the date of the first dose of trial intervention was used as baseline for the Eastern Cooperative Oncology Group (ECOG) performance-status score (range, 0 to 5, with higher scores indicating greater disability) and biomarker variables. "Missing data" refers to data that were not collected but would have been available for collection. "Data not available" refers to data that were not available for collection. Percentages may not total 100 because of rounding.

† Race and ethnic group were reported by the patient.

‡ Data for the number of organs involved and the presence or absence of liver metastases were based on blinded independent central review.

§ Local testing could be performed by means of tumor- or blood-based assays.

¶ The local microsatellite-instability status of microsatellite-stable, mismatch-repair proficient includes low microsatellite instability.

neutrophil count (in 34.1%), arthralgia (in 31.5%), and rash (in 30.2%) in the EC+mFOLFOX6 group; and diarrhea (in 50.2%) and nausea (in 49.8%) in the standard-care group (Table 2). The incidence of adverse events during treatment that were considered by the investigators to be related to treatment was similar across the groups (Table S9).

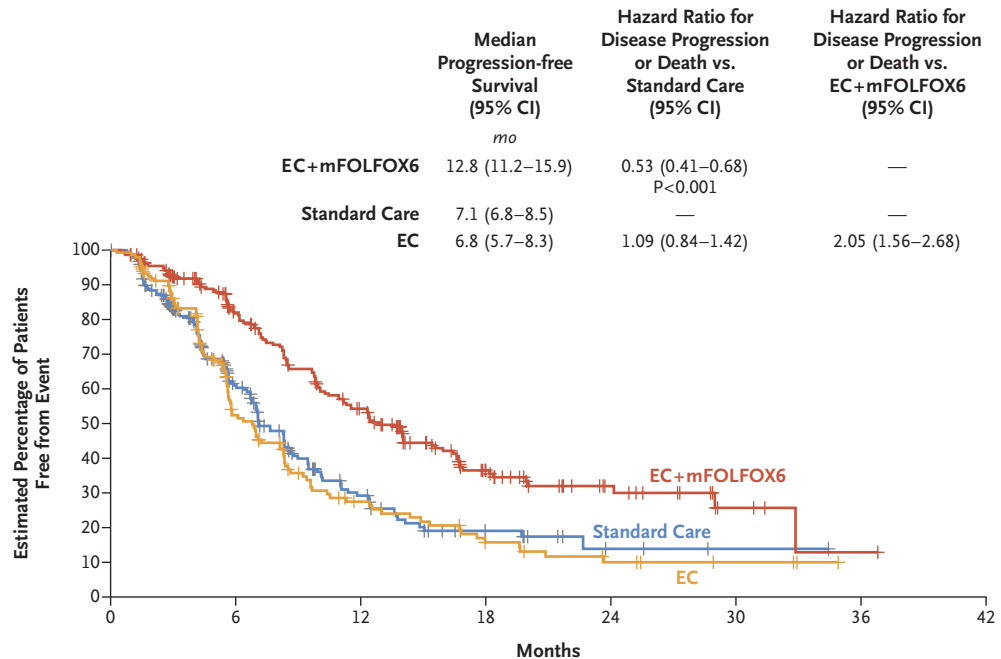
Adverse events of grade 3 or 4 occurred in 42.5% of the patients who received EC, in 81.5% of those who received EC+mFOLFOX6, and in 66.8% of those who received standard care. Grade 5 (fatal) adverse events occurred in 2.6% of the patients who received EC, in 4.3% of those who received EC+mFOLFOX6, and in 4.4% of those who received standard care. One patient in the standard-care group had a grade 5 adverse event that was considered by the investigators to be related to treatment. Serious adverse events during treatment occurred in 30.1% of the patients who received EC, in 46.1% of those who received EC+mFOLFOX6, and in 38.9% of those who received standard care. The most common serious adverse events from any cause are reported in Table 3, and the most common serious ad-

verse events that were considered by the investigators to be related to treatment are reported in Table S10.

Adverse events leading to permanent discontinuation of any trial intervention occurred in 13.1% of the patients in the EC group, in 26.7% of those in the EC+mFOLFOX6 group, and in 17.5% of those in the standard-care group. Adverse events leading to a dose reduction of any trial intervention occurred in 10.5%, 65.5%, and 54.1% of the patients, respectively. Permanent discontinuation of chemotherapy with or without bevacizumab (as appropriate for the treatment group) due to adverse events was reported in 20.7% of the patients in the EC+mFOLFOX6 group and in 17.5% of those in the standard-care group; a reduction in the dose of any of these interventions was reported in 59.9% and 54.1% of the patients, respectively.

## DISCUSSION

The BREAKWATER trial showed significant results for the two primary end points and the key

**A Progression-free Survival****No. at Risk**

EC+mFOLFOX6	236	156	96	39	16	4	1
Standard care	243	100	34	11	3	1	0
EC	158	60	24	12	6	3	0

**B Subgroup Analysis**

Subgroup	EC+mFOLFOX6 <i>no. of events/no. of patients</i>	Standard Care <i>no. of events/no. of patients</i>	Hazard Ratio for Disease Progression or Death (95% CI)
All patients (stratified analysis)	122/236	132/243	0.53 (0.41–0.68)
All patients (unstratified analysis)	122/236	132/243	0.51 (0.40–0.65)
Age			
<65 yr	78/150	71/139	0.51 (0.37–0.71)
≥65 yr	44/86	61/104	0.51 (0.34–0.75)
Sex			
Male	59/123	63/119	0.50 (0.35–0.72)
Female	63/113	69/124	0.53 (0.37–0.75)
ECOG performance-status score			
0	60/131	74/136	0.43 (0.30–0.61)
1	62/105	58/107	0.63 (0.44–0.90)
No. of organs involved			
≤2	52/119	66/127	0.40 (0.28–0.58)
≥3	70/117	66/116	0.64 (0.45–0.90)
Location of tumor			
Left side of colon	51/90	53/98	0.49 (0.33–0.73)
Right side of colon	71/146	79/145	0.52 (0.37–0.72)
Liver metastases			
Yes	87/147	86/160	0.60 (0.44–0.81)
No	35/89	46/83	0.36 (0.23–0.57)



**Figure 1 (facing page). Progression-free Survival According to Blinded Independent Central Review.**

Panel A shows Kaplan–Meier estimates of progression-free survival with encorafenib and cetuximab (EC), EC plus chemotherapy (oxaliplatin, leucovorin, and fluorouracil [mFOLFOX6]), and standard care (investigator's choice of chemotherapy). Progression-free survival according to blinded independent central review was one of the two primary end points in this trial. After a protocol amendment, enrollment into the EC group was discontinued prematurely. Analyses of EC as compared with standard care and with EC+mFOLFOX6 are descriptive; the confidence intervals are not adjusted for multiplicity and should not be interpreted as hypothesis tests. Tick marks indicate censored data. Panel B shows a forest plot of progression-free survival analyses in prespecified subgroups for the comparison of EC+mFOLFOX6 with standard care. The stratification factors at randomization were the Eastern Cooperative Oncology Group (ECOG) performance-status score (0 vs. 1; on a 5-point scale, with higher scores indicating greater disability) and geographic region (United States or Canada vs. Europe vs. the rest of the world); the numbers of patients in the ECOG-based subgroups are based on the stratification factor. Data for the number of organs involved and the presence or absence of liver metastases were based on blinded independent central review. The subgroup analyses are exploratory and descriptive in nature; the confidence intervals are not adjusted for multiplicity and should not be interpreted as hypothesis tests.

secondary end point, with significant improvements with EC+mFOLFOX6 over standard care with regard to objective response, progression-free survival, and overall survival among patients with untreated BRAF V600E–mutated metastatic colorectal cancer. The risk of disease progression or death in the EC+mFOLFOX6 group was nearly half the risk (47% lower) that was seen in the standard-care group. Treatment with EC+mFOLFOX6 resulted in risk of death that was half the risk (51% lower) that was seen in the standard-care group.

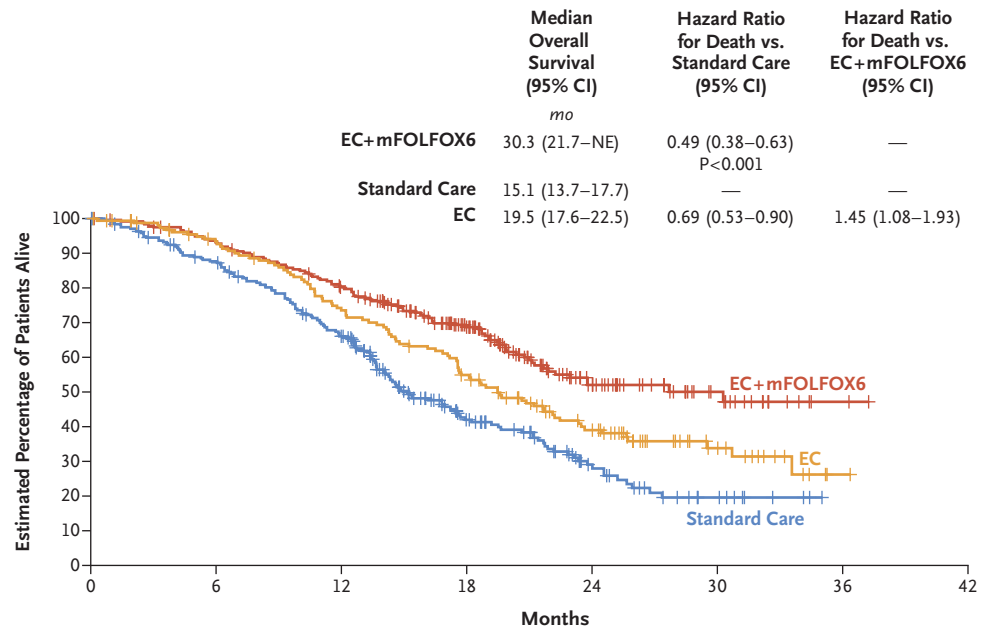
The early separation of the Kaplan–Meier curves for progression-free survival indicated an early clinical benefit in the EC+mFOLFOX6 group as compared with the standard-care group. The median overall survival was more than twice as long in the EC+mFOLFOX6 group as in the standard-care group, with early separation of the Kaplan–Meier curves. The survival advantage that had been observed at the previous interim analysis was sustained, which supports the sig-

nificant survival benefit in the EC+mFOLFOX6 group. The median overall survival in the EC+mFOLFOX6 group was 30.3 months, which is similar to the median overall survival that has been reported among patients with BRAF wild-type metastatic colorectal cancer; this finding was observed despite the historically poorer prognosis in BRAF-mutated metastatic colorectal cancer than in BRAF wild-type metastatic colorectal cancer.<sup>2,12</sup> The benefits with regard to both progression-free survival and overall survival with EC+mFOLFOX6 were observed across all the prespecified clinical subgroups, including in patients with liver metastases or with involvement of three or more organs.

The median second progression-free survival appeared to be prolonged with EC+mFOLFOX6 and, together with the data on overall survival, support the importance of a first-line treatment containing encorafenib to derive long-term clinical benefit. The subsequent anticancer treatments followed current real-world practices, with most of the standard-care group receiving subsequent BRAF inhibitor–based targeted treatments. In addition to the significantly higher percentage of patients with an objective response and to the data showing durable response, the analyses of progression-free and overall survival provide evidence for the importance of combining dual targeted therapy (EC) with chemotherapy in BRAF V600E–mutated colorectal cancer in the first-line context to improve patient outcomes.

The safety data continued to show that treatment with EC+mFOLFOX6 caused grade 3 or higher adverse events in more than three quarters of the patients, although the adverse events were largely manageable, as indicated by the incidence of treatment discontinuation. The safety profile of this combination therapy was consistent with that known for each agent, and the incidence of dose reduction or discontinuation of chemotherapy was not substantially higher with EC+mFOLFOX6 than with standard care.

Enrollment in the EC group was closed on the basis of the low likelihood of this combination therapy showing superiority over standard care after the results of the phase 2 ANCHOR study of EC plus binimetinib were published.<sup>21</sup> Progression-free and overall survival data from the

**A Overall Survival****No. at Risk**

EC+mFOLFOX6	236	216	182	121	48	17	2	0
Standard care	243	202	147	64	27	9	0	0
EC	158	137	107	78	44	16	1	0

**B Subgroup Analysis**

Subgroup	EC+mFOLFOX6 no. of deaths/no. of patients	Standard Care no. of deaths/no. of patients	Hazard Ratio for Death (95% CI)
All patients (stratified analysis)	94/236	148/243	0.49 (0.38–0.63)
All patients (unstratified analysis)	94/236	148/243	0.48 (0.37–0.62)
Age			
<65 yr	56/150	85/139	0.44 (0.31–0.62)
≥65 yr	38/86	63/104	0.54 (0.36–0.82)
Sex			
Male	54/123	71/119	0.59 (0.42–0.85)
Female	40/113	77/124	0.38 (0.26–0.56)
ECOG performance-status score			
0	42/131	76/136	0.42 (0.29–0.62)
1	52/105	72/107	0.54 (0.38–0.77)
No. of organs involved			
≤2	32/119	66/127	0.39 (0.25–0.59)
≥3	62/117	82/116	0.52 (0.38–0.73)
Location of tumor			
Left side of colon	38/90	62/98	0.48 (0.32–0.72)
Right side of colon	56/146	86/145	0.49 (0.35–0.68)
Liver metastases			
Yes	73/147	104/160	0.58 (0.43–0.78)
No	21/89	44/83	0.31 (0.18–0.52)

0.2 1.0 2.0

EC+mFOLFOX6  
BetterStandard Care  
Better

**Figure 2 (facing page). Overall Survival.**

Panel A shows Kaplan–Meier estimates of overall survival with EC, EC+mFOLFOX6, and standard care. Overall survival as the key secondary end point was assessed between the EC+mFOLFOX6 group and the standard-care group. Because the result of the interim analysis of overall survival was significant, no further statistical test will be performed. After a protocol amendment, enrollment into the EC group was discontinued prematurely. Analyses of EC as compared with standard care and with EC+mFOLFOX6 are descriptive; the confidence intervals are not adjusted for multiplicity and should not be interpreted as hypothesis tests. Tick marks indicate censored data. NE denotes could not be estimated. Panel B shows a forest plot of overall analyses in prespecified subgroups for the comparison of EC+mFOLFOX6 with standard care. The subgroup analyses are exploratory and descriptive in nature; the confidence intervals are not adjusted for multiplicity and should not be interpreted as hypothesis tests. The arrow indicates that the 95% confidence interval extends outside the graphed area.

EC group underscore the need for an intensive first-line regimen, such as EC+mFOLFOX6, to control aggressive tumor growth. Nevertheless, EC therapy did lead to a numerically higher percentage of patients with an objective response, longer median overall survival, and early separation of the Kaplan–Meier curves for overall survival as compared with standard care. However, the median overall survival appeared to be shorter in the EC group than in the EC+mFOLFOX6 group. First-line EC may be considered for patients who are unable to receive chemotherapy.

EC with FOLFIRI is currently being investigated in the ongoing cohort 3 portion of the BREAKWATER trial, building on the preliminary encouraging results from the safety lead-in portion.<sup>15</sup> In addition, with regard to patients with BRAF V600E–mutated tumors that were also MSI-H or dMMR, who were excluded from the current trial (unless the patient was ineligible to receive

**Table 2. Most Frequent Adverse Events during Treatment (Safety Analysis Set).\***

Event	EC (N = 153)		EC+mFOLFOX6 (N = 232)		Standard Care (N = 229)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients with event (percent)</i>					
Nausea	31 (20.3)	2 (1.3)	125 (53.9)	7 (3.0)	114 (49.8)	9 (3.9)
Anemia	32 (20.9)	10 (6.5)	107 (46.1)	35 (15.1)	58 (25.3)	9 (3.9)
Diarrhea	28 (18.3)	2 (1.3)	97 (41.8)	3 (1.3)	115 (50.2)	11 (4.8)
Decreased appetite	25 (16.3)	1 (0.7)	87 (37.5)	5 (2.2)	62 (27.1)	3 (1.3)
Vomiting	22 (14.4)	2 (1.3)	84 (36.2)	9 (3.9)	51 (22.3)	5 (2.2)
Neutrophil count decreased	2 (1.3)	1 (0.7)	79 (34.1)	44 (19.0)	67 (29.3)	39 (17.0)
Arthralgia	53 (34.6)	1 (0.7)	73 (31.5)	6 (2.6)	12 (5.2)	1 (0.4)
Rash	27 (17.6)	1 (0.7)	70 (30.2)	3 (1.3)	9 (3.9)	0
Asthenia	28 (18.3)	1 (0.7)	68 (29.3)	12 (5.2)	34 (14.8)	3 (1.3)
Pyrexia	26 (17.0)	2 (1.3)	67 (28.9)	5 (2.2)	36 (15.7)	1 (0.4)
Peripheral neuropathy	2 (1.3)	0	64 (27.6)	18 (7.8)	54 (23.6)	8 (3.5)
Constipation	22 (14.4)	1 (0.7)	63 (27.2)	1 (0.4)	52 (22.7)	1 (0.4)
Peripheral sensory neuropathy	3 (2.0)	0	62 (26.7)	16 (6.9)	54 (23.6)	8 (3.5)
Fatigue	33 (21.6)	2 (1.3)	61 (26.3)	6 (2.6)	64 (27.9)	8 (3.5)
Neutropenia	3 (2.0)	2 (1.3)	56 (24.1)	35 (15.1)	57 (24.9)	23 (10.0)
Alopecia	13 (8.5)	0	53 (22.8)	0	26 (11.4)	0
Platelet count decreased	3 (2.0)	0	53 (22.8)	3 (1.3)	32 (14.0)	4 (1.7)
Lipase increased	10 (6.5)	5 (3.3)	52 (22.4)	40 (17.2)	27 (11.8)	14 (6.1)
Abdominal pain	25 (16.3)	5 (3.3)	47 (20.3)	11 (4.7)	53 (23.1)	3 (1.3)

\* The safety analysis set included all the patients who received at least one dose of trial drug. The most frequent adverse events during treatment shown here are those reported in more than 20% of the patients in the EC+mFOLFOX6 group.

**Table 3. Most Frequent Serious Adverse Events during Treatment (Safety Analysis Set).\***

Event	EC (N=153)	EC+mFOLFOX6 (N=232)	Standard Care (N=229)
<i>number of patients with event (percent)</i>			
Intestinal obstruction	6 (3.9)	11 (4.7)	5 (2.2)
Pyrexia	0	9 (3.9)	3 (1.3)
Anemia	0	8 (3.4)	1 (0.4)
Disease progression	4 (2.6)	8 (3.4)	1 (0.4)
Abdominal pain	3 (2.0)	6 (2.6)	7 (3.1)
Vomiting	1 (0.7)	6 (2.6)	1 (0.4)
Sepsis	1 (0.7)	4 (1.7)	1 (0.4)
Alanine aminotransferase increased	0	3 (1.3)	1 (0.4)
Ascites	0	3 (1.3)	0
Ileus	2 (1.3)	3 (1.3)	4 (1.7)
Pneumonia	0	3 (1.3)	5 (2.2)
Pulmonary embolism	0	3 (1.3)	1 (0.4)
Small intestinal obstruction	1 (0.7)	3 (1.3)	1 (0.4)
Urinary tract infection	6 (3.9)	3 (1.3)	2 (0.9)

\* The most frequent adverse events during treatment shown here are those reported in more than 1% of the patients in the EC+mFOLFOX6 group.

immune checkpoint inhibitors), the SEAMARK trial (NCT05217446) is evaluating first-line EC with pembrolizumab as compared with pembrolizumab alone in patients with BRAF V600E-mutated and MSI-H–dMMR metastatic colorectal cancer.<sup>22</sup>

This trial showed an improved survival benefit with EC+mFOLFOX6 as compared with standard care as a first-line treatment in patients with BRAF V600E-mutated metastatic colorectal cancer.

Supported by Pfizer, with support from Ono Pharmaceutical, Merck (Darmstadt, Germany), and Eli Lilly, and by a Cancer Center Core Grant (P30 CA008748) from the National Cancer Institute, National Institutes of Health.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the participating patients and their families, as well as the staff at the participating sites, and Eleanor Porteous, M.Sc., and Akshaya Srinivasan, Ph.D., of Nucleus Global, an Inizio company, for medical writing assistance, funded by Pfizer.

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