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Encorafenib, Cetuximab and mFOLFOX6 in BRAF-mutant Colorectal Cancer

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for the BREAKWATER trial investigators

Abstract

BACKGROUND: The open-label, phase 3 BREAKWATER study evaluated first-line encorafenib plus cetuximab with or without chemotherapy (oxaliplatin, leucovorin, and 5-FU) (EC±mFOLFOX6) vs. standard of care (SOC; chemotherapy with or without bevacizumab) in BRAF V600E-mutant metastatic colorectal cancer (mCRC), an aggressive subtype with poor prognosis. BREAKWATER previously met one of its dual primary endpoints, objective response rate by blinded independent central review (60.9% [EC+mFOLFOX6] vs. 40.0% [SOC], odds ratio=2.443, one-sided P=0.0008), leading to accelerated FDA approval of EC+mFOLFOX6 for patients with BRAF V600E-mutant mCRC, including in the first-line setting. We report here the primary analysis of progression-free survival and an updated interim analysis of overall survival.

METHODS: In BREAKWATER, patients with previously untreated BRAF V600E-mutant mCRC were randomized to receive EC, EC+mFOLFOX6 or SOC. The dual primary endpoints were objective response rate and progression-free survival by blinded independent central review. The key secondary endpoint was overall survival.

RESULTS: BREAKWATER met its other dual primary endpoint, demonstrating significant progression-free survival improvement with EC+mFOLFOX6 vs. SOC: hazard ratio (HR) 0.53 (95% confidence interval [CI] 0.407, 0.677; two-sided P<0.0001); median progression-free survival 12.8 vs. 7.1 months. Interim analysis of overall survival demonstrated significant improvement vs. SOC: HR 0.49 (95% CI 0.375, 0.632; two-sided P<0.0001); median overall survival 30.3 vs. 15.1 months. Serious treatment-emergent adverse event rates were 46.1% vs. 38.9%; safety profiles were consistent with those known for each agent.

CONCLUSION: BREAKWATER demonstrated statistically significant improvements in progression-free and overall survival with first-line EC+mFOLFOX6 vs. SOC in patients with BRAF V600E-mutant mCRC. (Funded by Pfizer, Inc; ClinicalTrials.gov number, NCT04607421.)

INTRODUCTION

Approximately 8–12% of metastatic colorectal cancers (mCRCs) harbor *BRAF* V600E mutations.[1,2] BRAF V600E-mutant mCRC has emerged as a distinct mCRC subtype characterized by poor prognosis versus BRAF wild-type disease and lower responses to chemotherapy.[1,2] Encorafenib is a highly selective, ATP-competitive, small molecule BRAF inhibitor with anti-proliferative and apoptotic activity in tumor cells expressing *BRAF* V600E mutations and has prolonged pharmacodynamic activity compared with other approved BRAF inhibitors.[3,4] In CRC, BRAF inhibition can cause rapid pathway feedback reactivation through epidermal growth factor receptor (EGFR), attenuating its activity.[5,6] The value of simultaneously targeting BRAF with EGFR inhibition to overcome reactivation has been previously shown.[6–9]

Based on results from BEACON[10], encorafenib plus cetuximab, an anti-EGFR monoclonal antibody, was established as standard of care (SOC) for previously treated BRAF V600E-mutant mCRC.[11] In the first-line setting, chemotherapy with or without a biologic agent (e.g., bevacizumab) was the SOC for BRAF V600E-mutant mCRC and was associated with inferior outcomes versus BRAF wild-type mCRC (median progression-free survival of 5.8 vs. 9.2 months; median overall survival of 11.1 vs. 23.7 months).[12,13] A first-line activation pathway-targeted treatment that can demonstrate improved efficacy in BRAF V600E-mutant mCRC is needed.

BREAKWATER (NCT04607421) is a phase 3 study evaluating encorafenib plus cetuximab (EC) with or without chemotherapy (oxaliplatin, leucovorin, and 5-FU [mFOLFOX6]) (EC±mFOLFOX6) vs. SOC, investigator's choice of chemotherapy (mFOLFOX6; irinotecan, oxaliplatin, leucovorin, and 5-FU [FOLFOXIRI]; or oxaliplatin and capecitabine [CAPOX]) with or without bevacizumab, for the first-line treatment of patients with BRAF V600E-mutant mCRC.[14] Results from the safety lead-in portion of BREAKWATER showed encouraging response rates and progression-free survival of EC+mFOLFOX6 or EC plus irinotecan, leucovorin, and 5-FU (FOLFIRI).[15,16] BREAKWATER previously met one of the dual primary endpoints, objective response rate by blinded independent central review in the objective response rate analysis set (n=220), demonstrating statistically significant improvement in confirmed objective response rate with EC+mFOLFOX6 vs. SOC (60.9% vs. 40.0%, odds ratio=2.443, one-sided P-value=0.0008) at data cutoff (December 22, 2023). Responses were rapid and durable. [14] Based on these results, EC+mFOLFOX6 was granted accelerated approval by the US Food and Drug Administration (FDA), as part of the FDA's Project FrontRunner. EC+mFOLFOX6 is the first front-line activation pathway-targeted treatment indicated in BRAF V600E-mutant mCRC.

Reported here is the primary analysis of progression-free survival by blinded independent central review, the second dual primary endpoint, along with the updated interim analysis of

overall survival, safety, and descriptive analyses of other secondary endpoints. An interactive infographic is available at https://www.breakwaterphase3-infographic.com/.

METHODS

TRIAL OVERSIGHT

BREAKWATER enrolled in 28 countries. It was designed and overseen by the sponsor and a steering committee. An independent data monitoring committee oversaw the study for unblinded safety monitoring. BREAKWATER was supported by Pfizer, Inc. The protocol, including amendments, is available at NEJM.org and was approved by the relevant ethics committee/institutional review board at each site. BREAKWATER was performed in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines, applicable International Conference on Harmonization Good Clinical Practice guidelines, 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 study data. The first draft of the manuscript was developed using third-party medical writing support, provided by the sponsor, in collaboration with the authors. The authors assume responsibility for the accuracy and completeness of the data and analyses, and for the fidelity of the trial to the protocol.

TRIAL DESIGN, PATIENTS, AND TREATMENT

BREAKWATER is an ongoing, open-label, global, randomized, phase 3 trial.

Patients who were ≥16 years of age (where permitted locally), with histologically or cytologically confirmed colorectal adenocarcinoma that had evidence of Stage IV metastatic disease, measurable disease (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1)[17] and presence of a *BRAF* V600E mutation assessed by local (using either tissue or blood) or central laboratory testing when enrolled. Exclusion criteria included prior systemic treatment for metastatic disease, prior BRAF or EGFR inhibitor, symptomatic brain metastases, microsatellite instability-high/mismatch repair deficient tumors (MSI-H/dMMR) (unless ineligible to receive immune checkpoint inhibitors), or a *RAS* mutation. The protocol includes additional details (available at NEJM.org). Informed consent was obtained from patients before enrollment.

Patients were randomized 1:1:1 to receive EC (encorafenib 300 mg orally once daily; cetuximab 500 mg/m^2 intravenously once every 2 weeks), EC+mFOLFOX6 (encorafenib 300 mg orally once daily; cetuximab 500 mg/m^2 intravenously once every 2 weeks; oxaliplatin 85 mg/m^2 intravenously, leucovorin 400 mg/m^2 intravenously, and 5-FU 400 mg/m^2 intravenous bolus, then 5-FU 2400 mg/m^2 continuous intravenous infusion over 46–48 hours, all once every 2 weeks [mFOLFOX6; 28-day cycle]), or investigator's choice SOC (mFOLFOX6 with or without bevacizumab; FOLFOXIRI with or without bevacizumab; CAPOX with or without bevacizumab; dosing reported previously).[14] All assigned study treatments were administered until discontinuation criteria (including disease progression, unacceptable toxicity, withdrawal of consent, or death) were met. Following a protocol

amendment, EC arm enrollment was stopped and patients were randomized 1:1 to receive EC+mFOLFOX6 or SOC.

Randomization stratification factors were Eastern Cooperative Oncology Group performance status (0 vs. 1) (a 5-point scale where higher numbers reflect greater disability) and region (US/Canada vs. Europe vs. Rest of World). Randomization was implemented by Interactive Response Technology (details available in the protocol available at NEJM.org).

ENDPOINTS

The dual primary endpoints are objective response rate (in the first 110 patients randomized in the EC+mFOLFOX6 and SOC arms, respectively [objective response rate subset]) and progression-free survival both by blinded independent central review between the EC+mFOLFOX6 and SOC arms. Objective response rate was previously reported with an interim analysis of overall survival as part of an accelerated approval pathway.[14] Progression-free survival is defined as the time from the date of randomization to the earliest documented disease progression per RECIST 1.1[17] or death due to any cause.

The key secondary endpoint is overall survival (EC+mFOLFOX6 vs. SOC), defined as the time from the date of randomization to death due to any cause. Other secondary endpoints include time to response, duration of response, progression after next line of therapy, patient-reported outcomes, pharmacokinetics, safety, and biomarker endpoints.

Progression-free survival after the next line of therapy is defined as the time from the date of randomization to the date of discontinuation of next-line treatment after first objective progressive disease by investigator assessment, to second objective disease progression, or death from any cause, whichever occurs first.

Adverse events were coded using Medical Dictionary for Regulatory Activities v27.1,[18] and severity of adverse events was graded using National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.[19]

STATISTICAL ANALYSIS

The primary endpoint of progression-free survival by blinded independent central review was analyzed in all patients randomized using one-sided alpha of 0.023. One-sided alpha of 0.001 was used for the primary analysis of the other dual primary endpoint, objective response rate (Table S1).[14] The primary analysis of progression-free survival was preplanned to occur after ≥230 events for the EC+mFOLFOX6 and SOC arms and ≥12 months after the completion of enrollment of the phase 3 portion of the study; this number of events was required to have at least 85% power to detect an HR of 0.67 using a one-sided stratified log-rank test at a significance level of 0.023. The sample size (235 patients per arm) was determined based on the assumption of an HR of 0.67 under the exponential model assumptions with median progression-free survival of 7 and 10.4 months in the SOC and EC+mFOLFOX6 arms.

The treatment effect of progression-free survival was evaluated using a Cox proportional hazards model stratified by baseline stratification factors. The HR and its corresponding

95% confidence interval (CI) were reported. The Kaplan–Meier approach was used to estimate median progression-free survival for each arm; the 95% CIs were calculated using the Brookmeyer–Crowley method.

Following a pre-specified hierarchical testing procedure to control the family-wise type I error rate,[20] an interim analysis of the key secondary endpoint of overall survival in all randomized patients could be conducted using a portion of the one-sided alpha of 0.023 if results of the progression-free survival primary analysis were significant, or a portion of the one-sided alpha of 0.001 if progression-free survival results were not significant. The treatment effect of overall survival was evaluated using a Cox proportional hazards model stratified by baseline stratification factors.

The objective response rate, time to response, and duration of response were updated and analyzed in all patients randomized; all analyses are descriptive.

While hypothesis testing was one-sided, two-sided p-values and two-sided 95% confidence intervals are reported in the manuscript per conventional reporting.

RESULTS

PATIENTS

Patients were enrolled between November 16, 2021, and December 22, 2023 in the phase 3 portion;[14] 158, 236, and 243 patients were randomized to the EC, EC+mFOLFOX6, and SOC arms, respectively (Fig. S1). In the SOC arm, 197 of 243 (81.1%) patients received bevacizumab with chemotherapy. Baseline demographics and disease characteristics are reported in Table 1.[14]

EFFICACY

The data cut off for the analyses was January 6, 2025. The median follow-up for progression-free survival (95% CI) was 16.8 months (15.1, 18.4) in the EC+mFOLFOX6 arm and 9.8 months (8.5, 13.0) in the SOC arm. The median progression-free survival (95% CI) was 12.8 months (11.2, 15.9) and 7.1 months (6.8, 8.5) in the EC+mFOLFOX6 and SOC arms, respectively, HR 0.53 (95% CI 0.407, 0.677; two-sided P<0.0001) (Fig. 1A, S2). Predefined subgroup analyses of progression-free survival were consistent with that observed for the overall population (Fig. 1B). Investigator-assessed progression-free survival also showed consistent treatment effects (Table S2). In the EC arm, the median progression-free survival was 6.8 months (95% CI 5.7, 8.3; Fig. 1A), with a median follow-up of 18.0 months (95% CI 10.9, 25.2).

Upon achieving the dual primary endpoint of progression-free survival, a pre-specified updated interim analysis for overall survival (key secondary endpoint) was performed, which met the superiority threshold. 242 overall survival events (81.5% of 297 events expected for the final analysis) had occurred at the time of the data cutoff; in the EC+mFOLFOX6 and SOC arms (94 [39.8%] and 148 [60.9%], respectively). The median follow-up for overall survival (95% CI) was 21.8 months (20.4, 23.4) in the EC+mFOLFOX6 arm, and 22.2 months (18.9, 23.5) in the SOC arm. The median overall survival (95% CI) was 30.3 months

(21.7, not estimable) and 15.1 months (13.7, 17.7) in the EC+mFOLFOX6 and SOC arms, respectively; HR 0.49 (95% CI 0.375, 0.632; two-sided P<0.0001) (Fig. 2A, S3). In the EC+mFOLFOX6 and SOC arms the probability of survival was 80.1% vs. 66.0% at 12 months and 52.0% vs. 29.0% at 24 months, respectively. Predefined subgroup analyses of overall survival were consistent with that observed for the overall population (Fig. 2B). In the EC arm, the median overall survival was 19.5 months (95% CI 17.6, 22.5; Fig. 2A), with a median follow up of 26.3 months (95% CI 25.3, 29.2).

In all randomized patients in the EC+mFOLFOX6 and SOC arms, confirmed objective response rate (95% CI) was 65.7% (59.4, 71.4) and 37.4% (31.6, 43.7); median time to response (range) was 7.0 weeks (5.1 to 103.6) and 7.3 weeks (5.4 to 48.0); and median duration of response (95% CI) was 13.9 months (10.9, 18.5) and 10.8 months (7.6, 13.4), respectively (Table S3). In the EC arm, confirmed objective response rate, median time to response, and median duration of response were, 45.6% (95% CI 38.0, 53.3), 6.6 weeks (range 4.3 to 86.4), and 7.0 months (95% CI 4.2, 11.6), respectively.

SUBSEQUENT SYSTEMIC ANTICANCER TREATMENTS AND PROGRESSION AFTER NEXT LINE OF THERAPY

At data cutoff, among patients who discontinued treatment, 63.9% (108 out of 169) and 61.2% (139 out of 227) received subsequent systemic anticancer treatment in the EC+mFOLFOX6 and SOC arms, respectively; this was 73.3% in the EC arm (Table S4, Fig. S1). The majority of patients in the EC and EC+mFOLFOX6 arms received subsequent chemotherapies. Of the 139 patients in the SOC arm who received any subsequent systemic anticancer treatment, 100 (71.9%) received BRAF inhibitor-based subsequent therapies (Table S4).

The median time to PFS2 (95% CI) was 20.7 months (19.0, 23.9) and 12.7 months (11.2, 13.7) in the EC+mFOLFOX6 and SOC arms, respectively, and 14.3 months (12.7, 16.6) in the EC arm (Table S5).

SAFETY

The median duration of treatment (range) was 27.0 weeks (2.0 to 153.6), 49.8 weeks (1.3 to 161.9), and 25.9 weeks (2.0 to 150.0) in the EC, EC+mFOLFOX6, and SOC arms, respectively (Table S6); 12 (7.6%), 67 (28.4%), and 16 (6.6%) patients were still on study treatment at data cutoff, respectively.

A safety summary is reported in Table S7. Treatment-emergent adverse events occurred in 97.4%, 100%, and 99.1% of patients in the EC, EC+mFOLFOX6, and SOC arms, respectively. The most frequent (≥30% of patients) treatment-emergent adverse events were arthralgia (34.6%) in the EC arm; nausea (53.9%), anemia (46.1%), diarrhea (41.8%), decreased appetite (37.5%), vomiting (36.2%), neutrophil count decreased (34.1%), arthralgia (31.5%), and rash (30.2%) in the EC+mFOLFOX6 arm; and diarrhea (50.2%) and nausea (49.8%) in the SOC arm (Table 2). Similar rates of treatment-related adverse events were reported (Tables S7 and S8).

Grade 3/4 adverse events occurred in 42.5%, 81.5%, and 66.8% of patients, respectively; grade 5 (fatal) adverse events in 2.6%, 4.3%, and 4.4%, only one patient in the SOC arm experienced a grade 5 treatment-related adverse event (Table S7). Serious treatment-emergent adverse events occurred in 30.1%, 46.1%, and 38.9% of patients, respectively (Table S7). The most common all-causality and related serious adverse events are reported in Table 3 and Table S9, respectively.

Adverse events leading to permanent discontinuation of any study intervention occurred in 13.1%, 26.7%, and 17.5% of patients, respectively. Adverse events leading to dose reduction of any study intervention occurred in 10.5%, 65.5%, and 54.1% of 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% and 17.5% of patients in the EC+mFOLFOX6 and SOC arms; dose reduction of any of these interventions were reported in 59.9% and 54.1%, respectively (Table S7).

DISCUSSION

BREAKWATER has met both dual primary endpoints and the key secondary endpoint, showing statistically significant improvements with EC+mFOLFOX6 over the SOC arm in objective response rate, progression-free and overall survival in previously untreated BRAF V600E-mutant mCRC. The risk of disease progression or death in the EC+mFOLFOX6 arm was nearly halved (47% lower) vs. the SOC arm. Treatment with EC+mFOLFOX6 resulted in risk of death that was half (51% lower) of that in the SOC arm.

The early separation of the progression-free survival Kaplan–Meier curves indicates an early clinical benefit in the EC+mFOLFOX6 arm vs. the SOC arm. Survival advantage was further demonstrated by a median overall survival more than doubled in the EC+mFOLFOX6 arm vs. the SOC arm with early separation of the overall survival Kaplan–Meier curves observed at the prior interim analysis was sustained, supporting the significant survival benefit in the EC+mFOLFOX6 arm. Notably, median overall survival in the EC+mFOLFOX6 arm was 30.3 months, which is similar to the median overall survival reported in BRAF wild-type mCRC, despite the historically poor prognosis in BRAF-mutant vs wild-type mCRC.[2,12] Both the progression-free and overall survival benefits of EC+mFOLFOX6 were observed across all predefined clinical subgroups, including in patients with liver metastases or ≥3 organs involved. Median progression-free survival after second line therapy was prolonged with EC+mFOLFOX6, and together with overall survival data, 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 SOC arm receiving subsequent BRAF inhibitor-based targeted treatments. In addition to the significant objective response rate improvement and durable response, progression-free and overall survival data provide evidence for the importance of combining dual targeted therapy (encorafenib and cetuximab) with chemotherapy in BRAF V600E-mutant CRC in the first-line setting to improve patient outcomes.

The safety data continued to show that EC+mFOLFOX6 caused grade 3 or higher adverse events in more than half that patients but the adverse events were largely reversible. The

safety profile was consistent with that known for each agent and no substantial increase in chemotherapy dose reduction or discontinuation was needed.

EC arm enrollment was closed based on the low likelihood of EC demonstrating superiority versus SOC following the results of the phase 2 ANCHOR study of encorafenib, cetuximab, and binimetinib.[21] Progression-free and overall survival data from the EC arm underscore the need for an intensive first-line regimen, such as EC+mFOLFOX6, to control aggressive tumor growth. Nevertheless, EC did show a numerically higher objective response rate, longer median overall survival and early separation of overall survival Kaplan–Meier curves. However, median overall survival was shorter in the EC arm compared with EC+mFOLFOX6 arm. First-line EC may be considered for patients who are unable to tolerate chemotherapy.

EC plus FOLFIRI is currently being investigated in the ongoing cohort 3 portion of BREAKWATER, building on the preliminary encouraging results from the safety-lead in.[15] Additionally, in patients whose BRAF V600E-mutant tumors were also MSI-H or dMMR who were excluded from BREAKWATER (unless ineligible to receive immune checkpoint inhibitors), SEAMARK (NCT05217446) is evaluating first-line EC with pembrolizumab vs. pembrolizumab alone in patients with BRAF V600E-mutant and MSI-H/dMMR mCRC.[22]

BREAKWATER demonstrated an improved survival benefit with EC+mFOLFOX6 as a first-line treatment for patients with BRAF V600E-mutant mCRC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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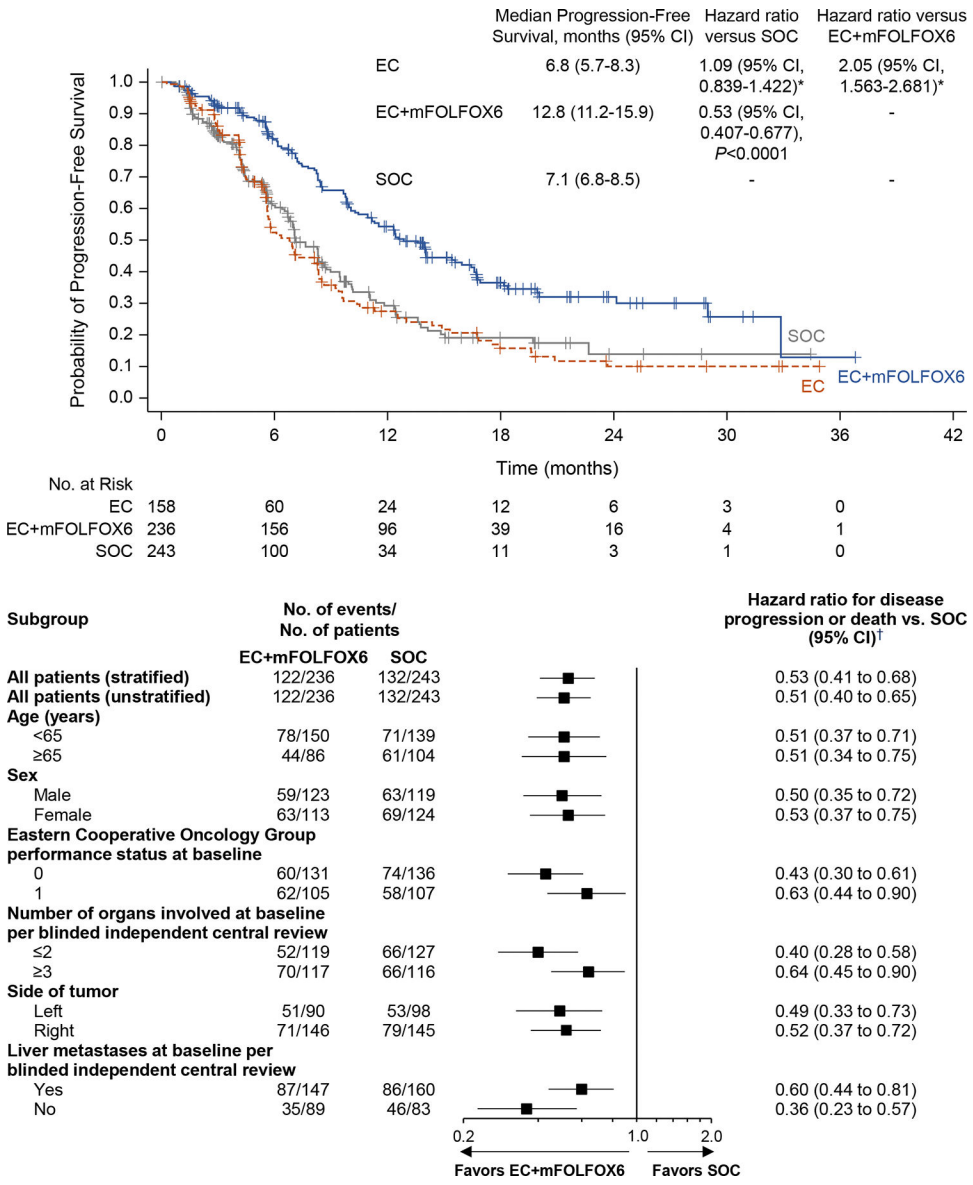

Figure 1. Analysis of Progression-Free Survival by Blinded Independent Central Review.

Panel A shows Kaplan–Meier estimates of progression-free survival in the EC, EC+mFOLFOX6 and SOC arms. **Panel B** shows a forest plot of the analyses in pre-specified subgroups in the EC+mFOLFOX6 and SOC arms.

*Analyses of EC versus SOC and EC versus EC+mFOLFOX6 are descriptive. CIs are not adjusted for multiplicity and should not be mistaken for hypothesis tests. Following a protocol amendment, enrollment into the EC arm was discontinued prematurely.

†Subgroup analyses are exploratory and descriptive in nature; CIs are not adjusted for multiplicity and should not be interpreted as hypothesis tests.

CI, confidence interval; EC, encorafenib and cetuximab; EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin and 5-FU; HR, hazard ratio; SOC, standard of care.

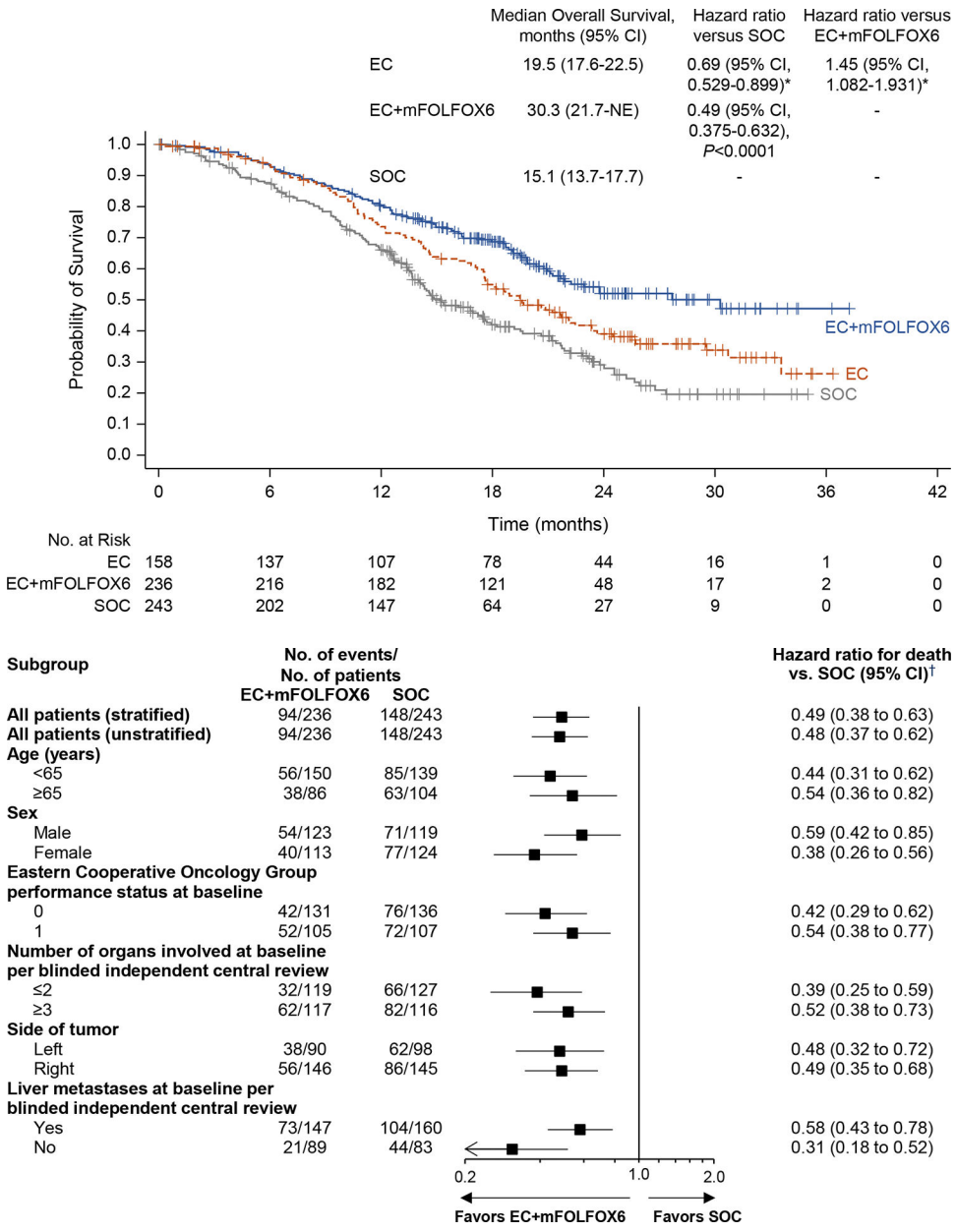

Figure 2. Analysis of Overall Survival.

Panel A shows Kaplan–Meier estimates of overall survival in the EC, EC+mFOLFOX6 and SOC. **Panel B** shows a forest plot of the analyses in pre-specified subgroups in the EC+mFOLFOX6 and SOC arms.

Because the result of the interim analysis of overall survival was statistically significant, no further statistical test will be performed.

*Analyses of EC versus SOC and EC versus EC+mFOLFOX6 are descriptive. CIs are not adjusted for multiplicity and should not be mistaken for hypothesis tests. Following a protocol amendment, enrollment into the EC arm was discontinued prematurely.

†Subgroup analyses are exploratory and descriptive in nature; CIs are not adjusted for multiplicity and should not be interpreted as hypothesis tests.

CI, confidence interval; EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin and 5-FU; HR, hazard ratio; SOC, standard of care.

Table 1.

Characteristics of Patients at Baseline in the EC, EC+mFOLFOX6, and SOC Arms [*]

Characteristic	EC N = 158	EC+mFOLFOX6 N = 236	SOC N = 243
Age — yr			
Median	59.0	60.0	62.0
Range	26.0–84.0	24.0–81.0	28.0–84.0
Sex — no. (%)			
Male	79 (50.0)	123 (52.1)	119 (49.0)
Female	79 (50.0)	113 (47.9)	124 (51.0)
Race — no. (%)			
White	88 (55.7)	141 (59.7)	144 (59.3)
Asian	64 (40.5)	88 (37.3)	91 (37.4)
Multiracial	0	0	2 (0.8)
Black or African American	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)
Side of tumor — no. (%)			
Left	69 (43.7)	90 (38.1)	98 (40.3)
Right	89 (56.3)	146 (61.9)	145 (59.7)
Stage at initial diagnosis — no. (%)			
Stage I	4 (2.5)	3 (1.3)	2 (0.8)
Stage II	7 (4.4)	13 (5.5)	10 (4.1)
Stage III	24 (15.2)	38 (16.1)	45 (18.5)
Stage 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)
Eastern Cooperative Oncology Group performance status — no. (%)			
0	79 (50.0)	128 (54.2)	131 (53.9)
1	74 (46.8)	104 (44.1)	98 (40.3)
Missing	5 (3.2)	4 (1.7)	14 (5.8)
Central BRAF V600E status (tumor tissue) — no. (%) [‡]			

Characteristic	EC N = 158	EC+mFOLFOX6 N = 236	SOC N = 243
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)
Not available	7 (4.4)	6 (2.5)	16 (6.6)
Local microsatellite instability/mismatch repair deficiency status — no. (%) [§]			
High microsatellite instability/mismatch repair deficiency	0	1 (0.4)	0
Microsatellite stable/proficient mismatch repair	152 (96.2)	229 (97.0)	227 (93.4)
Not available	6 (3.8)	6 (2.5)	16 (6.6)
Carcinoembryonic antigen at baseline — no. (%)			
≤5 μg/L	50 (31.6)	64 (27.1)	63 (25.9)
>5 μg/L	102 (64.6)	167 (70.8)	163 (67.1)
Missing	6 (3.8)	5 (2.1)	17 (7.0)
C-reactive protein at baseline — no. (%)			
≤10 mg/L	91 (57.6)	125 (53.0)	118 (48.6)
>10 mg/L	61 (38.6)	105 (44.5)	108 (44.4)
Missing	6 (3.8)	6(25	17 (7.0)

EC, encorafenib and cetuximab; EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin and 5-FU; SOC, standard of care.

[*] The last assessment before the date of first dose of study intervention for ECOG and biomarker endpoints was used as baseline.

[†] Number of organs and presence of liver metastases are based on blinded independent central review data for the phase 3 portion of the study.

[‡] Local testing could be performed by tumor or blood-based assays.

[§] Local microsatellite instability status of microsatellite stable/proficient mismatch repair includes low microsatellite instability.

Table 2.

Most Frequent Treatment-Emergent Adverse Events (Reported in More Than 20% of Patients in the EC+mFOLFOX6 Arm)

Adverse Event	EC N = 153		EC+mFOLFOX6 N = 232		SOC N = 229	
Treatment-emergent adverse events — no. (%)						
	Any grade	**Grade 3–4**	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
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 decrease	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)
Neuropathy peripheral	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)

EC, encorafenib and cetuximab; EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin and 5-FU; SOC, standard of care.

Table 3.

Most Frequent Serious Treatment-Emergent Adverse Events (Reported in More Than 1% of Patients in the EC+mFOLFOX6 Arm)

Adverse Event	EC N = 153	EC+mFOLFOX6 N = 232	SOC N = 229
Treatment-emergent adverse events — no. (%)			
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)
ALT 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)

ALT, Alanine aminotransferase; EC, encorafenib and cetuximab; EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin and 5-FU; SOC, standard of care.