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Encorafenib, cetuximab and chemotherapy in BRAF-mutant colorectal cancer: a randomized phase 3 trial

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Encorafenib + cetuximab (EC) is approved for previously treated BRAF V600E-mutant metastatic colorectal cancer (mCRC) based on the BEACON phase 3 study. Historically, first-line treatment of BRAF V600E-mutant mCRC with chemotherapy regimens has had limited efficacy. The phase 3 BREAKWATER study investigated EC+mFOLFOX6 versus standard of care (SOC) in patients with previously untreated BRAF V600E mCRC. The dual primary endpoint of progression-free survival is event driven; data were not mature at data cutoff. BREAKWATER met the other dual primary endpoint of objective response rate, demonstrating significant and clinically relevant improvement in objective response rate (EC+mFOLFOX6: 60.9%; SOC: 40.0%; odds ratio, 2.443; 95% confidence interval (CI): 1.403–4.253; 99.8% CI: 1.019–5.855; one-sided $P = 0.0008$). Median duration of response was 13.9 versus 11.1 months. At this first interim analysis of overall survival, the hazard ratio was 0.47 (95% CI: 0.318–0.691; repeated CI: 0.166–1.322). Serious adverse event rates were 37.7% versus 34.6%. The safety profiles were consistent with those known for each agent. BREAKWATER demonstrated a significantly improved response rate that was durable for first-line EC+mFOLFOX6 versus SOC in patients with BRAF V600E mCRC. ClinicalTrials.gov identifier: NCT04607421.

BRAF V600E mutations occur in 8–12% of metastatic colorectal cancers (mCRCs)[1,2]; the presence of these mutations has emerged as a distinct subtype that is characterized by poor prognosis compared with wild-type disease and resistance to standard chemotherapy regimens[1,2]. *BRAF* V600E mutations are found in multiple tumor types, and BRAF inhibitors in combination with MEK inhibitors are part of the standard of care (SOC) in BRAF-mutant melanoma and non-small cell lung cancer[3,4].

Encorafenib is a highly selective, ATP-competitive small-molecule BRAF inhibitor with anti-proliferative and apoptotic activity in tumor cells expressing *BRAF* V600E and has prolonged pharmacodynamic activity compared with other approved BRAF inhibitors[5,6]. BRAF V600E inhibition causes rapid pathway feedback reactivation through the epidermal growth factor receptor (EGFR)[7,8]; previous clinical trials targeting BRAF simultaneously with EGFR inhibition have shown the value of this combination in targeting MAPK signaling[9,10]. Encorafenib plus cetuximab, an anti-EGFR monoclonal antibody, is approved for previously treated BRAF V600E-mutant mCRC based on results from the BEACON study[11]. Median overall survival was 8.4 months, the objective response

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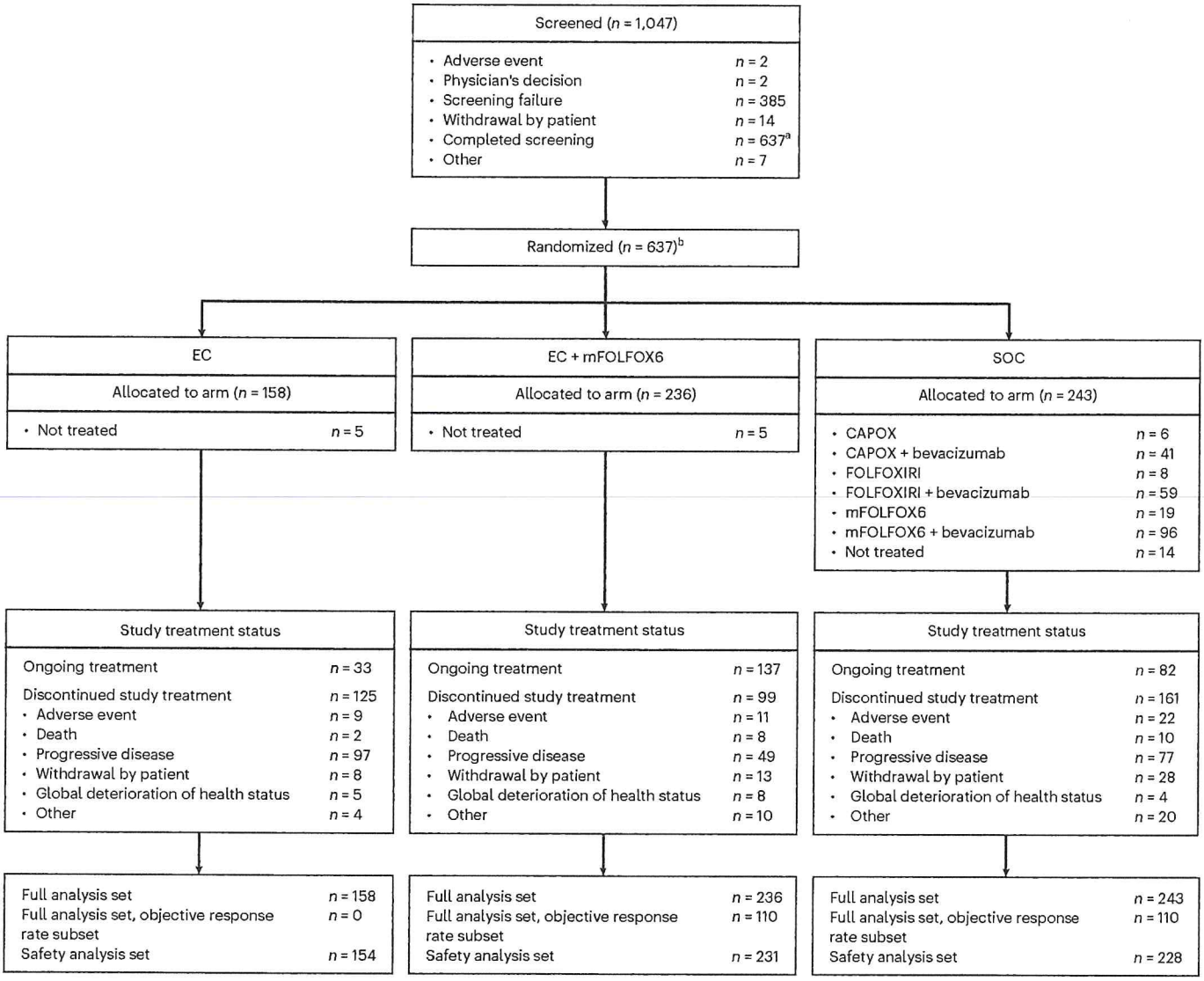

Fig. 1 | Patient disposition. CAPOX, oxaliplatin and capecitabine; EC, encorafenib and cetuximab; mFOLFOX6, oxaliplatin, leucovorin and 5-FU; FOLFOXIRI, irinotecan, oxaliplatin, leucovorin and 5-FU; mCRC, metastatic colorectal cancer; SOC, standard of care. [a]One participant who was randomized to the EC+mFOLFOX6 arm (but never treated) was inadvertently entered as withdrawal by subject on the screening case report form page. [b]Following closure of the EC arm, randomization was 1:1 to the EC+mFOLFOX6 and SOC arms.

rate was 20%, median progression-free survival was 4.2 months and no new safety signals were observed with encorafenib plus cetuximab[9].

Despite this promising option of targeted treatments in the second and later lines as demonstrated in the BEACON study, first-line chemotherapies with or without a biologic agent (eg, bevacizumab) have had limited efficacy for BRAF V600E-mutant mCRC[12]. Furthermore, the addition of bevacizumab with doublet and triplet chemotherapy has been debated due to tolerability concerns[13]. There are currently no first-line activation pathway-targeted treatments indicated for patients with BRAF V600E-mutant mCRC; therefore, a treatment that can demonstrate improved efficacy in the first-line setting is needed given the poor prognosis compared with BRAF wild-type mCRC.

BREAKWATER (NCT04607421) is a phase 3 study evaluating encorafenib plus cetuximab with or without standard chemotherapy (oxaliplatin, leucovorin and 5-FU (mFOLFOX6) (EC±mFOLFOX6) versus 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-mutabt mCRC. Data from the safety lead-in portion demonstrated encouraging response rates and progression-free survival of encorafenib and cetuximab with chemotherapy (mFOLFOX6 or irinotecan, leucovorin and 5-FU (FOLFIRI))[14].

Reported here are one of the dual primary endpoints, objective response rate and the first interim analysis of overall survival, duration of response, time to response and safety in the EC+mFOLFOX6 and SOC arms from the phase 3 portion. The second dual primary endpoint, progression-free survival, is event driven; the required number of events needed for analysis had not yet been achieved at the time of writing and will be reported later. Additional planned secondary endpoints not reported in this paper are progression after next line of therapy, patient-reported outcomes, pharmacokinetics and biomarker endpoints. An interactive infographic is available at https://www.breakwaterphase3-infographic.com/.

Results

Patients

Patients were enrolled between 16 November 2021 and 22 December 2023 in the phase 3 portion of the study. Eligible patients had previously

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Table 1 | Baseline demographics and disease characteristics

	EC+mFOLFOX6 (*n*=236)	SOC (*n*=243)	Total (*n*=479)
Median age (range), years	60.0 (24–81)	62.0 (28–84)	61.0 (24–84)
Male, *n* (%)	123 (52.1)	119 (49.0)	242 (50.5)
Female, *n* (%)	113 (47.9)	124 (51.0)	237 (49.5)
Race, *n* (%)			
White	141 (59.7)	144 (59.3)	285 (59.5)
Asian	88 (37.3)	91 (37.4)	179 (37.4)
Multiracial	0	2 (0.8)	2 (0.4)
Black or African American	0	1 (0.4)	1 (0.2)
Not reported	7 (3.0)	5 (2.1)	12 (2.5)
Body site, *n* (%)			
Colon	191 (80.9)	192 (79.0)	383 (80.0)
Rectum	24 (10.2)	27 (11.1)	51 (10.6)
Cecum	21 (8.9)	24 (9.9)	45 (9.4)
Side of tumor, *n* (%)			
Left	89 (37.7)	98 (40.3)	187 (39.0)
Right	147 (62.3)	145 (59.7)	292 (61.0)
Stage at initial diagnosis, *n* (%)			
I	3 (1.3)	2 (0.8)	5 (1.0)
II	13 (5.5)	10 (4.1)	23 (4.8)
III	37 (15.7)	43 (17.7)	80 (16.7)
IV	183 (77.5)	188 (77.4)	371 (77.5)
Primary tumor resection, *n* (%)			
Complete	116 (49.2)	105 (43.2)	221 (46.1)
Partial	14 (5.9)	13 (5.3)	27 (5.6)
None	106 (44.9)	125 (51.4)	231 (48.2)
No. of organs involved, *n* (%)[a]			
≤2	122 (51.7)	129 (53.1)	251 (52.4)
≥3	114 (48.3)	114 (46.9)	228 (47.6)
Liver metastases, *n* (%)[a]	144 (61.0)	156 (64.2)	300 (62.6)
Eastern Cooperative Oncology Group performance status, *n* (%)			
0	129 (54.7)	131 (53.9)	260 (54.3)
1	103 (43.6)	98 (40.3)	201 (42.0)
Missing	4 (1.7)	14 (5.8)	18 (3.8)
Central BRAF V600E status (tumor tissue), *n* (%)			
Detected	226 (95.8)	224 (92.2)	450 (93.9)
Indeterminate	0	1 (0.4)	1 (0.2)
Not detected	4 (1.7)	2 (0.8)	6 (1.3)
Not available	6 (2.5)	16 (6.6)	22 (4.6)
Local microsatellite instability/mismatch repair deficiency status, *n* (%)			
High microsatellite instability/mismatch repair deficiency	1 (0.4)	0	1 (0.2)
Microsatellite stable/proficient mismatch repair	229 (97.0)	227 (93.4)	456 (95.2)
Not available	6 (2.5)	16 (6.6)	22 (4.6)
Carcinoembryonic antigen at baseline, *n* (%)			
≤5 μg liter^{-1}	65 (27.5)	63 (25.9)	128 (26.7)
>5 μg liter^{-1}	166 (70.3)	163 (67.1)	329 (68.7)
Missing	5 (2.1)	17 (7.0)	22 (4.6)
C-reactive protein at baseline, *n* (%)			
≤10 mg liter^{-1}	125 (53.0)	119 (49.0)	244 (50.9)
>10 mg liter^{-1}	105 (44.5)	107 (44.0)	212 (44.3)
Missing	6 (2.5)	17 (7.0)	23 (4.8)

EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin and 5-FU. [a]Number of organs and presence of liver metastases are based on blinded independent central review data for the phase 3 portion of the study.

Table 2 | Confirmed objective response rate, time to treatment and duration of response by blinded independent central review

	EC+mFOLFOX6 (*n*=110)	SOC (*n*=110)
Confirmed best overall response, *n* (%)		
Complete response	3 (2.7)	2 (1.8)
Partial response	64 (58.2)	42 (38.2)
Stable disease	31 (28.2)	34 (30.9)
Non-complete response/non-progressive disease	3 (2.7)	4 (3.6)
Progressive disease	3 (2.7)	9 (8.2)
Not evaluable	6 (5.5)	19 (17.3)
Confirmed objective response rate (95% CI), %[a]	60.9 (51.6–69.5)	40.0 (31.3–49.3)
Odds ratio (95% CI; 99.8% CI)[b]	2.443 (1.403–4.253; 1.019–5.855)	
One-sided *P* value	0.0008	
	n=67	*n*=44
Median time to response (range), weeks	7.1 (5.7–53.7)	7.3 (5.4–48.0)
Estimated median duration of response (range), months	13.9 (8.5–NE)	11.1 (6.7–12.7)
Patients with a duration of response of ≥6 months, *n* (%)	46 (68.7)	15 (34.1)
Patients with a duration of response of ≥12 months, *n* (%)	15 (22.4)	5 (11.4)

CI, confidence interval; EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin and 5-FU; NE, not estimable. [a]Defined as complete response or partial response according to RECIST 1.1 recorded from the date of randomization until the date of the first documentation of progression of disease, death or start of subsequent anticancer therapy; both complete response and partial response must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. [b]Asymptotic CI used.

untreated BRAF V600E-mutant mCRC in the metastatic setting, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and Eastern Cooperative Oncology Group performance status 0-1. Data reported here are for the EC+mFOLFOX6 and SOC arms; data from the EC arm will be reported at a later date. Patient disposition is shown in Fig. 1; 236 patients were randomized to the EC+mFOLFOX6 arm and 243 were randomized to the SOC arm in the phase 3 portion of the study. At data cutoff (22 December 2023), study treatment was ongoing in 137 patients in the EC+mFOLFOX6 arm and 82 in the SOC arm. A summary of important protocol deviations is reported in Supplementary Table 1.

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	Number of responders/ Number of patients		Objective response rate (%)[a]		Odds ratio (95% CI)[b]
	EC+mFOLFOX6	SOC	EC+mFOLFOX6	SOC	
Age (years)					
<65	41/64	22/61	64.1	36.1	3.160 (1.432–7.010)
≥65	26/46	22/49	56.5	44.9	1.595 (0.658–3.883)
Gender					
Male	36/57	20/50	63.2	40.0	2.571 (1.099–6.050)
Female	31/53	24/60	58.5	40.0	2.114 (0.934–4.803)
Eastern Cooperative Oncology Group performance status at baseline					
0	37/56	26/56	66.1	46.4	2.247 (0.981–5.178)
1	30/54	18/54	55.6	33.3	2.500 (1.070–5.880)
Number of organs involved at baseline per blinded independent central review					
≤2	32/58	20/58	55.2	34.5	2.338 (1.037–5.301)
≥3	35/52	24/52	67.3	46.2	2.402 (1.010–5.758)
Side of tumor					
Left	28/43	17/46	65.1	37.0	3.184 (1.232–8.313)
Right	39/67	27/64	58.2	42.2	1.909 (0.901–4.053)
Liver metastases at baseline per blinded independent central review					
Yes	47/69	31/71	68.1	43.7	2.757 (1.310–5.836)
No	20/41	13/39	48.8	33.3	1.905 (0.704–5.210)

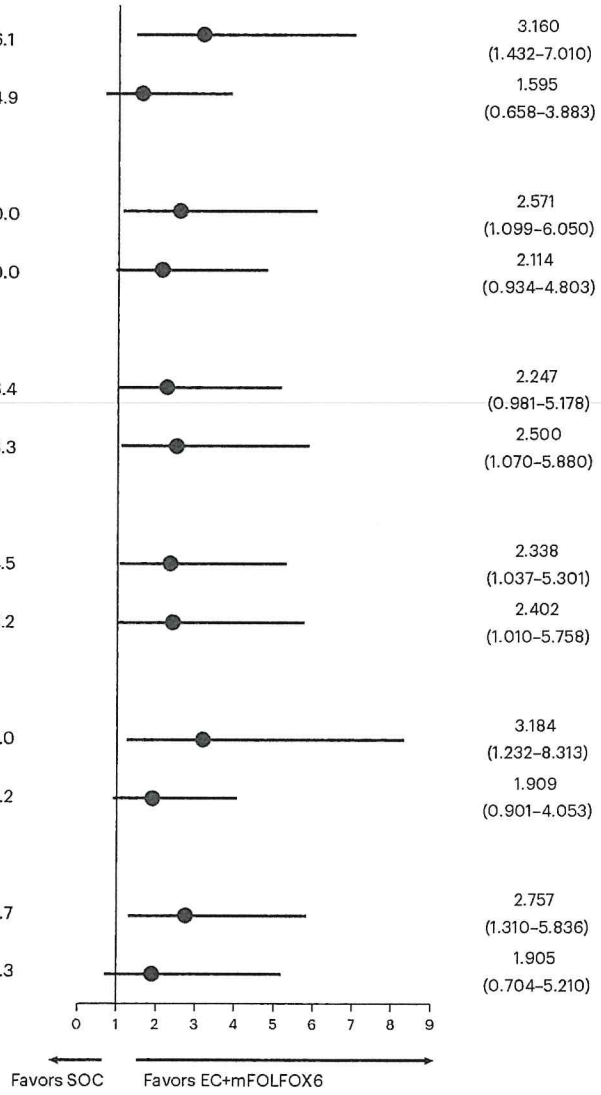

Fig. 2 | Subgroup analyses of confirmed objective response rate by blinded independent central review. Odds ratios (center) are presented with 95% CI (error bars). EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin and 5-FU. [a]Percentages were calculated based on the number of participants in the objective response rate subset of all randomized patients in each treatment group. [b]Objective response rate calculated based on the number of participants in the objective response rate subset of all randomized patients within each treatment group and subgroup. The odds ratio was estimated using the Mantel–Haenszel method. The exact CI was calculated.

Baseline demographics and disease characteristics were similar across arms (Table 1). The median age was 61 years, 49.5% of patients were female and 42.0% of patients had an Eastern Cooperative Oncology Group performance status of 1. The majority of patients had tumors that were on the right (61.0%), and most were microsatellite stable/proficient mismatch repair (95.2%).

Treatment

The median duration of treatment was 28.1 weeks (range: 1.3–107.4) in the EC+mFOLFOX6 arm and 20.4 weeks (range: 1.1–98.3) in the SOC arm (Extended Data Table 1). Median duration of treatment and relative dose intensities for each drug in each arm are reported in Extended Data Table 1 and Extended Data Table 2.

Efficacy

In the objective response rate subset of all randomized patients, the dual primary endpoint of confirmed objective response rate by blinded independent central review was met (60.9% (95% confidence interval (CI): 51.6–69.5) versus 40.0% (95% CI: 31.3–49.3) in the EC+mFOLFOX6 and SOC arm, respectively; odds ratio = 2.443 (95% CI: 1.403–4.253; 99.8% CI: 1.019–5.855), one-sided $P = 0.0008$) (Table 2). Predefined subgroup analyses of objective response rate showed consistency in results (Fig. 2). The median time to response by blinded independent central review was 7.1 weeks (range: 5.7–53.7) versus 7.3 weeks (range: 5.4–48.0), respectively (Table 2). The median duration of response was 13.9 months (95% CI: 8.5-not estimable) versus 11.1 months (95% CI: 6.7–12.7), respectively (Table 2). The proportion of patients with a duration

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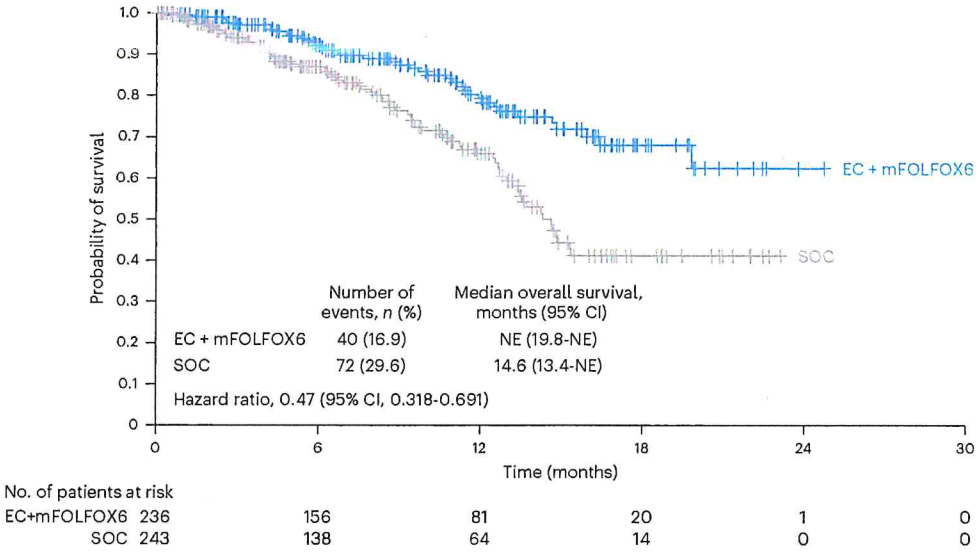

Fig. 3 | Overall survival. Hazard ratio repeated CI: 0.166–1.322.

of response of ≥6 months was 68.7% and 34.1%, respectively, and the proportion of patients with a duration of response of ≥12 months was 22.4% and 11.4%, respectively (Table 2). Data by investigator assessment also showed consistent treatment effects (Extended Data Table 3).

Upon achieving the dual primary endpoint of objective response rate, the key secondary endpoint of overall survival was formally tested in all randomized patients following the prespecified plan with one-sided alpha of 0.000000083, calculated as a portion of the nominal one-sided alpha of 0.001 based on the observed number of deaths (40 (16.9%) deaths in the EC+mFOLFOX6 arm; 72 (29.6%) deaths in the SOC arm). The median overall survival follow-up was 10.3 months (95% CI: 8.6–11.6) in the EC+mFOLFOX6 arm and 9.8 months (95% CI: 7.5–11.3) in the SOC arm. At this interim analysis of overall survival, the overall survival hazard ratio was 0.47 (95% CI: 0.318–0.691; repeated CI: 0.166–1.322)[15]; statistical significance was not achieved at this time ($P = 0.0000454$, one-sided alpha of 0.000000083). The median overall survival was not estimable (95% CI: 19.8 to not estimable) versus 14.6 months (95% CI: 13.4-not estimable), respectively (Fig. 3). The landmark overall survival rates were 92.3% versus 87.1% at 6 months and 79.5% versus 66.1% at 12 months.

Subsequent systemic anticancer treatments

Approximately half of the patients who discontinued study treatment received subsequent systemic anticancer treatment by the data cutoff. The majority of patients in the EC+mFOLFOX6 arm received subsequent chemotherapies, especially FOLFIRI-based combination. The majority of patients from the SOC arm received BRAF inhibitor-based subsequent therapies (Extended Data Table 4).

Safety

A safety summary is reported in Table 3 and Extended Data Table 5. Treatment-emergent adverse events occurred in 99.6% versus 97.8% of patients in the EC+mFOLFOX6 arm versus in the SOC arm, respectively. Similar rates of treatment-related adverse events were reported (Extended Data Table 5). The most frequent (≥30% of patients based on the EC+mFOLFOX6 arm) treatment-emergent adverse events were nausea (51.1% in the EC+mFOLFOX6 arm versus 48.2% in the SOC arm), anemia (36.4% versus 22.8%, respectively), diarrhea (34.2% versus 46.9%, respectively), decreased appetite (33.3% versus 25.0%, respectively), vomiting (33.3% versus 21.1%, respectively) and neutrophil count decreased (32.0% versus 28.1%, respectively) (Table 3).

Grade 3/4 adverse events occurred in 74.0% of patients in the EC+mFOLFOX6 arm versus 61.0% in the SOC arm; grade 3/4 treatment-related adverse events occurred in 69.7% versus 53.9% of patients, respectively (Extended Data Table 5).

Overall, there were 38 (16.5%) deaths in the EC+mFOLFOX6 arm and 69 (30.3%) deaths in the SOC arm; the disease under study was the most common cause (35 [15.2%] deaths in the EC+mFOLFOX6 arm versus 60 (26.3%) deaths in the SOC arm, respectively). Grade 5 (fatal) adverse events occurred in 4.3% versus 4.4% of patients, respectively; grade 5 treatment-related adverse events occurred in 0% versus 0.4% of patients, respectively (Extended Data Table 5).

Serious treatment-emergent adverse events occurred in 37.7% versus 34.6% of patients in the EC+mFOLFOX6 versus SOC arms, respectively (Extended Data Table 6). The most common serious adverse events are reported in Extended Data Table 6. Serious treatment-related adverse events occurred in 18.2% versus 19.3% of patients, respectively (Extended Data Table 6).

Adverse events leading to permanent discontinuation of any study intervention occurred in 20.8% versus 14.9% of patients in the EC+mFOLFOX6 versus SOC arms, respectively. Adverse events leading to dose reduction of any study intervention occurred in 61.0% versus 47.8% of patients, respectively. Permanent discontinuation of chemotherapy with or without bevacizumab (as appropriate for the treatment group) due to adverse event was reported in 15.6% of patients in the EC+mFOLFOX6 arm and 14.9% of patients in the SOC arm; dose reduction of any of these interventions were reported in 55.8% and 47.8%, respectively (Extended Data Table 5).

Discussion

BREAKWATER has met one of its dual primary endpoints, objective response rate, demonstrating a statistically significant and clinically relevant benefit in objective response rate by blinded independent central review with EC+mFOLFOX6 versus SOC. At the time of this analysis, data also showed a point estimate of overall survival hazard ratio of 0.47 for EC+mFOLFOX6 versus SOC; however, 16.9% of patients in the EC+mFOLFOX6 arm and 29.6% of patients in the SOC arm had an event at data cutoff for this first interim analysis and did not achieve the prespecified statistical significance. BREAKWATER is ongoing and once the required number of events specified in the protocol have occurred, the primary analysis of progression-free survival, the other dual primary endpoint, will be conducted and subsequently reported.

Investigator-assessed objective response rates were consistent with the objective response rates by blinded independent central review. Secondary endpoints showed the response to EC+mFOLFOX6

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Table 3 | Most common all-causality treatment-emergent adverse events (≥10% of patients in any arm) by preferred term

	EC+mFOLFOX6 (*n*=231)		SOC (*n*=228)	
	Any grade	Grade≥3	Any grade	Grade≥3
Any adverse event	230 (99.6)	181 (78.4)	223 (97.8)	149 (65.4)
Nausea	118 (51.1)	6 (2.6)	110 (48.2)	7 (3.1)
Anemia	84 (36.4)	25 (10.8)	52 (22.8)	8 (3.5)
Diarrhea	79 (34.2)	3 (1.3)	107 (46.9)	8 (3.5)
Neutrophil count decreased	74 (32.0)	42 (18.2)	64 (28.1)	38 (16.7)
Decreased appetite	77 (33.3)	5 (2.2)	57 (25.0)	3 (1.3)
Vomiting	77 (33.3)	8 (3.5)	48 (21.1)	5 (2.2)
Asthenia	62 (26.8)	10 (4.3)	33 (14.5)	3 (1.3)
Pyrexia	60 (26.0)	4 (1.7)	31 (13.6)	1 (0.4)
Peripheral sensory neuropathy	57 (24.7)	13 (5.6)	49 (21.5)	5 (2.2)
Rash	57 (24.7)	2 (0.9)	6 (2.6)	0
Fatigue	56 (24.2)	6 (2.6)	57 (25.0)	6 (2.6)
Neuropathy peripheral	54 (23.4)	16 (6.9)	48 (21.1)	6 (2.6)
Arthralgia	51 (22.1)	2 (0.9)	8 (3.5)	0
Neutropenia	51 (22.1)	34 (14.7)	51 (22.4)	21 (9.2)
Alopecia	49 (21.2)	0	23 (10.1)	0
Constipation	47 (20.3)	1 (0.4)	44 (19.3)	1 (0.4)
Platelet count decreased	46 (19.9)	3 (1.3)	28 (12.3)	4 (1.8)
White blood cell count decreased	42 (18.2)	13 (5.6)	32 (14.0)	8 (3.5)
Lipase increased	46 (19.9)	34 (14.7)	22 (9.6)	12 (5.3)
Weight decreased	40 (17.3)	2 (0.9)	19 (8.3)	0
Skin hyperpigmentation	39 (16.9)	0	5 (2.2)	0
Abdominal pain	38 (16.5)	7 (3.0)	47 (20.6)	3 (1.3)
Dermatitis acneiform	35 (15.2)	2 (0.9)	1 (0.4)	0
Hypokalemia	30 (13.0)	4 (1.7)	22 (9.6)	7 (3.1)
Aspartate aminotransferase increased	29 (12.6)	2 (0.9)	25 (11.0)	3 (1.3)
Dry skin	29 (12.6)	0	8 (3.5)	0
Headache	29 (12.6)	1 (0.4)	17 (7.5)	0
Mucosal inflammation	29 (12.6)	4 (1.7)	22 (9.6)	1 (0.4)
Paresthesia	28 (12.1)	6 (2.6)	18 (7.9)	3 (1.3)
Dysgeusia	27 (11.7)	0	31 (13.6)	0
Epistaxis	27 (11.7)	0	28 (12.3)	0
Hypomagnesemia	27 (11.7)	2 (0.9)	9 (3.9)	1 (0.4)
Stomatitis	27 (11.7)	4 (1.7)	32 (14.0)	3 (1.3)
Alanine aminotransferase increased	26 (11.3)	3 (1.3)	22 (9.6)	3 (1.3)
Myalgia	26 (11.3)	0	9 (3.9)	0
Thrombocytopenia	26 (11.3)	0	18 (7.9)	0
Neurotoxicity	25 (10.8)	11 (4.8)	18 (7.9)	0
Palmar-plantar erythrodysesthesia syndrome	25 (10.8)	3 (1.3)	18 (7.9)	2 (0.9)
Pruritus	24 (10.4)	0	4 (1.8)	0
Hypoalbuminemia	23 (10.0)	1 (0.4)	13 (5.7)	0
Insomnia	23 (10.0)	0	13 (5.7)	0

was rapid and durable. The percentage of patients with a duration of response beyond 6 or 12 months approximately doubled in the EC+mFOLFOX6 arm compared with the SOC arm. These early overall survival data showed a clear separation between the arms in the Kaplan-Meier curves, despite the number of deaths at data cutoff and data were not statistically significant at this first interim analysis. Follow-up is ongoing, with planned additional interim and final analysis. The subsequent system anticancer treatments reported in the study are similar to the current real-world practice. The majority of the patients in the SOC arm received a BRAF inhibitor-based subsequent anticancer treatment. Thus, the observed difference in overall survival is evaluated against a valid current SOC.

Subgroup analyses of objective response rates by blinded independent central review showed the clinical benefit of EC+mFOLFOX6 was seen across all key clinical subgroups; notably, clinical benefit was observed regardless of presence of liver metastases.

Trials of chemotherapy plus cetuximab or bevacizumab, BRAF inhibitor monotherapy, BRAF inhibitors with MEK inhibitors, and BRAF inhibitors with chemotherapy have shown limited benefit over the current SOC for patients with BRAF V600E-mutant mCRC[7,10,12,16–23]. Our data highlight the importance of combining dual targeted therapy (encorafenib and cetuximab) with chemotherapy in BRAF V600E-mutant CRC to improve patient outcomes in the first-line setting. It is currently unknown what specific mechanisms are responsible for the observed clinical benefit of EC and chemotherapy compared with chemotherapy alone. The combination of cytotoxic chemotherapy, which has a nonselective antitumor effect, and targeted therapy may overcome intratumor heterogeneity through an additive effect, targeting different cell populations, and ultimately improving clinical outcomes. Ongoing exploratory analyses may provide further insights into predictive biomarkers for this combination therapy.

Safety data showed that EC+mFOLFOX6 was generally tolerable, with a safety profile consistent with that known for each agent. Patients in the EC+mFOLFOX6 arm had a longer duration of treatment and maintained high relative dose intensities. The addition of EC to chemotherapy was generally tolerable without significant increase in chemotherapy dose reduction or discontinuation.

Recent data suggest that combining chemotherapy with targeted therapy may prevent the emergence of resistance alterations and allow for prolonged antitumor efficacy, these preclinical data support the rationale for the BREAKWATER study to combine EC with chemotherapy in BRAF V600E-mutant mCRC[24,25]. The long duration of response achieved in the BREAKWATER trial with EC+mFOLFOX6 suggests the potential for prolonged effect of the combination. Despite these promising data, there is a further need to characterize the mechanisms of resistance to help improve outcomes in patients who ultimately progress on treatment. A retrospective, exploratory, clinical and molecular analysis of the BEACON study characterized potential biological determinants underlying response and acquired resistance to BRAF-targeted therapy, with or without MEK inhibition, in BRAF V600E-mutant mCRC[26]. Future biomarker analyses of the BREAKWATER study may shed light on the resistance mechanism by comparing chemotherapy plus targeted therapy versus chemotherapy or targeted therapy alone.

Based on the results from the phase 2 ANCHOR study of encorafenib, cetuximab and binimetinib[27], it was suggested that the likelihood to demonstrate superiority in the EC arm versus the SOC arm was relatively low. This low likelihood, together with the fact that the majority of patients with BRAF V600E-mutant mCRC require an intensive first-line regimen to control the aggressive tumor growth, supports the investigation of EC+mFOLFOX6, and led to the early closure of EC arm enrollment.

BREAKWATER excluded patients with MSI-H or dMMR tumors unless ineligible to receive immune checkpoint inhibitors due to a preexisting medical condition. The programmed death 1 inhibitor pembrolizumab has shown clinical benefit as a first-line therapy for

MSI-H or dMMR mCRC[28]. SEAMARK is an ongoing phase 2 study evaluating first-line EC with pembrolizumab versus pembrolizumab alone in patients with BRAF V600E-mutant and MSI-H/dMMR mCRC[29].

Furthermore, the phase 3 portion of this study only investigated EC in combination with mFOLFOX6. As previously mentioned, the safety lead-in portion evaluated EC plus mFOLFOX6 or FOLFIRI in a small number of patients and showed encouraging results[14,30]. BREAKWATER is further evaluating EC plus FOLFIRI versus FOLFIRI with or without bevacizumab in the ongoing cohort 3 portion.

BREAKWATER showed substantially improved clinical benefit with EC+mFOLFOX6 as a first-line treatment for patients with BRAF V600E-mutant mCRC. These encouraging data support this regimen to potentially become the new SOC in BRAF V600E-mutant mCRC; prespecified analyses of mature progression-free survival and overall survival data are planned.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-024-03443-3.

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Methods

Trial oversight

BREAKWATER enrolled in 28 countries. It was designed and overseen by a steering committee, representatives of the sponsor, and an independent data monitoring committee. BREAKWATER was supported by Pfizer, Inc. Informed consent from patients was obtained prior to enrollment. The protocol, including amendments and was approved by the relevant ethics committee/institutional review board at each site (See Supplementary Information). 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. The listing of investigators who conducted the study is provided in the Supplementary Information. Data collection and analysis were performed by the sponsor in collaboration with the authors. The authors had access to the study data. The authors, in collaboration with the sponsor, made the decision to submit the results for publication. 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 and this report to the protocol.

Patients

BREAKWATER enrolled patients who were at least 16 years of age (where permitted locally), with histologically or cytologically confirmed colorectal adenocarcinoma that had evidence of Stage IV metastatic disease, measurable disease (RECIST 1.1)[31] and presence of a *BRAF* V600E mutation assessed by local or central laboratory testing. *BRAF* V600E mutation status was confirmed retrospectively by the central laboratory using tumor tissue collected within 2 years prior to study enrollment if not done at screening. Patients were eligible if they had not received prior systemic treatment for metastatic disease (prior [neo] adjuvant therapy was considered to be metastatic treatment if relapse or metastasis <6 months from the end of [neo]adjuvant therapy) and were ineligible if they previously received any selective BRAF inhibitor or any EGFR inhibitor. Eligible patients had an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate bone marrow, hepatic, and renal function. Patients with symptomatic brain metastases, microsatellite instability-high/mismatch repair deficient tumors (MSI-H/dMMR; unless ineligible to receive immune checkpoint inhibitors due to a preexisting medical condition), or a *RAS* mutation were excluded.

Trial design and treatment

Patients were randomized 1:1:1 to the EC arm (encorafenib 300 mg orally once daily; cetuximab 500 mg/m^2 intravenously once every 2 weeks), EC+mFOLFOX6 arm (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 h, all once every 2 weeks (mFOLFOX6; 28-day cycle)) or investigator's choice SOC arm (mFOLFOX6 with or without bevacizumab (per prescribing instructions); irinotecan 165 mg/m^2 intravenously, oxaliplatin 85 mg/m^2 intravenously, leucovorin 400 mg/m^2 intravenously and 5-FU 2,400 or 3,200 mg/m^2 continuous intravenous infusion over 46–48 h, all once every 2 weeks (FOLFOXIRI; 28-day cycle) with or without bevacizumab (per prescribing instructions); oxaliplatin 130 mg/m^2 intravenously once every 3 weeks (21-day cycle) and capecitabine 1,000 mg/m^2 orally twice daily (days 1–14) (CAPOX) with or without bevacizumab (per prescribing instructions)). Following a protocol amendment, enrollment to the EC arm was stopped and patients were randomized 1:1 to the EC+mFOLFOX6 or SOC arms.

Randomization stratification factors were Eastern Cooperative Oncology Group performance status (0 versus 1) and region (US/Canada versus Europe versus Rest of World). Randomization was completed by Interactive Response Technology; sites contacted the Interactive Response Technology prior to the start of study intervention administration for each patient, and sites recorded the study intervention assignment on the applicable case report form required.

Endpoints

The dual primary endpoints are objective response rate and progression-free survival by blinded independent central review between the EC+mFOLFOX6 and SOC arms, to be evaluated independently. Objective response rate is defined as confirmed complete response or partial response according to RECIST 1.1 (ref. 31) recorded from randomization until the date of the first documentation of progression of disease, death or start of subsequent anticancer therapy; both complete response and partial response must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. Progression-free survival is defined as the time from the date of randomization to the earliest documented disease progression per RECIST 1.1 (ref. 31) or death due to any cause.

The key secondary endpoint is overall survival between the EC+mFOLFOX6 and SOC arms, 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.

Adverse events were coded using Medical Dictionary for Regulatory Activities v26.1 (ref. 32), and severity of adverse events was graded using National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 (ref. 33).

Statistical analysis

The statistical analysis plan includes a detailed methodology for the statistical analyses of the data collected in this study. The sample size of 235 patients per arm was determined based on statistical assumptions for progression-free survival analysis. An overall one-sided alpha of 0.024 was unequally divided between the two dual primary endpoints.

One of the dual primary endpoints of objective response rate by blinded independent central review was analyzed in the objective response rate subset, comprised of the first 110 patients randomized in the EC+mFOLFOX6 arm and the SOC arm respectively. This sample size of 220 patients provided 90% power to test the odds ratio at a one-sided alpha of 0.001, assuming an objective response rate by blinded central review of 35% and 65% for the EC+mFOLFOX6 and SOC arms, respectively. Objective response rate was calculated along with the corresponding two-sided 95% Wilson score CI. The treatment effect between arms was measured using an odds ratio stratified by baseline stratification factors and its 99.8% and 95% CI and tested using a stratified Cochran–Mantel–Haenszel statistics at the one-sided alpha of 0.001.

Following a prespecified hierarchical testing procedure to control the family-wise type I error rate, an interim analysis of the key secondary endpoint of overall survival on all randomized patients would only be conducted if the dual primary endpoint of objective response by blinded independent central review is achieved, using a portion of the nominal one-sided alpha of 0.001. The treatment effect of overall survival was evaluated using a Cox proportional hazards model stratified by baseline stratification factors. The hazard ratio and its corresponding 95% CI were reported.

The other dual primary endpoint of progression-free survival was allocated one-sided alpha of 0.023 and will be analyzed once the required number of events has been observed.

Statistical analyses were performed using SAS version 9.4 or higher.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The analyses in this paper were based on a data cutoff of 22 December 2023.

Upon reasonable request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (that is, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Author contributions

S.K., T.Y., E.V.C., C.E., T.W.K., H.S.W., J.D., F.C., R.Y., T.S.M. and J.T. undertook the data acquisition. Xiaoxi Zhang performed the statistical analysis. All authors analyzed and interpreted the data, reviewed the paper and gave approval for submission. All authors were accountable for all aspects of the work.

Competing interests

S.K. has stock and other ownership interests in Lylon, Lutris, MolecularMatch and Navire; a consulting or advisory role at AbbVie, Amal Therapeutics, AstraZeneca/MedImmune, Bayer Health, Bicara Therapeutics, Boehringer Ingelheim, Boston Biomedical, Carina Biotech, Daiichi Sankyo, EMD Serono, Endeavor BioMedicines, Flame Biosciences, Genentech, Gilead Sciences, GSK, HalioDx, Holy Stone Healthcare, Inivata, Ipsen, Iylon, Jacobio, Jazz Pharmaceuticals, Lilly, Lutris, Merck, Mirati Therapeutics, Natera, Novartis, Numab, Pfizer, Pierre Fabre, Redx Pharma, Repare Therapeutics, Servier and Xilis and received research funding from Amgen, Array BioPharma, Biocartis, Daiichi Sankyo, EMD Serono, Genentech/Roche, Guardant Health, Lilly, MedImmune, Novartis and Sanofi. T.Y. receives honoraria from Bayer Yakuhin, Chugai Pharma, Merck KGaA, MSD, Ono Pharmaceutical, Sumitomo and Takeda and research funding from Amgen, Boehringer Ingelheim, Chugai Pharma, Daiichi Sankyo, Eisai, FALCO Biosystems, Genomedia, Molecular Health, MSD, Nippon Boehringer Ingelheim, Ono Pharmaceutical, Pfizer, Roche Diagnostics, Sanofi, Sumitomo Dainippon, Sysmex and Taiho Pharmaceutical. E.V.C. has a consulting or advisory role at AbbVie, Agenus, ALX, Amgen, Arcus Biosciences, Astellas Pharma, AstraZeneca, Bayer, BeiGene, BioNTech, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Debiopharm, ElmediX, Eisai, GSK, Hookipa Biotech, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Mirati, Novartis, Nordic, Pierre Fabre, Pfizer, Roche, Seagen, Servier, Simcere, Takeda, Taiho Pharmaceutical and Terumo. C.E. has a consulting role at Bayer, Boston Scientific, GlaxoSmithKline, HalioDx, Merck, Mirati, Hookipa, J&J, Natera, Roche, Seagen, Taiho and Veloxis and receives research funding (to VUMC) from Elevar, Hutchinson, Merck and Pfizer. T.W.K. receives research funding (institutional) from AstraZeneca, Sanofi and Roche/Genentech. H.S.W. has a consulting or advisory role at Amgen, Bayer, Bristol Myers Squibb (Celgene), Boehringer Ingelheim (DMC), BTG, EXACT Therapeutics, Erytech Pharma, Incyte, Merck KGaA, Oaktree Life Sciences, OncoSil, Pfizer, Pierre Fabre, Roche/Genentech, Seagen, Servier, Shire, Sirtex Medical, Takeda (Hutchinson Med) and Zymeworks and recieves research funding (institutional) from Merck KGaA, MSD, Pfizer and Sirtex Medical. J.D. has a consulting or advisory role at Amgen, Bayer, BeiGene, Daiichi Sankyo, Eisai, GSK, Merck KGaA and Pierre Fabre and receives research funding from AstraZeneca/MedImmune, BeiGene, Bionomics, Bristol Myers Squibb, GSK, Lilly, Novartis and Roche. F.C. has a consulting or advisory role at Amgen, Bayer, Merck KGaA, Pfizer and Roche/Genentech and receives research funding from Amgen, Bayer, Bristol Myers Squibb, Ipsen, Merck KGaA, MSD, Roche/Genentech, Servier and Symphogen. R.Y. has a consulting or advisory role at Array BioPharma/Pfizer, Mirati Therapeutics, Zai Lab and Amgen and receives research funding from Array BioPharma, Boehringer Ingelheim, Mirati Therapeutics, Pfizer and Daiichi Sankyo. T.S.M. has a consulting or advisory role at AstraZeneca, Pierre Fabre and Vertex; receives research funding (institutional) from Almac Diagnostics, AstraZeneca, Merck KgAA and PsiOxus Therapeutics; and has a patent pending. E.B., Xiaoxi Zhang and G.F. are employees of and have stock and other ownership interests in Pfizer. Xiaosong Zhang is an employee of and has stock and other ownership interests in Pfizer and has patents, royalties or other intellectual property via Johns Hopkins University. J.T. has a consulting or advisory role at Array BioPharma, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai Pharma, Daiichi Sankyo, F. Hoffmann-La Roche, Genentech, HalioDx, Hutchison MediPharma, Ikena Oncology, Inspirna, IQVIA, Lilly, Menarini, Merck Serono, Merus, Mirati Therapeutics, MSD, NeoPhore, Novartis, Ona Therapeutics, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Scandion Oncology, Scorpion Therapeutics, Seagen, Servier, Taiho Pharmaceutical, Tessa Therapeutics and TheraMyc and has other relationships with Amgen, Array Biopharma, BeiGene, Boehringer Ingelheim, BMS, Cancer Research UK, Celgene, Debiopharm, F. Hoffman-La Roche, Fundación Científica de la Asociación Española Contra el Cáncer, Genentech, HalioDx, Hutchinson Medipharma, Imedex, Janssen-Cilag, MedImmune, Medscape, Menarini, Merck Health KGaA, MJH Life Sciences, MSD, Merus, Mirati, Novartis, Oniria Therapeutics, PeerView Institute for

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Additional information

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Extended Data Table 1 | Median duration of treatment

EC+mFOLFOX6 n=231						
	Encorafenib (n=229)	Cetuximab (n=230)	Fluorouracil (n=231)	Leucovorin (n=231)	Oxaliplatin (n=231)	Regimen (n=231)
Median (range), weeks	27.57 (0.43-107.43)	27.07 (1.29-107.43)	24.86 (1.29-107.43)	24.86 (1.29-107.43)	18.86 (1.29-76.57)	28.14 (1.29-107.43)

SOC n=228							
	Fluorouracil (n=181)	Leucovorin (n=179)	Irinotecan (n=66)	Oxaliplatin (n=228)	Capecitabine (n=47)	Bevacizumab (n=195)	Regimen (n=228)
Median (range), weeks	20.43 (1.29-96.57)	20.14 (1.29-96.57)	21.36 (2.00-96.57)	16.71 (1.14-98.29)	17.00 (1.14-98.14)	20.00 (1.14-98.29)	20.36 (1.14-98.29)

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

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Extended Data Table 2 | Relative dose intensity

EC+mFOLFOX6 n=231					
	Encorafenib (n=229)	Cetuximab (n=230)	Fluorouracil (n=231)	Leucovorin (n=231)	Oxaliplatin (n=231)
Median (range), %	91.7 (3.0-100.7)	94.2 (38.4-199.4†)	82.7 (46.6-102.8)	94.1 (47.0-199.4†)	84.2 (41.6-201.9†)

SOC n=228						
	Fluorouracil (n=181)	Leucovorin (n=179)	Irinotecan (n=66)	Oxaliplatin (n=228)	Capecitabine (n=47)	Bevacizumab (n=195)
Median (range), %	90.3 (50.2-116.4)	98.8 (61.4-200.5†)	87.2 (47.6-120.5)	92.4 (42.2-204.9†)	68.6 (22.2-104.5)	99.3 (33.1-201.9†)

EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin, and 5-FU; SOC, standard of care. Relative dose intensity = 100 × (cumulative dose ÷ planned cumulative dose). Planned cumulative is sum of all doses assuming all doses are administered at the protocol-specified dose. † Patients who received only 2 doses and whose second dose was received prior to the planned date (still within protocol allowed window) leading to only 1 planned dose in the calculation.

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Extended Data Table 3 | Confirmed objective response rate, time to treatment, and duration of response by investigator assessment

	EC+mFOLFOX6 n=110	SOC n=110
Confirmed best overall response, n (%)		
Complete response	12 (10.9)	3 (2.7)
Partial response	59 (53.6)	41 (37.3)
Stable disease	31 (28.2)	38 (34.5)
Non-complete response/non progressive-disease	0	0
Progressive disease	1 (0.9)	12 (10.9)
Not evaluable	7 (6.4)	16 (14.5)
Confirmed objective response rate (95% CI), %*	64.5 (55.3-72.9)	40.0 (31.3-49.3)
Odds ratio (95% CI)	2.828 (1.548-5.040)	
One-sided *P*-value	0.0001	
	n=71	n=44
Median time to response (range), weeks	6.9 (5.6-93.1)	7.1 (5.4-24.6)
Estimated median duration of response (range), months	12.5 (9.4-NE)	8.3 (5.5-11.3)
Patients with a duration of response of ≥6 months, n (%)	49 (69.0)	22 (50.0)
Patients with a duration of response of ≥12 months, n (%)	17 (23.9)	6 (13.6)

* Defined as complete response or partial response according to RECIST 1.1 recorded from the date of randomization until the date of the first documentation of progression of disease, death, or start of subsequent anticancer therapy; both complete response and partial response must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

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Extended Data Table 4 | Subsequent systemic anticancer treatments by drug category

Patients, n (%)	EC+mFOLFOX6 n=236	SOC n=243
Participants with any subsequent systemic anticancer treatment	51 (21.6)	82 (33.7)
FOLFIRI ± combination	22 (9.3)	19 (7.8)
Single agent chemotherapy ± combination	11 (4.7)	10 (4.1)
BRAF inhibitor ± combination	8 (3.4)	52 (21.4)
FOLFOX ± combination	6 (2.5)	6 (2.5)
Other	6 (2.5)	5 (2.1)
Trifluridine/tipiracil ± VEGF inhibitor	2 (0.8)	0
CAPOX ± combination	1 (0.4)	1 (0.4)
FOLFOXIRI ± combination	1 (0.4)	2 (0.8)
Immunotherapy	0	1 (0.4)
Regorafenib	0	1 (0.4)

Classified using the WHODD GLOBALB3 MAR2023 coding dictionary.

https://doi.org/10.1038/s41591-024-03443-3

Extended Data Table 5 | Safety summary

Patients, n (%)	EC+mFOLFOX6 n=231	SOC n=228
Adverse event	230 (99.6)	223 (97.8)
Treatment-related adverse event	228 (98.7)	212 (93.0)
Adverse event related to encorafenib	196 (84.8)	1 (0.4)
Adverse event related to cetuximab	197 (85.3)	1 (0.4)
Adverse event related to other study intervention*	223 (96.5)	212 (93.0)
Grade 3/4 adverse event	171 (74.0)	139 (61.0)
Treatment-related adverse event	161 (69.7)	123 (53.9)
Grade 5 adverse event	10 (4.3)	10 (4.4)
Treatment-related adverse event	0	1 (0.4)†
Serious adverse event	87 (37.7)	79 (34.6)
Treatment-related adverse event	42 (18.2)	44 (19.3)
Adverse event leading to permanent discontinuation of any study treatment	48 (20.8)	34 (14.9)
Permanent discontinuation of encorafenib due to adverse event	27 (11.7)	N/A
Permanent discontinuation of cetuximab due to adverse event	30 (13.0)	N/A
Permanent discontinuation of other study intervention* due to adverse event	36 (15.6)	34 (14.9)
Adverse event leading to dose reduction of any study treatment	141 (61.0)	109 (47.8)
Dose reduction of encorafenib due to adverse event	51 (22.1)	N/A
Dose reduction of cetuximab due to adverse event	14 (6.1)	N/A
Dose reduction of other study intervention* due to adverse event	129 (55.8)	109 (47.8)
Adverse event leading to dose interruption of any study treatment	196 (84.8)	146 (64.0)
Dose interruption of encorafenib due to adverse event	131 (56.7)	N/A
Dose interruption of cetuximab due to adverse event	135 (58.4)	N/A
Dose interruption of other study intervention* due to adverse event	175 (75.8)	146 (64.0)

EC+mFOLFOX6, encorafenib and cetuximab plus oxaliplatin, leucovorin, and 5-FU; N/A, not applicable; SOC, standard of care. * Other study intervention includes: irinotecan, oxaliplatin, leucovorin or levo-leucovorin, fluorouracil (bolus or infusion), capecitabine, and bevacizumab (as appropriate for the treatment group). † Sepsis (preferred term).

https://doi.org/10.1038/s41591-024-03443-3

Extended Data Table 6 | Most common serious all-causality treatment-emergent adverse events (≥1% of patients in any arm) by preferred term

	EC+mFOLFOX6 n=231	SOC n=228
Any adverse event	87 (37.7)	79 (34.6)
Disease progression	8 (3.5)	0
Intestinal obstruction	8 (3.5)	5 (2.2)
Pyrexia	8 (3.5)	3 (1.3)
Anemia	6 (2.6)	1 (0.4)
Vomiting	6 (2.6)	1 (0.4)
Abdominal pain	4 (1.7)	7 (3.1)
Sepsis	4 (1.7)	1 (0.4)
Alanine aminotransferase increased	3 (1.3)	1 (0.4)
Febrile neutropenia	3 (1.3)	8 (3.5)
Ileus	2 (0.9)	3 (1.3)
Pneumonia	2 (0.9)	4 (1.8)
Acute kidney injury	1 (0.4)	3 (1.3)
Myocardial infarction	0	3 (1.3)

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

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Our web collection on statistics for biologists contains articles on many of the points above.

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Data collection	Inform database
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The analyses in this paper were based on a data cutoff of December 22, 2023.
Upon reasonable request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs

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Reporting on sex and gender	The self-reported sex of patients was collected along with other demographics categories; gender was not collected. 50.5% were male and 49.5% were female. Objective response rates in male and female patients were prespecified and reported in Figure 2.
Population characteristics	Patients with histologically or cytologically confirmed, metastatic CRC with the BRAF V600E mutation who had not received treatment systemic treatment for metastatic disease. The patient population was mostly male (50.5%) and White (59.5%), with a median age of 61.0 years. Most patients' tumors were located in the colon (80.0%) and were right-sided (61.0%), other characteristics are reported in a table in the manuscript.
Recruitment	Participants were recruited by investigators at each participating study site. Sites typically present the study to the oncology physicians at the site who then offer participation of the study to patients that they believe may be eligible. Although there may be some selection bias on the part of the physician and/or the patient, this is difficult to control, is not expected to be higher on this study than on other similar clinical trials, and is unlikely to substantially impact results. Participants were not compensated for study participation, although certain trial-related expenses (e.g., hotel rooms, transportation) were reimbursed for some patients.
Ethics oversight	The trial was approved by the institutional review board or independent ethics committee at each participating center.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	637 patients were randomized to the phase 3 portion of the study. This manuscript reports data from 479 patients in the EC+FOLFOX and SOC arms.
Data exclusions	No data were exclused
Replication	Not applicable as this is a clinical trial.
Randomization	Patients were assigned using a Interactive Response Technology; randomization was stratified by ECOG and region.
Blinding	Not applicable as this was an open-label study.

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Clinical trial registration	NCT04607421
Study protocol	The latest version of the protocol is included in the submission as supplementary information.
Data collection	Data were collected at various sites in 28 countries. Patients were enrolled between November 16, 2021 and December 22, 2023. The data cut off was December 22, 2023.
Outcomes	This analysis reports objective response, response duration and time to response (by blinded independent central review and by investigator), overall survival, and safety.

Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial

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Summary

Background CheckMate 8HW prespecified dual primary endpoints, assessed in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status: progression-free survival with nivolumab plus ipilimumab compared with chemotherapy as first-line therapy and progression-free survival with nivolumab plus ipilimumab compared with nivolumab alone, regardless of previous systemic treatment for metastatic disease. In our previous report, nivolumab plus ipilimumab showed superior progression-free survival versus chemotherapy in first-line microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer in the CheckMate 8HW trial. Here, we report results from the prespecified interim analysis for the other primary endpoint of progression-free survival for nivolumab plus ipilimumab versus nivolumab across all treatment lines.

Methods CheckMate 8HW is a randomised, open-label, international, phase 3 trial at 128 hospitals and cancer centres across 23 countries. Immunotherapy-naive adults with unresectable or metastatic colorectal cancer across different lines of therapy and microsatellite instability-high or mismatch repair-deficient status per local testing were randomly assigned (2:2:1) to nivolumab plus ipilimumab (nivolumab 240 mg, ipilimumab 1 mg/kg, every 3 weeks for four doses; then nivolumab 480 mg every 4 weeks; all intravenously), nivolumab (240 mg every 2 weeks for six doses, then 480 mg every 4 weeks; all intravenously), or chemotherapy with or without targeted therapies. The dual independent primary endpoints were progression-free survival by blinded independent central review with nivolumab plus ipilimumab versus chemotherapy (first line) and progression-free survival by blinded independent central review with nivolumab plus ipilimumab versus nivolumab (all lines) in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer. This study is registered with ClinicalTrials.gov (NCT04008030).

Findings Between Aug 16, 2019, and April 10, 2023, 707 patients were randomly assigned to nivolumab plus ipilimumab (n=354) or nivolumab alone (n=353). 296 (84%) of 354 patients in the nivolumab plus ipilimumab group and 286 (81%) of 353 patients in the nivolumab group were centrally confirmed to have microsatellite instability-high or mismatch repair-deficient status. At the data cutoff on Aug 28, 2024, median follow-up (from randomisation to data cutoff) was 47·0 months (IQR 38·4 to 53·2). Nivolumab plus ipilimumab treatment showed significant and clinically meaningful improvement in progression-free survival versus nivolumab (hazard ratio 0·62, 95% CI 0·48–0·81; p=0·0003). Median progression-free survival was not reached with nivolumab plus ipilimumab (95% CI 53·8 to not estimable) and was 39·3 months with nivolumab (22·1 to not estimable). Treatment-related adverse events of any grade occurred in 285 (81%) of 352 patients receiving nivolumab plus ipilimumab and in 249 (71%) of 351 patients receiving nivolumab; grade 3 or 4 treatment-related adverse events occurred in 78 (22%) and 50 (14%) patients, respectively. There were three treatment-related deaths: one event of myocarditis and pneumonitis each in the nivolumab plus ipilimumab group and one pneumonitis event in the nivolumab group.

Interpretation Nivolumab plus ipilimumab showed superior progression-free survival versus nivolumab across all treatment lines, with a manageable safety profile, in patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer. These results, together with the first-line results of superior progression-free survival with nivolumab plus ipilimumab versus chemotherapy, suggest nivolumab plus ipilimumab as a potential new standard of care for patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer.

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Research in context

Evidence before this study

On Nov 19, 2024, we searched PubMed for articles published between Jan 1, 2019, and Nov 19, 2024, with no language restrictions, reporting primary results from phase 3 trials of immune checkpoint inhibitors for the treatment of microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer using the search string "((MSI-H[Title/Abstract]) OR (dMMR[Title/Abstract])) AND (colorectal cancer[Title/Abstract]) AND ((metastatic[Title/Abstract]) OR (advanced[Title/Abstract])) AND ((phase 3[Title/Abstract]) OR (phase III[Title/Abstract]))", filtering for clinical trial articles only. We also searched the American Society of Clinical Oncology and the European Society for Medical Oncology websites for abstracts published between Jan 1, 2021, and Nov 19, 2024, with no language restrictions, using the search terms "MSI-H", "dMMR", and "metastatic colorectal cancer", identifying primary results of phase 3 clinical trial abstracts published since 2021. These searches identified KEYNOTE-177 as the only phase 3 clinical trial investigating an immune checkpoint inhibitor in microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer with published primary results before CheckMate 8HW. In the KEYNOTE-177 study, significant improvement in progression-free survival with pembrolizumab monotherapy versus chemotherapy was observed in previously untreated patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer. Based on these results, clinical practice guidelines for metastatic colorectal cancer have since recommended pembrolizumab as the standard of care for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer in the first-line setting. At the first prespecified interim analysis from CheckMate 8HW, nivolumab plus ipilimumab showed superior progression-free survival compared with chemotherapy in the first-line setting, with manageable safety.

Added value of this study

To our knowledge, CheckMate 8HW is the first phase 3, randomised trial to investigate the use of dual-agent immunotherapy versus single-agent immunotherapy in patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer. Nivolumab plus ipilimumab showed a clinically meaningful and significant progression-free survival benefit and a significantly higher response rate compared with nivolumab monotherapy in this patient population. Progression-free survival benefit was also observed across evaluated subgroups. A higher incidence of treatment-related adverse events was observed with nivolumab plus ipilimumab versus nivolumab; the safety profile of nivolumab plus ipilimumab was manageable and no new safety signals were reported.

Implications of all the available evidence

The results from the CheckMate 8HW trial establish the efficacy and manageable safety of dual-agent immunotherapy versus single-agent immunotherapy for the treatment of microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer. Coupled with the data from nivolumab plus ipilimumab versus chemotherapy in the first-line setting, these results support nivolumab plus ipilimumab as a potential new standard of care in patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer.

Introduction

Tumours with high microsatellite instability, mismatch repair deficiency, or both are found in approximately 4–7% of patients with metastatic colorectal cancer and are associated with poor outcomes with chemotherapy with or without targeted therapies.[1–4] The treatment of microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer has advanced substantially with the introduction of immune checkpoint inhibitors.[5–7] Pembrolizumab, a PD-1 inhibitor, showed improved progression-free survival versus chemotherapy in patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer in the first-line setting.[8] However, there remains an unmet need in this population, as 45 (29%) of 153 patients treated with pembrolizumab had progressive disease as best overall response, and 48% and 42% were progression-free and alive at 2 years and 3 years of follow-up, respectively.[8,9]

In the phase 2, non-randomised CheckMate 142 study, nivolumab, a PD-1 inhibitor, plus ipilimumab, a cytotoxic T-lymphocyte antigen 4 inhibitor, showed promising efficacy, including long-term survival benefit, and manageable safety in previously treated and untreated immunotherapy-naive patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer.[10–13] Indirect comparisons of non-randomised cohorts within CheckMate 142 suggested better outcomes with nivolumab plus ipilimumab than with nivolumab monotherapy and underscored the importance of determining the potential benefit of dual-agent immunotherapy versus single-agent immunotherapy in the treatment of microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer in a randomised setting.[11,14] The ongoing, phase 3, international, randomised CheckMate 8HW trial was designed to evaluate nivolumab plus ipilimumab compared with nivolumab monotherapy or chemotherapy with or without targeted therapy in patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer. At the previous prespecified interim analysis (median follow-up 31·5 months), nivolumab plus ipilimumab showed superior progression-free survival compared with chemotherapy in the first-line setting (median progression-free survival not reached

[95% CI 38·4 to not estimable] *vs* 5·9 months [4·4–7·8]; hazard ratio [HR] 0·21 [95% CI 0·13–0·35]; p<0·0001 with the use of a two-sided stratified log-rank test), meeting one of the dual primary endpoints of this study.[15,16] Progression-free survival at 24 months was 72% with nivolumab plus ipilimumab versus 14% with chemotherapy. In this study, we report results from the prespecified interim analysis of the other dual primary endpoint of progression-free survival for nivolumab plus ipilimumab compared with nivolumab monotherapy across all lines of therapy. Additionally, we present longer follow-up results of progression-free survival for nivolumab plus ipilimumab compared with chemotherapy in the first-line setting.

Methods

Study design and participants

This randomised, open-label, international, phase 3 trial was done at 128 hospitals and cancer centres in 23 countries (appendix p 2). Patients were enrolled in the trial if they were aged at least 18 years and had received a diagnosis of unresectable or metastatic colorectal cancer and high microsatellite instability or mismatch repair deficiency (or both) status per local testing. Sex data were self-reported by the trial participants, with male or female options provided for participant's sex at birth. Patients were enrolled across different lines of therapy and study enrolment occurred in two sequential parts: part 1 was open to patients across all treatment lines and part 2 was open to patients with no previous treatment for metastatic disease after completion of part 1. Patients who had received neoadjuvant or adjuvant therapy (or both) and had disease recurrence within 6 months after completion of therapy were considered to have received one previous treatment. Patients who had received triplet therapy combining fluorouracil, oxaliplatin, and irinotecan were considered to have received two previous treatments. Presence of measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were required for eligibility. ECOG performance status is assessed on a five-point scale, with 0 indicating no performance restrictions and higher scores indicating greater disability. Patients who had received previous immunotherapies (anti-PD-1, anti-PD-L1 or anti-PD-L2, anti-cytotoxic T-lymphocyte antigen-4, or any other antibody or drug targeting T-cell co-stimulation or checkpoint pathways) were excluded. Additional eligibility criteria are provided in the appendix (p 8).

The trial was done in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the principles of the Declaration of Helsinki. The protocol (appendix pp 25–410) was approved by the institutional review board or independent ethics committee at each site. All patients provided written informed consent. An independent data monitoring committee evaluated the trial interim analysis results. This study is registered with ClinicalTrials.gov, NCT04008030.

Randomisation and masking

Patients with zero or one previous treatment for metastatic disease were randomly assigned (2:2:1) to one of three treatment groups: nivolumab plus ipilimumab, nivolumab alone, or investigator's choice of chemotherapy with or without targeted therapies. Patients with two or more previous treatments for unresectable or metastatic disease were randomly assigned (1:1) to either nivolumab plus ipilimumab or nivolumab alone. In part 1 enrolment (across all treatment lines), patients were stratified at randomisation by tumour location (right *vs* left) and the number of previous treatments for unresectable or metastatic disease (0 *vs* 1 *vs* ≥2). In part 2 enrolment (the first-line setting), randomisation was stratified by tumour sidedness (right *vs* left) only.

The treatment allocation list was developed by the study sponsor (Bristol Myers Squibb). Patients were centrally randomly assigned by use of an interactive response technology system with a permuted blocks method (block size of 5). CheckMate 8HW was an open-label trial, and the treatments administered to the patients remained unmasked.

See Online for appendix

Procedures

For patients receiving nivolumab plus ipilimumab, nivolumab 240 mg in combination with ipilimumab 1 mg/kg of bodyweight was administered intravenously every 3 weeks for the first 12 weeks (up to four total doses of ipilimumab), followed by nivolumab 480 mg monotherapy every 4 weeks. Those randomly assigned to receive nivolumab monotherapy received nivolumab 240 mg intravenously every 2 weeks for the first 12 weeks, followed by nivolumab 480 mg monotherapy every 4 weeks. Investigator's choice of chemotherapy with or without targeted therapies was administered per the dosing and administration schedule specified in the protocol. Optional crossover to nivolumab (240 mg every 2 weeks for the first 12 weeks, followed by 480 mg every 4 weeks) plus ipilimumab (1 mg/kg of bodyweight every 6 weeks) was permitted for patients with disease progression in the chemotherapy group (as determined by blinded independent central review). Treatments were discontinued at disease progression, withdrawal of consent, or unacceptable toxicity. Patients in the nivolumab or nivolumab plus ipilimumab groups received study treatment for a maximum of 2 years (including patients who crossed over to nivolumab plus ipilimumab). The 2-year treatment duration was based on data suggesting that 2 years of PD-1 checkpoint inhibition might be sufficient for long-term benefit,[8,13,14] alongside data showing a shorter treatment duration in patients with advanced non-small-cell lung cancer was associated with an increased risk of progression.[17]

Additional details on the trial design and schedule of assessments are provided in the appendix (p 8) and protocol (pp 25–410), respectively.

Outcomes

This study had independent dual primary endpoints of progression-free survival by blinded independent central review per RECIST version 1.1 in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient unresectable or metastatic colorectal cancer. One primary endpoint was progression-free survival for nivolumab plus ipilimumab versus chemotherapy in the first-line setting and the other was progression-free survival for nivolumab plus ipilimumab versus nivolumab across all lines of therapy. The primary efficacy population for this trial was patients with microsatellite instability-high or mismatch repair-deficient status confirmed centrally either by the immunohistochemistry assay mismatch repair immunohistochemistry panel pharmDx (Dako Omnis; codes GE079, GE087, GE085, GE086; Agilent, Santa Clara, CA, USA) or PCR-based Idylla MSI Test (Biocartis; Mechelen, Belgium). Key secondary endpoints included overall survival, progression-free survival as determined by investigator assessment, progression-free survival as determined by blinded independent central review in all patients who underwent random assignment, and objective response (a confirmed best overall complete or partial response according to RECIST version 1.1) as determined by investigator and blinded independent central review. The trial is ongoing to assess secondary endpoints according to the hierarchical testing plan (appendix p 9), including progression-free survival for nivolumab plus ipilimumab versus nivolumab in the first-line setting, which did not meet the prespecified statistical criteria for significance at this interim analysis, as determined by the data monitoring committee, and therefore remains masked until its final analysis. Key exploratory endpoints included safety and health-related quality of life, measured with the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life questionnaire (QLQ-C30). The prespecified within-group minimally important mean changes from baseline in EORTC QLQ-C30 score for Global Health Status were 10 for improvement and –10 for deterioration. Health-related quality of life analyses were done in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status who received at least one administration of study treatment and had patient-reported outcome data. Further details on central microsatellite instability-high or mismatch repair-deficient confirmation, PD-L1 testing procedures, safety, and health-related quality of life analyses are provided in the appendix (pp 9–10).

Adverse events, including those related to study treatment, were assessed in all patients who received at least one dose of study treatment. These events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

To control the overall type I error at 0·05, the α was initially split between the dual primary endpoints, with 0·044 for progression-free survival in nivolumab plus ipilimumab versus chemotherapy (first line) and 0·006 for nivolumab plus ipilimumab versus nivolumab (across all lines). Progression-free survival with first-line nivolumab plus ipilimumab versus chemotherapy met the prespecified statistical criteria at the Oct 12, 2023 data cutoff.[16] Therefore, an α of 0·024 was passed to the nivolumab plus ipilimumab versus nivolumab (across all lines) analysis, for an overall α of 0·03. With a group sequential design for progression-free survival endpoints, the α distribution between interim analysis and final analysis was determined based on the actual number of progression-free survival events per blinded independent central review observed at the interim analysis and the target number of events at final analysis, using Lan-DeMets α spending function with O'Brien-Fleming boundaries. Under these assumptions, approximately 564 patients (randomly assigned in a 1:1 ratio to the nivolumab plus ipilimumab and nivolumab groups) were expected to provide approximately 96·8% power for an assumed HR of 0·635, with an overall type I error of 0·03 (two-sided), after approximately 319 events were observed. The interim analysis was planned 60 months after random assignment of the first patient in the study, and approximately 240 events were projected to have occurred at that time (information fraction 75%).

If progression-free survival per blinded independent central review in nivolumab plus ipilimumab versus nivolumab (all lines) met the prespecified statistical significance, an α of 0·006 would be passed to the secondary endpoint, objective response rate per blinded independent central review, for the same groups. Based on an assumed 18% difference in objective response rate between nivolumab plus ipilimumab and nivolumab in all lines, 564 randomly assigned patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status were expected to provide approximately 93% power with an overall type I error of 0·006 (two-sided) to show a statistically significant difference between these groups.

Progression-free survival per blinded independent central review was compared between nivolumab plus ipilimumab and nivolumab via a two-sided stratified log-rank test. Median progression-free survival with 95% CIs and rates at fixed timepoints were estimated using Kaplan–Meier methods. The HRs and associated 95% CIs were estimated using a stratified Cox proportional hazards model using the randomised group as a single covariate. Objective response rates were

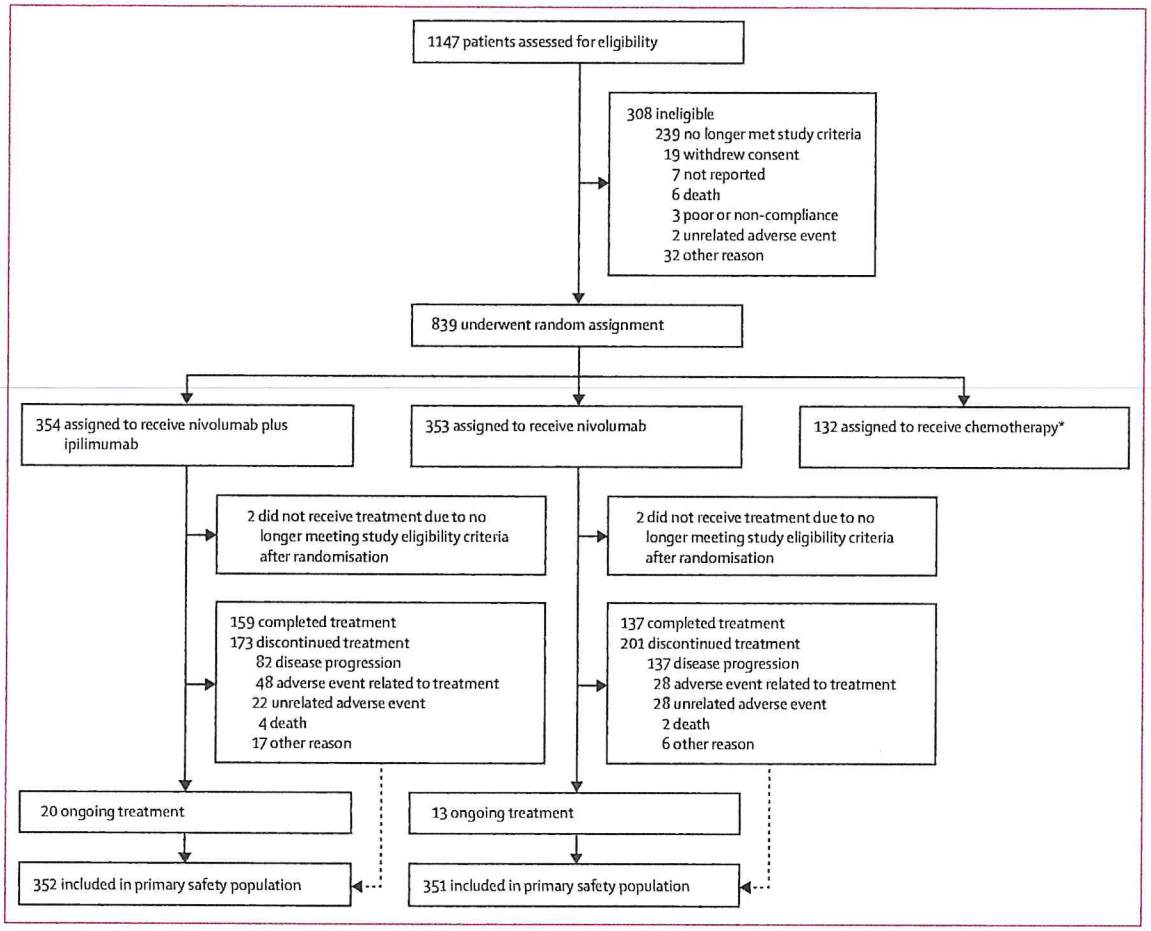

Figure 1: Trial profile
*Part 1 of enrolment was open for longer than part 2; therefore there is a different sample size for this analysis than previously reported.[16]

compared using a two-sided stratified Cochran–Mantel–Haenszel test. Difference in objective response rates with a 95% CI was calculated. Additional details on the statistical methods and testing procedures are in the appendix (p 9). Statistical analyses were done using SAS version 9.04.

Role of the funding source

Bristol Myers Squibb (the sponsor of the study), in collaboration with Ono Pharmaceutical, funded the trial, provided the trial agents, and collaborated with the academic authors on the trial design and on the collection, analysis, and interpretation of the data. Medical writing support, including development of the first draft of the manuscript under the guidance of the authors, was funded by the sponsor.

Results

Between Aug 16, 2019, and April 10, 2023, 839 patients with unresectable or metastatic microsatellite instability-high or mismatch repair-deficient colorectal cancer by local testing were randomly assigned to receive nivolumab plus ipilimumab (354 patients), nivolumab (353 patients), or chemotherapy (132 patients) across all lines of therapy (figure 1). 202 (57%) of 354 patients in the nivolumab plus ipilimumab group, 201 (57%) of 353 patients in the nivolumab group, and 101 (77%) of 132 patients in the chemotherapy group were previously untreated. Baseline patient demographics and disease characteristics were similar between the two treatment groups (table 1). 296 (84%) of 354 patients in the nivolumab plus ipilimumab group and 286 (81%) of 353 patients in the nivolumab group were centrally confirmed to have microsatellite instability-high or mismatch repair-deficient status (table 1; appendix p 11) and constituted the primary efficacy population. 125 (18%) of 707 randomly assigned patients did not have central confirmation of their microsatellite instability-high or mismatch repair-deficient status due to microsatellite stable status, mismatch repair proficiency of their tumours, or other reasons (table 1). Patient demographics and baseline characteristics of patients

	Nivolumab plus ipilimumab group (n=354)	Nivolumab group (n=353)
Age, years		
Median (IQR)	62 (52–70)	63 (51–70)
<65	199 (56%)	193 (55%)
≥65	155 (44%)	160 (45%)
Sex		
Male	162 (46%)	190 (54%)
Female	192 (54%)	163 (46%)
Race		
White	311 (88%)	305 (86%)
Asian	27 (8%)	36 (10%)
Black or African American	4 (1%)	7 (2%)
Other	12 (3%)	5 (1%)
Geographical region		
USA, Canada, or Europe	251 (71%)	246 (70%)
Asia	26 (7%)	33 (9%)
Rest of world	77 (22%)	74 (21%)
Eastern Cooperative Oncology Group performance status		
0	192 (54%)	183 (52%)
1	162 (46%)	170 (48%)
Disease stage at initial diagnosis*		
Stage I	2 (1%)	4 (1%)
Stage II	65 (18%)	61 (17%)
Stage III	133 (38%)	129 (37%)
Stage IV	152 (43%)	158 (45%)
Not reported	2 (1%)	1 (<1%)
Disease stage at study entry		
Stage IVA	129 (36%)	132 (37%)
Stage IVB	110 (31%)	98 (28%)
Stage IVC	114 (32%)	122 (35%)
Not reported	1 (<1%)	1 (<1%)
Number of previous lines of therapy†		
0	202 (57%)	201 (57%)
1	67 (19%)	67 (19%)
≥2	85 (24%)	85 (24%)
Tumour sidedness‡		
Right	241 (68%)	240 (68%)
Left	113 (32%)	113 (32%)
Sites of metastases by blinded independent central review§		
Liver	140 (40%)	149 (42%)
Lung	85 (24%)	99 (28%)
Peritoneum	143 (40%)	126 (36%)
Centrally confirmed microsatellite instability-high or mismatch repair-deficient status		
Yes	296 (84%)	286 (81%)
No	58 (16%)	67 (19%)
MSS and pMMR	41 (12%)	40 (11%)
MSS or pMMR¶	8 (2%)	10 (3%)
Other‖	9 (3%)	17 (5%)
PD-L1 expression**		
<1%	255 (72%)	264 (75%)
≥1%	74 (21%)	63 (18%)
***BRAF*, *KRAS*, and *NRAS* mutation status**		
BRAF, *KRAS*, and *NRAS* all wild type	83 (23%)	103 (29%)
BRAF mutant	106 (30%)	85 (24%)
KRAS or *NRAS* mutant	83 (23%)	89 (25%)
BRAF and *KRAS* or *NRAS* mutant	9 (3%)	2 (1%)
Unknown	73 (21%)	74 (21%)
Clinical history of Lynch syndrome		
Yes	48 (14%)	49 (14%)
No	217 (61%)	207 (59%)
Unknown	86 (24%)	91 (26%)
Not reported	3 (1%)	6 (2%)
Previous systemic therapies		
Any previous systemic therapy	218 (62%)	213 (60%)
Previous systemic therapy setting		
Neoadjuvant	18/218 (8%)	16/213 (8%)
Adjuvant	116/218 (53%)	94/213 (44%)
Metastatic	124/218 (57%)	137/213 (64%)

(Table 1 continues in next column)

(Continued from previous column)

Data are n (%) or n/N (%), unless otherwise indicated. CRF=case report form. IRT=interactive response technology. MSS=microsatellite stable. pMMR=mismatch repair proficient. *Disease stage not reported in two patients in the nivolumab plus ipilimumab group and one patient in the nivolumab group. †Numbers here are using IRT criteria—numbers from the CRF were 193 (55%) untreated at metastatic stage, 82 (23%) one line, and 78 (22%) two or more lines in the nivolumab plus ipilimumab group, and 184 (52%) untreated at metastatic stage, 86 (24%) one line, and 83 (24%) two or more lines in the nivolumab group. ‡Numbers here are using IRT criteria—numbers of patients from the CRF were 244 (69%) patients with right tumour sidedness and 110 (31%) with left tumour sidedness in the nivolumab plus ipilimumab group, and 244 (69%) patients with right tumour sidedness and 109 (31%) with left tumour sidedness in the nivolumab group. §Metastatic sites not reported in three patients in the nivolumab plus ipilimumab group and two patients in the nivolumab group; patients could have more than one site of metastasis. ¶In the nivolumab plus ipilimumab group, six patients had pMMR tumours and were not tested for microsatellite instability; two patients had MSS tumours and could not be evaluated for mismatch repair status. In the nivolumab group, seven patients had pMMR tumours and were not tested for microsatellite instability; three patients had MSS tumours and could not be evaluated for mismatch-repair status. ‖26 patients were not evaluable or not tested for both microsatellite instability and mismatch repair status (nine patients in the nivolumab plus ipilimumab group and 17 patients in the nivolumab group). **Tumour cell PD-L1 expression indeterminate, not evaluable, or not available for 25 patients in the nivolumab plus ipilimumab group and 26 patients in the nivolumab group.

Table 1: **Patient demographics and disease characteristics at baseline in all randomly assigned patients**

within the primary efficacy population were similar to those from the all randomised population (table 1; appendix p 11).

At the data cutoff on Aug 28, 2024, median follow-up (from randomisation to data cutoff) was 47·0 months (IQR 38·4–53·2). 703 patients received treatment: 352 in the nivolumab plus ipilimumab group and 351 in the nivolumab group. Among treated patients, 296 (159 [45%]

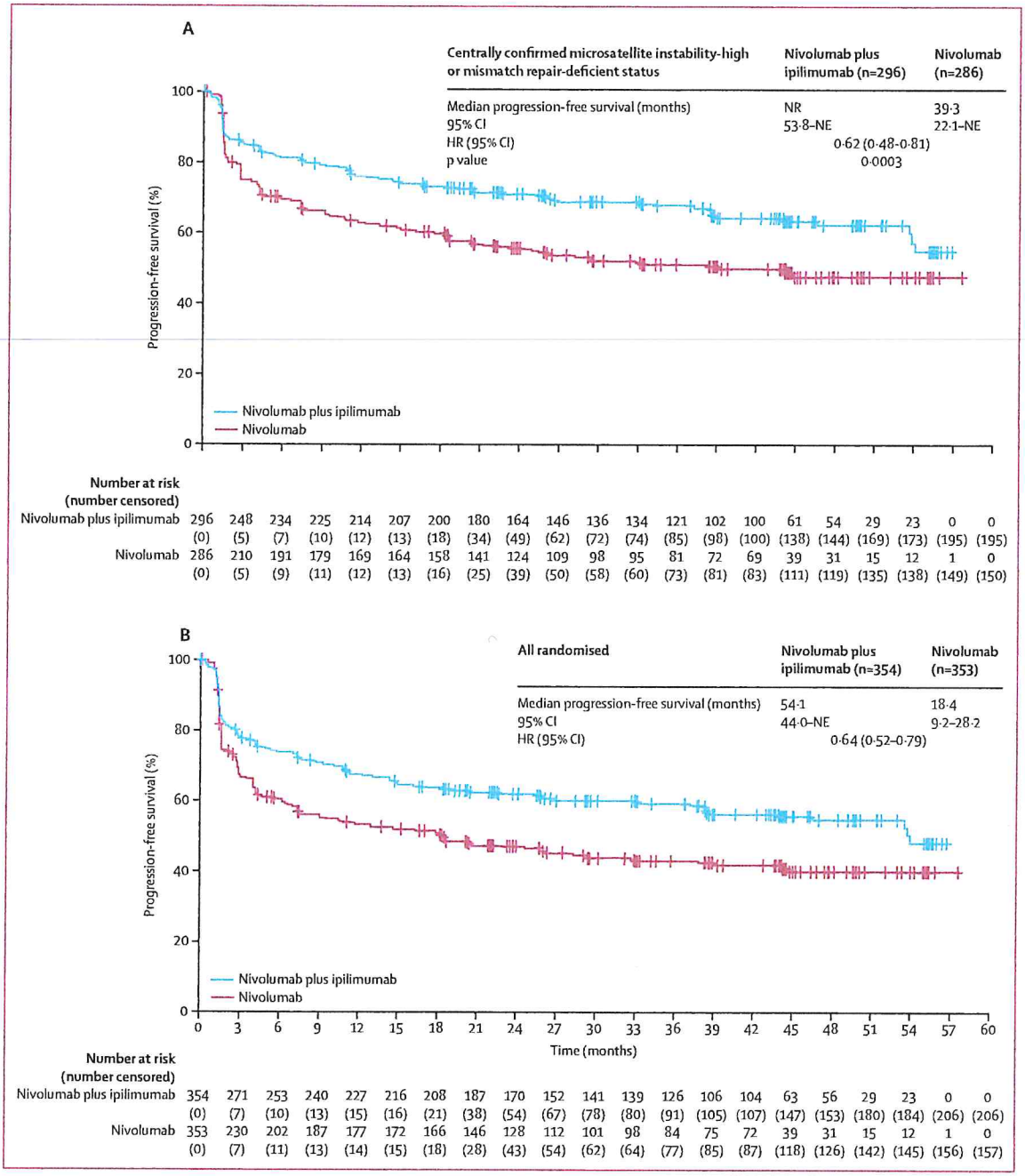

Figure 2: **Progression-free survival by blinded independent central review with nivolumab plus ipilimumab versus nivolumab**
(A) Patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status. The boundary for statistical significance was p<0·0095. (B) All patients who underwent randomisation. For both patient populations, stratified Cox proportional hazard model by tumour sidedness (left *vs* right) and previous lines of therapy (0 *vs* 1 *vs* ≥2) per interactive response technology was used. Vertical dashes indicate censored data. HR=hazard ratio. NE=not estimable. NR=not reached.

of 352 patients in the nivolumab plus ipilimumab group and 137 [39%] of 351 patients in the nivolumab group) completed 2 years of treatment. 173 (49%) of 352 patients in the nivolumab plus ipilimumab group and 201 (57%) of 351 patients in the nivolumab group discontinued treatment. Treatment discontinuation due to disease progression was reported in 82 (23%) of 352 patients in the nivolumab plus ipilimumab group and 137 (39%) of 351 patients in the nivolumab group (figure 1). A trial profile of treated patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status is shown in the appendix (p 17).

	Number of events/number of patients		Unstratified HR for progression-free survival (95% CI)
	Nivolumab plus ipilimumab	Nivolumab	
Age (years)			
<65	51/164	70/157	0·60 (0·42–0·87)
≥65	50/132	66/129	0·66 (0·46–0·96)
Sex			
Male	47/135	76/149	0·60 (0·42–0·87)
Female	54/161	60/137	0·67 (0·47–0·98)
Region			
USA, Canada, and Europe	76/209	105/206	0·63 (0·47–0·84)
Asia	4/23	10/29	0·40 (0·13–1·29)
Rest of world	21/64	21/51	0·73 (0·40–1·33)
Eastern Cooperative Oncology Group performance status			
0	51/164	60/149	0·69 (0·47–1·00)
1	50/132	76/137	0·60 (0·42–0·85)
Tumour sidedness			
Left	25/80	32/72	0·62 (0·37–1·04)
Right	76/216	104/214	0·64 (0·47–0·86)
Liver metastases*			
Yes	37/104	51/106	0·68 (0·44–1·03)
No	64/190	85/178	0·60 (0·43–0·83)
Peritoneal metastases*			
Yes	44/126	53/100	0·55 (0·37–0·82)
No	57/168	83/184	0·67 (0·48–0·94)
Tumour cell PD-L1 expression			
≥1%	21/72	21/61	0·77 (0·42–1·42)
<1%	74/214	111/213	0·57 (0·43–0·77)
***BRAF/KRAS/NRAS* mutation status**			
BRAF, *KRAS*, and *NRAS* all wild-type	26/75	37/81	0·64 (0·39–1·06)
BRAF mutant	34/98	41/81	0·62 (0·39–0·97)
KRAS or *NRAS* mutant	22/57	31/68	0·76 (0·44–1·31)
Unknown	16/59	26/55	0·48 (0·26–0·91)
Lynch syndrome			
Yes	19/43	18/40	0·90 (0·47–1·72)
No	54/172	78/162	0·56 (0·40–0·80)
Unknown	28/78	36/78	0·71 (0·43–1·16)
Overall	**101/296**	**136/286**	**0·63 (0·49–0·82)**

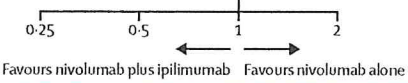

Figure 3: **Progression-free survival by blinded independent central review in key subgroups of patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status**

Unstratified HRs are reported for patient subgroup analyses. Based on Kaplan–Meier estimates; rates not computed for subgroups with less than ten patients per treatment group. HR=hazard ratio. *Metastatic sites were determined by blinded independent central review and were not reported in three patients in the nivolumab plus ipilimumab group and two patients in the nivolumab group; patients could have more than one site of metastasis.

Nivolumab plus ipilimumab treatment showed significant and clinically meaningful improvement in progression-free survival versus nivolumab in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (HR 0·62, 95% CI 0·48 to 0·81; p=0·0003 by two-sided stratified log-rank test; figure 2). Median progression-free survival was not reached with nivolumab plus ipilimumab (95% CI 53·8 to not estimable) and was 39·3 months with nivolumab (22·1 to not estimable; figure 2). The estimated proportions of patients in the nivolumab plus ipilimumab group who were alive and progression-free at 12 months, 24 months, and 36 months were 76% (95% CI 71 to 80), 71% (95% CI 65 to 76), and 68% (95% CI 62 to 73), respectively; corresponding rates with nivolumab were 63% (95% CI 57 to 68), 56% (95% CI 49 to 61), and 51% (95% CI 45 to 57). In prespecified subgroup analyses, progression-free survival generally favoured nivolumab plus ipilimumab versus nivolumab (figure 3).

	Nivolumab plus ipilimumab group (n=296)	Nivolumab group (n=286)	p value
Objective response rate (95% CI)	209 (71%) [65–76]	165 (58%) [52–64]	0·0011
Best overall response			..
Complete response	90 (30%)	80 (28%)	..
Partial response	119 (40%)	85 (30%)	..
Stable disease	40 (14%)	53 (19%)	..
Progressive disease	30 (10%)	54 (19%)	..
Unevaluable	17 (6%)	14 (5%)	..
Median time to response, months (IQR)	2·8 (1·4–4·2)	2·8 (1·5–4·2)	..
Median duration of response, months (95% CI)	NR (NE)	NR (NE)	..

Data are n (%), unless otherwise indicated. NE=not estimable. NR=not reached.

Table 2: **Best overall response by blinded review in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status**

	Nivolumab plus ipilimumab group (n=352)		Nivolumab group (n=351)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any treatment-related adverse event	285 (81%)	78 (22%)	249 (71%)	50 (14%)
Treatment-related serious adverse event	65 (18%)	55 (16%)	29 (8%)	24 (7%)
Treatment-related adverse event leading to discontinuation of any drug in the regimen	48 (14%)	33 (9%)	21 (6%)	14 (4%)
Treatment-related deaths*	2 (1%)	..	1 (<1%)	..
Treatment-related adverse events reported in ≥5% of patients in either group				
Pruritus	91 (26%)	0	63 (18%)	0
Diarrhoea	71 (20%)	3 (1%)	59 (17%)	2 (1%)
Hypothyroidism	61 (17%)	2 (1%)	31 (9%)	0
Asthenia	58 (16%)	2 (1%)	44 (13%)	2 (1%)
Fatigue	42 (12%)	1 (<1%)	35 (10%)	1 (<1%)
Hyperthyroidism	40 (11%)	0	16 (5%)	0
Arthralgia	38 (11%)	1 (<1%)	23 (7%)	0
Adrenal insufficiency	34 (10%)	8 (2%)	12 (3%)	3 (1%)
Rash	34 (10%)	3 (1%)	29 (8%)	1 (<1%)
Increased alanine aminotransferase	31 (9%)	6 (2%)	21 (6%)	3 (1%)
Increased aspartate aminotransferase	27 (8%)	3 (1%)	17 (5%)	3 (1%)
Hypophysitis	20 (6%)	10 (3%)	3 (1%)	3 (1%)
Increased lipase	18 (5%)	6 (2%)	14 (4%)	7 (2%)
Nausea	18 (5%)	0	18 (5%)	0

Data are n (%). All events between the first dose of treatment and 30 days after the last dose of treatment were reported. *Treatment-related adverse events leading to death were reported regardless of timeframe.

Table 3: **Treatment-related adverse events in all treated patients who received at least one dose of the assigned treatment**

Improvements in progression-free survival with nivolumab plus ipilimumab versus nivolumab were consistent among all randomly assigned patients (HR 0·64, 95% CI 0·52 to 0·79); median progression-free survival in all randomly assigned patients was 54·1 months (95% CI 44·0 to not estimable) with nivolumab plus ipilimumab and 18·4 months (9·2 to 28·2) with nivolumab (figure 2). The findings from the analysis of progression-free survival according to investigator assessment in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status were consistent with the findings from the blinded independent central review (median not reached [95% CI 54·1 months to not estimable] and 38·1 months [95% CI 27·2 months to not estimable], respectively; HR 0·62, 95% CI 0·48 to 0·80; appendix p 18); concordance between progression-free survival by blinded independent central review and by investigator assessment was 88% in the nivolumab plus ipilimumab group and 89% in the nivolumab group when comparing total numbers of events (disease progression or death) and censored cases.

The objective response rate by blinded independent central review was significantly higher with nivolumab plus ipilimumab versus nivolumab in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status (209 [71%] of 296 patients; 95% CI 65–76 and 165 [58%] of 286 patients; 52–64, respectively; p=0·0011; table 2). Complete responses were reported in 90 (30%) of 296 patients in the nivolumab plus ipilimumab group and 80 (28%) of 286 patients in the nivolumab group; progressive disease as best response was reported in 30 (10%) patients and 54 (19%) patients, respectively (table 2). Median duration of response was not reached for either of the treatment groups; median time to response was similar across both groups (2·8 months [IQR 1·4–4·2] for nivolumab plus ipilimumab and 2·8 months [1·5–4·2] for nivolumab; table 2; appendix p 20). Among response-evaluable patients (patients with target lesion assessment at baseline and at least one on-treatment tumour assessment) with centrally confirmed microsatellite instability-high or mismatch repair-deficient status, 217 (77%) of 281 in the nivolumab plus ipilimumab group and 169 (62%) of 273 in the nivolumab group had at least a 30% reduction in the sum of diameters of target lesions from baseline (appendix p 21). In prespecified subgroup analyses, objective response rate was higher with nivolumab plus ipilimumab versus nivolumab (appendix p 22). Objective responses by blinded independent central review in all randomly assigned patients were consistent with those from patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status (appendix p 14).

At this updated analysis (Aug 28, 2024 data cutoff and minimum follow-up of 16·7 months), nivolumab plus ipilimumab continued to show progression-free survival benefit versus chemotherapy in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status in the first-line setting with longer follow-up. Median progression-free survival was 54·1 months (95% CI 54·1 to not estimable) in the nivolumab plus ipilimumab group and 5·9 months (4·4 to 7·8) in the chemotherapy group (HR 0·21, 95% CI 0·14 to 0·31; appendix p 23). The 24-month progression-free survival rate with longer follow-up was 74% (95% CI 67 to 80) with nivolumab plus ipilimumab and 11% (4 to 21) with chemotherapy; 36-month progression-free survival rates were 69% (61 to 76) and 11% (4 to 21), respectively.

Among all treated patients, the overall median duration of treatment was 20·5 months (IQR 3·8–23·6) in the nivolumab plus ipilimumab group (20·5 months [3·8–23·6] for nivolumab and 2·1 months [2·1–2·1] for ipilimumab) and 16·4 months (3·7–23·5) in the nivolumab group (appendix p 13). The median number of ipilimumab doses received by those in the nivolumab plus ipilimumab group was four (IQR 4–4); 288 (82%) of 352 patients received all four doses of ipilimumab.

Adverse events of any grade and any cause occurred in 349 (99%) of 352 patients in the nivolumab plus ipilimumab group and in 336 (96%) of 351 patients in the nivolumab group; adverse events of grade 3 or 4 occurred in 168 (48%) patients and 151 (43%) patients, respectively (appendix p 15). Treatment-related adverse events of any grade occurred in 285 (81%) of 352 patients receiving nivolumab plus ipilimumab and in 249 (71%) of 351 patients receiving nivolumab; grade 3 or 4 treatment-related adverse events occurred in 78 (22%) and 50 (14%) patients, respectively (table 3). The most common treatment-related adverse event was pruritus, which occurred in 91 (26%) of 352 patients receiving nivolumab plus ipilimumab and 63 (18%) of 351 patients receiving nivolumab alone. Treatment-related adverse events which led to treatment discontinuation of any drug in the regimen occurred in 48 (14%) of 352 patients and 21 (6%) of 351 patients (table 3). The most common grade 3 or 4 immune-mediated adverse events in the nivolumab plus ipilimumab and nivolumab groups were diarrhoea or colitis (12 [3%] of 352 patients and eight [2%] of 351 patients, respectively), hypophysitis (11 [3%] of 352 patients and four [1%] of 351 patients, respectively), and adrenal insufficiency (ten [3%] of 352 patients and three [<1%] of 351 patients, respectively). A summary of immune-mediated adverse events is in the appendix (p 16).

Among the 703 patients who received at least one dose of treatment, 252 deaths were reported (103 [29%] of 352 patients in the nivolumab plus ipilimumab group and 149 [42%] of 351 patients in the nivolumab group). The most common cause of death in both groups was disease progression. There were three treatment-related deaths: one event of myocarditis and pneumonitis each in the nivolumab plus ipilimumab group and one pneumonitis event in the nivolumab group (table 3).

Improvements from baseline in health-related quality of life were observed in both the nivolumab plus ipilimumab and nivolumab groups as measured by the EORTC QLQ-C30 Global Health Status subscale (appendix p 24). Mean change from baseline scores were positive in both treatment groups, with the nivolumab plus ipilimumab group reaching the prespecified threshold for meaningful change starting at week 21 and remaining at or near the within-group minimally important change from baseline of 10 at most timepoints starting from week 21.

Discussion

To our knowledge, CheckMate 8HW is the first randomised, phase 3 trial in microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer to report superior progression-free survival and objective response rate with the dual-immune checkpoint inhibitors, nivolumab plus ipilimumab compared with single-agent immunotherapy (nivolumab). Nivolumab plus ipilimumab showed significant and clinically meaningful improvement in progression-free survival versus nivolumab monotherapy across all lines of therapy in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer. In our study, progression-free survival rates were higher with nivolumab plus ipilimumab versus nivolumab. In prespecified subgroup analyses, progression-free survival favoured nivolumab plus ipilimumab versus nivolumab. In patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status, progression-free survival by blinded independent central review was robust and supported by investigator assessment, with a high degree of concordance between these assessments. Furthermore, progression-free survival by blinded independent review in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status was also consistent with data for all randomly assigned patients, where microsatellite instability-high or mismatch repair-deficient status was determined by local tests. The progression-free survival outcomes with nivolumab plus ipilimumab in all randomly assigned patients in this study are also consistent with data from patients receiving nivolumab plus ipilimumab in the phase 2 CheckMate 142 trial, in which local confirmation of microsatellite instability-high or mismatch repair-deficient status was done.[11,14] In the first 3 months after random assignment, there was a more pronounced decline in progression-free survival in the all randomised group compared with patients who had centrally confirmed microsatellite instability-high or mismatch repair-deficient status. This observation could be attributed to the presence of misdiagnosed patients by local testing among the all randomised population. 99 (14%) of 707 patients had microsatellite stable or mismatch repair-proficient status according to central testing. Given that this patient group

has been observed to be more resistant to immune checkpoint inhibitors,[18,19] broad adoption of validated immunohistochemistry and PCR-based (or next-generation sequencing) testing is paramount. However, analysis of the all randomised group presents an opportunity to estimate the efficacy and safety of nivolumab and ipilimumab in a real-world context in which clinicians use various tests, including those that are locally developed, to identify patients with microsatellite instability-high or mismatch repair-deficient colorectal cancer.

Previously, we reported improved progression-free survival with first-line nivolumab plus ipilimumab versus chemotherapy in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer, one of the dual primary endpoints from CheckMate 8HW.[16] In the longer follow-up analyses reported here, first-line nivolumab plus ipilimumab continued to show progression-free survival benefit over chemotherapy with higher 2-year and 3-year progression-free survival rates with nivolumab plus ipilimumab.[15,16] The 2-year and 3-year landmark progression-free survival rates with nivolumab plus ipilimumab observed in CheckMate 8HW were similar in the first-line and all-lines settings.

In the CheckMate 8HW study, there was a significant and clinically meaningful improvement in objective response rate with nivolumab plus ipilimumab versus nivolumab across all lines of therapy in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status. Furthermore, addition of ipilimumab led to reduced rates of progressive disease as best response. Objective response rates among those with locally tested high microsatellite instability or mismatch repair deficiency were similar to those from CheckMate 142.[10,13] To our knowledge, the objective response rate observed in CheckMate 8HW for nivolumab plus ipilimumab across all lines of therapy in centrally confirmed microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer is the highest reported in a randomised setting. Responses to treatment were durable in both the nivolumab plus ipilimumab and nivolumab groups, and median duration of response was not reached in both groups. The high complete response rate in this study suggests cure can be achieved in a proportion of patients, even in a metastatic setting. Future exploration of this hypothesis could include potential landmark analyses of progression-free survival and overall survival by best overall response, as well as biomarker analyses assessing correlations between radiographic response and circulating tumour DNA.

In the nivolumab group in our study, for all randomly assigned patients with local high microsatellite instability or mismatch repair deficiency assessment and mixed number of previous lines of therapy, the efficacy results were similar to those from previously untreated patients receiving pembrolizumab in KEYNOTE-177.[8,9,20] Rates of primary progressive disease were also similar to KEYNOTE-177, in which high microsatellite instability or mismatch repair deficiency was locally determined, although it is important to note that the proportion of patients with misdiagnosed microsatellite instability-high or mismatch repair-deficient status in KEYNOTE-177 is unknown. The outcomes observed across all lines in our study might be driven by previously untreated patients, due to a large proportion of patients receiving study treatment in the first-line setting; however, at the time of database lock, efficacy outcomes by line of therapy remain masked.

Safety of nivolumab plus ipilimumab was consistent with the profile observed in previously reported results comparing nivolumab plus ipilimumab with chemotherapy[16] and with the known profiles of each individual component. The incidence of drug-related adverse events was higher in the nivolumab plus ipilimumab group compared with the nivolumab group. The most frequently reported drug-related adverse events were pruritus, diarrhoea, and hypothyroidism with nivolumab plus ipilimumab and pruritus, diarrhoea, and asthenia with nivolumab. Particularly noteworthy was the higher incidence of immune-mediated endocrine adverse events in the nivolumab plus ipilimumab group compared with the nivolumab group, most of which were grade 1 and 2. However, a proportion of patients had resolution of these events with or without the need for ongoing hormone replacement therapy. Additionally, there were higher rates of drug-related adverse events leading to discontinuation with nivolumab plus ipilimumab, although patients were able to continue with nivolumab after early discontinuation of ipilimumab. Despite these differences in safety between the treatment groups, patients had improvements from baseline in health-related quality of life with nivolumab plus ipilimumab and nivolumab. The mean changes from baseline in EORTC QLQ-C30 Global Health Status scores remained close to the prespecified threshold for meaningful change with nivolumab plus ipilimumab and nivolumab at most timepoints from week 21 onward, showing the efficacy with nivolumab plus ipilimumab compared with nivolumab was not at the expense of diminished health-related quality of life.

It is important to note the limitations of this trial. First, as the trial was open label, it is conceivable that there were biases in reporting of treatment assessments; however, the high degree of concordance between blinded independent central review and the investigator assessment of progression-free survival suggests that the open-label design did not affect efficacy assessments. Second, due to the relatively shorter duration of minimum follow-up for the current interim analysis, some secondary endpoints, such as duration of response, remain immature; these will be addressed with additional follow-up. Third, patient numbers in some of the prespecified subgroups were low, limiting data interpretation. Additionally, although subgroup analyses for assessment of progression-free

survival and objective response rates by line of treatment would have been of interest, treatment lines remain masked at this time because these data are not yet mature, in line with the hierarchical testing plan. Finally, although progression-free survival is an established endpoint to assess clinical benefit with immunotherapy in microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer, overall survival data remain masked at this time and will be valuable to further contextualise these study results.

In conclusion, to our knowledge this is the first randomised phase 3 trial to investigate the use of dual-agent immunotherapy versus single-agent immunotherapy in patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer, contributing to the body of evidence across multiple indications that dual-agent immunotherapy shows clinical benefit compared with single-agent immunotherapies.[21,22] The significant progression-free survival and objective response benefits reported here with nivolumab plus ipilimumab over nivolumab support use across lines of therapy in this setting. The safety of nivolumab plus ipilimumab was consistent with the established profiles of each individual drug, and no new safety concerns were identified. Taken together, these results strongly support nivolumab plus ipilimumab as a potential new standard of care in microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer.

Contributors

TA, H-JL, LHJ, TY, JL, EC, TCh, ML, LJ, SIB, and SL contributed to the concept and design of the study in collaboration with Bristol Myers Squibb. TA, EE, H-JL, LHJ, YT, EVC, RG-C, DT, GAM, MS, CdlF, MLL, TY, JL, JLMM, LD, GT, MC, EG, MIB, RJ, TCi, FA, EC, ML, and SL were involved in data collection. EC, TCh, ML, SIB, and LJ were responsible for data analysis. All authors were involved in critical data interpretation and reviewed and edited the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors reviewed the final version of the manuscript to be submitted and agree with its content and submission. All authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Declaration of interests

TA reports consulting or advisory roles for Amgen, Aptitude Health, Astellas Pharma, Bristol Myers Squibb, GamaMabs Pharma, Gritstone Bio, Gilead Sciences, GlaxoSmithKline, MSD Oncology, Nordic Bioscience, Seagen, Servier, Pfizer, Pierre Fabre, Takeda-Lundbeck, Tesaro, and Transgene; receiving honoraria from Amgen, Bristol Myers Squibb, MSD Oncology, Merck Serono, GlaxoSmithKline, Pierre Fabre, Roche-Genentech, Sanofi, Seagen, Servier, and Ventana Medical Systems; a data monitoring committee role for Inspirna; being President of the ARCAD foundation (Aide à la recherché en cancérologie digestive), a member of the ACCENT Collaborative Group and Gercor; and travel or accommodation expenses from Bristol Myers Squibb, MSD Oncology, Takeda, and Servier. 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Data sharing

Bristol Myers Squibb will honour legitimate requests for clinical trial data from qualified researchers who submit an in-scope proposal approved by the independent review committee. Before data are released, the researcher(s) must sign a data sharing agreement, after which de-identified and anonymised datasets can be accessed within a secure portal. The Bristol Myers Squibb policy on data sharing can be found at https://www.bms.com/researchers-andpartners/independent-research/data-sharing-request-process.html.

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LBA125

Rapid Oral Abstract Session

Low-dose aspirin to reduce recurrence rate in colorectal cancer patients with PI3K pathway alterations: 3-year results from a randomized placebo-controlled trial.

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Background: Colorectal cancer (CRC) affects 1.9 million individuals globally each year. Among patients with stage II-III CRC, 20-40% develop metastatic disease. Aspirin lowers the incidence of adenomas and CRC in high-risk patients. In addition, observational studies suggest that post-diagnosis aspirin treatment improves disease-free survival (DFS) in unselected populations. Furthermore, retrospective findings indicate that somatic PIK3CA mutations predict treatment response, but requires validation in randomized trials. **Methods:** The ALASCCA trial was a randomized, double-blind, multicenter, placebo-controlled trial with two parallel arms, across 33 hospitals in Sweden, Denmark, Finland, and Norway. Patients with stage I-III rectal cancer or stage II-III colon cancer exhibiting somatic alterations in the PI3K signaling pathway were included. Patients were randomized to receive either 160 mg of aspirin daily or placebo, initiated within three months post-surgery and continued for three years. To detect a hazard ratio (HR) of 0.36 for the primary outcome of time to recurrence (TTR) assessed at 3 years, with 80% power and a two-sided alpha of 0.05, 150 patients with PIK3CA mutations in exon 9 and/or 20 ("Group A") were required per arm. An additional 300 patients with other somatic PI3K pathway driver alterations (PIK3CA outside exon 9/20, PIK3R1, or PTEN; "Group B") were required for secondary analyses. A stratified Cox proportional hazards model was fitted for the primary efficacy analysis. **Results:** A total of 3508 patients were screened for somatic alterations in the PI3K pathway. Of the 2980 patients with conclusive genomic analyses, 1103 patients (37%) had an alteration in the PI3K pathway: 515 patients (17.3%) in Group A and 588 patients (19.7%) in Group B. In total, 626 patients were randomized. After three years of follow-up, the HRs for TTR comparing aspirin to placebo were 0.49 (95% CI; 0.24-0.98; p=0.044) in Group A and 0.42 (95% CI; 0.21-0.83; p=0.013) in Group B. For DFS, the HRs were 0.61 (95% CI; 0.34-1.08; p=0.091) in Group A, and 0.51 (95% CI; 0.29-0.88; p=0.017) in Group B. Three patients experienced aspirin-related severe adverse events (one GI-bleeding, one hematoma, one allergic reaction). **Conclusions:** Primary endpoint was met. Adjuvant treatment with 160 mg aspirin daily for three years reduced recurrence rate in CRC patients with somatic alterations in the PI3K signaling pathway. These findings could lead to immediate changes in clinical praxis for about a third of CRC patients. Clinical trial information: NCT02647099. Research Sponsor: Swedish Research Council; Swedish Cancer Society; ALF (regional agreement on medical training and clinical research between the Stockholm County Council and Karolinska Institutet.); Private Donation; Stockholm Cancer Society.