874eP

First-line (1L) encorafenib + cetuximab + mFOLFOX6 in patients with BRAF V600E-mutant metastatic colorectal cancer (mCRC) in China: results from the phase 3 BREAKWATER study

Xicheng Wang,[1] Ying Yuan,[2] Zhiyu Chen,[3] Jun Zhang,[4] Qi Wang,[5] Xianling Liu,[6] Yongqiang Li,[7] Zuoxing Niu,[8] Xiaoping Qian,[9] Yan Li,[10] Ting Xu,[1] Yihui Zhu,[11] Hui Zhang,[11] Nan Li,[11] Xiaosong Zhang,[12] Lin Shen[1]

[1]Beijing Cancer Hospital, Beijing, China; [2]The Second Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou, China; [3]Fudan University Shanghai Cancer Center, Shanghai, China; [4]Ruijin Hospital Shanghai Jiao Tong University School of Medicine, Shanghai, China; [5]The Third Xiangya Hospital of Central South University, Changsha, China; [6]The Second Xiangya Hospital of Central South University, Changsha, China; [7]Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China; [8]Shandong Cancer Hospital, Jinan, China; [9]Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China; [10]Chongqing University Cancer Hospital, Chongqing, China; [11]Pfizer Inc, Shanghai, China; [12]Pfizer Inc, South San Francisco, CA, USA

Objectives

- We present exploratory efficacy and safety data with EC+mFOLFOX6 vs control (chemotherapy ± bevacizumab) as first-line therapy for patients with BRAF V600E-mutant mCRC enrolled in the BREAKWATER study in China

Conclusions

- For Chinese patients with untreated BRAF V600E-mutant mCRC enrolled in BREAKWATER, EC+mFOLFOX6 showed improved ORR, PFS, and OS vs control, consistent with results of the global study
- In this subgroup of patients, safety of EC+mFOLFOX6 was manageable, in line with the overall trial population, and as expected for each agent

Plain Language Summary
Please scan this Quick Response (QR) code with your smartphone to view a plain language summary. If you do not have a smartphone, access the plain language summary via the internet at: https://scientificpubs.congressposter.com/pls/ys362dm21y7yczp4

Electronic Poster
Copies of this poster obtained through QR codes are for personal use only and may not be reproduced without written permission of the authors. If you do not have a smartphone, access the poster via the internet at: https://scientificpubs.congressposter.com/p/ys362dm21y7yczp4

References: **1.** Tabernero J, et al. *Am Soc Clin Oncol Educ Book.* 2022;42:254-263. **2.** Tran B, et al. *Cancer.* 2011;117:4623-4632. **3.** Delord JP, et al. *Clin Cancer Res.* 2017;23:5339-5348. **4.** Stuart DD, et al. *Cancer Res.* 2012;72(8_Suppl):3790. **5.** Kopetz S, et al. *N Engl J Med.* 2019;381:1632-1643. **6.** Wang X, et al. *J Clin Oncol.* 2024; 42 (17_Suppl): LBA3559. **7.** Kopetz S, et al. *Nat Med.* 2025;31:901-908. **8.** Élez E, et al. *N Engl J Med.* 2025;392:2425-2437. **9.** BRAFTOVI (encorafenib). Prescribing information. US Food and Drug Administration; 2024.

Abbreviations: AE, adverse event; BICR, blinded independent central review; CAPOX, capecitabine/oxaliplatin; CTCAE, Common Terminology Criteria for Adverse Events, CEA, carcinoembryonic antigen; CRP, C-reactive protein; dMMR, deficient mismatch repair; DOR, duration of response; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; FOLFOXIRI, fluorouracil/leucovorin/oxaliplatin/irinotecan; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; RECIST, Response Evaluation Criteria in Solid Tumors; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event; TTR, time to response.

Acknowledgments: The authors thank the participating patients and their families, as well as the staff at the participating sites. BREAKWATER was sponsored by Pfizer and was conducted with support from ONO Pharmaceutical, Merck KGaA, Darmstadt, Germany, and Eli Lilly and Company. Medical writing support was provided by Radhika Das Chakraborty, PhD, of Nucleus Global, an Inizio Company, and was funded by Pfizer.

Disclosures/COIs: **Xicheng Wang** reports research funding from Pfizer (Inst). **Ying Yuan** reports research funding from Pfizer (Inst). **Zhiyu Chen** reports research funding from Pfizer (Inst). **Jun Zhang** reports research funding from Pfizer (Inst). **Qi Wang** reports research funding from Pfizer (Inst). **Xianling Liu** reports research funding from Pfizer (Inst). **Yongqiang Li** reports research funding from Pfizer (Inst). **Zuoxing Niu** reports research funding from Pfizer (Inst). **Xiaoping Qian** reports research funding from Pfizer (Inst). **Yan Li** reports research funding from Pfizer (Inst). **Ting Xu** reports research funding from Pfizer (Inst). **Yihui Zhu** reports employment with Pfizer; and stock and other ownership interests in Pfizer. **Hui Zhang** reports employment with Pfizer; and stock and other ownership interests in Pfizer. **Nan Li** reports employment with Pfizer; and stock and other ownership interests in Pfizer. **Xiaosong Zhang** reports employment with Pfizer; stock and other ownership interests in Pfizer; and patents, royalties, and other intellectual property with Johns Hopkins University. **Lin Shen** reports research funding from Beigene and Pfizer (Inst).

Presented at ESMO 2025; Oct 17-21, 2025; Berlin, Germany.

Background

- BRAF V600E mutations occur in 8% to 12% of patients with mCRC and are associated with poor prognosis[1,2]
- Encorafenib is a highly selective, ATP-competitive, BRAF inhibitor with prolonged pharmacodynamic activity compared with other approved BRAF inhibitors[3,4]
- Encorafenib plus cetuximab was approved in China in 2025 for BRAF V600E-mutant mCRC in the second- and third-line settings based on results from the BEACON (NCT02928224) study and bridging study NAUTICAL CRC (NCT05004350)[5,6]
- BREAKWATER (NCT04607421) is a phase 3 study evaluating EC with or without mFOLFOX6 vs control (investigator's choice of chemotherapy with mFOLFOX6/FOLFOXIRI/CAPOX ± bevacizumab) in previously untreated BRAF V600E-mutant mCRC[7,8]
  - EC+mFOLFOX6 demonstrated clinically meaningful and statistically significant improvements in ORR by BICR and PFS by BICR (dual primary endpoints) and OS (key secondary endpoint) vs control
    - Confirmed ORR by BICR: 60.9% versus 40.0% (odds ratio=2.44, 1-sided *P*=0.0008)
    - PFS by BICR: 12.8 vs 7.1 months (HR 0.53; 1-sided *P*<0.0001)
    - OS: 30.3 vs 15.1 months (HR 0.49; 1-sided *P*<0.0001)
  - Safety data showed that EC+mFOLFOX6 was generally tolerable, with a safety profile consistent with that known for each agent, and that there was no substantial increase in chemotherapy dose reduction or discontinuation vs control[7,8]
  - EC+mFOLFOX6 was granted accelerated approval by the US FDA as part of Project FrontRunner for patients with BRAF V600E-mutant mCRC, including in the first-line setting[9]; this was followed by several recent full approvals in countries in Latin America and conditional approval in Canada
  - EC+mFOLFOX6 is practice changing as a new SOC for BRAF V600E-mutant mCRC in the first-line setting

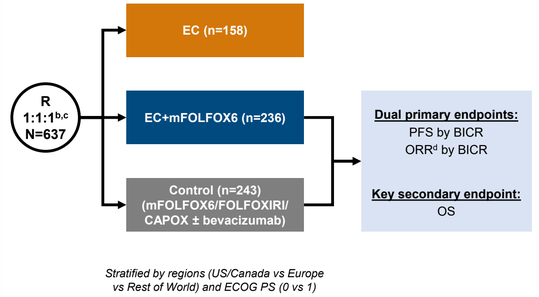
Methods

- BREAKWATER is an open-label, multicenter, phase 3 study in patients with previously untreated BRAF V600E-mutant mCRC (**Figure 1**)
- Eligible patients with untreated BRAF V600E-mutant mCRC were randomized 1:1:1 to receive EC, EC+mFOLFOX6, or control
  - Following a protocol amendment, EC arm enrollment was stopped and patients were randomized 1:1 to receive EC+mFOLFOX6 or control
- The data cutoff date was January 6, 2025
- The dual primary endpoints were ORR and PFS by BICR; the key secondary endpoint was OS
- Adverse events were characterized by type and severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03
- For the current post hoc exploratory analysis, outcomes were evaluated for EC+mFOLFOX6 and control in patients enrolled in China

Figure 1. Study Design for BREAKWATER

Inclusion criteria
- Age ≥16 years (or ≥18 years based on country)[a]
- No prior systemic treatment for metastatic disease
- Measurable disease (RECIST 1.1)
- BRAF V600E-mutant mCRC by local or central laboratory testing
- ECOG PS 0 or 1
- Adequate bone marrow, hepatic, and renal function

Exclusion criteria
- Prior BRAF or EGFR inhibitors
- Symptomatic brain metastases
- MSI-H/dMMR tumors (unless patients were ineligible to receive immune checkpoint inhibitors due to a preexisting medical condition)
- Presence of a *RAS* mutation



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

Results

- In the BREAKWATER study, there were 36 and 42 patients in the EC+mFOLFOX6 and control arms, respectively, in China
- At the data cutoff, 28 patients (77.8%) in the EC+mFOLFOX6 arm and 40 patients (95.2%) in the control arm had discontinued study treatment
- Baseline characteristics were generally balanced between treatment arms (**Table 1**)

Table 1. Key Demographic and Baseline Disease Characteristics

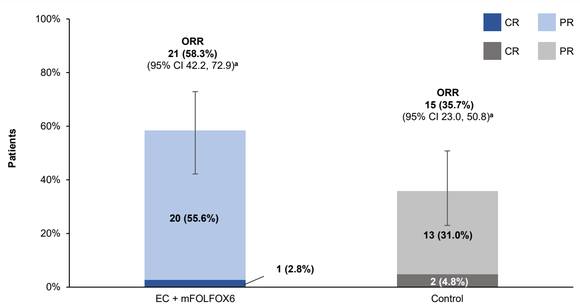
	EC+mFOLFOX6 n=36	Control n=42
Age, median (range), years	58.50 (30-80)	60.50 (33-74)
Sex, n (%)		
Male	22 (61.1)	27 (64.3)
Female	14 (38.9)	15 (35.7)
ECOG PS, n (%)[a]		
0	13 (36.1)	19 (45.2)
1	22 (61.1)	22 (52.4)
Side of tumor, n (%)		
Left	17 (47.2)	23 (54.8)
Right	19 (52.8)	19 (45.2)
No. of organs involved, n (%)[b]		
≤2	18 (50.0)	23 (54.8)
≥3	18 (50.0)	19 (45.2)
Liver metastases, n (%)		
Yes	23 (63.9)	28 (66.7)
No	13 (36.1)	14 (33.3)
CEA at baseline, n (%)[a]		
≤5 μg/L	13 (36.1)	12 (28.6)
>5 μg/L	22 (61.1)	29 (69.0)
CRP at baseline, n (%)[a]		
≤10 mg/L	23 (63.9)	25 (59.5)
>10 mg/L	12 (33.3)	16 (38.1)

Data cutoff: January 6, 2025.
[a]Data was missing for 1 patient in EC+mFOLFOX6 arm and 1 patient in control arm. [b]Based on BICR.

Efficacy

- Confirmed ORR by BICR was improved with EC+mFOLFOX6 vs control (58.3% vs 35.7%; odds ratio 2.52 [95% CI 1.01, 6.29]) (**Figure 2** and **Table 2**)
- Median TTR was 1.5 months and median DOR was 15.4 months for EC+mFOLFOX6 (**Table 2**)
- PFS by BICR was longer with EC+mFOLFOX6 vs control (10.0 vs 7.1 months, HR 0.63 [95% CI 0.33, 1.21]) (**Figure 3**)
- Similarly, OS was also improved with EC+mFOLFOX6 vs control (NE vs 13.4 months, HR 0.34 [95% CI 0.18, 0.66]) (**Figure 4**)
- Improved ORR, PFS, and OS with EC+mFOLFOX6 vs chemotherapy in the subgroup of patients enrolled in China were consistent with what was observed in the overall population

Figure 2. ORR by BICR



	n=36	n=42
Odds ratio	**2.52** 95% CI 1.01, 6.29[b]	

Data cutoff: January 6, 2025.
[a]Wilson method used. [b]Odds ratio estimated using the Mantel-Haenszel method.

Table 2. TTR and DOR by BICR

Responders	EC+mFOLFOX6 n=21	Control n=15
TTR, median (range), months	1.5 (1.2-3.0)	1.6 (1.4-3.4)
DOR,[a] median (95% CI), months	15.4 (8.5, 18.5)	11.1 (4.3, NE)
Patients with DOR ≥6 months, n (%)	15 (71.4)	4 (26.7)
Patients with DOR ≥12 months, n (%)	10 (47.6)	2 (13.3)

Data cutoff: January 6, 2025. [a]Based on the Brookmeyer and Crowley method.

Figure 3. PFS by BICR

Median follow-up
EC+mFOLFOX6: 17.8 mo (95% CI 9.8, 21.5)
Control: 7.2 mo (95% CI 5.6, 9.8)

	EC+mFOLFOX6 n=36	Control n=42
No. of events, n (%)	19 (52.8)	20 (47.6)
Median PFS[a]	**10.0 mo** (95% CI 7.1, 19.9)	**7.1 mo** (95% CI 5.7, 9.5)
PFS hazard ratio[b]	**0.63** (95% CI 0.33, 1.21)	

Data cutoff: January 6, 2025. [a]Based on the Brookmeyer and Crowley method. [b]Hazard ratio based on Cox proportional hazards model.

Figure 4. OS

Median follow-up
EC+mFOLFOX6: 20. 5 mo (95% CI 19.0, 23.0)
Control: 26.3 mo (95% CI 21.3, 29.1)

	EC+mFOLFOX6 n=36	Control n=42
No. of events, n (%)	13 (36.1)	30 (71.4)
Median OS[a]	**NE** (95% CI 18.7, NE)	**13.4 mo** (95% CI 11.0, 14.5)
OS hazard ratio[a]	**0.34** (95% CI 0.18, 0.66)	

Data cutoff: January 6, 2025. [a]Based on the Brookmeyer and Crowley method. [b]Hazard ratio based on Cox proportional hazards model.

Safety

- A safety summary for the EC+mFOLFOX6 and control groups is shown in **Table 3**
  - Serious TEAEs with EC+mFOLFOX6 and control, respectively, occurred in 37.1% and 34.1% of patients in the safety analysis set
- The 3 most common any grade TEAEs in the EC+mFOLFOX6 arm included anemia (65.7%), white blood cell count decreased (65.7%), and neutrophil count decreased (62.9%) (**Table 4**)
  - The 3 most common grade 3/4 TEAEs in the EC+mFOLFOX6 arm included lipase increased (31.5%), neutrophil count decreased (22.8%), and anemia (20.0%)
- Permanent discontinuation of other study treatments (irinotecan, oxaliplatin, leucovorin or levo-leucovorin, 5-FU, capecitabine, or bevacizumab) due to TEAEs was similar for EC+mFOLFOX6 and control (20.0% and 17.1%, respectively) (**Table 5**)

Table 3. Safety Summary

Patients, n (%)	EC+mFOLFOX6 n=35	Control n=41
All cause		
TEAE	35 (100.0)	41 (100.0)
Grade 3 or 4 TEAE	28 (80.0)	29 (70.7)
Grade 5 TEAE	1 (2.9)[a]	0
Serious TEAE	13 (37.1)	14 (34.1)
TEAE leading to dose reduction of any study treatment	22 (62.9)	18 (43.9)
TEAE leading to dose interruption of any study treatment	30 (85.7)	32 (78.0)
TEAE leading to permanent discontinuation of any study treatment	11 (31.4)	7 (17.1)
Treatment related		
AE related to any drug	35 (100.0)	39 (95.1)
Grade 3 or 4 TRAE	26 (74.3)	27 (65.9)
Grade 5 TRAE	0	0
Serious AE related to any drug	8 (22.9)	8 (19.5)

[a]The Grade 5 TEAE was intestinal obstruction and was not related to study treatment.

Table 4. Most Frequent (≥30% in the EC+mFOLFOX6 Arm) All-Cause TEAEs

	EC+mFOLFOX6 n=35		Control n=41	
TEAEs, n (%)	**Any grade**	**≥Grade 3**	**Any grade**	**≥Grade 3**
Anemia	23 (65.7)	7 (20.0)	19 (46.3)	1 (2.4)
White blood cell count decreased	23 (65.7)	4 (11.4)	23 (56.1)	6 (14.6)
Neutrophil count decreased	22 (62.9)	8 (22.8)	23 (56.1)	12 (29.3)
Platelet count decreased	20 (57.1)	2 (5.7)	17 (41.5)	1 (2.4)
Decreased appetite	19 (54.3)	0	15 (36.6)	0
Nausea	19 (54.3)	0	20 (48.8)	0
Alanine aminotransferase increased	17 (48.6)	1 (2.9)	13 (31.7)	1 (2.4)
Vomiting	17 (48.6)	0	16 (39.0)	2 (4.9)
Aspartate aminotransferase increased	16 (45.7)	1 (2.9)	15 (36.6)	1 (2.4)
Hypoalbuminemia	16 (45.7)	0	10 (24.4)	0
Lipase increased	15 (42.9)	11 (31.5)	4 (9.8)	1 (2.4)
Weight decreased	12 (34.3)	0	6 (14.6)	0
Constipation	11 (31.4)	0	3 (7.3)	0
Hypokalemia	11 (31.4)	0	7 (17.1)	3 (7.3)

Table 5. Dose Modifications due to AEs

Patients, n (%)	EC+mFOLFOX6 n=35	Control n=41
Dose reduction		
Encorafenib	10 (28.6)	–
Cetuximab	4 (11.4)	–
Other study treatment[a]	20 (57.1)	18 (43.9)
Dose interruption		
Encorafenib	20 (57.1)	–
Cetuximab	20 (57.1)	–
Other study treatment[a]	26 (74.3)	32 (78.0)
Discontinuation		
Encorafenib	4 (11.4)	–
Cetuximab	4 (11.4)	–
Other study treatment[a]	7 (20.0)	7 (17.1)

[a]Irinotecan, oxaliplatin, leucovorin or levo-leucovorin, fluorouracil, capecitabine, and bevacizumab (as appropriate for the treatment group).