Targeted Therapy Combo Nearly Doubles Time Without Disease Progression for Patients With Advanced Colorectal Cancer

Adding Braftovi plus Erbitux to chemotherapy reduced the risk of disease progression or death by more than half.

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- Cohort 3 of the BREAKWATER trial evaluated encorafenib plus cetuximab with FOLFIRI chemotherapy.
- Updated results demonstrate improved progression-free survival, better overall survival and consistent side effects with earlier analyses.
- Findings build on earlier data showing improved responses and survival outcomes.
- In February, the FDA approved the BREAKWATER regimen with FOLFIRI as a first-line option for BRAF V600E-mutant metastatic colorectal cancer.

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Updated results from the Phase III BREAKWATER trial, led by researchers at The University of Texas MD Anderson Cancer Center, demonstrated a 56% reduction in the risk of disease progression or death for patients with BRAF V600E mutant metastatic colorectal cancer treated with a targeted therapy combination.

The data was presented [May 30] at the 2026 American Society of Clinical Oncology (ASCO) Annual Meeting by lead author, Scott Kopetz, MD, PhD, professor of Gastrointestinal Medical Oncology and associate vice president of Translational Integration. Findings also were published in Annals of Oncology.

This update builds on earlier BREAKWATER results with mFOLFOX6, providing additional evidence

supporting the Food and Drug Administration (FDA) approval of the triplet combination of encorafenib, cetuximab and fluorouracil chemotherapy for patients with BRAF V600E-mutant metastatic colorectal cancer, further demonstrating the benefit of targeted combination strategies in this difficult-to-treat disease.

“These results demonstrate that this regimen substantially improves disease control and survival outcomes compared with standard chemotherapy and supports its use as a new standard-of-care option for patients with BRAF-mutant metastatic colorectal cancer,” Kopetz said.

Which therapies did the BREAKWATER regimen assess and what does the updated data show?

The Cohort 3 portion of the Phase 3 BREAKWATER trial evaluated a combination of therapies targeting unique features of BRAF-mutant colorectal cancer, including:

- Encorafenib [Braftovi], a BRAF-targeted therapy
- Cetuximab [Erbitux], an EGF- targeted therapy
- FOLFIRI, a chemotherapy combination of 5-flurouracil and irinotecan commonly used for colorectal cancers

The study compared this combination against standard chemotherapy treatment, with or without bevacizumab, in patients with previously untreated metastatic colorectal cancer harboring the BRAF V600E mutation.

Patients treated with encorafenib and cetuximab plus FOLFIRI experienced significantly improved outcomes. Median progression-free survival – the length of time patients lived without their disease getting worse – was 15.2 months, compared with 8.3 months for patients receiving standard therapy.

The treatment also helped people live longer overall. Nearly 75% of patients receiving treatment with the combination were alive at 18 months, compared with just over 50% of those who received standard therapy. At the time researchers analyzed the data, the median overall survival for patients on the new regimen had not yet been reached, indicating many patients continued to benefit from treatment.

Treatment was generally well tolerated, and side effects were consistent with what is already known about the individual therapies. No new safety concerns were identified.

Why is the BREAKWATER trial important for colorectal cancer patients?

For patients with this aggressive type of colorectal cancer, the BREAKWATER regimen showed that adding targeted therapy to chemotherapy can help people live significantly longer and keep their cancer under control. It represents one of the most significant treatment advances for this patient group in years.

The findings reinforce the growing role of biomarker-driven treatment strategies in metastatic colorectal cancer, which contributed to the FDA approval of this treatment regimen.

Researchers now are focused on long-term follow-up and refining targeted treatment strategies to further improve outcomes for patients with BRAF-mutant colorectal cancer.

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The study was sponsored by Pfizer Inc., and Kopetz disclosed consulting for Pfizer and receiving research funding from the company. A full list of collaborating authors and their disclosures can be found in the full paper in Annals of Oncology.

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