# CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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## Targeting *BRAF* V600E Mutations in Metastatic Colorectal Cancer

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**H&O** How common is *BRAF* V600E–mutated colorectal cancer (CRC)?

**SK** *BRAF* V600E mutations occur in approximately 5% to 7% of patients with metastatic CRC. That percentage is higher in earlier-stage disease.

**H&O** What makes *BRAF* V600E–mutated CRC biologically distinct from other subtypes of CRC?

**SK** *BRAF* V600E CRC arises from a premalignancy state different from that of many other CRCs. It is defined by flat sessile serrated adenomas, and nearly all cases exhibit high levels of epigenetic dysregulation. Clinically, it behaves distinctly from other forms of CRC, with different patterns of metastases. It is more likely to spread to the peritoneum, retroperitoneal lymph nodes, and brain, although brain metastases are still not common. We think of *BRAF* V600E CRC as representing a distinct branch of the genealogic tree of CRC.

The activity of standard chemotherapy regimens, whether administered as first-, second-, or third-line therapy, is greatly reduced in the setting of *BRAF* V600E CRC. Fortunately, outcomes have improved with the advent of BRAF-targeted therapies.

**H&O** What is the prognosis for someone with *BRAF* V600E CRC?

**SK** Before the addition of targeted therapies, the median survival of patients with this form of cancer was approximately 1 year. Thanks to the development of BRAF inhibitors for certain patients with CRC and an understanding of how to deploy them, we have been seeing increases in median survival to an estimated 2 1/2 years, with outcomes continuing to improve. Nonetheless, we need to acknowledge that some patients' disease never responds to therapy, and it can move more quickly and aggressively than average in some cases.

**H&O** When should patients with CRC be tested for *BRAF* V600E mutations in clinical practice?

**SK** The current guidelines state that patients should be tested at the time metastatic CRC is diagnosed. Back when we had approval for BRAF inhibitors only in later-line settings, it was reasonable to plan on doing testing after initial therapy had begun. But now, patients need to be tested immediately upon diagnosis, and that information should be used in initial decision-making regarding treatment.

**H&O** What is the role of liquid biopsy in testing?

**SK** Liquid biopsy with circulating tumor DNA (ctDNA) is very sensitive in CRC; its performance is excellent in patients with newly diagnosed disease. Not only can the use of ctDNA help us understand the molecular subtype of the tumor, the results usually are available much sooner than with tissue testing. As a result, ctDNA is the first and preferred testing modality in my practice. Still, molecular testing can take time. If we are dealing with aggressive metastatic disease, sometimes we will provide an initial cycle of folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin (FOLFOX) before we have the results of

the biomarker testing. That way, by cycle 2 we can tailor the therapy better according to the patient's molecular subtype.

**H&O** What treatment options are available for the first-line treatment of *BRAF* V600E–mutated CRC?

**SK** Our options for first-line treatment depend on whether high microsatellite instability (MSI-H) or mismatch repair deficiency (MMRd) is present. If the cancer is MSI-H or MMRd, the patient can benefit from a combination of a programmed death 1 (PD-1) inhibitor and a cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitor, regardless of *BRAF* mutation status.

In patients whose disease is microsatellite stable and who have a *BRAF* mutation, the current standard of care is the BRAF inhibitor encorafenib (Braftovi, Pfizer) and the epidermal growth factor receptor (EGFR) inhibitor cetuximab (Erbitux, Lilly) plus a modified FOLFOX regimen (mFOLFOX6). This combination received full US Food and Drug Administration (FDA) approval in February 2026 on the basis of the BREAKWATER study.[1] Cohort 3 of this study is looking at the first-line use of encorafenib and cetuximab (EC) plus a different chemotherapy backbone—leucovorin, fluorouracil, and irinotecan (FOLFIRI)—and has demonstrated similar results. On the basis of these results, the recent FDA approval included an option to use either the FOLFOX or FOLFIRI backbone.[2]

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Several years ago, we were using triplet cytotoxic regimens such as folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) with bevacizumab for patients with *BRAF* mutations. However, subgroup analyses have shown that EC + FOLFOX is superior to even this triplet cytotoxic regimen and is now the standard of care for first-line treatment.

**H&O** What options are available for second-line treatment in *BRAF* V600E–mutated CRC?

**SK** EC is approved for use as second-line treatment in patients who have CRC with a *BRAF* mutation if they did not receive it in the first line for whatever reason. Sequencing does matter, however, and we know that patients derive the greatest survival benefit from BRAF-targeted therapy when they receive it in the first-line setting.

Standard chemotherapy is another option for second-line treatment, although the benefits are reduced in patients who have a *BRAF* mutation. For example, an option for a patient who received EC plus FOLFOX as first-line treatment is FOLFIRI plus bevacizumab.

**H&O** Could you go into more detail regarding the BREAKWATER trial, including the most recent results from cohort 3?

**SK** The BREAKWATER study previously reported its primary endpoint, which was overall survival with EC plus FOLFOX vs standard care, which consisted of doublet or triplet chemotherapy with or without bevacizumab. This study demonstrated improvement in the overall response rate with EC plus FOLFOX vs standard care, from 40.0 to 60.9 months,[3] and in progression-free survival, from 7.1 to 12.8 months.[2] In addition, it found that EC plus FOLFOX doubled median overall survival from 15.1 to 30.3 months.[2] This was the first time we were able to achieve a median survival of 2 1/2 years in this population.

Not all patients are candidates for FOLFOX in the first-line treatment of metastatic disease, however. Patients who received FOLFOX or capecitabine plus oxaliplatin (CAPOX) as adjuvant treatment for earlier-stage disease before recurrence will want a different regimen for second-line treatment, as will those who have neuropathy or other comorbidities. Patient or provider preference is also a valid reason to choose FOLFIRI over FOLFOX.

The FOLFIRI cohort of the BREAKWATER study was enrolled after completion of the primary phase 3 study. In this cohort, 147 patients were randomized to EC plus FOLFIRI or standard-of-care chemotherapy. The EC/FOLFIRI regimen led to a substantial improvement in the overall response rate, at 64.4% vs 39.2%, and a trend toward improved overall survival, with a hazard ratio of 0.49. These findings are similar to what we saw in the original BREAKWATER cohort. We will be presenting further updates of cohort 3 at the 2026 American Society of Clinical Oncology (ASCO) Annual Meeting, but these findings support the idea of being able to choose between FOLFOX and FOLFIRI as a backbone with EC. As previously mentioned, EC plus FOLFIRI received

FDA approval, and I expect that this regimen will be incorporated into our National Comprehensive Cancer Network (NCCN) treatment guidelines soon. Having more options for our patients is helpful. The results of cohort 3 of BREAKWATER have already changed my practice.

**H&O** How do the side effect profiles of EC-based regimens compare with those of standard chemotherapy?

**SK** We see some rash with the EC regimen, although interestingly, we see less rash than we do with cetuximab alone or cetuximab and chemotherapy. We have some data showing that BRAF inhibition can actually reduce skin toxicity rates by blunting some of the inflammatory responses to EGFR inhibition. The use of encorafenib does increase the rates of anemia and arthralgia, which are classic side effects of BRAF inhibitors, but these tend to be mild and transient. Overall, we see no difference in discontinuation rates when we add EC to a chemotherapy backbone.

**H&O** Are any emerging targets or novel combinations being explored for *BRAF* V600E CRC?

**SK** We have preclinical and translational data suggesting that the addition of EC to FOLFOX chemotherapy is changing the mechanisms of resistance that we see in these patients. We are seeing much less resistance to BRAF inhibition in these patients, which is changing what we believe about what resistance patterns look like. The combinatorial synergy may help explain why the combination of EC and chemotherapy works so much better in the first line than chemotherapy followed by EC. We still want to know how we can do better in this space, however. For example, how do we further inhibit the mitogen-activated protein kinase (MAPK) pathway to target resistance? A phase 1b study is looking at adding the extracellular signal–regulated kinase (ERK) inhibitor ulixertinib to EC in patients with metastatic CRC who have previously received EGFR- or BRAF-directed therapy (NCT05985954). Another study is looking at the use of the bromodomain inhibitor ZEN003694 in combination with EC in patients who have relapsed or refractory metastatic CRC and a *BRAF* V600 mutation (NCT06102902). The phase 2 SWOG2107 study is looking at the addition of nivolumab (Opdivo, Bristol Myers Squibb) to EC in patients who have *BRAF*-mutated CRC with microsatellite stability (NCT05308446).

**H&O** Is there anything you would like to emphasize?

**SK** I would like to emphasize 2 points. First, we need to be testing our patients with metastatic CRC immediately at diagnosis and determining their *BRAF* V600 mutation and MSI/MMR status. Second, we need to act on the results of that testing by targeting BRAF in the first line whenever appropriate because sequencing does matter.

***Disclosures***

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## References

1. Elez E, Yoshino T, Shen L, et al; BREAKWATER Trial Investigators. Kopetz S; BREAKWATER Trial Investigators. Encorafenib, cetuximab, and mFOLFOX6 in BRAF-mutated colorectal cancer. *N Engl J Med.* 2025;392(24):2425-2437.
2. Kopetz S, Wasan HS, Yoshino T, et al. BREAKWATER: Primary analysis of first-line (1L) encorafenib + cetuximab (EC) + FOLFIRI in BRAF V600E-mutant metastatic colorectal cancer (mCRC) [ASCO GI abstract 13] *J Clin Oncol.* 2026;44(suppl 2).
3. Kopetz S, Yoshino T, Van Cutsem E, et al. BREAKWATER: analysis of first-line encorafenib + cetuximab + chemotherapy in BRAF V600E-mutant metastatic colorectal cancer [ASCO GI abstract 16]. *J Clin Oncol.* 2025;43(suppl 4).