News Release

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# European Commission Approves Erbitux® (cetuximab) in Combination with Encorafenib and FOLFOX for First-Line Treatment of Metastatic Colorectal Cancer with BRAF V600E Mutation

- **ERBITUX in combination with encorafenib and FOLFOX is the first and only approved targeted regimen for the first-line treatment of adult patients with BRAF V600E-mutant mCRC**
- **The approval is based on the pivotal Phase 3 BREAKWATER trial, which demonstrated statistically significant and clinically meaningful improvements in both progression-free survival (PFS) and overall survival (OS) compared to standard chemotherapy with or without bevacizumab**
- **ERBITUX confirms its status as the pioneering anti-EGFR therapy in mCRC, now approved across different patient populations and multiple lines of therapy**

DARMSTADT, Germany, July 14, 2026 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced that the European Commission (EC) approved an update to the Erbitux (cetuximab) EU label on June 26, 2026. Erbitux is now indicated in combination with encorafenib for patients with BRAF V600E-mutant metastatic colorectal cancer (mCRC) — both in first-line treatment in combination with FOLFOX (BREAKWATER regimen) and for patients who have received prior systemic therapy (BEACON regimen).

The first-line approval is based on results from the Phase 3 BREAKWATER trial, which showed that the cetuximab–encorafenib–FOLFOX combination delivered statistically significant and clinically meaningful improvements in the dual primary endpoints of objective response rate (ORR) and PFS, as well as a significant overall survival benefit — reducing the risk of death by 51% versus chemotherapy with or without bevacizumab.

”The approval of Erbitux in combination with encorafenib and FOLFOX marks an important milestone for patients with BRAF V600E-mutant mCRC who can now benefit from a first targeted treatment option in the first-line setting,” said Matthias Wernicke, Head of Global Therapeutic Area Specialty Care, in the healthcare business sector of Merck KGaA, Darmstadt, Germany. “BRAF V600E-mutant mCRC is associated with a historically poor prognosis and limited effective options. This approval reinforces Erbitux as the backbone of anti-EGFR therapy in colorectal cancer — and reflects our ongoing commitment to addressing unmet needs for patients across the full treatment continuum.”

BREAKWATER (NCT04607421) is a Phase 3, randomized, active-controlled, open-label, multicenter trial evaluating encorafenib in combination with cetuximab and FOLFOX in participants with previously untreated BRAF V600E-mutant mCRC. The trial was conducted by Pfizer, in collaboration with Merck KGaA, Darmstadt, Germany, and Ono Pharmaceutical. The combination of cetuximab, encorafenib and FOLFOX received accelerated FDA approval in December 2024 for treatment-naïve patients based on ORR data, and full FDA approval in February 2026 based on PFS and OS data — with the indication expanded to include fluorouracil-based chemotherapy (FOLFOX or FOLFIRI).

The BREAKWATER regimen demonstrated statistically significant and clinically meaningful improvements across all key endpoints versus standard-of-care chemotherapy (FOLFOX/FOLFOXIRI/CAPOX with or without bevacizumab).[1,2] Median PFS was 12.8 months versus 7.1 months (HR 0.53; 95% CI: 0.41–0.68; P<0.001), representing a 47% reduction in the risk of progression or death. Overall survival was likewise significantly improved, with a median OS of 30.3 months versus 15.1 months (HR 0.49; 95% CI: 0.38–0.63; P<0.001) — a 51% reduction in the risk of death, more than doubling median overall survival compared to

standard care. Confirmed ORR was 65.7% (95% CI: 59.4–71.4) in the BREAKWATER arm versus 37.4% (95% CI: 31.6–43.7) in the control arm. Safety profiles were consistent with those previously established for each individual agent; serious adverse events occurred in 46.1% versus 38.9% in the standard-care arm. The cetuximab–encorafenib–FOLFOX regimen has been endorsed as first-line standard of care by the April 2026 ESMO Clinical Practice Guidelines (Recommendation Grade I, A) for patients with metastatic colorectal cancer harboring the BRAF V600E mutation.[3]

While the BREAKWATER regimen redefines first-line therapy, the Phase 3 BEACON CRC trial confirmed Erbitux as a standard of care in second-line and beyond. The combination of Erbitux and encorafenib — also approved by the EC on June 26, 2026 for patients with BRAF V600E-mutant mCRC who have received prior systemic therapy — significantly improved OS versus the irinotecan-based control (median 9.3 vs. 5.9 months; HR 0.61; 95% CI: 0.48–0.77; p<0.0001), reducing the risk of death by 39%.[4,5] This regimen maintains quality of life with no increase in Grade ≥3 adverse events versus standard chemotherapy.

Erbitux is the first and only anti-EGFR therapy approved for both RAS wild-type and BRAF V600E-mutant mCRC patients — supporting patients throughout their treatment journey and across multiple lines of therapy.

Colorectal cancer remains a major global health challenge. It is the third most commonly diagnosed cancer worldwide and the second leading cause of cancer-related deaths, with 1.92 million new cases and approximately 900,000 deaths recorded in 2022 alone.[6] Projections indicate cases will increase by more than 85% and mortality will double in coming decades. Of patients presenting with metastatic disease — approximately 20% at diagnosis — 5-year survival remains at only 16.2%.

BRAF V600E mutations occur in approximately 8–12% of patients with mCRC and are associated with a particularly poor prognosis, with mortality risk more than double that of patients without the mutation. Extending the indication of Erbitux to this patient population represents a meaningful step toward more personalized and effective treatment — addressing a significant and clinically important unmet need.

With this dual approval — first-line (BREAKWATER) and second-line (BEACON) — Erbitux is now established as the pioneering anti-EGFR backbone across the mCRC treatment continuum. This milestone underscores Merck KGaA, Darmstadt, Germany's commitment to driving innovation in oncology and improving outcomes for patients with difficult-to-treat cancers.

**Local HCP Declaration**
Pierre Fabre, which holds the commercialization rights for BRAFTOVI (encorafenib) in Europe, submitted the BREAKWATER data to European Medical Agency (EMA) and received EC approval on June 22,2026. The BEACON regimen was already approved under BRAFTOVI since June 2020.

**About BREAKWATER Study**
BREAKWATER is a Phase 3, randomized, open-label, multicenter trial , whose findings support a targeted, first-line approach for patients with BRAF V600E-mutant mCRC.[2] The combination of ERBITUX, encorafenib, and the FOLFOX regimen significantly improved outcomes versus standard of care, with a 47% reduction in the risk of progression or death (HR 0.53) and a 51% reduction in the risk of death (HR 0.49). The data also show a meaningful increase in the ORR and a median OS of over 30 months in the experimental arm, underscoring the value of combined inhibition of BRAF and EGFR pathways in this poor-prognosis population and suggesting this treatment strategy as a new first-line standard of care.

**About BEACON Study**
BEACON CRC is a randomised, open-label, global Phase 3 trial evaluating the efficacy and safety of ERBITUX in combination with encorafenib ± binimetinib in patients with BRAF V600E-mutant mCRC whose disease has progressed after one or two prior regimens. BEACON CRC is the first Phase 3 trial designed to test a BRAF combination targeted therapy in BRAF V600E-mutant mCRC.

The data showed that ERBITUX in combination with encorafenib significantly improved OS in patients with BRAF V600E-mutant mCRC (median 9.3 months vs 5.9 months; HR: 0.61; 95% CI: 0.48–0.77; $p<0.0001$) and reduced the risk of death by 39%, compared with the ERBITUX plus irinotecan-containing regimen (control) arm. Data also showed that, besides improving OS, ERBITUX-encorafenib resulted in no worsening in quality of life or increase in grade 3 AEs versus irinotecan-based chemotherapy–cetuximab.[4,5]

**About Cetuximab (ERBITUX®)**
Cetuximab is an IgG1 monoclonal antibody targeting the epidermal growth factor receptor (EGFR). As a monoclonal antibody, the mode of action of Cetuximab is distinct from standard non-selective chemotherapy treatments in that it specifically targets and binds to the EGFR. This binding inhibits the activation of the receptor and the subsequent signal-transduction pathway, which results in reducing both the invasion of normal tissues by tumor cells and the spread of tumors to new sites. It is also believed to inhibit the ability of tumor cells to repair the damage caused by chemotherapy and radiotherapy and to inhibit the formation of new blood vessels inside tumors, which appears to lead to an overall suppression of tumor growth. Based on in vitro evidence, Cetuximab also targets cytotoxic immune effector cells towards EGFR-expressing tumor cells (antibody-dependent cell-mediated cytotoxicity [ADCC]).

Cetuximab has already obtained market authorization in over 100 countries worldwide for the treatment of RAS wild-type metastatic colorectal cancer and for the treatment of squamous cell carcinoma of the head and neck. Merck KGaA, Darmstadt, Germany licensed the right to market ERBITUX (Cetuximab), a registered trademark of ImClone LLC, outside the U.S. and Canada from ImClone LLC, a wholly owned subsidiary of Eli Lilly and Company, in 1998.

**About Merck KGaA, Darmstadt, Germany**
Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across life science, healthcare and electronics. More than 62,000 employees work to make a positive difference to millions of people's lives every day by creating more joyful and sustainable ways to live. From providing products and services that accelerate drug development and manufacturing as well as discovering unique ways to treat the most challenging diseases to enabling the intelligence of devices – the company is everywhere. In 2025, Merck KGaA, Darmstadt, Germany, generated sales of € 21.1 billion in 65 countries.

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[2] Kopetz S, et al. Encorafenib, cetuximab and chemotherapy in BRAF-mutant colorectal cancer: a randomized phase 3 trial. *Nat Med.* 2025;31:901–908.
[3] Cremolini C, et al. on behalf of the ESMO Guidelines Committee. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2026. doi: https://doi.org/10.1016/j.annonc.2026.03.005.
[4] Kopetz S, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. *N Engl J Med.* 2019. PMID: 31566309.
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[6] World Health Organization. Colorectal cancer: Key facts. Accessed 14 July 2026. https://www.who.int/news-room/fact-sheets/detail/colorectal-cancer.