Real-world use of encorafenib + cetuximab (EC) in patients with *BRAF*^{V600E}-mutant metastatic colorectal cancer (mCRC): a pooled analysis of European observational studies

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Introduction

- Approximately 8–12% of patients with metastatic colorectal cancer (mCRC) have a *BRAF*^{V600E} mutation,[1] which is associated with limited response to conventional therapies and a poor prognosis.[2, 3]
- The European Society for Medical Oncology (ESMO) guidelines for mCRC recommend encorafenib + cetuximab (EC) after prior systemic therapy as standard of care for these patients.[4]
- While some real-world data from this rare patient population are available,[5-9] additional data would allow a better understanding of the disease and assist in improving patient care; in particular, combining data from several real-world studies would provide a large and centralised dataset from which robust conclusions could be drawn.

Methods

- This was a retrospective, longitudinal pooled analysis of five European real-world observational studies (BERING CRC [Austria/Germany/Switzerland]; B-REAL [France], CATAMARAN [the Netherlands], CONFIDENCE [Spain], Italian GONO Cohort [Italy]) conducted between 2020 and 2024.
- Data from all adults (aged ≥18 years) who received EC after prior systemic therapy for *BRAF*^{V600E}-mutant mCRC in each study were pooled.
- The data were collected from the date of EC initiation (with some data collected at initial CRC diagnosis) to the end of the observation period in each study (end of follow-up or death, whichever occurred first).
- Clinical and patient characteristics, treatments patterns and sequencing, *BRAF* testing, and effectiveness and safety of EC were evaluated.
- The study was conducted according to the Guidelines of Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, the European Union General Data Protection Regulation (EU GDPR), and any applicable national guidelines.
- Patient data were pseudonymised and, according to applicable regulations, patients were informed that their data would be reused.

Results

- The pooled analysis population was comprised of 709 patients (**Figure 1**), of whom 54.4% were female, 65.9% had a right-sided tumour, and 70.9% had synchronous disease at initial diagnosis (**Table 1**).

Figure 1. Patient flow.

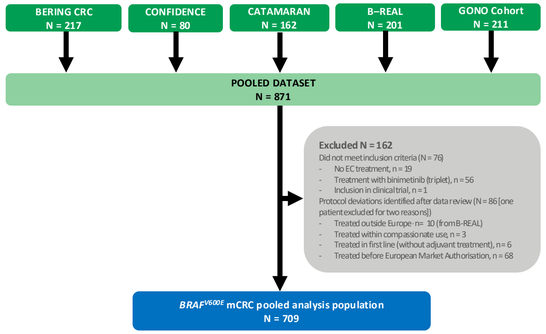


Table 1. Baseline demographic and clinical characteristics of the study cohort.

Characteristic	N = 709
Sex, n (%)	*n = 708*
Male	323 (45.6)
Female	385 (54.4)
Age at EC initiation, years[a]	
Median (range)	65 (26–90)
Age category at EC initiation, years	
≤60	247 (34.8)
60 to <70	223 (31.5)
≥70	239 (33.7)
ECOG PS at EC initiation, n (%)	*n = 637*
0–1	502 (78.8)
≥2	135 (21.2)
Primary tumour histology, n (%)	*n = 515*
Carcinoma[b]	505 (98.0)
Medullary carcinoma	1 (0.2)
Signet ring cell carcinoma	6 (1.2)
Other	3 (0.6)
Tumour sidedness, n (%)	*n = 707*
Right	466 (65.9)
Left	235 (33.2)
Both	6 (0.8)
Surgery for primary tumour, n (%)	
Yes	394 (55.6)
No	315 (44.4)
Time to metastases, n (%)	
Metachronous	206 (29.1)
Synchronous	503 (70.9)
Time from colorectal cancer diagnosis to EC initiation[c], months	
Median (range)	13.5 (1.1–177.1)
Time from mCRC diagnosis to EC initiation[d], months	*n = 547*
Median (range)	9.9 (0.1–122.3)
Number of metastatic sites at EC initiation[e], n (%)	*n = 708*
1	259 (36.6)
2	230 (32.5)
≥3	219 (30.9)
Metastatic site at EC initiation[f], n (%)	*n = 679*
Liver	425 (62.6)
Peritoneum	361 (53.2)
Lymph nodes	181 (26.7)
Lung	147 (21.6)
Brain	10 (1.5)
Other[g]	109 (16.1)

[a]Age at initiation of treatment calculated as: difference between date of treatment initiation and date of birth/365.25. [b]Adenocarcinoma + mucinous adenocarcinoma, + mucinous carcinoma. [c]Time from diagnosis calculated as: (date of treatment initiation – date of CRC diagnosis)/30.4375. [d]Time from metastatic diagnosis calculated as: (date of treatment initiation – date of mCRC diagnosis)/30.4375. [e]For BERING CRC, GONO, CONFIDENCE and B-REAL, the number of metastatic sites was derived based on raw metastases locations; for CATAMARAN, collected number was used. [f]Patients could report multiple sites. [g]Other sites included bone, ovary, skin, pancreas, adrenal gland, local recurrence, abdominal wall, and bladder. CRC, colorectal cancer; EC, encorafenib + cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRC, metastatic colorectal cancer.

- All patients in the study cohort had a *BRAF*^{V600E} mutation.
- The most commonly used tissue for *BRAF* testing (details available for 194 patients) was archival primary tumour (76.8%), with the most commonly used testing methods being next generation sequencing (61.1%), polymerase chain reaction (16.1%) and immunohistochemistry (7.0%).
- Microsatellite instability (MSI) testing was performed in 90.8% of patients prior to EC treatment initiation, and 9.2% of these patients had tumours that were MSI-high.
- The median time from mCRC diagnosis to EC initiation was 9.9 months.
- Most patients (66.1%) initiated EC as second-line therapy, with 21.3% receiving it as third-line and 7.9% as fourth-line or later; 4.7% of patients received EC after prior systemic treatment (early relapse during or after adjuvant treatment).

Effectiveness

- In the patients who could be assessed, the overall response rate (complete response + partial response) was 28.0% (**Table 2**).

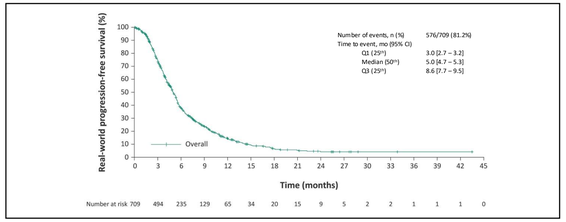
Table 2. Treatment activity of encorafenib + cetuximab.

Response, n (%)	Analysis population (N=709)
Complete response	7 (1.4)
Partial response	131 (26.6)
Stable disease	180 (36.5)
Progressive disease	157 (31.8)
Not evaluable	18 (3.7)
Missing[a]	216

[a]Tumor response not collected for 164 patients in CATAMARAN and 43 patients in BERING CRC. Data were missing for 9 patients (3 patients in B-REAL and 5 in GONO).

- Median progression-free survival (PFS) was 5.0 (95% confidence interval [CI] 4.7–5.3) months (**Figure 2**).
- PFS rates (95% CI) at 6, 12, and 24 months were 38.1% (34.4–41.9), 14.4% (11.7–17.5), and 4.2% (2.4–6.7), respectively.

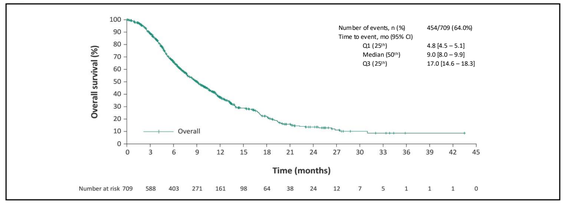
Figure 2. Progression-free survival.



CI, confidence interval; Q, quartile.

- At a median (95% CI) follow-up of 14.3 (13.2–16.3) months, median overall survival (OS) was 9.0 (95% CI 8.0–9.9) months (**Figure 3**).
- OS rates (95% CI) at 6, 12, and 24 months were 66.5% (62.7–70.0), 37.4% (33.3–41.4), and 13.6% (10.1–17.6), respectively.

Figure 3. Overall survival.



CI, confidence interval; Q, quartile.

Key findings on prognostic factors

- PFS
  - Good prognostic factors:
    - Prior primary tumour resection (hazard ratio [HR] 0.77, 95% CI 0.6–0.9)
    - Absence of liver metastases (HR 0.77, 95% CI 0.6–0.9)
    - ECOG PS <2 (HR 0.66, 95% CI 0.5–0.9)
  - Poor prognostic factors:
    - Synchronous metastases (HR 1.29, 95% CI 1.05–1.60)
    - ECOG PS ≥2 (HR 2.74, 95% CI 1.85–4.07)
    - ≥3 metastatic sites (HR=1.30, 95% CI 1.07–1.58)
- OS
  - Poor prognostic factors:
    - Synchronous metastases (HR 1.55; 95% CI 1.2–2.0)
    - ECOG PS ≥2 (HR 4.96, 95% CI 2.7–9.3)
    - ≥3 metastatic sites (HR 1.38, 95% CI 1.1–1.8)

Safety

- Safety data were collected from 547 patients; no new safety signals were observed.
- During EC treatment, 85.2% of patients had at least one adverse event (AE) of any grade.
- Most patients experienced AEs of low grade; 27.4% experiencing at least one AE that was grade ≥3.
- The most frequent AEs of any grade (in >10% of patients) were fatigue (21.9%), decreased appetite (19.7%), asthenia (19.0%), nausea (18.1%), anaemia (17.2%), arthralgia (12.6%), rash (12.6%), skin toxicity (11.9%) and vomiting (10.8%).
- The most frequent AEs of grade ≥3 were anaemia (2.9%), asthenia (2.7%), general physical health deterioration (1.5%), abdominal pain (1.5%), decreased appetite (1.3%), and intestinal obstruction, upper abdominal pain, nausea, vomiting and arthralgia (1.1% each).

Conclusions

- **This analysis of data from the largest available real-world cohort of European patients with *BRAF*^{V600E}-mutant mCRC underscores the aggressive nature of this type of disease, and the need for molecular testing at diagnosis to ensure an optimal treatment strategy.**
- **The effectiveness of EC in the study cohort was consistent with the efficacy results of the phase III BEACON CRC study.[10, 11]**
- **Prior primary tumour surgery and absence of liver metastases were associated with more favourable PFS outcomes in EC-treated patients; Presence of synchronous metastases, multiple metastatic sites and higher ECOG are linked with poorer prognoses for PFS and OS.**
- **No new safety signals were observed.**

Acknowledgments

- Study sponsored by Pierre Fabre Laboratories.
- All authors contributed to and approved this poster. Professional medical writing and editorial assistance was provided by Kate Palmer of Springer Healthₙ, funded by Pierre Fabre.

Conflicts of interest

- Advisory board or consultant role with Astra Zeneca, Bicara Therapeutics, BMS, GSK, Lilly, Merck, Mirati, MSD, Nordic Pharma, Roche, Pfizer, Pierre Fabre, Revolution Medicine, Rottapharm, Takeda, and Tempus. Invited speaker with compensation for Amgen, Bayer, Merck Serono, MSD, Pierre Fabre Servier, Takeda; Research grants by Amgen, Merck, Pierre Fabre, Roche, Seagen (Pfizer), Servier, and Tempus.

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Presented at the ESMO Gastrointestinal Cancers Congress 2025, 2 to 5 July 2025 in Barcelona, Spain.

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