Original article

# Encorafenib in Combination With Cetuximab After Systemic Therapy in Patients With $BRAF^{V600E}$ Mutant Metastatic Colorectal Cancer: German Health Technology Assessment-Driven Analyses From the BEACON CRC Study

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## Abstract

**The German Health Technology Assessment (HTA) helps the clinician by giving an additional evaluation of the clinical evidence of a substance in the light of a risk benefit assessment. In the HTA a "hint for a considerable additional benefit" of encorafenib + cetuximab compared to the ACT in BRAFV600E-mutant mCRC patients was granted. This treatment is considered the new standard of care for these patients.**

**Background:** Purpose of this analysis was to report data of the BEACON CRC trial used in the German Health Technology Assessment (HTA) and previously unpublished data focusing on the dual blockade (encorafenib + cetuximab) and appropriate comparative therapy (ACT/control: cetuximab + irinotecan-based chemotherapy) of patients with $BRAF^{V600E}$-mutant mCRC. **Materials and Methods:** Analyses included overall survival (OS) and time-to-event analyses of morbidity and safety. **Results:** A total of 220 patients received encorafenib + cetuximab and 221 patients ACT/control. Median OS was 9.3 (encorafenib + cetuximab) versus 5.9 months (ACT/control) (stratified hazard ratio ($HR_{strat}$): 0.61 [95% confidence interval: 0.48-0.77]). Time-to-response (TTR) showed a statistically significant advantage for encorafenib + cetuximab compared to ACT/control ($HR_{strat}$ [95% CI]: 10.46 [3.75; 29.15]; $P < .0001$). Median progression-free survival 2, ie, PFS after initiation of subsequent treatment after completion of study treatment, was 8.3 (dual blockade) versus 5.3 months (ACT/control), representing a statistically significant benefit for the dual blockade ($HR_{strat}$ [95% CI]: 0.62 [0.48; 0.78]; $P < .0001$). The statistically significant advantage for diarrhea (EORTC QLQ-C30) reached clinical relevance (LS-mean [95% CI]; *P*-value / Hedges'g [95% CI]: -12.61 [-17.75; -7.47]; $P < .0001$ / -0.53 [-0.74; -0.31]). The time-to-event analyses showed a statistically significant benefit for the dual blockade for serious

*Abbreviations:* ACT, Appropriate comparative therapy; AE, Adverse event; AESI, Adverse event of special interest; BIRC, Blinded Independent Central Review Committee; BOR, Best overall response; BRAF, V-raf murine sarcoma viral oncogene homolog B1; CEA, Carcinoembryonic antigen; CI, Confidence interval; CRC, Colorectal cancer; CRP, C-reactive protein CTCAE, Common Terminology Criteria for Adverse Events; DOR, Duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, Epidermal growth factor receptor; EMA, European Medicines Agency; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, European Quality of Life 5 Dimensions questionnaire; ESMO, European Society for Medical Oncology; FACT-C, Functional Assessment of Cancer Therapy-Colon cancer; FACT-G, Functional Assessment of Cancer Therapy-General; FOLFIRI, Folinic acid, fluorouracil, and irinotecan; G-BA, German Federal Joint Committee; $HR_{strat}$, Stratified hazard ratio; $HR_{unstrat}$, Unstratified hazard ratio; HTA, Health Technology Assessment; IQWiG, Institute for Quality and Efficiency in Health Care; IRI, Irinotecan; LS, Least square; MAPK, Mitogen-activated protein kinase; mCRC, Metastatic colorectal cancer; MMRM, Mixed model for repeated measures; mOS, Median overall survival; MSI, Microsatellite instability; n.c., Not calculable; n.r., Not reached; ORR, Overall response rate; OR, Odds ratio; OS, Overall survival; PCR, Polymerase chain reaction; PFS, Progression free survival; PFS2, Progression free survival 2; PGIC, Patient Global Impression of Change; PPE, Palmar-plantar erythrodysesthesia; PS, Performance status; REML, Restricted Maximum Likelihood; SAE, Serious adverse event; SOC, System organ class; TFST, Time to first subsequent therapy; TSST, Time to second subsequent therapy; TTR, Time to response; VAS, Visual analog scale.

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adverse events (AE), severe AEs and AEs leading to discontinuation. **Conclusion:** In the HTA, the German G-BA granted a "hint for a considerable additional benefit" of encorafenib + cetuximab compared to the ACT in BRAF$^{V600E}$-mutant mCRC patients. This treatment is considered the new standard of care for these patients.

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**Keywords:** BRAF$^{V600E}$-mutation, Irinotecan, Overall survival, Progression-free survival, Time-to-event

## Introduction

Colorectal cancer (CRC) is among the 3 leading cancer entities in Europe[1] showing an incidence of more than 500,000 new cases and causing approximately 250,000 deaths in both male and female patients in 2020.[2] Across all stages, the 5-year survival rate is approximately 60%.[3] However, approximately 20% of the patients present with distant metastases[4,5] at primary diagnosis, and during disease course, almost half of the patient population will develop metastatic disease (mCRC).[6] Once distant metastases are present, the median overall survival (mOS) is around 30 months[7] and less than 10% of the patients will survive the next 5 years[4]. In the current European Society for Medical Oncology (ESMO) guidelines, combination regimens with cytotoxic and targeted therapy are recommended for the treatment of patients with unresectable mCRC.[7] These include 5-fluoruracil plus folinic acid (FUFA), irinotecan (IRI), oxaliplatin (OX), anti-VEGF/VEGFR agents (bevacizumab, aflibercept, ramucirumab) and anti-EGFR antibodies (cetuximab and panitumumab).[7] More recently, immune checkpoint inhibitors have been added to the therapeutic arsenal in mCRC with high microsatellite instability (MSI-H).[8-10]

The BRAF$^{V600E}$-mutation, a constitutive activator of the BRAF-kinase and RAS/RAF/MEK/ERK signaling pathway triggering increased cell proliferation and survival,[11] is detected in approximately 8%-12% of mCRC-cases[12-14] and represents a marker of poor prognosis.[15-18] Due to incomplete epidermal growth factor receptor (EGFR)-mediated inhibition of MAPK signaling and potentially further mechanisms,[19,20] BRAF inhibitor monotherapy achieves low response rates in BRAF-mutant mCRC.[21-23] Preclinical and clinical studies suggested improved efficacy of treatment regimens that combine BRAF and EGFR inhibitors.[19,20,24,25]

In early clinical trials, the dual blockade combination of the EGFR antibody cetuximab with the BRAF inhibitor encorafenib has shown promising efficacy with respect to progression-free (PFS) and overall survival (OS).[26]

Core study results of the BEACON CRC study on efficacy (OS, overall response rate (ORR), best overall response (BOR), duration of response (DOR) and PFS) as well as safety have been previously published.[27,28] The present manuscript presents results from time-to-event analyses that have not been published so far. We focus on data of BRAF$^{V600E}$-mutant mCRC patients having received dual blockade treatment with encorafenib plus cetuximab compared to investigators' choice of either cetuximab combined with irinotecan (IRI) alone or cetuximab in combination with folinic acid plus fluorouracil plus IRI (FOLFIRI). FOLFIRI or irinotecan both in combination with cetuximab were regarded as being in line with appropriate comparative therapy (ACT) as defined by the German Federal Joint Committee (G-BA).

The time-to-event analyses have been used for the Benefit Assessment of Medicinal Products with New Active Ingredients (German Health Technology Assessment (HTA)) according to the requirements defined by the G-BA[29,30] and in accordance with the general methods defined by the German Institute for Quality and Efficiency in Health Care (IQWiG).[31]

## Materials and Methods

The BEACON CRC study was a global, multicenter, randomized, open-label, controlled phase III trial to evaluate the efficacy and safety of encorafenib plus cetuximab plus binimetinib (triple blockade; not subject of this paper since the registered combination does not include binimetinib) or dual blockade compared to the control treatment in patients with BRAF$^{V600E}$-mutant mCRC after 1 or 2 previous treatment regimens. Primary endpoints were ORR and OS regarding the triple blockade versus control. OS regarding the dual blockade versus control served as a key secondary endpoint, on which the study was powered. Based on a test hierarchy, the endpoints ORR, OS and PFS of both the triple blockade and the dual blockade were alpha-controlled. Details on the study design were reported earlier.[27,28]

All analyses presented here are based on the second data cutoff dated August 15th, 2019.

The following major endpoints relevant for the German HTA were analyzed: OS, PFS, DOR, patient-reported outcomes, and safety (AEs and serious adverse events (SAEs)).

### *Statistical Analysis*

Time-to-event endpoint and incidence analyses were performed on the intention-to-treat population and safety evaluations were done on the Safety Analysis Set. Details on the statistical analysis methods have been published previously.[27,28]

In addition to time-to-event analyses, patient-reported endpoints based on the European Quality of Life 5 Dimensions questionnaire (EQ-5D visual analog scale (VAS)), European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, and Functional Assessment of Cancer Therapy-Colon cancer (FACT-C) and -General (FACT-G) were also analyzed by means of Mixed effect Model Repeat Measurement (MMRM). Based on a random-intercept random-slope model, the adjusted means (Least Square [LS] mean estimator) for the changes from baseline both for each visit when assessments were done by treatment group and for the overall assessment period was calculated. The treatment difference was established based on adjusted mean difference (LS mean



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**Table 1** Baseline Characteristics of the Patients in the Dual Blockade-Group and the Control Group[28]

| Characteristic | Encorafenib/Cetuximab (n = 220) | Control (n = 221) |
|---|---|---|
| Sex, n (%) | | |
| Male | 114 (52) | 94 (43) |
| Female | 106 (48) | 127 (57) |
| Median age (range), years | 61 (30-91) | 60 (27-91) |
| ECOG PS, n (%) | | |
| 0 | 112 (51) | 108 (49) |
| 1 | 104 (47) | 113 (51) |
| 2 | 4 (2) | 0 (0) |
| Location of primary tumor, n (%) | | |
| Left colon (includes rectum) | 83 (38) | 68 (31) |
| Right colon | 110 (50) | 119 (54) |
| Others[a] | 27 (12) | 34 (15) |
| ≥ 3 organs involved, n (%) | 103 (47) | 98 (44) |
| Presence of liver metastases, n (%) | 134 (61) | 128 (58) |
| Primary tumor removed, n (%) | | |
| Completely resected | 123 (56) | 122 (55) |
| Partially resected or unresected | 97 (44) | 99 (45) |
| Prior lines of therapy, n (%) | | |
| 1 | 146 (66) | 145 (66) |
| 2[b] | 74 (34) | 76 (34) |
| Prior oxaliplatin, n (%) | 210 (95) | 201 (91) |
| MSI-H[c], n (%) | 19 (9) | 12 (5) |
| CEA baseline value > 5 mg/L, n (%) | 153 (70) | 178 (81) |
| CRP baseline value > 10 mg/L, n (%) | 79 (36) | 90 (41) |

Abbreviations: CEA = carcinoembryonic antigen; CRP = C-reactive protein; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MSI-H = microsatellite instability high (high).
[a] Other refers to patients with primary tumor in both left and right sides of colon and those with unknown location of primary tumor.
[b] One patient in the control arm received more than 2 prior lines of therapy.
[c] Based on assessment by polymerase chain reaction (PCR), 17% of patients were not evaluable or had missing MSI measurement by PCR.

estimator) and calculated by means of Restricted Maximum Likelihood (REML) analysis with unstructured covariance matrix. For the evaluation of clinical relevance of statistically significant treatment differences, Hedges'g were used. Treatment differences were deemed clinically relevant in case the Hedges'g 95% confidence interval (CI) was completely, ie, over its full range, above 0.2 or below -0.2, respectively.

The analyses presented here were performed according to the regulations of the German HTA methodology. As such, these data were not adjusted for multiple testing. Thus, the observation of significant *P*-values may also result from chance which should be considered when interpreting the individual data. Nevertheless, in the context of this report and in alignment with the regulations of the German HTA methodology, *P*-values <.05 are referred to as significant.

## Results

Between May 2017 and January 2019, a total of 665 patients were enrolled. 220 patients were randomized to the dual blockade, 221 patients to the control group. Baseline demographic and clinical characteristics were well balanced in both treatment arms (see Table 1).

Based on the pre-defined primary analysis (first data cutoff, Feb. 2019; median follow-up regarding OS 7.8 months), the study met its primary endpoints with ORR 26% (95% CI: 18-35) regarding the triple blockade versus 2% (95% CI: <1-7) in the control arm ($P < .001$) and median OS 9.0 versus 5.4 months, respectively (HR) [95% CI]: 0.52 [0.39; 0.70]; $P < .001$). Regarding the confirmatory analysis of the dual blockade versus control, ORR was 20% (95% CI: 13-29) versus 2% (95% CI: <1-7) ($P < .001$) and median OS was 8.4 versus 5.4 months, respectively (HR) [95% CI]: 0.60 [0.45; 0.79]; $P < .001$).[27]

These results were confirmed after a median follow-up of 12.8 months (second data cutoff, August 2019), with an OS of 9.3 months (95% CI: 8.0; 11.3) for the dual blockade and 5.9 months in the control arm (95% CI: 5.1; 7.1) (stratified hazard ratio ($HR_{strat}$) [95% CI]: 0.61 [0.48; 0.77]). Consistently, ORR in the dual blockade arm was 20% (95% CI: 15-25) versus 2% (95% CI: <1-5) in the control arm ($P < .001$) based on this update analysis.[28]

The median **time to response** (TTR) has not been established in either treatment arm since the response rate did not reach the 50% level. The event time analysis shows a statistically significant advantage for the dual blockade treatment compared to the control arm (stratified hazard ratio ($HR_{strat}$) [95% CI]: 10.46 [3.75; 29.15]; $P <$



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**Table 2** MMRM Analyses of the Patient Reported Outcome Assessments (Only Statistically Significant Results are Shown)

| Parameter | LS-Mean [95% CI] | *P*-value | Hedges'g [95% CI] |
|---|---|---|---|
| EORTC QLQ-C30 – functional scale | | | |
| Global health status | 3.92 [0.26; 7.57] | .036 | 0.23 [0.02; 0.44] |
| EORTC QLQ-C30 – symptom scales | | | |
| Diarrhea | -12.61 [-17.75; -7.47] | <.0001 | -0.53 [-0.74; -0.31] |
| Nausea/vomiting | -4.62 [-7.75; -1.48] | .004 | -0.31 [-0.52; -0.11] |
| Loss of appetite | -6.72 [-12.07; -1.38] | .014 | -0.27 [-0.48; -0.06] |
| Constipation | -5.68 [-10.08; -1.28] | .012 | -0.28 [-0.48; -0.07] |
| FACT-G | | | |
| Global health score | 3.78 [1.05; 6.50] | .007 | 0.29 [0.09; 0.50] |
| FACT-C | | | |
| Physical wellbeing | 1.62 [0.70; 2.54] | <.001 | 0.37 [0.16; 0.58] |

Abbreviations: CI = confidence interval; FACT-C = Functional Assessment of Cancer Therapy-Colon cancer; FACT-G = Functional Assessment of Cancer Therapy-General; LS = least square.

.0001). For the 43 patients in the dual blockade arm with a response, the median TTR was 1.5 months, for the 4 responding patients in the control arm median TTR was 2.0 months (descriptive analysis).

The median **progression-free survival 2** (PFS2, ie time between randomization and progression or death after initiation of a subsequent treatment line after completion of study treatment) was 8.3 months in the dual blockade arm and 5.3 months in the control arm with a statistically significant benefit for the dual blockade compared to the control ($HR_{strat}$ [95% CI]: 0.62 [0.48; 0.78]; $P < .0001$). Hence, the prolongation of the median PFS by 2.8 months with dual blockade was sustained in the median PFS2.

The overall MMRM analyses of the patient-reported outcome assessments showed statistically significant differences (all in favor of the dual blockade) for the key parameters of the EORTC QLQ-C30 (functional scale: global health status; symptom scales: diarrhea, nausea/vomiting, loss of appetite, constipation) and FACT-C (FACT-G: global health score; physical well-being) (LS-mean [95% CI]; *P*-value / Hedges'g [95% CI]) (see Table 2).

Only the EORTC QLQ-C30 symptom scale for diarrhea reached the level of clinical relevance (LS-mean [95% CI]; *P*-value / Hedges'g [95% CI]: -12.61 [-17.75; -7.47]; $P < .0001$ / -0.53 [-0.74; -0.31]).

Details on mortality and morbidity results of the dual blockade treatment versus the control group are shown in Table 3.

Statistically significant differences in favor of the dual blockade treatment were demonstrated with respect to frequency and time to onset of SAEs: median time to onset 12.0 months (dual blockade) versus 5.2 months (control) after treatment start, $HR_{unstrat}$ [95% CI]: 0.65 [ 0.47; 0.89]; $P = .0075$; for AEs leading to treatment discontinuation: median time to onset not calculable, $HR_{unstrat}$ [95% CI]: 0.36 [0.21; 0.63], $P = .0002$; as well as for severe AEs (grade 3 or higher): median time to onset 4.7 months (dual blockade) versus 1.4 months (control) after treatment start, $HR_{unstrat}$ [95% CI]: 0.47 [0.36; 0.62], $P < .0001$.

In the time-to-event analyses of all AEs (median time to onset 0.1 months (dual blockade) versus 0.1 months (control) after treatment start; $HR_{unstrat}$ [95% CI]: 0.93 [0.76; 1.13]; $P = .304$) and non-severe AEs (grade 1-2) (median time to onset not calculable; $HR_{unstrat}$ [95% CI]: 1.21 [0.88; 1.67]; $P = .2371$) there were no statistically significant differences between the treatment groups.

Considering frequent AEs, statistically significant differences in time-to-event analyses between the treatment arms in favor of the dual blockade group were found for a number of events. These included the gastrointestinal tract ($HR_{unstrat}$ [95% CI]: 0.64 [0.51; 0.80]; $P < .0001$; in particular diarrhea, nausea, vomiting, and stomatitis), skin and subcutaneous tissue ($HR_{unstrat}$ [95% CI]: 0.71 [0.57; 0.90]; $P = .0050$; in particular dermatitis acneiform, alopecia, and skin fissures) and blood count ($HR_{unstrat}$ [95% CI]: 0.41 [0.28; 0.61]; $P < .0001$; particularly neutropenia) and other, individual events (in particular hypokalemia, paronychia, pulmonary embolism).

There were statistically significant differences between the treatment arms to the disadvantage of the dual blockade treatment relating to the nervous system ($HR_{unstrat}$ [95% CI]: 2.05 [1.44; 2.92]; $P < .0001$; in particular headache), skeletal muscles/connective tissue/bones ($HR_{unstrat}$ [95% CI]: 2.09 [1.48; 2.96]; $P < .0001$; especially arthralgia, myalgia, pain in the extremities), overall benign and malign neoplasms (predominantly melanocytic nevi and papillomas of the skin) ($HR_{unstrat}$ [95% CI]: 9.03 [3.63; 22.50]; $P < .0001$), and overall eye disorders ($HR_{unstrat}$ [95% CI]: 2.93 [1.41; 6.09]; $P = .0025$).

For all other frequent AEs, there were no statistically significant differences between the treatment arms regarding the time-to-event analysis.

In addition, considering individual AEs that were of special interest (AESI), there was a statistically significant difference for myopathy to the disadvantage of the dual blockade (all myopathy events: median time to onset not calculable; $HR_{unstrat}$ [95% CI]: 4.84 [1.88; 12.48]; $P = .0003$; non-severe myopathy events: median time to onset not calculable; $HR_{unstrat}$ [95% CI]: 4.75 [1.84; 12.26]; $P = .0004$). Most of the events were not severe; severe myopathy only occurred in 1 case in the dual blockade arm (no case in the control arm); SAEs of myopathy did not occur.

There was a statistically significant benefit for the dual blockade treatment for palmar-plantar erythrodysesthesia (PPE): any PPE AE:



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**Table 3** Time-to-Event Analyses of the Dual Blockade Treatment Versus Control

| BEACON CRC | Dual Blockade Median Months [95% CI] | Control Treatment Median Months [95% CI] | Dual Blockade vs. Control $HR_{strat}$ [95% CI]; *P*-value |
|---|---|---|---|
| OS | 9.3 [8.0; 11.3] | 5.9 [5.1; 7.1] | 0.61 [0.48; 0.77]; <.0001 |
| DOR (BIRC) | 5.6 [4.1; 8.3] | 5.6 [2.6; n.c.] | 1.88 [0.40; 8.96]; .4266 |
| TTR (BIRC) | n.c. [n.c.; n.c.] | n.c. [n.c.; n.c.] | 10.46 [3.75; 29.15]; <.0001 |
| PFS (BIRC) | 4.3 [4.1; 5.5] | 1.5 [1.5; 1.9] | 0.44 [0.35; 0.55]; <.0001 |
| PFS2 | 8.3 [7.7; 9.8] | 5.3 [4.6; 6.2] | 0.62 [0.48; 0.78]; <.0001 |
| TFST | 5.6 [4.9; 6.6] | 3.0 [2.5; 3.5] | 0.61 [0.49; 0.75]; <.0001 |
| TSST | 8.8 [8.0; 10.3] | 5.1 [4.6; 5.8] | 0.60 [0.48; 0.75]; <.0001 |

Abbreviations: BIRC = Blinded Independent Central Review Committee; CI = confidence interval; DOR = duration of response; $HR_{strat}$ = stratified hazard ratio; n.c. = not calculable; OS = overall survival; PFS = progression free survival, ie, time between randomization and progression or death during study treatment; PFS2 = progression free survival 2, ie, time between randomization and progression or death after initiation of a subsequent treatment line after completion of study treatment; TFST = time to first subsequent therapy; TSST = time to second subsequent therapy; TTR = time to response.

median time to onset not calculable; $HR_{unstrat}$ [95% CI]: 0.45 [0.20; 1.00]; $P = .0439$; non-severe PPE events: median time to onset not calculable; $HR_{unstrat}$ [95% CI]: 0.40 [0.17; 0.90]; $P = .0233$. Most of the events were non-severe; a severe event only occurred in 1 case in the dual blockade arm (no case in the control arm). There were no reports about SAEs of a PPE.

For further details, see Table 4.

## Discussion

Into the BEACON CRC study, systemically pretreated patients with $BRAF^{V600E}$-mutant mCRC were enrolled. Evidence with regard to the treatment of this patient population was limited before BEACON, which represents the first randomized phase III trial in this setting. Therefore, the currently available German S3 guidelines only recommend an early initiation of intensified chemotherapy for patients with $BRAF^{V600E}$ mutation due to their poor prognosis or – based on very limited data at the time of guideline development – the inclusion into a clinical study.[12] From the S3 guidelines, no clear recommendation can be derived for subsequent therapies, leaving the specific treatment choice dependent on individual factors such as general health condition, comorbidities, tumor characteristics and the type and number of previous therapies. At European level, the current ESMO pocket guidelines on metastatic colorectal cancer from September 2021 already recommend the combination of encorafenib and cetuximab in pre-treated BRAF-mutant patients.

This article focuses on previously unpublished data from the BEACON CRC study and the comparison of the results from the dual blockade arm consisting of encorafenib plus cetuximab versus investigators' choice of FOLFIRI plus cetuximab or IRI plus cetuximab.

From the updated analyses based on the cut-off from August 2019,[28] the authors of the BEACON study concluded that the dual blockade treatment offers a benefit regarding mortality and morbidity with improved **OS** (dual blockade median [95% CI]: 9.3 months [8.0; 11.3]; control median [95% CI]: 5.9 months [5.1; 7.1]; $P < .0001$), **ORR** (dual blockade median [95% CI]: 19.5% [15; 25]; control median [95% CI]: 1.8% [<1; 5]; $P < .0001$), and **PFS** (dual blockade median [95% CI]: 4.3 months [4.1; 5.5]; control median [95% CI]: 1.5 months [1.5; 1.9]; $P < .0001$) compared to the chemotherapy-based control.[28]

On the basis of this clinical trial, encorafenib in combination with cetuximab was granted approval for use in $BRAF^{V600E}$-mutant mCRC upon systemic therapy by the European Medicines Agency (EMA) and Swissmedic (June and December 2020, respectively).[32,33] In addition, the BEACON CRC study also constituted the basis for the German HTA of encorafenib performed by the G-BA and the IQWiG. Based on the mortality results, the G-BA concluded that taking into account the poor survival prognosis for patients with BRAF-mutant tumors as well as their advanced stage of disease and treatment, the extent of the achieved prolongation in OS is regarded as a significant improvement in therapeutic benefit. Accordingly, for the endpoint category mortality, a hint for a considerable additional benefit of encorafenib in combination with cetuximab compared to the final ACT as defined by the G-BA, ie, including cetuximab plus IRI or FOLFIRI, was acknowledged and attributed by the G-BA.[34]

For the evaluation of the endpoint category "morbidity," PFS (which relates to the "morbidity" component "disease progression"), symptomatology (symptom scales of the EORTC QLQ-C30, Patient Global Impression of Change (PGIC)), and health status (using EQ-5D VAS) were reviewed. The G-BA stated that PFS was assessed solely by means of radiologic procedures and determined according to the RECIST criteria, ie, on the basis of asymptomatic, not directly patient-relevant findings without primarily considering clinical symptoms.

The G-BA agreed that the morbidity endpoints showed an advantage for the treatment with the dual blockade based on a relevantly lower burden of the symptom "diarrhea[34]."

In terms of safety and tolerability, time-to-event analyses of AEs were used by the G-BA in its assessments. Statistically significant differences in favor of the dual blockade were acknowledged for serious AEs, AEs that led to treatment discontinuation and for AEs in the system organ class (SOC) "Skin and subcutaneous tissue diseases." In addition, for severe AEs (Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3) an advantage for the dual blockade was stated.[34] Accordingly, the G-BA concluded that the results on side effects showed exclusively positive effects for the dual blockade.[34]



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**Table 4** Overview of Adverse Events (Only Statistically Significant Results are Shown)

| BEACON CRC | Dual Blockade Median Time to Onset (Months) [95% CI] % Patients | Control Median Time to Onset (Months) [95% CI] % Patients | Dual Blockade vs. Control $HR_{unstrat}$ [95% CI] *P*-value |
|---|---|---|---|
| AEs | | | |
| SAE | 12.0 [5.9; n.c.] 39.8 | 5.2 [3.2; n.c.] 39.9 | **0.65 [0.47; 0.89] .008** |
| AE grade ≥ 3-4 | 4.7 [3.9; 6.4] 57.4 | 1.4 [1.1; 2.1] 64.2 | **0.47 [0.36; 0.62] <.001** |
| AE leading to treatment discontinuation | n.r. [17.5; n.c.] 12.0 | n.r. [8.1; n.c.] 17.1 | **0.36 [0.21; 0.63] .0002** |
| AESI | | | |
| AESI: Myopathy | n.r. [15.9; n.r.] 16.7 | n.r. [n.r.; n.r.] 2.6 | ***4.84 [1.88; 12.48] .0003*** |
| AESI: PPE | n.r. [n.r.; n.r.] 5.1 | n.r. [n.r.; n.r.] 7.8 | **0.45 [0.20; 1.00] .0439** |
| Frequent SAEs Gastrointestinal | 22.8 [22.8; n.r.] 16.7 | n.r. [n.r.; n.r.] 18.1 | **0.58 [0.36; 0.93] .0233** |
| Frequent severe AEs Gastrointestinal | 22.8 [22.8; n.c.] 19.4 | 9.4 [4.4; n.c.] 26.9 | **0.40 [0.26; 0.61] <.0001** |
| Selected AEs (ie most frequent in the respective SOC) | | | |
| *SOC Gastrointestinal disorders* | *0.7 [0.5; 1,1] 81.5* | *0.2 [0.1; 0.3] 82.9* | **0.64 [0.51; 0.80] <.0001** |
| Diarrhea | 10.3 [6.4; 18.8] 38.4 | 2.1 [1.1; n.r.] 48.7 | **0.45 [0.33; 0.62] <.0001** |
| *SOC Skin and subcutaneous tissue disorders* | *0.9 [0.7; 1.2] 75.9* | *0.5 [0.4; 0.6] 73.1* | **0.71 [0.57; 0.90] .0050** |
| Dermatitis acneiform | n.c. [13.0; n.c.] 30.1 | n.c. [2.8; n.c.] 39.9 | **0.56 [0.40; 0.78] .0006** |
| *SOC Blood and lymphatic system disorders* | *n.c. [12.0; n.c.] 23.1* | *n.c. [4.1; n.c.] 34.7* | **0.41 [0.28; 0.61] <.0001** |
| Neutropenia | n.c. [n.c.; n.c.] 1.4 | n.c. [n.c.; n.c.] 18.7 | **0.05 [0.01; 0.15] <.0001** |
| SOC Nervous system disorders | 7.4 [2.6; n.c.] 49.1 | 9.9 [7.7; n.c.] 23.3 | ***2.05 [1.44; 2.92] <.0001*** |
| *Headache* | n.c. [n.c.; n.c.] 19.9 | n.c. [n.c.; n.c.] 2.6 | ***7.27 [2.87; 18.42] <.0001*** |
| *SOC Musculoskeletal and connective tissue disorders* | *4.2[2,8; 5,2] 56.5* | *NE [4.9; n.c.] 23.3* | ***2.09 [1.48; 2.96]; <.0001*** |
| *Arthralgia* | n.c. [n.c.; n.c.] 22.7 | n.c. [13.5; n.c.] 1.6 | ***10.16 [3.15; 32.79] <.0001*** |
| *SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps)* | n.c. [10.3; n.c.] 29.6 | n.c. [n.c.; n.c.] 2.6 | ***9.03 [3.63; 22.50] <.0001*** |
| *SOC Eye disorders* | *n.c. [15.6; n.c.] 19.9* | *n.c. [11.6; n.c.] 4.7* | ***2.93 [1.41; 6.09] .0025*** |

Statistically significant differences in favor of the dual blockade group are highlighted in bold font and in favor of the control group in bold-italic font, respectively.
Abbreviations: AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; $HR_{unstrat}$ = unstratified hazard ratio; n.c. = not calculable; n.r. = not reached; PPE = palmar-plantar erythrodysesthesia; SAE = serious adverse event; SOC = system organ class.

In summary, the G-BA saw a hint for a considerable additional benefit for $BRAF^{V600E}$-mutant mCRC patients who have received prior systemic therapy for the treatment with encorafenib in combination with cetuximab versus IRI + cetuximab or FOLFIRI + cetuximab.[34] The time-to-event analysis performed in the context of the German HTA added value assessment was based on the appropriate comparator as defined by the German HTA authority and thus formed the basis for subsequent price negotiations specifically in Germany.

## Conclusions

Prior to the approval of encorafenib in combination with cetuximab, an established standard treatment was not available for the assessed indication. This chemotherapy-free dual blockade treatment is considered the new standard of care for patients with $BRAF^{V600E}$-mutant mCRC after systemic pretreatment.[28] The pivotal BEACON CRC study is the first and up to now the only phase III study in this poor prognostic patient population. The HTA assessment by the German G-BA on the dual blockade stated



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a statistically significant and clinically relevant benefit compared to the control treatment, in particular regarding the prolongation of overall survival as well as with regard to the side effect "diarrhea," severe AEs (grade 3 or higher), SAEs, and AEs that lead to treatment discontinuation. Accordingly, the G-BA granted encorafenib in combination with cetuximab a "hint for a considerable additional benefit" in its German HTA-resolution compared to the final ACT, ie, including cetuximab in combination with IRI alone or with FOLFIRI. This additional benefit applies to the overall population of patients in the indication.

The analyses performed in the context of the German HTA might form a relevant basis for HTA decision making in other regions as well as for individual treatment decisions by physicians and patients.

### *Clinical Practice Points*

- For BRAF V600E mutant metastatic colorectal cancer, encorafenib plus cetuximab is considered the standard of care after any systemic treatment.
- Within the phase-III BEACON trial, median OS was significantly longer reaching 9.3 (encorafenib + cetuximab) versus 5.9 months (ACT/control) (stratified hazard ratio (HRstrat): 0.61 [95% confidence interval: 0.48-0.77]).
- The German Health Technology Assessment (HTA) evaluated the BEACON trial with respect to a risk benefit assessment and granted a "hint for a considerable additional benefit," giving additional reliability of the use of encorafenib plus cetuximab within this patient group.

## Compliance With Ethics Guidelines – Ethics Approval and Consent to Participate

The BEACON CRC study was conducted in accordance with the requirements of each country's regulatory authorities as well as the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Council for Harmonisation. All patients who participated in the trial provided written informed consent. This trial was approved by the institutional review board or independent ethics committee at each center.

The trial was registered at clinicaltrials.gov under the registration number NCT02928224.

## Availability of data and materials

The anonymized data from the clinical study is archived according to the ICH-GCP requirements at Pierre Fabre Pharma in Boulogne-Billancourt, France, and will not be made public as the data is confidential.

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Supplemental Figure S1: Disclaimer of warranties and limitation of liability for Supplemental Figure S1 apply.

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2022.04.002.

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