Original Study

Adverse Events Associated with Encorafenib Plus Cetuximab in Patients with BRAFV600E-mutant Metastatic Colorectal Cancer: An in-depth Analysis of the BEACON CRC Study

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Abstract

Encorafenib+cetuximab is approved for metastatic colorectal cancer (CRC) with a mutated *BRAF*^{V600E} gene. We examined the adverse events (AEs) of this therapy seen during the phase 3 BEACON CRC study. In 220 patients, encorafenib+cetuximab was well tolerated, with dermatological toxicities the most common AE. Most AEs were more common in women, mild-to-moderate in severity, occurred early and resolved rapidly.

Background: The BRAF inhibitor encorafenib in combination with cetuximab was recently approved for patients with *BRAF*^{V600E}-mutated (*BRAF*^{V600E}mut) metastatic colorectal cancer (mCRC). Approval was based on positive results from the phase 3 BEACON CRC study in *BRAF*^{V600E}mut mCRC patients who had progressed after 1–2 previous regimens. This analysis provides a detailed examination of the adverse events (AEs) of interest (AEIs) with encorafenib+cetuximab in the BEACON study to aid gastrointestinal oncologists, given the limited experience with this combination. **Materials and Methods:** AEIs, including dermatological AEs, arthralgia/myalgia, nausea/vomiting, diarrhea, abdominal pain, fatigue/asthenia and nephrotoxicity, were examined in the doublet therapy group. Clinical characteristics associated with these AEs, AE grade, time to onset and time to resolution were also studied. **Results:** Safety analysis included 216/220 patients randomized to doublet therapy. The most commonly occurring AEI was dermatological toxicity (75.5%), followed by arthralgia/myalgia (56.0%) and fatigue/asthenia (56.0%). Other than nephrotoxicity (7 patients; 5/7 with Grade 3 or 4), most AEs were Grade 1 or 2. Most AEs were more common in women than men (nausea/vomiting, diarrhea, abdominal pain, dermatological AEs, and arthralgia/myalgia). Nausea/vomiting, abdominal pain and fatigue/asthenia were more common in patients aged ≥70 years. Most AEs developed early, within the first 1–2 months of treatment, and resolved within 1–2 weeks. In addition, survival outcomes were better in patients experiencing arthralgia/myalgia or dermatological toxicities. **Conclusion:** This analysis indicated that, except for rare cases of nephrotoxicity, encorafenib+cetuximab is well tolerated in most patients, with most AEIs being mild-to-moderate in severity, occurring early and resolving rapidly.**Clinical Trial Registration:** the BEACON study (ClinicalTrials.gov, NCT02928224; EudraCT, 2015-005805-35)

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Introduction

BRAF mutations are detected in 8–12% of colorectal cancers (CRCs),[1-5] although this proportion varies from ~5–21%.[6-9] Ninety-five percent of CRCs with *BRAF* mutations harbor the V600E mutation (*BRAF*^{V600E}mut), a marker for poor outcomes, including greater risk of recurrence after surgery, high rate of peritoneal metastasis and reduced survival.[10,11]

BRAF inhibitors have been used widely for treating *BRAF*-mutated metastatic melanoma but have only recently gained approval in *BRAF*^{V600E}mut metastatic CRC (mCRC); experience with these agents among gastrointestinal oncologists is limited. The BRAF inhibitor encorafenib was approved in 2020 in combination with cetuximab in patients with *BRAF*^{V600E}mut mCRC after prior systemic treatment by the European Medicines Agency, US Food and Drug Administration and other regula-

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tory agencies.[12-14] This approval was based on the phase 3 BEACON CRC study data, which showed that either triplet therapy with encorafenib+binimetinib+cetuximab or doublet therapy with encorafenib+cetuximab significantly prolonged survival and improved response rates compared with standard chemotherapy plus cetuximab.[15] Efficacy outcomes were not significantly better with the triplet versus doublet regimen, and the overall toxicity was higher.[9] Therefore, the approved regimen for treatment of *BRAF*^{V600E}mut mCRC beyond first line is encorafenib+cetuximab in most regions globally. Indeed, the combination is recommended in the European Society for Medical Oncology (ESMO) guidelines for BRAF^{V600E}mut, pre-treated mCRC.[16]

Here, we conducted a detailed analysis of adverse events (AEs) of interest (AEIs), regardless of causality, occurring in patients who received encorafenib+cetuximab in the BEACON study, with the aim of providing physicians and their support teams with improved knowledge to assist the clinical management of patients with *BRAF*^{V600E}mut mCRC.

Materials and Methods

Study Design

The BEACON study (ClinicalTrials.gov: NCT02928224; EudraCT: 2015-005805-35) has been described previously.[15] Briefly, this was a multicenter, randomized, open-label, phase 3 study in patients with *BRAF*^{V600E}mut mCRC who had progressed after one or two previous regimens. The BEACON study was carried out in accordance with the Declaration of Helsinki. Ethics approval was obtained by the institutional review board or independent ethics committees at the appropriate centers. Written informed consent was provided by all patients. Patients were randomized in a 1:1:1 ratio to one of three groups: triplet therapy with encorafenib+binimetinib+cetuximab; doublet therapy with encorafenib+cetuximab; or control, where patients received investigator's choice of either cetuximab+irinotecan or cetuximab+FOLFIRI (folinic acid, fluorouracil and irinotecan). Patients in the doublet therapy group received oral encorafenib (300 mg/day) and cetuximab (400 mg/m^2 initial dose, then 250 mg/m^2 weekly) until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy or death.

Outcomes

The current analysis examines, in detail, the incidence and prevalence of the most frequent AEs and unusual AEIs in the group receiving doublet therapy with encorafenib+cetuximab, regardless of causality. AEIs, defined as uncommon/unique AEs or commonly occurring AEs with this combination, included dermatological AEs, arthralgia/myalgia, nausea/vomiting, diarrhea, abdominal pain, fatigue/asthenia and nephrotoxicity. In this analysis, AEs were grouped according to Medical Dictionary for Regulatory Activities (MedDRA)-derived terms (version 21.0; See Supplementary Table S1 for definitions of the AEs).

The following parameters were examined: grade of AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03; incidence of AEs (number of patients affected) by age (<70 vs ≥70 years) and sex (male vs female); percentage of patients who required 0, 1 or >1 reduction in the dose of encorafenib or cetuximab, or treatment interruption; time course and time to onset of AEs of any Grade and AEs of Grade ≥3; and time to resolution of AEI. The definitions describing dose interruptions or reductions are presented in the Supplementary Methods.

Statistical Analysis

The incidence of AEIs was summarized using descriptive statistics (number of individuals and percentages). Kaplan-Meier curves were constructed for the time to onset and time to resolution of each AEI. Not having an AE was classified as censored, with the censor time corresponding to the earliest of the following dates: end of treatment + 30 days; database cut-off date (August 2019); start date of a new anticancer therapy; last contact date; or death. The time to onset in all AE groups was analyzed for all Grades together and Grade 3 or 4 AEs specifically. If the AE was not resolved it was censored, and the end date was imputed as the earliest of the following: cut-off date; last contact date; date of death; or end of treatment date + 30 days. Median and 95% confidence intervals (CIs) were calculated for time to onset and time to resolution. The correlation between the incidence of AEs (AEIs, and any AE ≥Grade 3 from each AEI group) and efficacy outcomes (overall survival [OS] and progression-free survival [PFS]) in patients receiving doublet therapy was assessed. The log rank test was used to compare OS and PFS between patients with at least one AE with those without AEs, both in the encorafenib+cetuximab and the control arm. The differences between the overall incidence of AEs ≥Grade 3 or the incidence of AE ≥Grade 3 from each AEI group and age or sex were assessed using the Chi-squared test when applicable. Descriptive analyses were used to summarize the incidence of dose interruption and dose reduction by age or sex, and the median time to onset of any AE by age or sex.

Results

Patient Demographics

Overall, 220 patients were randomized to doublet therapy (114 males and 106 females; median [range] age 61 [30–91] years). Patients in this group had an Eastern Cooperative Oncology Group performance status of 0 (n=112), 1 (n=104) or 2 (n=4). Four patients did not receive the allocated treatment, so the safety analysis set comprised 216 patients. The median duration of follow up (from treatment start to data cut-off) for the current safety analysis was 14.9 months.

Overall Incidence of AEs

In the most-recent BEACON CRC study update, AEs were reported in 212/216 patients receiving encorafenib+cetuximab (98.1%), and 124 patients (57.4%) developed a Grade ≥3 AE.[9] The most common AEs (any grade) reported in the main trial were abnormal creatinine levels (n=116; 53.7%), reduced hemoglobin (n=85; 39.4%), diarrhea (n=83; 38.4%), nausea (n=82; 38.0%), fatigue only (n=72; 33.3%), decreased appetite (n=67; 31.0%), and acneiform dermatitis (n=65; 30.1%).[9]

Among the AEIs, as defined and grouped for the current analysis and based on the number of events, dermatological AEs were the most common, with 439 events reported in 163 patients (75.5%).

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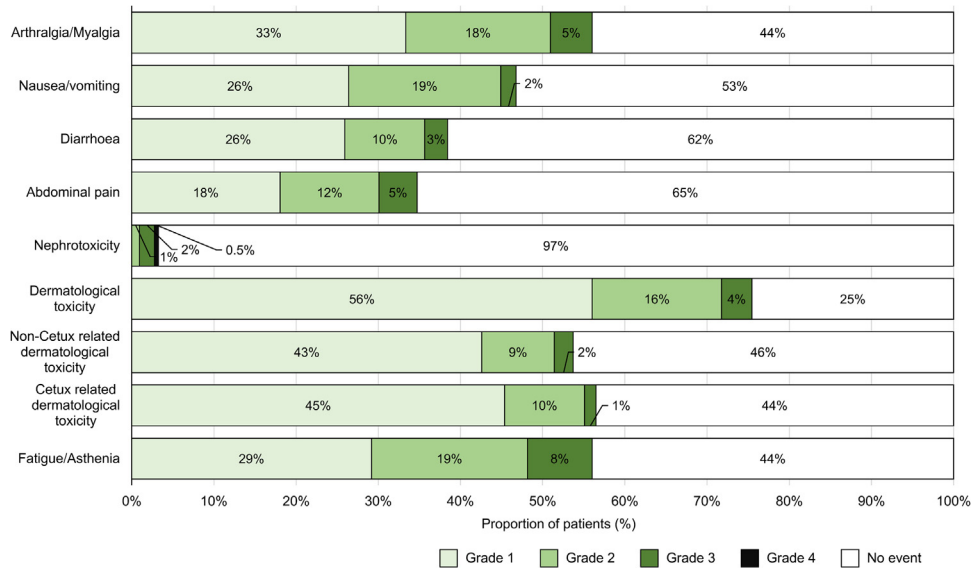
Table 1 Overall Incidence of Adverse Events (AEs) of any Grade and Incidence by Age and Sex

AEs, n (%)		By Sex			By Age Group		
	Overall (n=216)	Males (n=112)	Females (n=104)	P-value	<70 Years (n=166)	≥70 Years (n=50)	P-value
Any AE	**212 (98.1)**	**108 (96.4)**	**104 (100.0)**	**0.0075**	**162 (97.6)**	**50 (100.0)**	**0.7475**
Dermatological toxicity	163 (75.5)	82 (73.2)	81 (77.9)	0.4254	128 (77.1)	35 (70.0)	0.3058
Arthralgia/myalgia	121 (56.0)	53 (47.3)	68 (65.4)	0.0075	92 (55.4)	29 (58.0)	0.7475
Nausea/vomiting	101 (46.8)	43 (38.4)	58 (55.8)	0.0105	71 (42.8)	30 (60.0)	0.0323
Diarrhea	83 (38.4)	38 (33.9)	45 (43.3)	0.1585	63 (38.0)	20 (40.0)	0.7941
Abdominal pain	75 (34.7)	30 (26.8)	45 (43.3)	0.0110	54 (32.5)	21 (42.0)	0.2176
Nephrotoxicity	7 (3.2)	5 (4.5)	2 (1.9)	0.2920	5 (3.0)	2 (4.0)	0.7295
Fatigue/asthenia	121 (56.0)	63 (56.3)	58 (55.8)	0.9433	87 (52.4)	34 (68.0)	0.0515

Figure 1 Incidence of adverse events by category and grade. Cetux, cetuximab.



Of the 439 dermatological AEIs, 49.9% were considered to be related to cetuximab (in the authors' opinion). The second most common AEI was arthralgia/myalgia (264 events in 121 patients; 56.0%), and 121 patients (56.0%) developed 229 events classified as fatigue/asthenia (Table 1). Most AEIs in this analysis were Grade 1 or 2, with <10% of patients experiencing Grade 3 AEs for each of the categories other than nephrotoxicity (Figure 1).

Although creatinine increase was frequent in the study population (53.7%), it was generally mild and related to diarrhea and dehydration. However, nephrotoxicity with acute kidney injury was observed in seven patients (3.2%; Grade 2: n=2, Grade 3: n=4, Grade 4: n=1).

Nausea/vomiting, diarrhea, abdominal pain, dermatological AEs and arthralgia/myalgia tended to occur more frequently (>5% difference in incidence) in women than in men (Table 1). Nephrotoxicity occurred more often in men than in women (4.5% vs 1.9%). Nausea/vomiting, abdominal pain, and fatigue/asthenia were more common in patients aged ≥70 years (Table 1).

The efficacy of the combination treatment appears to be associated with the development of some AEIs (Table 2). OS and PFS were significantly longer in patients receiving encorafenib+cetuximab who experienced arthralgia/myalgia or a dermatological toxicity (whether related to cetuximab or not), versus those who did not experience these AEIs. Further, PFS was significantly longer in patients who experienced diarrhea versus those who did not. In patients receiving the control treatment, OS and PFS were significantly longer in those experiencing abdominal pain and dermatological toxicity (whether related to cetuximab or not), and PFS was significantly longer in those patients experiencing nausea/vomiting, diarrhea and fatigue, versus those who did not experience these AEIs. PFS was also significantly longer in control arm-treated patients who experienced any AEI of ≥Grade 3 versus those who did not.

There was no significant difference in the incidence of AEIs of ≥Grade 3 between male and female patients or between patients aged <70 years and ≥70 years (Supplementary Table S2). While

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Table 2 Overall Survival (OS) and Progression-free Survival (PFS) in Patients Receiving encorafenib + Cetuximab or Control Treatment who did and did not experience Adverse Events of Interest (AEIs)

AEIs, n (%)	Encorafenib + Cetuximab (n=216)				Control (n=193)			
	Patients with ≥1 AE	Patients Without AEs	OS, p-value[a]	PFS, p-value[a]	Patients with ≥1 AE	Patients Without AEs	OS, p-value[a]	PFS, p-value[a]
Any AEI of ≥grade 3	51 (23.6)	165 (76.4)	0.0602	0.4408	59 (30.6)	134 (69.4)	0.6506	**0.0490**
Arthralgia/myalgia	121 (56.0)	95 (44.0)	**0.0042**	**0.0191**	39 (20.2)	154 (79.8)	0.4798	0.1868
Nausea/vomiting	101 (46.8)	115 (53.2)	0.6999	0.1579	102 (52.8)	91 (47.2)	0.9132	**0.0097**
Diarrhea	83 (38.4)	133 (61.6)	0.0889	**0.0115**	94 (48.7)	99 (51.3)	0.1416	**0.0073**
Abdominal pain	75 (34.7)	141 (65.3)	0.7664	0.5418	66 (34.2)	127 (65.8)	**0.0462**	**0. 0023**
Nephrotoxicity	7 (3.2)	209 (96.8)	0.3112	0.3032	6 (3.1)	187 (96.9)	0.1538	0.3936
Dermatological toxicity	163 (75.5)	53 (24.5)	**0.0001**	**0.0003**	137 (71.0)	56 (29.0)	**<0.0001**	**0.0002**
Not cetuximab related	116 (53.7)	100 (46.3)	**0.0017**	**0.0003**	50 (25.9)	143 (74.1)	**0.0104**	**0.0001**
Cetuximab related	122 (56.5)	94 (43.5)	**<0.0001**	**0.0018**	126 (65.3)	67 (34.7)	**<0.0001**	**<0.0001**
Fatigue	121 (56.0)	95 (44.0)	0.9642	0.7138	101 (52.3)	92 (47.7)	0.1080	**<0.0001**

[a] p-value derived from the log rank test, comparing patients who did versus those who did not experience an AE. Values in bold are statistically significant.

there was no significant difference in the incidence of AEs of ≥Grade 3 between male and female patients, the incidence was significantly higher in patients ≥70 years compared to those <70 years (72.0% vs 53.0%; p=0.017; Supplementary Table S2).

Dose Interruptions and Reductions

The median dose intensities were 291.7 mg/day and 409.2mg/week for encorafenib and cetuximab, respectively.

Encorafenib was interrupted at least once in 91/216 patients (42.1%) and cetuximab in 93/216 patients (43.1%). Forty patients (18.5%) had only a single interruption of encorafenib and 38 (17.6%) had a single interruption of cetuximab, while 51 (23.6%) and 55 (25.5%) patients had more than one interruption of encorafenib and cetuximab, respectively. Permanent discontinuation of one drug was generally associated with permanent discontinuation of the other.

Age (<70 or ≥70 years) did not significantly impact the overall incidence of dose interruptions of encorafenib or cetuximab (41.6–48.0% across all groups; Supplementary Table S3), or whether treatment was interrupted once (16.3–26.0%) or more than once (18.0–26.0%). Sex did not impact the overall incidence of dose interruptions of cetuximab (42.0% in males vs 44.2% in females; Supplementary Table S3), or whether treatment was interrupted once (16.1% vs 19.2%) or more than once (25.9% vs 25.0%). However, treatment with encorafenib was interrupted significantly more frequently in females than males (51.0% vs 33.9%, respectively; *P*= 0.0495), although sex had no impact on whether the interruption happened once (25.0% vs 12.5%) or more than once (26.0% vs 21.4%).

Encorafenib dosage was reduced in 26/216 patients (12.0%; 1 dose reduction: n=11 [5.1%], >1 dose reduction: n=15 [6.9%]). Cetuximab dosage was reduced in 10 patients (4.6%; 1 dose reduction: n=9 [4.2%], >1 dose reduction: n=1 [0.5%]).

Age (<70 years or ≥70 years) and sex had no impact on the overall incidence of dosage reduction, or on whether the reduction occurred once or more than once, for either encorafenib or cetuximab (Supplementary Table S4). However, the patient numbers were small in all groups.

Although nephrotoxicity was the least common AEI, it was associated with the highest rate of dose interruption (42.9%; n=3) or dose discontinuation (28.6%; n=2) due to its potential clinical impact (Supplementary Table S5).

Time to AE Onset

Most AEIs developed within the first 1–2 months of treatment; thereafter the rate of AEI onset slowed (Figure 2A, 2B).

Median time to AE onset was 0.56 months (Q1-Q3 0.30–1.18) for dermatological toxicity, 1.12 months (Q1-Q3 0.16–3.22) for arthralgia/myalgia, 0.53 months (Q1-Q3 0.07–2.63) for nausea/vomiting, 1.81 months (Q1-Q3 0.26–3.75) for diarrhea, 1.22 months (Q1-Q3 0.46–3.38) for abdominal pain, and 3.12 months (Q1-Q3 0.26–4.73) for nephrotoxicity. Grade ≥3 AEs occurred in a stochastic pattern over the study period (Figure 2B). Median time to onset of Grade ≥3 AEs was 1.43 months (Q1-Q3 0.87–3.61) for dermatological toxicity, 3.78 months (Q1-Q3 2.53–7.92) for arthralgia/myalgia, 4.90 months (Q1-Q3 2.76–5.68) for diarrhea, and 0.66 months (Q1-Q3 0.26–4.73) for nephrotoxicity. In contrast, the median time to onset for Grade ≥3 nausea/vomiting occurred soon after the start of treatment (0.08 months; 95% CI 0.05–0.11). The median time to onset of all grade abdominal pain was similar to the onset of grade ≥3 abdominal pain (3.32 months; 95% CI 2.25–4.30).

The prevalence of dermatological AEs and arthralgia/myalgia tended to increase over time, but the prevalence of nausea/vomiting, diarrhea, abdominal pain and nephrotoxicity was generally similar throughout 12 months of treatment (Supplementary Figure S1a). When comparing dermatological AEs commonly associated with cetuximab treatment (in the authors' opinion) with those unrelated, cetuximab related toxicities plateau within the first few weeks of treatment while non-cetuximab related toxicities gradually increase over the first couple of months (Supplementary Figures S1b, S1c).

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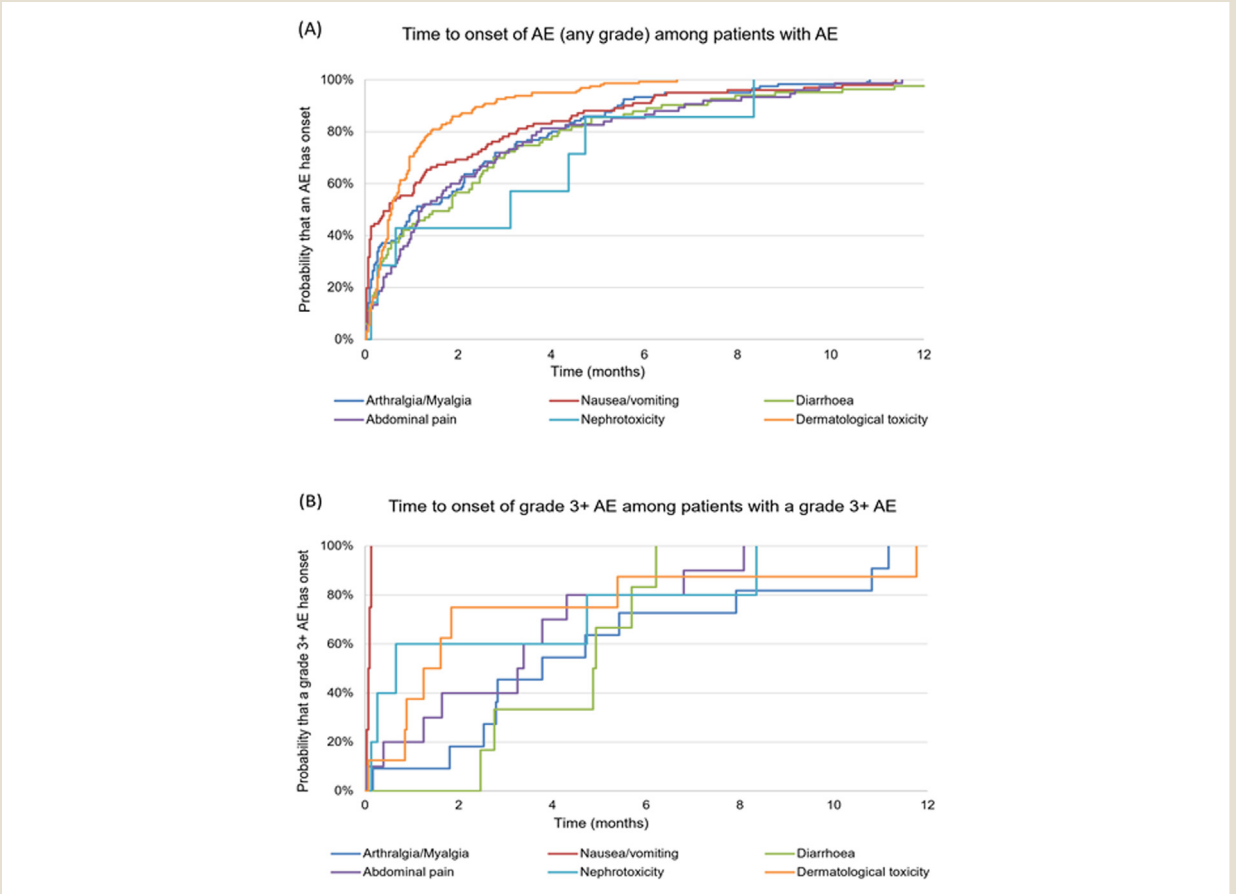
Figure 2 Kaplan-Meier curves for the time to onset of (A) any grade adverse event (AE) among patients with AE and (B) grade 3 and 4 AEs among patients with a grade 3 and higher AE.



There was no significant difference in the median time to onset of any AE in males versus females (0.1 months [Q1-Q3 0.07–0.13] vs 0.03 months [Q1-Q3 0.03–0.07]), or in patients aged <70 years versus ≥70 years (0.07 months [Q1-Q3 0.07–0.13] vs 0.03 months [Q1-Q3 0.03–0.1]). Subgroups of AEs had insufficient numbers of patients to compute the median time to onset.

Time to AE Resolution

Most AEs resolved within 1–2 weeks (Figure 3), but dermatological AEs and arthralgia/myalgia resolved gradually after a median of 3.14 (95% CI 2.14–4.71) and 6.00 (95% CI 3–16) weeks, respectively. Due to the low number of nephrotoxicity events (n=7), no formal analysis was undertaken. However, nephrotoxicity resolved completely in 5/7 patients within the 1 month of follow up available for these patients.

Discussion

This comprehensive analysis, based on the AEIs from the BEACON study, confirms that encorafenib+cetuximab is generally tolerable in patients with *BRAF*^{V600E}mut mCRC. The additional analyses performed on the AEIs differ from previously published BEACON tolerability data because these analyses are more in depth, e.g. the timing of onset of AEIs, sex and age differences, correlation between efficacy and outcomes, and because data were pooled, e.g. data for different types of dermatological AEs, providing a clinically pragmatic approach towards understanding the tolerability of this new treatment. The most common AEIs (dermatological AEs, arthralgia/myalgia, fatigue/asthenia, nausea/vomiting, diarrhea and abdominal pain) were generally mild-to-moderate in severity; Grade ≥3 events were relatively uncommon with no significant differences seen by sex or age. Except for fatigue/asthenia, the frequency of AEIs were higher in women, while patients aged ≥70 years tended to have higher incidences of fatigue/asthenia, nausea/vomiting and abdominal pain. Certain toxicities also seemed to be associated with better efficacy, with patients who experienced arthralgia/myalgia or dermatological toxicities having significantly better outcomes than those who did not experience these toxicities. Previous data have also shown a link between cetuximab-related skin toxicities and treatment outcomes in patients with mCRC.[17] Most AEIs developed in the first few months of treatment and resolved within 1–2 weeks, although dermatological AEs and arthralgia/myalgia resolution was slower (3 and 6 weeks, respectively). These data are generally consistent with the known safety and tolerability profile of encorafenib when used in mCRC and other indications.[15,18] Unlike encorafenib,

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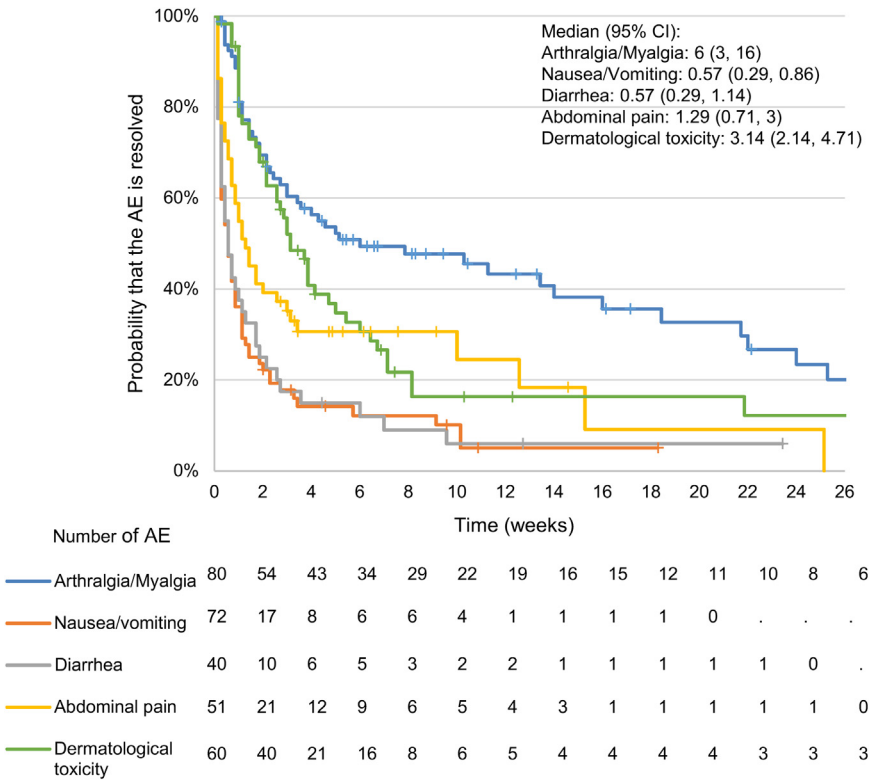
Figure 3 Kaplan-Meier curves for the time to resolution of AEIs. AEI, adverse events of interest; CI confidence interval.



cetuximab has been used to treat mCRC for more than a decade, usually in combination with chemotherapy, so clinicians are familiar with its safety/tolerability profile.

In metastatic melanoma, BRAF inhibitors are combined with mitogen-activated protein kinase (MEK) inhibitors.[19] The phase III COLUMBUS study reported fatigue/asthenia, arthralgia/myalgia, dermatological and gastrointestinal events as common AEs in patients receiving encorafenib+binimetinib (MEK inhibitor).[20] In the BEACON study, gastrointestinal (diarrhea, nausea and vomiting) or dermatological (acneiform dermatitis, dry skin, rash, stomatitis and pruritus) AEs occurred at a higher incidence with triplet therapy than doublet therapy except for arthralgia, myalgia and musculoskeletal pain which occurred with a higher incidence with doublet therapy.[15] Mild-to-moderate dermatological AEs are usually manageable with topical moisturizers, hydrocortisone or tetracyclines, diarrhea with anti-diarrheals, nausea/vomiting with antiemetics and arthralgia/myalgia with paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs).[21] However, due to possible treatment-associated diarrhea and dehydration, NSAIDs should be used with caution and only after failure of level 1 painkillers. Since most of these AEs occur early in the treatment course, patients should be made aware of them before starting therapy and be given appropriate advice and self-management support. Moreover, most AEIs resolve within 1–2 weeks of onset and very few patients need to discontinue treatment, further highlighting that AEIs are generally manageable and successful reinstitution of dosing with encorafenib is invariably achievable. At the first appearance of a Grade 3 or 4 AEI, a short-term interruption of 1–2 weeks is recommended, to establish if treatment should be resumed with a dose reduction, rather than permanent discontinuation.

Frequently reported increased serum creatinine in the BEACON trial was generally mild and associated with diarrhea and related dehydration, whereas direct nephrotoxicity was rare with this combination. In the current analysis only 7/216 patients (3.2%) developed Grade ≥2 nephrotoxicity, leading to treatment discontinuation in 2/7 patients. The cause of this nephrotoxicity is most likely multifactorial. Cetuximab is associated with diarrhea and electrolyte disturbances (hypomagnesaemia and hypokalemia) which may affect renal function; however, it is unclear to what degree cetuximab contributed to nephrotoxicity in the BEACON study. Some symptoms of nephrotoxicity may have also been related to the patients' underlying mCRC (including diarrhea and dehydration) or concomitant medications. Tumor-associated myelosuppression and infection may also have contributed, particularly in one patient with pyelonephritis. Although not predefined as an AEI in this analysis, increased creatinine levels (most likely related to diarrhea and dehydration) was the most common AE in an updated analysis of BEACON, experienced by 53.7% of patients receiving encorafenib+cetuximab,[9] while its frequency was comparatively low (2.0%) with encorafenib in patients with locally

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advanced unresectable or metastatic *BRAF*^{V600E}mut melanoma.[20] Thus, given the specific patient population and multiple contributing factors, nephrotoxicity, while rare, should be monitored and managed appropriately.

The strengths of our study were the large cohort of patients and the grouping of similar AEs into categories, as well as a longitudinal assessment of their onset of timing and duration; unlike the BEACON publication which presented toxicity by strict NCI-CTCAE definitions and was based only on the worst toxicity grade experienced by each patient. Our method of presentation might therefore be more informative for clinicians in daily practice due to the additional perspective provided, and might counteract investigator differences in the classification of similar AEs. Additionally, the new data on the time to onset and resolution of AEIs might help oncologists in planning toxicity prophylaxis and the re-evaluation of patients affected by AEs.

The bias in this post hoc analysis was minimized by including data from all patients in the doublet therapy group of the BEACON study. Nonetheless, the BEACON study had restrictive inclusion criteria, so the findings may not be generalizable to a heterogeneous real-world population of patients with *BRAF*^{V600E}mut mCRC.

Despite their frequency, the AEIs were generally mild-to-moderate in severity and resolved rapidly, except for the rare cases of nephrotoxicity. The good tolerance profile of encorafenib+cetuximab is particularly important if we consider the second-line setting and the palliative intent of the treatment. The majority of patients who receive this therapy in a real-world setting will have received a first-line chemotherapy combination and will therefore be burdened by more frequent and clinically relevant AEs. In addition, they might be symptomatic due to disease progression. Considering these two factors, in our opinion, the possibility of offering them a combination that is not only effective, but also well tolerated, is particularly relevant.

Conclusion

Analysis of BEACON CRC study data shows that encorafenib+cetuximab is deliverable to most patients with *BRAF*^{V600E}mut mCRC without the need for dose reduction, interruption or discontinuation. To optimize patient care, oncologists should become familiar with the toxicity profile of this new regimen, which is recommended in the ESMO guidelines for BRAF^{V600E}mut, pre-treated mCRC[16].

Authors' Contributions

J. Taieb, C. Castagné, J. Desai, G. Folprecht, S. Khan, E. Polo Marques, and H. Wasan: conceptualization. J. Taieb, J. Desai, G. Folprecht, E. Polo Marques, and S. Lonardi: resources. J. Taieb, C. Castagné, and S. Khan: methodology. C. Castagné and S. Khan: validation. S. Khan: project administration. H. Wasan and J. Desai were members of the BEACON CRC steering committee. All authors: writing- review and editing. All authors approved the final version of the manuscript for publication.

Clinical Practice Points

- The *BRAF*^{V600E} mutation (*BRAF*^{V600E}mut) is a prognostic marker in metastatic colorectal cancer (mCRC), with patients experiencing poor outcomes, including a greater risk of recurrence after surgery, a high rate of peritoneal metastasis and reduced overall survival.
- BRAF inhibitors have been used widely for treating *BRAF*-mutated metastatic melanoma but have only recently gained approval, in combination with cetuximab, in *BRAF*^{V600E}mut mCRC. Therefore, experience with this combination of agents is limited among gastrointestinal oncologists.
- We examined the adverse events (AEs) of this combination seen during the phase 3 BEACON study. In general, encorafenib+cetuximab was well tolerated, with dermatological toxicities being the most common AE and some toxicities (arthralgia/myalgia and dermatological toxicities) linked to better outcomes in patients. Most AEs were more common in women, mild-to-moderate in severity, occurred early and resolved rapidly.
- This analysis shows that encorafenib+cetuximab can be used in most patients with *BRAF*^{V600E}mut mCRC without the need for dose reductions, interruptions, or discontinuations. Oncologists should become familiar with the toxicity profile of this regimen to optimize patient care with this combination.

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Pierre Fabre medical staff was involved in the concept of this post hoc analysis and interprétation of data and in the writing of the report for this work. The BEACON trial was sponsored by Pfizer and was conducted with support from Merck KGaA Darmstadt, Germany (for sites outside of North America), ONO Pharmaceutical, and Pierre Fabre. The authors had access to all data in the study and were responsible for submission of this paper for publication.

Data Availability Statement

The data generated during this study are available from the corresponding author upon reasonable request.

Disclosure

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J. Taieb has received honoraria as a speaker and/or in an advisory role from Roche Genentech, Merck KGaA, Sanofi, Merck Sharp Dohme, Novartis, Astra Zeneca, Servier, Pierre Fabre and Amgen. S. Lonardi has received honoraria as a speaker and/or in an advisory role from Roche Merck KGaA, MSD, Astra Zeneca, Servier, Pierre Fabre, Amgen, Lilly, Incyte, Daiichi-Sankyo, Bristol-Myers Squibb and GlaxoSmithKline. J. Desai has participated in consulting and/or advisory roles for Pierre Fabre, Merck KGA, Bayer, GlaxoSmithKline, BeiGene, Amgen; and has received research funding (institutional) from: Roche, GlaxoSmithKline, Novartis, BeiGene, Lilly, Bristol-Myers Squibb, and AstraZeneca. G. Folprecht has participated in consulting and/or advisory roles from Pierre Fabre, Merck KGA, Bayer, GlaxoSmithKline, Beigene, Amgen; and received research funding (all institutional) from: Roche, GlaxoSmithKline, Novartis, BeiGene, Lilly, Bristol-Myers Squibb and AstraZeneca. C. Gallois has participated in consulting and/or advisory boards for Servier and Sanofi, and has received support for travel to meetings from Amgen. E. Polo Marques declares no conflict of interest. S Khan is an employee of Pierre

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2022.12.003.

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