



# Nursing care and management of adverse events for patients with *BRAF*<sup>V600E</sup>-mutant metastatic colorectal cancer receiving encorafenib in combination with cetuximab: a review

Matthew Fowler<sup>1</sup> · Helene Tობback<sup>2</sup> · Alice Karuri<sup>3</sup> · Paz Fernández-Ortega<sup>4</sup>

Received: 8 July 2022 / Accepted: 5 January 2023 / Published online: 7 March 2023  
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2023

## Abstract

Encorafenib is a B-Raf proto-oncogene serine/threonine-protein kinase (BRAF) inhibitor, approved in the EU and USA, in combination with the epidermal growth factor receptor (EGFR) inhibitor cetuximab, for the treatment of patients with *BRAF*<sup>V600E</sup>-mutant metastatic colorectal cancer (mCRC). In the pivotal BEACON CRC trial, patients achieved longer survival with encorafenib in combination with cetuximab vs. conventional chemotherapy. This targeted therapy regimen is also generally better tolerated than cytotoxic treatments. However, patients may present with adverse events unique to the regimen and characteristic of BRAF and EGFR inhibitors, which produce their own set of challenges. Nurses play an essential role in navigating the care of patients with *BRAF*<sup>V600E</sup>-mutant mCRC and managing adverse events that patients may experience. This includes early and efficient identification of treatment-related adverse events, subsequent management of adverse events and education of patients and their caregivers around key adverse events. This manuscript aims to provide support to nurses managing patients with *BRAF*<sup>V600E</sup>-mutant mCRC receiving encorafenib in combination with cetuximab, by summarising potential adverse events and providing guidance on how to manage them. Special attention will be paid to the presentation of key adverse events, dose modifications that may be required, practical recommendations and supportive care measures.

**Keywords** Nursing role · *BRAF* Mutation · Encorafenib · Cetuximab · Toxicity · Colorectal cancer

## Abbreviations

ADL	Activities of daily living	CK	Creatine kinase
ALP	Alkaline phosphatase	CRC	Colorectal cancer
ALT	Alanine aminotransferase increase	CT	Computed tomography
AST	Aspartate aminotransferase increase	ECG	Electrocardiogram
BL	Baseline	EGFR	Epidermal growth factor receptor
BRAF	B-Raf proto-oncogene serine/threonine-protein kinase	FOLFIRI	Folinic acid, fluorouracil and irinotecan
BRAF (gene)	v-Raf murine sarcoma viral oncogene homolog B	Hb	Haemoglobin
BRAF <sup>WT</sup>	BRAF wild type	IV	Intravenous
BRAT	Bananas, rice, apples and toast	LLN	Lower limit of normal
BSA	Body surface area	MAPK	Mitogen-activated protein kinase
		mCRC	Metastatic colorectal cancer
		NA	Not applicable
		OS	Overall survival
		QTc	Corrected QT interval
		RAS	Rat sarcoma virus
		ULN	Upper limit of normal

✉ Matthew Fowler  
matthew.fowler@nhs.net

<sup>1</sup> University Hospitals of Derby and Burton NHSFT, Uttoxeter Road, DE22 3NE Derby, UK

<sup>2</sup> UZ Leuven, Gasthuisberg Campus, Leuven, Belgium

<sup>3</sup> Barts and the London NHS Trust, London, UK

<sup>4</sup> Institut Català d'Oncologia, Granvia de l'Hospitalet, L'Hospitalet de Llobregat, Barcelona, Spain

## Background

In Europe, colorectal cancer (CRC) is both the second most diagnosed cancer and the second biggest cause of death, accounting for 500,000 cases and 138,000 deaths

in 2018 [1]. Despite improved efforts in screening, it is estimated that > 20% of patients present with metastatic CRC (mCRC) and out of those diagnosed with localised CRC, 50–60% will go on to develop metastases [2–4]. This is a major contributor to the high death rates reported in CRC; the 5-year survival rate for mCRC is just 12% with a median overall survival (OS) of 30 months [4–6]. It is widely accepted that sporadic CRC arises due to accumulation of both genetic and epigenetic alterations of the genome. Particularly, CRC is associated with the activation of oncogenes, such as Kirsten rat sarcoma viral oncogene homolog and v-Raf murine sarcoma viral oncogene homolog B (BRAF), which have roles in regulating proliferation, differentiation and cell growth [7, 8]. These mutations not only help drive the development of CRC but can also act as biomarkers, determining prognosis and response to treatment [5]. Due to their predictive and prognostic roles, European guidelines recommend RAS and BRAF mutational testing upon diagnosis of mCRC [9].

BRAF mutations are present in 8–12% of mCRC cases; the majority of these (~ 95%) result from a valine to glutamate mutation known as V600E [5, 10]. The BRAF<sup>V600E</sup> mutation forms a protein that is 500-fold more active than wild-type BRAF (BRAF<sup>WT</sup>) [11]. This results in constitutive activation of the mitogen-activated protein kinase (MAPK) signalling pathway through downstream phosphorylation of protein kinases, which drive tumour cell proliferation and survival [8]. BRAF<sup>V600E</sup>-mutant mCRC is associated with right-sided primary tumours, advanced age, female sex, late-stage and aggressive disease that has a limited response to the standard of care treatment. In mCRC, BRAF<sup>V600E</sup> mutations are a key prognostic biomarker for poor outcomes resulting in a two-fold increase in mortality compared with BRAF<sup>WT</sup> mCRC [12].

### Treating BRAF<sup>V600E</sup>-mutant mCRC

Doublet or triplet chemotherapy regimens plus the VEGF inhibitor, bevacizumab, are recommended as first-line treatment for BRAF-mutant mCRC, although it should be noted Bevacizumab is not available across all of Europe. These cytotoxic combinations provide moderate benefits in first-line for BRAF<sup>V600E</sup>-mutant mCRC, but limited benefits at second-line and beyond [8]. Therefore, European guidelines recommend a BRAF inhibitor, encorafenib, in combination with an epidermal growth factor receptor (EGFR) inhibitor, cetuximab, in patients with BRAF<sup>V600E</sup>-mutant mCRC who have received prior systemic therapy [9]. Unlike in melanoma, responses to BRAF inhibitor monotherapy were suboptimal in BRAF<sup>V600E</sup>-mutant mCRC. BRAF inhibition triggers a feedback loop in CRC cells, whereby rapid activation of upstream EGFR

reinstates MAPK activation, resulting in continued cell proliferation [8, 13]. In preclinical and early clinical trials, addition of an EGFR inhibitor alongside a BRAF inhibitor resulted in synergistic inhibition of tumour growth, overcoming the feedback loop. Adding a MEK inhibitor has also reported a similar increase in anti-tumour activity [12, 14–17].

These early trials prompted the pivotal Phase III, open-label BEACON CRC trial. Patients with BRAF<sup>V600E</sup>-mutant mCRC who had received prior systemic therapy were randomly assigned 1:1:1 to receive encorafenib plus the MEK inhibitor, binimetinib, in combination with cetuximab (triplet), encorafenib in combination with cetuximab (doublet) or the investigators choice of irinotecan/fluorouracil, irinotecan and leucovorin plus cetuximab (control). Median OS was 9.3 months with both triplet and doublet combinations vs. 5.9 months for the control [8]. Overall response rate was greatest in the triplet group (26.8%) vs. the doublet (19.5%) and the control (1.8%). However, adverse events were also highest in the triplet group compared with doublet and control regimens, with grade ≥ 3 adverse events reported in 65.8%, 57.4% and 64.2% of patients, respectively [8]. It was concluded that the doublet regimen was sufficient to maximise OS benefit with an acceptable adverse event profile [8]. Data from BEACON CRC formed the basis for the EU and US approval of encorafenib in combination with cetuximab for patients with BRAF<sup>V600E</sup>-mutant mCRC who had received prior systemic treatment [18, 19].

For mCRC, the recommended dose of encorafenib is 300 mg, taken orally as four 75 mg capsules once daily. Encorafenib does not need to be refrigerated and can be taken at home [20, 21]. Nurses may use telemonitoring to check patients are taking the medication as directed to ensure full benefit of encorafenib; telemonitoring has been applied to other patient groups, with significantly improved self-management and medication adherence [22–24].

The official administration guidelines recommend cetuximab is given as a weekly intravenous (IV) infusion, initially at 400 mg/m<sup>2</sup> (120-min infusion), then 250 mg/m<sup>2</sup> (60-min infusion) for subsequent doses. Weekly infusions mean frequent visits to the hospital for patients, perpetuating treatment fatigue. Consequently, some centres administer cetuximab bi-weekly, which is more convenient for both the patient and treating institution [25–27]. Available data suggest bi-weekly cetuximab, at 500 mg/m<sup>2</sup>, has an equivalent pharmacokinetic, efficacy and safety profile to weekly administration. However, these results come from patients treated with cetuximab alongside chemotherapy and not encorafenib, so further data are needed to confirm the efficacy of bi-weekly cetuximab in this setting [25–27].

In general, targeted treatments are better tolerated than conventional cytotoxic agents. However, their characteristic

patterns of adverse events differ from conventional treatment, presenting unique challenges [28]. Nurses are crucial in educating patients and caregivers on the disease, available treatments and the nature, recognition and severity of any possible adverse events. This can help ensure potential adverse events are managed promptly so maximum treatment benefit is achieved. The objective of this manuscript is to provide an overview of adverse events observed in patients with *BRAF*<sup>V600E</sup>-mutant mCRC receiving encorafenib in combination with cetuximab, guidance on adverse event management, suggestions for supportive care to aid the management and prevention of adverse events, and tips for educating patients and caregivers.

### Encorafenib in combination with cetuximab: overview of adverse events

The most frequently occurring adverse events reported with BRAF inhibitors are dermatological and can develop within days of treatment [8, 29, 30]. Pyrexia can also occur following BRAF inhibitor treatment and may be due to an inflammatory response [8, 29–31]. Similarly, arthralgia, commonly reported in patients receiving BRAF inhibitors, may originate from this inflammatory response [8, 29, 30, 32]. Gastrointestinal events are also commonly associated with BRAF inhibitors. The MAPK pathway has a role in regulating chloride secretion in normal gastrointestinal mucosa and therefore BRAF inhibition may increase chloride secretion, inducing diarrhoea [8, 33]. Cardiovascular side effects have

been associated with BRAF inhibitors, possibly due to non-specific interference with MAPK signalling. In cardiovascular cells, MAPK inhibition leads to oxidative stress and cell death, affecting the formation of blood vessels [30, 33, 34].

As with BRAF inhibitors, the most frequently occurring adverse events associated with EGFR inhibitors are skin disorders, although they present differently. This association with skin disorders is not surprising as EGFR is involved in the development and physiology of the epidermis. Evidence suggests an association between EGFR inhibitors and mucosal toxicity, possibly due to immunological factors [28]. Electrolyte imbalances, particularly hypomagnesaemia, often arise from compromised renal magnesium retention and are frequently reported in patients receiving cetuximab. The IV administration of cetuximab may also be associated with potentially severe infusion-related reactions; for example, anaphylactic reactions are assumed to be because of non-specific cytokine release from immune cells [28].

Table 1 summarises the most frequent adverse events seen in patients with *BRAF*<sup>V600E</sup>-mutant mCRC receiving encorafenib in combination with cetuximab in BEACON CRC. Diarrhoea was the most frequently reported adverse event of any grade, followed by nausea and fatigue. Among abnormal laboratory values associated with adverse events, creatinine increase (54%) and haemoglobin decrease (39%) were very common [8]. The National Cancer Institute Common Terminology Criteria for Adverse Events and associated grading scales for key adverse events observed in this setting can be found in the supplementary material.

**Table 1** The most common adverse events observed with encorafenib in combination with cetuximab in the BEACON CRC trial [8]

Adverse events occurring in $\geq 20\%$ (any grade) or $\geq 3\%$ (grade $\geq 3$ ) <sup>a</sup> %	Encorafenib in combination with cetuximab $n = 216$		Control <sup>b</sup> $n = 193$	
	Any grade	Grade $\geq 3$	Any grade	Grade $\geq 3$
Diarrhoea	38	3	49	10
Nausea	38	< 1	44	2
Fatigue	33	4	28	5
Decreased appetite	31	1	29	3
Dermatitis acneiform	30	< 1	40	3
Abdominal pain	28	3	28	5
Vomiting	27	1	32	3
Asthenia	24	4	28	5
Arthralgia	23	1	2	0
Headache	20	0	3	0
Selected abnormal laboratory values associated with adverse events, %				
Creatinine increase	54	3	38	1
Haemoglobin decrease	39	6	46	5
Bilirubin increase	8	3	9	3

<sup>a</sup>Regardless of causality; any-grade adverse events that occurred in  $\geq 20\%$  of patients receiving encorafenib in combination with cetuximab; grade  $\geq 3$  adverse events that occurred in  $\geq 3\%$  of patients receiving encorafenib in combination with cetuximab

<sup>b</sup>Patients in the control group received either investigator's choice of cetuximab and irinotecan or cetuximab and FOLFIRI (folinic acid, fluorouracil and irinotecan). CRC colorectal cancer

## Encorafenib in combination with cetuximab: guidance for managing adverse events

General guidance should be given to patients commencing treatment with encorafenib in combination with cetuximab to minimise adverse events and maximise treatment efficacy. During treatment with encorafenib, patients are advised to keep hydrated. Encorafenib should be taken at the same time every day, and the capsule swallowed whole with water. If a dose is missed, it can be taken up to 12 h before the next dose. If taken within 12 h of the next dose, patients should skip that dose and take their next dose at the regular time [20].

Certain medicinal products, such as ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole and hormonal contraceptives, should be co-administered with caution and grapefruit juice should be avoided due to interaction with the enzyme CYP3A4, which metabolises encorafenib, or the enzyme UGT1A1, which is inhibited by encorafenib. The full list of medicinal products to be administered with caution can be found in the BRAFTOVI® SmPC [20].

Encorafenib may reduce the efficacy of hormonal contraceptives; therefore, alternative methods, such as barrier contraception, should be used during encorafenib treatment and for  $\geq 1$  month after the last dose. Females should not receive treatment if pregnant or breastfeeding. Males should be informed of the potential risk for impaired sperm production [20].

Prior to the first infusion of cetuximab, healthcare professionals must ensure the patient takes premedication consisting of an antihistamine and a corticosteroid at least 1 h before cetuximab administration. Premedication is recommended before all subsequent infusions. The patient must have the first cetuximab dose administered slowly (not exceeding 5 mg/min) and vital signs closely monitored for 2 h. Following doses can be infused faster, without exceeding 10 mg/min, with close monitoring during and for at least 1 h afterwards. Resuscitation equipment should be available during this time [35]. It is crucial that patients are told to inform nurses immediately of any suspected side effects they may be experiencing at the time of infusion or during monitoring.

Infusion-related reactions may occur during the first infusion, up to several hours afterwards or during subsequent infusions. Patients should be monitored for signs of severe infusion-related reactions and should be warned of the potential for late-onset reactions. Symptoms can include bronchospasm, changes in blood pressure, itchy rash, loss of consciousness or shock and, in rare cases, chest pain leading to myocardial infarction or cardiac arrest. Patients should have their urea, serum electrolyte levels (including magnesium, potassium and calcium) and creatinine levels measured prior to each cetuximab treatment [35].

In clinical practice, several investigations are required before, during and after treatment with encorafenib in combination with cetuximab (Fig. 1). Dose and treatment schedules may need to be adapted according to the test outcomes to ensure the safety and efficacy of the regimen is maintained [20, 35].

### Skin conditions

Following treatment with encorafenib in combination with cetuximab, patients may experience skin reactions (Fig. 2). Skin rash, one of the most frequently occurring adverse events associated with BRAF inhibition, generally comprises several conditions, such as maculopapular exanthema, papulopustular exanthema and eczema [20, 33]. Melanocytic nevi are mostly benign neoplasms formed from the proliferation of pigment-producing cells in the skin [36]. During BRAF inhibition, pre-existing melanocytic nevi may change and new, eruptive nevi may also develop [37]. Changes in pre-existing melanocytic lesions usually do not have the *BRAF*<sup>V600E</sup> mutation but *BRAF* mutations are shown in up to 80% of acquired nevi [37–40]. Melanocytic nevi associated with BRAF inhibitors have increased melanin pigmentation and deep HMB-45 expression (Fig. 2b) [37].

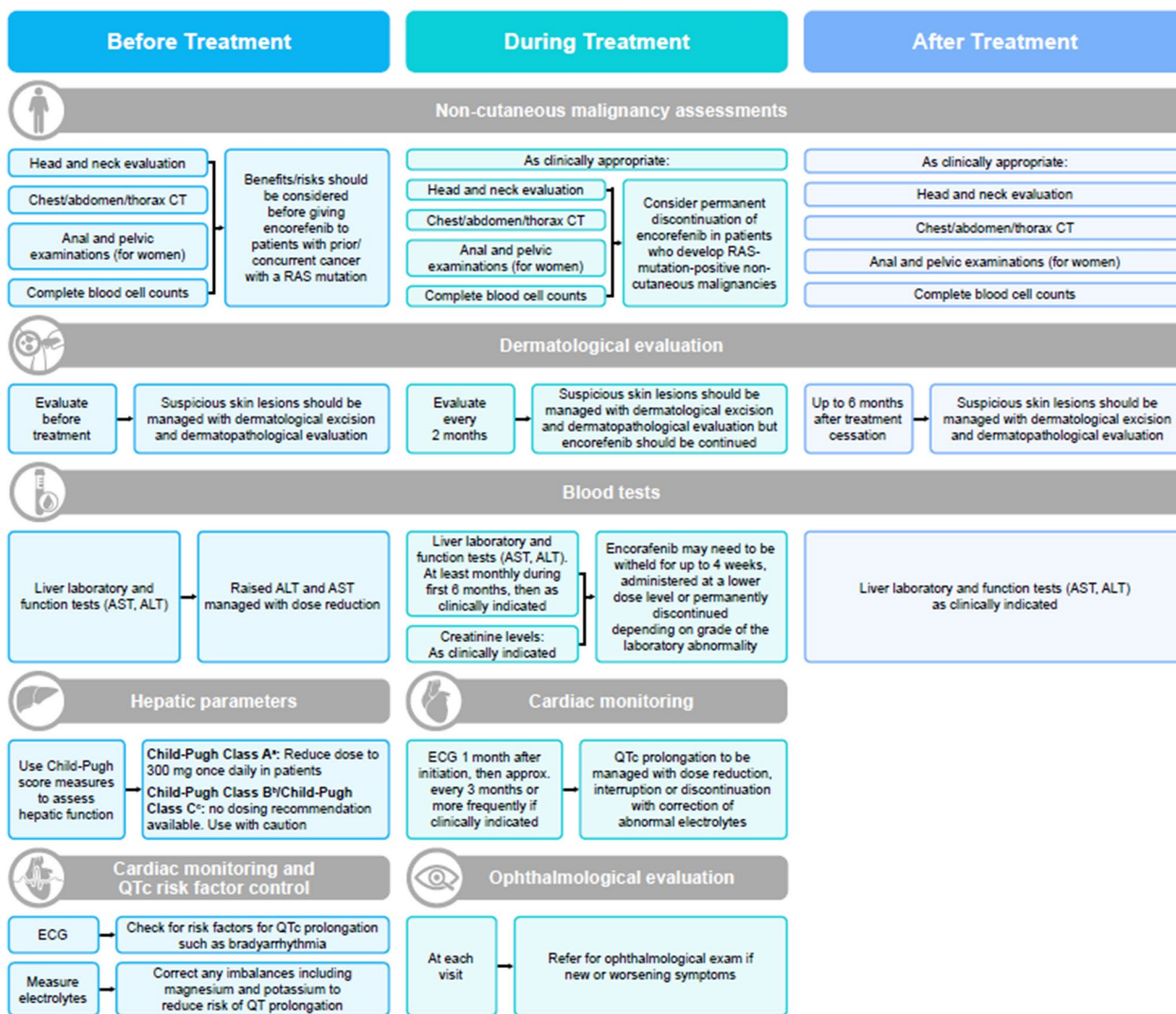
Acneiform dermatitis, a skin rash with a flat discoloured area or raised bumps resembling acne, frequently occurs in patients treated with cetuximab [20, 33, 35, 42]. Skin reactions develop in  $> 80\%$  of patients who receive cetuximab, with  $\sim 15\%$  classed as severe, including cases of skin necrosis [35].

Skin adverse events affected over three-quarters of patients receiving encorafenib in combination with cetuximab in BEACON CRC, which were predominantly mild or moderate (Table 2) [8]. Of the 216 patients receiving this treatment, 30% reported dermatitis acneiform of any grade, with one grade  $\geq 3$  event. Dose modifications and treatment discontinuations due to skin-related adverse events were rare in BEACON CRC [8].

### Monitoring and dose modifications

The severity of cutaneous adverse events may be overestimated by oncologists, causing premature discontinuation and reducing patient access to potentially lifesaving treatment [44, 45]. Therefore, an interdisciplinary approach between dermatologists, oncologists and oncology nurses trusted by the patient is imperative [45]. Dermatological evaluations should be performed prior to treatment with encorafenib in combination with cetuximab and every 4 weeks before a new encorafenib prescription is dispensed [20]. Patients may have their skin assessed more frequently and should be instructed to immediately inform their physicians or nurses if new skin lesions develop. Suspicious skin lesions should





**Fig. 1** Recommendations for the monitoring of patients along with appropriate actions before, during and after treatment with encorafenib in combination with cetuximab [20]. **a** Mild hepatic, **b** moderate hepatic impairment, **c** severe hepatic impairment. *ALT*

alanine aminotransferase increase, *AST* aspartate aminotransferase increase, *CT* computed tomography, *ECG* electrocardiogram, *QTc* corrected QT interval, *RAS* rat sarcoma virus

be managed with excision and dermatopathological evaluation [20, 35]. Encorafenib dose modification guidance for managing rash adverse events is shown in Fig. 3a. Modifications are not recommended for new primary cutaneous malignancies or melanocytic nevi [43].

Cetuximab dose modification guidance is the same for any single type of skin adverse event. For grade  $\geq 3$ , interrupt treatment until improvement to grade  $\leq 2$ . At first incidence of severe skin reactions, treatment may resume at full dose when the reaction has resolved to grade  $\leq 2$ . Following second and third occurrences of severe skin reactions, cetuximab must be interrupted and resumed at a lower dose level (200 mg/m<sup>2</sup> after second occurrence and 150 mg/m<sup>2</sup>

after third) when resolved to grade  $\leq 2$ . If severe skin reactions occur a fourth time or are not resolved to grade  $\leq 2$ , permanent discontinuation is required [35].

**Practical recommendations and supportive care measures**

Many practical measures can be suggested to the patient to reduce the incidence and severity of skin adverse events [20, 43]. Some patients may require referral to dermatologists for skin biopsies but for optimal management of skin adverse events, dermatologist liaison is key [20, 43, 45]. Patients should avoid sun exposure, ensuring they wear a hat and sunscreen that blocks both ultraviolet A

### a. Rash associated with BRAF inhibitor



### b. Cutaneous neoplasms associated with BRAF inhibitors



### c. Rash with cetuximab administration



**Fig. 2** Example images of skin disorders patients may experience when receiving encorafenib in combination with cetuximab [37, 41]. *BRAF* v-Raf murine sarcoma viral oncogene homolog B

and ultraviolet B rays with SPF  $\geq 30$  [46]. Moisturising creams should be used at least twice daily, within 15 min of showering and with every hand wash. Creams containing salicylic acid, urea, ammonium or lactic acid are recommended as they soften skin and enable water retention [46, 47]. These creams may be administered prophylactically to prevent rashes or as treatment once the rash has developed. Products that can irritate or are abrasive to the skin, such as soaps, detergents, fragranced creams, sponges, bath scrubs and loofahs must be avoided [46].

For a mild rash, topical corticosteroids (e.g. mometasone cream) and/or topical antibiotics (e.g. erythromycin) may be required. If a moderate rash develops, topical erythromycin or clindamycin plus topical mometasone or topical

pimecrolimus and oral antibiotics should be considered. For a severe rash, having consulted a dermatologist, oral prednisolone or oral isotretinoin may be used [43]. In addition, primary prophylaxis with doxycycline or minocycline may reduce the severity of rashes related to cetuximab [48].

For many patients, skin reactions negatively affect their body image and quality of life [42]. Forty-one percent of patients with CRC treated with cetuximab who developed a cutaneous skin rash reported psychological distress and in 47% of these cases, this affected their willingness to go out in public [49, 50]. Furthermore, patients reported facing a loss of privacy due to the rash increasing the difficulty of concealing an illness [45]. Therefore, it is imperative that emotional support and guidance are administered alongside physical treatment.

**Table 2** Dose reductions and discontinuations of encorafenib in combination with cetuximab due to key adverse events observed in the BEACON CRC trial [8, 43]

	Encorafenib in combination with cetuximab <i>n</i> = 216		Control <sup>a,b</sup> <i>n</i> = 193	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
<b>Skin-related adverse events</b>				
Adverse event, % <sup>c,d</sup>				
Dermatitis acneiform	30	< 1	40	3
Melanocytic nevus	16	0	0	0
Rash	15	0	15	2
Dry skin	13	0	8	< 1
Pruritus	11	0	5	0
Dose reduction, % <sup>c</sup>				
Encorafenib	1	0	NA	NA
Cetuximab	0	0	2	1
Discontinuation of any study drug due to any skin adverse event, % <sup>c</sup>	0	0	2	1
<b>Musculoskeletal-related adverse events</b>				
Adverse event, % <sup>c</sup>				
Arthralgia	23	1	2	0
Myalgia	15	< 1	2	0
Musculoskeletal pain	13	0	2.6	0
Dose reduction, % <sup>c</sup>				
Encorafenib				
Arthralgia	1	< 1	NA	NA
Myalgia	< 1	0	NA	NA
Cetuximab	0	0	0	0
Discontinuation of any study drug due to any arthralgia or myalgia, %	0	0	0	0
<b>Laboratory abnormalities</b>				
Adverse event, % <sup>c</sup>				
ALT increase (IU/L)	19	< 1	30	4
AST increase (IU/L)	19	2	22	3
Bilirubin increase (mmol/L)	8	3	9	3
Creatine kinase increase (IU/L)	4	0	7	< 1
Creatinine increase (mmol/L)	54	3	38	1
Haemoglobin decrease (g/L)	40	6	46	5
<b>General adverse events</b>				
Adverse event, % <sup>c</sup>				
Fatigue	33	4	28	5
Asthenia	24	4	28	5
Headache	20	0	3	0
Pyrexia	19	1	15	< 1
Dyspnoea	13	1	10	3
Dose reduction, % <sup>c</sup>				
Encorafenib <sup>e</sup>				
Fatigue	1	0	NA	NA
Asthenia	1	< 1	NA	NA
Cetuximab	0	0	0	0
Discontinuation of any study drug, %				
Fatigue	< 1 <sup>f</sup>	< 1 <sup>f</sup>	< 1 <sup>g</sup>	0
Asthenia	0	0	1	0

ALT alanine aminotransferase increase, AST aspartate aminotransferase increase, CRC, colorectal cancer, NA not applicable

<sup>a</sup>Patients in the control group received either investigator's choice of cetuximab and irinotecan or cetuximab and folinic acid, fluorouracil and irinotecan (FOLFIRI)

<sup>b</sup>As per the protocol, patients in the control arm did not receive routine skin evaluations

<sup>c</sup>Regardless of causality; data indicate the percentage of patients

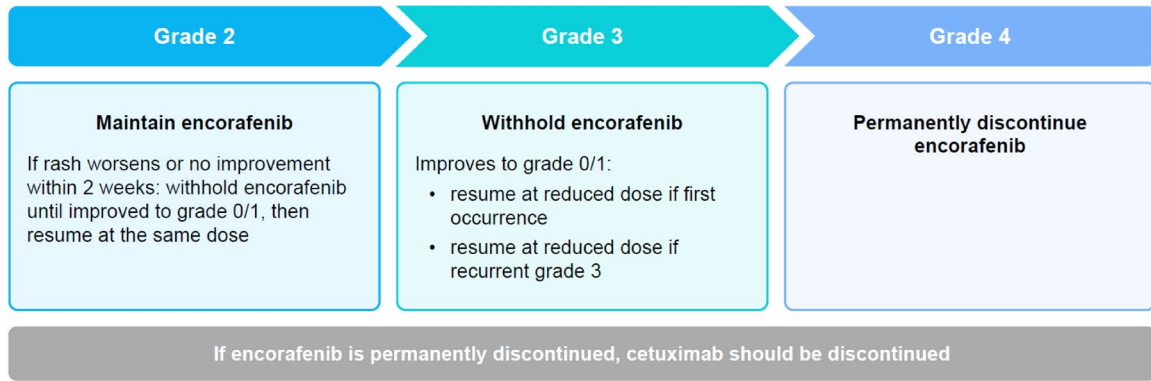
<sup>d</sup>Skin adverse events that occurred in ≥ 10% of patients receiving encorafenib in combination with cetuximab

<sup>e</sup>No dose reductions were required for pyrexia or headache

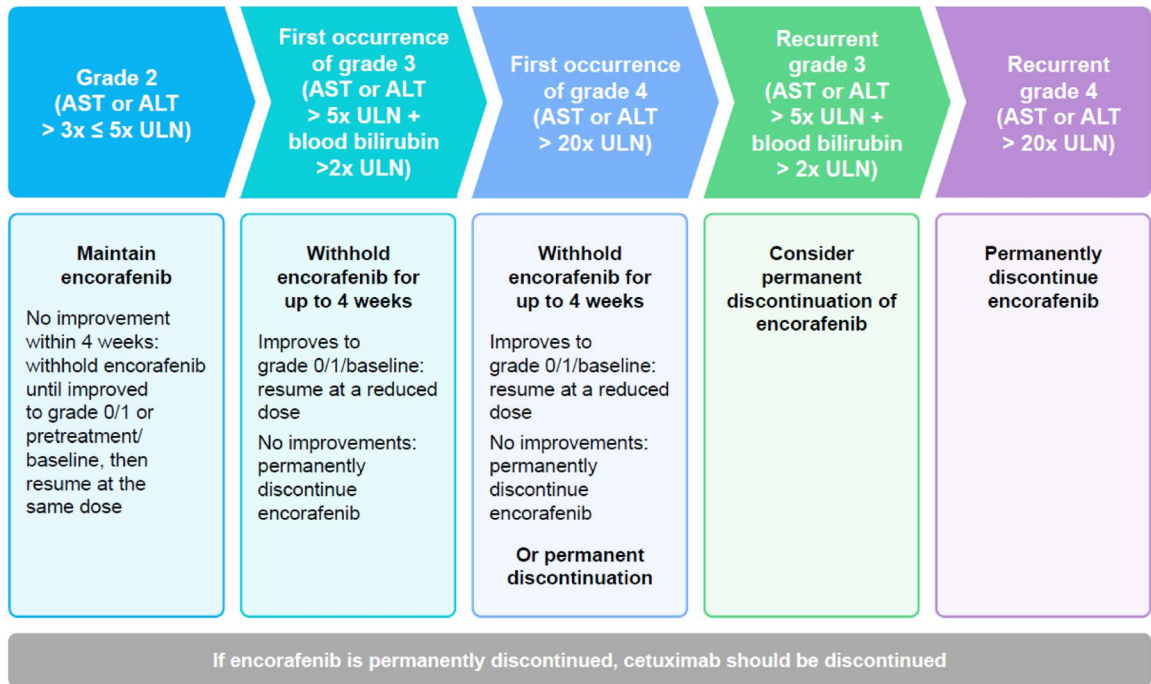
<sup>f</sup>One patient discontinued cetuximab as a result of fatigue; there were no discontinuations of any drug due to pyrexia or headache

<sup>g</sup>There were no discontinuations of any drug due to pyrexia or headache

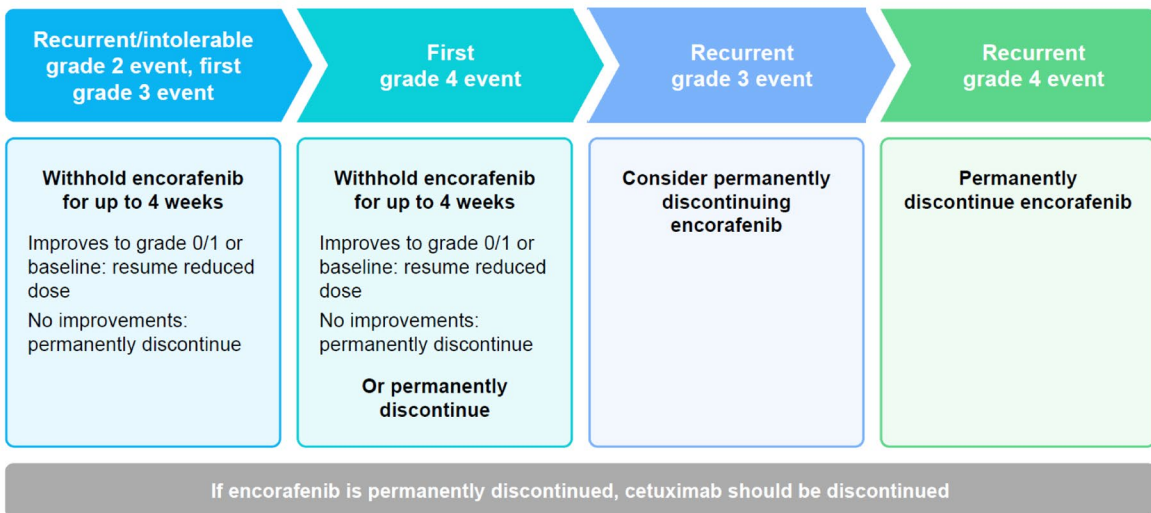
a. Encorafenib dose modifications for rash adverse events



b. Encorafenib dose modifications for liver laboratory abnormalities



c. Encorafenib dose modifications for other/general adverse events





**Fig. 3** Encorafenib dose modifications for the management of key adverse events [20, 43]. **a** Encorafenib dose modifications for rash adverse events. **b** Encorafenib dose modifications for liver laboratory abnormalities. **c** Encorafenib dose modifications for other/general adverse events. ALT alanine aminotransferase increase, AST aspartate aminotransferase increase, *ULN* upper limit of normal

### Musculoskeletal pain

Musculoskeletal side effects are common with encorafenib treatment, primarily arthralgia and myalgia. However, back pain, pain in extremities, muscular weakness and muscle spasms have also been reported [20, 32, 33]. In BEACON CRC, patients treated with encorafenib in combination with cetuximab experienced musculoskeletal pain (13%) arthralgia (23%) and myalgia (15%) [8]. Myalgia and arthralgia were generally mild or moderate in severity and grade  $\geq 3$  events were rare, resulting in very few dose modifications and no discontinuation of treatment (Table 2) [8, 43].

### Monitoring and dose modifications

Encorafenib dose modification guidance for managing musculoskeletal events follows general adverse event management guidance (Fig. 3b).

### Practical recommendations and supportive care measures

For mild symptoms of arthralgia or myalgia, patients should be advised to rest the area of pain and consider stretching, gentle exercise, massage and relaxation techniques [51]. Pain relief or low-dose corticosteroids may be used. For severe musculoskeletal events, rheumatologists should be consulted as patients may require intra-articular or high-dose steroids [33].

### Laboratory abnormalities

A range of laboratory abnormalities may be observed with encorafenib in combination with cetuximab [20]. The grading criteria for laboratory abnormalities are provided in the supplementary material.

Increases in liver laboratory values, alkaline phosphatase, bilirubin, alanine aminotransferase and aspartate aminotransferase may be observed with BRAF inhibitors [30]. In addition, creatinine elevation, which signifies impaired renal function, has been frequently reported with encorafenib monotherapy or in combination. Observed renal failure (acute kidney injury and renal impairment) is generally associated with vomiting and dehydration, due to contributing factors such as diabetes and hypertension. Elevated blood creatine kinase levels and decreased haemoglobin levels have similarly been reported in patients receiving encorafenib combinations [20].

Progressively decreasing serum magnesium levels and eventual hypomagnesaemia, due to lack of magnesium reabsorption in the kidneys, occurs frequently with cetuximab, potentially leading to heart arrhythmias, muscle weakness and psychotic symptoms [35, 52].

Over half of the patients in BEACON CRC experienced abnormal creatinine laboratory values when treated with encorafenib in combination with cetuximab. Renal, urinary and laboratory abnormalities in this group were largely mild and moderate in severity [8]. No events resulted in dose modification or discontinuation as renal or urinary adverse events were rare [43]. Liver and haematological laboratory abnormalities were more common in the control group compared with the encorafenib in combination with cetuximab group (Table 2) [8].

### Monitoring and dose modifications

Reference ranges for laboratory values may vary between institutions. Therefore, nurses should be aware of their own centre's reference ranges. For renal abnormalities (Fig. 3b), blood creatinine should be monitored as clinically indicated and creatinine elevation managed with dose modification or discontinuation. For liver laboratory abnormalities (Fig. 3c), values should be monitored before initiation of encorafenib and at least monthly during the first 6 months, then as clinically indicated [8].

For the hypomagnesaemia reported with cetuximab administration, electrolyte tests should be carried out prior to treatment, particularly for elderly patients, with re-examination once every 2–4 weeks [52]. If the patient presents with low magnesium, monitoring should increase to once weekly [53]. Grade 1 hypomagnesaemia (0.6–0.7 mmol/L) is usually asymptomatic and doesn't require treatment. Magnesium replacement is normally required for any patient with a Grade 2 hypomagnesaemia (0.4–0.5 mmol/L) and local guidelines should be followed [52, 54].

### Practical recommendations and supportive care measures

Nurses should advise patients to maintain appropriate fluid intake during treatment. Any urinary tract infections should be treated promptly. Patients must be evaluated for alternative causes of renal dysfunction and treated accordingly. Nephrologist consultation should be considered as required [43].

If magnesium is between 0.5 and 0.6 mmol/L and the patient is asymptomatic and able to tolerate oral supplementation, then this should be the preferred route for replacement. When magnesium levels are  $<0.5$  mmol/L then the IV replacement should be considered, although local guidelines should be adhered to [55]. Oral magnesium salts often cause or worsen diarrhoea and nurses should advise administration with or after food to minimise incidence and severity. If

## CHECKLIST: Encorafenib in combination with cetuximab

### Treatment

- Patients have been informed:
  - that encorafenib in combination with cetuximab is a targeted treatment and specifically targets the *BRAF<sup>V600E</sup>* mutation in their tumour
  - that encorafenib in combination with cetuximab is different to chemotherapy

### Starting treatment

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• Have all necessary pre-treatment investigations been carried out?</li> <li><input type="checkbox"/> Non-cutaneous malignancy assessments           <ul style="list-style-type: none"> <li>- Head and neck evaluation</li> <li>- Chest/abdomen CT scan</li> <li>- Complete blood cell counts</li> </ul> </li> <li><input type="checkbox"/> Dermatological evaluation           <ul style="list-style-type: none"> <li>- Examination for suspicious skin lesions</li> </ul> </li> <li><input type="checkbox"/> Blood tests           <ul style="list-style-type: none"> <li>- Liver laboratory and function tests (AST, ALT)</li> </ul> </li> <li><input type="checkbox"/> Cardiac monitoring           <ul style="list-style-type: none"> <li>- ECG</li> <li>- Electrolyte correction</li> <li>- QT prolongation</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• Patients have been informed about           <ul style="list-style-type: none"> <li><input type="checkbox"/> keeping hydrated during treatment</li> <li><input type="checkbox"/> how to store encorafenib in combination with cetuximab</li> <li><input type="checkbox"/> how to take encorafenib in combination with cetuximab</li> <li><input type="checkbox"/> any medications and foods to avoid</li> <li><input type="checkbox"/> contraception</li> <li><input type="checkbox"/> contraindications</li> </ul> </li> </ul> |
|---|---|

### Adverse event management

- Patients understand:
  - the most common adverse events that may occur, such as skin disorders, pyrexia, gastrointestinal events, cardiovascular toxicity, arthralgia, myalgia, mucosal toxicity, electrolyte imbalances and infusion reactions
  - how to recognise these key adverse events i.e., the signs and symptoms
  - what to do if they experience these signs or symptoms and who to inform
  - how these adverse events will be managed and treated
  - what they can do to help manage these adverse events
  - that if they experience X, Y, Z, they should contact their nurse or doctor immediately

### Emergencies

- Patients know:
  - in case of vomiting, they should not take an additional encorafenib dose and should take the next scheduled dose
  - any encorafenib doses omitted for adverse events or any other reason can be taken up to 12 hours prior to the next dose
  - who to contact in an emergency
  - when they should contact their nurse or doctor, and when they should go straight to hospital

### Information

- Patients have been:
  - given any suitable printed handouts e.g., patient information guide on encorafenib with cetuximab
  - directed to websites for further information
    - the following online sources may be useful to recommend to your patients seeking more information and for sharing experiences with other patients:
      - [www.esmo.org/for-patients/patient-guides/colorectal-cancer](http://www.esmo.org/for-patients/patient-guides/colorectal-cancer): European Society for Medical Oncology (ESMO) provides a colorectal cancer guide for patients
      - [www.macmillan.org.uk](http://www.macmillan.org.uk): MacMillan Cancer Support provides support and information on cancer treatments
      - [www.maggies.org](http://www.maggies.org): Maggie's provides free online support for anyone with cancer and their family
      - [www.digestivecancers.eu](http://www.digestivecancers.eu): Digestive Cancers Europe (DiCE) is an organisation representing and connecting patients with digestive cancer, including colorectal cancer.
      - [www.europecancer.org](http://www.europecancer.org): European Cancer Organisation is a patient advocacy group for the European cancer community.
    - Patients should also be directed to support available in their local area
  - Given contact details for both during- and out-of-office hours

**Fig. 4** Checklist for nurses and their patients with BRAF<sup>V600E</sup>-mutant mCRC being treated with encorafenib in combination with cetuximab. *ALT* alanine aminotransferase increase, *AST* aspartate aminotransferase increase, *BRAF* B-Raf proto-oncogene serine/threonine-protein kinase, *CT* computed tomography, *ECG* electrocardiogram

oral magnesium is not appropriate, a parenteral magnesium replacement can be considered using a magnesium sulphate infusion [55]. Follow-up blood tests should be taken as indicated by the patient's medical team.

### General adverse events

General disorders, such as fatigue, dyspnoea, pyrexia and headaches, are frequently reported with single-agent BRAF inhibitors or in combination [20, 30]. Fatigue is associated with many oral kinase inhibitors [30]. The effects are often downplayed, but chronic fatigue can have a damaging impact on quality of life and may increase as treatment progresses [30, 56]. Nurses should consider other contributing factors, including disease progression, infection, depression, haematological and biochemical laboratory abnormalities, and increased hospital visits, all of which are physically and mentally draining [30, 56].

Around a third of patients in BEACON CRC experienced fatigue when treated with encorafenib in combination with cetuximab, 20% experienced headaches and 19% experienced pyrexia. These events rarely required dose modifications or discontinuations (Table 2) [8, 43].

### Monitoring and dose modifications

Encorafenib dose modifications for managing general adverse events are shown in Fig. 3b. Of note, pyrexia experienced with targeted therapy is often better tolerated compared with pyrexia observed with chemotherapy, as they have different causes [30]. Pyrexia associated with targeted therapies, such as BRAF inhibitors, is possibly due to inflammation triggered by the inhibitor, whereas pyrexia associated with chemotherapy is largely due to neutropenic sepsis, where an infection is producing the fever [30]. Therefore, uncomplicated pyrexia in patients treated with targeted therapy is often well managed and, without complicating factors or sepsis, patients manage the fever at home with paracetamol, steroids and/or temporary dose interruption [30]. However, it is still important that patients experiencing pyrexia call the hotline team or designated local 24/7 number and are triaged as necessary to avoid missing sepsis.

### Practical recommendations and supportive care measures

For patients with chronic but tolerable diarrhoea, dietary modifications are advised including eating small and frequent

meals, introduction of a 'BRAT' diet (bananas, rice, apples and toast) and stopping lactose-containing products. Treatment with the anti-diarrheal loperamide can also be considered, once infective causes have been excluded [30, 43]. For pyrexia, oral antibiotics and IV fluids can be administered as needed. Paracetamol can be administered with caution as can mask fever [30]. For general adverse events, advise patients to drink plenty of fluids, eat healthily, exercise regularly if possible and rest. Pain relief can be used as appropriate [43].

### Patient and caregiver education

Education has become an important part of nursing care and involves counselling, informing and training patients [57]. Nurses have a role in educating patients and their caregivers on the disease and treatments they are receiving and possible adverse events. When switching to encorafenib in combination with cetuximab after prior systemic therapy, patients may have many questions and concerns. Nurses play a pivotal role in mitigating concerns and providing education on this treatment and its differentiation from other therapies. Patients may have previously received or be aware of chemotherapy and immunotherapy and nurses should be prepared to discuss how targeted therapy differs, including efficacy profiles, adverse event profiles and administration routes.

Patients also need to be aware of possible adverse events with encorafenib in combination with cetuximab, including signs and symptoms, to identify such events for efficient and effective management. Patients should also understand preventative measures and adverse events management, should these adverse events arise. Patients and their primary caregivers must be made aware of contacts for advice on adverse events and when to go to the hospital. Often, this is a hospital hotline providing a 24-h nurse-led telephone service.

The COVID-19 pandemic has exemplified how circumstances can make it difficult to reach patients and caregivers, so equipping patients and caregivers with the right information upfront is crucial. Increased patient education will contribute to efficient identification of adverse events and their timely management, leading to an improved quality of life, increased adherence to treatment and, therefore, maximal treatment benefits. Checklists that nurses can go through with patients would implement a formalised process ensuring patients are receiving all the correct information in a timely manner. A checklist could also improve confidence for both nurses and patients that processes for preventing and managing adverse events are completed accurately and thoroughly. Figure 4 shows an example checklist specifically for nurses and their patients with BRAF<sup>V600E</sup>-mutant mCRC being treated with encorafenib in combination with cetuximab.

## Conclusions

Nurses play an important role in managing and caring for patients with *BRAF*<sup>V600E</sup>-mutant mCRC. Nurses are pivotal in the prevention, early and efficient identification and subsequent management of treatment-related adverse events. This increases adherence to treatment by enabling patients to remain on treatment at the most optimal doses and duration, therefore maximising the treatment benefit and outcomes. An important part of the efficient identification and management of adverse events is the education of patients and their caregivers, which nurses can provide during the day-to-day management of patients. With efficient identification, management or even prevention of adverse events, patients should be able to remain on encorafenib in combination with cetuximab and obtain maximal treatment benefits.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00520-023-07579-9>.

**Acknowledgements** Medical writing support was provided by Paige Johnson and Danielle Walsh of Meditech Media and Chrysalis Medical Communications, both part of Nucleus Global Ltd., and was funded by Pierre Fabre. The authors were responsible for all content and editorial decisions.

**Author contribution** The authors were responsible for all content and editorial decisions. All authors were involved in material preparation, writing, reviewing, editing and conceptualization of the manuscript. All authors reviewed and commented on each version of the manuscript. All authors read and approved the final version of the manuscript.

**Funding** Medical writing support was provided by Paige Johnson and Danielle Walsh of Meditech Media and Chrysalis Medical Communications, both part of Nucleus Global Ltd., and was funded by Pierre Fabre. The authors were responsible for all content and editorial decisions. The authors received no payment for the development of this manuscript. Pierre Fabre checked the manuscript for scientific accuracy only.

## Declarations

**Ethics approval** This manuscript does not report a scientific study; therefore, no ethics approval is required.

**Consent to participate** This manuscript does not report a scientific study; therefore, no informed consent was obtained.

**Consent for publication** The authors affirm that their patients provided informed consent for publication of the patient images in Fig. 2c.

**Competing interests** Mathew Fowler (corresponding author) was an advisory board member for Vygon and received honoraria from Sanofi. Helene Tobback, Alice Karuri and Paz Fernandez-Ortega have no relevant financial or non-financial interests to disclose.

## References

1. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, Gavin A, Visser O, Bray F (2018) Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 103:356–387
2. Chiorean EG, Nandakumar G, Fadelu T, Temin S, Alarcon-Rozas AE, Bejarano S, Croitoru A-E, Grover S, Lohar PV, Odhiambo A (2020) Treatment of patients with late-stage colorectal cancer: ASCO resource-stratified guideline. *JCO Glob Oncol* 6:414–438
3. Christensen TD, Jensen SG, Larsen FO, Nielsen DL (2018) Systematic review: incidence, risk factors, survival and treatment of bone metastases from colorectal cancer. *J Bone Oncol* 13:97–105
4. Pretzsch E, Bösch F, Neumann J, Ganschow P, Bazhin A, Guba M, Werner J, Angele M (2019) Mechanisms of metastasis in colorectal cancer and metastatic organotropism: hematogenous versus peritoneal spread. *J Oncol* 2019:7407190
5. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K et al (2016) ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 27:1386–1422
6. Xie Y-H, Chen Y-X, Fang J-Y (2020) Comprehensive review of targeted therapy for colorectal cancer. *Signal Transduct Targeted Ther* 5:1–30
7. Dinu D, Dobre M, Panaitescu E, Bîrlă R, Iosif C, Hoara P, Caragui A, Boeriu M, Constantinoiu S, Ardeleanu C (2014) Prognostic significance of KRAS gene mutations in colorectal cancer-preliminary study. *J Med Life* 7:581
8. Tabernero J, Grothey A, Van Cutsem E, Yaeger R, Wasan H, Yoshino T, Desai J, Ciardiello F, Loupakis F, Hong YS (2021) Encorafenib plus cetuximab as a new standard of care for previously treated BRAF V600E-mutant metastatic colorectal cancer: Updated Survival results and subgroup analyses from the BEACON study. *J Clin Oncol* 39:273–284
9. ESMO (2020) ESMO pocket guidelines: Lower gastrointestinal cancer. Available at: [http://interactiveguidelines.esmo.org/esmo-web-app/home/gl\\_home.php?GL=45](http://interactiveguidelines.esmo.org/esmo-web-app/home/gl_home.php?GL=45). Accessed September 2021
10. Taieb J, Lapeyre-Prost A, Laurent Puig P, Zaanani A (2019) Exploring the best treatment options for BRAF-mutant metastatic colon cancer. *Br J Cancer* 121:434–442
11. Bond CE, Whitehall VL (2018) How the BRAF V600E mutation defines a distinct subgroup of colorectal cancer: molecular and clinical implications. *Gastroenterol Res Pract* 2018:925075
12. Corcoran RB, André T, Atreya CE, Schellens JH, Yoshino T, Bendell JC, Hollebecque A, McRee AJ, Siena S, Middleton G (2018) Combined BRAF, EGFR, and MEK inhibition in patients with BRAFV600E-mutant colorectal cancer. *Cancer Discov* 8:428–443
13. Roviello G, D'Angelo A, Petrioli R, Roviello F, Cianchi F, Nobili S, Mini E, Lavacchi D (2020) Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. *Transl Oncol* 13:100795
14. Corcoran RB, Ebi H, Turke AB, Coffee EM, Nishino M, Cogdill AP, Brown RD, Della Pelle P, Dias-Santagata D, Hung KE (2012) EGFR-mediated reactivation of MAPK signaling contributes to insensitivity of BRAF-mutant colorectal cancers to RAF inhibition with vemurafenib. *Cancer Discov* 2:227–235
15. Hong DS, Morris VK, El Osta B, Sorokin AV, Janku F, Fu S, Overman MJ, Piha-Paul S, Subbiah V, Kee B, Tsimberidou AM, Fogelman D, Bellido J, Shureiqi I, Huang H, Atkins J, Tarcic G, Sommer N, Lanman R et al (2016) Phase IB Study of vemurafenib in combination with irinotecan and cetuximab in patients with metastatic colorectal cancer with BRAFV600E mutation. *Cancer Discov* 6:1352–1365
16. Prahallad A, Sun C, Huang S, Di Nicolantonio F, Salazar R, Zecchin D, Beijersbergen RL, Bardelli A, Bernards R (2012) Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature* 483:100–103



17. Van Cutsem E, Huijberts S, Grothey A, Yaeger R, Cuyle P-J, Elez E, Fakih M, Montagut C, Peeters M, Yoshino T (2019) Binimetinib, encorafenib, and cetuximab triplet therapy for patients with BRAF V600E-mutant metastatic colorectal cancer: safety lead-in results from the phase III BEACON Colorectal Cancer Study. *J Clin Oncol* 37:1460
18. FDA (2020) FDA approves encorafenib in combination with cetuximab for metastatic colorectal cancer with a BRAF V600E mutation. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-combination-cetuximab-metastatic-colorectal-cancer-braf-v600e-mutation>. Accessed September 2021
19. Pierre Fabre Medicament (2020) Pierre Fabre receives European approval for BRAFTOVI® (encorafenib). Available at: [https://www.pierre-fabre.com/en/press\\_release/pierre-fabre-receives-european-approval-for-braftovir-encorafenib](https://www.pierre-fabre.com/en/press_release/pierre-fabre-receives-european-approval-for-braftovir-encorafenib). Accessed September 2021
20. Pierre Fabre Medicament (2020) BRAFTOVI® (encorafenib). Summary of product characteristics Available at: [https://www.ema.europa.eu/en/documents/product-information/braftovi-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/braftovi-epar-product-information_en.pdf)
21. Pfizer (2020) Taking BRAFTOVI + MEKTOVI. Available at: <https://www.braftovimektovi.com/taking-braftovi-mektovi/>
22. Aikens JE, Trivedi R, Aron DC, Piette JD (2015) Integrating support persons into diabetes telemonitoring to improve self-management and medication adherence. *J Gen Intern Med* 30:319–326
23. Riegel B, Stephens-Shields A, Jaskowiak-Barr A, Daus M, Kimmel SE (2020) A behavioral economics-based telehealth intervention to improve aspirin adherence following hospitalization for acute coronary syndrome. *Pharmacoepidemiology and drug safety* 29:513–517
24. Turner AP, Sloan AP, Kivlahan DR, Haselkorn JK (2014) Telephone counseling and home telehealth monitoring to improve medication adherence: results of a pilot trial among individuals with multiple sclerosis. *Rehabil Psychol* 59:136
25. Hergert J (2021) Biweekly Cetuximab offers a convenient dosing option in mCRC. Available at: <https://www.onclive.com/view/biweekly-cetuximab-offers-a-convenient-dosing-option-in-mcrc>. Accessed September 2021
26. Matsuda A, Yamada T, Jmjitrongs S, Shinji S, Ohta R, Sonoda H, Kamonvarapitak T, Sekiguchi K, Miyashita M, Suzuki H, Yoshida H (2020) Comparison between biweekly and weekly cetuximab in patients with metastatic colorectal cancer: a meta-analysis. *Anticancer Res* 40:3469–3476
27. Zekri J, Farag K, Al-Saadi R, Ashour M, Haggag R (2016) Safety and efficacy of biweekly cetuximab based chemotherapy for patients with metastatic colorectal cancer. *J Unexplored Med Data* 1:15–20
28. Hofheinz R-D, Segart S, Safont MJ, Demonty G, Prenen H (2017) Management of adverse events during treatment of gastrointestinal cancers with epidermal growth factor inhibitors. *Critical Reviews in Oncology/Hematology* 114:102–113
29. Sanchez JN, Wang T, Cohen MS (2018) BRAF and MEK inhibitors: use and resistance in BRAF-mutated cancers. *Drugs* 78:549–566
30. Welsh SJ, Corrie PG (2015) Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol* 7:122–136
31. Livingstone E, Zimmer L, Vaubel J, Schadendorf D (2014) BRAF, MEK and KIT inhibitors for melanoma: adverse events and their management. *Chin Clin Oncol* 3:29–29
32. Mackin AG, Pecan PE, Dinsmore AL, Patnaik JL, Gonzalez R, Robinson WA, Palestine AG (2019) Inflammatory side effects of BRAF and MEK inhibitors. *Melanoma Res* 29:522–526
33. Heinzerling L, Eigentler TK, Fluck M, Hassel JC, Heller-Schenck D, Leipe J, Pauschinger M, Vogel A, Zimmer L, Gutzmer R (2019) Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management. *ESMO Open* 4:e000491
34. Mincu RI, Mahabadi AA, Michel L, Mrotzek SM, Schadendorf D, Rassaf T, Totzeck M (2019) Cardiovascular adverse events associated with BRAF and MEK inhibitors: a systematic review and meta-analysis. *JAMA Network Open* 2:e198890–e198890
35. Merck (2020) ERBITUX® (cetuximab) Summary of product characteristics available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/erbitux>
36. Damsky W, Bosenberg M (2017) Melanocytic nevi and melanoma: unraveling a complex relationship. *Oncogene* 36:5771–5792
37. Mochel MC, Hammond MR, Frederick DT, Alora-Palli MB, Piris A, Flaherty KT, Hoang MP (2015) Melanocytic nevi excised during B-Raf proto-oncogene (BRAF) inhibitor therapy: a study of 19 lesions from 10 patients. *J Am Acad Dermatol* 73(491–499):e492
38. Dalle S, Poulalhon N, Debarbieux S, Zaharia D, Mihm MC, Lacouture ME, Rosen A, Marghoob AA, Busam KJ, Depaepe L (2013) Tracking of second primary melanomas in vemurafenib-treated patients. *JAMA Dermatol* 149:488–490
39. Göppner D, Müller J, Krüger S, Franke I, Gollnick H, Quist SR (2014) High incidence of naevi-associated BRAF wild-type melanoma and dysplastic naevi under treatment with the class I BRAF inhibitor vemurafenib. *Acta Derm Venereol* 94:517–520
40. Zimmer L, Hillen U, Livingstone E, Lacouture ME, Busam K, Carvajal RD, Egberts F, Hauschild A, Kashani-Sabet M, Goldinger SM (2012) Atypical melanocytic proliferations and new primary melanomas in patients with advanced melanoma undergoing selective BRAF inhibition. *J Clin Oncol* 30:2375
41. Rubin KM (2017) MAPK pathway-targeted therapies: care and management of unique toxicities in patients with advanced melanoma. *Clin J Oncol Nurs* 21:699–709
42. Urban C, Anadkat MJ (2013) A review of cutaneous toxicities from targeted therapies in the treatment of colorectal cancers. *J Gastrointest Oncol* 4:319
43. Tabernero J, Velez L, Trevino TL, Grothey A, Yaeger R, Van Cutsem E, Wasan H, Desai J, Ciardiello F, Yoshino T (2020) Management of adverse events associated with encorafenib plus cetuximab in patients with BRAF V600E mutant metastatic colorectal cancer (The BEACON CRC Study). *Hemoglobin* 39:46
44. Hassel JC, Kripp M, Al-Batran S, Hofheinz R-D (2010) Treatment of epidermal growth factor receptor antagonist-induced skin rash: results of a survey among German oncologists. *Onkologie* 33:94–98
45. Lacouture M, Sibaud V (2018) Toxic side effects of targeted therapies and immunotherapies affecting the skin, oral mucosa, hair, and nails. *Am J Clin Dermatol* 19:31–39
46. Cancer Net (2019) Skin conditions. Available at: <https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/skin-conditions>. Accessed August 2020
47. Dermatology AAo (2019) Sunscreen FAQs. Available at: <https://www.aad.org/public/everyday-care/sun-protection/sunscreen-patients/sunscreen-faqs>. Accessed November 2021
48. Ocvirk J, Heeger S, McCloud P, Hofheinz R-D (2013) A review of the treatment options for skin rash induced by EGFR-targeted therapies: Evidence from randomized clinical trials and a meta-analysis. *Radiol Oncol* 47:166
49. Romito F, Giuliani F, Cormio C, Tulipani C, Mattioli V, Colucci G (2010) Psychological effects of cetuximab-induced cutaneous rash in advanced colorectal cancer patients. *Support Care Cancer* 18:329–334
50. Wu PA, Balagula Y, Lacouture ME, Anadkat MJ (2011) Prophylaxis and treatment of dermatologic adverse events from epidermal growth factor receptor inhibitors. *Curr Opin Oncol* 23:343–351
51. Cancer Net (2018) Muscle aches. Available at: <https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/skin-conditions>

- [ts-cancer/managing-physical-side-effects/muscle-aches](#). Accessed August 2020
52. Zhang B, Fang C, Deng D, Xia L (2018) Research progress on common adverse events caused by targeted therapy for colorectal cancer. *Oncol Lett* 16:27–33
  53. Peniket A, Maoche N (2015) Guidelines for the management of hypomagnesaemia in adult clinical haematology patients. Available at: <http://nssg.oxford-haematology.org.uk/oxford/clinical-care/H-95-guidelines-for-management-of-hypomagnesaemia-in-adult-clinical-haematology.pdf>. Accessed September 2021
  54. NCI (2017) Common terminology criteria for adverse events (CTCAE), version 5.0 Available at: [https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)
  55. Preece D (2020) How is acute hypomagnesaemia treated in adults? Available at: [https://www.sps.nhs.uk/wp-content/uploads/2016/01/UKMI\\_QA\\_How\\_is\\_acute\\_hypomagnesemia\\_treated\\_in\\_adults\\_update\\_Nov\\_2020.pdf](https://www.sps.nhs.uk/wp-content/uploads/2016/01/UKMI_QA_How_is_acute_hypomagnesemia_treated_in_adults_update_Nov_2020.pdf). Accessed September 2021
  56. Cancer Net (2020) Fatigue. Available at: <https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/fatigue>. Accessed August 2020
  57. Strupeit S, Buß A, Dassen T (2013) Effectiveness of nurse-delivered patient education interventions on quality of life in outpatients: a systematic review. *Appl Nurs Res* 26:232–238

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.