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Treatment experience with encorafenib plus binimetinib for *BRAF* V600-mutant metastatic melanoma: management insights for clinical practice

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For patients with locally advanced or metastatic melanoma who have *BRAF* V600 activating mutations, combination therapy with BRAF and MEK inhibitors is now the standard of care. The combination of encorafenib, a highly selective adenosine triphosphate–competitive BRAF inhibitor, plus binimetinib, a potent, selective, allosteric, non–adenosine triphosphate-competitive MEK1/2 inhibitor, was approved by the US Food and Drug Administration for unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations based on data from the phase III COLUMBUS study (NCT01909453). Clinical data evaluating BRAF and MEK inhibitor combinations in advanced melanoma indicate a specific profile of adverse events that includes serious retinopathy, skin disorders, and cardiovascular toxicities. Here we provide an overview of the rationale for combining BRAF and MEK inhibitors for the treatment of melanoma, long-term safety results from COLUMBUS, and guidance on managing the most common adverse events associated with this combination based on clinical experience. Proactive and appropriate management of adverse events can allow for longer treatment durations and may result in better treatment outcomes. *Melanoma Res* 33: 406–416 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

The treatment landscape for melanoma has changed dramatically over the last 10 years. Prior to 2010, chemotherapy agents and cytokines were the most commonly used treatments. The efficacy of these agents was poor, with an estimated survival of 6–9 months [1]. Since then, several new treatments – BRAF, MEK, immune checkpoint inhibitors; and Talimogene laherparepvec – have been approved and have greatly improved tumor responses and overall survival (OS) in patients with this aggressive cancer [2].

This review focuses on BRAF and MEK inhibitors and the rationale for combining them for melanoma treatment, summarizes long-term safety results from the phase III COLUMBUS study (NCT01909453), and provides guidance on managing the most common adverse events associated with this combination based on clinical experience. Correctly managing adverse events can allow longer treatment durations and may result in better treatment outcomes.

With these points in mind, the choice of treatment regimen is key and largely guided by the safety profile and convenience amongst oncologists. It is the experiences of the authors here that when a choice for a combination is made, the early toxicities are managed by withholding therapy or dose reductions; however, if issues persist beyond one or two attempts at dose modification then we would switch to another combination.

BRAF inhibitors

BRAF is a serine/threonine protein kinase in the RAF/MEK/ERK serine-threonine kinase cascade (MAPK signaling pathway). This pathway regulates cellular functions including growth, proliferation, differentiation, and survival. *BRAF* mutations, most commonly V600E or V600K, are found in about half of cutaneous melanomas [3–6]. *BRAF*-mutant melanomas have a worse prognosis and greater likelihood of metastasizing to the brain than *BRAF* wild-type melanomas [7,8].

The discovery of *BRAF* mutations and the knowledge of how they contribute to melanoma progression have led to the development of small-molecule inhibitors of BRAF, such as vemurafenib, dabrafenib, and encorafenib. Vemurafenib was the first to be approved in 2011 based on data from the BRIM-3 study (NCT01006980), in

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which vemurafenib treatment resulted in a median OS of 13.6 versus 9.7 months with dacarbazine [hazard ratio 0.81; 95% confidence interval (CI), 0.67–0.98] [9,10]. In the BREAK-3 study (NCT01227889), dabrafenib demonstrated a median OS of 20.0 versus 15.6 months with dacarbazine (hazard ratio 0.77; 95% CI, 0.52–1.13) after a median follow-up of 16.9 months [11]. Finally, in COLUMBUS, encorafenib 300 mg once daily treatment arm showed a median OS of 23.5 versus 16.9 months with vemurafenib (hazard ratio 0.61; 95% CI, 0.48–0.79) [12]. Increased OS with encorafenib can be explained by its long dissociation half-life (10 times longer than dabrafenib or vemurafenib), allowing sustained targeted inhibition and enhanced antitumor activity while reducing paradoxical activation of MAPK pathways in normal tissue [13,14]. Although BRAF inhibitor monotherapy improved efficacy, there were concerns regarding the development of resistance and adverse events.

MEK inhibitors

The discovery of *BRAF* mutations and the success of BRAF inhibitors also led to the development of MEK inhibitors and their evaluation as treatments for melanoma. Over the last decade, the US Food and Drug Administration (FDA) approved three MEK inhibitors for melanoma treatment: trametinib, binimetinib, and cobimetinib [15–17]. Only trametinib is approved as monotherapy for *BRAF* V600-mutant melanoma; in the phase III METRIC study (NCT01245062), median OS with trametinib was 15.6 versus 11.3 months with chemotherapy (dacarbazine or paclitaxel; hazard ratio 0.84; 95% CI, 0.63–1.11) [17,18]. There are no phase III studies of binimetinib monotherapy in patients with *BRAF*-mutant melanoma; however, in the phase III NEMO study (NCT01763164) in patients with *NRAS*-mutant melanoma, median OS with binimetinib was 11.0 versus 10.1 months with dacarbazine (hazard ratio 1.00, 95% C,I 0.75–1.33) [19]. There are no phase III studies of cobimetinib monotherapy in melanoma. In a phase I study that enrolled 74 patients with advanced solid tumors, treatment with single-agent cobimetinib resulted in partial responses in seven patients; all but one had *BRAF* V600E-mutant melanoma [20].

Combining BRAF and MEK inhibitors

The main resistance mechanism to BRAF inhibitors is via persistent activation or reactivation of the MAPK pathway [5]. Inhibiting two proteins in this pathway was, therefore, explored as an option to prevent tumor resistance and encourage more sustained treatment responses. Compared with BRAF inhibitor monotherapy, dual inhibition of the MAPK pathway with BRAF and MEK inhibitors has shown improved efficacy and reduced toxicities associated with paradoxical MAPK pathway reactivation [21–23]. Combination treatment with MEK inhibitors mitigates the risk of secondary cutaneous malignancies and other hyperproliferative skin lesions associated with BRAF inhibitor monotherapy [5].

Currently, three FDA-approved BRAF + MEK inhibitor combinations are available for the treatment of advanced *BRAF*-mutant melanoma: vemurafenib + cobimetinib, dabrafenib + trametinib, and encorafenib + binimetinib [15,16,24]. In the phase III coBRIM study (NCT01689519), median OS with vemurafenib + cobimetinib was 22.3 versus 17.4 months with vemurafenib alone (hazard ratio 0.70; 95% CI, 0.55–0.90) [25]. In the phase III COMBI-d study (NCT01584648), median OS with dabrafenib + trametinib was 25.1 versus 18.7 months with dabrafenib alone (hazard ratio 0.71; 95% CI, 0.55–0.92) [26]. Finally, in COLUMBUS, encorafenib + binimetinib treatment resulted in a median OS of 33.6 versus 23.5 months with encorafenib alone (hazard ratio 0.81; 95% CI, 0.61–1.06) [21]. Clinical data for encorafenib + binimetinib are discussed in the next section.

With BRAF + MEK inhibitors, class effects such as gastrointestinal and cutaneous adverse events, myalgia, and arthralgia occur; however, each combination has a unique safety profile [27,28]. Photosensitivity reactions and pyrexia were more common with vemurafenib + cobimetinib and dabrafenib + trametinib, respectively, than with encorafenib + binimetinib. Furthermore, hypertension, cough, and chills were more common with dabrafenib + trametinib; diarrhea, arthralgia, rash, and increased alanine aminotransferase were more common with vemurafenib + cobimetinib; and elevated blood creatine phosphokinase was more common with encorafenib + binimetinib. Vemurafenib + cobimetinib is also associated with more grade ≥3 adverse events than other combinations [29]. Adverse events may result in treatment interruptions, dose reductions, modifications, or discontinuation, which can lead to earlier resistance development. Therefore, proactive management of adverse events is essential to ensure that patients derive the most treatment benefit.

Encorafenib + binimetinib in clinical studies

Phase Ib/II study

Safety data for encorafenib + binimetinib have been reported from an open-label, dose-finding, phase Ib/II study (NCT01543698) in 126 patients with *BRAF* V600E-mutant solid tumors, including BRAF inhibitor-naive and BRAF inhibitor-treated metastatic melanoma [30]. Median duration of therapy was 11.1 (range 0.8–26.4) months in the BRAF inhibitor-naive group ($n = 42$) and 4.3 (range 0.2–23.2) months in the BRAF inhibitor-treated group ($n = 26$). All patients in phase II experienced adverse events. The most common adverse events (all grades) occurring in ≥25% of patients in BRAF inhibitor-naive and inhibitor-treated melanoma populations, respectively, were diarrhea (45%, 54%), nausea

(48%, 42%), vomiting (33%, 35%), pyrexia (33%, 23%), arthralgia (31%, 27%), fatigue (29%, 39%), increased alanine aminotransferase (31%, 23%), and constipation (26%, 19%). Most adverse events were mild or moderate. The rates of grade 3 and 4 events, respectively, for these adverse events, were as follows: diarrhea (2%, 4%), nausea (5%, 12%), vomiting (5%, 12%), pyrexia (5%, 0%), arthralgia (0%, 0%), fatigue (0%, 4%), increased alanine aminotransferase (12%, 4%), and constipation (0%, 0%) [30].

Phase III COLUMBUS study

The two-part, multicenter, randomized, open-label, phase III COLUMBUS study included patients with locally advanced unresectable or metastatic *BRAF* V600-mutant melanoma who were untreated or progressed on or after first-line immunotherapy [21]. In Part 1, patients were randomized (1 : 1 : 1) to encorafenib 450 mg once daily + binimetinib 45 mg twice daily, encorafenib 300 mg once daily, or vemurafenib 960 mg twice daily [21]. Full details of the study design and efficacy results have been published [12,21]. At data cutoff (November 2018), 98.4% experienced any adverse event, and 68.2% experienced grade 3/4 adverse events with encorafenib + binimetinib. Most adverse events were mild or moderate (grade 1/2). The incidence of grade 3/4 adverse events ranged from 0 to 2.6%, except for increased blood creatine phosphokinase (7.8%) and pyrexia (3.6%) (Table 1; Fig. 1a) [12]. Adverse events led to discontinuation in 16%, 15%, and 17% of patients and dose reduction or interruption in 55%, 71%, and 62% of patients in the encorafenib + binimetinib, encorafenib, and vemurafenib arms, respectively [12].

Table 1 Summary of adverse events reported in ≥20% of patients treated with encorafenib 450 mg once daily + binimetinib 45 mg twice daily in COLUMBUS (*N* = 192) [12]

Adverse event, *n* (%)	All grades	Grade 3/4
Gastrointestinal disorders		
Nausea	84 (43.8)	4 (2.1)
Diarrhea	74 (38.5)	5 (2.6)
Vomiting	61 (31.8)	4 (2.1)
Constipation	48 (25.0)	0
Decreased appetite	19 (9.9)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	55 (28.6)	2 (1.0)
Myalgia	31 (16.1)	0
Pain in extremity	23 (12.0)	2 (1.0)
General disorders and administration site conditions		
Fatigue	57 (29.7)	4 (2.1)
Asthenia	42 (21.9)	3 (1.6)
Pyrexia	38 (19.8)	7 (3.6)
Skin and subcutaneous tissue disorders		
Dry skin	31 (16.1)	0
Rash	31 (16.1)	3 (1.6)
Hyperkeratosis	29 (15.1)	1 (0.5)
Alopecia	28 (14.6)	0
Pruritus	24 (12.5)	1 (0.5)
Palmoplantar keratoderma	19 (9.9)	0
Hand-foot syndrome	14 (7.3)	0
Keratosis pilaris	9 (4.7)	0
Photosensitivity	7 (3.6)	1 (0.5)
Other		
Increased blood creatine phosphokinase	50 (26.0)	15 (7.8)
Headache	49 (25.5)	4 (2.1)

Data cutoff: November 2018.

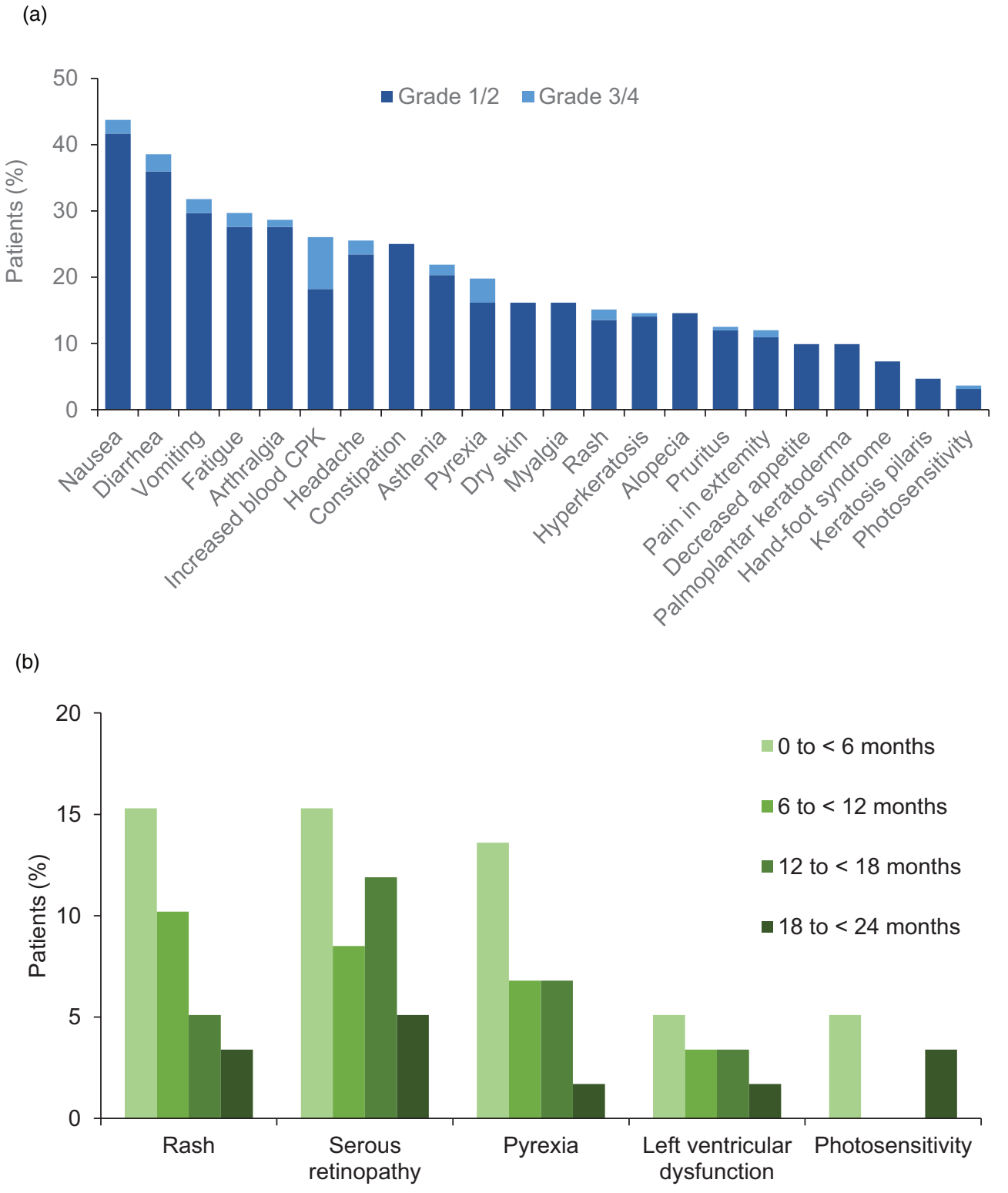
The most frequently reported adverse events with encorafenib + binimetinib (all grades, ≥20% of patients) were gastrointestinal disorders, including nausea (43.8%), diarrhea (38.5%), vomiting (31.8%), and constipation (25.0%; Table 1; Fig. 1a) [12]. Other common adverse events included arthralgia, myalgia, fatigue, headache, pyrexia, and skin and subcutaneous tissue disorders. Arthralgia and myalgia occurred in 28.6 and 16.1% of patients, respectively [12]. Most events were mild or moderate; the incidence of grade 3/4 arthralgia and myalgia was 1 and 0%, respectively [12].

Fatigue, headache, and pyrexia events with encorafenib + binimetinib were generally mild. Incidence of all-grade fatigue, headache, and pyrexia was 29.7%, 25.5%, and 19.8%, respectively; the incidence of grade 3/4 events was 2.1% each for fatigue and headache, and 3.6% for pyrexia. Incidence of pyrexia was highest during the first 6 months of therapy (13.6%; Fig. 1b) [12].

The most common skin and subcutaneous tissue disorders reported with encorafenib + binimetinib were rashes (16.1%), dry skin (16.1%), hyperkeratosis (15.1%), and pruritus (12.5%). Lower incidences of palmoplantar keratoderma (9.9%), hand-foot syndrome (7.3%), and keratosis pilaris (4.7%) occurred. The incidence of rash was highest during the first 6 months of therapy (15.3%) and decreased to 3.4% during 18–<24 months (Fig. 1b). Photosensitivity (any grade) was reported in 3.6% of patients; one patient experienced a grade 3/4 event [12]. Serous retinopathy was reported in 23% of patients; of the 59 patients who received encorafenib + binimetinib for ≥24 months, the incidence ranged from 15.3% in the first 6 months to 5.1 to 11.9% during each 6-month period thereafter, up to 24 months [12]. In COLUMBUS, left ventricular dysfunction (LVD) was assessed by multigated acquisition scan (MUGA) or echocardiogram on day 1 of cycles 2, 3, 6, and 9, and every 12 weeks thereafter [31]. The incidence of LVD decreased throughout the study; 5.1%, 3.4%, 3.4%, and 1.7% of patients had LVD during months 0–<6, 6–<12, 12–<18, and 18–<24, respectively (Fig. 1b) [12].

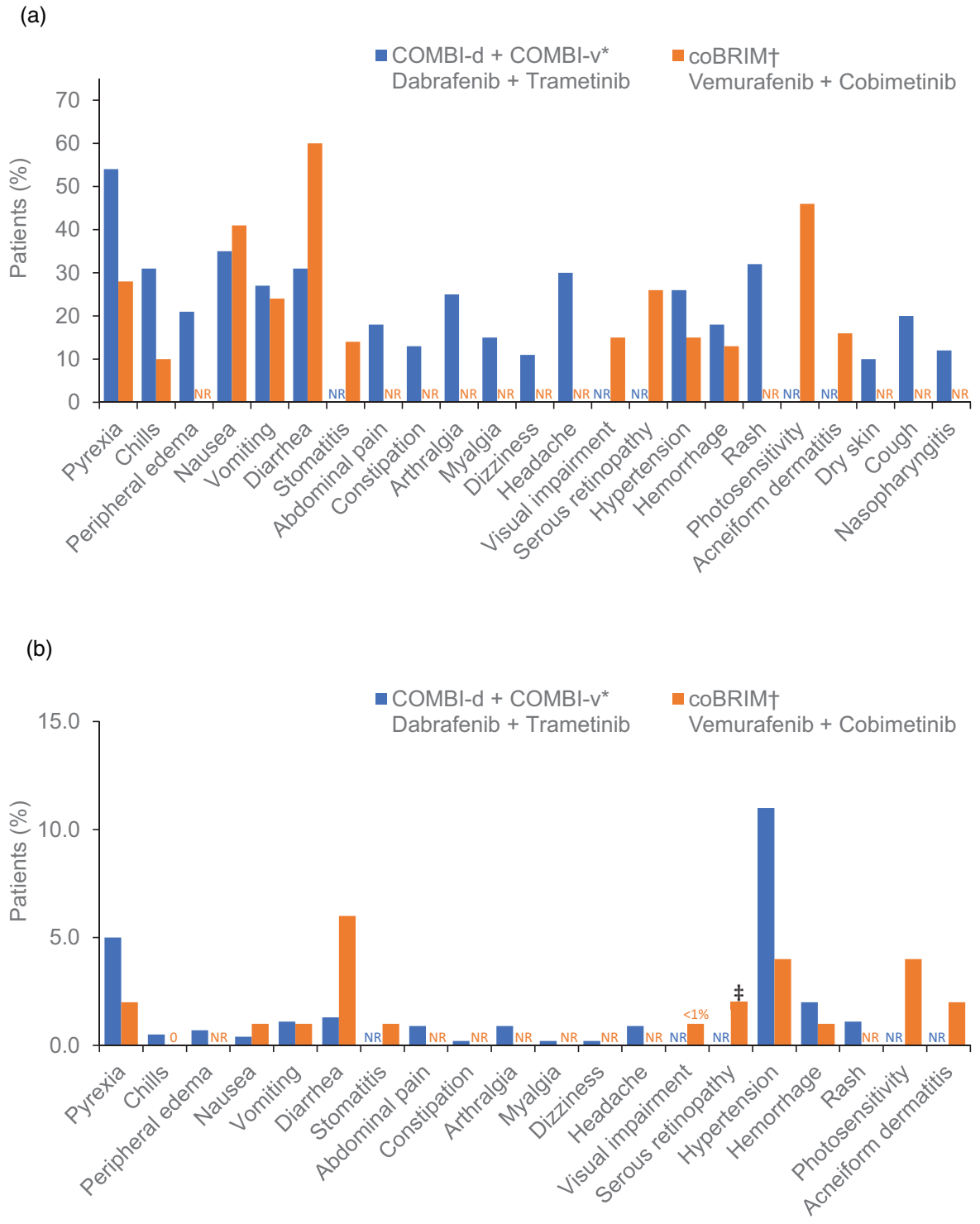
The rates of serous retinopathy, LVD, and skin disorders with encorafenib + binimetinib in COLUMBUS were largely consistent with those observed in other BRAF/MEK inhibitor studies (Fig. 2) [12,25,32]. Although no direct comparisons by randomized trials are available, rates of pyrexia (19.8%) and photosensitivity (3.6%) with encorafenib + binimetinib were similar or lower than those reported for other BRAF/MEK inhibitor combinations [12,31]. In the COMBI-d study of dabrafenib + trametinib, all-grade photosensitivity rates ranged from 3

Fig. 1



(a) Summary of adverse events reported in ≥20% of patients treated with encorafenib 450 mg once daily + binimetinib 45 mg twice daily in COLUMBUS. (b) Incidence of select adverse events of interest occurring in the first 24 months in patients treated with encorafenib 450 mg once daily + binimetinib 45 mg twice daily in COLUMBUS [12]. The denominator of each category is 59, which is the total number of patients treated with encorafenib 450 mg once daily + binimetinib 45 mg twice daily for at least 24 months. Patients who had the same adverse event in multiple time ranges are counted in each time range. CPK, creatine phosphokinase.

Fig. 2



Summary of adverse events reported in ≥10% of patients receiving combination therapy [44–46]. *The comparator arm in COMBI-d was dabrafenib + placebo and in COMBI-v was single-agent vemurafenib. These graphs show the pooled incidence of select adverse events occurring in ≥10% (all grades) of patients ($N = 559$) treated with dabrafenib + trametinib and the incidence of adverse events occurring in ≥10% (all grades) of patients receiving trametinib + dabrafenib and at a higher incidence (≥5% for all grades or ≥2% for grades 3–4) than in patients receiving single-agent dabrafenib; †The comparator arm in coBRIM was vemurafenib + placebo [44,45]. These graphs show the incidence of adverse events occurring in ≥10% (all grades) of patients ($N = 247$) receiving cobimetinib + vemurafenib and at a higher incidence (≥5% for all grades or ≥2% for grades 3–4) than patients receiving vemurafenib; ‡Combines chorioretinopathy (13% all grades; <1% grades 3–4) and retinal detachment (12% all grades; 2% grades 3–4) [46]. NR, not reported.

Table 2 Management of adverse events reported with encorafenib + binimetinib in patients with advanced *BRAF* V600E-mutant melanoma [15,33–38]

Adverse event	Signs and symptoms	Supportive care, monitoring, and management
Nausea or vomiting	Loss of appetite, dehydration, malnutrition, electrolyte imbalance, weakness, weight loss	Ensure fluid replacement to avoid dehydration Frontline therapy for moderate to high emetic potential: 5-HT3 receptor antagonists (granisetron, ondansetron, or dolasetron) Breakthrough nausea agents include: dexamethasone, lorazepam, metoclopramide, olanzapine, prochlorperazine Monitor QT prolongation on ECG if prescribing olanzapine, metoclopramide, or 5-HT3 receptor antagonists Modify the dose of encorafenib and binimetinib or discontinue therapy
Diarrhea	Dehydration, malnutrition, electrolyte imbalance, low immune function, inflammation, abdominal pain	Standard supportive care, including dietary modification (eat frequent small meals, increase fluid intake, replace lost salts, reduce fiber consumption) Consider treatment with loperamide, diphenoxylate/atropine, octreotide, or codeine Rule out infectious etiologies Modify or delay the dose of encorafenib/binimetinib until symptoms resolve to grade ≤1 or baseline; restart at a lower dose If needed, hospitalize for intravenous rehydration and electrolyte replacement Check a stool culture if diarrhea persists for >24 h; consider antibiotics if fever or grade 3/4 neutropenia occur with diarrhea If needed, discontinue therapy Consider colonoscopy to assess for colitis and exclude infectious cause
Myalgia/arthralgia	Muscle pain, joint pain	Advise patients to take simple analgesics or NSAIDs Myositis or vasculitis may require medium/high-dose corticosteroids Withhold encorafenib until grade ≤1; optimize analgesia with NSAIDs Restart encorafenib at a reduced dose upon recovery If symptoms recur, withhold encorafenib until grade ≤1; consider adding low-dose corticosteroid (according to local policy) to reduce encorafenib dose further If symptoms persist to grade >2 despite two dose reductions, consider switching to a different BRAF inhibitor Doses can be up-titrated if symptoms improve later For persistent muscle pain, consider checking creatine kinase level for rhabdomyolysis Consider rheumatology consultation if appropriate, especially if considering intra-articular or high-dose steroids; if refractory to steroids, consider leflunomide or methotrexate after rheumatology consult
Fatigue	Generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities	Advise patients to rest when necessary, particularly during the early stages of treatment Consider treatment with low-dose steroids Ensure other possible causes of fatigue are investigated and treated
Pyrexia	Elevation of body temperature above 38.0 °C or 100.4 °F	Start standard supportive care (drink plenty of fluids; consider treatment with over-the-counter acetaminophen or NSAIDs) Rule out infectious cause Rapidly treat any infections Check full blood count and blood pressure If fever persists, add NSAIDs to acetaminophen or temporarily stop encorafenib and binimetinib until fever grade ≤1, then restart at the same dose on first occasion and a lower dose on subsequent occasion For symptomatic, recurrent, or refractory fever, consider low-dose prednisolone Consider discontinuing therapy if fever persists and no other cause is found Consider intravenous fluids and hospital admission if systemically unwell
Headache	Marked discomfort in various parts of the head, not confined to the area of distribution of any nerve	Use over-the-counter NSAIDs Ensure adequate fluid intake
Skin and subcutaneous tissue disorders	Hyperkeratosis (calluses and corns), dry skin, hair loss, pruritus, hand-foot syndrome (redness, swelling, or pain on palms of hands or soles of feet)	For dry skin and hyperkeratosis, apply bland emollients and topical keratolytics, if needed For hand-foot syndrome, administer topical steroids as outlined below Consider referral to dermatologist
Rash	Erythematous macules and papules with or without pruritus typically presenting on the trunk but can spread to the extremities	For mild rash, use bland emollients or topical corticosteroids (e.g. hydrocortisone 2.5% cream) For moderate rash, use mid-potency topical steroids (e.g. triamcinolone 0.1% cream) For severe rash, consider high-potency topical steroids (e.g. clobetasol 0.05% cream), oral prednisone 0.5 mg/kg/day (up to 60 mg/day) for 5–7 days, and referral to a dermatologist If needed, administer oral antihistamines If rash does not improve within 2 weeks, withhold therapy until grade ≤1 severity; restart at same dose after first occurrence, or at the next lower dose for recurrent rash Discontinue therapy for severe forms (including Stevens-Johnson syndrome or toxic epidermal necrolysis) If needed, hospitalize for intravenous hydration and electrolyte replacement

(*Continued*)

Table 2
(*Continued*)

Adverse event	Signs and symptoms	Supportive care, monitoring, and management
Photosensitivity	Photodistributed erythema with or without pain, tenderness, edema, desquamation, or blisters	Prophylactic broad-spectrum sunscreen SPF > 30 [UV B] plus 5-star UV B rating UV avoidance and use of UV-protective clothing For sunburn, consider topical glucocorticosteroids and NSAIDs Consult a dermatologist If needed, modify the dose of encorafenib and binimetinib or discontinue therapy
Eye disorders	Blurred vision, loss of vision, or other vision changes; seeing colored dots; seeing blurred outline around objects; eye pain; eye swelling or redness	Consider topical NSAID or carbonic anhydrase inhibitors for symptom relief Consult an ophthalmologist Perform symptom-driven diagnostic measures If needed, modify the dose or discontinue therapy
Left ventricular dysfunction	Decrease in LVEF below the institutional LLN with an absolute decrease in LVEF ≥ 10% below baseline as detected by echocardiogram or multigated acquisition scan	Withhold binimetinib for up to 4 weeks; remeasure LVEF: if improved to near-normal value, resume at a lower dose; if not improved to normal after two dose reductions, permanently discontinue Consult a cardiologist If needed, discontinue therapy Permanently discontinue binimetinib if patient has symptomatic congestive heart failure or absolute decrease in LVEF >20% from baseline that is also below LLN

5-HT3, 5-hydroxytryptamine-3 receptor antagonist; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; SPF, sun protection factor; UV, ultraviolet.

to 4%; in the coBRIM study, the rate of photosensitivity for cobimetinib + vemurafenib was 34% [25,32]. Rates of pyrexia in COMBI-d and coBRIM were 59 and 29%, respectively [25,32].

In COLUMBUS, differences in adverse event rates were evaluated for three subgroups: age, race (including those of Japanese and Asian ethnicity), sex, and those with brain metastases. In the pooled Combo population, adverse events of any grade that were reported more frequently (with a >10% difference in incidence) in patients aged <75 years (n = 259) than in those aged ≥75 years (n = 25) were arthralgia (23.8 vs. 12.0%) and hyperkeratosis (10.8 vs. 0%). Adverse events of any grade that were reported more frequently (at least three patients and >25% difference in incidence) in patients aged ≥75 years than those aged <75 years were diarrhea (60.0 vs. 35.8%) and asthenia (36.0 vs. 9.3%).

In the Combo pooled population, 261 patients were male and 172 patients were female. There were no adverse events reported more frequently (>10% difference in incidence) in male patients than in female patients. Adverse events of any grade that were reported more frequently in female patients than male patients were nausea (49.4 vs. 35.6%), diarrhea (44.8 vs. 32.2%), fatigue (37.8 vs. 26.8%) and vomiting (34.9 vs. 24.1%).

With regard to safety and race, there were too few patients in the Asian (n = 9) or other race (n = 14) categories to make data comparisons interpretable. In the Combo pooled population, there were 45 and 388 patients who did and did not have brain metastasis at baseline, respectively. There were no clinically relevant differences in adverse events of any grade in patients with and without baseline brain metastases.

Management of adverse events with encorafenib + binimetinib in clinical practice

Prior to initiating therapy with encorafenib + binimetinib, patients and caregivers should be educated to anticipate select adverse events so proactive management can occur. Proactive guidance regarding dietary modifications, fluid intake, skin hydration with bland emollients, and standard supportive care (e.g. hydration to mitigate fatigue, arthralgia/myalgia, headaches, nausea/vomiting, diarrhea, and laboratory abnormalities) should be given. Patients should be encouraged to keep a diary of adverse events to discuss with their healthcare provider to elicit further guidance as needed. Further to this, telemedicine has become a valuable tool for supporting patients through any adverse events they experience. It has facilitated more timely communication and earlier interventions in the experience of physicians in this study. Although this is anecdotal, it should still be considered.

It is worth highlighting that it can be extremely difficult to distinguish efficacy differentials when switching between different combinations for an individual patient. Physicians should also consider that if a patient has interrupted targeted therapy for an extended period, they may be re-sensitized to the approach. Additional responses observed in that setting are hard to discern whether they are related to a new combination or simply the re-sensitization.

At treatment initiation and during routine visits, physicians should monitor liver function, electrolytes, creatinine with creatine phosphokinase, echocardiogram or MUGA, full blood count, and ECG, and perform dermatologic and ophthalmologic evaluations. Ophthalmic evaluation should include best-corrected visual acuity,

Amsler grid testing, slit-lamp examination (with attention to the anterior chamber, and to rule out anterior and posterior intraocular inflammation), dilated fundus exam (with attention to the posterior chamber and retina), and optical coherence tomography of the macula to diagnose subclinical serous retinopathy that might not affect best-corrected vision or cause metamorphopsia.

Approaches to managing key adverse events reported with encorafenib + binimetinib (Table 2) are discussed below [15,33–38]. An overview of encorafenib + binimetinib dose modification steps in approved product labeling is in Table 3 [15,37].

Gastrointestinal disorders

The majority of gastrointestinal events reported with encorafenib + binimetinib have been mild or moderate, therefore symptoms are usually managed on an outpatient basis [34,35]. Encorafenib and binimetinib have a moderate to high emetic risk; the National Comprehensive Cancer Network (NCCN) recommends prophylaxis with 5-hydroxytryptamine-3 (5-HT3) receptor antagonists (granisetron, ondansetron, or dolasetron), which may be administered before anticancer therapy and continued daily, per patient and provider preference. Other NCCN-recommended standard supportive therapy for breakthrough nausea and vomiting include antiemetics such as dexamethasone, lorazepam, metoclopramide, olanzapine, or prochlorperazine. Olanzapine, metoclopramide, and 5-HT3 receptor antagonists may prolong QT intervals; therefore, patients should be monitored by ECG [38]. Dietary modifications to manage diarrhea include eating frequent small meals, increasing fluid intake, replacing lost salts, and reducing fiber consumption [34,35]. Treatment with loperamide, diphenoxylate/atropine, octreotide, or codeine should also be considered [34,35]. Infectious origins (i.e. *Clostridium difficile* or other bacterial/viral infections) should be ruled out. For persistent diarrhea, a colonoscopy with colonic biopsies should be considered [34]. Dose interruption, adjustment, or discontinuation is recommended for persistent symptoms or grade ≥3 events, in addition to symptomatic treatment [15,37].

Musculoskeletal disorders

Arthralgia and myalgia are the most common musculoskeletal disorders with encorafenib + binimetinib. To manage mild symptoms, patients should be advised to use simple analgesics or NSAIDs; treatment with low-dose oral anti-inflammatory drugs or steroids, particularly for patients with prior steroid treatment, may be necessary [34,35]. For grade ≥3 events or persistent symptoms, dose interruption, adjustments, or treatment discontinuation is recommended [15,37]. Switching to an alternative BRAF inhibitor should be considered if symptoms persist despite dose adjustments. Referral to a rheumatologist is recommended for select cases [34,35].

Table 3 Encorafenib and binimetinib modification and dose reduction guidance based on the approved product labelinga [15,37]

Adverse event	Dose modification
Nausea, vomiting, diarrhea, fatigue, myalgia/arthralgia, pyrexia, headache, hand-foot syndrome	Recurrent grade 2 or first occurrence of any grade 3: withhold encorafenib and binimetinib for up to 4 weeks If improvement to grade ≤1 or to pretreatment/baseline level, resume at reduced dose If no improvement, permanently discontinue encorafenib and binimetinib First occurrence of any grade 4: permanently discontinue encorafenib and binimetinib or withhold for up to 4 weeks If improvement to grade ≤1 or to pretreatment/baseline level, then resume at reduced dose If no improvement, permanently discontinue encorafenib and binimetinib Recurrent grade 3: consider permanently discontinuing encorafenib and binimetinib Recurrent grade 4: permanently discontinue encorafenib and binimetinib
Skin (other than hand-foot syndrome)	Grade 2: if no improvement within 2 weeks, withhold encorafenib and binimetinib until grade ≤1. Resume encorafenib at same dose. Resume binimetinib at same or reduced dose if first occurrence or reduce dose if recurrent Grade 3: Withhold encorafenib and binimetinib until grade ≤1. Resume at same dose if first occurrence, or reduce dose if recurrent Grade 4: Permanently discontinue encorafenib and binimetinib

Dose reduction steps
Encorafenib
First dose reduction: 300 mg (four 75-mg capsules orally once daily)
Second dose reduction: 225 mg (three 75-mg capsules orally once daily)
Subsequent modification: Permanently discontinue if unable to tolerate encorafenib 225 mg (three 75-mg capsules once daily)
Binimetinib
First dose reduction: 30 mg orally twice daily (two 15-mg tablets orally twice daily)
Subsequent modification: Permanently discontinue if unable to tolerate binimetinib 30 mg orally twice daily
Discontinuation
If encorafenib is permanently discontinued, discontinue binimetinib. If binimetinib is withheld, reduce encorafenib to a maximum dose of 300 mg (four 75-mg capsules orally once daily) until binimetinib is resumed

[a]For full details on dosage modifications, please consult the Prescribing Information or Summary of Product Characteristics [15,37].

Fatigue, pyrexia, and headache

Fatigue, pyrexia, and headache with encorafenib + binimetinib are typically mild or moderate and can be managed with standard supportive care. After infectious causes are excluded, grade 3/4 pyrexia is usually managed with treatment interruption, with occasional administration of antibiotics, antipyretics, or steroids [34,35].

Skin and subcutaneous tissue disorders

The most common skin and subcutaneous tissue disorders with encorafenib + binimetinib are hyperkeratosis, rash, and dry skin. Maculopapular rash or morbilliform drug eruptions – presenting as centrally distributed macules and papules, and sometimes associated with pruritus – may occur [39]. Although photosensitivity is uncommon, patient education and ongoing management are important to mitigate the effects. Patients should be informed about erythema nodosum, a common skin disorder that is typically managed with supportive measures (e.g. patient education, topical therapy, NSAIDs) but may require systemic steroids. Guidance for managing rash, photosensitivity, and sunburn is outlined in Table 2. Mild and moderate skin disorders may be relieved with topical emollients and corticosteroids. More severe cases may require oral antibiotics, steroids, retinoids, or dermatologist referral. To prevent photosensitivity reactions, patients should use broad-spectrum sunscreens, including lip balm and ultraviolet (UV)-protective clothing, and avoid exposure to high UV levels [34–36].

Serous retinopathy

Serous retinopathy and other retinal alterations collectively known as MEK-induced retinopathy are a class effect of MEK inhibitors. Serous retinopathy is characterized by fluid accumulation or edema between the outer retinal layer and the retinal pigment epithelium. This fluid accumulation may cause transient visual disturbances such as reduced visual acuity, dyschromatopsia, and photophobia as early as 24–48 h after initiating treatment, but may occur at any time [40]. Typically, serous retinopathy is asymptomatic or minimally symptomatic (grade 1/2) and does not result in treatment interruption, functional deficits, or structural changes of the eye [41]. Most cases do not require pharmacologic intervention, are self-limiting, and resolve after 1–2 months; however, dose interruption can be considered for patients with decreased vision; topical NSAIDs or carbonic anhydrase inhibitors can be used for symptomatic relief [40]. In COLUMBUS, routine ophthalmic testing was performed for the encorafenib + binimetinib group at all regularly scheduled visits during treatment [31]; however, in real-world practice, asymptomatic patients do not undergo ocular examination; therefore, only ocular toxicities that are symptomatic or exacerbated may be identified. Educating patients regarding the reversible and self-limiting nature of this toxicity is important to decrease apprehension and anxiety regarding continued therapies.

Left ventricular dysfunction

Decreased left ventricular ejection fraction appears to be induced by MEK inhibitors; furthermore, BRAF + MEK inhibitors are associated with a higher risk of cardiovascular adverse events than treatment with BRAF inhibitor monotherapy [42]. Although various explanations for this increased risk have been suggested, the exact mechanism is unknown. Potential mechanisms may result from interference with the cardioprotective role of the MAPK pathway, leading to impaired physiological mechanisms related to myocytes [42]. Patients with cardiovascular risk factors should be monitored closely by ECG when treated with encorafenib + binimetinib [15,37]. LVD is usually managed by dose interruption or reduction and is generally manageable without treatment discontinuation. Treatment should be discontinued if improvement is not seen with dose modifications or for LVD grade ≥3 [34–36]. Symptomatic LVD should be managed by a cardiologist.

Discussion

Long-term treatment with encorafenib + binimetinib is generally well tolerated in patients with *BRAF*-mutant melanoma. Awareness of the unique safety profile of encorafenib + binimetinib and regular monitoring can help clinicians anticipate and manage adverse events, prolong the duration of therapy, and, consequently, prolong the benefit of this combination. Encorafenib + binimetinib provides long-term benefits [median OS 33.6 months (95% CI, 24.4–39.2)] for patients with advanced *BRAF* V600E-mutant metastatic melanoma [12]. Adverse events reported with this combination in COLUMBUS were mostly mild or moderate [12]. Of note, the various BRAF and MEK inhibitors licensed for *BRAF* V600-mutant metastatic melanoma appear to have different safety and tolerability profiles that may affect clinical practice [34,35]. Incidences of serous retinopathy, LVD, and skin disorders are similar to those observed in other BRAF + MEK inhibitor studies, whereas differences are evident in the rates of pyrexia and photosensitivity [12,25,32]. Some differences in the adverse event profile can potentially be explained by the ability of encorafenib to suppress the MAPK pathway in tumor cells that express several mutated forms of *BRAF* kinase as well as its long dissociation half-life; furthermore, the shorter half-life of binimetinib compared with other MEK inhibitors may allow for quicker resolution of adverse events following treatment interruption [13–15,43].

Although clinical trials define monitoring guidelines and restrictions, this does not reflect adverse event management practices in the real world. For encorafenib + binimetinib, common adverse events such as gastrointestinal disorders, musculoskeletal disorders, fatigue, pyrexia, headache, and skin-related disorders are manageable with supportive care and temporary dose interruptions. With proactive adverse event management, patients can

be encouraged to stay on treatment to derive the most benefit from encorafenib + binimetinib.

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Conflicts of interest

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