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REVIEW

A Practical Review of Encorafenib and Binimetinib Therapy Management in Patients with BRAF V600E-Mutant Metastatic Non-Small Cell Lung Cancer

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ABSTRACT

According to current guidelines, targeted therapy with a combination of BRAF plus MEK inhibitors is the preferred first-line treatment for patients with BRAF V600E-mutant metastatic non-small cell lung cancer (NSCLC). In the open-label, single-arm, phase 2 PHAROS trial (NCT03915951), the combination of encorafenib, a potent BRAF inhibitor, and binimetinib, a potent MEK inhibitor, demonstrated durable antitumor activity with a manageable safety profile in this patient population. On the basis of the results of this study, the combination of encorafenib plus binimetinib was approved by the US Food and Drug Administration on October 11, 2023, for patients with BRAF V600E-mutant metastatic NSCLC. In this review, we summarize the efficacy and safety of encorafenib plus binimetinib from the PHAROS study. In addition, we discuss strategies to manage adverse reactions with this combination therapy with the intent of minimizing unnecessary treatment discontinuations in these patients.

Keywords: Adverse reaction management; Binimetinib; BRAF; Encorafenib; Non-small cell lung cancer

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Key Summary Points

The BRAF plus MEK inhibitor combination of encorafenib plus binimetinib is indicated for the treatment of BRAF V600E-mutant metastatic non-small cell lung cancer.

Adverse reactions experienced with encorafenib plus binimetinib in clinical trials were well managed with dose modifications.

There is a need for resources detailing management of adverse reactions with encorafenib plus binimetinib in a clinical setting.

We describe approaches for managing select adverse reactions as determined by published clinical trial data as well as opinion of an expert panel of oncologists with years of experience treating patients with metastatic non-small cell lung cancer receiving targeted therapy.

The goal of adverse reaction management is minimizing treatment discontinuations.

INTRODUCTION

Approximately 85% of patients with lung cancer are diagnosed with non-small cell lung cancer (NSCLC), and most NSCLCs have an adenocarcinoma histology [1–3]. To date, multiple actionable biomarkers with approved therapies have been identified, including oncogenic alterations in *ALK*, *BRAF* V600E, *EGFR*, *HER2*, *KRAS*, *MET*, *NTRK*, *RET*, *ROS1*, and expression of programmed death ligand 1 [4–7]. *BRAF* mutations occur in various solid tumors, including melanoma (≈ 40%), thyroid (≈ 33%), colorectal (CRC; ≈ 9%), and NSCLC (≈ 2–4%) [3, 8]. The *BRAF* gene encodes a kinase involved in the mitogen-activated protein kinase (MAPK) signaling pathway, which regulates cellular processes, including growth, differentiation, proliferation, and survival [9, 10]. *BRAF* mutations are grouped into three classes based on dimerization status and kinase activity level [9, 11]. While class I mutations occur exclusively at codon 600, resulting in a constitutively active BRAF monomer, class II and III mutations occur at non-V600 codons, resulting in constitutively active and kinase-dead or kinase-impaired dimers, respectively [11]. Class I mutations account for the majority of *BRAF* mutations (≈ 77%) in melanoma, whereas NSCLC has a more even distribution, with class I, II, and III mutations accounting for 31–45%, 32–34%, and 23–31% of BRAF-mutant NSCLCs, respectively [8, 12]. The most common *BRAF* mutation in NSCLC, which accounts for approximately 2% of all NSCLCs, is a class I mutation that replaces the valine at codon 600 with glutamic acid (V600E), resulting in an approximately 500-fold increase in kinase activity [8, 11, 13]. When considering treatment options for NSCLC, identification of oncogenic alterations is critically important since targeted therapy has improved outcomes for many actionable mutations, including BRAF V600E-mutant NSCLC [3, 14–16]. Therefore, all patients with advanced or metastatic NSCLC should undergo broad-based molecular testing, as recommended by current guidelines [5, 7].

Available Treatments for BRAF V600E-Mutant Metastatic NSCLC

Clinical investigation of targeted therapy for BRAF V600E-mutant NSCLC began with BRAF inhibitor monotherapy (vemurafenib, dabrafenib) [17, 18]. However, clinical benefit of monotherapy was limited by acquired resistance, which reactivates the MAPK pathway [19]. The addition of a MEK inhibitor (trametinib, binimetinib) to a BRAF inhibitor provided dual inhibition of the MAPK pathway and prolonged antitumor activity with a tolerable safety profile [15, 20, 21]. Dabrafenib plus trametinib was approved as the first BRAF plus MEK inhibitor targeted therapy for patients with BRAF V600E-mutant metastatic NSCLC (mNSCLC) in 2017 [22]. Encorafenib plus binimetinib was

approved in October 2023 as the second BRAF and MEK inhibitor combination for this patient population [23]. Currently approved BRAF inhibitors inhibit monomers, and binding to one protomer in a dimer can cause paradoxical activation of the second protomer [9, 24]. Therefore, BRAF monomer inhibitors are not effective for inhibiting class II or III dimers [9, 25]. Novel drugs that inhibit dimers or disrupt dimerization are currently under investigation in preclinical and ongoing clinical trials and have even demonstrated initial efficacy against all three classes of *BRAF* mutations in preclinical models [25–27].

Guidelines for BRAF V600E-mutant NSCLC recommend BRAF and MEK inhibitors as the preferred first-line treatment and immunotherapy, chemotherapy, or a combination as alternative options [5, 7]. Although some clinicians prescribe immunotherapy with or without chemotherapy in the first-line setting, data from studies of immunotherapy or chemotherapy for patients with BRAF V600E-mutant NSCLC are limited with retrospective analyses, small population sizes, and conflicting results [12, 13, 28, 29]. Given the recent approval of encorafenib plus binimetinib for patients with BRAF V600E-mutant mNSCLC [23], we summarize the efficacy and safety profile of this combination therapy and address management of adverse reactions (ARs) in the clinical setting. These management approaches were determined by oncologists on the basis of their experience treating patients with mNSCLC receiving targeted therapy. This article is based on previously conducted studies and does not contain any new studies with human participants.

PHAROS Study: Efficacy and Safety

The phase 2 PHAROS (NCT03915951) study enrolled 59 treatment-naïve and 39 previously treated patients with BRAF V600E-mutant mNSCLC [15]. The key inclusion and exclusion criteria for the study are described in Supplementary Materials Table S1 [30]. Patients received orally administered encorafenib 450 mg once daily plus orally administered binimetinib 45 mg twice daily until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, or death. Tumor response was determined by independent radiology review (IRR, also called independent review committee) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [15, 31]. For treatment-naïve patients, objective response rate (ORR) by IRR was 75%, median duration of response (DOR) was not estimable (NE), and median time to response was 1.9 months (Table 1) [15]. Median duration of follow-up for progression-free survival (PFS) by IRR was 18.2 months, median PFS was NE, and median overall survival (OS) was NE. For previously treated patients, ORR by IRR was 46%, median DOR was 16.7 months, and median time to response was 1.7 months. Median duration of follow-up for PFS by IRR was 12.8 months, median PFS was 9.3 months, and median OS was NE.

In the published primary analysis of PHAROS, safety data were reported as treatment-related adverse events and resulting dose modifications [15]. However, the US Food and Drug Administration (FDA) labels report all-causality ARs that occurred in $\geq$ 10% of patients in PHAROS and resulting dose modifications [31, 32]. Safety analysis of the 98 patients revealed that the most common ARs reported in $\geq$ 25% of patients included fatigue, nausea, diarrhea, musculoskeletal pain, vomiting, abdominal pain, visual impairment, dyspnea, rash, constipation, and cough (Table 2) [31, 32]. Pyrexia was reported in 22% of patients, with no grade 3 or 4 events. Serious ARs occurred in 38% of patients; ARs occurring in $\geq$ 2% of patients were hemorrhage (6%); diarrhea (4%); anemia, dyspnea, and pneumonia (3% each); and arrhythmia, device-related infection, edema, myocardial infarction, and pleural effusion (2% each). Dose modifications were generally related to gastrointestinal (GI) ARs. For encorafenib, ARs led to dose interruption in 59% of patients with diarrhea (17%) as the most common, dose reduction in 30% of patients with diarrhea and nausea (8% each) as the most common, and permanent discontinuation in 16% of patients with diarrhea and musculoskeletal pain (3% each) as the most common

Table 1 Summary of efficacy data from PHAROS [15]

	Treatment-naïve (n = 59)	Previously treated (n = 39)
ORR by IRR[a] (95% CI), %	75 (62–85)	46 (30–63)
Best overall response by IRR, %		
CR	15	10
PR	59	36
SD	17	33
PD	3	8
Not evaluable	5	13
DOR, median (95% CI), months	NE (23.1–NE)	16.7 (7.4–NE)
Time to response, median (range), months	1.9 (1.1–19.1)	1.7 (1.2–7.3)
Duration of follow-up for PFS by IRR, median (95% CI), months	18.2 (16.4–22.3)	12.8 (9.0–19.8)
PFS, median (95% CI), months	NE (15.7–NE)	9.3 (15.7–NE)
OS, median, months	NE	NE

CI confidence interval, *CR* complete response, *DOR* duration of response, *IRR* independent radiology review, *NE* not estimable, *ORR* objective response rate, *OS* overall survival, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *SD* stable disease
[a]Primary efficacy end point

[31]. For binimetinib, ARs led to dose interruption in 62% of patients with diarrhea (17%) as the most common, dose reduction in 33% of patients with diarrhea (8%) as the most common, and permanent discontinuation in 17% of patients with diarrhea (3%) as the most common [32]. Treatment-related ARs led to dose interruption, dose reduction, and permanent discontinuations of both encorafenib plus binimetinib in 44%, 24%, and 15% of patients, respectively [15].

Dabrafenib plus Trametinib for Patients with BRAF V600E-Mutant mNSCLC

In the updated analysis of the phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant mNSCLC, the ORR and median PFS were 64% and 10.8 months in treatment-naïve patients (n = 36) and 68% and 10.2 months in previously treated patients (n = 57) [14]. According to the US FDA label, the most common ARs in the overall population (n = 93) were pyrexia (55%), fatigue (51%), and nausea (45%) (Supplementary Materials Table S2) [33, 34]. While the incidence of cutaneous squamous cell carcinoma (SCC) was 12% with dabrafenib monotherapy in a previous trial, SCC was reported in 4% of patients receiving dabrafenib plus trametinib [18, 20]. The most common treatment-emergent laboratory abnormalities were hyperglycemia (71%), increased alkaline phosphatase (64%), and increased aspartate aminotransferase (AST; 61%) [33, 34]. For dabrafenib, ARs led to dose interruption in 62% of patients with pyrexia (27%) as the most common, dose reduction in 35% of patients with pyrexia (10%) as the most common, and permanent discontinuation in 18% of patients with pyrexia, decreased ejection fraction, and respiratory distress (2% each) as the most common [33]. For trametinib, ARs led

to dose interruption in 57% of patients with pyrexia (16%) as the most common, dose reduction in 30% of patients with pyrexia (5%) as the most common, and permanent discontinuation in 19% of patients with pyrexia, decreased ejection fraction, and respiratory distress (2% each) as the most common [34]. Management strategies for ARs associated with dabrafenib plus trametinib have been summarized in previous publications, and the strategies generally focus on patient education, proactive evaluations, supportive care, and dose modifications [35, 36]. Pyrexia was the leading cause for dose modifications for patients treated with dabrafenib plus trametinib [33, 34]. Therefore, there is an emphasis on managing pyrexia for patients receiving dabrafenib plus trametinib [35, 36].

Encorafenib plus Binimetinib for Patients with Other Solid Tumors

In 2018, encorafenib plus binimetinib was approved by the US FDA for BRAF V600E/K-mutant unresectable or metastatic melanoma [37]. This approval was based on the phase 3 COLUMBUS study, which evaluated encorafenib (n = 194), encorafenib plus binimetinib (n = 192), and vemurafenib (n = 191) [37, 38]. According to the US FDA labels, the most common ARs were fatigue (43%), nausea (41%), and vomiting (30%) (Supplementary Materials Table S3) [31, 32]. The most common laboratory abnormalities were increased creatinine (93%), increased gamma glutamyl transferase (45%), and anemia (36%). For encorafenib, ARs led to dose interruption in 30% of patients with nausea and vomiting (7% each) as the most common, dose reduction in 14% of patients with arthralgia, fatigue, and nausea (2% each) as the most common, and permanent discontinuations in 5% of patients with hemorrhage (2%) as the most common [31]. For binimetinib, ARs led to dose interruption in 33% of patients with left ventricular dysfunction (6%) as the most common, dose reduction in 19% of patients with left ventricular dysfunction and serous retinopathy (3% each) as the most common, and permanent discontinuations in 5% of

Table 2 ARs and laboratory abnormalities reported in ≥ 10% of patients in PHAROS [31, 32]

AR or laboratory abnormality (n = 98)	Any grade[a]	Grade 3/4[a]
General disorders, %		
Fatigue[b]	61	8
Edema[c]	23	1
Pyrexia	22	0
Gastrointestinal disorders, %		
Nausea	58	3
Diarrhea[d]	52	7
Vomiting	37	1
Abdominal pain[e]	32	1
Constipation	27	0
Musculoskeletal and connective tissue disorders, %		
Musculoskeletal pain[f]	48	4
Ocular disorders, %		
Visual impairment[g]	29	2
Skin and subcutaneous tissue disorders, %		
Rash[h]	27	3
Pruritus[i]	16	0
Dry skin	13	0
Alopecia	12	0
Respiratory, thoracic, and mediastinal disorders, %		
Dyspnea[j]	27	8
Cough[k]	26	0
Nervous system disorders, %		
Dizziness[l]	17	1
Headache	11	0
Metabolism and nutrition disorders, %		
Decreased appetite	14	1
Vascular disorders, %		
Hemorrhage[m]	12	4
Hypertension	10	5

Table 2 continued

AR or laboratory abnormality (n = 98)	Any grade[a]	Grade 3/4[a]
Cardiac disorders, %		
Left ventricular dysfunction/cardiomyopathy[n]	11	1
Investigations, %		
Weight increased	11	1
Psychiatric disorders, %		
Insomnia	10	0
Laboratory abnormalities[o], %		
Creatinine increased	91	3
Hyperglycemia	48	6
Anemia	47	11
CPK increased	41	3
Lipase increased	40	14
ALT increased	34	9
Hypoalbuminemia	32	0
AST increased	31	10
ALP increased	31	3
Hyperkalemia	31	2
Hyponatremia	26	11
Lymphopenia	24	6
Serum amylase increased	22	1
Thrombocytopenia	20	1
Hypocalcemia	12	2
Neutropenia	12	1
Leukopenia	12	0

Table 2 continued

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AR* adverse reaction, *AST* aspartate aminotransferase, *CPK* creatine phosphokinase, *FDA* US Food and Drug Administration

[a]Grades per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03

[b]Fatigue includes fatigue and asthenia

[c]Edema includes edema peripheral, generalized edema, swelling, localized edema, and face edema

[d]Diarrhea includes diarrhea and colitis

[e]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, and epigastric discomfort

[f]Musculoskeletal pain includes back pain, arthralgia, pain in extremity, myalgia, musculoskeletal chest pain, non-cardiac chest pain, and neck pain

[g]Visual impairment includes vision blurred, visual impairment, vitreous floaters, photophobia, visual acuity reduced, and photopsia

[h]Rash includes rash, rash macular, rash maculo-papular, rash papular, rash pustular, dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, eczema, and skin exfoliation

[i]Pruritus includes pruritus and pruritus genital

[j]Dyspnea includes dyspnea and dyspnea exertional

[k]Cough includes cough and productive cough

[l]Dizziness includes dizziness and balance disorder

[m]Hemorrhage includes anal hemorrhage, hemothorax, gastrointestinal hemorrhage, hematochezia, hematuria, hemoptysis, hemorrhage intracranial, hyphema, small intestinal hemorrhage, upper gastrointestinal hemorrhage, and vaginal hemorrhage. There was one grade 5 AR of hemorrhage that occurred

[n]Left ventricular dysfunction/cardiomyopathy includes ejection fraction decreased, cardiac failure, and cardiac failure congestive

[o]Laboratory abnormalities are based on the number of patients with available baseline and at least one on-treatment laboratory test. Laboratory abnormalities were included separately from the ARs on the FDA label

Table 3 Pharmacokinetic data

Parameter	Encorafenib [31]	Binimetinib [32]
Drug formulation	75 mg capsule	15 mg tablet
Recommended dose	450 mg QD	45 mg BID
Bioavailability, %	86	50
Median T_{max}, hours	2	1.6
Mean $t_{1/2}$, hours	3.5	3.5
Effect of food	High-fat meal 30 min prior to administration delayed absorption but had no clinically relevant effect on drug exposure [54]	No effect on drug exposure
Drug interactions	Coadministration with strong or moderate CYP3A inhibitors may increase encorafenib plasma concentrations	None
	Avoid coadministration	
	If unavoidable, reduce encorafenib dose	
	Coadministration with strong or moderate CYP3A4 inducers may decrease encorafenib plasma concentrations and subsequently efficacy	
	Avoid coadministration	
	Coadministration with sensitive CYP3A4 substrates may decrease plasma concentrations and subsequently efficacy of those substrates	
	Coadministration with OATP1B1, OATP1B3, or BCRP substrates may increase concentrations and potentially toxicity of those substrates	
	Monitor patients and consider adjusting doses of those substrates	
	Coadministration with drugs that prolong QT/QTc interval should be avoided	

BCRP breast cancer resistance protein, *BID* twice a day, *CYP* cytochrome P450, *OATP* organic anion transporting polypeptide, *QD* once a day, *QTc* corrected *QT* interval, $t_{1/2}$ half-life, T_{max} time to maximum concentration

patients with hemorrhage (2%) as the most common [32].

The PHAROS study demonstrated that the safety profile and pharmacokinetic data (Table 3) for encorafenib plus binimetinib were generally consistent with those reported in previous melanoma studies [15, 39, 40]. Direct comparisons between the clinical trials cannot be made because of differences in trial designs, populations, and analyses; however, dose modification rates vary between melanoma and NSCLC [31, 32]. For patients with BRAF V600E-mutant mNSCLC, GI ARs were the most common reason for both encorafenib and binimetinib dose modifications. For patients with BRAF V600E/K-mutant melanoma, GI ARs, arthralgia, fatigue, and nausea were the most common reasons for encorafenib dose

modifications and left ventricular dysfunction, serous retinopathy, and hemorrhage were the most common reasons for binimetinib dose modifications.

Encorafenib, in combination with cetuximab, is approved for patients with previously treated BRAF V600E-mutant metastatic CRC [31]. This approval was based on the phase 3 BEACON study, which compared encorafenib plus cetuximab with or without binimetinib (n = 224 and n = 220, respectively) with investigator's choice of chemotherapy plus cetuximab (n = 221) in patients with previously treated BRAF V600E-mutant CRC [41, 42]. Management strategies for ARs associated with this treatment combination were previously published [43].

MANAGEMENT OF ENCORAFENIB PLUS BINIMETINIB–ASSOCIATED ARS IN CLINICAL PRACTICE TREATING PATIENTS WITH BRAF V600E-MUTANT NSCLC

While clinical trials monitor and manage ARs [44], this publication outlines real-world strategies for healthcare providers. Providing healthcare providers with management strategies can potentially improve the patient's experience on treatment, decrease incidence of permanent discontinuations, increase duration of treatment, and improve treatment outcomes [35, 44, 45]. While the NSCLC indication for encorafenib plus binimetinib was recently approved, this combination has been used to treat patients in standard of care with melanoma since 2018 [23, 37]. Therefore, clinicians have years of experience managing the associated ARs, and AR management strategies for patients with melanoma have been previously published [44, 45]. These AR management strategies for patients with BRAF V600E-mutant mNSCLC were developed on the basis of clinical data from the PHAROS trial and recommendations from oncologists experienced in treating patients for NSCLC with encorafenib plus binimetinib along with prior recommendations for treating patients with melanoma.

Prior to beginning treatment with encorafenib plus binimetinib, patients and caregivers should be educated on the potential ARs and what to do should they occur [44]. Special attention should be given to Gl ARs as these are common reasons for dose interruption and reduction [31, 32]. Patients should keep track of ARs between appointments to discuss with their healthcare providers. Baseline and recurring evaluations should be conducted for liver function, electrolytes, creatinine with creatine phosphokinase (CPK), echocardiogram or multiple gated acquisition (MUGA) scan, and dermatologic examinations [31, 32]. Ophthalmologic evaluations should be done at regular intervals and when assessing new or worsening symptoms. Patients with certain comorbidities (e.g., cardiovascular risks) should be closely monitored.

Some ARs can be managed with lifestyle changes or over-the-counter (OTC) medications (Table 4) [44]. However, dose modifications are typically recommended for higher grade or recurrent ARs, and recommendations for general ARs are summarized in Fig. 1 [31, 32]. Starting doses and dose modifications are similar for patients with NSCLC or melanoma; however, for patients with BRAF V600E/K-mutant melanoma, if there is moderate or severe hepatic impairment, the recommended starting dose for binimetinib is 30 mg instead of 45 mg [31, 32]. For BRAF V600E-mutant metastatic CRC, the recommended starting dose of encorafenib is 300 mg instead of 450 mg and the minimum dose is 150 mg instead of 225 mg [31]. ARs of hepatotoxicity, uveitis, dermatologic conditions, cardiomyopathy, new primary malignancy, corrected QT interval (QTc) prolongation, rhabdomyolysis, serous retinopathy, retinal vein occlusion, venous thromboembolism, and interstitial lung disease have specific dose modification recommendations (Fig. 2). Some ARs are associated with either encorafenib or binimetinib and necessitate dose modification of that agent alone (Fig. 2b, c). If encorafenib is permanently discontinued, binimetinib should be discontinued [32]. If binimetinib is withheld, encorafenib should be reduced to a maximum of 300 mg once daily [31]. The following sections describe ARs

Table 4 Clinical management of select adverse reactions

Adverse reaction group	Evaluations	Management strategies
General disorders	Rule out other causes (e.g., infection, anemia) [44, 48]	For fatigue, rest when necessary [44] and exercise when tolerable
	Monitor for dehydration	For peripheral edema, compression and elevation may help relieve swelling [45]
		For mild (100.4–102.2 °F or 38.0–39.0 °C) to moderate (> 102.3–104.0 °F or > 39.0–40.0 °C) pyrexia, OTC medications (e.g., acetaminophen, NSAIDs) and fluids to maintain hydration [44, 47]
		For pyrexia that is symptomatic, recurrent, refractory, or grade ≥ 3 (> 104.0 °F or 40 °C), consider treatment interruptions, antibiotics, antipyretics, or low-dose corticosteroids (e.g., prednisone) [44, 47, 48]
Gastrointestinal disorders	Rule out other causes (e.g., infection) [45]	Diet changes (e.g., frequent, small meals and reducing fiber consumption) [44]
	Monitor for dehydration	Maintaining liquid intake; sports drinks are excellent for hydration and replacing electrolytes
		Antiemetics (e.g., dexamethasone, lorazepam, metoclopramide, olanzapine, prochlorperazine, 5-HT_3 receptor antagonists) [44, 49]
		Exercise caution with coadministration; patients receiving olanzapine, metoclopramide, or 5-HT_3 receptor antagonists should be monitored for QTc prolongation with ECG [31, 49]
		Anti-diarrheal medication (e.g., loperamide, diphenoxylate/atropine, octreotide) [44]

Table 4 continued

Adverse reaction group	Evaluations	Management strategies
Musculoskeletal and connective tissue disorders	CPK and creatinine levels should be monitored throughout treatment [32]	Medication (e.g., analgesics, NSAIDs, low-dose anti-inflammatory drugs, or steroids) [44], physical therapy, stretching, and hot and cold compresses
		For select cases, a rheumatologist may be consulted, especially when considering intra-articular or high-dose steroids [44, 45]
		If a patient is refractory to steroids, leflunomide or methotrexate may be considered after a rheumatologist consult [44, 45]
Hepatotoxicity	Baseline and monthly liver function tests [31, 32]	Follow dose modification guidance in Figs. 1 and 2
	Rule out alternative causes (e.g., infection or liver injury) [45]	
Ocular disorders	Ophthalmologic evaluations should be done at regular intervals [31, 32]	Topical NSAIDs or carbonic anhydrase inhibitors [44]
	In clinical practice, asymptomatic patients might not undergo ophthalmologic evaluations; it is best to use clinical judgment	Ophthalmology consultation [44]
Skin and subcutaneous tissue disorders	Healthcare providers should assess the patient's skin before, during (every 2 months), and up to 6 months after treatment with encorafenib [31]	For mild rashes, creams, emollients, topical corticosteroids (e.g., hydrocortisone) [44], changes in clothing, or lotions
	In clinical practice, ongoing dermatologic evaluations every 3 to 6 months are suggested	For moderate to severe rashes, topical steroids (e.g., triamcinolone, clobetasol), prednisone, antihistamines, or referral to a dermatologist [44]
		For photosensitivity, proactive protection with broad-spectrum sunscreen and lip balm, ultraviolet-protective clothing, avoiding sun exposure [44], and avoiding alcohol-based fragrances or lotions
		Proactive skin checks for new warts, sores that bleed or do not heal, and changes to moles [31]

Table 4 continued

Adverse reaction group	Evaluations	Management strategies
Cardiac disorders	Monitor cardiac function (echocardiogram, MUGA) before treatment, 1 month after beginning treatment, and every 2 to 3 months during treatment [31, 32] Monitor electrolytes [31]	Consult cardiology [44]

5-HT$_3$ 5-hydroxytryptamine-3, *CPK* creatine phosphokinase, *ECG* electrocardiogram, *MUGA* multiple gated acquisition, *NSAID* nonsteroidal anti-inflammatory drug, *OTC* over the counter

a

Severity	Occurrence	Encorafenib plus Binimetinib Dose Modifications
Grade 2	Recurrent	Withhold for ≤4 weeks • If improved to grade ≤1 or baseline, resume at reduced dose • If no improvement, permanently discontinue
Grade 3	First	
	Recurrent	Consider permanent discontinuation
Grade 4	First	Permanently discontinue, or Withhold for ≤4 weeks • If improved to grade ≤1 or baseline, resume at reduced dose • If no improvement, permanently discontinue
	Recurrent	Permanently discontinue

b

	Encorafenib (QD)	Binimetinib (BID)
Initial dose, mg	450	45
First reduction, mg	300	30 (minimum dose)
Second reduction, mg	225 (minimum dose)	-
If unable to tolerate minimum dose	Discontinue along with binimetinib	Discontinue; while withholding, reduce encorafenib to maximum dose of 300 mg QD

Fig. 1 Dose modifications for AR management [31, 32]. **a** Recommendations for general ARs. **b** Encorafenib and binimetinib dose reduction schema. *AR* adverse reaction, *BID* twice daily, *QD* once daily

a

Adverse Reaction	Severity	Encorafenib plus Binimetinib Dose Modifications
Hepatotoxicity (ALT or AST increased)	Grade 2	Maintain dose • If no improvement within 2 (binimetinib) or 4 (encorafenib) weeks, withhold until grade ≤1 or baseline levels, then resume at same dose
	Grade 3 or 4	Follow general AR dose modifications (**Figure 1**)
Uveitis	Grade 1 or 2	If no response to ocular therapy, withhold for ≤6 weeks • If improved, resume at same or reduced dose • Otherwise, permanently discontinue
	Grade 3	Withhold for ≤6 weeks • If improved, resume at same or reduced dose • Otherwise, permanently discontinue
	Grade 4	Permanently discontinue
Dermatologic	Grade 2	If no improvement within 2 weeks, withhold until grade ≤1, then resume at same dose if first occurrence or reduced dose if recurrent
	Grade 3	Withhold until grade ≤1 • Resume at same dose if first occurrence • Resume at reduced dose if recurrent
	Grade 4	Permanently discontinue
Cardiomyopathy	Symptomatic congestive heart failure or absolute decrease in LVEF of >20% from baseline and below LLN	Reduce encorafenib by one dose level • If LVEF improves to at least LLN and absolute decrease to ≤10% compared with baseline occurs, continue at reduced dose • If no improvement, withhold until improvement to at least institutional LLN and absolute decrease to ≤10% compared with baseline occurs, then resume at reduced dose or reduce an additional level Permanently discontinue binimetinib

b

Adverse Reaction	Severity	Encorafenib Dose Modifications
New primary malignancy	Non-cutaneous RAS mutation-positive malignancies	Permanently discontinue
QTc prolongation	QTcF of >500 ms and ≤60 ms above baseline	Withhold until QTcF is ≤500 ms and resume at reduced dose • If recurrent, permanently discontinue
	QTcF of ≥500 ms and ≥60 ms above baseline	Permanently discontinue

c

Adverse Reaction	Severity	Binimetinib Dose Modifications
Rhabdomyolysis or CPK elevations	Grade 4 asymptomatic CPK elevation	Withhold for ≤4 weeks • If improved to grade ≤1, resume at reduced dose • If not resolved within 4 weeks, permanently discontinue
	Any-grade CPK elevation with either symptoms or renal impairment	
Serous retinopathy	Symptomatic serous retinopathy/retinal pigment epithelial detachments	Withhold for ≤10 days • If improvement and asymptomatic, resume at same dose • If no improvement, resume at lower dose or permanently discontinue
Retinal vein occlusion	Any grade	Permanently discontinue
Venous thromboembolism	Uncomplicated DVT or PE	Withhold • If improves to grade ≤1, resume at reduced dose • If no improvement, permanently discontinue
	Life-threatening PE	Permanently discontinue
Interstitial lung disease	Grade 2	Withhold for ≤4 weeks • If improved to grade ≤1, resume at reduced dose • If not resolved within 4 weeks, permanently discontinue
	Grade 3 or 4	Permanently discontinue

Cardiomyopathy	Asymptomatic, absolute decrease in LVEF is >10% from baseline and below LLN	Withhold for ≤4 weeks and evaluate LVEF every 2 weeks
		• Resume at reduced dose if all the following are present:
		  • LVEF of ≥LLN
		  • Absolute decrease of ≤10% from baseline
		  • No symptoms
		If LVEF does not recover within 4 weeks, permanently discontinune

◀**Fig. 2** Dose modifications for specific ARs [31, 32]. **a** ARs that require encorafenib plus binimetinib dose modifications. **b** ARs that require encorafenib dose modifications. **c** ARs that require binimetinib dose modifications. *ALT* alanine aminotransferase, *AR* adverse reaction. *AST* aspartate aminotransferase, *CPK* creatine phosphokinase, *DVT* deep vein thrombosis, *LLN* lower limit of normal, *LVEF* left ventricular ejection fraction, *PE* pulmonary embolism, *QTc* corrected QT interval, *QTcF* Fridericia correction formula

observed in PHAROS and corresponding management strategies.

General Disorders

General disorders, comprising systemic instead of localized reactions, were the most common group of ARs, including fatigue (61%), edema (23%), and pyrexia (22%) (Table 2) [31, 32]. For fatigue, management strategies include resting when necessary [44] and exercising when tolerable (Table 4). The appropriate level of physical activity should be determined by several factors, including anemia, comorbidities, and safety (e.g., fall risk) [46]. Additionally, referral for rehabilitation (e.g., physical therapy, occupational therapy, physical medicine) or nutrition consultation should be considered. For edema, compression and elevation may help relieve swelling [45]. For pyrexia, all reported pyrexia events in PHAROS were grade ≤ 2 [31, 32]. For mild to moderate pyrexia (100.4–104.0 °F or 38.0–40.0 °C), management strategies include OTC medications (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]) and fluids to maintain hydration [44, 47]. While severe to life-threatening pyrexia (grade ≥ 3 [104.0 °F or 40 °C]) was not reported in PHAROS, it was reported by 4% of patients receiving encorafenib plus binimetinib in previous melanoma trials [31, 32, 47]. Management strategies that can be considered for symptomatic, recurrent, refractory, or grade ≥ 3 pyrexia include treatment interruptions, antibiotics, antipyretics, or low-dose corticosteroids (e.g., prednisone) [44, 48]. Alternative causes for these ARs, such as infection, disease progression, or a hematologic abnormality (e.g., anemia), should also be considered and addressed accordingly. Although most general disorder ARs in PHAROS were grade ≤ 2, dose modifications were required by some patients [31, 32]. Dose modifications are recommended for ARs that are either recurrent grade 2 or any occurrence of grade ≥ 3 (Fig. 1).

Gastrointestinal ARs

GI ARs are class effects associated with BRAF plus MEK inhibitors and are typically mild or moderate [31, 32, 44, 45]. In PHAROS, GI effects included nausea (58%), diarrhea (52%), vomiting (37%), abdominal pain (32%), and constipation (27%) (Table 2) [31, 32]. Most GI ARs can be managed with non-pharmacological or pharmacological strategies on an outpatient basis [44]. Non-pharmacological management strategies include dietary changes, such as eating frequent, small meals and reducing fiber consumption (Table 4) [44]. Encorafenib and binimetinib can be taken with or without food [31, 32]. Eating a small meal with treatment may help with nausea. No data evaluating the impact of fasting on efficacy and tolerability of encorafenib plus binimetinib for patients from PHAROS are available. Hydration is critical given the potential for loss of fluids through vomiting and diarrhea to lead to dehydration, hypotension, or, in severe incidences, kidney failure [45]. Sports drinks are an option for remaining hydrated and replacing electrolytes.

OTC medications, antiemetics (e.g., dexamethasone, lorazepam, metoclopramide, olanzapine, prochlorperazine, 5-hydroxytryptamine-3 [5-HT_3] receptor antagonists), and anti-diarrheal medications (e.g., loperamide, diphenoxylate/atropine, octreotide) can be used to relieve GI symptoms [44, 49]. When prescribing drugs for coadministration, healthcare providers should consider all current medications and be cautious of potential drug interactions. Encorafenib is associated with QTc prolongation, so when administered with other drugs that may prolong QT intervals (e.g., olanzapine, metoclopramide, 5-HT_3 receptor antagonists), patients should be monitored by

electrocardiogram [31, 49]. Dexamethasone is a CYP3A4 inducer and may lower encorafenib plasma concentration and subsequently efficacy [31, 50]. Other causes of GI effects, such as infections (e.g., *Clostridium difficile*) or progressive disease, should also be considered [45]. Although most GI ARs in PHAROS were grade ≤ 2, they were the most common reasons for dose interruptions, reductions, and permanent discontinuations for both encorafenib and binimetinib [31, 32]. Dose modifications are recommended for GI ARs that are either recurrent grade 2 or any occurrence of grade ≥ 3 (Fig. 1).

Musculoskeletal and Connective Tissue Disorders

Musculoskeletal pain, which included events such as back pain, arthralgia, myalgia, and noncardiac chest pain, was reported by 48% of patients [31, 32]. Although not reported in PHAROS, arthritis occurred in 1% and 2% of patients receiving encorafenib with and without binimetinib, respectively, in a prior melanoma trial; polyarthritis occurred in 2% of patients receiving encorafenib, including grade 3 in 1% [38]. Medication (e.g., analgesics, NSAIDs, low-dose anti-inflammatory drugs, or steroids) [44], physical therapy, stretching, and hot and cold compresses may relieve pain and swelling of joints. Moderate- to high-dose steroids should be considered for severe ARs, including myositis or vasculitis [44, 45]. A rheumatologist consultation may be recommended for select cases, including if considering intra-articular or high-dose steroids. If a patient is refractory to steroids, leflunomide or methotrexate may be considered after a rheumatologist consultation. Recurring or severe musculoskeletal ARs should be managed with dose modifications (Fig. 1) [31, 32].

In addition to musculoskeletal pain, increased CPK was a laboratory abnormality observed in 41% of patients, including grade ≥ 3 in 3% of patients [31, 32]. Increased CPK may be a potential sign of rhabdomyolysis, which is the rapid breakdown of skeletal muscle and has been associated with encorafenib plus binimetinib treatment in previous trials with melanoma (0.1%) [32, 51]. CPK and creatinine levels should be measured prior to initiating treatment and periodically throughout treatment [32]. If a patient has asymptomatic grade 4 CPK elevation ($> 10 \times$ upper limit of normal) or any-grade symptomatic CPK elevation or renal impairment, binimetinib should be withheld ≤ 4 weeks (Fig. 2c) [32, 47]. If CPK levels have improved to grade ≤ 1 ($\leq 2.5 \times$ upper limit of normal), binimetinib can be resumed at a reduced dose. However, if there is no improvement, binimetinib should be permanently discontinued and the dose of encorafenib adjusted [31, 32, 47]. In clinical practice, if the patient has low-grade symptomatic CPK but is otherwise doing well, it would be considered reasonable to continue treatment under close observation.

Hepatotoxicity

Hepatotoxicity manifests as increased liver enzymes in laboratory tests, including alanine aminotransferase (ALT) and AST. ALT was increased in 34% of patients, with grade 3 or 4 in 9% [31, 32]. AST was increased in 31% of patients, with grade 3 or 4 in 10%. Patients should be aware of the possible signs of liver dysfunction, such as jaundice, dark or brown urine, nausea, vomiting, loss of appetite, fatigue, bruising, and bleeding [31, 32]. Liver function should be evaluated prior to treatment and monthly throughout treatment [31, 32]. Specific dose modification guidance for ALT and AST elevations is found in Fig. 2a. A differential diagnosis should be conducted, and alternative causes considered, such as liver injury or infection [45].

Ocular Disorders

Ocular disorders are class effects associated with BRAF and MEK inhibitors [35, 44]. Visual impairment was observed in 29% of patients, with grade ≥ 3 events in 2% of patients (Table 2) [31, 32]. Additionally, serous retinopathy without blindness (2%) and uveitis (1%) were reported in PHAROS. In previous

clinical trials with encorafenib plus binimetinib for patients with melanoma, serous retinopathy without blindness (20%), uveitis (4%), and retinal vein occlusion (0.1%) were reported. Visual symptoms should be assessed at each visit, and ophthalmologic evaluations should be performed at regular intervals and as directed for new visual disturbances. Safety has not been determined for patients with a history of or risk factors for retinal vein occlusion [32]. In clinical practice, asymptomatic patients might not undergo ophthalmologic evaluations [31, 32]. However, this approach may differ, and it is best to use clinical judgment when determining when ophthalmologic examinations are necessary. Patients should be educated about the possibility of changes to their vision and be advised to inform their healthcare provider. For symptomatic relief, management strategies include topical NSAIDs or carbonic anhydrase inhibitors [44]. For some cases, an ophthalmologist may be consulted. Symptomatic serous retinopathy or retinal pigment epithelial detachments should be managed by withholding binimetinib for up to 10 days (Fig. 2c) [32]. If the condition improves and is asymptomatic, binimetinib should be resumed at a reduced dose. However, if the condition does not improve, binimetinib could be resumed at a reduced dose or discontinued.

Skin and Subcutaneous Tissue Disorders

Dermatologic ARs are considered a class effect of both BRAF and MEK inhibitors (Table 2, Supplementary Materials Table S3) [35, 44]. In PHAROS, dermatological ARs included rash (27%), pruritus (16%), dry skin (13%), and alopecia (12%) [31, 32]. It is important for patients to inform their healthcare provider about any skin changes immediately [31, 32]. Management strategies for mild rashes include creams, emollients, topical corticosteroids (e.g., hydrocortisone) [44], changes in clothing, or lotions. Moderate to severe cases may require additional medications, such as topical steroids (e.g., triamcinolone, clobetasol), prednisone, antihistamines, or referral to a dermatologist [44]. Photosensitivity was reported by 4% of patients in a previous trial of encorafenib plus binimetinib for melanoma [52]. Patients should proactively prevent photosensitive reactions by applying broad-spectrum sunscreen and lip balm, wearing ultraviolet-protective clothing, avoiding sun exposure [44], and avoiding alcohol-based fragrances or lotions. Dose modifications for general dermatologic ARs are summarized in Fig. 2a.

New skin cancers, including cutaneous SCC and basal cell carcinoma, are associated with encorafenib and other BRAF inhibitors [21, 31, 53]. In PHAROS, cutaneous SCC and skin papilloma each occurred in 2% of patients [31]. The incidence of SCC is decreased by the addition of MEK inhibitors [20, 53]. For instance, in previous trials with encorafenib monotherapy and encorafenib plus binimetinib for patients with melanoma, cutaneous SCC occurred in 8% and 3% of patients, respectively [31]. Proactive management is important as the median onset to first occurrence for cutaneous SCC with encorafenib plus binimetinib for patients with melanoma was 5.8 months. Patients should proactively check their skin for any changes (e.g., new wart, a sore that bleeds or does not heal, changes to a mole) and alert their healthcare provider. Healthcare providers should check the patient's skin before treatment and every 2 months during treatment and up to 6 months after treatment. In clinical practice, ongoing dermatologic evaluations every 3 to 6 months are suggested. Dose modifications are not recommended for new primary cutaneous malignancies, but non-cutaneous malignancies can also occur. Patients should be monitored for symptoms of non-cutaneous malignancies, and encorafenib should be discontinued for RAS-mutant non-cutaneous malignancies (Fig. 2b).

Cardiac Disorders

In PHAROS, cardiomyopathy manifesting as left ventricular dysfunction was reported in 11% of patients, with grade 3 in 1% (Table 2) [31, 32]. In a previous melanoma trial, left ventricular dysfunction occurred in 7% of patients, with grade 3 in 2% and a median time to onset of 3.6 months. Cardiomyopathy resolved in 82%

and 87% of patients in NSCLC and melanoma trials, respectively. Ejection fraction should be assessed by echocardiogram or MUGA scan before initiating treatment, 1 month after treatment initiation, and every 2 to 3 months during treatment. Safety of encorafenib plus binimetinib has not been evaluated in patients with baseline ejection fraction that is < 50% or below institutional lower limit of normal. In addition, dose-dependent QTc prolongation has been associated with encorafenib treatment, with an increase in QTcF to > 500 ms in 2.1% of patients in PHAROS [31]. Electrolytes should be evaluated, and abnormalities should be remedied. Close monitoring should be instituted for patients with cardiovascular risks, including current or risk for developing QTc prolongation [31, 32]. Patients who experience a decrease in left ventricular ejection fraction or prolongation in QTc need to be carefully assessed, and treatment should be withheld, dose reduced, or permanently discontinued on the basis of severity and recurrence as outlined in Fig. 2. Consultation with a cardiologist should also be considered [44].

CONCLUSION

In the PHAROS study, encorafenib plus binimetinib was an effective therapy option for patients with BRAF V600E-mutant mNSCLC and was generally well tolerated, with most ARs being grade ≤ 2 [15, 31, 32]. ARs were generally managed with dose interruptions or dose reductions, with ARs resulting in permanent discontinuation of encorafenib or binimetinib in only 16% and 17% of patients, respectively. The safety profile was generally consistent with that observed in patients with BRAF V600E- or V600K-mutant unresectable or metastatic melanoma. The 5-year updated analysis from that trial demonstrated continued tolerability with no new safety concerns [52]. Management of ARs associated with encorafenib plus binimetinib involves proactive communication, supportive care, and occasional dose modifications. Proactive AR management may prevent unnecessary treatment discontinuations and enable patients to remain on encorafenib and binimetinib while deriving clinical benefit.

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Declarations

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