Optimizing Treatment of *BRAF* V600E–Mutant Metastatic NSCLC With Encorafenib and Binimetinib: A Practical Resource for Advanced Practice Providers

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

The *BRAF* V600E mutation aberrantly activates the mitogen-activated protein kinase (MAPK) pathway, subsequently resulting in uncontrolled cellular proliferation, survival, and dedifferentiation. Approximately 2% of patients with non–small cell lung cancer (NSCLC) have a *BRAF* V600E mutation. BRAF and MEK inhibitor combination therapy targets two kinases within the MAPK pathway. Encorafenib (Braftovi) and binimetinib (Mektovi) are potent oral inhibitors of BRAF and MEK, respectively. With the recent US Food and Drug Administration approval of encorafenib plus binimetinib, adult patients with *BRAF* V600E–mutated metastatic NSCLC have an additional treatment option. In the phase II PHAROS study, encorafenib plus binimetinib achieved the primary endpoint of objective response rate by independent review committee and exhibited a manageable safety profile in this patient population. This article provides an overview of the efficacy and safety of encorafenib plus binimetinib and uses a fictional patient case to illustrate the role of advanced practice providers in providing individualized patient care and identifying and managing adverse reactions.

CASE STUDY

The patient case described is fictional and does not represent actual events or a response from an actual patient. The authors developed this fictional case for educational purposes only.

Ruth, a 68-year-old white woman, was diagnosed with metastatic non–small cell lung cancer (mNSCLC; Figure 1). Her presenting symptoms were dyspnea, hemoptysis, chest pain, and weight loss without any changes to activity or diet. She has a 20 pack-year history of smoking and quit 10 years prior to presentation. Her concurrent medical conditions included hypertension, hyperlipidemia, gastroesophageal reflux disease, and chronic obstructive pulmonary disease; her corresponding medications were amlodipine (Norvasc), rosuvastatin (Crestor), famotidine (Pepcid), and fluticasone (Flovent). She had no family history of cancer.

Ruth underwent CT scans of the chest, abdomen, and pelvis, which revealed an abnormal mass on her lungs. A tissue biopsy revealed NSCLC with adenocarcinoma histology. Additional imaging scans (PET and MRI) revealed that the cancer had metastasized to distant lymph nodes and bones but not to the brain. Next-generation sequencing with a multiple-gene panel identified a *BRAF* V600E mutation (Figure 2), and immunohistochemistry analysis revealed programmed death ligand 1 (PD-L1) expression of 60%. Based on her presenting symptoms, her Eastern Cooperative Oncology Group performance status at diagnosis was 1. Ruth's physician initiated an oral combination of encorafenib (Braftovi) 450 mg once daily and binimetinib (Mektovi) 45 mg twice daily.

The *BRAF* gene encodes a kinase involved in the mitogen-activated protein kinase signaling pathway, which regulates cellular processes, such as cell growth, differentiation, and proliferation (Figure 3; Ottaviano et al., 2021; Yaeger & Corcoran, 2019). *BRAF* mutations occur in various solid tumor types, including melanoma, thyroid, colorectal, and non–small cell lung cancer (NSCLC; Owsley et al., 2021). *BRAF* mutations occur in approximately 2% to 4% of patients with NSCLC and are divided into Class I, II, and III mutations accounting for 31% to 45%, 32% to 34%, and 23% to 31% of cases, respectively (Barlesi et al., 2016; Dagogo-Jack et al., 2019; Owsley et al., 2021). Class I mutations occur at codon 600 (V600), in which valine is substituted for another amino acid, resulting in a constitutively active BRAF monomer; glutamic acid substitution (V600E) is the most common *BRAF* mutation in NSCLC, accounting for approximately 30% to 50% of *BRAF* mutations in NSCLC cases (Cardarella et al., 2013; Sheikine et al., 2018; Smiech et al., 2020). Class II and III mutations occur at various non-V600 codons to form either constitutively active or kinase-impaired dimers, respectively (Smiech et al., 2020). Given that *BRAF* V600E is a targetable mutation with approved therapies, all patients with advanced nonsquamous NSCLC should receive broad-based molecular testing, including for *BRAF* mutations, as recommended by guidelines (Baik et al., 2017; Hendriks et al., 2023; National Comprehensive Cancer Network [NCCN], 2023). Molecular testing should be considered for patients with squamous NSCLC.

Clinical characteristics of patients with *BRAF*-mutant NSCLC vary by the class of mutation, and epidemiological patterns are unclear due to the rarity of *BRAF* mutations in NSCLC (Abdayem & Planchard, 2022; Dagogo-Jack et al., 2019). Adenocarcinoma is the predominant histology, occurring in > 85% of patients with *BRAF*-mutant NSCLC (Barlesi et al., 2016; Dagogo-Jack et al., 2019; Riely et al., 2023). While *BRAF* mutations are often identified in patients who currently smoke or formerly smoked (> 75%), several studies suggest that the association is weaker with *BRAF* V600E than with other *BRAF* mutations (Barlesi et al., 2016; Cardarella et al., 2013; Marchetti et al., 2011).

TREATMENT LANDSCAPE

Approved targeted therapies are only effective for the Class I *BRAF* V600E mutation; no agents are currently approved for Class II or III *BRAF* mutations (NCCN, 2023; Yaeger & Corcoran, 2019). BRAF inhibitor (vemurafenib [Zelboraf] or dabrafenib [Tafinlar]) monotherapy demonstrated initial efficacy but provided a limited survival benefit in patients with *BRAF* V600E–mutant NSCLC (Figure 3; Mazieres et al., 2020; Planchard

Name: Ruth

DOB: 05-31-1955

Age: 68

Sex: Female

Ethnicity: White

Notes: Ruth lives with her husband, and her two daughters live 20 minutes away. Strong support system.

Presentation

- Dyspnea
- Hemoptysis
- Chest pain
- Weight loss without changes to activity or diet

History and Lifestyle

- Formerly smoked (20 pack-years); quit ≈10 years ago
- Moderately active
- Occasional alcohol
- No family history of cancer or other conditions
- Knee surgery (age 58 years)

Comorbidities and Concurrent Medications

- Hypertension, managed with amlodipine (Norvasc) 5 mg orally once daily
- Hyperlipidemia, managed with rosuvastatin (Crestor) 10 mg orally once daily
- GERD, managed with famotidine (Pepcid)
- COPD, managed with fluticasone (Flovent) 88 µg orally (inhalation) twice daily

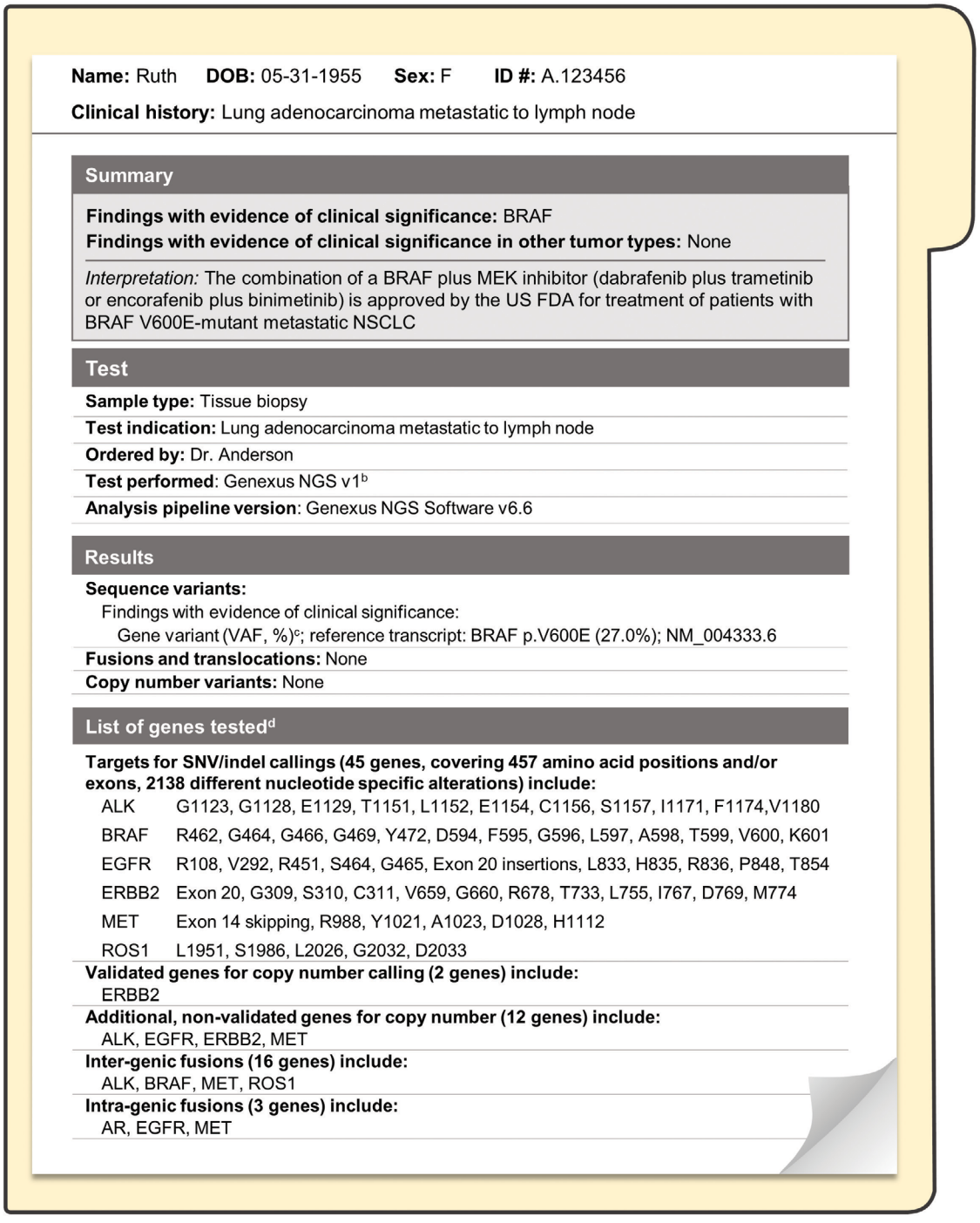
Assessment and Diagnosis

- Stage IV non-small cell lung cancer
- **Metastases:** distant lymph nodes and bones
- **Tissue biopsy:** *BRAF* V600E mutation
- **IHC:** PD-L1 expression of 60%
- **ECOG PS:** 1
- **Brain metastases:** no

Treatment Plan

- No prior systemic treatment
- Encorafenib (Braftovi; 450 mg orally once daily) plus binimetinib (Mektovi; 45 mg orally twice daily)

Figure 1. Patient case study summary. COPD = chronic obstructive pulmonary disease; DOB = date of birth; ECOG PS = Eastern Cooperative Oncology Group performance status; GERD = gastroesophageal reflux disease; IHC = immunohistochemistry; PD-L1 = programmed cell death ligand 1.



Name: Ruth **DOB:** 05-31-1955 **Sex:** F **ID #:** A.123456

Clinical history: Lung adenocarcinoma metastatic to lymph node

Summary

Findings with evidence of clinical significance: BRAF
Findings with evidence of clinical significance in other tumor types: None

Interpretation: The combination of a BRAF plus MEK inhibitor (dabrafenib plus trametinib or encorafenib plus binimetinib) is approved by the US FDA for treatment of patients with BRAF V600E-mutant metastatic NSCLC

Test

Sample type: Tissue biopsy
Test indication: Lung adenocarcinoma metastatic to lymph node
Ordered by: Dr. Anderson
Test performed: Genexus NGS v1[b]
Analysis pipeline version: Genexus NGS Software v6.6

Results

Sequence variants:
Findings with evidence of clinical significance:
Gene variant (VAF, %)[c]; reference transcript: BRAF p.V600E (27.0%); NM_004333.6
Fusions and translocations: None
Copy number variants: None

List of genes tested[d]

Targets for SNV/indel callings (45 genes, covering 457 amino acid positions and/or exons, 2138 different nucleotide specific alterations) include:

ALK	G1123, G1128, E1129, T1151, L1152, E1154, C1156, S1157, I1171, F1174,V1180
BRAF	R462, G464, G466, G469, Y472, D594, F595, G596, L597, A598, T599, V600, K601
EGFR	R108, V292, R451, S464, G465, Exon 20 insertions, L833, H835, R836, P848, T854
ERBB2	Exon 20, G309, S310, C311, V659, G660, R678, T733, L755, I767, D769, M774
MET	Exon 14 skipping, R988, Y1021, A1023, D1028, H1112
ROS1	L1951, S1986, L2026, G2032, D2033

Validated genes for copy number calling (2 genes) include:
ERBB2
Additional, non-validated genes for copy number (12 genes) include:
ALK, EGFR, ERBB2, MET
Inter-genic fusions (16 genes) include:
ALK, BRAF, MET, ROS1
Intra-genic fusions (3 genes) include:
AR, EGFR, MET

Figure 2. Simplified NGS report summary for patient.[a] DOB = date of birth; F = female; ID = identification; NGS = next-generation sequencing; NSCLC = non–small cell lung cancer; SNV = single nucleotide variant; US FDA = United States Food and Drug Administration; VAF = variant allele frequency.
[a]This report is a simplified fictional NGS report based on a typical report provided to the authors.
[b]Genexus NGS assay utilizes a targeted, amplicon-based NGS assay for detecting select regions across 50 genes for the identification of key genomic alterations.
[c]VAF is the percentage of observed sequence reads that match the specified variant.
[d]For simplicity, this list is not comprehensive and only includes examples of genes tested.

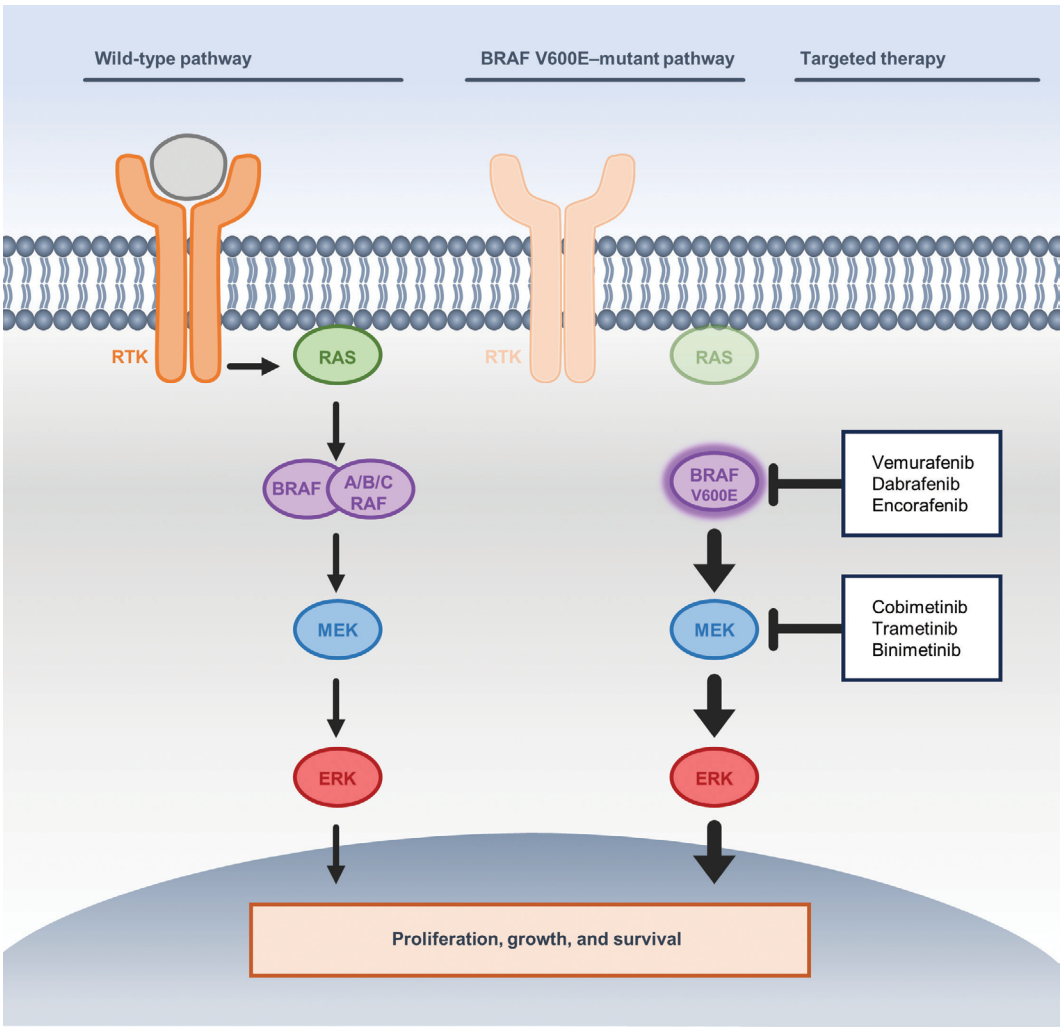


Figure 3. Mitogen-activated protein kinase (MAPK) pathway. In the wild-type pathway, RAS activates BRAF, which forms homo- or heterodimers and subsequently activates MAPK kinase (MEK). In *BRAF* V600E–mutant cells, *BRAF* V600E is a constitutively active monomer. Current targeted therapy includes BRAF monomer inhibitors (vemurafenib, dabrafenib, and encorafenib) and MEK inhibitors (cobimetinib, trametinib, and binimetinib). RTK = receptor tyrosine kinase.

et al., 2016a; Subbiah et al., 2020). Combining a MEK (downstream of BRAF in the mitogen-activated protein kinase pathway) inhibitor, such as trametinib (Mekinist) or binimetinib (Mektovi), with a BRAF inhibitor improved efficacy outcomes and provided a favorable safety profile (Planchard et al., 2016b; Planchard et al., 2017; Riely et al., 2023; Subbiah et al., 2020). Combinations of BRAF and MEK inhibitors, dabrafenib plus trametinib and encorafenib (Braftovi) plus binimetinib, are approved therapies for patients with *BRAF* V600E–mutant metastatic NSCLC (mNSCLC); these targeted therapy combinations have also been approved for other indications (Table 1; Array BioPharma Inc, 2018a; Koelblinger et al., 2018; Novartis Pharmaceuticals Corporation, 2013b; Tran & Cohen, 2020). Current guidelines recommend either dabrafenib plus trametinib or encorafenib plus binimetinib as the preferred first-line treatment for *BRAF* V600E–mutant mNSCLC as well as for subsequent therapy in patients who received another therapy in the first-line setting (NCCN, 2023).

Table 1. Approved Targeted Therapy Combinations for *BRAF* V600E–Mutant Tumors

Combination	Indications
Dabrafenib (Tafinlar) plus trametinib (Mekinist)	*BRAF* V600E– or V600K–mutant unresectable or metastatic melanoma
	Adjuvant treatment following complete resection for patients with *BRAF* V600E– or V600K–mutant melanoma with involvement of lymph node(s)
	BRAF V600E–mutant metastatic NSCLC
	BRAF V600E–mutant locally advanced or metastatic anaplastic thyroid cancer with no satisfactory locoregional treatment options
	BRAF V600E–mutant unresectable or metastatic solid tumors in previously treated adult and pediatric patients (aged ≥ 1 year) with no satisfactory alternative option
	BRAF V600E–mutant low-grade glioma in pediatric patients (aged ≥ 1 year) who require systemic therapy
Encorafenib (Braftovi) plus binimetinib (Mektovi)	*BRAF* V600E– or V600K–mutant unresectable or metastatic melanoma
	BRAF V600E–mutant metastatic NSCLC in adult patients
Encorafenib (Braftovi) plus cetuximab (Erbitux)	*BRAF* V600E–mutant metastatic colorectal cancer in previously treated adult patients

Note. NSCLC = non–small cell lung cancer. Information from Novartis Pharmaceuticals Corporation (2013a); Array BioPharma Inc (2018a).

Current guidelines also recommend chemotherapy, immunotherapy, or a combination of immunotherapy and chemotherapy as additional treatment options for *BRAF* V600E–mutant mNSCLC (Hendriks et al., 2023; NCCN, 2023). Efficacy and safety data for immunotherapy and chemotherapy in patients with *BRAF*-mutant NSCLC are limited; available data are from retrospective analyses of a small number of patients (Cardarella et al., 2013; Dagogo-Jack et al., 2019; Dudnik et al., 2018; Guisier et al., 2020; Mazieres et al., 2019). Some studies showed that patients with *BRAF* V600E mutations or those without a smoking history have poorer outcomes with immunotherapy than those with *BRAF* non-V600E mutations or a smoking history (Dudnik et al., 2018; Mazieres et al., 2019). High PD-L1 expression is a potential indicator of immunotherapy response, and high PD-L1 expression (≥ 50%) in patients with mNSCLC is more common with *BRAF* V600E mutations (approximately 42%–48%) than with most other oncogenes (e.g., approximately 9%–19% with *EGFR* mutations; Dudnik et al., 2018; Hsu et al., 2022; Negrao et al., 2021). Pembrolizumab (Keytruda), a programmed cell death protein 1 antibody that blocks the PD-L1 pathway, is approved by the US Food and Drug Administration (FDA) for patients with PD-L1–expressing mNSCLC tumors although not specifically for patients with a *BRAF* V600E mutation (Pai-Scherf et al., 2017).

ENCORAFENIB PLUS BINIMETINIB FOR *BRAF* V600E–MUTANT METASTATIC NSCLC: EFFICACY

PHAROS, a phase II, single-arm, open-label study, enrolled 59 treatment-naive and 39 previously treated patients with *BRAF* V600E–mutant mNSCLC (Table 2; Riely et al., 2023). Patients received oral encorafenib 450 mg once daily plus oral 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 version 1.1. In treatment-naive patients, objective response rate by IRR was 75%, median duration of response was not estimable (NE), and median time to response was 1.9 months. Median duration of follow-up for progression-free survival (PFS) by IRR was 18.2 months, median PFS was NE, and median overall survival was NE. In previously treated patients, objective response rate by IRR was 46%, median duration of response 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 overall survival was NE.

Table 2. Summary of Efficacy of Encorafenib Plus Binimetinib in the PHAROS Study

	Treatment-naive (*n* = 59)	Previously treated (*n* = 39)
ORR by IRR (95% CI), %	75 (62–85)	46 (30–63)
CR	15	10
PR	59	36
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 (6.2–NE)
OS, median, months	NE	NE

Note. CI = confidence interval; CR = complete response; DOR = duration of response; IRR = independent radiology review; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response. Information from Riely et al. (2023).

CASE STUDY CONTINUED: EFFICACY OUTCOMES

Approximately 2 months after beginning treatment with encorafenib plus binimetinib, Ruth had a follow-up visit to determine the efficacy of treatment and assess safety. She noted improvements in her respiratory and other baseline symptoms. Full systemic restaging with CT scans of her chest, abdomen, and pelvis was performed to remeasure the lesions (Figure 4). Based on a 35% decrease in tumor lesions per Response Evaluation Criteria in Solid Tumors version 1.1, she had achieved a partial response. Ruth returned for restaging every 2 months and received MRI brain scans every 6 months. At Ruth's 16-month appointment, she mentioned experiencing breathing difficulties that began the prior week. The worsening of her respiratory symptoms coincided with tumor growth that was evident when her 16-month scans were compared with her 2-month scans, which indicated that her mNSCLC had progressed. Therefore, Ruth discontinued encorafenib plus binimetinib treatment. As tumor tissue was not available, a liquid biopsy was performed to evaluate potential mechanisms of acquired resistance to inform the next treatment options.

ENCORAFENIB PLUS BINIMETINIB: SAFETY AND TOLERABILITY

In the PHAROS study, safety analysis revealed a manageable safety profile in patients (*n* = 98) who received encorafenib plus binimetinib (Riely et al., 2023). While the published paper reported treatment-related adverse events and resulting dose modifications, the FDA labels report all-causality adverse reactions (ARs) that occurred in ≥ 10% of patients in PHAROS and dose modifications (Figure 5, Table 3; Array BioPharma Inc, 2018a, 2018b; Riely et al., 2023). The most common (≥ 25%) ARs were fatigue (61%), nausea (58%), diarrhea (52%), musculoskeletal pain (48%), vomiting (37%), abdominal pain (32%), visual impairment (29%), dyspnea (27%), rash (27%), constipation (27%), and cough (26%; Array BioPharma Inc, 2018a, 2018b). All-causality pyrexia occurred in 22% of patients, was grade 1 and 2, and resulted in one dose interruption and no dose reductions or permanent discontinuations (Riely et al., 2023). Serious ARs occurred in 38% of patients, with hemorrhage (6%) being the most common (Array BioPharma Inc, 2018a, 2018b). The safety profile of encorafenib plus binimetinib in PHAROS was generally consistent with the known safety profile of the combination in patients with *BRAF* V600E– or V600K–mutant unresectable or metastatic cutaneous melanoma (Dummer et al., 2018; Riely et al., 2023; Table 4).

ROLE OF THE APP IN ADVERSE REACTION MANAGEMENT

Advanced practice providers (APPs) play an essential role throughout a patient's cancer care. As treatment selection is complex, when choosing

Name: Ruth **DOB:** 05-31-1955 **Rx:** Enco (450 mg once daily) + bini (45 mg twice daily)

Efficacy Highlights	
Month 2	Partial response • Sum of diameters: 35% decrease from baseline
Month 16	Disease progression • Sum of diameters: 21% increase compared with 2-month scans Treatment discontinued

Adverse Reactions and Interventions	
Week 2	Nausea without vomiting or abdominal pain (grade 1) • Prescribed prochlorperazine (Compazine) to be taken 10 mg orally as needed • Advised to eat small, frequent meals and snacks and to hydrate
	Fatigue; naps are helpful (grade 1) • Advised to nap when needed and incorporate light physical activity if tolerated
	Normal laboratory study results
	Notes: Scheduled follow-up appointment in 2 weeks and advised patient to call if symptoms worsened.
Week 4	Nausea worsened; food intake has decreased but weight is stable (grade 2)
	Fatigue affecting daily activities; naps no longer restorative (grade 2)
	Dry mucous membranes
	BP slightly decreased • Given IV fluids • Instructed to monitor BP at home daily • Given parameters for withholding antihypertensive medication
	Notes: Instructed patient to withhold treatment until improvement. Patient reported improvement via phone call 2 days later.
Week 5	BP within normal limits while on antihypertensive medication
	Improvement in baseline pain and dyspnea
	Notes: Since symptoms improved to near baseline, restart treatment at reduced doses: encorafenib (300 mg once daily) and binimetinib (30 mg twice daily)

Figure 4. Patient response to treatment, including efficacy and safety. Bini = binimetinib; BP = blood pressure; DOB = date of birth; enco = encorafenib; IV = intravenous; Rx = prescription.

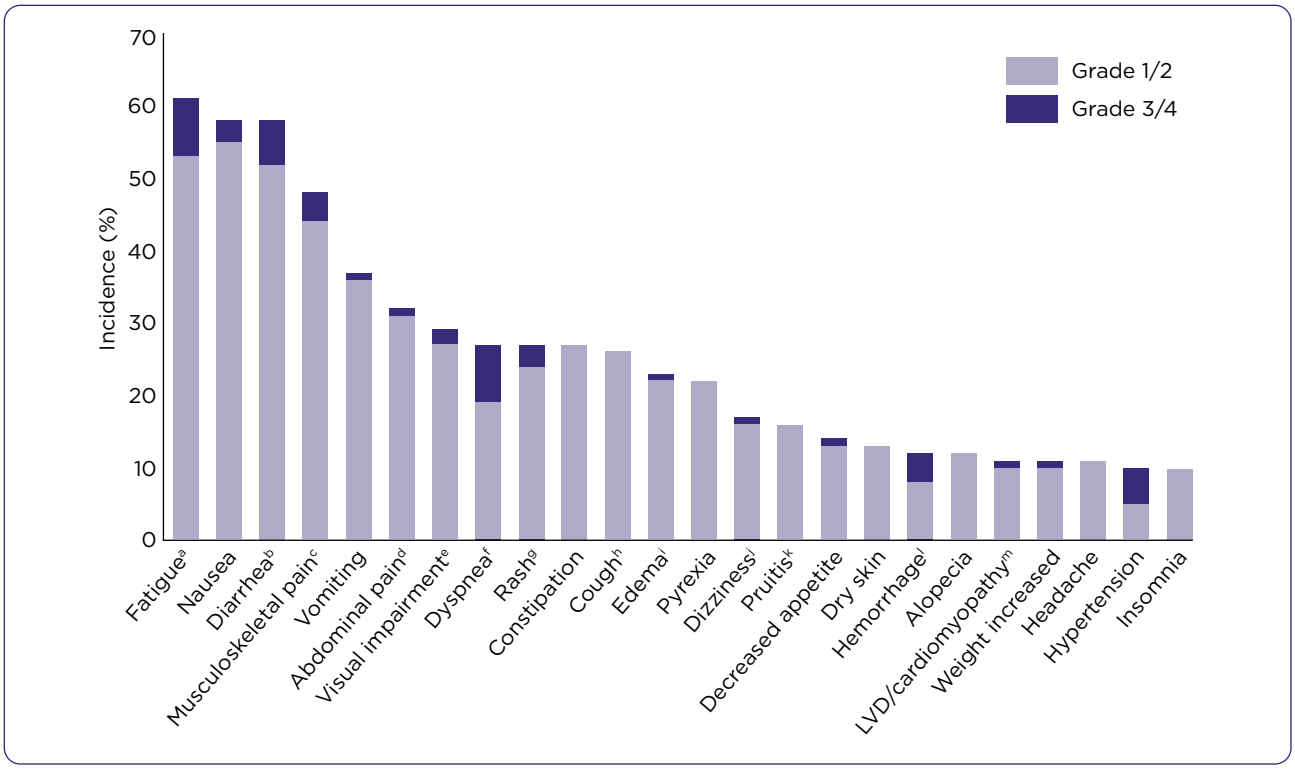


Figure 5. All-causality ARs reported by ≥ 10% of patients in the PHAROS study. AR = adverse reaction; LVD = left ventricular dysfunction. Information from Array BioPharma Inc (2018a, 2018b).
[a]Includes fatigue and asthenia.
[b]Includes diarrhea and colitis.
[c]Includes back pain, arthralgia, pain in extremity, myalgia, musculoskeletal chest pain, noncardiac chest pain, and neck pain.
[d]Includes abdominal pain, upper abdominal pain, abdominal discomfort, and epigastric discomfort.
[e]Includes blurred vision, visual impairment, vitreous floaters, photophobia, reduced visual acuity, and photopsia.
[f]Includes dyspnea and exertional dyspnea.
[g]Includes rash, macular rash, maculopapular rash, papular rash, pustular rash, dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, eczema, and skin exfoliation.
[h]Includes cough and productive cough.
[i]Includes peripheral edema, generalized edema, swelling, localized edema, and face edema.
[j]Includes dizziness and balance disorder.
[k]Includes pruritus and genital pruritus.
[l]Includes anal hemorrhage, hemothorax, gastrointestinal hemorrhage, hematochezia, hematuria, hemoptysis, intracranial hemorrhage, hyphema, small intestinal hemorrhage, upper gastrointestinal hemorrhage, and vaginal hemorrhage. One grade 5 hemorrhage occurred.
[m]Includes decreased ejection fraction, cardiac failure, and congestive cardiac failure.

the optimal personalized approach for each patient, many factors should be considered, including medical history, disease characteristics, and ability to take certain drugs. Relevant patient history may include smoking history, comorbidities, and current medications. An accurate baseline history, including review of symptoms and physical examination, can help in grading and attributing changes in condition after therapy initiation and guide focused interviews and examinations for new or worsening symptoms. A review of medications is important to avoid drug-drug interactions. While binimetinib has no reported drug interactions, coadministration of encorafenib with strong or moderate CYP3A4 inhibitors (e.g., itraconazole [Sporanox]) may increase

Table 3. Dose Modifications of Encorafenib or Binimetinib as a Result of All-Causality Adverse Reactions in the PHAROS study (*n* = 98)[a]

Dose modification	Encorafenib	Binimetinib
Dose interruptions, %	59	62
Most common ARs (%)	Diarrhea (17) Nausea (13) Musculoskeletal pain (8) Fatigue (8) AST increased (7) ALT increased (6) Anemia (6) Hemorrhage (6) Vomiting (6) Acute kidney injury (5)	Diarrhea (17) Nausea (15) Fatigue (9) AST increased (7) ALT increased (6) Anemia (6) Musculoskeletal pain (6) Vomiting (6) Acute kidney injury (5) Hemorrhage (5) LV dysfunction/cardiomyopathy (5)
Dose reductions, %	30	33
Most common ARs (%)	Diarrhea (8) Nausea (8) AST increased (5) Fatigue (5)	Diarrhea (8) Nausea (6) AST increased (5)
Permanent discontinuation, %	16	17
Most common ARs (%)	Diarrhea (3) Musculoskeletal pain (3) Fatigue (2) Rash (2) Nausea (2) Visual impairment (2) Vomiting (2)	Diarrhea (3) Musculoskeletal pain (2) LV dysfunction/cardiomyopathy (2) Fatigue (2) Nausea (2) Rash (2) Visual impairment (2) Vomiting (2)

Note. ALT = alanine aminotransferase; AR = adverse reaction; AST = aspartate aminotransferase; LV = left ventricular. Information from Riely et al. (2023); Array BioPharma Inc (2018a, 2018b).
[a]In PHAROS, treatment-related adverse events led to dose interruption, dose reduction, and permanent discontinuations of both encorafenib and binimetinib in 44%, 24%, and 15% of patients, respectively.

the risk of adverse reactions; coadministration of encorafenib with strong CYP3A4 inducers (e.g., rifamycin [Aemcolo]) may decrease efficacy (Array BioPharma Inc, 2018a, 2018b; Janssen Pharmaceuticals, 2024; RedHill Biopharma Ltd, 2024; US Food and Drug Administration, 2023a).

Biomarker identification informs the selection of first-line treatment based on guideline recommendations, and biomarker testing has been associated with improved patient outcomes (Bhandari et al., 2023; Waterhouse et al., 2021). Baseline biomarker screening should be conducted for all patients with advanced or metastatic non-squamous NSCLC regardless of patient characteristics (e.g., smoking history, age, sex) prior to initiation of first-line treatment (Baik et al., 2017; Bhandari et al., 2023; Waterhouse et al., 2021). The testing rates for *BRAF* mutations fall behind that of other oncogenes (Waterhouse et al., 2021). A retrospective real-world study showed that a higher proportion of patients with *BRAF*-mutant NSCLC received discordant first-line treatment compared with other biomarkers (Bhandari et al., 2023). Next-generation sequencing (NGS) simultaneously tests multiple genes using little tumor tissue, and it has become the preferred biomarker screening method (Hoffman et al., 2023). In addition to molecular characteristics, it is important to assess disease-related characteristics, including burden of disease (e.g., presence of brain metastases), symptom burden, and symptom distress.

The ability to take medications can be influenced by a patient's functional or performance status, patient support system, financial capacity, ability to adhere to complex treatment regimens, and route of administration (e.g., oral vs.

Table 4. Safety Profile of Encorafenib Plus Binimetinib in Patients With *BRAF* V600E– or V600K–Mutant Unresectable or Metastatic Cutaneous Melanoma

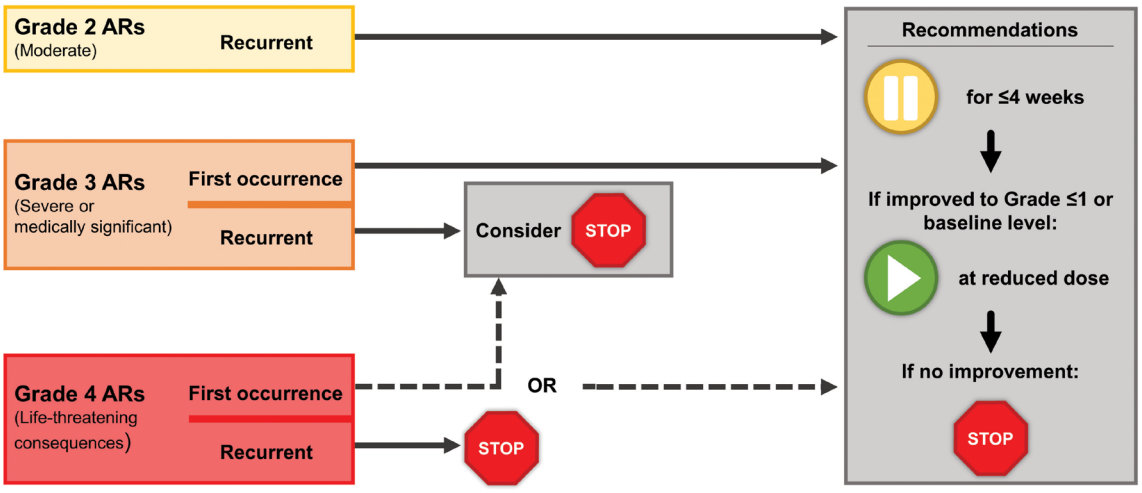
Most common (≥ 25%) all-causality ARs		
AR	**Incidence, %**	**Median time to onset, days**
Fatigue	43	NA
Nausea	41	29
Diarrhea	36	29
Vomiting	30	57
Abdominal pain	28	NA
Arthralgia	26	85
Pyrexia[a]	18	85
Dose modifications resulting from all-causality ARs		
Dose modification	**Encorafenib**	**Binimetinib**
Dose interruptions, %	30	33
Most common ARs (%)	Nausea (7) Vomiting (7) Pyrexia (4)	LV dysfunction (6) Serous retinopathy (5)
Dose reductions, %	14	19
Most common ARs (%)	Arthralgia (2) Fatigue (2) Nausea (2)	LV dysfunction (3) Serous retinopathy (3) Colitis (2)
Permanent discontinuation, %	5	5
Most common ARs (%)	Hemorrhage (2) Headache (1)	Hemorrhage (2) Headache (1)

Note. AR = adverse reaction; LV = left ventricular. Information from Array BioPharma Inc (2018a, 2018b); Gogas et al. (2019).
[a]Pyrexia was included due to particular interest in the incidence of this AR for BRAF plus MEK inhibitors.

infusion). Functional or performance status, indicative of mobility, is an important consideration when choosing treatments that require numerous appointments. Oral drugs can be more convenient for patients; however, they may be a concern for people with an inability to swallow.

Prior to initiating treatment, APPs educate patients and their caregivers on the appropriate dosage, administration, and most common ARs and encourage patients and their caregivers to openly talk to their health-care team about ARs and how to manage them. Advanced practice providers proactively inquire about ARs throughout the treatment course and modify the dose of therapy as needed. During treatment, listening to and addressing the concerns of patients and caregivers will ensure that a patient knows what to expect and is comfortable reporting ARs to a health-care provider.

Some of the common ARs associated with encorafenib plus binimetinib can be managed with lifestyle changes (e.g., exercise to reduce fatigue, hydration for headaches, diet changes for gastrointestinal ARs) or over-the-counter medications (e.g., lotion or creams for rash, fluids and medications for vomiting and diarrhea; Augustyn et al., 2023; Baik et al., 2024). Dose modifications may lead to resolution of the AR, which would enable those who are deriving benefit to remain on therapy and potentially experience increased quality of life. General recommendations for dose modifications for AR management are found in Figure 6 (Array BioPharma Inc, 2018a, 2018b). A subset of ARs have specific encorafenib or binimetinib dose modification recommendations (Table 5). If encorafenib is permanently discontinued, binimetinib should also be discontinued (Array BioPharma Inc, 2018b). If binimetinib is discontinued, encorafenib should be reduced to a maximum dose of 300 mg (Array BioPharma Inc, 2018a).



Dose Modifications

	Initial dose, mg	First reduction, mg	Second reduction, mg	Unable to tolerate minimum dose
Encorafenib (once daily)	450	300	225	STOP Along with binimetinib
Binimetinib (twice daily)	45	30	-	STOP While withholding, reduce encorafenib to maximum dose of 300 mg once daily

Resume Withhold STOP Permanently discontinue

Figure 6. Dose modifications for management of ARs with encorafenib plus binimetinib. Dose modifications are recommended for any occurrence of higher-grade (≥ 3) or recurrent grade 2 ARs. Recommendations are for both encorafenib and binimetinib. Information from Array BioPharma Inc (2018a, 2018b). AR = adverse reaction.

CASE STUDY CONTINUED: IMPACT OF PATIENT CHARACTERISTICS ON TREATMENT PLAN

Since Ruth's mNSCLC was positive for the *BRAF* V600E mutation, her oncologist selected encorafenib plus binimetinib as her first-line treatment. Most of her concurrent medications posed no risk of potential drug interactions. However, Ruth was monitored closely for rosuvastatin-associated ARs (e.g., myopathy, rhabdomyolysis), as coadministration with encorafenib plus binimetinib may increase rosuvastatin plasma concentrations and subsequent ARs (Array BioPharma Inc, 2018a; AstraZeneca Pharmaceuticals LP, 2003). When discussing medication regimens, Ruth admitted that she can be forgetful. However, her husband and two daughters provided her with a pill sorter, set alarms on her cell phone, and followed up to ensure she kept to the schedule. Her daughters provided immense support and alternated taking Ruth to appointments. Her strong support system would enable her to adhere to the prescribed encorafenib plus binimetinib regimen.

CASE STUDY CONTINUED: ADVERSE REACTIONS EXPERIENCED DURING TREATMENT AND MANAGEMENT

At her toxicity assessment 2 weeks after initiation of therapy, Ruth noted intermittent nausea without vomiting or abdominal pain (Figure 4). She reported fatigue (grade 1), which required an occasional nap during the day; she did not previously need to

Table 5. ARs Specific to Encorafenib or Binimetinib That Require Dose Modifications

Encorafenib dose modifications for AR management[a]	
New primary malignancies	
Noncutaneous *RAS*-mutant 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
Binimetinib dose modification for specific AR management[b]	
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
Serous retinopathy	
Symptomatic serous retinopathy/retinal pigment epithelial detachments	Withhold for ≤ 10 days • If improved and asymptomatic, resume same dose • If not improved, resume at lower dose or permanently discontinue
Retinal vein occlusion	
Any grade	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
Rhabdomyolysis or CPK elevations	
Grade 4 asymptomatic CPK elevation or any-grade CPK elevation with either symptoms or renal impairment	Withhold for ≤ 4 weeks • If improved to grade ≤ 1, resume at reduced dose • If not resolved within 4 weeks, permanently discontinue
Cardiomyopathy	
Asymptomatic; absolute decrease in LVEF of > 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 discontinue

Note. AR = adverse reaction; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; DVT = deep vein thrombosis; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; PE = pulmonary embolism; QTc = correct QT interval; QTcF = Fridericia Correction Formula. Information from Array BioPharma Inc (2018a, 2018b).

[a]When administered with binimetinib, dose modifications of encorafenib are not recommended for the following ARs: new primary cutaneous malignancies, ocular events (except uveitis, iritis, and iridocyclitis), interstitial lung disease/pneumonitis, CPK level elevation, rhabdomyolysis, and venous thromboembolism.

[b]When administered with encorafenib, dose modifications of binimetinib are not recommended for the following ARs: palmar-plantar erythrodysesthesia syndrome, noncutaneous *RAS*-mutant malignancies, and QTc prolongation.

☞ *Continued on the next page*

Table 5. ARs Specific to Encorafenib or Binimetinib That Require Dose Modifications (cont.)

Specific ARs that may require encorafenib and binimetinib dose modifications	
Uveitis	
Grade 1 or 2	If no response following ocular therapy, withhold for ≤ 6 weeks • If improved, resume at same or reduced dose • If not improved, permanently discontinue
Grade 3	Withhold for ≤ 6 weeks • If improved, resume at same or reduced dose • If not improved, permanently discontinue
Grade 4	Permanently discontinue
Dermatologic	
Grade 2	If no improvement within 2 weeks, withhold until grade ≤ 1, then resume same dose if first occurrence or reduced dose if recurrent
Grade 3	Withhold until grade ≤ 1 • If first occurrence, resume at same dose • If recurrence, reduce dose
Grade 4	Permanently discontinue
Hepatoxicity (increased AST or ALT level)	
Grade 2	Maintain dose • If no improvement within 2 (binimetinib) or 4 (encorafenib) weeks, withhold until grade ≤ 1 or return to baseline levels, then resume same dose
Grade 3 or 4	Follow recommendations for general ARs (Figure 6)
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 institutional 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

Note. AR = adverse reaction; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; DVT = deep vein thrombosis; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; PE = pulmonary embolism; QTc = correct QT interval; QTcF = Fridericia Correction Formula. Information from Array BioPharma Inc (2018a, 2018b).

[a]When administered with binimetinib, dose modifications of encorafenib are not recommended for the following ARs: new primary cutaneous malignancies, ocular events (except uveitis, iritis, and iridocyclitis), interstitial lung disease/pneumonitis, CPK level elevation, rhabdomyolysis, and venous thromboembolism.

[b]When administered with encorafenib, dose modifications of binimetinib are not recommended for the following ARs: palmar-plantar erythrodysesthesia syndrome, noncutaneous *RAS*-mutant malignancies, and QTc prolongation.

take naps. She felt that her energy improved post nap. Her laboratory study results were unremarkable. She was prescribed oral prochlorperazine (Compazine) 10 mg to be taken as needed and was encouraged to consume small, frequent meals and snacks and to hydrate. Supportive measures for fatigue were reviewed, such as napping when needed and light physical activity as tolerated. While Ruth reported that side effects were tolerable, she was grateful for the recommended management strategies. She was asked to return in 2 weeks for another assessment.

During the 2 weeks, Ruth's nausea worsened (grade 2). She was eating less, but her weight remained stable. Her mucous membranes were dry, and her blood pressure was slightly decreased.

The fatigue worsened, and naps were no longer restorative. She was unable to participate in her typical daily activities, such as walking her dog, due to feeling tired (grade 2). At this time point, encorafenib and binimetinib were withheld, and she was given intravenous fluids, instructed to monitor her blood pressure at home daily, and given parameters for withholding her antihypertensive medication. Ruth was reevaluated in 2 days by phone. Her symptoms were beginning to improve. She was seen in the clinic after 1 week, and symptoms were close to those seen at baseline. Her blood pressure was within normal limits due to antihypertensive therapy. She was reporting some improvement in baseline pain and dyspnea. Given the overlap in side effects of both drugs, the encorafenib dose was reduced to 300 mg once daily, and the binimetinib dose was reduced to 30 mg twice daily.

Throughout the remaining duration of Ruth's treatment with encorafenib plus binimetinib, her health-care providers continued to monitor her ARs. In addition to fatigue and nausea continuing intermittently throughout treatment, Ruth experienced occasional muscle pain that never exceeded grade 1. Ongoing communication with her health-care providers and supportive measures were successful in managing her ARs, enabling Ruth to remain on treatment. At Ruth's 16-month appointment, she described difficulty catching her breath on several occasions during the previous week. Imaging revealed that her worsening respiratory symptoms coincided with tumor growth, and Ruth was instructed to discontinue encorafenib and binimetinib.

DISCUSSION

Targeted therapy with BRAF and MEK inhibitors has established efficacy and safety profiles in patients with *BRAF* V600E–mutant mNSCLC (Planchard et al., 2022; Riely et al., 2023). Ruth's fictional case illustrates an example of the efficacy, safety, and tolerability of encorafenib plus binimetinib in patients with *BRAF* V600E–mutant mNSCLC. In the PHAROS study, encorafenib plus binimetinib demonstrated durable (≥ 12 months) antitumor activity in treatment-naive and previously treated patients (Riely et al., 2023). The safety profile of encorafenib plus binimetinib was generally tolerable, with most ARs being grade ≤ 2 (Array BioPharma Inc, 2018a, 2018b). The combination of encorafenib and binimetinib received FDA approval in October 2023 and is listed in guidelines as a preferred first-line therapy and subsequent option, offering patients with *BRAF* V600E–mutant metastatic NSCLC a new treatment option (NCCN, 2023; US Food and Drug Administration, 2023b). As encorafenib plus binimetinib therapy enters the clinical setting, APPs have an essential role in ensuring that patients receive optimal care. Rapport and clear communication between the APP and patient are essential to effectively identify and manage ARs. The ultimate goal is to continue therapy when patients have responded to treatment and ensure acceptable quality of life.

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Ms. Goodwin reports no conflicts of interest. Ms. Orbaugh participates in a speakers bureau for Lilly, Gilead, AstraZeneca, Daiichi Sankyo Inc, CTI BioPharma, Regeneron, Bristol Myers Squibb, Pfizer, and MorphoSys. Dr. Duncan is an employee of Pfizer. Ms. Stumpf reports no conflicts of interest.

References

Abdayem, P. A., & Planchard, D. (2022). Ongoing process in *BRAF*-mutated non-small cell lung cancer. *Clinical Advances in Hematology & Oncology, 20*(11), 662–672.

Array BioPharma Inc. (2018a). Braftovi (encorafenib) package insert. https://www.accessdata.fda.gov/spl/data/c2eedf4c-59b6-43ed-9820-a5621fa3e18f/c2eedf4c-59b6-43ed-9820-a5621fa3e18f.xml

Array BioPharma Inc. (2018b). Mektovi (binimetinib) package insert. https://www.accessdata.fda.gov/spl/data/4e0f2551-01a9-46c6-8019-bd5535c09ee6/4e0f2551-01a9-46c6-8019-bd5535c09ee6.xml

AstraZeneca Pharmaceuticals LP. (2003). Crestor (rosuvastatin) package insert. https://www.accessdata.fda.gov/spl/data/18053149-18b6-427b-b740-5541f6ed2000/18053149-18b6-427b-b740-5541f6ed2000.xml

Augustyn, K., Joseph, J., Patel, A. B., Razmandi, A., Ali, A. N., & Tawbi, H. A. (2023). Treatment expereince with encorafenib plus binimetinib for BRAF V600-mutant metastatic melanoma: Management insights for clinical practice. *Melanoma Research, 33*(5), 406–416. https://doi.org/10.1097/CMR.0000000000000891

Baik, C., Cheng, M. L., Dietrich, M., Gray, J. E., & Karim, N. A. (2024). A practical review of encorafenib and binimetinib therapy management in patients with BRAF V600E-mutant metastatic non-small cell lung cancer. *Advances in Therapy, 41*(7), 2586–2605. https://doi.org/10.1007/s12325-024-02839-4

Baik, C. S., Myall, N. J., & Wakelee, H. A. (2017). Targeting *BRAF*-mutant non-small cell lung cancer: from molecular profiling to rationally designed therapy. *The Oncologist, 22*(7), 786–796. https://doi.org/10.1634/theoncologist.2016-0458

Barlesi, F., Mazieres, J., Merlio, J., Debieurve, D., Mosser, J., Lena, H., & Ouaik, L. (2016). Routine molecular profiling of cancer: results of a one-year nationwide program at the French Cooperative Thoracic Intergroup (IFCT) for advanced non-small cell lung cancer (NSCLC) patients. *The Lancet, 387*(10026), 1415–1426. https://doi.org/10.1016/S0140-6736(16)00004-0

Bhandari, N. R., Hess, L. M., He, D., & Peterson, P. (2023). Biomarker testing, treatment, and outcomes in patients with advanced/metastatic non-small cell lung cancer using a real-world database. *Journal of the National Comprehensive Cancer Network, 21*(9), 934–944 e931. https://doi.org/10.6004/jnccn.2023.7039

Cardarella, S., Ogino, A., Nishino, M., Butaney, M., Shen, J., Lydon, C.,...Janne, P. A. (2013). Clinical, pathologic, and biologic features associated with *BRAF* mutations in non-small cell lung cancer. *Clinical Cancer Research, 19*(16), 4532–4540. https://doi.org/10.1158/1078-0432.CCR-13-0657

Dagogo-Jack, I., Martinez, P., Yeap, B. Y., Ambrogio, C., Ferris, L. A., Lydon, C.,...Awad, M. M. (2019). Impact of *BRAF* mutation class on disease characteristics and clinical outcomes in *BRAF*-mutant lung cancer. *Clinical Cancer Research, 25*(1), 158–165. https://doi.org/10.1158/1078-0432.CCR-18-2062

Dudnik, E., Peled, N., Nechushtan, H., Wollner, M., Onn, A., Agbarya, A.,...Israel Lung Cancer Group. (2018). *BRAF* mutant lung cancer: programmed death ligand 1 expression, tumor mutational burden, microsatellite instability status, and response to immune check-point inhibitors. *Journal of Thoracic Oncology, 13*(8), 1128–1137. https://doi.org/10.1016/j.jtho.2018.04.024

Dummer, R., Ascierto, P. A., Gogas, H. J., Arance, A., Mandala, M., Liszkay, G.,...Flaherty, K. T. (2018). Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with *BRAF*-mutant melanoma (COLUMBUS): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncology, 19*(5), 603–615. https://doi.org/10.1016/S1470-2045(18)30142-6

Gogas, H. J., Flaherty, K. T., Dummer, R., Ascierto, P. A., Arance, A., Mandala, M.,...Robert, C. (2019). Adverse events associated with encorafenib plus binimetinib in the COLUMBUS study: Incidence, course and management. *European Journal of Cancer, 119*, 97–106. https://doi.org/10.1016/j.ejca.2019.07.016

Guisier, F., Dubos-Arvis, C., Vinas, F., Doubre, H., Ricordel, C., Ropert, S.,...Bylicki, O. (2020). Efficacy and safety of anti-PD-1 immunotherapy in patients with advanced NSCLC with *BRAF*, *HER2*, or *MET* mutations or *RET* translocation: GFPC 01-2018. *Journal of Thoracic Oncology, 15*(4), 628–636. https://doi.org/10.1016/j.jtho.2019.12.129

Hendriks, L. E., Kerr, K. M., Menis, J., Mok, T. S., Nestle, U., Passaro, A.,...Reck, M. (2023). Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology, 34*(4), 339–357. https://doi.org/10.1016/j.annonc.2022.12.009

Hoffman, P., Roden, A. C., Chung, J. H., & Planchard, D. (2023). IASLC atlas of molecular testing for targeted therapy in lung cancer.

Hsu, K. H., Tseng, J. S., Yang, T. Y., Chen, K. C., Su, K. Y., Yu, S. L.,...Chang, G. C. (2022). PD-L1 strong expressions affect the clinical outcomes of osimertinib in treatment naive advanced *EGFR*-mutant non-small cell lung cancer patients. *Science Reports, 12*(1), 9753. https://doi.org/10.1038/s41598-022-13102-7

Janssen Pharmaceuticals, Inc. (2024). Sporanox (itraconazole) package insert. https://www.accessdata.fda.gov/spl/data/115d4f3d-303d-e42c-e063-6294a90a7d9e/115d4f3d-303d-e42c-e063-6294a90a7d9e.xml

Koelblinger, P., Thuerigen, O., & Dummer, R. (2018). Development of encorafenib for *BRAF*-mutated advanced melanoma. *Current Opinion in Oncology, 30*(2), 125–133. https://doi.org/10.1097/CCO.0000000000000426

Marchetti, A., Felicioni, L., Malatesta, S., Grazia Sciarrotta, M., Guetti, L., Chella, A.,...Buttitta, F. (2011). Clinical features and outcome of patients with non-small-cell lung cancer harboring *BRAF* mutations. *Journal of Clinical Oncology, 29*(26), 3574–3579. https://doi.org/10.1200/JCO.2011.35.9638

Mazieres, J., Cropet, C., Montane, L., Barlesi, F., Souquet, P. J., Quantin, X.,...Blay, J. Y. (2020). Vemurafenib in non-small-cell lung cancer patients with *BRAF*(V600) and *BRAF*(nonV600) mutations. *Annals of Oncology, 31*(2), 289–294. https://doi.org/10.1016/j.annonc.2019.10.022

Mazieres, J., Drilon, A., Lusque, A., Mhanna, L., Cortot, A. B., Mezquita, L.,...Gautschi, O. (2019). Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: Results from the IMMUNOTARGET registry. *Annals of Oncology, 30*(8), 1321–1328. https://doi.org/10.1093/annonc/mdz167

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Negrao, M. V., Skoulidis, F., Montesion, M., Schulze, K., Bara, I., Shen, V.,...Heymach, J. V. (2021). Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. *Journal for Immunotherapy Cancer, 9*(8), e002891. https://doi.org/10.1136/jitc-2021-002891

Novartis Pharmaceuticals Corporation. (2013a). Mekinist (trametinib) package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204114s025lbl.pdf

Novartis Pharmaceuticals Corporation. (2013b). Tafinlar (dabrafenib) package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202806s025lbl.pdf

Ottaviano, M., Giunta, E. F., Tortora, M., Curvietto, M., Attade-

mo, L., Bosso, D.,...Simeone, E. (2021). *BRAF* gene and melanoma: back to the future. *International Journal of Molecular Sciences, 22*(7), 3474. https://doi.org/10.3390/ijms22073474

Owsley, J., Stein, M. K., Porter, J., In, G. K., Salem, M., O'Day, S.,...VanderWalde, A. (2021). Prevalence of class I-III *BRAF* mutations among 114,662 cancer patients in a large genomic database. *Experimental Biology and Medicine, 246*(1), 31–39. https://doi.org/10.1177/1535370220959657

Pai-Scherf, L., Blumenthal, G. M., Li, H., Subramaniam, S., Mishra-Kalyani, P. S., He, K.,...Pazdur, R. (2017). FDA approval summary: Pembrolizumab for treatment of metastatic non-small cell lung cancer: first-line therapy and beyond. *The Oncologist, 22*(11), 1392–1399. https://doi.org/10.1634/theoncologist.2017-0078

Planchard, D., Besse, B., Groen, H. J. M., Hashemi, S. M. S., Mazieres, J., Kim, T. M.,...Johnson, B. E. (2022). Phase 2 study of dabrafenib plus trametinib in patients with *BRAF* V600E-mutant metastatic NSCLC: Updated 5-Year survival rates and genomic analysis. *Journal of Thoracic Oncology, 17*(1), 103–115. https://doi.org/10.1016/j.jtho.2021.08.011

Planchard, D., Besse, B., Groen, H. J. M., Souquet, P. J., Quoix, E., Baik, C. S.,...Johnson, B. E. (2016b). Dabrafenib plus trametinib in patients with previously treated *BRAF*(V600E)-mutant metastatic non-small cell lung cancer: An open-label, multicentre phase 2 trial. *The Lancet Oncology, 17*(7), 984–993. https://doi.org/10.1016/S1470-2045(16)30146-2

Planchard, D., Kim, T. M., Mazieres, J., Quoix, E., Riely, G., Barlesi, F.,...Johnson, B. E. (2016a). Dabrafenib in patients with *BRAF*(V600E)-positive advanced non-small-cell lung cancer: A single-arm, multicentre, open-label, phase 2 trial. *The Lancet Oncology, 17*(5), 642–650. https://doi.org/10.1016/S1470-2045(16)00077-2

Planchard, D., Smit, E. F., Groen, H. J. M., Mazieres, J., Besse, B., Helland, A.,...Johnson, B. E. (2017). Dabrafenib plus trametinib in patients with previously untreated *BRAF*(V600E)-mutant metastatic non-small-cell lung cancer: An open-label, phase 2 trial. *The Lancet Oncology, 18*(10), 1307–1316. https://doi.org/10.1016/S1470-2045(17)30679-4

RedHill Biopharma Ltd. (2024). Aemcolo (rifamycin) package insert. https://www.accessdata.fda.gov/spl/data/9377a845-abf1-4c32-84e6-51ee3473c9d2/9377a845-abf1-4c32-84e6-51ee3473c9d2.xml

Riely, G. J., Smit, E. F., Ahn, M. J., Felip, E., Ramalingam, S. S., Tsao, A.,...Johnson, B. E. (2023). Phase II, open-label study of encorafenib plus binimetinib in patients with *BRAF*(V600)-mutant metastatic non-small-cell lung cancer. *Journal of Clinical Oncology, 41*(21), 3700–3711. https://doi.org/10.1200/JCO.23.00774

Sheikine, Y., Pavlick, D., Klempner, S. J., Trabucco, S. E., Chung, J. H., Rosenzweig, M.,...Peled, N. (2018). *BRAF* in lung cancers: Analysis of patient cases reveals recurrent *BRAF* mutations, fusions, kinase duplications, and concurrent alterations. *JCO Precision Oncology, 2*, PO.17.00172. https://doi.org/10.1200/PO.17.00172

Smiech, M., Leszczynski, P., Kono, H., Wardell, C., & Taniguchi, H. (2020). Emerging *BRAF* mutations in cancer progression and their possible effects on transcriptional networks. *Genes (Basel), 11*(11), 1342. https://doi.org/10.3390/genes11111342

Subbiah, V., Baik, C., & Kirkwood, J. M. (2020). Clinical development of BRAF plus MEK inhibitor combinations. *Trends in Cancer, 6*(9), 797–810. https://doi.org/10.1016/j.trecan.2020.05.009

Tran, B., & Cohen, M. S. (2020). The discovery and development of binimetinib for the treatment of melanoma. *Expert Opinion on Drug Discovery, 15*(7), 745–754. https://doi.org/10.1080/17460441.2020.1746265

US Food and Drug Administration. (2023a). Drug development and drug interactions | table of substrates, inhibitors, and inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-2

US Food and Drug Administration. (2023b). FDA approves encorafenib with binimetinib for metastatic non-small cell lung cancer with a BRAF V600E mutation. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-binimetinib-metastatic-non-small-cell-lung-cancer-braf-v600e-mutation

Waterhouse, D. M., Tseng, W. Y., Espirito, J. L., & Robert, N. J. (2021). Understanding contemporary molecular biomarker testing rates and trends for metastatic NSCLC among community oncologists. *Clinical Lung Cancer, 22*(6), e901–e910. https://doi.org/10.1016/j.cllc.2021.05.006

Yaeger, R., & Corcoran, R. B. (2019). Targeting alterations in the RAF-MEK pathway. *Cancer Discovery, 9*(3), 329–341. https://doi.org/10.1158/2159-8290.CD-18-1321