Phase II, open-label study of encorafenib plus binimetinib in patients with BRAFV600-mutant metastatic non-small-cell lung cancer

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ABSTRACT

PURPOSE The combination of encorafenib (BRAF inhibitor) plus binimetinib (MEK inhibitor) has demonstrated clinical efficacy with an acceptable safety profile in patients with *BRAF*$^{V600E/K}$-mutant metastatic melanoma. We evaluated the efficacy and safety of encorafenib plus binimetinib in patients with *BRAF*^{V600E}-mutant metastatic non–small-cell lung cancer (NSCLC).

METHODS In this ongoing, open-label, single-arm, phase II study (ClinicalTrials.gov identifier: NCT03915951), patients with *BRAF*^{V600E}-mutant metastatic NSCLC received oral encorafenib 450 mg once daily plus binimetinib 45 mg twice daily in 28-day cycles. The primary end point was confirmed objective response rate (ORR) by independent radiology review (IRR). Secondary end points included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival, time to response, and safety.

RESULTS At data cutoff, 98 patients (59 treatment-naïve and 39 previously treated) with *BRAF*^{V600E}-mutant metastatic NSCLC received encorafenib plus binimetinib. Median duration of treatment was 9.2 months with encorafenib and 8.4 months with binimetinib. ORR by IRR was 75% (95% CI, 62 to 85) in treatment-naïve and 46% (95% CI, 30 to 63) in previously treated patients; median DOR was not estimable (NE; 95% CI, 23.1 to NE) and 16.7 months (95% CI, 7.4 to NE), respectively. DCR after 24 weeks was 64% in treatment-naïve and 41% in previously treated patients. Median PFS was NE (95% CI, 15.7 to NE) in treatment-naïve and 9.3 months (95% CI, 6.2 to NE) in previously treated patients. The most frequent treatment-related adverse events (TRAEs) were nausea (50%), diarrhea (43%), and fatigue (32%). TRAEs led to dose reductions in 24 (24%) and permanent discontinuation of encorafenib plus binimetinib in 15 (15%) patients. One grade 5 TRAE of intracranial hemorrhage was reported. Interactive visualization of the data presented in this article is available at the PHAROS dashboard (https://clinical-trials.dimensions.ai/pharos/).

CONCLUSION For patients with treatment-naïve and previously treated *BRAF*^{V600E}-mutant metastatic NSCLC, encorafenib plus binimetinib showed a meaningful clinical benefit with a safety profile consistent with that observed in the approved indication in melanoma.

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INTRODUCTION

Targeting oncogenic drivers with small-molecule inhibitors is an effective treatment strategy for some patients with non–small-cell lung cancer (NSCLC).[1] BRAF (v-Raf murine sarcoma viral oncogene homolog B) is a serine/threonine kinase that is involved in the MAP/ERK signaling pathway.[2] Somatic activating mutations in *BRAF* occur in approximately 3%-5% of patients with NSCLC.[2,3] The majority of *BRAF* mutations occur on codon 600 (*BRAF*^{V600}), with most leading to a *BRAF*^{V600E} mutation, accounting for 50% of all *BRAF* mutations in lung cancer.[4,5] *BRAF*^{V600} mutations are class I *RAS*-independent mutations that confer sensitivity to BRAF

CONTEXT

Key Objective

This primary analysis of the phase II PHAROS study evaluated the activity and safety of encorafenib plus binimetinib in treatment-naïve and previously treated patients with *BRAF*^{V600}-mutant metastatic non–small-cell lung cancer (NSCLC).

Knowledge Generated

The primary end point of objective response rate (ORR) by independent radiology review was met, with an ORR of 75% in treatment-naïve and 46% in previously treated patients with *BRAF*^{V600E}-mutant metastatic NSCLC. Encorafenib plus binimetinib showed a meaningful clinical benefit with a safety profile consistent with that observed in the approved indication in melanoma.

Relevance *(T.E. Stinchcombe)*

Encorafenib and binimetinib is a new treatment option for patients with *BRAF*^{V600E}-mutant metastatic NSCLC.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

inhibition.[6] *BRAF* mutations also occur in patients with other solid tumors, including melanoma, colorectal cancer, papillary thyroid cancer, diffuse gliomas, and cholangiocarcinoma.[7-9]

Encorafenib is an oral, selective, reversible small-molecule RAF kinase inhibitor, with a long dissociation half-life of >30 hours.[10,11] Binimetinib is an oral, ATP-uncompetitive, reversible inhibitor of MEK1 and MEK2 activation.[11,12] In patients with *BRAF*$^{V600E/K}$-mutant metastatic melanoma, encorafenib in combination with binimetinib demonstrated clinical benefit with an acceptable safety profile.[13,14] Median progression-free survival (PFS) was 14.9 months in patients treated with encorafenib plus binimetinib compared with 7.3 months with single-agent vemurafenib, another BRAF inhibitor.[13] In a trial of dabrafenib and trametinib in patients with advanced melanoma, the median PFS was 9.3 months with dabrafenib plus trametinib and 8.8 months with single-agent dabrafenib.[15] In another phase III trial, coBRIM, the median PFS was 9.9 months with vemurafenib plus cobimetinib and 6.2 months with vemurafenib.[16] Objective response rate (ORR), PFS, and overall survival (OS) observed with encorafenib plus binimetinib in the COLUMBUS trial were comparable with those seen with other BRAF plus MEK inhibitors in patients with *BRAF*^{V600}-mutant metastatic melanoma.[13,15-19]

Dabrafenib plus trametinib is a standard treatment in patients with *BRAF*^{V600E}-mutant metastatic NSCLC that has been approved by regulatory agencies.[1,20] These approvals were based on the results of a single-arm phase II study, in which treatment with dabrafenib plus trametinib led to meaningful antitumor activity and a manageable safety profile in this patient population.[21,22] ORR by independent review committee was 64% in treatment-naïve patients and 63% in previously treated patients; median PFS was 14.6 and 8.6 months, respectively. Given the observed efficacy and safety profile of encorafenib plus binimetinib in patients with *BRAF*^{V600}-mutant metastatic melanoma, this combination therapy was assessed in this phase II trial in patients with *BRAF*^{V600E}-mutant metastatic NSCLC.

METHODS

Study Design and End Points

PHAROS (ClinicalTrials.gov identifier: NCT03915951) is an ongoing, single-arm, open-label, multicenter phase II trial evaluating the efficacy and safety of encorafenib plus binimetinib in treatment-naïve and previously treated patients with *BRAF*^{V600}-mutant metastatic NSCLC. Patients were treated with encorafenib 450 mg once daily plus binimetinib 45 mg twice daily, administered orally in 28-day cycles. Treatment was administered until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, or death. Patients permanently discontinuing treatment with binimetinib were allowed to continue treatment with encorafenib; however, those permanently discontinuing treatment with encorafenib were required to discontinue treatment with binimetinib. Patients who discontinued treatment for reasons other than progressive disease were followed for disease status after the end of treatment.

The study was performed in accordance with the requirements of the applicable local regulatory authorities and International Conference on Harmonisation Good Clinical Practice Guidelines. An institutional review board or independent ethics committee approved the Protocol (online only) and all amendments. All patients provided written informed consent.

Details of the study end points were published previously.[11] The primary end point was confirmed ORR, assessed

according to RECIST version 1.1 (RECIST 1.1) by independent radiology review (IRR). Secondary efficacy end points included confirmed ORR by investigator assessment; duration of response (DOR), disease control rate (DCR), PFS, and time to response by IRR and investigator assessment; and OS and safety. Exploratory end points included pharmacokinetic and biomarker assessments. Efficacy end points were assessed separately in treatment-naïve and previously treated patients. Safety end points, including treatment-related adverse events (TRAEs) and serious adverse events (AEs), were assessed in the overall patient population.

Patients

Adult patients (age 18 years and older) with histologically confirmed stage IV or recurrent NSCLC, measurable disease on the basis of RECIST 1.1, and an Eastern Cooperation Oncology Group performance status (ECOG PS) of 0 or 1 were included in the study. Patients were enrolled into two study groups: treatment-naïve and previously treated. Patients with prior first-line platinum-based chemotherapy or platinum-based chemotherapy plus anti–PD-1/PD-L1 inhibitor treatment were enrolled in the previously treated group. Patients who received more than one prior line of treatment in the advanced setting were excluded. Tumor samples were required to have *BRAF*^{V600} class I mutations by next-generation sequencing (NGS)– or polymerase chain reaction (PCR)–based local testing before enrollment. *BRAF*^{V600} mutations were retrospectively confirmed by FoundationOne CDx (Foundation Medicine, Cambridge, MA).[23] Patients who had prior treatment with a BRAF or MEK inhibitor, other driver alterations (eg, *EGFR* mutation, *ALK* rearrangement, or *ROS1* rearrangement), untreated symptomatic brain metastasis, or leptomeningeal disease were excluded. Patients with untreated small brain metastases (<5 mm) and previously treated brain metastases were eligible if they were asymptomatic and had stable intracranial disease for ≥28 days before the first dose of study treatment.

Assessments

Tumors were assessed according to RECIST 1.1 at screening, every 8 weeks for 12 months, and every 12 weeks thereafter until disease progression or end of the study. A magnetic resonance imaging scan of the brain was required for all patients at screening to determine brain metastases at baseline. Subsequent brain imaging was required for patients with brain metastases at baseline. Radiologic disease follow-up was continued in patients who permanently discontinued study treatment for a reason other than disease progression. Radiologic images were reviewed by investigators and by independent radiologists (for end points by IRR). The OS follow-up visits continued every 12 weeks after the last treatment dose until withdrawal of consent, loss to follow-up, death, or end of study.

Both AEs and serious AEs were monitored throughout treatment and during the 30-day post-treatment follow-up. In patients who started new anticancer therapy within 30 days after the end of study treatment, safety follow-up was continued until the start of the new therapy.

Statistical Analyses

ORR was defined as the proportion of patients with a confirmed best overall response of complete response (CR) or partial response (PR). For the primary efficacy end point, the study was designed to test the null hypothesis of ORR ≤ 39% in treatment-naïve patients (n = 60, assuming an alternative target rate of 65% and 1-sided $\alpha \leq .025$), which was considered not sufficiently clinically meaningful to warrant further investigation in this indication where similar therapies are already available, and ≤20% in previously treated patients (n = 37, assuming an alternative target rate of 45% and 1-sided $\alpha \leq .025$) with *BRAF*^{V600E}-mutant metastatic NSCLC; details were published previously.[11,24,25] The two-sided 95% CI for ORR and DCR was calculated using the Clopper-Pearson method. The Kaplan-Meier method was used to estimate DOR, PFS, and OS. Univariable logistic regression using Firth's method was used to test for associations between mutation and response in the overall, treatment-naïve, and previously treated patient population for the most frequently mutated genes (ie, requiring eight or more alterations overall and five or more alterations in subgroups for subgroup-specific tests). Patients who were not evaluable for response were excluded from the analysis, unless there was evidence of early progression or death, in which case they were included as nonresponders. Significance was evaluated at a false discovery rate–corrected *P* value of .05 using the Benjamini-Hochberg method (Data Supplement, online only).

Safety data were summarized descriptively. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. The safety set included all patients who received at least one dose of drugs. The pharmacokinetic parameters of encorafenib and binimetinib were estimated using a population model–based approach (Appendix 1, online only).

RESULTS

Patient Characteristics

Between June 4, 2019, and June 2, 2022, 98 patients from 56 centers in five countries were enrolled in this study and were treated with encorafenib plus binimetinib. Of these, 59 patients were treatment-naïve and 39 were previously treated. In the overall patient population, the median age was 70 years, 88% were White, 53% were women, 30% had never smoked, 73% had an ECOG PS of 1, 97% had adenocarcinoma, and 8% had baseline brain metastases (Table 1). All patients had a *BRAF*^{V600E} mutation; one patient in the previously treated group had both *BRAF*^{V600E} and *BRAF*^{V600D} mutations in their

TABLE 1. Patient Characteristics

Characteristic	Treatment-Naïve (n = 59)	Previously Treated (n = 39)	Overall (N = 98)
Age, years, median (range)	68 (47-83)	71 (53-86)	70 (47-86)
Sex, No. (%)			
Women	33 (56)	19 (49)	52 (53)
Men	26 (44)	20 (51)	46 (47)
Ethnicity, No. (%)			
White	53 (90)	33 (85)	86 (88)
Asian	3 (5)	4 (10)	7 (7)
Black	1 (2)	2 (5)	3 (3)
American Indian	1 (2)	0	1 (1)
Unknown	1 (2)	0	1 (1)
ECOG PS, No. (%)			
0	19 (32)	7 (18)	26 (27)
1	40 (68)	32 (82)	72 (73)
Smoking status, No. (%)			
Current	8 (14)	5 (13)	13 (13)
Former	33 (56)	23 (59)	56 (57)
Never	18 (31)	11 (28)	29 (30)
BRAF V600 status, No. (%)			
V600E	59 (100)	39 (100)	98 (100)
V600D[a]	0	1 (3)	1 (1)
Method of local *BRAF* testing, No. (%)			
PCR	15 (25)	11 (28)	26 (26)
Tissue NGS	44 (75)	27 (69)	71 (72)
Plasma NGS	0	1 (3)	1 (1)
Tumor histology, No. (%)			
Adenocarcinoma	57 (97)	38 (97)	95 (97)
Squamous cell carcinoma	1 (2)	1 (3)	2 (2)
Other	1 (2)	0	1 (1)
Brain metastases, No. (%)			
No	55 (93)	35 (90)	90 (92)
Yes	4 (7)	4 (10)	8 (8)
Prior systemic treatment for metastatic disease, No. (%)	0	39 (100)	39 (40)
Immunotherapy	NA	24 (62)[b]	24 (24)[b]
Monotherapy PD-(L)1	NA	12 (31)	12 (12)
Combination PD-(L)1[c]	NA	12 (31)	12 (12)
Chemotherapy	NA	18 (46)	18 (18)
Prior radiotherapy, No. (%)			
No	50 (85)	22 (56)	72 (73)
Yes	9 (15)	17 (44)	26 (27)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; NGS, next-generation sequencing; PCR, polymerase chain reaction.

[a]Comutation with V600E.

[b]Three patients were also included in the immunotherapy group as they had first-line chemotherapy followed by immunotherapy.

[c]With chemotherapy or other immunotherapy.

tumor tissue. In the overall patient population, the median duration of treatment was 9.2 months (range, 0-35.1) with encorafenib and 8.4 months (range, 0-35.1) with binimetinib. In treatment-naïve patients, the median duration of treatment was 15.1 months (range, 0-35.1) with encorafenib and 14.4 months (range, 0-35.1) with binimetinib. In previously treated patients, the median duration of treatment was 5.4 months (range, 0.1-31.2) for both encorafenib and binimetinib. At the data cutoff of September 22, 2022, treatment was ongoing in 25 (42%) treatment-naïve patients and in eight (21%) previously treated patients (Appendix Fig A1, online only).

Antitumor Activity

The ORR by IRR was 75% (95% CI, 62 to 85) in treatment-naïve patients, with nine CRs and 35 PRs. In previously treated patients, the ORR was 46% (95% CI, 30 to 63), with four CRs and 14 PRs (Table 2). The primary end point was met in both treatment-naïve and previously treated groups. The median time to response by IRR was 1.9 months (range, 1.1-19.1) in treatment-naïve patients and 1.7 months (range, 1.2-7.3) in previously treated patients, corresponding to the time of the first tumor assessment. At the time of this analysis, the median DOR by IRR was not estimable (NE; 95% CI, 23.1 to NE) in treatment-naïve patients and 16.7 months (95% CI, 7.4 to NE) in previously treated patients. Durable responses lasting ≥12 months were observed in 59% of treatment-naïve and 33% of previously treated patients. After 24 weeks, the DCR was 64% (95% CI, 51 to 76) in treatment-naïve patients and 41% (95% CI, 26 to 58) in previously treated patients. In the treatment-naïve and previously treated groups, 18 and 21 patients, respectively, discontinued treatment within 6 months—mostly because of disease progression (Appendix Fig A2, online only).

The ORRs by IRR were generally comparable across subgroups, including age, sex, and ECOG PS (Appendix Table A1, online only). The ORRs in current (n = 8), former (n = 33), and never (n = 18) smokers, respectively, were 50%, 76%, and 83% in treatment-naïve patients. In previously treated patients, the ORRs in current (n = 5), former (n = 23), and never (n = 11) smokers were 20%, 52%, and 46%, respectively. In patients with baseline brain metastases noted by the investigator, all four treatment-naïve patients had a systemic CR or PR, but none of the four previously treated patients had a systemic objective response by IRR. One patient from each group experienced intracranial progression by IRR. In previously treated patients, those who received prior immunotherapy (n = 24) had an ORR of 58%, and those who did not receive prior immunotherapy (n = 15) had an ORR of 27%. In these patients, ORRs on prior therapies were 24% in patients on immunotherapy in first line (n = 21) and 22% in those who received chemotherapy alone in first line (n = 18).

Investigator-assessed ORR in treatment-naïve patients was 63% (95% CI, 49 to 75), with two CRs and 35 PRs. In previously treated patients, the investigator-assessed ORR was

TABLE 2. Efficacy End Points by IRR and Investigator Assessment

End Point	Treatment-Naïve (n = 59)	Previously Treated (n = 39)
Best overall response by IRR, No. (%)		
CR	9 (15)	4 (10)
PR	35 (59)	14 (36)
Stable disease	10 (17)	13 (33)
Progressive disease	2 (3)	3 (8)
Not evaluable	3 (5)	5 (13)
ORR % (95% CI)	75 (62 to 85)	46 (30 to 63)
DCR % at 24 weeks (95% CI)	64 (51 to 76)	41 (26 to 58)
DOR, months, median (95% CI)	NE (23.1 to NE)	16.7 (7.4 to NE)
DOR ≥ 12 months, No./n (%)	26/44 (59)	6/18 (33)
DOR ≥ 24 months, No./n (%)	7/44 (16)	3/18 (17)
Time to response, months, median (range)	1.9 (1.1-19.1)	1.7 (1.2-7.3)
PFS, months, median (95% CI)	NE (15.7 to NE)	9.3 (6.2 to NE)
Best overall response by investigator assessment, No. (%)		
CR	2 (3)	1 (3)
PR	35 (59)	15 (38)
Stable disease	16 (27)	13 (33)
Progressive disease	4 (7)	6 (15)
Not evaluable	2 (3)	4 (10)
ORR % (95% CI)	63 (49 to 75)	41 (26 to 58)
DOR, months, median (95% CI)	23.1 (17.7 to NE)	NE (11.9 to NE)
DOR ≥ 12 months, No./n (%)	23/37 (62)	7/16 (44)
DOR ≥ 24 months, No./n (%)	6/37 (16)	3/16 (19)
Time to response, months, median (range)	1.8 (1.4-14.0)	1.8 (0.8-9.2)

NOTE. Interactive visualization of the data presented in this article is available at the PHAROS dashboard (https://clinical-trials.dimensions.ai/pharos/).[26]

Abbreviations: CR, complete response; DCR, disease control rate; DOR, duration of response; IRR, independent radiology review; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

41% (95% CI, 26 to 58), with one CR and 15 PRs (Table 2, Fig 1).

The median duration of follow-up for PFS by IRR was 18.2 months (95% CI, 16.4 to 22.3) in treatment-naïve patients and 12.8 months (95% CI, 9.0 to 19.8) in previously treated patients. The median PFS by IRR was NE (95% CI, 15.7 to NE) in the treatment-naïve group and 9.3 months (95% CI, 6.2 to NE) in the previously treated group (Fig 2). At the time of data cutoff, 17 deaths (29%) had occurred in the treatment-naïve group and 13 deaths (33%) had occurred in the previously treated group; the median OS was NE for both patient groups.

Safety

Overall, all-causality AEs occurred in 97 (99%) of 98 patients (Appendix Table A2, online only). TRAEs of any grade, grade 3, and grade 4 occurred in 92 (94%), 37 (38%), and three (3%) of 98 patients, respectively (Table 3). The most frequently reported TRAEs (≥20%) of any grade were nausea

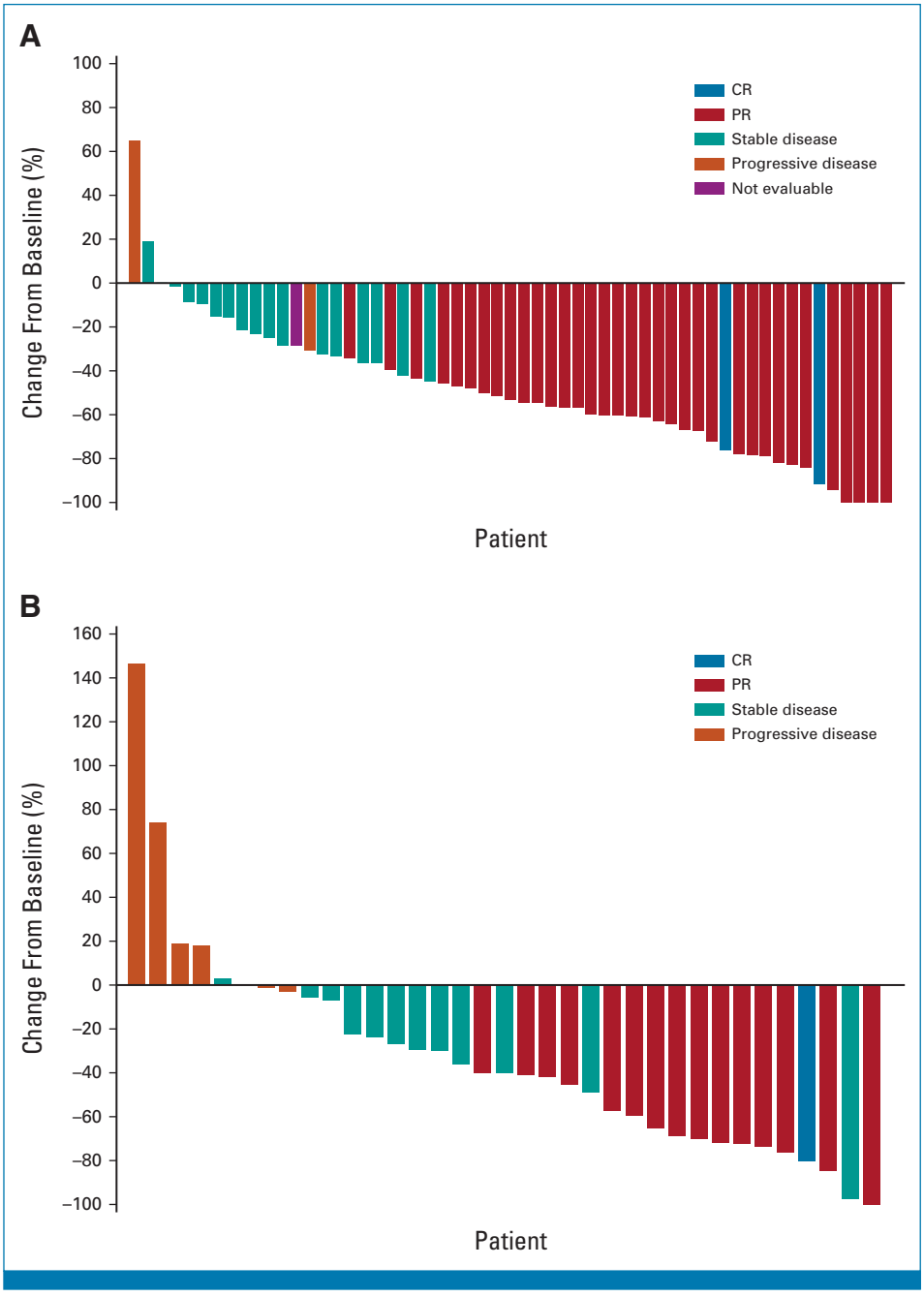

FIG 1. Maximum change from baseline in the sum of diameters of target lesions by investigator assessment in (A) treatment-naïve patients (n = 57) and (B) previously treated patients (n = 35). Patients for whom an assessment response was not evaluable at all tumor assessments were not included in this analysis. CR, complete response; PR, partial response.

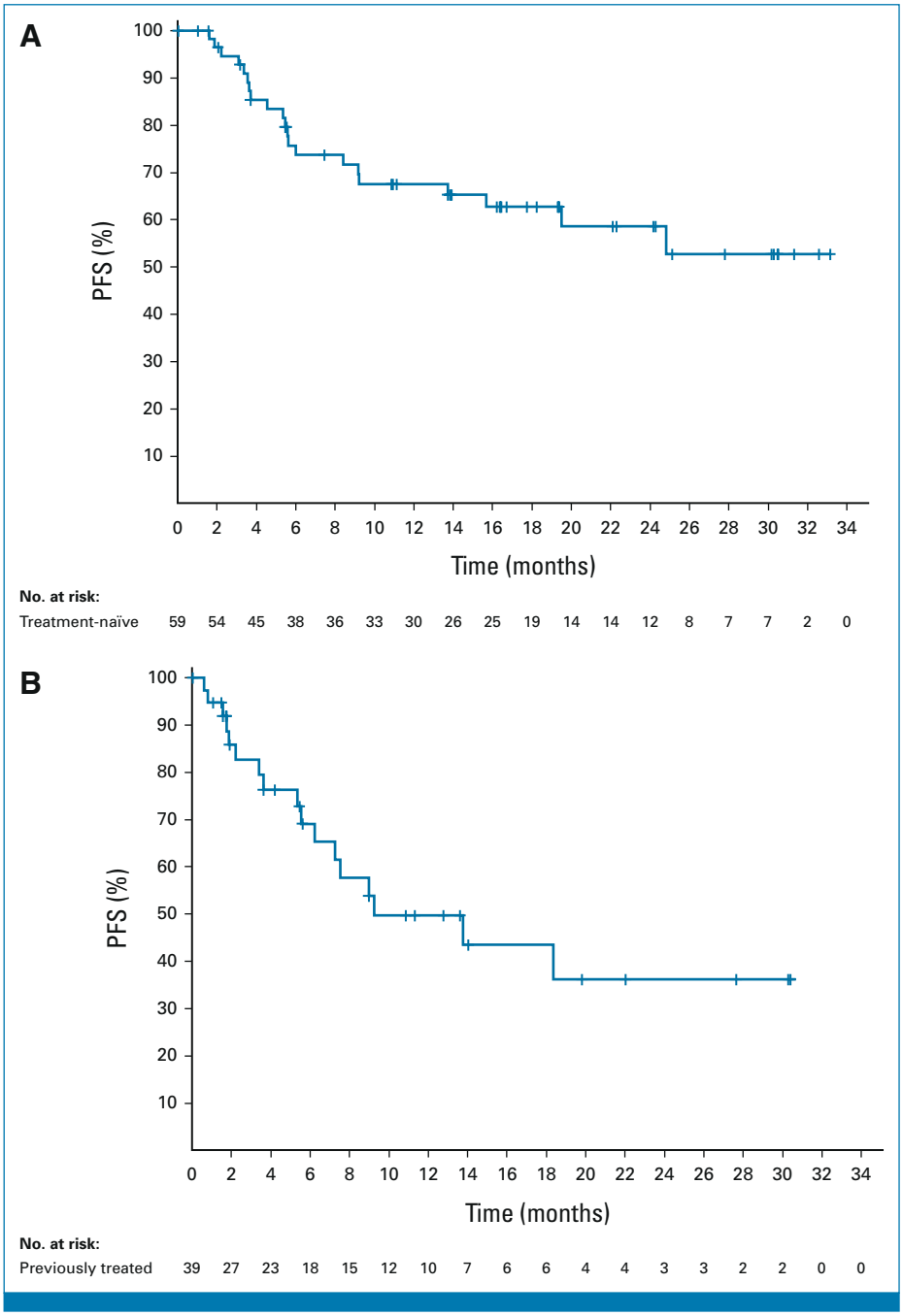

FIG 2. PFS by independent radiology review in (A) treatment-naïve patients and (B) previously treated patients. PFS, progression-free survival.

(50%), diarrhea (43%), fatigue (32%), and vomiting (29%). AEs led to dosing interruption of both encorafenib and binimetinib in 43 of 98 patients (44%)—most commonly (≥10%) because of nausea (12%) and diarrhea (11%; Appendix Table A3, online only). TRAEs led to dose reduction of both encorafenib and binimetinib in 24 of 98 patients (24%) and led to permanent discontinuation in 15 of 98 (15%) patients (Appendix Tables A4 and A5, online only). The most frequent TRAEs that led to permanent discontinuation were diarrhea, nausea, and vomiting (two patients each). Treatment-related serious AEs occurred in 14% of patients, with the most common being colitis (3%). Death occurred in 30 patients (31%); the primary reasons for death were disease progression (24%), AE (2%), or other causes (4%). One patient died due to intracranial hemorrhage, which was assessed as treatment related by the investigator.

Biomarker Analyses

All tissue samples were positive for *BRAF* mutation by local tissue NGS (n = 71), PCR (n = 26), or plasma NGS (n = 1) testing. In the central FoundationOne CDx testing, *BRAF*

TABLE 3. Incidence of TRAEs of Any Grade ≥10% in All Patients

	Overall (N = 98)		
AE Preferred Term	Any Grade	Grade 3	Grade 4
Any TRAEs, No. (%)	92 (94)	37 (38)	3 (3)[a]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Vision blurred	17 (17)	1 (1)	0
Constipation	13 (13)	0	0
ALT increased	12 (12)	5 (5)	0
AST increased	12 (12)	7 (7)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Peripheral edema	11 (11)	0	0
Abdominal pain	10 (10)	0	0
Alopecia	10 (10)	0	0
Asthenia	10 (10)	3 (3)	0
Dry skin	10 (10)	0	0

Abbreviation: TRAE, treatment-related adverse event.
[a]Grade 4 TRAEs were colitis, disseminated intravascular coagulation, increased gamma-glutamyl transferase, and hyponatremia. One patient can have multiple TRAEs.

status was confirmed, and other mutations potentially interacting with treatment were assessed using data from a targeted sequencing panel applied to all available baseline biopsy samples; 80 (82%) samples (48 treatment-naïve and 32 previously treated) were analyzed for genomic alterations. Samples from five patients, which were positive for *BRAF* mutation by local testing, were not found to have a *BRAF* mutation on central testing (Fig 3); subsequent inspection indicated that the apparent discordance was due to stringent criteria for *BRAF* mutation status used by the central testing laboratory. Of these five patients, two had a PR, two had stable disease, and one had progressive disease. The most frequent genomic alterations identified at baseline, in addition to *BRAF*, included *SETD2* and *TP53* (43% each), *SMAD4* (21%), *ATM*, *MLL2*, *CSF1R*, *SMARCA4* (14% each), and *CDKN2A* (11%; Fig 3). None of these alterations were associated with outcome after false discovery correction (corrected $P < .05$) in the overall patient population, treatment-naïve, or previously treated analysis sets (Appendix Fig A3, online only). Some alterations—such as *FLT1* (10%) and *CDKN2A*—showed potential associations with a lower likelihood of response in some comparisons (uncorrected $P < .05$).

Pharmacokinetic Analyses

The geometric mean exposures, calculated as AUC-time curve over the dosing interval at steady state were 12,100 ng·h/mL for encorafenib and 2,210 ng·h/mL for binimetinib (Appendix Table A6, online only). The pharmacokinetic data results from this study are consistent with those observed for other tumor types.

Interactive visualization of the data presented in this article is available at the PHAROS dashboard (https://clinical-trials.dimensions.ai/pharos/).[26]

DISCUSSION

To our knowledge, this phase II trial represents the first clinical trial of encorafenib plus binimetinib in patients with *BRAF*^{V600E}-mutant metastatic NSCLC. The combination of encorafenib plus binimetinib showed substantial antitumor activity in patients with *BRAF*^{V600E}-mutant metastatic NSCLC. The protocol-defined primary end point was met, with an ORR of 75% in treatment-naïve and 46% in previously treated patients. Objective responses were durable with the lower limit of the 95% CI of 23.1 months (median DOR was NE) in treatment-naïve patients, with 25 patients (42%) still on therapy, and a median DOR of 16.7 months in previously treated patients, with eight patients (21%) still on therapy.

Effective targeted therapeutic options are limited in this patient population, making the results from this study clinically important. Currently, to our knowledge, dabrafenib plus trametinib is the only approved targeted therapy available for patients with *BRAF*^{V600}-mutant metastatic NSCLC.[1] In the 5-year update of the phase II study of dabrafenib plus trametinib, investigator-assessed ORRs were similar between treatment-naïve patients (64%) and previously treated patients (68%); median DORs were 10.2 and 9.8 months, respectively.[27] The similarity in response rates for first-line and second-line therapy differs from observations in the current study. Higher response rates in treatment-naïve patients have been previously noted with multiple other targeted therapies.[28,29] The high ORR observed with encorafenib plus binimetinib in the treatment-naïve group suggests that patients with *BRAF*^{V600}-mutant metastatic NSCLC should receive targeted therapies as their initial therapy.

Currently, to our knowledge, no clinical trials have prospectively evaluated the efficacy and safety of immunotherapies in this patient population. Unlike in other oncogene-driven cancers such as *EGFR*-mutant, *ALK*-, *ROS1*-, or *RET*-translocated tumors, immune checkpoint inhibitors may have activity in *BRAF*-mutant metastatic NSCLC.[30] In a retrospective study, the ORR for immune checkpoint inhibitor monotherapy was 24% in previously treated patients with *BRAF*-mutant metastatic NSCLC.[30] However, targeted therapy is the preferred treatment in patients with *BRAF*^{V600E} mutations.[31]

In this study, previously treated patients who had received prior immunotherapy seemed to have numerically better rates of objective response to encorafenib plus binimetinib than those who did not receive prior immune checkpoint

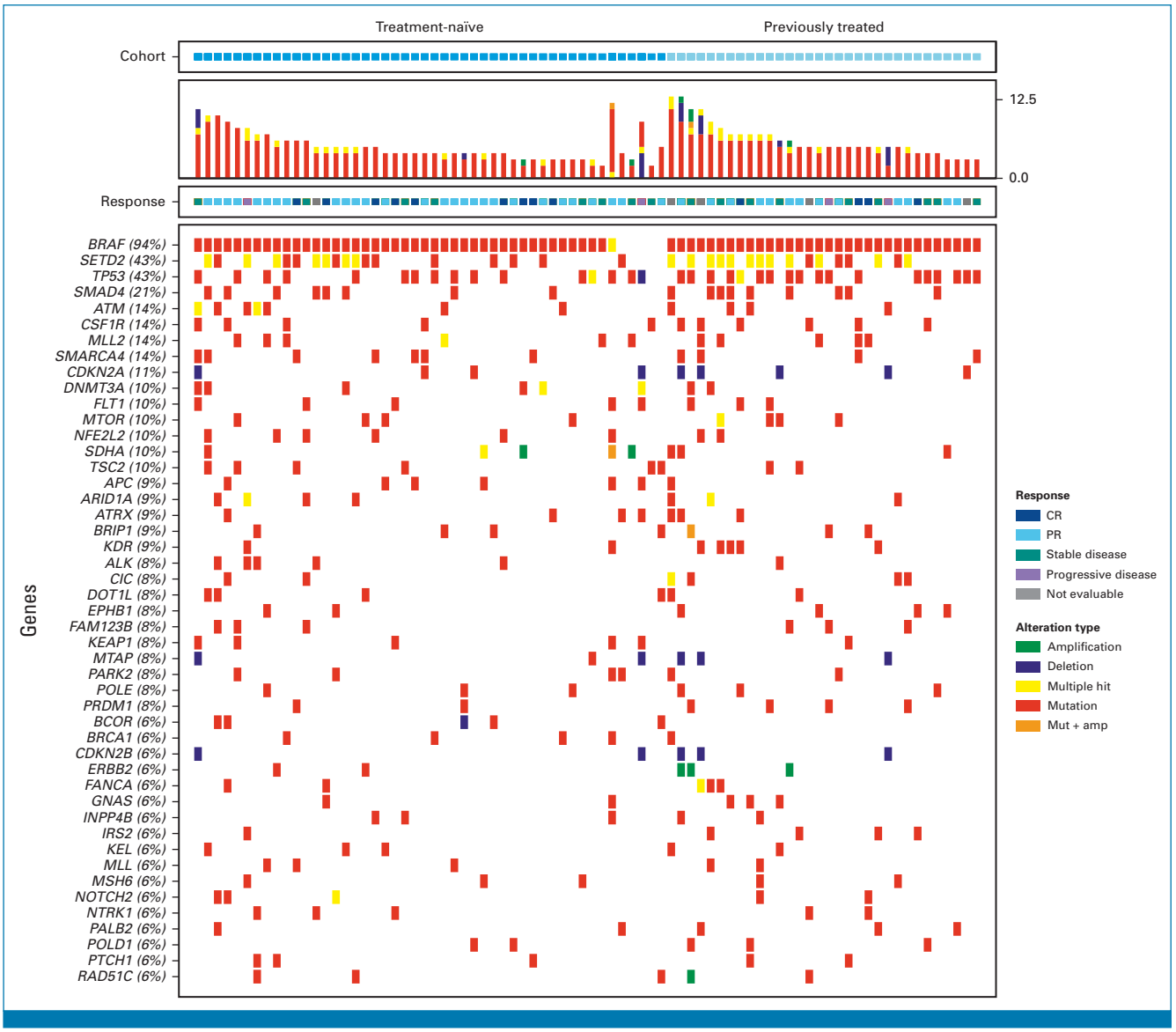

FIG 3. Tumor molecular alterations in baseline biopsy samples from treatment-naïve and previously treated patients. The most frequently altered genes (altered in five or more cases) are shown. The bar plot on top represents the number of alterations among the displayed genes for each patient, colored by the alteration type. Amp, amplification; CR, complete response; Mut, mutation; PR, partial response.

inhibitors. This may have been due to several confounding factors or partially attributed to the immune response. The efficacy of MAP kinase inhibition is partly explained by immunologic mechanisms, including enhanced CD8+ T-cell recruitment, increased expression of major histocompatibility complex class I, reduced activity of regulatory T cells, and decreased expression of PD-L1.[32] It may be possible that inhibition of the MAP kinase pathway by BRAF plus MEK inhibitors may restore the immune response and help enhance clinical outcomes. Although the sample size was small, encorafenib plus binimetinib showed antitumor activity in four of eight patients with baseline brain metastases (all four of the treatment-naïve patients and none of the previously treated patients had an objective response). To our knowledge, this study is the first to show intracranial activity with BRAF plus MEK inhibitors in patients with *BRAF*^{V600E}-mutant metastatic NSCLC. Encorafenib plus binimetinib has also shown intracranial response in patients with baseline brain metastases in *BRAF*-mutant melanoma.[33]

Toxicity is a particularly important factor to consider when presented with different treatment options. Older patients can be more susceptible to AEs and are more likely to discontinue treatment because of AEs[34]; the median age of patients in this study was 70 years. The toxicity and overall tolerability of encorafenib when given as a monotherapy are substantially ameliorated when encorafenib is given in combination with binimetinib.[10,13] Although the available BRAF plus MEK inhibitors have overlapping safety profiles, there are notable differences in frequency of these AEs. Pyrexia (56%), nausea (51%), and vomiting (41%) were the most common AEs reported with dabrafenib plus

trametinib.[27] With encorafenib plus binimetinib, nausea (50%), diarrhea (43%), and fatigue (32%) were the most common TRAEs. Dabrafenib plus trametinib is associated with a higher frequency of pyrexia than observed with encorafenib plus binimetinib in this study. With dabrafenib and trametinib, 64% of treatment-naïve and 46% of previously treated patients experienced all-causality pyrexia.[21,22] Pyrexia, reported in 16% of patients, was also the most common serious AE observed. By contrast, with encorafenib plus binimetinib, all-causality pyrexia occurred in 22% of patients in the current study (Appendix Table A2). Pyrexia (treatment-related) was the cause of dose interruption of encorafenib plus binimetinib in one patient but did not result in dose reduction or permanent treatment discontinuation. With encorafenib plus binimetinib, TRAEs led to dose interruption, dose reduction, and permanent discontinuation of both drugs in 44%, 24%, and 15% of patients, respectively. In the COLUMBUS trial for patients with melanoma, the most common AEs with the combination of encorafenib and binimetinib were nausea (41%), diarrhea (36%), and vomiting (30%); pyrexia occurred in 18% of patients, similar to the 22% frequency of pyrexia observed in patients with NSCLC.[13] Overall, the safety profile of encorafenib plus binimetinib was manageable and consistent with the known safety profile observed in patients with *BRAF*$^{V600E/K}$-mutant metastatic melanoma.[13]

In this study, we used a targeted NGS panel to confirm *BRAF*^{V600E} mutations, identify the most common concurrent alterations, and explore whether pretreatment molecular alterations could identify patients either more or less likely to benefit from encorafenib plus binimetinib. Although patients commonly had concurrent baseline mutations in a number of genes, with those in *SETD2*, *TP53*, and *SMAD4* occurring most frequently, these alterations were not significantly associated with response to treatment.[23] As larger data sets become available, it will be important to assess whether these lower-frequency alterations are associated with patient outcomes.[35]

Although the patient numbers were small and 95% CIs are overlapping, the ORRs appear to be lower for current smokers in this study. Smoking can induce CYP1A2 isoform, which has been shown to lower the exposure to binimetinib and may explain the lower response in this study.[36,37] Patients with smoking history often have more comutations, as observed in a large retrospective study[38]; in the current study, comutations were not associated with patient outcomes. Additional data are needed to assess the impact of smoking on response to encorafenib plus binimetinib and determine the optimal treatment for patients with *BRAF* mutations with smoking history.

In conclusion, results of the PHAROS study show that encorafenib plus binimetinib had antitumor activity and an acceptable safety profile consistent with that seen in the approved indication in melanoma. Encorafenib plus binimetinib represents a potential new treatment option for patients with *BRAF*^{V600E}-mutant metastatic NSCLC.

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Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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Phase II, Open-Label Study of Encorafenib Plus Binimetinib in Patients With *BRAF*^{V600}-Mutant Metastatic Non–Small-Cell Lung Cancer

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Consulting or Advisory Role: Novartis, Daiichi Sankyo, Checkpoint Therapeutics, G1 Therapeutics, Jazz Pharmaceuticals, GlaxoSmithKline, Genentech, AstraZeneca, Hummingbird Diagnostics, BlueDot, Merus NV, Abdera Therapeutics, Simcere

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No other potential conflicts of interest were reported.

APPENDIX 1. PHARMACOKINETIC METHODS

Plasma concentration-time profiles and pharmacokinetic parameter estimates for encorafenib and binimetinib were collected through blood samples, dependent on their protocol version, measured predose (within 30 minutes before dose) on day 15 of cycle 1 and day 1 of cycle 2 and postdose (0.5, 1.5, 3, and 6 hours after dose) on day 1 and day 15 of cycle 1, or on day 1 of the first six cycles with a predose (within 30 minutes before dose) measurement.

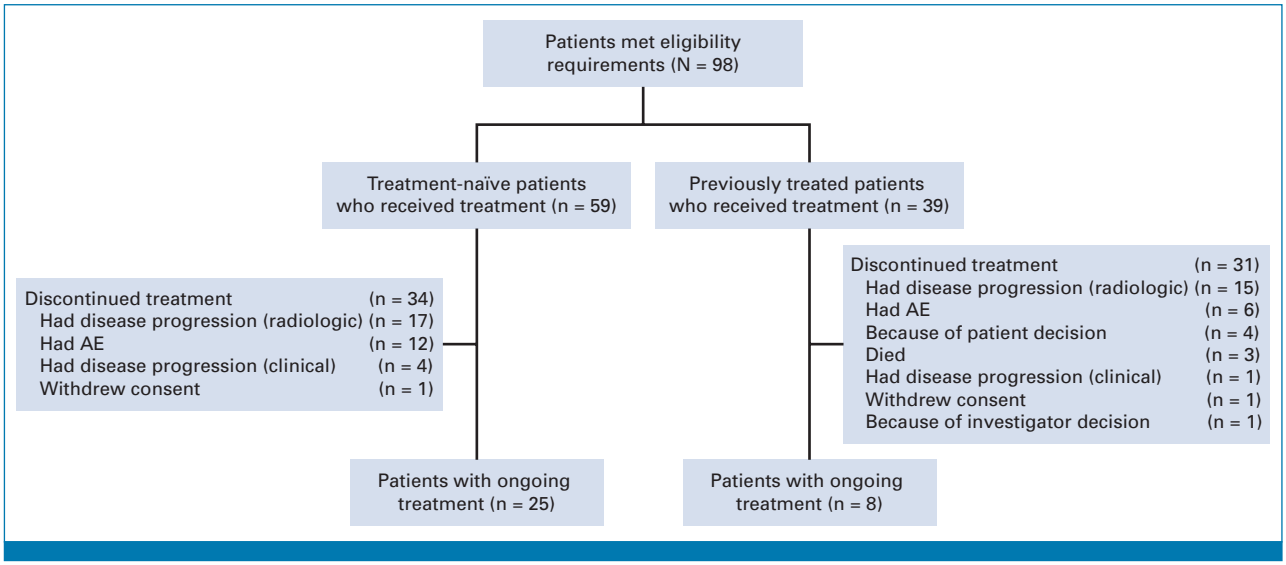

FIG A1. Patient disposition flow chart. AE, adverse event.

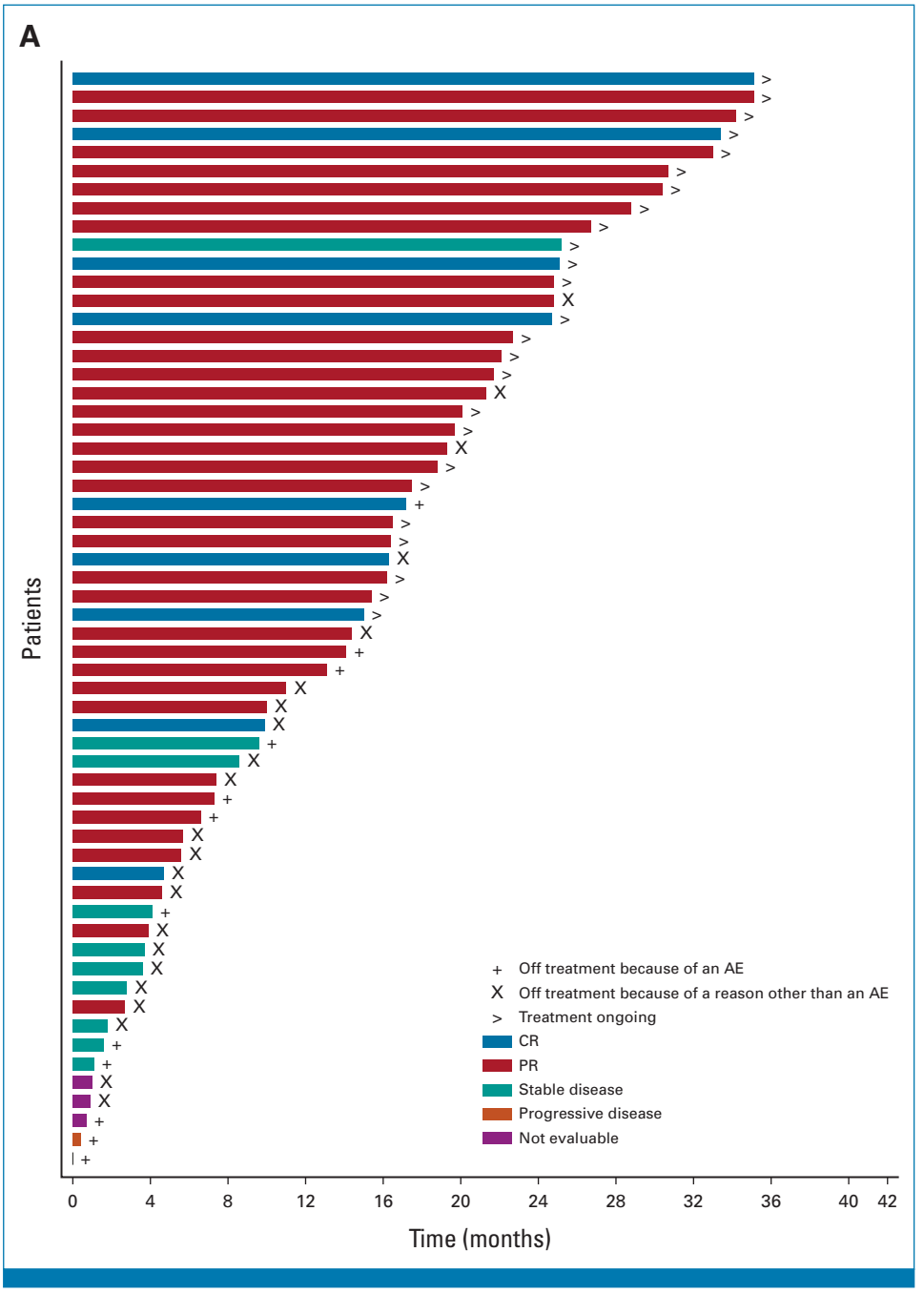

FIG A2. Duration of exposure and best overall response by independent radiology review in (A) treatment-naïve patients and (B) previously treated patients. AE, adverse event; CR, complete response; PR, partial response. (continued on following page)

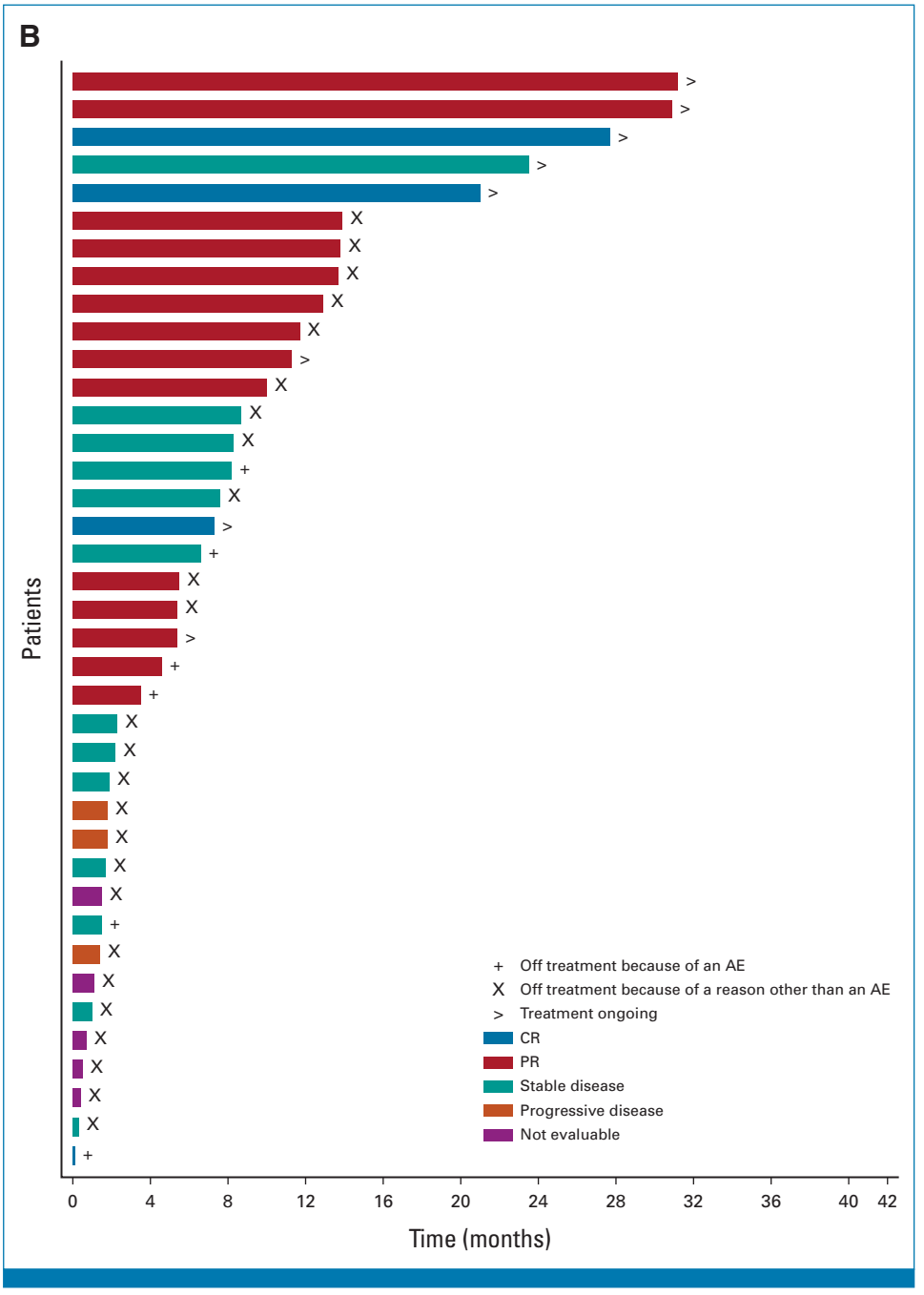

FIG A2. (Continued).

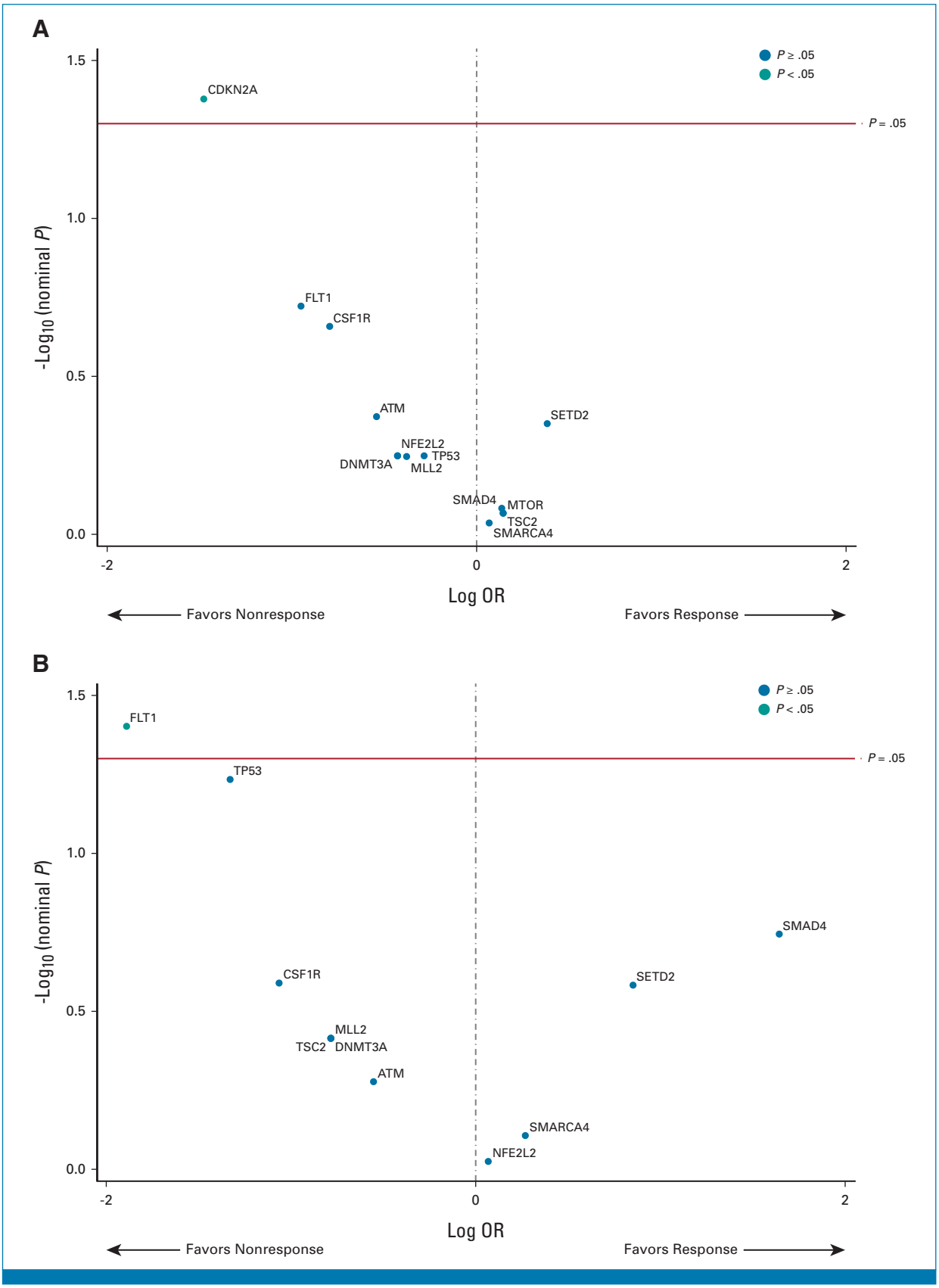

FIG A3. Volcano plots of genomic alterations (A) in the overall patient population (n = 77), (B) in treatment-naïve patients (n = 47), and (C) in previously treated patients (n = 30). Excluded patients with unevaluable response and without postbaseline assessments because of other reasons, irrespective of gene and *BRAF* gene. (continued on following page)

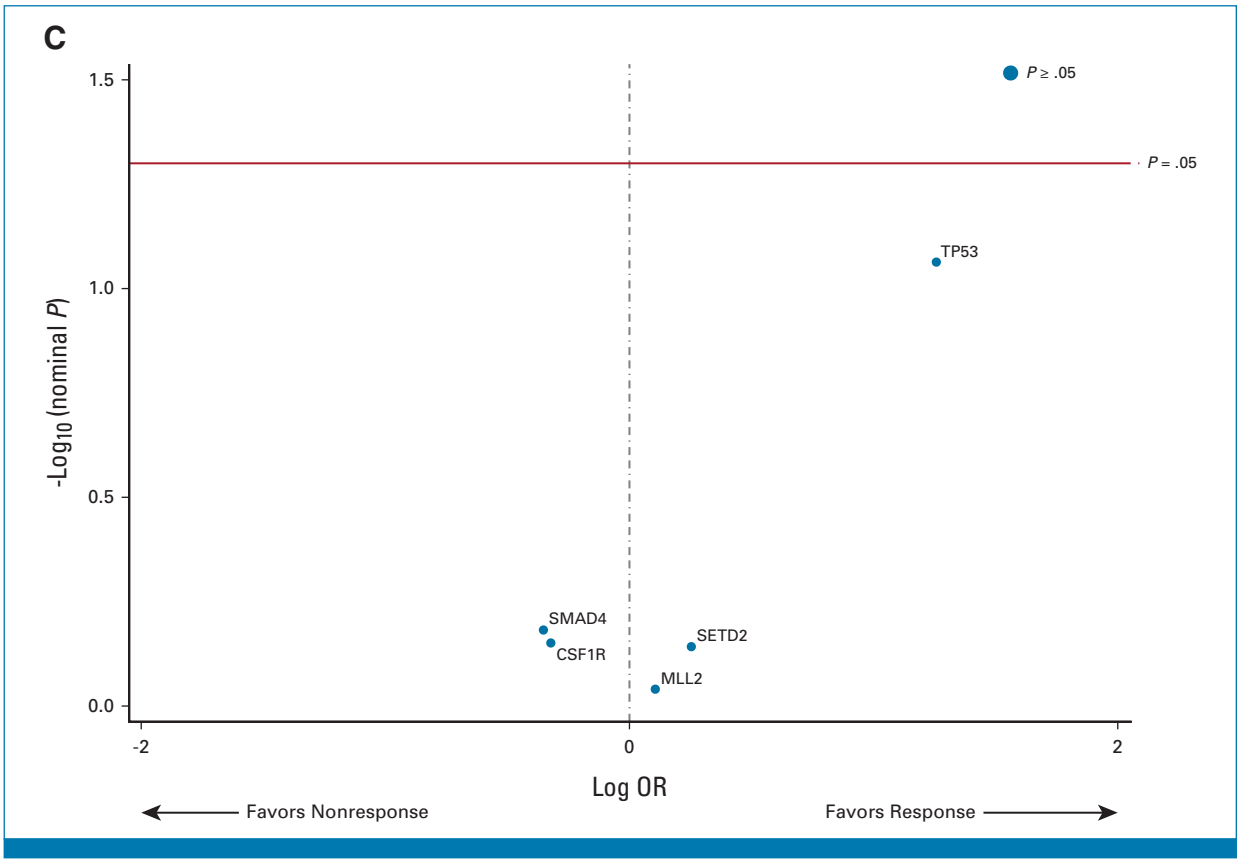

FIG A3. (Continued). Included genes altered in eight or more cases with evaluable responses for overall patient population. Included genes altered in five or more cases for treatment-naïve and previously treated patients. *P* values are based on likelihood ratio test. OR, odds ratio.

TABLE A1. ORR by Independent Radiology Review in Subgroups

Characteristic	Treatment-Naïve		Previously Treated	
	No.	ORR % (95% CI)	No.	ORR % (95% CI)
Age group, years				
<65	23	73.9 (51.6 to 89.8)	13	38.5 (13.9 to 68.4)
≥65	36	75.0 (57.8 to 87.9)	26	50.0 (29.9 to 70.1)
Sex				
Women	33	69.7 (51.3 to 84.4)	19	47.4 (24.4 to 71.1)
Men	26	80.8 (60.6 to 93.4)	20	45.0 (23.1 to 68.5)
ECOG PS				
0	19	73.7 (48.8 to 90.9)	7	85.7 (42.1 to 99.6)
1	40	75.0 (58.8 to 87.3)	32	37.5 (21.1 to 56.3)
Smoking status				
Current	8	50.0 (15.7 to 84.3)	5	20.0 (0.5 to 71.6)
Former	33	75.8 (57.7 to 88.9)	23	52.2 (30.6 to 73.2)
Never	18	83.3 (58.6 to 96.4)	11	45.5 (16.7 to 76.6)
Brain metastases				
No	55	72.7 (59.0 to 83.9)	35	51.4 (34.0 to 68.6)
Yes	4	100 (39.8 to 100.0)	4	0
Previously treated with immunotherapy				
Yes		NA	24	58.3 (36.6 to 77.9)
No		NA	15	26.7 (7.8 to 55.1)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; ORR, objective response rate.

TABLE A2. All-Causality Adverse Events of Any Grade ≥15% in All Patients

Adverse Event	Overall (N = 98)
Any-grade, No. (%)	97 (99)
Nausea	57 (58)
Diarrhea	50 (51)
Fatigue	45 (46)
Vomiting	36 (37)
Anemia	30 (31)
Constipation	26 (27)
Dyspnea	25 (26)
Pyrexia	22 (22)
Peripheral edema	21 (21)
Abdominal pain	20 (20)
Back pain	20 (20)
Vision blurred	20 (20)
Cough	17 (17)
Asthenia	16 (16)
Blood creatinine increased	16 (16)
Dizziness	16 (16)
Arthralgia	15 (15)
AST increased	15 (15)
Blood creatine phosphokinase increased	15 (15)
Lipase increased	15 (15)
Pruritus	15 (15)

TABLE A3. Treatment-Related Adverse Events Leading to Dose Interruption of Both Encorafenib and Binimetinib

Adverse Event	Overall (N = 98)
Any-grade, No. (%)	43 (44)
Nausea	12 (12)
Diarrhea	11 (11)
ALT increased	6 (6)
AST increased	6 (6)
Vomiting	6 (6)
Fatigue	4 (4)
Anemia	3 (3)
Colitis	3 (3)
Acute kidney injury	2 (2)
Arthralgia	2 (2)
Asthenia	2 (2)
Blood alkaline phosphatase increased	2 (2)
Chills	2 (2)
Glomerular filtration rate decreased	2 (2)
Hyponatremia	2 (2)
Rash maculopapular	2 (2)
Abdominal discomfort	1 (1)
Abdominal pain	1 (1)
Amylase increased	1 (1)
Atrial fibrillation	1 (1)
Blood creatine phosphokinase increased	1 (1)
Blood creatinine increased	1 (1)
Cholelithiasis	1 (1)
Cognitive disorder	1 (1)
Decreased appetite	1 (1)
Dehydration	1 (1)
Dizziness	1 (1)
Dysgeusia	1 (1)
Ejection fraction decreased	1 (1)
Generalized edema	1 (1)
Hypertransaminasemia	1 (1)
Lipase increased	1 (1)
Liver disorder	1 (1)
Liver function test increased	1 (1)
Malaise	1 (1)
Muscular weakness	1 (1)
Myalgia	1 (1)
Noncardiac chest pain	1 (1)
Pain in extremity	1 (1)
Platelet count decreased	1 (1)
Pruritus	1 (1)
Pyrexia	1 (1)
Rash	1 (1)
Retinal detachment	1 (1)
Squamous cell carcinoma of skin	1 (1)

(continued on following page)

TABLE A3. Treatment-Related Adverse Events Leading to Dose Interruption of Both Encorafenib and Binimetinib (continued)

Adverse Event	Overall (N = 98)
Stomatitis	1 (1)
Upper GI hemorrhage	1 (1)
Vision blurred	1 (1)
Visual impairment	1 (1)

TABLE A4. Treatment-Related Adverse Events Leading to Dose Reduction of Both Encorafenib and Binimetinib

Adverse Event	Overall (N = 98)
Any-grade, No. (%)	24 (24)
Diarrhea	6 (6)
Nausea	6 (6)
AST increased	5 (5)
ALT increased	4 (4)
Anemia	2 (2)
Abdominal pain	1 (1)
Acute kidney injury	1 (1)
Asthenia	1 (1)
Blood alkaline phosphatase increased	1 (1)
Blood creatinine increased	1 (1)
Constipation	1 (1)
Decreased appetite	1 (1)
Generalized edema	1 (1)
Lipase increased	1 (1)
Liver disorder	1 (1)
Myalgia	1 (1)
Peripheral edema	1 (1)
Pruritus	1 (1)
Rash	1 (1)
Rash maculopapular	1 (1)
Vision blurred	1 (1)
Vomiting	1 (1)

TABLE A5. Treatment-Related Adverse Events Leading to Discontinuation of Both Encorafenib and Binimetinib

Adverse Event	Overall (N = 98)
Any-grade, No. (%)	15 (15)
Diarrhea	2 (2)
Nausea	2 (2)
Vomiting	2 (2)
Arthralgia	1 (1)
Asthenia	1 (1)
Atrial fibrillation	1 (1)
Blood creatine phosphokinase increased	1 (1)
Blood creatinine increased	1 (1)
Cardiac failure	1 (1)
Cerebrovascular accident	1 (1)
Colitis	1 (1)
Ejection fraction decreased	1 (1)
Fatigue	1 (1)
Glomerular filtration rate decreased	1 (1)
Myalgia	1 (1)
Pain in extremity	1 (1)
Photophobia	1 (1)
Rash	1 (1)
Rash maculopapular	1 (1)
Ulcerative keratitis	1 (1)
Vitreous floaters	1 (1)

TABLE A6. Pharmacokinetic Parameters of Encorafenib and Binimetinib in Plasma Samples

	Encorafenib		Binimetinib	
Parameter (units)	No.	Cycle 1 Day 15	No.	Cycle 1 Day 15
AUCtau (ng·h/mL)	49	12,100 (94.0)	51	2,210 (47.3)
Cmax (ng/mL)	50	3,110 (128.0)	52	546 (61.1)

NOTE. Dosing interval (tau) is 24 hours for encorafenib and 12 hours for binimetinib. Geometric mean (geometric % coefficient of variation) values are presented.
Abbreviations: AUCtau, AUC-time curve over a dosing interval; Cmax, maximum concentration.