Zipalertinib in Patients With Epidermal Growth Factor Receptor Exon 20 Insertion-Positive Non–Small Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy With or Without Amivantamab

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ABSTRACT

PURPOSE To evaluate the safety and efficacy of zipalertinib, an irreversible epidermal growth factor receptor (EGFR) inhibitor, in pretreated patients with non–small cell lung cancer (NSCLC) harboring *EGFR* exon 20 insertion (ex20ins) mutations.

METHODS REZILIENT1 (ClinicalTrials.gov identifier: NCT04036682) is a phase I/II open-label trial enrolling patients with locally advanced or metastatic *EGFR* ex20ins-mutant NSCLC previously treated with platinum-based chemotherapy with/without ex20ins-targeted therapies. Asymptomatic, treated and untreated stable CNS metastases are permitted. We report data from patients treated with zipalertinib 100 mg twice daily. The primary end points are objective response rate (ORR) and duration of response (DOR) by independent central review.

RESULTS At data cutoff (December 10, 2024), 244 patients had received treatment with zipalertinib 100 mg twice daily. The primary efficacy population (8 months' follow-up) comprised patients who had received prior platinum-based chemotherapy without ex20ins-targeted therapy (125 patients), with amivantamab only (30 patients), or with amivantamab and other ex20ins-targeted therapy (21 patients). The confirmed ORR was 35.2% (95% CI, 28.2 to 42.8); median DOR was 8.8 months (95% CI, 8.3 to 12.7). Among patients who received prior platinum-based chemotherapy without ex20ins-targeted therapy, amivantamab only, or amivantamab and other ex20ins-targeted therapy, the confirmed ORR was 40%, 30%, and 14.3%, and median DOR was 8.8, 14.7, and 4.2 months, respectively. Among 68 patients with CNS metastases, the ORR was 30.9%. The most common grade ≥3 treatment-related adverse events were anemia (7%), pneumonitis and rash (2.5% each), and diarrhea, ALT increased, and platelet count decreased (2% each).

CONCLUSION Zipalertinib demonstrated clinically meaningful efficacy with a manageable safety profile in patients with *EGFR* ex20ins-mutant NSCLC who received prior platinum-based chemotherapy with or without amivantamab.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Mutations in the epidermal growth factor receptor (*EGFR*) are a major oncogenic driver that occur in approximately one-third of patients with non–small cell lung cancer (NSCLC), although there is marked variation across geographic regions.[1,2] Exon 20 insertions (ex20ins) represent the third most common *EGFR* mutation type after deletions in exon 19 and the L858R point mutation in exon 21 (together, termed "classical" mutations).[3-5]

CONTEXT

Key Objective

To assess the safety and efficacy of zipalertinib in patients with epidermal growth factor receptor (EGFR) exon 20 insertion (ex20ins)-mutant non–small cell lung cancer previously treated with platinum-based chemotherapy, with or without amivantamab.

Knowledge Generated

Meaningful clinical efficacy was observed in patients receiving zipalertinib 100 mg twice daily, as evidenced by an objective response rate (ORR) of 35.2% in the primary efficacy population. In exploratory analyses, patients previously treated with amivantamab without other ex20ins-targeted therapy achieved an ORR of 30%, supporting the efficacy of zipalertinib in the post-amivantamab setting. Levels of dermatologic and gastrointestinal toxicities typically associated with wild-type EGFR inhibition were low.

Relevance *(T.E. Stinchcombe)*

Zipalertinib, a novel EGFR exon 20 insertion targeting tyrosine kinase inhibitor, should become a treatment option for patients who have received platinum-based chemotherapy as well as prior amivantamab therapy.*

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

Although several tyrosine kinase inhibitors (TKIs) have been developed for the treatment of NSCLC harboring classical *EGFR* mutations,[6,7] most patients with ex20ins exhibit primary resistance to these EGFR TKIs.[3,6,8-11]

Until recently, platinum-based chemotherapy was the standard first-line treatment for patients with *EGFR* ex20ins-mutant NSCLC.[6] In 2021, amivantamab, an EGFR-MET bispecific antibody, received initial regulatory approval as monotherapy for patients who progressed on/after platinum-based chemotherapy on the basis of the results of the phase I CHRYSALIS trial.[12,13] More recently, amivantamab plus carboplatin and pemetrexed showed superior efficacy compared with chemotherapy alone in the phase III PAPILLON trial, leading to the approval of this regimen for the first-line treatment of patients with *EGFR* ex20ins-mutant NSCLC and providing a new standard-of-care for previously untreated patients.[12,14]

While amivantamab is an effective treatment for both previously treated and treatment-naive patients with *EGFR* ex20ins-mutant NSCLC,[13,14] it is associated with significant dermatologic and other toxicities.[15] Moreover, the development of primary or acquired resistance to amivantamab presents a further challenge for managing this patient population.[16,17] As such, there is a need for well-tolerated, orally administrated, targeted therapies with durable clinical benefit, particularly for patients with disease progression on prior amivantamab therapy.

Despite the availability of TKI treatment of NSCLC harboring classical *EGFR* mutations, no oral TKIs are currently approved for the treatment of *EGFR* ex20ins-mutant NSCLC.[18] Several ex20ins-active TKIs have been investigated; however, TKIs such as mobocertinib and poziotinib have shown modest efficacy in previously treated *EGFR* ex20ins-mutant NSCLC, and mobocertinib failed to improve efficacy versus chemotherapy in the first-line setting.[18-21]

Zipalertinib is an irreversible, oral EGFR TKI with a unique pyrolopyrimidine scaffold that potently inhibits cell growth and EGFR signaling in *EGFR* ex20ins-mutant human cancer cell lines and demonstrates improved selectivity for ex20ins-mutant versus wild-type *EGFR*.[22,23] In vitro, zipalertinib demonstrated a broader therapeutic window than other EGFR TKIs, suggesting it may reach higher serum and tissue concentrations before the development of dose-limiting, on-target toxicities.[23,24]

REZILIENT1 is a multipart, phase I/II study assessing the safety, tolerability, antitumor activity, and pharmacokinetics of zipalertinib in patients with recurrent or metastatic NSCLC harboring *EGFR* ex20ins mutations. Data from 73 patients enrolled in the phase I/IIa components of the trial showed encouraging antitumor activity with a manageable toxicity profile, and zipalertinib 100 mg twice daily was selected as the recommended dose for further clinical development.[25]

We report the primary efficacy and safety data from patients in REZILIENT1 who received monotherapy with zipalertinib 100 mg twice daily after prior platinum-based chemotherapy, with or without amivantamab.

METHODS

Study Design and Patients

REZILIENT1 (ClinicalTrials.gov identifier: NCT04036682) is a phase I/II, open-label, multicenter trial evaluating the safety and efficacy of oral zipalertinib in patients with locally advanced or metastatic *EGFR* ex20ins-mutant NSCLC who previously received platinum-based chemotherapy. The design of the phase I/IIa dose escalation and expansion components has been published previously.[25] We present data for patients who received at least 1 dose of zipalertinib 100 mg twice daily and were enrolled before or on April 25, 2024, to allow approximately 8 months of minimal follow-up by data cutoff (December 10, 2024).

Eligible patients were aged 18 years and older with locally advanced or metastatic NSCLC and documented *EGFR* ex20ins mutations as determined by local tests. They were required to have measurable disease per RECIST version 1.1 (v1.1), an Eastern Cooperative Oncology Group performance status of 0/1, and adequate organ function. Patients must have received prior treatment with platinum-based chemotherapy in the recurrent/metastatic setting, unless they had declined it or it was contraindicated, with no restrictions on the number of previous therapies. Prior EGFR TKIs were permitted if completed more than 8 days or five times the terminal phase half-life, whichever was longer, before the first dose of zipalertinib. Previous treatment with an agent approved by local regulatory authorities for *EGFR* ex20ins-mutant NSCLC was allowed in a subset of patients to explore the safety and efficacy of zipalertinib 100 mg twice daily after progression on ex20ins-targeted therapy. Patients with CNS metastases were eligible if they were asymptomatic, had been treated with surgery and/or radiation (if clinically indicated) or were untreated (if treatment was not clinically indicated) and were stable (ie, not requiring steroids or on a stable or decreasing dose for ≥4 weeks before the first dose of zipalertinib).

The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki and was reviewed and approved by the institutional review board at each participating site. All patients provided written informed consent.

Tumor imaging was performed at baseline, 6 weeks after initiation of treatment, and at 9-week intervals thereafter. Further details on procedures and assessments are provided in Appendix 1 (online only).

End Points

The primary end points were objective response rate (ORR) and duration of response (DOR), as determined by independent central review (ICR) per RECIST v1.1. Secondary end points included investigator-assessed ORR and DOR, disease control rate (DCR), clinical benefit rate (CBR), progression-free survival (PFS) determined by ICR and investigator assessment, overall survival (OS), antitumor activity in patients with known CNS disease, and safety and tolerability.

Statistical Analysis

The safety analysis set included all patients who received at least 1 dose of zipalertinib 100 mg twice daily, and the primary efficacy population included all patients who received at least 1 dose of zipalertinib 100 mg twice daily and started treatment before or on April 25, 2024 (ie, there were approximately 8 months of minimal follow-up before data cutoff on December 10, 2024).

Including 176 patients in the efficacy analysis provides >99% power to demonstrate that the lower bound value of the 95% CI for the observed ORR was >20% (historical control).[26,27] ORR was defined as the proportion of patients who achieved a confirmed complete response (CR) or partial response (PR) per RECIST v1.1 during the study and was assessed using the point estimate and 95% two-sided exact CI (Clopper-Pearson method). DOR was defined as the time between the first response and date of the first documented progressive disease, death, or, in the absence of these, last disease assessment. Nonparametric Kaplan-Meier method was used to estimate DOR, PFS, and OS.

Exploratory subgroup analyses were performed in patients who received prior amivantamab with or without other ex20ins-targeted therapy and by CNS involvement (brain metastases) at baseline.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Population

In total, 244 patients were enrolled and treated with zipalertinib 100 mg twice daily (Fig 1). At the data cutoff, 62.3% of patients had permanently discontinued treatment with zipalertinib, most commonly because of disease progression (32.8%) or treatment-emergent adverse events (TEAEs, 16.4%; treatment-related adverse events [TRAEs] in 8.2%). In total, 43.9% of patients discontinued the study, including 32% who died.

Baseline demographic and disease characteristics were similar between patients previously treated with platinum-based chemotherapy without ex20ins-targeted therapy (n = 143) and those who had received prior ex20ins-targeted therapy (n = 101), except for a slightly younger age, higher prevalence of baseline CNS/brain metastases, and a higher number of prior treatments in the latter subgroup (Table 1).

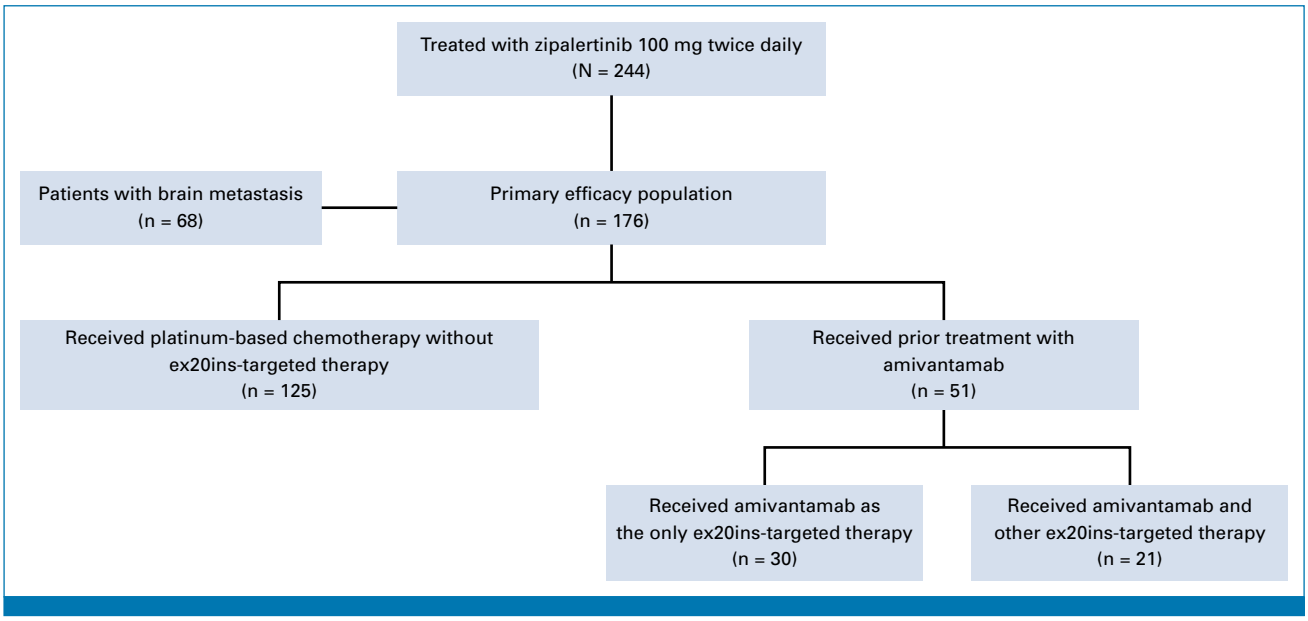

FIG 1. Flow diagram and analysis groups. The safety analysis set includes all patients who received at least 1 dose of zipalertinib 100 mg twice daily. The primary efficacy population includes patients treated with oral zipalertinib 100 mg twice daily before or on April 25, 2024 (approximately 8 months of minimum follow-up before data cutoff on December 10, 2024). Patients either received prior platinum-based chemotherapy without prior ex20ins-targeted therapy or amivantamab with or without other ex20ins-targeted therapies. ex20ins, exon 20 insertions.

Among the 93.4% of patients who had received prior chemotherapy, the most common agents included pemetrexed, carboplatin, and cisplatin (84%, 79.5%, and 22.1% of patients, respectively). Overall, 46.3% of patients had received prior immunotherapy with a PD-(L)1 inhibitor with or without another immunotherapy.

Among the 143 patients who received prior platinum-based chemotherapy without ex20ins-targeted therapy, 37 (25.9%) had received prior targeted therapy, most commonly osimertinib (9.1%). Among the 101 patients who received prior ex20ins-targeted therapy, 83 (82.2%) had received amivantamab (either as the only ex20ins-targeted therapy [53 patients] or with other ex20ins-targeted therapy [30 patients] such as mobocertinib, BLU-451, poziotinib, or sunvozertinib; Table 1). Of the 53 patients who received amivantamab without other ex20ins-targeted therapy, 49 had also received prior chemotherapy, mostly as sequential treatments (six patients received concurrent amivantamab plus chemotherapy).

Efficacy

Of the 244 treated patients, 176 were included in the primary efficacy population, comprising 125 patients treated with prior platinum-based chemotherapy without ex20ins-targeted therapy and 51 who had received prior amivantamab with or without prior chemotherapy (30 received amivantamab as the only ex20ins-targeted therapy and 21 received amivantamab and other ex20ins-targeted therapy; Fig 1.)

In the primary efficacy population, the confirmed ORR per ICR was 35.2% (95% CI, 28.2 to 42.8), including 1 patient with a CR and 61 patients with a PR (Table 2; Fig 2); median DOR was 8.8 months (95% CI, 8.3 to 12.7; Appendix Fig A1A). The DCR and CBR were 89.2% (95% CI, 83.7 to 93.4) and 64.2% (95% CI, 56.6 to 71.3), respectively. Per investigator assessment, the confirmed ORR, DCR, and CBR were 38.1% (95% CI, 30.9 to 45.7), 90.9% (95% CI, 85.7 to 94.7), and 67% (95% CI, 59.6 to 73.9), respectively, and median DOR was 9.9 months (95% CI, 8.3 to 29.0; Appendix Table A1). The median time to response by ICR and investigator assessment was 44.0 days (range, 31-295) and 42.0 days (range, 31-862), respectively.

Among the 125 patients who received prior platinum-based chemotherapy only, the confirmed ORR per ICR and investigator assessment was 40% (95% CI, 31.3 to 49.1) and 40.8% (95% CI, 32.1 to 49.9), respectively (Table 2; Appendix Table A1). The median DOR was 8.8 months (95% CI, 8.3 to 12.7) per ICR and 10.4 months (95% CI, 8.3 to 29.0) per investigator assessment.

Efficacy was also explored in patients who received prior ex20ins-targeted therapy. Among all 51 patients with prior amivantamab with or without other ex20ins-targeted TKIs, the confirmed ORR according to ICR was 23.5% (95% CI, 12.8 to 37.5) and the median DOR was 8.5 months (95% CI, 4.2 to 14.8; Table 3). For patients who received prior amivantamab without other ex20ins-targeted therapy, the confirmed ORR per ICR was 30% (95% CI, 14.7 to 49.4), with a median DOR of 14.7 months. For those receiving amivantamab and other

TABLE 1. Baseline Demographic and Disease Characteristics

Characteristic	Platinum-Based Chemotherapy Without ex20ins-Targeted Therapy (n = 143)	Prior ex20ins-Targeted Therapy (n = 101)	Total (N = 244)
Age, years, median (range)	66.0 (36-86)	62.0 (31-85)	65.0 (31-86)
Aged <65 years, No. (%)	61 (42.7)	60 (59.4)	121 (49.6)
Aged ≥65 years, No. (%)	82 (57.3)	41 (40.6)	123 (50.4)
Sex, No. (%)			
Male	56 (39.2)	31 (30.7)	87 (35.7)
Female	87 (60.8)	70 (69.3)	157 (64.3)
Race, No. (%)			
White	51 (35.7)	47 (46.5)	98 (40.2)
Black or African American	5 (3.5)	7 (6.9)	12 (4.9)
Asian	77 (53.8)	45 (44.6)	122 (50.0)
Other	1 (0.7)	1 (1.0)	2 (0.8)
Not reported	9 (6.3)	1 (1.0)	10 (4.1)
Region, No. (%)			
United States	40 (28.0)	39 (38.6)	79 (32.4)
Europe	35 (24.5)	23 (22.8)	58 (23.8)
Asia	68 (47.6)	39 (38.6)	107 (43.9)
Disease stage, No. (%)			
Stage III	7 (4.9)	2 (2.0)	9 (3.7)
Stage IV	136 (95.1)	99 (98.0)	235 (96.3)
Cell type, No. (%)			
Adenocarcinoma	140 (97.9)	96 (95.0)	236 (96.7)
Squamous cell carcinoma	1 (0.7)	1 (1.0)	2 (0.8)
Large cell carcinoma	0	1 (1.0)	1 (0.4)
Other[a]	2 (1.4)	3 (3.0)	5 (2.0)
ECOG performance status, No. (%)			
0	45 (31.5)	33 (32.7)	78 (32.0)
1	98 (68.5)	68 (67.3)	166 (68.0)
Smoking history, No. (%)			
Former	55 (38.5)	32 (31.7)	87 (35.7)
Current	1 (0.7)	3 (3.0)	4 (1.6)
None	86 (60.1)	66 (65.3)	152 (62.3)
Unknown	1 (0.7)	0	1 (0.4)
CNS or brain metastases, No. (%)			
Yes	48 (33.6)	55 (54.5)	103 (42.2)
Number of prior systemic regimens, median (range)	1 (0-6)	2 (1-7)	2 (0-7)
Prior chemotherapy, No. (%)	132 (92.3)	96 (95.0)	228 (93.4)
Prior anti-PD-(L)1, No. (%)	67 (46.9)	46 (45.5)	113 (46.3)
Prior targeted therapy, No. (%)	37 (25.9)	101 (100)	138 (56.6)
Amivantamab	1 (0.7)[b]	83 (82.2)	84 (34.4)
Mobocertinib	0	40 (39.6)	40 (16.4)
Bevacizumab	14 (9.8)	16 (15.8)	30 (12.3)
Osimertinib	13 (9.1)	7 (6.9)	20 (8.2)
BLU-451	0	5 (5.0)	5 (2.0)
Cetuximab	4 (2.8)	0	4 (1.6)
Poziotinib	0	3 (3.0)	3 (1.2)
Sunvozertinib	0	3 (3.0)	3 (1.2)
Other	17 (11.9)	9 (8.9)	26 (10.7)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ex20ins, exon 20 insertions; NSCLC, non–small cell lung cancer.
[a]NSCLC or adenocarcinoma with squamous features.
[b]Patient mistakenly assigned from the prior amivantamab group.

TABLE 2. BOR per Independent Central Review

Outcome	Primary Efficacy Population (n = 176)	Platinum-Based Chemotherapy Without ex20ins-Targeted Therapy (n = 125)	Patients With Brain Metastases[a] (n = 68)
Confirmed BOR, No. (%)[b]			
CR	1 (0.6)	0	1 (1.5)
PR	61 (34.7)	50 (40.0)	20 (29.4)
Unconfirmed PR[c]	7 (4.0)	6 (4.8)	2 (2.9)
SD	88 (50.0)	55 (44.0)	37 (54.4)
PD	11 (6.3)	8 (6.4)	5 (7.4)
Not applicable	8 (4.5)	6 (4.8)	3 (4.4)
Confirmed ORR, No. (%) (95% CI)[d]	62 (35.2) (28.2 to 42.8)	50 (40.0) (31.3 to 49.1)	21 (30.9) (20.2 to 43.3)
DCR, No. (%) (95% CI)[e]	157 (89.2) (83.7 to 93.4)	111 (88.8) (81.9 to 93.7)	60 (88.2) (78.1 to 94.8)
CBR, No. (%) (95% CI)[f]	113 (64.2) (56.6 to 71.3)	85 (68.0) (59.1 to 76.1)	38 (55.9) (43.3 to 67.9)
Time to response, days, median (range)	44 (31-295)	44 (39-232)	98 (35-232)
DOR, months, median (95% CI)	8.8 (8.3 to 12.7)	8.8 (8.3 to 12.7)	8.3 (4.2 to 9.9)

NOTE. Patients were evaluable for response if they had received at least 1 dose of zipalertinib and had at least 1 postdose tumor assessment or had discontinued before the first efficacy assessment because of clinical disease progression or toxicity.
Abbreviations: BOR, best overall response; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DOR, duration of response; ex20ins, exon 20 insertions; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Patients with brain metastases included 44 patients with prior platinum-based chemotherapy without ex20ins-targeted therapy and 24 who received prior amivantamab with (nine patients) or without (15 patients) other ex20ins-targeted therapy.
[b]Response confirmed ≥4 weeks after response first noted.
[c]Patient had PR only at the last tumor assessment visit.
[d]Proportion of patients with confirmed CR or PR.
[e]Proportion of patients with CR, PR, or SD.
[f]Proportion of patients with CR, PR, or with SD lasting ≥24 weeks.

ex20ins-targeted therapy, the confirmed ORR was 14.3% (95% CI, 3.0 to 36.3) and median DOR was 4.2 months (Table 3). Clinical outcomes by prior amivantamab treatment per investigator assessment are summarized in Appendix Table A1.

Among the 68 patients with baseline brain metastases, the confirmed systemic ORR per ICR was 30.9% (95% CI, 20.2 to 43.3) and median DOR was 8.3 months (95% CI, 4.2 to 9.9; Appendix Fig A1B). The DCR and CBR were 88.2% (95% CI, 78.1 to 94.8) and 55.9% (95% CI, 43.3 to 67.9), respectively (Table 2).

With a median follow-up of 9.3 months, median PFS per ICR in the primary efficacy population was 9.4 months (95% CI, 7.4 to 10.0; Fig 3A), with landmark 6-month and 12-month progression-free rates of 63.8% and 29.9%, respectively. OS data were immature at the time of analysis; survival rates at 6 and 12 months were 84.1% and 69.3%, respectively (Figs 3A and 3B). For the 51 patients who received prior amivantamab, median PFS was 7.3 months (95% CI, 5.3 to 9.7; Appendix Fig A2), and for those with brain metastases, it was 7.3 months (95% CI, 5.3 to 9.5; Appendix Fig A3).

Safety and Tolerability

Among all 244 patients, the median duration of treatment exposure was 6.4 months (range, 0.03-51.8) at data cutoff. The median relative dose intensity was 94.1%.

Most of the patients had at least 1 TEAE (99.2%), with 223 (91.4%) patients experiencing a TRAE (grade ≥3 in 29.5% of patients; Table 4). The most common any-grade TRAEs (reported in ≥20% of patients) were paronychia (38.5%), rash (30.3%), dermatitis acneiform (24.6%), dry skin (24.6%), diarrhea (21.7%), and stomatitis (20.1%; Table 4). Among the reported grade 2 TRAEs, 17 (7%) patients had rash and 10 (4.1%) patients each had diarrhea and nausea. Twelve patients (4.9%) had treatment-related pneumonitis, five of whom had received prior immunotherapy (Appendix Table A2).

Anemia was the most common grade ≥3 TRAE, reported in 17 (7%) patients; other common grade ≥3 TRAEs (reported in at least five patients) included pneumonitis and rash (six [2.5%] patients each) and ALT increased, diarrhea, and platelet count decreased (five [2%] patients each; Appendix Table A3). Serious TRAEs were reported in 22 (9%) patients, most commonly pneumonitis (seven [2.9%] patients), followed by anemia, decreased appetite, hypoxia, and rash (two [0.8%] patients each). Two TRAEs, pneumonitis and hypoxia, led to death.

Dose modification due to TRAEs occurred in 103 (42.2%) patients, including 35 (14.3%) with a dose reduction and 96 (39.3%) with a dose interruption. TRAEs led to treatment discontinuation in 20 (8.2%) patients overall.

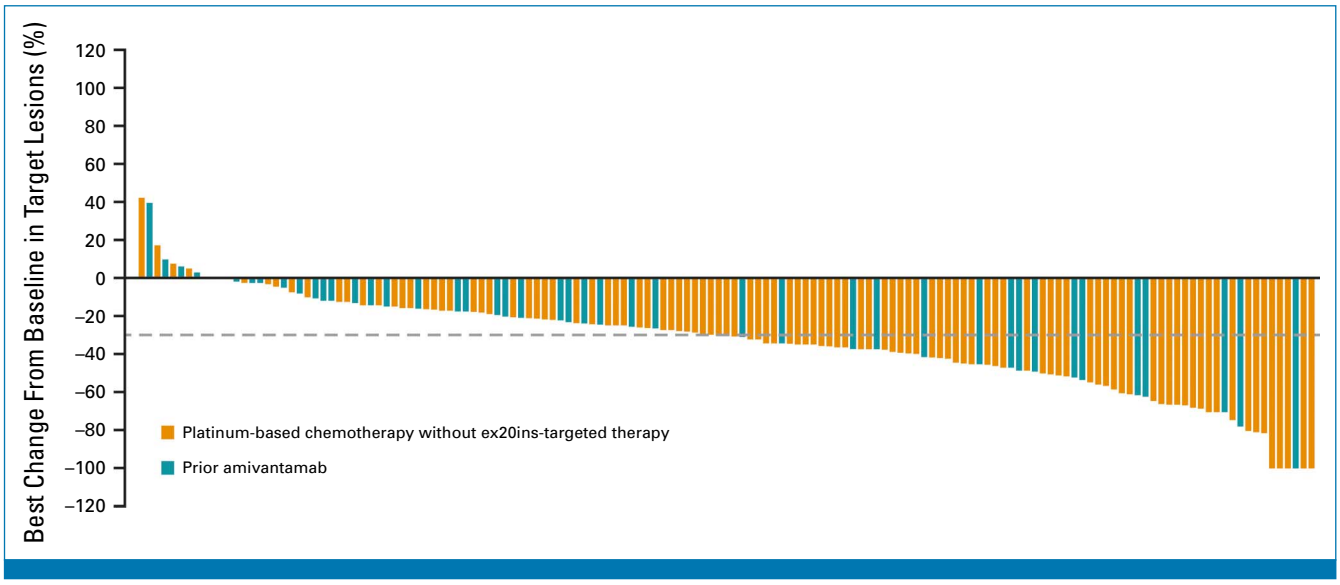

FIG 2. Best change from baseline in target lesions. ex20ins, exon 20 insertions.

DISCUSSION

Despite recent advances, including the approval of first-line amivantamab plus chemotherapy, there remains an unmet medical need for effective and well-tolerated targeted therapies for patients with previously treated recurrent or metastatic NSCLC harboring *EGFR* ex20ins mutations. In this phase I/II trial, zipalertinib provided meaningful clinical efficacy in this patient population, as evidenced by an ORR of 35.2% in the primary efficacy population, which exceeded the historical benchmark of approximately 20% with chemotherapy.[26,27] Responses were durable, with a median DOR of more than 8 months.

In patients who had received prior platinum-based chemotherapy without ex20ins-targeted therapy, the ORR was 40%, with a median DOR and PFS of 8.8 and 9.4 months, respectively. These findings are consistent with prior

TABLE 3. Efficacy of Zipalertinib in Patients With Prior Amivantamab Treatment per ICR

Outcome[a]	Prior Amivantamab Without Other ex20ins-Targeted Therapy (n = 30)	Prior Amivantamab and Other ex20ins-Targeted Therapy (n = 21)	Total (n = 51)
Confirmed BOR, No. (%)[b]			
CR	1 (3.3)	0	1 (2.0)
PR	8 (26.7)	3 (14.3)	11 (21.6)
Unconfirmed PR[c]	1 (3.3)	0	1 (2.0)
SD	19 (63.3)	14 (66.7)	33 (64.7)
PD	0	3 (14.4)	3 (5.9)
Confirmed ORR, No. (%) (95% CI)[d]	9 (30.0) (14.7 to 49.4)	3 (14.3) (3.0 to 36.3)	12 (23.5) (12.8 to 37.5)
DCR, No. (%) (95% CI)[e]	29 (96.7) (82.8 to 99.9)	17 (81.0) (58.1 to 94.6)	46 (90.2) (78.6 to 96.7)
CBR, No. (%) (95% CI)[f]	18 (60.0) (40.6 to 77.3)	10 (47.6) (25.7 to 70.2)	28 (54.9) (40.3 to 68.9)
Time to response, days, median (range)	43 (39-232)	98 (40-103)	44 (39-232)
DOR, months, median (95% CI)	14.7 (4.2 to NE)	4.2 (3.9 to NE)	8.5 (4.2 to 14.8)

Abbreviations: BOR, best overall response; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DOR, duration of response; ex20ins, exon 20 insertions; ICR, independent central review; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

[a]All per ICR except for 12-month OS rate. Patients were evaluable for response if they had received at least 1 dose of zipalertinib and had at least 1 postdose tumor assessment or had discontinued before the first efficacy assessment because of clinical disease progression or toxicity.

[b]Response confirmed ≥4 weeks after response first noted.

[c]Patient had PR only at the last tumor assessment visit.

[d]Proportion of patients with confirmed CR or PR.

[e]Proportion of patients with CR, PR, or SD.

[f]Proportion of patients with CR, PR, or with SD lasting ≥24 weeks.

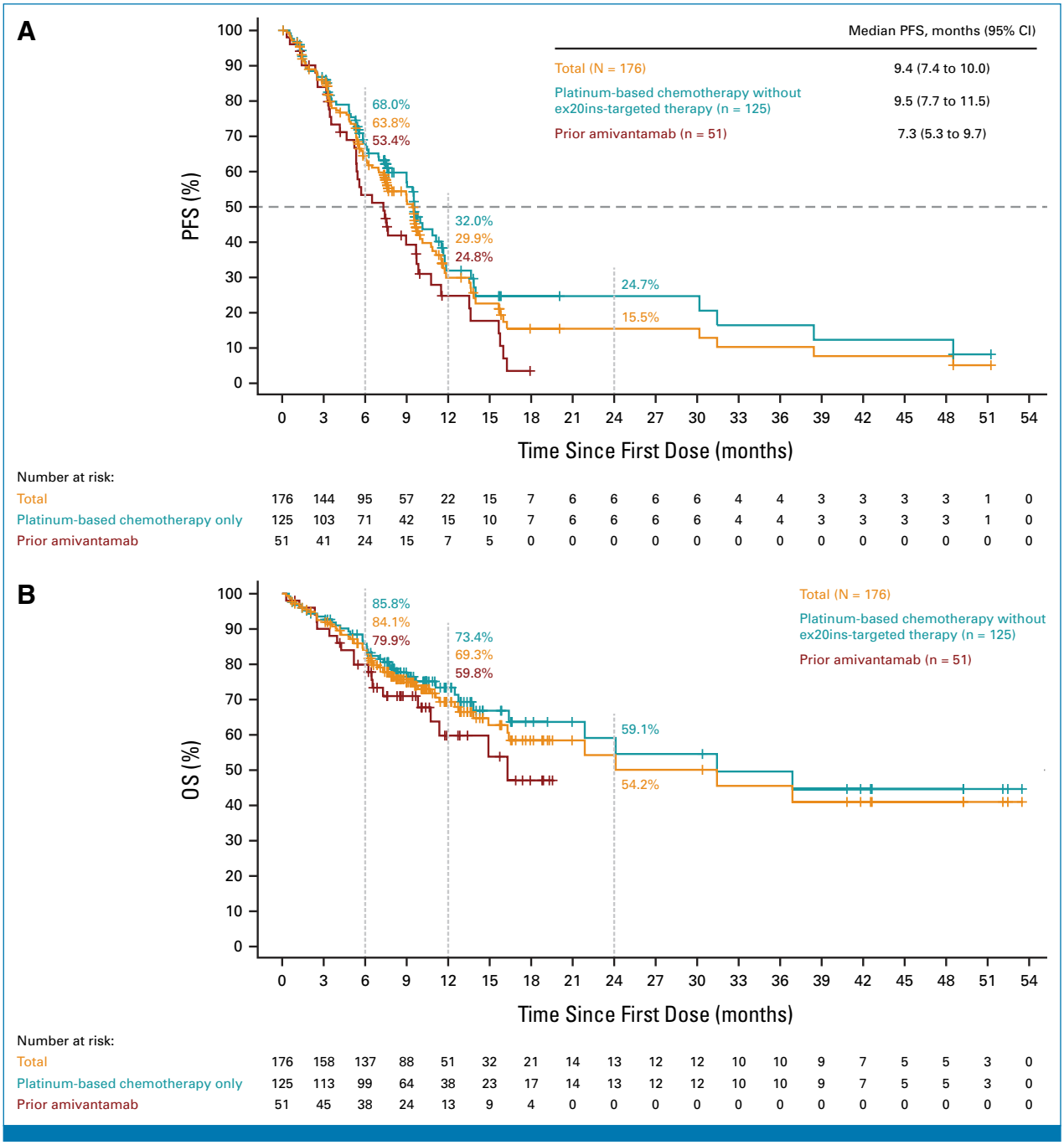

FIG 3. (A) Median PFS per independent central review and (B) OS. PFS was defined as the time between the day of the first dose of zipalertinib and first documentation of progressive disease or death, whichever occurred earlier. OS was defined as the time between the day of the first dose of zipalertinib and date of death due to any cause. ex20ins, exon 20 insertions; OS, overall survival; PFS, progression-free survival.

observations from the phase I/IIa components of REZILIENT1[25] and similar to those observed in the phase I CHRYSALIS trial of amivantamab monotherapy, in which the confirmed ORR was 40%, with a median DOR and PFS of 11.1 and 8.3 months, respectively.[13] The results are also comparable with those recently reported for sunvozertinib (confirmed ORR, 41%) and furmonertinib (ORR, 41%-50%).[28,29]

Exploratory subgroup analysis in this study showed that patients who had received prior treatment with amivantamab without other ex20ins-targeted therapy achieved an ORR of 30%, supporting the efficacy of zipalertinib in the postamivantamab setting, where there are currently no approved targeted therapeutic options. The efficacy of zipalertinib in this subgroup suggests limited cross-resistance between amivantamab as an antibody and zipalertinib as a

TABLE 4. Safety Summary

AE	Total (N = 244), No. (%)
Any TEAE	242 (99.2)
Grade ≥3 TEAE	137 (56.1)
Serious TEAE	104 (42.6)
Any TRAE	223 (91.4)
Grade ≥3 TRAE	72 (29.5)
Serious TRAE	22 (9.0)
TRAE leading to dose reduction	35 (14.3)
TRAE leading to dose interruption	96 (39.3)
TRAE leading to treatment discontinuation[a]	20 (8.2)
TRAEs leading to death	2 (0.8)

Any-Grade TRAEs Reported in ≥10% of Patients	Any Grade, No. (%)	Grade ≥3, No. (%)
Paronychia	94 (38.5)	0
Rash	74 (30.3)	6 (2.5)
Dermatitis acneiform	60 (24.6)	1 (0.4)
Dry skin	60 (24.6)	0
Diarrhea	53 (21.7)	5 (2.0)
Stomatitis	49 (20.1)	4 (1.6)
Anemia	48 (19.7)	17 (7.0)
Pruritus	44 (18.0)	1 (0.4)
Nausea	35 (14.3)	2 (0.8)
Rash maculopapular	34 (13.9)	3 (1.2)
Fatigue	29 (11.9)	0

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a]TRAEs leading to treatment discontinuation included pneumonitis (nine patients), anemia, asthenia, erythema multiforme, fatigue, interstitial lung disease, myocarditis, neutrophil count decreased, paronychia, platelet count decreased, pneumonia, rash, and Stevens-Johnson syndrome (one each).

TKI and has important implications regarding treatment sequencing. By comparison, reduced activity (ORR, 14.3%) was observed in the subgroup who received other ex20ins-targeting TKIs in addition to amivantamab. Although little is known regarding the mechanisms driving resistance to EGFR TKIs in patients with *EGFR* ex20ins-mutant NSCLC,[30] this observation may reflect the accumulation of resistance mutations that confer cross-resistance to other EGFR TKIs, resulting from selective pressure under prior EGFR TKI treatment.[30-32] Further work to characterize acquired resistance mechanisms to zipalertinib and other ex20ins-directed TKIs would help support effective patient management. With this goal in mind, biomarker analyses from the REZILIENT1 trial are ongoing.

Management of CNS metastases in patients with NSCLC remains a critical unmet need, especially among patients with *EGFR* ex20ins-mutant disease, for which the prognosis is particularly unfavorable.[3] It is notable, therefore, that zipalertinib demonstrated promising systemic efficacy (ORR, 30.9%) in patients with brain metastases. This finding is consistent with anecdotal cases of intracranial activity in a previous report[25] and provides further preliminary evidence that zipalertinib is active in this patient population. This study was not designed to assess the intracranial response rate; however, the activity of zipalertinib in patients with active or untreated brain metastases is currently being investigated in a dedicated cohort of the phase II REZILIENT2 study (ClinicalTrials.gov identifier: NCT05967689).

The safety profile of zipalertinib was consistent with previously reported data,[25] where the most common TRAEs were low-grade dermatologic toxicities. The incidence of high-grade TRAEs for on-target toxicities commonly associated with EGFR TKIs[33,34] was low, with grade ≥3 diarrhea and rash reported in only 2% and 2.5% of patients, respectively. Notably, the incidence of grade ≥3 treatment-related diarrhea with zipalertinib was lower than that reported for sunvozertinib in two phase II studies in patients with platinum-pretreated *EGFR* ex20ins-mutant NSCLC (17.1% in WU-KONG1 and 8% in WU-KONG6 studies).[28,35] Pneumonitis, another class effect of EGFR TKIs,[36] was a rare event with zipalertinib, and almost half of patients with pneumonitis had received prior anti-PD-(L)1 therapy, which has been shown to increase the likelihood of severe immune-related adverse events with subsequent EGFR TKI therapy.[37]

TRAEs with zipalertinib were generally reversible and manageable with dose modifications and/or supportive care, as reflected in the low rates of treatment discontinuation (8.2%). Overall, these findings support the tolerability of zipalertinib in patients with previously treated *EGFR* ex20ins-mutant NSCLC and suggest that zipalertinib offers effective target inhibition while limiting the dermatologic and gastrointestinal adverse events associated with wild-type EGFR inhibition.[38] Although zipalertinib had similar efficacy to that observed previously with amivantamab monotherapy,[13] the safety profiles of the two agents differ. In addition to the dermatologic and gastrointestinal toxicities associated with EGFR inhibition,[39] including high-grade diarrhea (2%)[13] and recurrent rash (3%),[13] amivantamab results in a high incidence of infusion-related reactions and associated need for premedication, as well as toxicities related to MET inhibition, such as hypoalbuminemia and peripheral edema,[13,39] which are not observed with zipalertinib. In patients receiving zipalertinib after amivantamab, there were no notable differences in safety outcomes compared with patients who had received prior chemotherapy without ex20ins-targeted therapy.

In conclusion, zipalertinib demonstrated clinically meaningful efficacy and a manageable safety profile in patients with *EGFR* ex20ins-mutant NSCLC who have received prior platinum-based chemotherapy, including in those

who received prior amivantamab. These findings support zipalertinib as a potential treatment option for patients with *EGFR* ex20ins-mutant NSCLC after progression on platinum-based chemotherapy, including those who are unresponsive to or experience disease progression on amivantamab.

Given this favorable risk-benefit ratio, the safety and efficacy of first-line zipalertinib is being investigated in combination with standard platinum-based chemotherapy in patients with locally advanced or metastatic *EGFR* ex20ins-mutant NSCLC in the phase III REZILIENT3 trial (ClinicalTrials.gov identifier: NCT05973773).[40]

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A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-25-00763. Aggregated clinical data may be shared with qualified requestor(s) but restrictions may apply on the availability of certain data. Such data is available to qualified requestors for use in rigorous, independent scientific research with scientific rationale and methodology, presence of a robust statistical analysis plan and publication plan with no potential conflicts of interest present. For approved requests, the data will be available beginning 2 years and ending 5 years following article publication. To submit a request, please contact https://cullinantx.com/contact.

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Zipalertinib in Patients With Epidermal Growth Factor Receptor Exon 20 Insertion–Positive Non–Small Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy With or Without Amivantamab

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Other Relationship: Astellas Pharma

No other potential conflicts of interest were reported.

APPENDIX 1. STUDY PROCEDURES

Zipalertinib was self-administered with or without food at a dose of 100 mg twice daily, at approximately the same time each day and with approximately 12 hours between doses. Dose interruption was allowed in the presence of clinically significant toxicity, and treatment could be discontinued or resumed (with or without a maximum of one dose reduction to 50 mg twice daily) depending on the severity of the adverse event.

Tumor imaging was performed at baseline, at 6 weeks after initiation of treatment, and at 9-week intervals thereafter, and response evaluation was conducted using RECIST version 1.1. Adverse events were monitored throughout the study and until 28 days after treatment discontinuation or initiation of a new anticancer therapy and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.

Archival or fresh tumor tissue and plasma samples (for circulating tumor DNA) were collected for all patients at baseline for confirmation of epidermal growth factor receptor ex20ins status, with plasma samples also collected during treatment and at progression to analyze changes to on-treatment mutational status compared with baseline and to investigate any evolving therapy-resistant mutations.

APPENDIX 2. INVESTIGATORS FOR REZILIENT1

Zofia Piotrowska, Helena Yu, Danny Nguyen, Alexander Spira, John Wrangle, Vamsidhar Velcheti, Mark Socinski, Rachel Sanborn, Gregory Kalemkerian, Nashat Gabrail, Ho Fun Victor Lee, Gerrina Ruiter, Egbert Smit, Daniel Shao Weng Tan, Ross Lai Kit Soo, James Chih-Hsin Yang, Gee-Chen Chang, Tsung-Ying Yang, Chao-Hua Chiu, Haruyasu Murakami, Hiroshi Tanaka, Yasushi Goto, Kazumi Nishino, Ryo Ariyasu, Shigeki Umemura, Haruko Daga, Annalisa Fontana, Lorenzo Antonuzzo, Antonio Passaro, Oscar Jose Juan-Vidal, Mariano Provencio Pulla, Gonzalo Fernández Hinojal, Manual Cobo Dols, Antonio Calles Blanco, Laura Mezquita Perez, Delvys Rodriguez Abreu, Enriqueta Felip Font, Maria Rosario Garcia Campelo, Ernesto Samuel Nadal Alforia, Tatiana Hernandez, Hyun Woo Lee, Se Hyun Kim, Byoung Yong Shim, Sang-We Kim, Sung Yong Lee, Young Saing Kim, Se-Hoon Lee, Ji-Youn Han

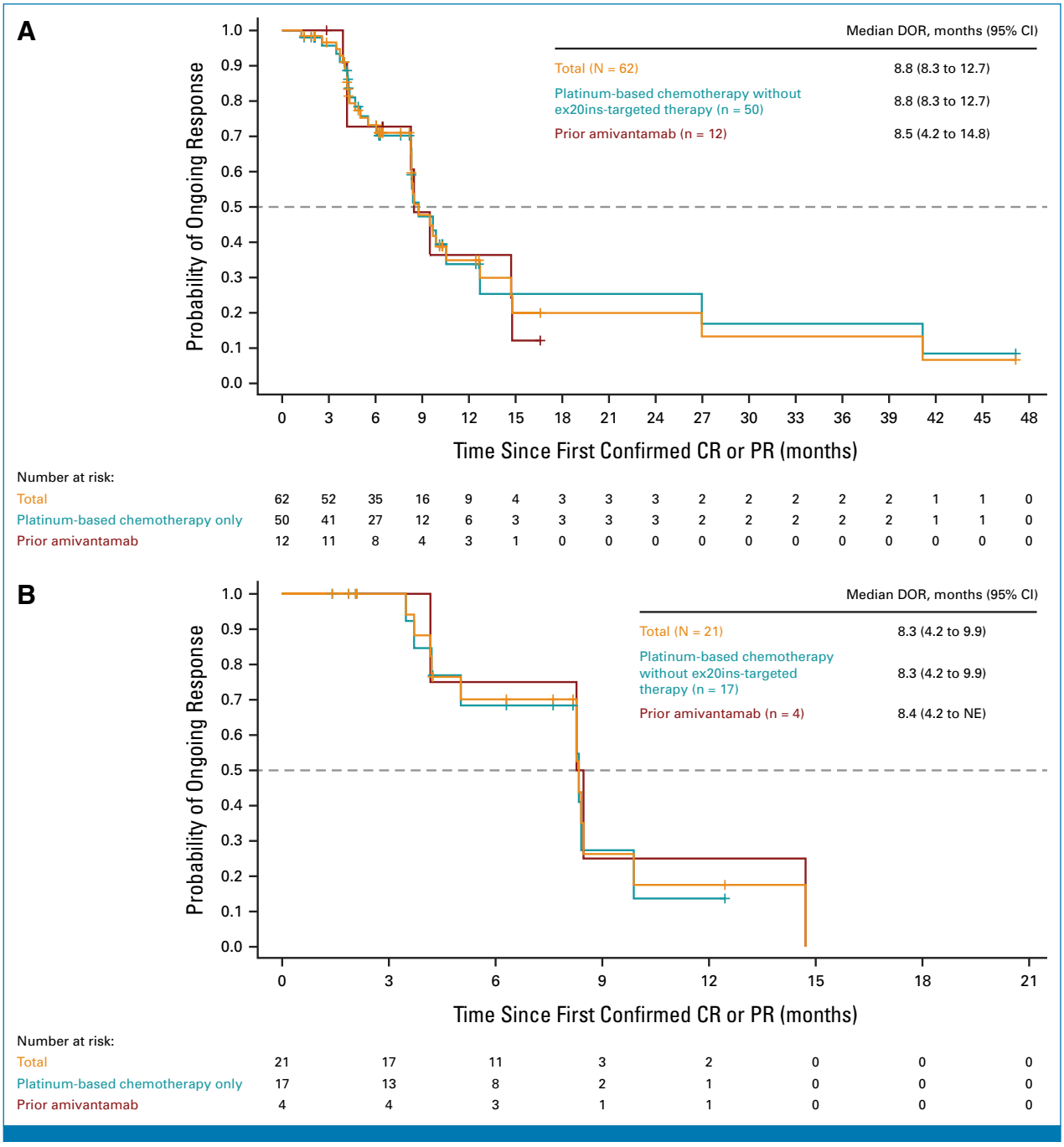

FIG A1. DOR per independent central review (A) in the primary efficacy population and (B) among patients with brain metastases. CR, complete response; DOR, duration of response; ex20ins, exon 20 insertions; NE, not evaluable; PR, partial response.

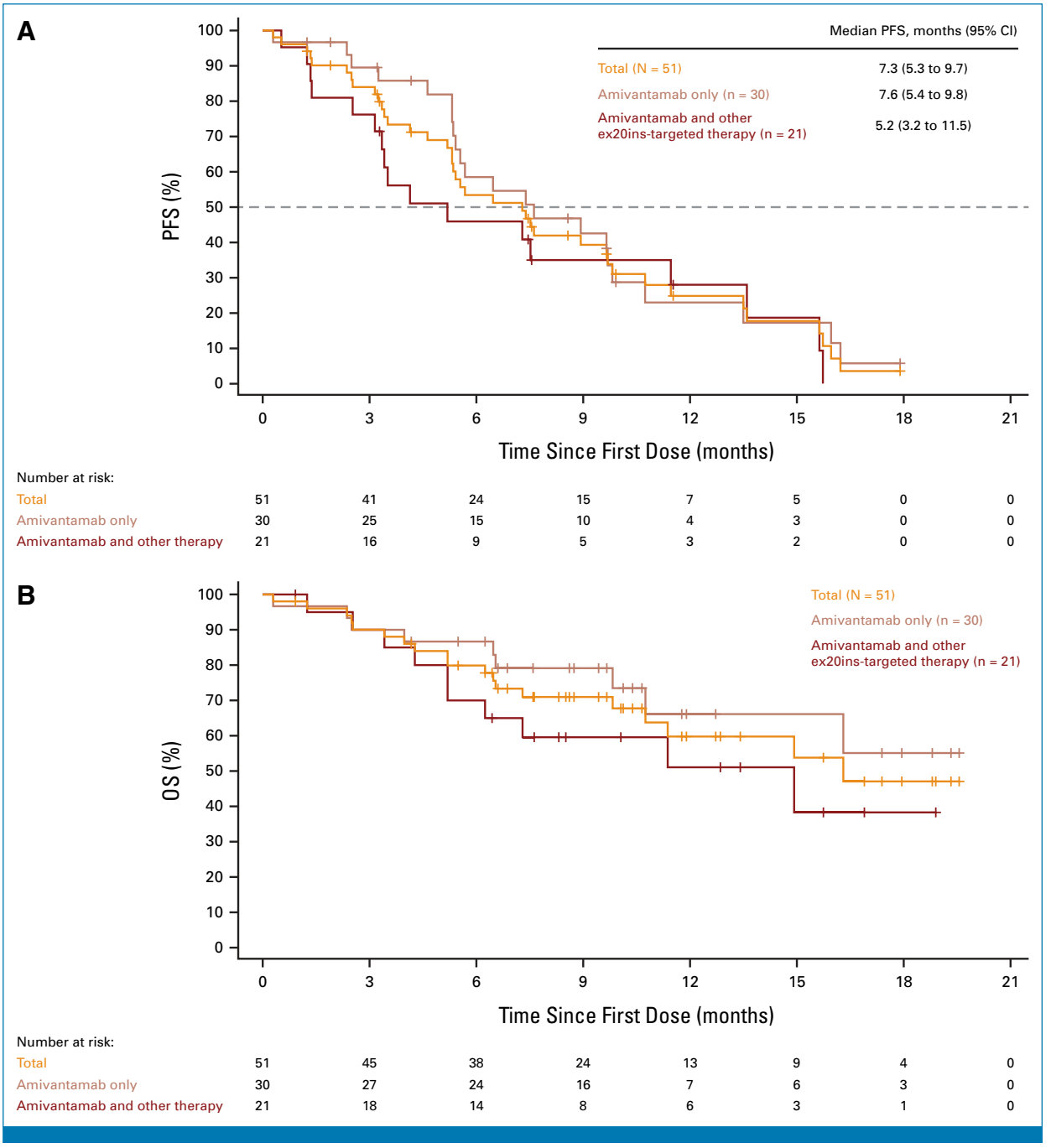

FIG A2. (A) Median PFS per independent central review and (B) OS in patients who received prior amivantamab. ex20ins, exon 20 insertions; OS, overall survival; PFS, progression-free survival.

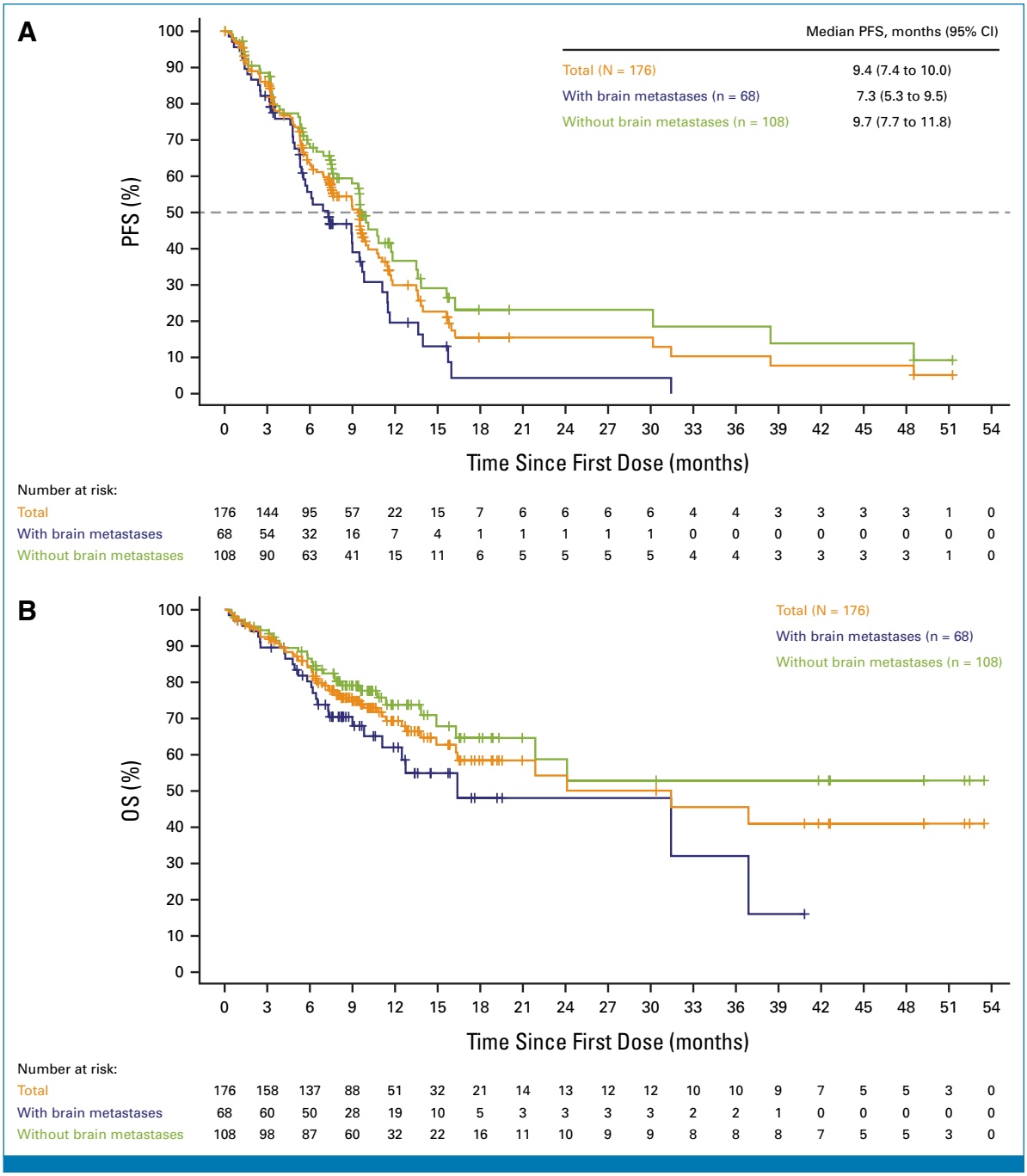

FIG A3. (A) Median PFS per independent central review and (B) OS in patients with brain metastases. OS, overall survival; PFS, progression-free survival.

TABLE A1. BOR per Investigator Assessment

Outcome	Primary Efficacy Population (n = 176)	Platinum-Based Chemotherapy Without ex20ins-Targeted Therapy (n = 125)	Prior Amivantamab (n = 51)	Prior Amivantamab Without Other ex20ins-Targeted Therapy (n = 30)	Prior Amivantamab and Other ex20ins-Targeted Therapy (n = 21)	Patients With Brain Metastases (n = 68)
Confirmed BOR, No. (%)[a]						
CR	2 (1.1)	1 (0.8)	1 (2.0)	1 (3.3)	0	1 (1.5)
PR	65 (36.9)	50 (40.0)	15 (29.4)	11 (36.7)	4 (19.0)	24 (35.3)
Unconfirmed PR[b]	5 (2.8)	3 (2.4)	2 (3.9)	2 (6.7)	0	2 (2.9)
SD	88 (50.0)	60 (48.0)	28 (54.9)	14 (46.7)	14 (66.7)	32 (47.1)
PD	7 (4.0)	5 (4.0)	2 (3.9)	0	2 (9.5)	5 (7.4)
Not evaluable	1 (0.6)	0	1 (2.0)	1 (3.3)	0	1 (1.5)
Not applicable	8 (4.5)	6 (4.8)	2 (3.9)	1 (3.3)	1 (4.8)	3 (4.4)
Confirmed ORR, No. (%) (95% CI)[c]	67 (38.1) (30.9 to 45.7)	51 (40.8) (32.1 to 49.9)	16 (31.4) (19.1 to 45.9)	12 (40.0) (22.7 to 59.4)	4 (19.0) (5.4 to 41.9)	25 (36.8) (25.4 to 49.3)
DCR, No. (%) (95% CI)[d]	160 (90.9) (85.7 to 94.7)	114 (91.2) (84.8 to 95.5)	46 (90.2) (78.6 to 96.7)	28 (93.3) (77.9 to 99.2)	18 (85.7) (63.7 to 97.0)	59 (86.8) (76.4 to 93.8)
CBR, No. (%) (95% CI)[e]	118 (67.0) (59.6 to 73.9)	90 (72.0) (63.3 to 79.7)	28 (54.9) (40.3 to 68.9)	17 (56.7) (37.4 to 74.5)	11 (52.4) (29.8 to 74.3)	40 (58.8) (46.2 to 70.6)
Time to response, days, median (range)	42 (31-862)	41 (31-862)	42 (36-169)	42 (36-169)	133 (39-168)	41 (34-169)
DOR, months, median (95% CI)	9.9 (8.3 to 29.0)	10.4 (8.3 to 29.0)	8.3 (4.2 to NE)	9.5 (4.2 to NE)	6.2 (3.0 to NE)	6.1 (4.2 to NE)

Abbreviations: BOR, best overall response; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DOR, duration of response; ex20ins, exon 20 insertions; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Response confirmed ≥4 weeks after response first noted.

[b]Patient had PR only at the last tumor assessment visit.

[c]Proportion of patients with confirmed CR or PR.

[d]Proportion of patients with CR, PR, or SD.

[e]Proportion of patients with CR, PR, or with SD lasting ≥24 weeks.

TABLE A2. Summary of Patients with Pneumonitis and Prior Treatment

Characteristic	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Patients, No.	3	3	5	0	1	12
Number of prior lines of therapy, range	1-2	1-2	1-2	—	6	1-6
Prior treatment, No.						
Platinum-based chemotherapy only	1	2	1	—	—	4
Immunotherapy + platinum-based chemotherapy	2	—	2	—	—	4
Amivantamab + platinum-based chemotherapy	—	1	2	—	—	3
Mobocertinib + amivantamab + immunotherapy + platinum-based chemotherapy	—	—	—	—	1	1

TABLE A3. Grade ≥3 TRAEs Reported in ≥Two Patients

Grade ≥3 TRAE	Total (N = 244), No. (%)
Anemia	17 (7.0)
Pneumonitis	6 (2.5)
Rash	6 (2.5)
ALT increased	5 (2.0)
Diarrhea	5 (2.0)
Platelet count decreased	5 (2.0)
Neutrophil count decreased	4 (1.6)
Stomatitis	4 (1.6)
Amylase increased	3 (1.2)
Hypoxia	3 (1.2)
Lymphocyte count decreased	3 (1.2)
Rash maculo-papular	3 (1.2)
AST increased	2 (0.8)
Decreased appetite	2 (0.8)
Hypersensitivity	2 (0.8)
Hypertension	2 (0.8)
Nausea	2 (0.8)
Neutropenia	2 (0.8)
Thrombocytopenia	2 (0.8)

Abbreviation: TRAE, treatment-related adverse event.