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Efficacy of zipalertinib in NSCLC patients with EGFR exon 20 insertion mutations who received prior platinum-based chemotherapy with or without amivantamab

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Disclosure

- **Consulting or Advisory Role:** AbbVie, Amgen, AstraZeneca, Bayer, Black Diamond Therapeutics, BMS, Daiichi Sankyo, Pfizer, Orion, Janssen, Merck, Taiho, Takeda
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Key Takeaways

1. Zipalertinib demonstrated clinically meaningful efficacy in patients with EGFR ex20ins-mutant NSCLC who received prior platinum-based chemotherapy, including those who also received prior amivantamab

2. Zipalertinib demonstrated a manageable safety profile in this patient population, consistent with previously reported data

3. These findings support zipalertinib as a potential treatment option for patients with EGFR ex20ins-mutant NSCLC after progression on platinum-based chemotherapy, including in the post-amivantamab setting, a significant and growing unmet need

EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertions; NSCLC, non-small cell lung cancer.

Background

Unmet need

Despite the approval of amivantamab for EGFR ex20ins-mutant NSCLC,[1] an unmet need remains for well-tolerated oral targeted therapies with durable clinical benefit

Zipalertinib: a novel EGFR TKI

Zipalertinib (CLN-081, TAS6417) is a novel EGFR TKI that showed promising clinical activity and manageable safety in a phase 1/2a study in patients with EGFR ex20ins-mutant NSCLC that progressed on platinum-based chemotherapy[2]

Here we report the primary data from the pivotal phase 2b REZILIENT1 study of zipalertinib in patients with advanced or metastatic EGFR ex20ins-mutant NSCLC who progressed after platinum-based chemotherapy with or without prior amivantamab

EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertions; NSCLC, non-small cell lung cancer, TKI, tyrosine kinase inhibitor.

1. Rybrevant (amivantamab-vmjw) injection, for intravenous use. Highlights of prescribing information. Horsham, PA: Janssen Biotech, 2024. **2.** Piotrowska Z, et al. *J Clin Oncol.* 2023;41(26):4218-4225.

REZILIENT1 Phase 2b study design

- REZILIENT1 is a phase 1/2, open-label, multicenter trial (NCT04036682)

Key eligibility criteria
- Age ≥18 years
- Locally advanced or metastatic NSCLC
- Documented EGFR exon 20 insertion
- ECOG PS 0 or 1
- Stable/asymptomatic CNS metastases allowed

Zipalertinib
100 mg PO BID

Prior platinum-based chemotherapy without prior ex20ins-targeted therapy

Prior platinum-based chemotherapy with prior amivantamab ± other ex20ins-targeted therapy

Primary endpoint:
- **ORR and DOR as assessed by blinded ICR per RECIST v1.1**

Secondary endpoints:
- ORR and DOR by investigator
- DCR
- CBR
- PFS by ICR and investigator
- OS
- Antitumor activity in patients with CNS disease
- Safety

- Safety analysis population: all patients who received ≥1 dose of zipalertinib 100 mg BID (N=244)
- Primary efficacy population: all patients who received ≥1 dose of zipalertinib 100 mg BID with ~8 months of minimum follow-up before data cutoff (December 10, 2024) (N=176)
- Patients were assigned to a cohort based on previous therapy (ie, platinum-based chemotherapy only or amivantamab)

BID, twice daily; CBR, clinical benefit rate; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertions; ICR, independent central review; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors.

Baseline demographic and disease characteristics

Characteristic	Platinum-based chemotherapy without ex20ins-targeted therapy (n=143)	Prior ex20ins-targeted therapy (n=101)	Safety population (N=244)
Age, y, median (range)	66 (36–86)	62 (31–85)	65 (31–86)
Aged <65 y / ≥65 y, No. (%)	61 (43) / 82 (57)	60 (59) / 41 (41)	121 (50) / 123 (50)
Female, No. (%)	87 (61)	70 (69)	157 (64)
Race, No. (%)[a]			
White	51 (36)	47 (47)	98 (40)
Black or African American	5 (4)	7 (7)	12 (5)
Asian	77 (54)	45 (45)	122 (50)
Disease stage III / IV, No. (%)	7 (5) / 136 (95)	2 (2) / 99 (98)	9 (4) / 235 (96)
Cell type, No. (%)[b]			
Adenocarcinoma	140 (98)	96 (95)	236 (97)
Squamous cell carcinoma	1 (1)	1 (1)	2 (1)
Large cell carcinoma	0	1 (1)	1 (1)
ECOG PS 0 / 1, No. (%)	45 (32) / 98 (69)	33 (33) / 68 (67)	78 (32) / 166 (68)
Smoking history, No. (%)[c]			
Former	55 (39)	32 (32)	87 (36)
Current	1 (1)	3 (3)	4 (2)
None	86 (60)	66 (65)	152 (62)
CNS/brain metastases, No. (%)	48 (34)	55 (55)	103 (42)

[a]Race was reported as other in 1 patient each in the platinum-based chemotherapy without ex20ins-targeted therapy and prior ex20ins-targeted therapy groups; race was not reported in 9 patients and 1 patient in the platinum-based chemotherapy without ex20ins-targeted therapy and prior ex20ins-targeted therapy groups, respectively. [b]Cell type was other (NSCLC or adenocarcinoma with squamous features) in 2 patients and 3 patients in the platinum-based chemotherapy without ex20ins-targeted therapy and prior ex20ins-targeted therapy groups, respectively. [c]Smoking history was unknown in 1 patient and no patients in the platinum-based chemotherapy without ex20ins-targeted therapy and prior ex20ins-targeted therapy groups, respectively.
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ex20ins, exon 20 insertions; NSCLC, non-small cell lung cancer.

Prior therapies

Characteristic	Platinum-based chemotherapy without ex20ins-targeted therapy (n=143)	Prior ex20ins-targeted therapy (n=101)	Safety population (N=244)
Median number of prior systemic regimens, No. (range)	1 (0–6)	2 (1–7)	2 (0–7)
Prior chemotherapy, No. (%)	132 (92)	96 (95)	228 (93)
Prior anti–PD-(L)1, No. (%)	67 (47)	46 (46)	113 (46)
Prior targeted therapy, No. (%)	37 (26)	101 (100)	138 (57)
Amivantamab	0	84 (83)	84 (34)
Mobocertinib	0	40 (40)	40 (16)
Bevacizumab	14 (10)	16 (16)	30 (12)
Osimertinib	13 (9)	7 (7)	20 (8)
BLU-451	0	5 (5)	5 (2)
Cetuximab	4 (3)	0	4 (2)
Poziotinib	0	3 (3)	3 (1)
Sunvozertinib	0	3 (3)	3 (1)
Other[a]	17 (12)	9 (9)	26 (11)
Prior brain radiation, No. (%)	18 (13)	15 (15)	33 (14)
Brain metastasis untreated, No. (%)	30 (21)	40 (40)	70 (29)

[a]Includes first/second generation EGFR tyrosine kinase inhibitors, ALK inhibitors, CDK4/6 inhibitors, NTRK/ROS1 inhibitors, angiokinase inhibitors.
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertions; PD-(L)1, programmed death-(ligand) 1.

Efficacy per ICR in all patients and subgroups

Median follow-up: 9.3 months

Outcome	Primary efficacy population (N=176)	Platinum-based chemotherapy without ex20ins-targeted therapy (n=125)	Prior amivantamab ± other ex20ins-target therapy (n=51)[a]
BOR, No. (%)[b]			
CR	1 (1)	0	1 (2)
PR	61 (35)	50 (40)	11 (22)
Unconfirmed PR[c]	7 (4)	6 (5)	1 (2)
SD	88 (50)	55 (44)	33 (65)
PD	11 (6)	8 (6)	3 (6)
Not evaluable[d]	8 (5)	6 (5)	0
Confirmed ORR, No. (%) [95% CI][e]	62 (35) [28–43]	50 (40) [31–49]	12 (24) [13–38]
DCR, No. (%) [95% CI][f]	157 (89) [84–93]	111 (89) [82–94]	46 (90) [79–97]
CBR, No. (%) [95% CI][g]	113 (64) [57–71]	85 (68) [59–76]	28 (55) [40–69]
Median time to response, days (range)	44 (31–295)	44 (39–232)	44 (39–232)
Median DOR, months (95% CI)	8.8 (8.3–12.7)	8.8 (8.3–12.7)	8.5 (4.2–14.8)

Patients were evaluable for response if they had received at least one dose of zipalertinib and had at least one post-dose tumor assessment or had discontinued prior to the first efficacy assessment due to clinical disease progression or toxicity. [a]Including 30 patients who received prior amivantamab without and 21 patients with other ex20ins-targeted therapy. [b]Response confirmed ≥4 weeks after response first noted. [c]Patients had PR but confirmatory scan had not yet been performed. [d]No post-baseline imaging. [e]Proportion of patients with confirmed CR or PR. [f]Proportion of patients with CR, PR, or SD. [g]Proportion of patients with CR, PR, or with SD lasting ≥24 weeks.
BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; ex20ins, exon 20 insertions; ICR, independent central review; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Efficacy per ICR in patients with prior amivantamab ± other ex20ins-target therapy

Outcome	Prior amivantamab without other ex20ins-targeted therapy (n=30)	Prior amivantamab and other ex20ins-targeted therapy (n=21)	Total (n=51)
BOR, No. (%)[a]			
CR	1 (3)	0	1 (2)
PR	8 (27)	3 (14)	11 (22)
Unconfirmed PR[b]	1 (3)	0	1 (2)
SD	19 (63)	14 (67)	33 (65)
PD	0	3 (14)	3 (6)
Confirmed ORR, No. (%) [95% CI][c]	9 (30) [15–49]	3 (14) [3–36]	12 (24) [13–38]
DCR, No. (%) [95% CI][d]	29 (97) [83–100]	17 (81) [58–95]	46 (90) [79–97]
CBR, No. (%) [95% CI][e]	18 (60) [41–77]	10 (48) [26–70]	28 (55) [40–69]
Median time to response, days (range)	43 (39–232)	98 (40–103)	44 (39–232)
Median DOR, months (95% CI)	14.7 (4.2–NE)	4.2 (3.9–NE)	8.5 (4.2–14.8)

Patients were evaluable for response if they had received at least one dose of zipalertinib and had at least one post-dose tumor assessment or had discontinued prior to the first efficacy assessment due to clinical disease progression or toxicity. [a]Response confirmed ≥4 weeks after response first noted. [b]Patients had PR but confirmatory scan had not yet been performed. [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.
BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; 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; PD, progressive disease; PR, partial response; SD, stable disease.

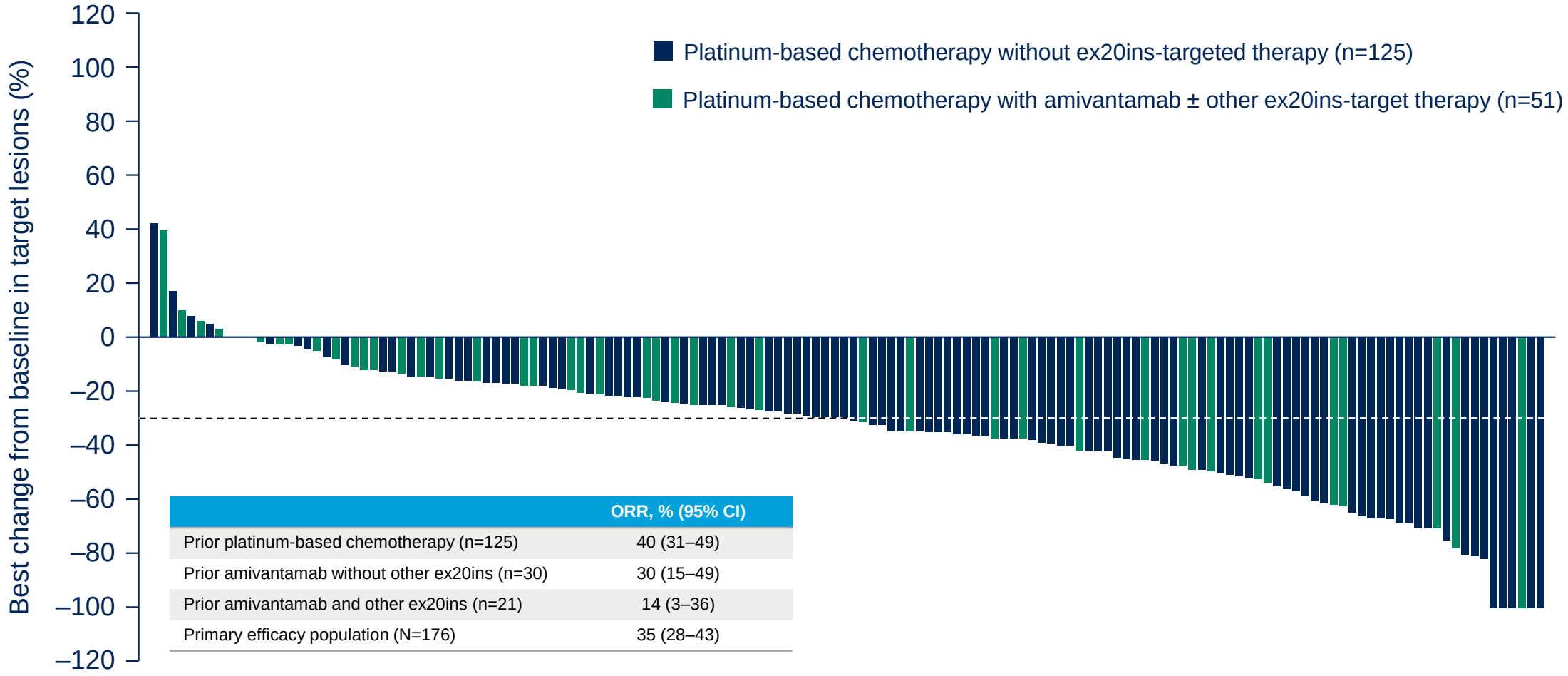
Efficacy per ICR in all patients and those with brain metastases

Outcome	Primary efficacy population (N=176)	Patients with brain metastases[a] (n=68)
BOR, No. (%)[b]		
CR	1 (1)	1 (2)
PR	61 (35)	20 (29)
Unconfirmed PR[c]	7 (4)	2 (3)
SD	88 (50)	37 (54)
PD	11 (6)	5 (7)
Not evaluable[d]	8 (5)	3 (4)
Confirmed ORR, No. (%) [95% CI][e]	62 (35) [28–43]	21 (31) [20–43]
DCR, No. (%) [95% CI][f]	157 (89) [84–93]	60 (88) [78–95]
CBR, No. (%) [95% CI][g]	113 (64) [57–71]	38 (56) [43–68]
Median time to response, days (range)	44 (31–295)	98 (35–232)
Median DOR, months (95% CI)	8.8 (8.3–12.7)	8.3 (4.2–9.9)

Patients were evaluable for response if they had received at least one dose of zipalertinib and had at least one post-dose tumor assessment or had discontinued prior to the first efficacy assessment due to clinical disease progression or toxicity. [a]Patients with brain metastases included 44 patients with prior platinum-based chemotherapy without ex20ins-targeted therapy and 24 who received prior amivantamab with (9 patients) or without (15 patients) other ex20ins-targeted therapy. [b]Response confirmed ≥4 weeks after response first noted. [c]Patients had PR but confirmatory scan had not yet been performed. [d]No post-baseline imaging. [e]Proportion of patients with confirmed CR or PR. [f]Proportion of patients with CR, PR, or SD. [g]Proportion of patients with CR, PR, or with SD lasting ≥24 weeks.

BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; ex20ins, exon 20 insertions; ICR, independent central review; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

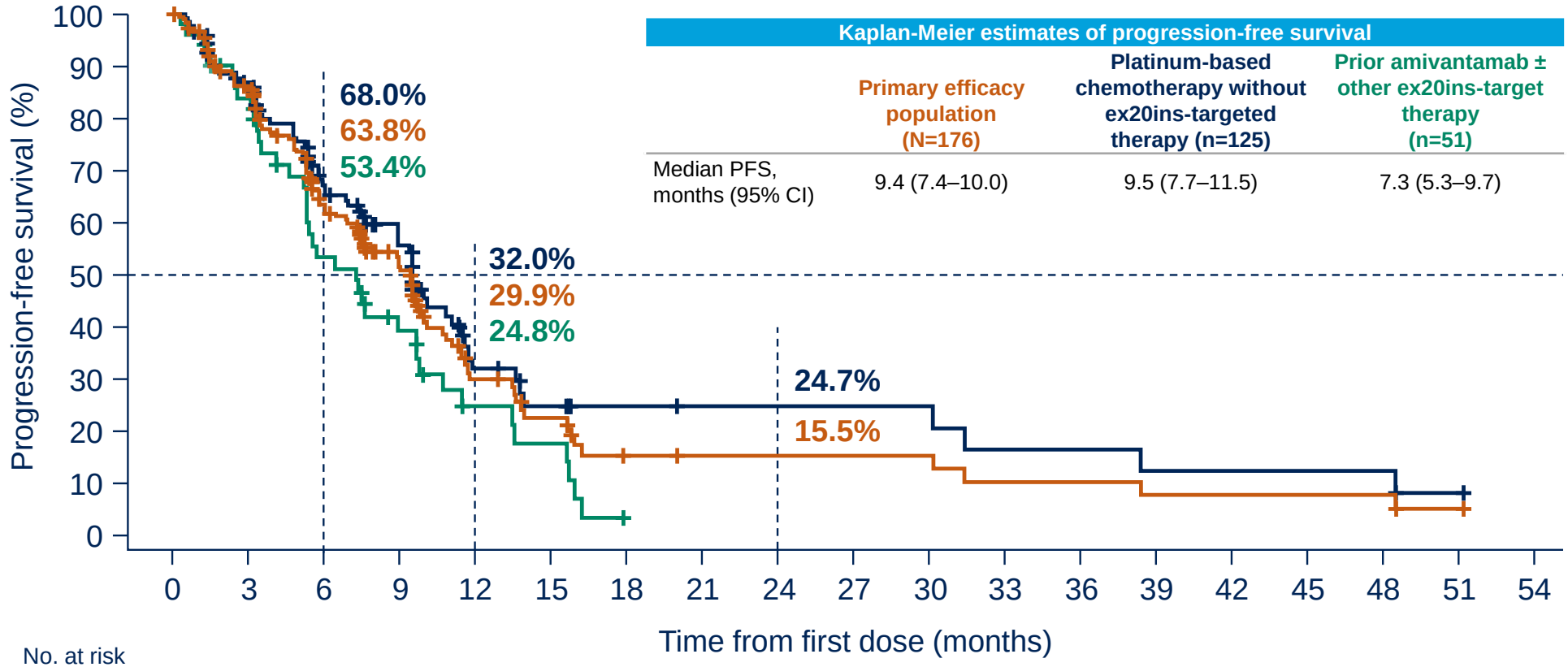
Best change from baseline in target lesions



	ORR, % (95% CI)
Prior platinum-based chemotherapy (n=125)	40 (31–49)
Prior amivantamab without other ex20ins (n=30)	30 (15–49)
Prior amivantamab and other ex20ins (n=21)	14 (3–36)
Primary efficacy population (N=176)	35 (28–43)

CI, confidence interval; ex20ins, exon 20 insertions; ORR, objective response rate.

Progression-free survival per ICR



Kaplan-Meier estimates of progression-free survival

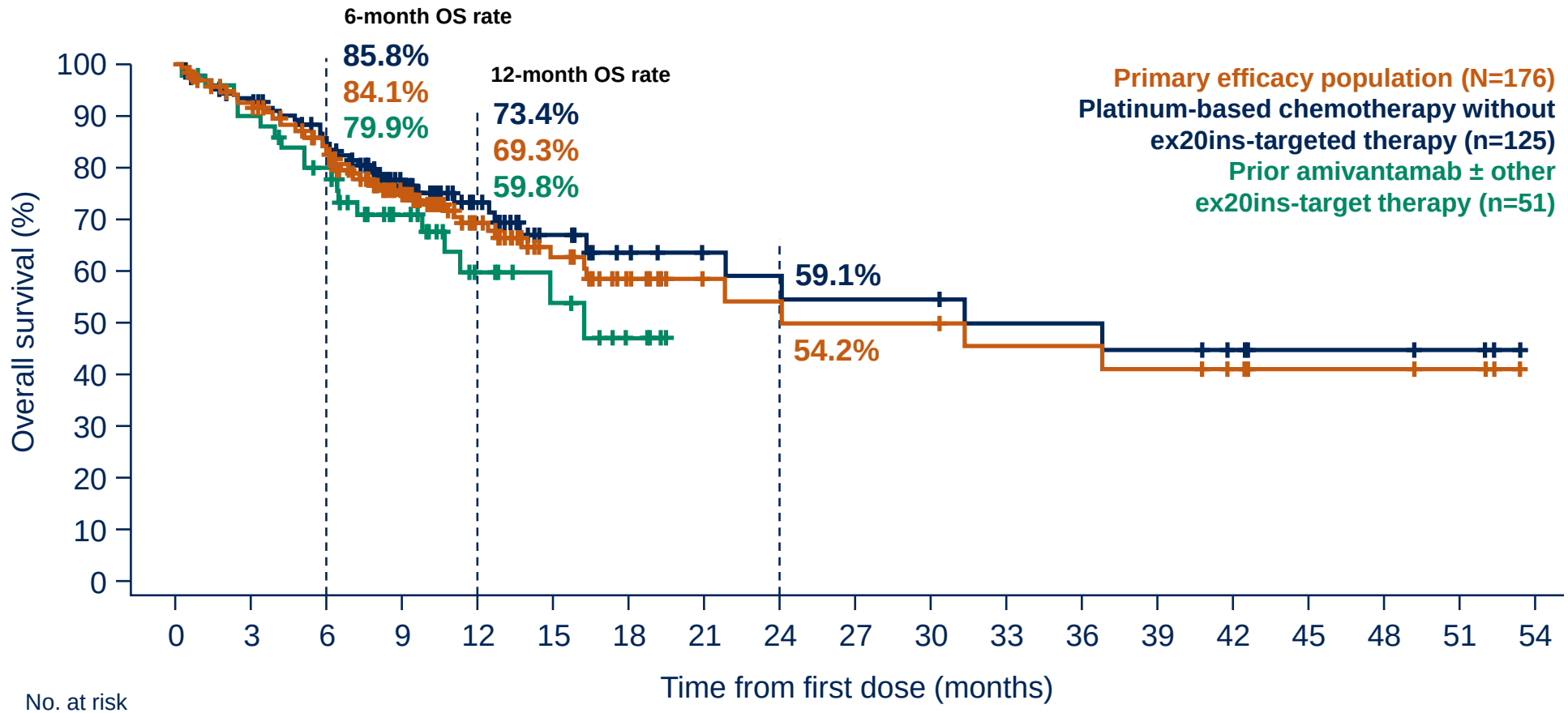
	Primary efficacy population (N=176)	Platinum-based chemotherapy without ex20ins-targeted therapy (n=125)	Prior amivantamab ± other ex20ins-target therapy (n=51)
Median PFS, months (95% CI)	9.4 (7.4–10.0)	9.5 (7.7–11.5)	7.3 (5.3–9.7)

No. at risk

Total	176	144	95	57	22	15	7	6	6	6	6	4	4	3	3	3	3	1	0
Platinum-based chemotherapy only	125	103	71	42	15	10	7	6	6	6	6	4	4	3	3	3	3	1	0
Prior amivantamab ± other ex20ins	51	41	24	15	7	5	0	0	0	0	0	0	0	0	0	0	0	0	0

Progression-free survival was defined as the time between the day of the first dose of zipalertinib and the first documentation of progressive disease or death, whichever occurred earlier.
CI, confidence interval; ex20ins, exon 20 insertions; ICR, independent central review; PFS, progression-free survival.

Overall survival



No. at risk																			
Total	176	158	137	88	51	32	21	14	13	12	12	10	10	9	7	5	5	3	0
Platinum-based chemotherapy only	125	113	99	64	38	23	17	14	13	12	12	10	10	9	7	5	5	3	0
Prior amivantamab ± other ex20ins	51	15	38	24	13	9	4	0	0	0	0	0	0	0	0	0	0	0	0

Overall survival was defined as the time between the day of the first dose of zipalertinib and the date of death due to any cause.
ex20ins, exon 20 insertion; OS, overall survival.

Summary of adverse events

AE, No. (%)	Safety population (N=244)
TEAEs	
Any TEAE	242 (99.2)
Grade ≥3 TEAE	137 (56.1)
TRAEs	
Any TRAE	223 (91.4)
Grade ≥3 TRAE	72 (29.5)
TRAE leading to treatment modification	
Dose reduction	35 (14.3)
Dose interruption	96 (39.3)
Treatment discontinuation[a]	20 (8.2)
TRAE leading to death	2 (0.8)

- Median duration of treatment exposure was 6.4 months (range, 0.03–51.8)
- Median relative dose intensity was 94.1%
- TRAEs leading to treatment discontinuation was 8%
- TRAEs that led to death were pneumonitis and hypoxia
  - Pneumonitis: 6 prior lines of treatment, including platinum-based chemotherapy, immunotherapy, amivantamab, mobocertinib, and medical history of thromboembolism and COVID-19
  - Hypoxia: 4 prior lines of treatment, including platinum-based chemotherapy, osimertinib, amivantamab, and lazertinib, and a medical history of thromboembolism and COVID-19

[a]TRAEs leading to treatment discontinuation included pneumonitis (9 patients), and anemia, asthenia, erythema multiforme, fatigue, interstitial lung disease, myocarditis, neutrophil/platelet count decreased, paronychia, pneumonia, rash, and Stevens-Johnson syndrome (1 patient each).
AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Most common treatment-related adverse events

Any-grade TRAEs reported in ≥10% of patients, No. (%)	Any grade	Grade 3
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

- Anemia was the most common grade 3 TRAE
- Other grade ≥3 TRAEs reported in ≥5 patients included pneumonitis and rash (6 patients [2.5%] each), and alanine aminotransferase increased, diarrhea, and platelet count decreased (5 patients [2.0%] each)
- Twelve patients (4.9%) had treatment-related pneumonitis, 5 of whom had received prior immunotherapy
  - Grade 1, n=3; grade 2, n=3; grade 3, n=5; grade 5, n=1

TRAE, treatment-related adverse event.

Conclusions

Efficacy

Zipalertinib demonstrated clinically meaningful efficacy in patients with EGFR ex20ins-mutant NSCLC who received prior platinum-based chemotherapy, including those who also received prior amivantamab

Safety

Zipalertinib demonstrated a manageable safety profile in this patient population, consistent with previously reported data[1]

Summary

These findings support zipalertinib as a potential treatment option for patients with EGFR ex20ins-mutant NSCLC that progressed on platinum-based chemotherapy, including in the post-amivantamab setting, a significant and growing unmet need

REZILIENT3, a confirmatory phase 3 study in 1L patients, is ongoing

1. Piotrowska Z, et al. *J Clin Oncol.* 2023;41(26):4218-4225.
EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertions; NSCLC, non-small cell lung cancer.

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The study has been simultaneously published in JCO with this presentation.

"Zipalertinib in Patients With EGFR Exon 20 Insertion-Positive NSCLC Previously Treated With Platinum-Based Chemotherapy With or Without Amivantamab"

Original Reports | Thoracic Oncology

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] Insertions in exon 20 of the *EGFR* gene (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]

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]