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# Zipalertinib in NSCLC Patients With *EGFR* Exon 20 Insertion Mutations Who Received Prior Amivantamab

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# REZILIENT1 Phase 2b Module C: Study Design

- Zipalertinib, a novel, irreversible, and selective EGFR ex20ins TKI, has been granted Breakthrough Therapy Designation by the US FDA after demonstrating promising antitumor efficacy and a favorable safety profile in a Phase 1/2a study (NCT04036682)[1]
- Module C of this Phase 2b study investigates the efficacy and safety of zipalertinib in patients who progressed on or after amivantamab, an emerging unmet medical need

**Key eligibility criteria**

- Locally advanced or metastatic NSCLC
- Documented *EGFR* ex20ins
- ***Progressed on or after amivantamab***
- ECOG PS 0 or 1
- Stable/asymptomatic brain metastases allowed

→

**Zipalertinib**
100 mg BID oral[a]

**Primary endpoint:**

- ORR and DOR per RECIST v1.1

**Secondary endpoints:**

- Safety
- PFS
- DCR

- At data cutoff on June 13, 2025, 84 patients were enrolled
- All patients had ≥9 months of follow-up

[a]Zipalertinib may be taken with or without food.
BID, twice daily; 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; FDA, Food and Drug Administration; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; US, United States.
1. Piotrowska Z, et al. J Clin Oncol. 2023;41:4218-4225.

# Demographic and Baseline Disease Characteristics

| Characteristics, n (%) | Amivantamab only[a] (n=54) | Amivantamab + other ex20ins-targeted therapy[b] (n=30) | Total (N=84) |
|---|---|---|---|
| Median age, y (range) | 62 (31–85) | 64 (33–78) | 62 (31–85) |
| Female | 37 (68.5) | 22 (73.3) | 59 (70.2) |
| Race | | | |
| Asian | 24 (44.4) | 14 (46.7) | 38 (45.2) |
| White | 24 (44.4) | 13 (43.3) | 37 (44.0) |
| ECOG PS 1 | 34 (63.0) | 22 (73.3) | 56 (66.7) |
| Median prior systemic regimens, n (range) | 2 (1–6) | 4 (2–7) | 3 (1–7) |
| Prior chemotherapy | 50 (92.6) | 30 (100) | 80 (95.2) |
| Prior anti–PD-1/L1 | 22 (40.7) | 16 (53.3) | 38 (45.2) |
| Prior amivantamab | 54 (100) | 30 (100) | 84 (100) |
| Prior other ex20ins-targeted therapy[b] | 0 | 30 (100) | 30 (36) |
| **History of brain metastases** | **31 (57.4)** | **15 (50.0)** | **46 (54.8)** |

[a]Amivantamab only: patients had previous amivantamab without or without chemotherapy, but no other ex20ins-targeted therapy.
[b]Other ex20ins-targeted therapy: mobocertinib (n=23); BLU-451 (n=5); sunvozertinib (n=2); poziotinib (n=3).
ECOG PS, Eastern Cooperative Oncology Group performance status; ex20ins, exon 20 insertions; PD-1/L1, programmed cell death protein 1/ligand 1.

# Efficacy per BICR

| Outcome, n (%) [95% CI] | Prior amivantamab only (n=54) | Prior amivantamab + other ex20ins-targeted therapy (n=30) | Total (N=84) |
|---|---|---|---|
| Confirmed best overall response | | | |
| CR | 0 | 0 | 0 |
| PR | 17 (31.5) [19.5–45.6] | 6 (20.0) [7.7–38.6] | 23 (27.4) [18.2–38.2] |
| Unconfirmed PR | 2 (3.7) [0.5–12.7] | 1 (3.3) [0.1–17.2] | 3 (3.6) [0.7–10.1] |
| SD | 28 (51.9) [37.8–65.7] | 17 (56.7) [37.4–74.5] | 45 (53.6) [42.4–64.5] |
| PD | 1 (1.9) [0.0–9.9] | 3 (10.0) [2.1–26.5] | 4 (4.8) [1.3–11.7] |
| NA | 6 (11.1) [4.2–22.6] | 3 (10.0) [2.1–26.5] | 9 (10.7) [5.0–19.4] |
| **Confirmed ORR (CR+PR)** | **17 (31.5) [19.5–45.6]** | **6 (20.0) [7.7–38.6]** | **23 (27.4) [18.2–38.2]** |
| DCR (CR+PR+SD) | 47 (87.0) [75.1–94.6] | 24 (80.0) [61.4–92.3] | 71 (84.5) [75.0–91.5] |
| CBR (CR+PR+SD ≥24 weeks) | 30 (55.6) [41.4–69.1] | 13 (43.3) [25.5–62.6] | 43 (51.2) [40.0–62.3] |
| Median DOR, months [95% CI] | 9.5 [6.2–NE] | 8.3 [3.9–NE] | 8.5 [6.2–14.8] |
| **Median PFS, months [95% CI]** | **7.4 [5.4–9.7]** | **5.2 [3.4–11.5]** | **6.5 [5.4–8.9]** |

In patients with brain metastases who received prior amivantamab only, the confirmed ORR was 29.0% (95% CI: 14.2%–48.0%)

BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DOR, duration of response; ex20ins, exon 20 insertion; NA, not available; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

# Most Common Treatment-Emergent Adverse Events

| TEAE (all grade) ≥10%, n (%) | Module C Amivantamab only (N=54) | Module C Amivantamab + other ex20ins-targeted therapy (N=30) | Module C Amivantamab overall (N=84) | |
|---|---|---|---|---|
| | | | All Grade | Grade ≥3 |
| ***Preferred Term*** | | | | |
| Paronychia | 22 (40.7) | 13 (43.3) | 35 (41.7) | 0 |
| Anemia | 19 (35.2) | 13 (43.3) | 32 (38.1) | 13 (15.5) |
| Rash | 20 (37.0) | 9 (30.0) | 29 (34.5) | 3 (3.6) |
| Nausea | 13 (24.1) | 11 (36.7) | 24 (28.6) | 1 (1.2) |
| Diarrhea | 11 (20.4) | 8 (26.7) | 19 (22.6) | 2 (2.4) |
| Dry skin | 13 (24.1) | 5 (16.7) | 18 (21.4) | 0 |
| Dermatitis acneiform | 11 (20.4) | 7 (23.3) | 18 (21.4) | 1 (1.2) |
| Dyspnea | 12 (22.2) | 5 (16.7) | 17 (20.2) | 5 (6.0) |
| Constipation | 8 (14.8) | 7 (23.3) | 15 (17.9) | 0 |
| Pruritus | 11 (20.4) | 4 (13.3) | 15 (17.9) | 0 |
| Cough | 11 (20.4) | 2 (6.7) | 13 (15.5) | 1 (1.2) |
| Vomiting | 7 (13.0) | 6 (20.0) | 13 (15.5) | 1 (1.2) |
| Stomatitis | 6 (11.1) | 6 (20.0) | 12 (14.3) | 2 (2.4) |
| Fatigue | 7 (13.0) | 4 (13.3) | 11 (13.1) | 0 |
| Pneumonia | 4 (7.4) | 7 (23.3) | 11 (13.1) | 9 (10.7) |
| Rash maculopapular | 6 (11.1) | 4 (13.3) | 10 (11.9) | 1 (1.2) |

TEAE, treatment-emergent adverse event.

# Conclusion

- Zipalertinib demonstrated promising efficacy in patients who progressed on or after prior chemotherapy and amivantamab without other EGFR ex20ins therapy:
  - ORR: 31.5%
  - DOR: 9.5 months
- Zipalertinib was well tolerated and demonstrated a manageable safety profile in patients who progressed on prior chemotherapy and amivantamab with or without other ex20ins-targeted therapy. No new safety signals have been identified

# Thank You

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