

Central Nervous System (CNS) Activity of Ziplertinib in Non-Small Cell Lung Cancer (NSCLC) Patients With Uncommon *EGFR* Mutations (*EGFR*mt)

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Introduction

- CNS metastases in patients with NSCLC harboring *EGFR* mutations are associated with poor prognosis¹
- There are limited treatment options for patients with NSCLC harboring *EGFR* ex20ins mutations with CNS metastases²
- Ziplertinib is an oral, highly selective, irreversible *EGFR* tyrosine kinase inhibitor (TKI) that has demonstrated clinical activity against advanced/metastatic NSCLC harboring *EGFR* ex20ins mutations in a phase 1/2 trial, including in patients with CNS metastases³⁻⁵
- Ziplertinib also demonstrated clinical activity in patients with locally advanced/metastatic NSCLC harboring other uncommon mutations, including L861Q, G719X, S768I, and compound mutations⁶
- Here we report follow-up results from Cohort C of the ongoing phase 2b REZILIENT2 trial (NCT05967689), focusing on patients with NSCLC harboring *EGFR* ex20ins or other uncommon mutations (including L861Q, G719X, S768I) and compound mutations, who have active newly diagnosed and/or progressing brain metastases and/or leptomeningeal disease (LMD)

Methods: Study Design

REZILIENT2 is a multicohort open-label, phase 2 trial (NCT05967689; EUDRA CT 2023-503865-48)

Eligibility

- Age ≥18 years with locally advanced/metastatic NSCLC
- Documented **ex20ins or other uncommon single or compound non-ex20ins *EGFR* mutations^a**
- Measurable disease per **RECIST v1.1** and CNS metastases by **RANO-BM**
- Active brain metastases:** newly diagnosed and/or progressing brain lesions (without CNS targeted therapy) and/or LMD
- ECOG PS 0 or 1
- Any prior line of therapy for advanced/metastatic disease

Endpoints (investigator assessed)

Primary:

- ORR per RECIST v1.1

Secondary:

- Intracranial ORR, intracranial DOR, and intracranial DCR per RANO-BM
- Safety

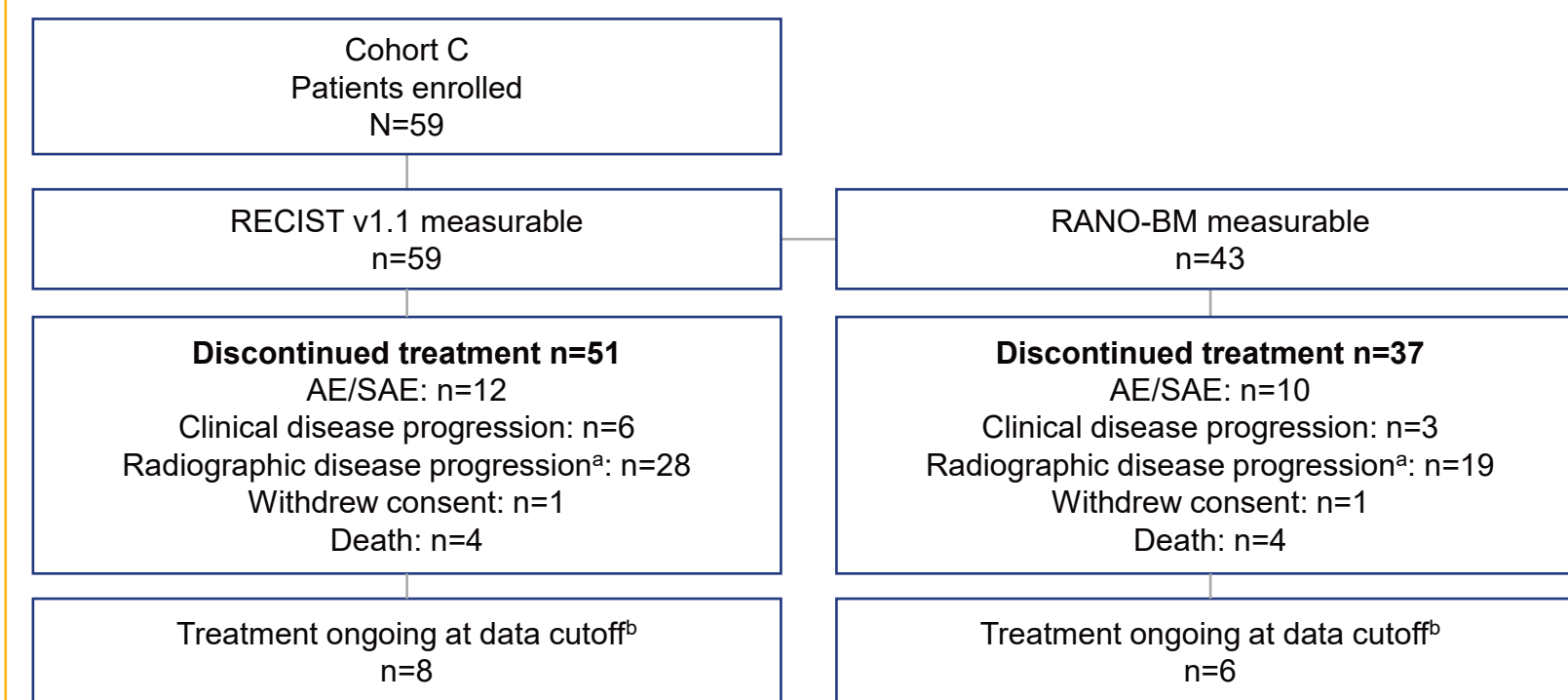
^aDetermined by local testing performed at a CLIA certified (US) or locally certified laboratory (outside the US). CNS, central nervous system; DCR, disease control rate (complete response + partial response + stable disease); DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; ex20ins, exon 20 insertion; LMD, leptomeningeal disease; NSCLC, non-small cell lung cancer; ORR, objective response rate (complete response + partial response); RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors.

- Data cutoff: June 27, 2026; study is ongoing
- Patients received ziplertinib at a starting dose of 100 mg orally twice daily until progressive disease or other withdrawal criteria
- Median number of cycles received was 7 (range, 1–35)

Results: Patients

- Of 59 enrolled patients, 43 were Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) measurable (**Figure 1**)

Figure 1. Patient disposition



^aDisease progression as per RECIST v1.1; ^bData cutoff: June 27, 2026. AE, adverse event; RANO-BM, Response Assessment in Neuro-oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event.

- Median age of patients was 62 years (range, 23–84) in both groups and the majority had ex20ins mutations (**Table 1**)
- 13/59 patients (22%) had LMD (**Table 1**)
- 27/43 RANO-BM measurable patients (63%) and 41/59 of all enrolled patients (69%) had not received prior CNS radiotherapy (**Table 2**)

Table 1. Patient demographics and disease characteristics

	Cohort C Total (N=59)	RANO-BM Measurable (n=43)
Median age (range), years	62 (23–84)	62 (23–84)
Female, n (%)	34 (58)	24 (56)
Race, n (%)		
White	30 (51)	24 (56)
Asian	21 (36)	13 (30)
Black or African American	1 (2)	1 (2)
Not collected	7 (12)	5 (12)
ECOG performance status 0/1	15 (25)/44 (75)	12 (28)/31 (72)
EGFR exon20 mutations, n (%)	40 (68) ^a	29 (67) ^a
A767_V769dup (ASV)	11 (19)	9 (21)
S768_D770dup (SVD)	4 (7)	3 (7)
N771_H773dup (NPH)	2 (3)	1 (2)
H773dup (H)	3 (5)	3 (7)
Other	22 (37)	15 (35)
Other EGFR mutations, n (%)	20 (34)	15 (35)
G719X	4 (7)	4 (9)
S768I	1 (2)	1 (2)
L861Q	3 (5)	1 (2)
E709X	1 (2)	1 (2)
Compound mutations	9 (15)	7 (16)
Other ^b	2 (3)	1 (2)
Leptomeningeal disease, n (%)	13 (22)	9 (21)

^aOne patient had more than one mutation. ^bOther EGFR mutations were G779F (n=1) and I740_K745dup (n=1). ECOG, Eastern Cooperative Group; EGFR, epidermal growth factor receptor; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases.

Table 2. Prior therapies

	Cohort C Total (N=59)	RANO-BM Measurable (n=43)
Patients with at least 1 prior systemic drug therapy, n (%)	46 (78)	32 (74)
Median number of prior therapies (range) ^a	2 (1–6)	2 (1–6)
Prior systemic therapies, n (%)		
0	13 (22)	11 (26)
1	16 (27)	11 (26)
2	13 (22)	9 (21)
≥3	17 (29)	12 (30)
Median number of prior lines of EGFR-TKI (range) ^b	1 (1–3)	1 (1–2)
Prior lines of EGFR-TKI therapies, n (%)		
0	34 (58)	24 (56)
1	16 (27)	13 (30)
2	8 (14)	6 (14)
≥3	1 (2)	0
Prior amivantamab therapy, n (%)	9 (15)	8 (19)
Prior CNS radiotherapy, n (%)	18 (31)	16 (37)
Time from end of therapy to first ziplertinib dose, range, months	1–62	1–62

^aRANO-BM, n=32; Total, N=46. ^bRANO-BM, n=19; Total, N=25. CNS, central nervous system; EGFR-TKI, epidermal growth factor receptor–targeted tyrosine kinase inhibitor; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases.

Results: Efficacy

At data cut-off

- For RANO-BM measurable patients (n=43), median time on treatment was 4.4 months (range, 0.3–21.4)
- 13/43 patients (ORR 30%; 95% CI: 56, 85) with measurable CNS disease had confirmed responses by RANO-BM criteria (including 2 intracranial complete response [CR]) (**Figures 2 and 3**)
 - Median intracranial duration of response (DOR) was 9.7 months (95% CI: 3.1, not evaluable [NE])
- Of the 13 patients with confirmed intracranial response
 - 10 patients had no prior CNS radiotherapy; the remaining 3 had prior CNS radiotherapy >8 months before the start of ziplertinib treatment
 - 3 patients also had LMD at baseline; median time on treatment was 6.8 months (range, 3.0–12.6)
- For RECIST measurable patients (N=59), median time on treatment was 4.4 months (range, 0.3–27.4)
- 18/59 patients (objective response rate [ORR] 31%; 95% CI: 19, 44) had confirmed systemic responses by RECIST v1.1 (**Figures 2 and 3**)
 - Median DOR was 8.4 months (95% CI: 4.4, 15.6)
- Long-term data show similar intracranial and systemic response rates

Figure 2. Responses

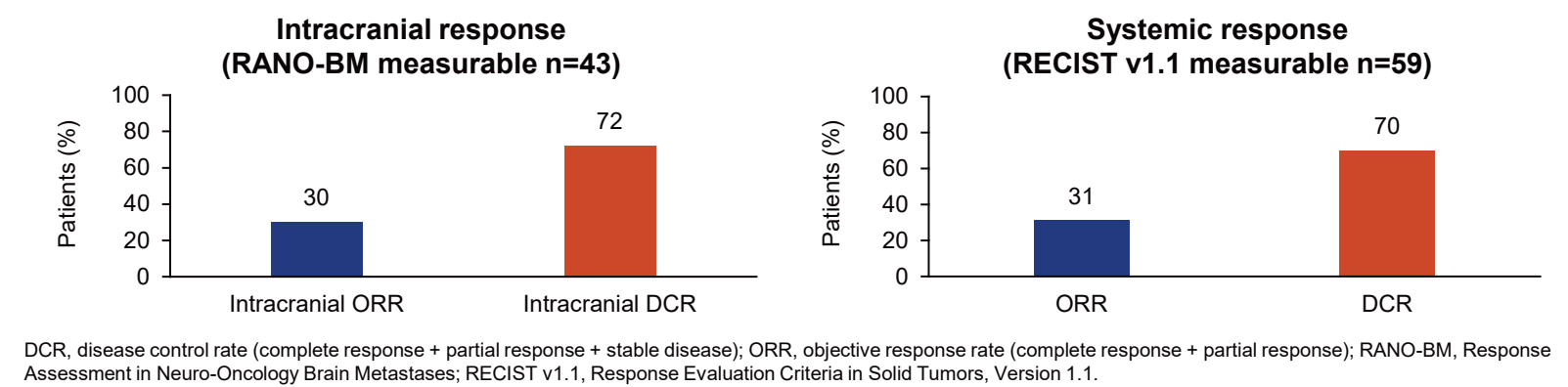
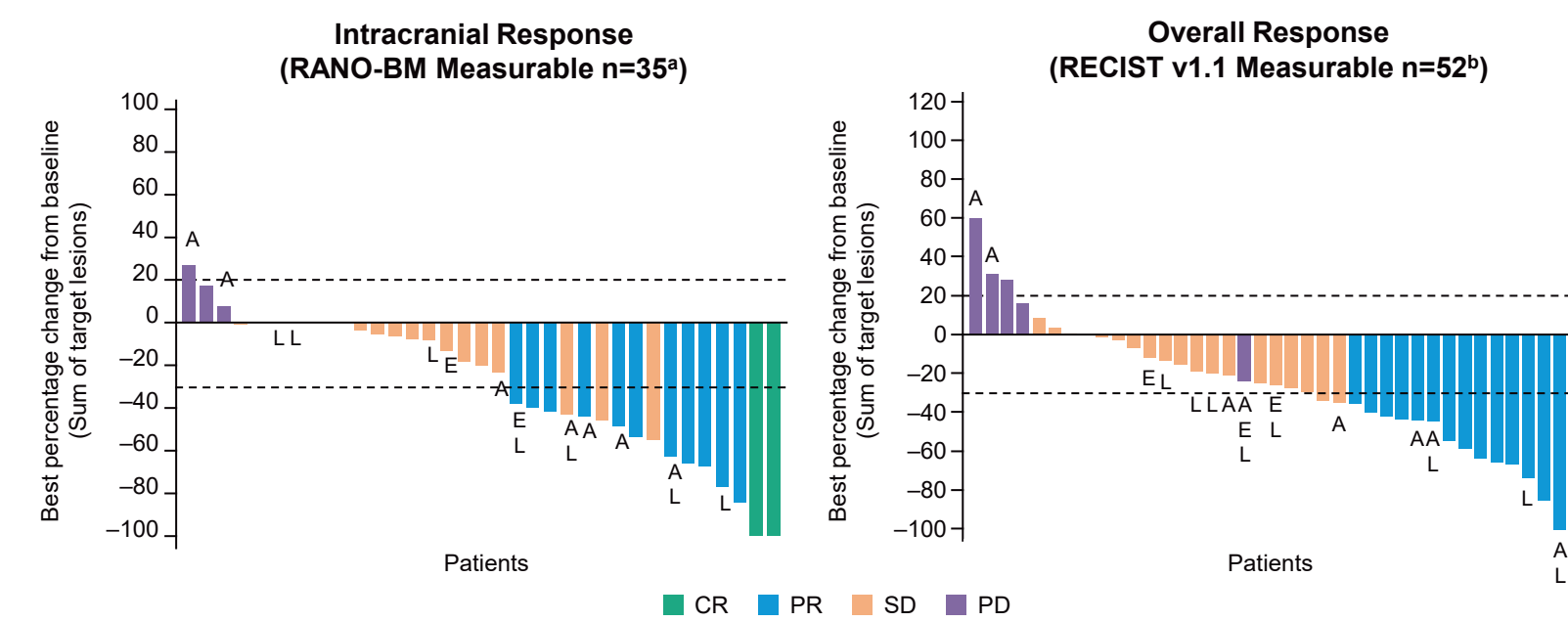


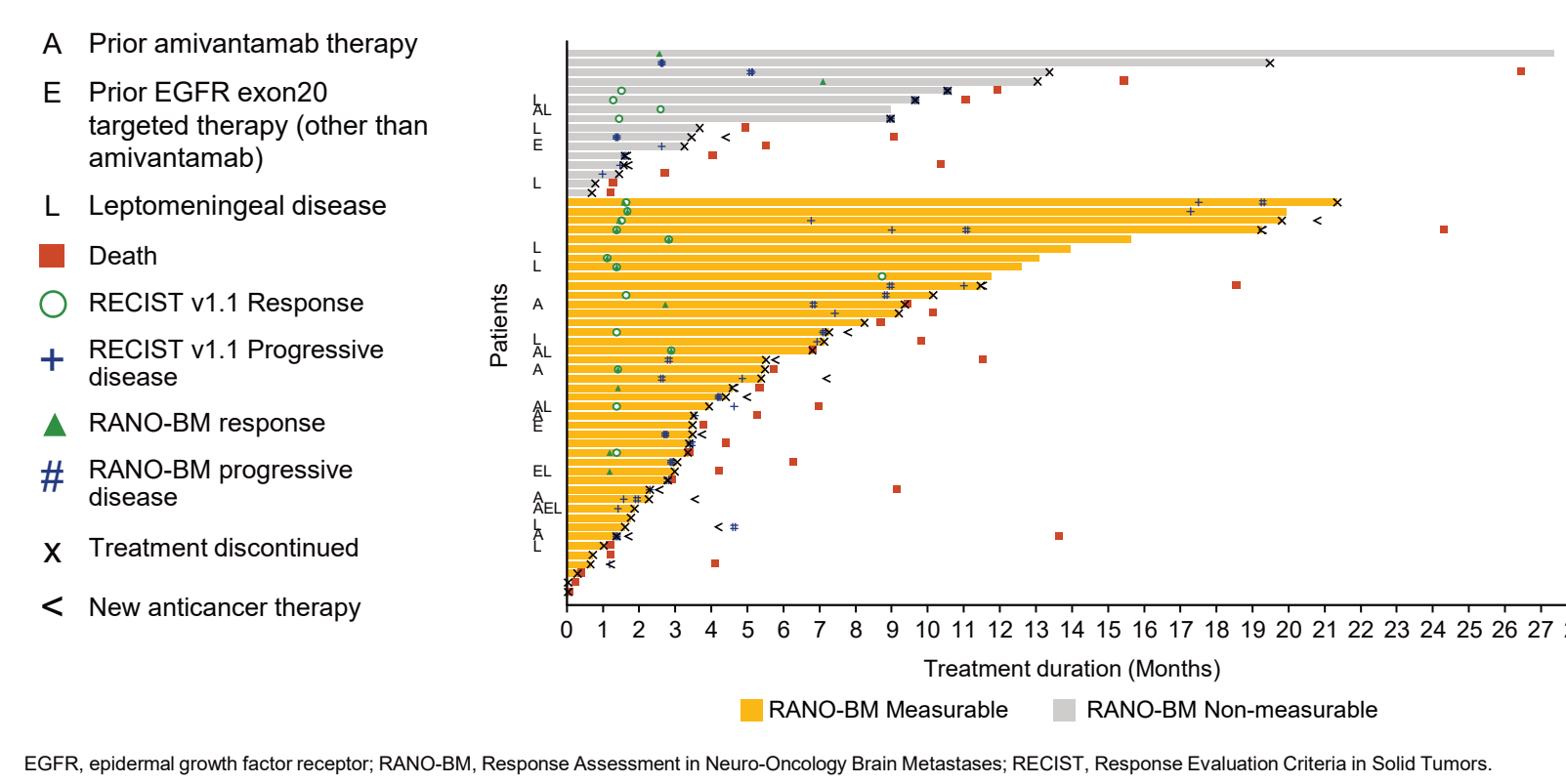
Figure 3. Best percentage change in target lesions



^a6 of 43 patients were not evaluable for response. ^b7 of 59 patients were not evaluable for response. A, prior amivantamab therapy; CR, complete response; E, prior EGFR exon20 targeted therapy (other than amivantamab); L, leptomeningeal disease; PD, progressive disease; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, Version 1.1; SD, stable disease.

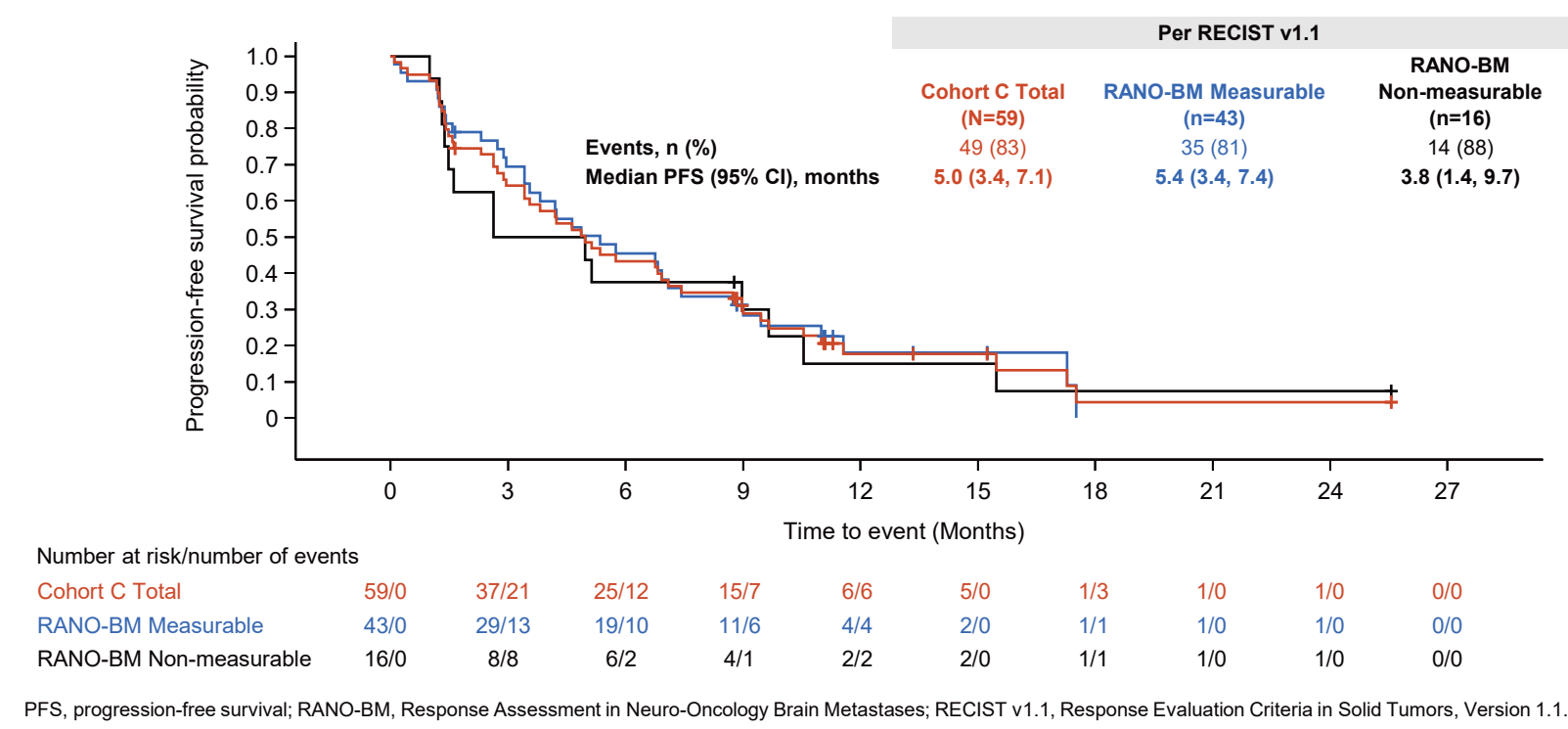
- Figure 4** shows treatment duration and individual patient responses by RANO-BM criteria and RECIST v1.1
- Ziplertinib demonstrated comparable systemic and intracranial activity in ex20ins NSCLC with brain metastases (RECIST v1.1 ORR 37.5%; RANO-BM ORR 34.5%)
- Responses occurred after prior amivantamab-only treatment (RECIST v1.1 4/7; RANO-BM 3/6). Antitumor activity after prior ex20ins TKIs was limited (RECIST 0/4; RANO-BM 1/3)
- In non-ex20ins NSCLC, predominantly pretreated with EGFR TKIs, response rates were modest (RECIST v1.1 3/19; RANO-BM 3/14)

Figure 4. Characterization of response



- Median PFS per RECIST v1.1 was 5.0 (95% CI: 3.4, 7.1) months for Cohort C total and 5.4 (95% CI: 3.4, 7.4) months for the RANO-BM measurable group (**Figure 5**)

Figure 5. Progression-free survival



Results: Safety

- Safety profile of ziplertinib 100 mg BID was consistent with previous studies (**Tables 3 and 4**)
- Low incidence of EGFR-related Grade ≥3 toxicity in both Cohort C total and RANO-BM measurable groups
- Grade ≥3 treatment-related adverse events (TRAEs) (in >1 patient) were dermatitis acneiform (n=3), amylase increase (n=2), and interstitial lung disease (n=2) in Cohort C total and dermatitis acneiform (n=2), and amylase increase (n=2) in the RANO-BM measurable group
- Adverse events were manageable (**Tables 3 and 4**)
- Dose reductions, interruptions, or treatment discontinuations due to TRAEs were reported in 7 (12%), 14 (24%), and 7 (12%) patient(s), respectively, in Cohort C total and 5 (12%), 10 (23%), and 5 (12%) patient(s), respectively, in the RANO-BM measurable group
- Grade ≥3 TRAEs leading to treatment discontinuation were interstitial lung disease (n=2), and pneumonitis, anaphylactic reaction, and nausea (n=1 each) in Cohort C total and pneumonitis, anaphylactic reaction, interstitial lung disease, and nausea (n=1 each) in the RANO-BM measurable group

Table 3. Treatment-related adverse events: Cohort C total (N=59)

Any-grade TRAEs in ≥15% of patients, n (%) (N=59)	Any Grade	Grade 1	Grade 2	Grade ≥3
≥1 TRAE	52 (88)	17 (29)	20 (34)	15 (25)
Paronychia	17 (29)	7 (12)	9 (15)	1 (2)
Dermatitis acneiform	13 (22)	5 (9)	5 (9)	3 (5)
Diarrhea	13 (22)	9 (15)	3 (5)	1 (2)
Stomatitis	12 (20)	10 (17)	2 (3)	0
Dry skin	10 (17)	5 (9)	5 (9)	0
Rash	10 (17)	4 (7)	6 (10)	0
Anemia	9 (15)	6 (10)	0	3 (5)

TRAEs, treatment-related adverse events.

Table 4. Treatment-related adverse events: RANO-BM evaluable (n=43)

Any-grade TRAEs in ≥15% of patients, n (%) (n=43)	Any Grade	Grade 1	Grade 2	Grade ≥3
≥1 TRAE	38 (88)	11 (26)	17 (40)	10 (23)
Paronychia	14 (33)	6 (14)	7 (16)	1 (2)
Diarrhea	11 (26)	7 (16)	3 (7)	1 (2)
Dermatitis acneiform	8 (19)	3 (7)	3 (7)	2 (5)
Rash	7 (16)	3 (7)	4 (9)	0
Stomatitis	7 (16)	7 (16)	0	0

RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; TRAEs, treatment-related adverse events.

CONCLUSIONS

- Ziplertinib demonstrated clinically meaningful intracranial antitumor activity, with a **30% intracranial ORR** by RANO-BM criteria in patients with NSCLC harboring *EGFR* ex20ins or other uncommon single or compound uncommon mutations
 - Ziplertinib also appears to demonstrate **activity in patients with LMD**
- Ziplertinib showed systemic (RECIST 1.1 ORR 37.5%) and intracranial (RANO-BM ORR 34.5%) **activity in patients with ex20ins NSCLC and brain metastases**
- In ex20ins NSCLC, responses occurred after prior amivantamab-only treatment (RECIST v1.1 4/7; RANO-BM 3/6); data in patients pretreated with ex20ins-targeted TKIs was limited
- Response rates were modest in predominantly EGFR TKI-pretreated non-ex20ins NSCLC; small subgroups limit interpretation
- The safety profile of ziplertinib was consistent with previous reports

Presenter Disclosures

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References

- Maitotra J, et al. *JAMA Oncol*. 2025;11:60–9.
- Watanabe N, et al. *Ann Transl Med*. 2022;10:1283.
- Hasako S, et al. *Mol Cancer Ther*. 2018;17:1648–58.
- Udagawa H, et al. *Mol Cancer Res*. 2019;17:2233–43.
- Piotrowska Z, et al. *J Clin Oncol*. 2025;43:2387–97.

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