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Activity of Zipalertinib Against Active Central Nervous System (CNS) Metastases in Patients With Non-Small Cell Lung Cancer (NSCLC) Harboring *EGFR* exon 20 insertion (ex20ins)/Other Uncommon Mutations

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Declaration of Interests

Consulting or Advisory Role: AstraZeneca, Daiichi Sankyo, Blueprint Medicines, Janssen, C4 Therapeutics, Cullinan Oncology, Black Diamond Therapeutics, Taiho Oncology, AbbVie, Novocure, Takeda, Bristol Myers Squibb/Roche, Orion Clinical

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Other Relationship: Astellas Pharma

Background

- CNS metastases in patients with NSCLC harboring *EGFR* mutations are associated with a poor prognosis[1]
- Zipalertinib is an oral, highly selective, irreversible EGFR 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 metastases[2–4]
- There are limited treatment options for patients with NSCLC harboring *EGFR* ex20ins mutations with CNS metastases[5]
- Here, we report preliminary results from Cohort C of the ongoing phase 2b REZILIENT2 trial (NCT05967689), focusing on patients with NSCLC harboring *EGFR* ex20ins or other uncommon mutations who have active newly diagnosed and/or progressing brain metastases and/or leptomeningeal disease

CNS, central nervous system; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

1. Malholtra J, et al. *JAMA Oncol*. 2025;11:60–9. 2. Hasako S, et al. *Mol Cancer Ther*. 2018;17:1648–58. 3. Udagawa H, et al. *Mol Cancer Res*. 2019;17:2233–43. 4. Piotrowska Z, et al. *J Clin Oncol*. 2025;43:2387–97. 5. Watanabe N, et al. *Ann Transl Med*. 2022;10:1283.

Zipalertinib Cohort for Patients With NSCLC Harboring Uncommon *EGFR* Mutations and Active CNS Metastases

Eligibility

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

- Patients received zipalertinib 100 mg orally twice daily until progressive disease or meeting other discontinuation criteria
- Total of **32 patients enrolled**, including **16 patients evaluable by RANO-BM** (data cutoff: February 17, 2025; study is ongoing)

CNS, central nervous system; DCR, disease control rate; DOR, intracranial 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; RANO-BM, Response Assessment in Neuro-oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumours.

Patient Baseline Characteristics

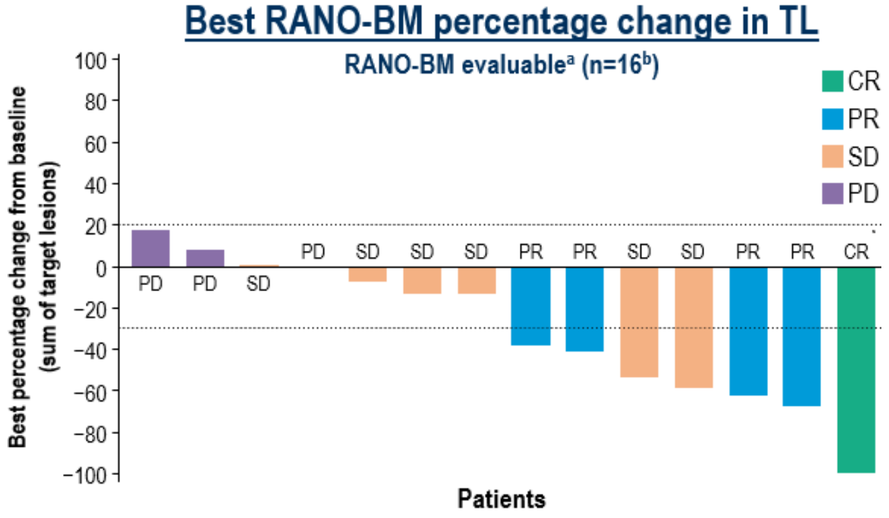
	RANO-BM evaluable (n=16)	Total (N=32)
Median (range) age, years	63.0 (23–75)	62.5 (23–83)
Female, n (%)	9 (56)	18 (56)
Race, n (%)		
Caucasian/White	10 (63)	16 (50)
Asian	5 (31)	14 (44)
Not collected	1 (6)	2 (6)
ECOG PS, n (%)		
0	6 (38)	9 (28)
1	10 (63)	23 (72)
Leptomeningeal disease, n (%)	3 (19)	6 (19)
***EGFR* exon 20 insertion mutations, n (%)**	9 (56)	21 (66)
Other *EGFR* mutations, n (%)	7[a] (44)	13[b] (41)
Median (range) lines of prior systemic therapy, n	2 (0–4)	2 (0–4)
Prior EGFR-TKI therapy, n (%)	9 (56)	14 (44)
Prior amivantamab therapy, n (%)	1 (6)	2 (6)

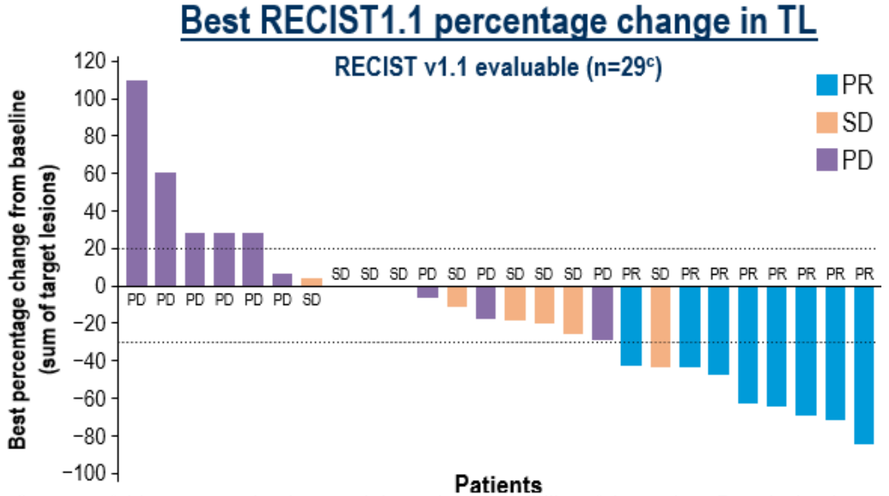
[a]G719X (1); S7681 (3); L861Q (1): complex (2); other (1). [b]G719X (3); S7681 (3); L861Q (3): complex (2); other (3).

- **A total of 62.5% of RANO-BM–evaluable patients** and 68.8% of all enrolled patients **had not received prior CNS radiotherapy**

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; RANO-BM, Response Assessment in Neuro-oncology Brain Metastases; TKI, tyrosine kinase inhibitor.

Preliminary Efficacy



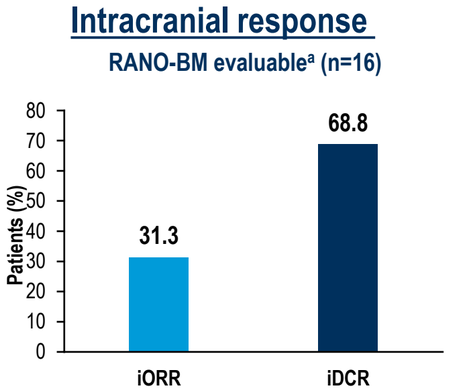


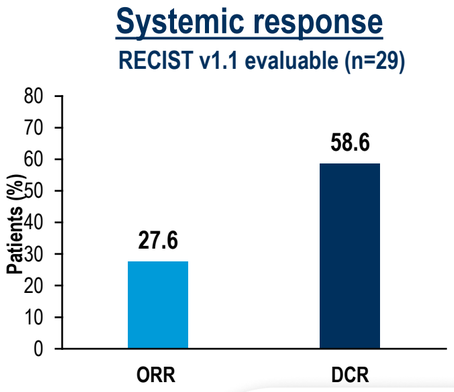
As of the data cut-off (study ongoing):

- 5/16 (**31.3%) patients with measurable CNS disease had confirmed responses by RANO-BM criteria** (including 1 intracranial CR)
- Among confirmed intracranial responders, **2/5 responders also had LMD at baseline**
- 4/5 patients with confirmed intracranial responses did not receive prior CNS radiotherapy
- Median intracranial DOR was 8.1 months (95% CI: 3.1, NE)

- 8/29 (27.6%) patients had a confirmed systemic responses according to RECIST v1.1
- Median DOR was 7.6 months (95% CI: 2.07, 9.07)

Preliminary data show similar intracranial and systemic response rates





*Newly diagnosed and/or progressive brain metastasis(es) measurable by RANO-BM criteria and not subjected to CNS-directed therapy, and/or LMD measurable or nonmeasurable by RANO-BM criteria and confirmed by a positive cerebrospinal fluid cytology, or unequivocal radiographic and/or clinical determination. [b]2/16 patients did not have post-baseline measurements. [c]3/29 patients did not have post-baseline measurements.

CI, confidence interval; CNS, central nervous system; CR, complete response; DCR, disease control rate; DOR, duration of response; LMD, leptomeningeal disease; NE, non-estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; RANO-BM, Response Assessment in Neuro-oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; TL, tumor lesion.

Safety

Any grade TRAEs in ≥ 15% of patients, n (%) (N=32)	Any grade	Grade 1	Grade 2	Grade ≥3
≥1 event	26 (81.3)	10 (31.3)	8 (25.0)	8 (25.0)
Paronychia	8 (25.0)	2 (6.3)	5 (15.6)	1 (3.1)
Dermatitis acneiform	7 (21.9)	3 (9.4)	3 (9.4)	1 (3.1)
Stomatitis	7 (21.9)	5 (15.6)	2 (6.3)	0
Anemia	6 (18.8)	3 (9.4)	0	3 (9.4)
Diarrhea	5 (15.6)	3 (9.4)	2 (6.3)	0
Dry skin	5 (15.6)	2 (6.3)	3 (9.4)	0
Rash	5 (15.6)	2 (6.3)	2 (6.3)	1 (3.1)

Safety profile of zipalertinib 100 mg BID was consistent with previous studies

- Low incidence of EGFR-related Grade ≥3 toxicity (i.e. no Grade ≥3 diarrhea)
- Grade ≥3 TRAEs (>1 incidence) included anemia (n=3) and ILD (n=2, 1 fatal)

Adverse events were manageable

- Dose reductions, interruptions, or treatment discontinuations were due to TRAEs in 1 (3.1%), 5 (15.6%), and 2 (6.3%) patient(s), respectively

BID, twice daily; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; TRAE, treatment-related adverse event.

Conclusions

- Zipalertinib demonstrated clinically meaningful intracranial antitumor activity, with a **31.3% intracranial ORR and 68.8% intracranial DCR** by RANO-BM criteria in patients with NSCLC harboring *EGFR* ex20ins or other uncommon single or compound uncommon mutations
    - Zipalertinib also appears to demonstrate **activity in patients with LMD**
- Intracranial response rate was similar to the systemic response rate in the reported population
- The safety profile of zipalertinib was consistent with previous reports
- Study is ongoing and full results from Cohort C of the REZILENT2 trial will be forthcoming in a future presentation

DCR, disease control rate; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; LMD, leptomeningeal disease; NSCLC, non-small cell lung cancer; ORR, objective response rate; RANO-BM, Response Assessment in Neuro-oncology Brain Metastases.

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