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Phase 2 Interim Results of Zipalertinib in Patients With NSCLC Harboring Uncommon Non-Exon 20 Insertion *EGFR* Mutations

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Background

- Patients with NSCLC harboring uncommon *EGFR* non-ex20ins have variable responses to currently approved EGFR TKIs, highlighting the need for novel treatment options[1,2]
- Zipalertinib is an oral, highly selective, irreversible EGFR TKI that has demonstrated preliminary clinical activity against ex20ins and preclinical activity against uncommon, non-ex20ins *EGFR*-mutated NSCLC[3–5]
- REZILIENT2 is a phase 2b, open-label, multicenter trial evaluating zipalertinib 100 mg BID in patients with locally advanced/metastatic NSCLC harboring ex20ins and uncommon single or compound *EGFR* mutations (NCT05967689)[6]
  - We present preliminary efficacy and safety data for NSCLC harboring uncommon, non-ex20ins *EGFR*mt[a]
  - Patients received zipalertinib 100 mg orally BID until progressive disease or meeting other withdrawal criteria

Cohort D inclusion criteria

- Age ≥18 years with locally advanced/ metastatic NSCLC
- Documented single or compound uncommon, non-ex20ins *EGFR* ECOG PS 0–1
- Stable brain metastases (leptomeningeal disease not allowed)
- Archival tissue available
- Any line of prior systemic therapy for advanced/metastatic disease

Endpoints:

Primary
- ORR (IR) per RECIST v1.1

Secondary
- DOR
- DCR
- Safety

[a]**Data cutoff: March 16–24, 2025**

BID, twice daily; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EGFRmt, epidermal growth factor receptor mutations; exon20ins, exon 20 insertion mutation; IR, investigator review; NSCLC, non-small cell lung cancer; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

1. Yang JC-H, et al. *Lancet Oncol.* 2015;16:830–8. 2. Wells L, Qin A. *Curr Treat Options Oncol*. 2023;24:1802–14. 3. Hasako S, et al. *Mol Cancer Ther*. 2018;17:1648–58. 4. Udagawa H, et al. *Mol Cancer Res*. 2019;17:2233–43.
5. Piotrowska Z, et al. *J Clin Oncol.* 2023;41:4218–25. 6. ClinicalTrials.gov. NCT05967689. https://clinicaltrials.gov/study/NCT05967689. Accessed July 2025

Results: Patient Baseline Characteristics

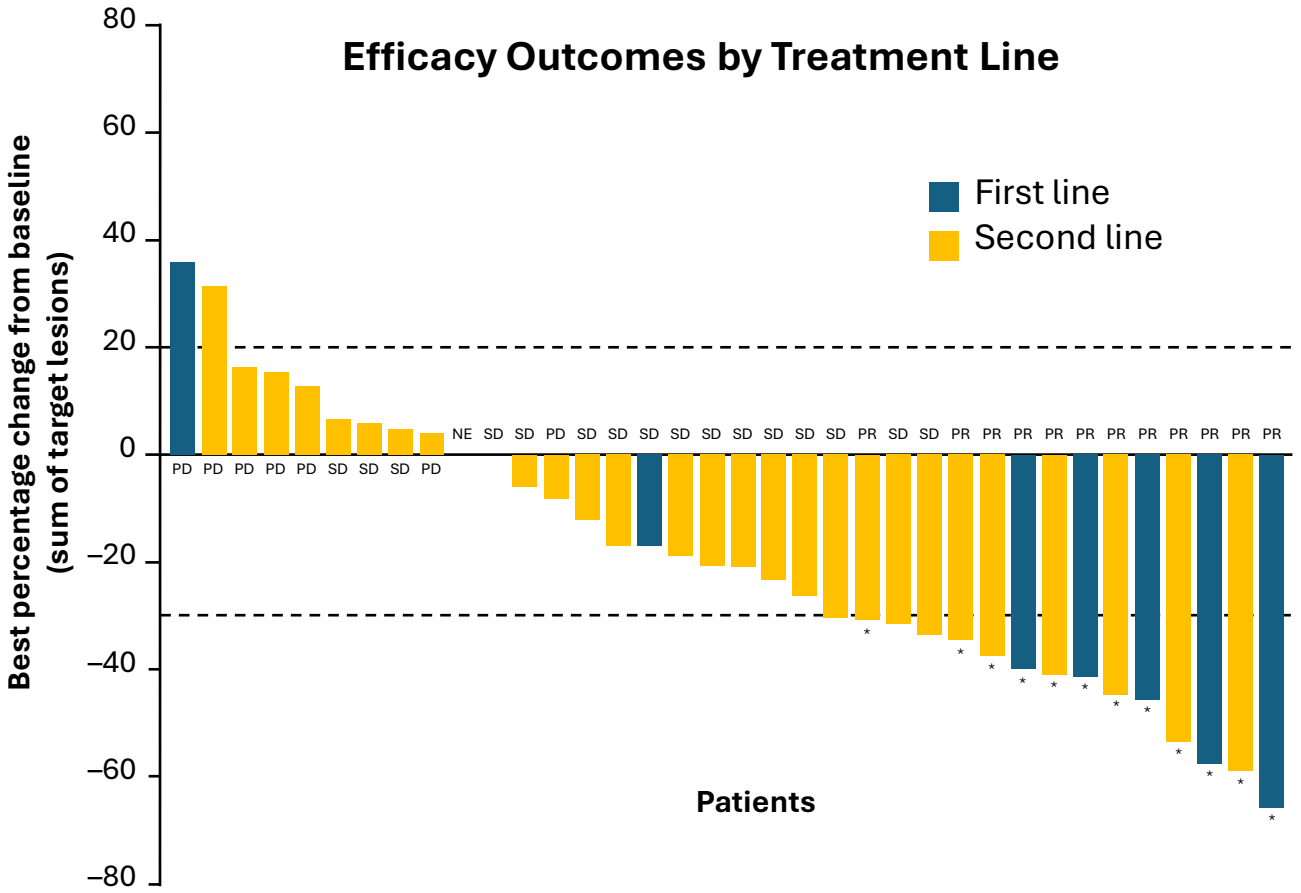
	Treatment-naïve (n=8)	Previously treated (n=32)	All patients (N=40)
Median age, years (range)	73 (56–80)	65.5 (47–85)	66 (47–85)
Female, n (%)	2 (25.0)	20 (62.5)	22 (55.0)
Race, n (%)			
Caucasian/White	1 (12.5)	7 (21.9)	8 (20.0)
Asian	6 (75.0)	18 (56.3)	24 (60.0)
Not collected	1 (12.5)	7 (21.9)	8 (20.0)
Median number of prior lines of systemic therapy, n (range)	-	2 (1–7)	2 (1–7)
Prior TKI, n (median [range])	-	1 (1–4) 30/32 pts	1 (1–4) 30/40 pts
Major single uncommon mutations, n (%)	6 (75.0)	17 (53.0)	23 (57.5)
G719X	2 (25.0)	9 (28.1)	11 (27.5)
S768I	0 (0)	2 (5.0)	2 (5.0)
L861Q	4 (50.0)	6 (18.7)	10 (25.0)
Other single uncommon mutations, n (%)[a]	1 (12.5)	5 (15.7)	6 (15.0)
Compound mutations,[b] n (%)	1 (12.5)	10 (31.3)	11 (27.5)
ECOG PS, n (%)			
0	2 (25.0)	4 (12.5)	6 (15.0)
1	6 (75.0)	28 (87.5)	34 (85.0)
Brain metastases, n (%)	1 (12.5)	11 (34.4)	12 (30.0)

[a]Other single uncommon mutations include L861R (n=2), E709_T710delinsD (n=2), K745_E746insVPVAIK (n=1), and S229C (n=1). [b]Refers to a combination of ≥2 *EGFR*mt, ≥1 of which is considered "uncommon," found in the same tumor (usually from the same allele or tumor sample).
ECOG PS, Eastern Cooperative Oncology Group performance status; Pts, patients; TKI, tyrosine kinase inhibitor.

Results: Efficacy

- **Confirmed ORR was 30%** (95% CI: 16.6, 46.5)
- **Median DOR was 7.75 months** (95% CI: 3.48, NE)
- DCR was 70% (95% CI: 53.5, 83.4)

	Treatment-naïve n=8	Previously treated n=32	All patients N=40
ORR, % (95% CI)	62.5 (24.5, 91.5)	21.9 (9.3, 40.0)	30.0 (16.6, 46.5)
DCR, % (95% CI)	75.0 (34.9, 96.8)	68.8 (50.0, 83.9)	70.0 (53.5, 83.4)
mDOR, month (95% CI)	7.75 (3.48, NE)	7.75 (3.48, NE)	7.75 (3.48, NE)



- **Anti-tumor activity was markedly higher in patients without prior EGFR TKI (ORR 62.5%) compared to pre-treated patients (ORR 23.3%, 30/32 patients with prior EGFR TKI treatment)**

CI, confidence interval; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; mDOR, median DOR; ORR, objective response rate; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Results: Safety (all patients)

- **Safety profile overall consistent with previous zipalertinib studies with no new safety signals detected**
  - Common (≥30%) related AEs included paronychia, dermatitis, stomatitis and anemia
  - Grade ≥3 related AEs were reported in 12 (30.0%) patients; no Grade ≥3 TRAE observed in more than 2 patients (≤ 5%)

	All grades n (%)	Grade ≥3 n (%)
Patients with ≥1 TRAE	38 (95.0)	12 (30.0)
Paronychia	19 (47.5)	2 (5.0)
Dermatitis acneiform	15 (37.5)	0
Stomatitis	13 (32.5)	1 (2.5)
Anemia	12 (30.0)	2 (5.0)
Diarrhea	9 (22.5)	0
Rash	8 (20.0)	1 (2.5)
Dry skin	6 (15.0)	0

- **Dose reductions, interruptions, or treatment discontinuations due to AEs occurred in 10 (25.0%), 19 (47.5%), and 6 (15.0%) patients, respectively; 1 treatment discontinuation was due to TRAE**
- **No treatment-related deaths were reported**

AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event

Conclusions

- Zipalertinib demonstrated preliminary clinical efficacy in patients with NSCLC harboring uncommon, non-ex20ins *EGFR*mt.
  - Clinically meaningful responses were observed in heavily pre-treated patients, with an ORR of 30.0% and a median DOR of 7.75 months
  - Increased anti-tumor activity was noted in treatment-naïve patients with a substantially higher ORR (62.5%)
- Zipalertinib 100mg BID was tolerable with a manageable safety profile, with no new safety signals
- Trial enrolment is ongoing, with a focus on further evaluating and confirming the observed preliminary efficacy

BID, twice daily; EGFR, epidermal growth factor receptor; *EGFR*mt, epidermal growth factor receptor mutations; ex20ins, exon 20 insertion mutation; NSCLC, non-small cell lung cancer; mDOR, median duration of response; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

Thank You

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