Updates in HER2 *(ERBB2)*-Mutant Metastatic Non-small Cell Lung Cancer Treatment:
Small Population, Big Unmet Need

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The FDA has now approved zongertinib, a kinase inhibitor indicated for the treatment of adult patients with unresectable or metastatic non-squamous NSCLC whose tumors have HER2 (*ERBB2*) tyrosine kinase domain activating mutations, as detected by an FDA-approved test, and who have received prior systemic therapy.* For U.S. Healthcare Professionals, please see full Prescribing Information.

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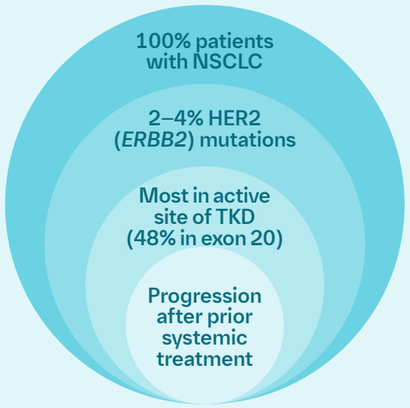
The clinical challenge in HER2 *(ERBB2)*-mutant mNSCLC[1-3]



Unmet needs in HER2 *(ERBB2)*-mutant mNSCLC[2-4]

- Limited treatment options, with significant toxicities
- Poor prognosis
- Need for HER2-targeted therapy

Beamion LUNG-1 Phase 1b Study [5,6]

HER2 TKD activating mutations

Cohorts:

Previously treated with chemo +/- IO (n=69) + HER2 mAb (N=71)	Previously treated with chemo ± IO and subsequent HER2-directed ADC (N=34)

Zongertinib:

- 120 mg once daily (two 60 mg tablets) for patients <90 kg
- 180 mg once daily (three 60 mg tablets) for patients ≥90 kg

Clinical activity in previously treated patients with TKD activating mutations[5,6]

Response rate and durability

Previously treated with chemo +/- IO (N=71)

75% ORR
58% DOR ≥6 months
6% complete response
69% partial response

Previously treated with chemo ± IO and subsequent HER2-directed ADC (N=34)

44% ORR
5.4 months median DOR
3% complete response
41% partial response

Safety[†‡]

Low discontinuation rate
2.9% due to AEs

Minimal dose reductions
7% of patients

Manageable drug-related AEs

Low rate of Grade 3:
Rash (1%)
Diarrhea (1%)

No Grade 5 AEs occurred

Intracranial activity

60% intracranial ORR in patients with measurable CNS metastases by BICR and had not received RT to the brain within 2 months prior to treatment as measured by RANO-BM (n=3 of 5)

Patient perspective[†]

Clinical response translates to patient benefit[7]

Symptom relief (NSCLC-SAQ)
60% improved by Cycle 5

Physical function (EORTC QLQ-C30)
53.3% improved by Cycle 5
Sustained improvements through Cycle 9

Coughing
>50% reported no coughing at Cycles 5 and 9 (versus **25%** baseline)

Dyspnea
30% of patients improved by Cycle 5

Patient satisfaction[6]

- **80–90%** of patients "not at all" or "a little" troubled by AEs
- **50%** never experienced diarrhea post-baseline
- **QOL maintained** regardless of response type

Conclusion

In previously treated patients with HER2 (*ERBB2*)-mutant mNSCLC, zongertinib demonstrated:

- Early and durable responses
- Intracranial activity in patients with CNS metastases
- Manageable safety profile with low discontinuation rates
- Sustained improvements in symptoms and functioning, and minimal reported treatment burden

Zongertinib addresses multiple dimensions of therapeutic benefit[5-7]

Clinical response + patient benefit = positive patient experience

Clinical response
75% ORR
58% DOR ≥6 months

Patient benefit
60% improved symtoms
53.3% improved physical function

Manageable safety and treatment continuation
Low discontinuation rates: 2.9% due to AEs
Minimal dose reductions: 7% of patients
No Grade 5 adverse reactions

Abbreviations:

ADC: antibody–drug conjugate; AE: adverse event; BICR: blinded independent central review; chemo: chemotherapy; CNS: central nervous system; DOR: duration of response; EGFR: epidermal growth factor receptor; EORTC QLQ-C30: 30-item European Organisation for Research and Treatment of Cancer-Quality of Life Group; HER2: human epidermal growth factor receptor 2; IO: immuno–oncology; mAb: monoclonal antibody; mNSCLC: metastatic non-small cell lung cancer; NSCLC: non-small cell lung cancer; NSCLC-SAQ: NSCLC Symptom Assessment Questionnaire; ORR: objective response rate; PFS: progression-free survival; QOL: quality of life; RANO-BM: Response Assessment in Neuro-Oncology for Brain Metastases; RT: radiotherapy; TKD: tyrosine kinase domain.

Footnotes:

*This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

†Assessed in 75 patients with TKD activating mutations and previously treated with chemotherapy ± IO.

‡The safety profile of zongertinib was similar across cohorts.

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