# Zongertinib in patients with previously treated HER2-mutant NSCLC and brain metastases at baseline: Beamion LUNG-1

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## Introduction

- Brain metastases in *HER2*-mutant NSCLC are associated with reduced quality of life and poor prognosis, with a median overall survival of <6 months[1]
- Approximately 20% of patients with *HER2*-mutant NSCLC present with brain metastases at diagnosis, and 50% of patients experience brain metastases in their lifetime.[1] Despite the high incidence rates, patients with active brain metastases are often excluded from clinical trials
- Zongertinib is an irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing wild-type EGFR, thereby limiting associated toxicities
- Zongertinib demonstrated clinically meaningful efficacy in patients with previously treated advanced *HER2*-mutant NSCLC in Phase Ib Cohort 1 of Beamion LUNG-1, including those with stable, asymptomatic brain metastases (intracranial ORR in 27 RANO-BM eligible patients: 41%)[2]

Beamion LUNG-1: NCT04886804. EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases

## Objectives

Here, we assessed the efficacy and safety of zongertinib in patients with *HER2*-mutant NSCLC with and without brain metastases at baseline, including stable, asymptomatic (Cohort 1) and active (Cohort 4) brain metastases

## Methods

**Phase Ib (dose expansion): patients with *HER2*-mutant advanced NSCLC**
**Selected dose after interim futility analysis: zongertinib 120 mg QD**

**Current analysis: patients with brain metastases at baseline**

**Cohort 1** — Previously treated* patients with TKD mutations, including those with stable, asymptomatic brain metastases at baseline

Primary endpoint: Objective response by BICR in all lesions (RECIST v1.1)

Secondary endpoints: Objective response and DC by BICR in CNS lesions (RANO-BM); DC, DOR, and PFS by BICR in all lesions (RECIST v1.1)

**Cohort 4** — Treatment-naïve or previously treated* patients with TKD mutations and active brain metastases at baseline

Primary endpoint: Objective response by BICR in CNS lesions (RANO-BM)

Secondary endpoints: DC, DOR, and PFS by BICR in CNS lesions (RANO-BM); objective response, DC, DOR, and PFS by BICR in all lesions (RECIST v1.1)

Additional cohorts not included in the current analysis:

**Cohort 2** — Treatment-naïve patients with TKD mutations

**Cohort 3** — Previously treated* patients with non-TKD mutations

**Cohort 5** — Patients previously treated with HER2-directed ADC and with TKD mutations

*Excluding those previously treated with a HER2-directed ADC
ADC, antibody–drug conjugate; BICR, blinded independent central review; CNS, central nervous system; DC, disease control; DOR, duration of response; PFS, progression-free survival; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TKD, tyrosine kinase domain

## Patients

As of March 26, 2025, 75 patients in Cohort 1 and 30 patients in Cohort 4 had received zongertinib 120 mg

| | Cohort 1 | | Cohort 4 |
|---|---|---|---|
| | No brain metastases n = 47 | Stable, asymptomatic brain metastases n = 28 | Active brain metastases N = 30 |
| Age, median (range), years | 60 (30–80) | 63 (32–80) | 59 (38–77) |
| Female, n (%) | 32 (68) | 19 (68) | 19 (63) |
| Race, n (%)* | | | |
| Asian | 26 (55) | 14 (50) | 15 (50) |
| Non-Asian | 20 (43) | 9 (32) | 10 (33) |
| No. of lines of prior systemic anticancer treatment, n (%) | | | |
| 0 | 2 (4)† | 1 (4)† | 10 (33) |
| 1 | 32 (68) | 11 (39) | 13 (43) |
| ≥2 | 13 (28) | 16 (57) | 7 (23) |
| No prior brain radiotherapy, n (%) | – | 17 (60) | 24 (80) |
| ECOG PS, n (%) | | | |
| 0 | 16 (34) | 12 (43) | 13 (43) |
| 1 | 31 (66) | 16 (57) | 17 (57) |

*Not reported: n = 1 in Cohort 1 no brain metastases group and n = 5 in both Cohort 1 and 4 brain metastases groups; †Patients had received previous treatment in an adjuvant context only. Prior treatment was allowed in the adjuvant setting; these patients were therefore considered as previously treated in the advanced/metastatic setting per protocol. ECOG PS, Eastern Cooperative Oncology Group performance status

## Key Findings and Conclusions

- Zongertinib demonstrated an intracranial ORR of 50% by RECIST v1.1 in patients with stable, asymptomatic brain metastases (Cohort 1)
- In a pooled analysis of patients with stable, asymptomatic or active brain metastases (Cohorts 1 and 4), zongertinib demonstrated encouraging intracranial efficacy by RANO-BM, with an ORR of 41%
- In patients who had not received any prior brain radiotherapy, zongertinib demonstrated an intracranial ORR of 44% by RANO-BM. Overall, 95% of these patients experienced a reduction in brain lesion size from baseline
- The systemic efficacy and safety profile of zongertinib was consistent in patients with and without brain metastases
- These findings underscore a clinically meaningful advancement in managing patients with brain metastases who have limited therapeutic options

## Confirmed intracranial response by RECIST v1.1 (Cohort 1)

**Zongertinib demonstrated promising intracranial responses by RECIST v1.1 in patients with stable, asymptomatic brain metastases in Cohort 1 (n = 8*)**

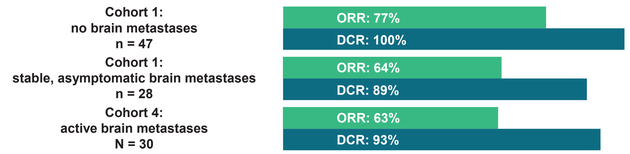

Median DOR,† months (95% CI)
12.5 (11.1–NC)

Intracranial response by RECIST v1.1 is not yet evaluable in patients with active brain metastases in Cohort 4

*Patients with RECIST v1.1–measurable CNS lesions; †Median follow-up for DOR: 16.6 months (95% CI: 11.0–16.6 months)
CI, confidence interval; DCR, disease control rate; NC, not calculable

## Confirmed systemic response by RECIST v1.1 (Cohorts 1 and 4)

**Zongertinib elicited strong systemic responses, with similar effectiveness in patients with no brain metastases and those with stable, asymptomatic or active brain metastases**




## Confirmed intracranial response by RANO-BM (Cohorts 1 and 4)

**In Cohort 4, the intracranial ORR by RANO-BM was 43% in patients with active brain metastases (N = 30)**

**In a pooled analysis of 58 patients with stable, asymptomatic or active brain metastases in Cohorts 1 and 4 (Cohort 1, n = 28; Cohort 4, n = 30), the intracranial ORR by RANO-BM was 41%; some of these patients had received prior brain radiotherapy**

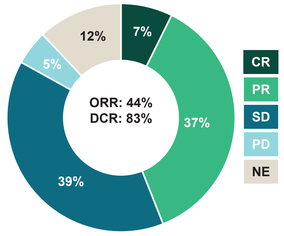
| Intracranial response, % | n = 58 |
|---|---|
| **ORR** | **41** |
| CR | 9 |
| PR | 33 |
| **DCR** | **83** |
| SD | 41 |
| PD | 7 |
| NE | 10 |

Median PFS (95% CI), months
8.2 (4.5–12.3)

CR, complete response; NE, not evaluable; PR, partial response; PD, progressive disease; SD, stable disease

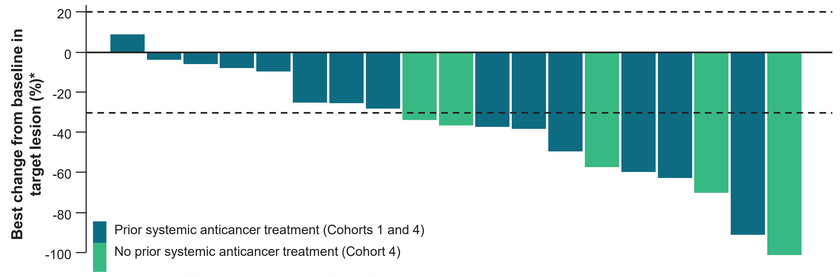
## Confirmed intracranial response by RANO-BM in patients without prior brain radiotherapy (Cohorts 1 and 4)

**Promising intracranial responses by RANO-BM occurred in patients with stable, asymptomatic or active brain metastases in Cohorts 1 and 4 who had not received prior radiotherapy (n = 41)**




Median PFS (95% CI), months
8.1 (4.1–12.3)

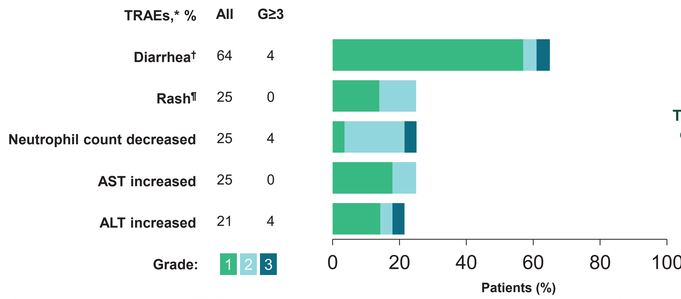
**Overall, 95% (18/19) of evaluable patients* who had not received prior brain radiotherapy experienced a reduction in brain lesion size from baseline**




*Patients with target lesions in the CNS at baseline, evaluable by RANO-BM, as assessed by the investigator

## Safety (Cohort 1)

**Cohort 1: stable, asymptomatic brain metastases (n = 28)**




**The TRAE profile was consistent with that in patients without brain metastases**

*As assessed by the investigator. TRAEs reported in >20% of patients in either group are included. Overall, 100%/21% of patients with stable, asymptomatic brain metastases and 96%/17% of patients with no brain metastases experienced any/G≥3 TRAEs; †Grouped term including diarrhea, gastroenteritis, and colitis; ¶Grouped term including rash, rash maculopapular, dermatitis acneiform, rash erythematous, rash pustular, butterfly rash, dermatitis, dermatitis allergic, and erythema
ALT, alanine aminotransferase; AST, aspartate aminotransferase; G, grade; TRAE, treatment-related adverse event

## References

**1.** Offin M, et al. Cancer 2019;125:4380–7; **2.** Heymach JV, et al. N Engl J Med 2025;392:2321–33

## Plain Language Summary

People with *HER2*-mutant non-small cell lung cancer often develop brain metastases, which are associated with poor quality of life and survival. New HER2-targeting medications are needed that work well in people with brain metastases

Zongertinib, a new drug that targets HER2, has shown strong activity with manageable side effects in people with *HER2*-mutant non-small cell lung cancer

This analysis of a large, international trial is evaluating how well zongertinib works in people with *HER2*-mutant non-small cell lung cancer and brain metastases

**Presented at the Florida Society of Clinical Oncology (FLASCO) meeting, Orlando, Florida, USA, October 23–25, 2025**

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Previously presented at the World Conference on Lung Cancer (WCLC) Meeting, Barcelona, Spain, September 6–9, 2025



This study was funded by Boehringer Ingelheim.
The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version. The authors did not receive payment related to the development of the poster. Medical writing support for the development of this poster, under the direction of the authors, was provided by Hannah Simmons, MSc, of Ashfield MedComms, and encored by Karina Silova, MSc, of Nucleus Global, an Inizio company, and funded by Boehringer Ingelheim

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