Zongertinib in treatment-naïve patients with *HER2*-mutant NSCLC, including those with active brain metastases: Beamion LUNG-1

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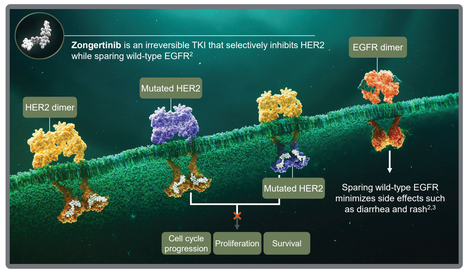
Background

- *HER2* mutations occur in approximately 2–4% of NSCLC cases and are associated with highly aggressive disease, a poor prognosis and a high incidence of brain metastases[1]
- Zongertinib is an orally administered, irreversible TKI that selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities[2,3]
- Zongertinib recently received accelerated approval in the United States for patients with unresectable or metastatic non-squamous NSCLC whose tumors have *HER2* (ERBB2) TKD activating mutations[4,5]

Prior to zongertinib, there was no approved HER2-targeted 1L therapy, a major unmet clinical need

Figure 1. Mechanism of Action of Zongertinib



1L, first line; EGFR, epidermal growth factor receptor; ERBB2, erb-b2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor.

Methods

Figure 2. Beamion LUNG-1 Study Design

Phase Ib (dose expansion): patients with advanced *HER2*-mutant NSCLC
In Phase Ia, the MTD was not reached at 360 mg QD
In Phase Ib, the selected dose after interim futility analysis was zongertinib 120 mg QD

Current analysis

Cohort 2 — Treatment-naïve patients with TKD mutations
Primary endpoint: Objective response by BICR (RECIST v1.1)

Cohort 4 — Treatment-naïve or previously treated patients with TKD mutations and active brain metastases at baseline
Primary endpoint: Objective response in CNS lesions by BICR (RANO-BM)

Here we present the efficacy and safety of zongertinib 120 mg as 1L therapy, as well as findings in patients with active brain metastases

Additional cohorts not included in the current analysis

Cohort 1 — Previously treated 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

1L, first line; ADC, antibody-drug conjugate; BICR, blinded independent central review; CNS, central nervous system; HER2, human epidermal growth factor receptor 2; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; QD, once daily; RANO-BM, response assessment in neuro-oncology brain metastases; RECIST, response evaluation criteria in solid tumors; TKD, tyrosine kinase domain.

Patients

Baseline patient and disease characteristics

- In Cohort 2, 74 treatment-naïve patients received zongertinib 120 mg
  - 58% were ≥65 years old
  - 35% had a history of tobacco exposure
  - 30% had baseline brain metastases
- In Cohort 4, 30 patients with active brain metastases had received zongertinib 120 mg
  - 27% were treatment-naïve†

Characteristic	Cohort 2: Treatment-naïve patients N=74‡	Cohort 4: Patients with active brain metastases N=30
Age, median (range), years	67 (35–88)	59 (38–77)
Age group, n (%)		
65–<75 years	30 (41)	6 (20)
≥75 years	13 (18)	2 (7)
Female, n (%)	37 (50)	19 (63)
Race, n (%)§		
Asian	34 (46)	15 (50)
Non-Asian	33 (45)	10 (33)
ECOG PS, n (%)		
0	34 (46)	13 (43)
1	40 (54)	17 (57)
Tobacco use, n (%)¶		
Never	47 (64)	19 (63)
Former	25 (34)	10 (33)
Current	1 (1)	1 (3)
Brain metastases, n (%)	22 (30)**	30 (100)
HER2 TKD mutation type, n (%)		
A775_G776insYVMA	50 (68)	17 (57)
Other	24 (32)	13 (43)

Data cut-off: August 21, 2025.
‡Seven patients did not receive any prior lines of therapy, irrespective of treatment intent; 1 additional patient was treated with curative-adjuvant chemotherapy, with sufficient time elapsed before the start of the trial; †two patients had received prior treatment and had protocol deviations; §not reported: Cohort 2, n=7; Cohort 4, n=5; ¶not reported: Cohort 2, n=1; **patients with stable, asymptomatic brain metastases were eligible.
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; TKD, tyrosine kinase domain.

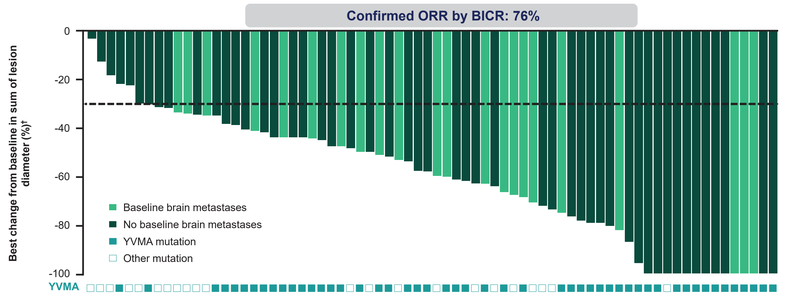
Conclusions and Future Directions

- Zongertinib demonstrated clinically meaningful benefit in patients with advanced *HER2*-mutant NSCLC, including in patients with active brain metastases, with a manageable safety profile and notably few grade ≥3 TRAEs
  - Given as 1L therapy, the confirmed ORR by BICR was 76%; median PFS and DoR were 14.4 months and 15.2 months
  - Zongertinib also showed intracranial responses in patients with active brain metastases (47% ORR; RANO-BM), including in those with no prior brain radiotherapy (59% ORR; RANO-BM)
- Zongertinib recently received accelerated approval in the United States for patients with unresectable or metastatic non-squamous NSCLC whose tumors have *HER2* (ERBB2) TKD activating mutations
- Beamion LUNG-2 (NCT06151574) is a Phase III randomized study evaluating first-line zongertinib versus standard of care in patients with unresectable, locally advanced or metastatic *HER2*-mutant NSCLC; target enrollment has been reached
- Beamion LUNG-3 (NCT07195695), a Phase III randomized study investigating zongertinib as adjuvant monotherapy versus standard of care in patients with early-stage, resectable *HER2*-mutant NSCLC, is ongoing

1L, first line; BICR, blinded independent central review; DoR, duration of response; ERBB2, erb-b2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; RANO-BM, response assessment in neuro-oncology brain metastases; TKD, tyrosine kinase domain; TRAE, treatment-related adverse event.

Efficacy

Figure 3. Zongertinib in 1L Treatment-Naïve Patients: Tumor Response



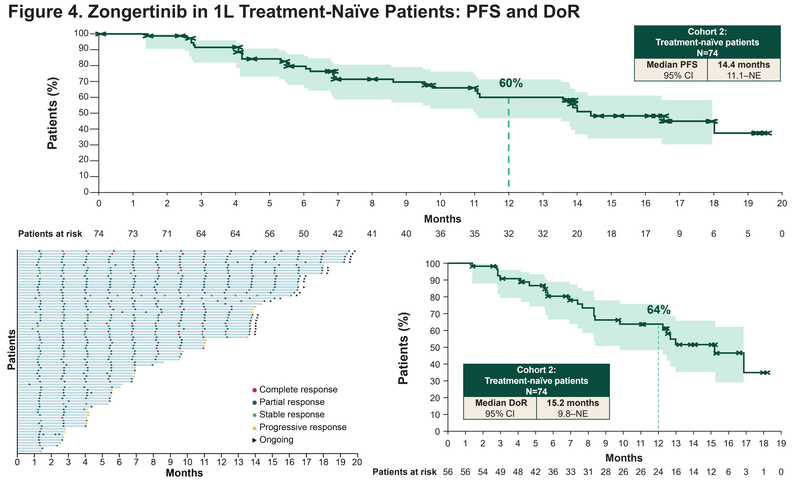
Confirmed response by BICR (RECIST v1.1)	Cohort 2: Treatment-naïve patients N=74
ORR	**76%**
CR, n (%)	8 (11)
PR, n (%)	48 (65)
DCR	**96%**
SD, n (%)	15 (20)
PD, n (%)	1 (1)‡

- Median time to objective response was 1.4 months (95% CI, 1.1 to 6.9)

1L zongertinib demonstrated clinical benefit in all patients, irrespective of *HER2* mutation type

Median follow-up for DoR: 13.8 months (95% CI, 12.4–15.3). Median best percentage change in sum of lesion diameter was -59% (range, -4% to -100%).
†two patients were not evaluable for response (images were not available); ‡PD due to non-target lesion progression.

Figure 4. Zongertinib in 1L Treatment-Naïve Patients: PFS and DoR

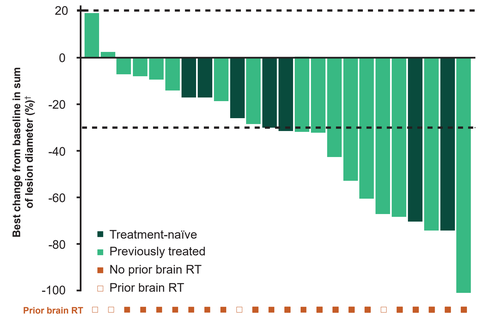


Responses to zongertinib were durable, the majority were observed at the first assessment

Median follow-up for PFS: 15.2 months (95% CI, 13.7–16.5); median follow-up for DoR: 13.8 months (95% CI, 12.4–15.3).

Figure 5. Zongertinib in Patients with Active Brain Metastases: Intracranial Tumor Response

Confirmed intracranial response by BICR (RANO-BM)	Cohort 4: Active brain metastases N=30	No prior brain RT and confirmed measurable intracranial disease n=17
ORR	**47%**	**59%**
CR, n (%)	2 (7)	1 (6)
PR, n (%)	12 (40)	9 (53)
DCR	**87%**	**94%**
SD, n (%)	12 (40)	6 (35)
NE, n (%)	4 (13)	1 (6)
Median DoR	**6.9 months**	**6.2 months**
95% CI	2.9–NE	2.7–NE
Median PFS	**8.2 months**	NE
95% CI	4.1–11.3	NE



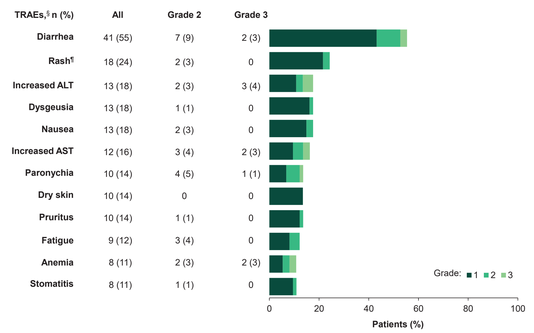
Zongertinib showed intracranial activity in patients with active, untreated brain metastases

For Cohort 4 (n=30): median follow-up for DoR: 11.8 months (95% CI, 4.2–NE) and median follow-up for PFS: 9.6 months (95% CI, 6.9–NE).
†Patients who had a baseline assessment and at least one post-baseline assessment (from at least one central reader).
1L, first line; BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RANO-BM, response assessment in neuro-oncology brain metastases; RECIST, response evaluation criteria in solid tumors; RT, radiotherapy; SD, stable disease.

Safety

- Zongertinib had a manageable safety profile in treatment-naïve patients (Cohort 2): TRAEs were reported in 67 (91%) patients, with grade ≥3 TRAEs in 14 (19%) patients
  - Most common grade ≥3 TRAE was increased ALT
  - Low rates of grade ≥3 diarrhea and rash
  - AEs leading to dose reduction occurred in 12 (16%) patients†
  - AEs leading to discontinuation occurred in 7 (9%) patients‡

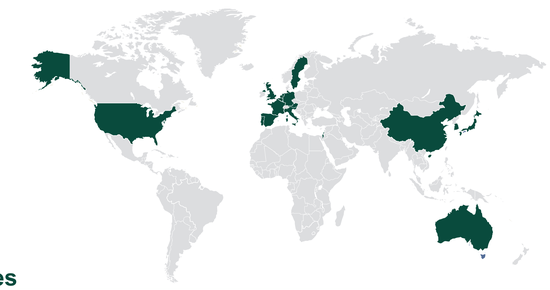
Figure 6. Zongertinib Safety Profile in Treatment-Naïve Patients



Median duration of treatment: 14.0 months (range, 0–21.0); two cases (3%) of ILD/pneumonitis were reported (both grade 2); there was one grade 4 TRAE (decreased neutrophil count) and no grade 5 TRAEs; The safety profile of patients with active brain metastases (cohort 4) consistent with the overall Beamion LUNG-1 patient population.
†AEs leading to dose reduction were: increased ALT, increased AST (both n=3), diarrhea, decreased ejection fraction (both n=2), anemia, increased blood bilirubin, hypertransaminasemia, lower GI hemorrhage, peripheral neuropathy, paronychia and vomiting (all n=1); ‡AEs leading to dose discontinuation were: decreased ejection fraction (n=2), increased ALT, anemia, increased AST, diarrhea, pericardial effusion and pneumonitis (all n=1); §TRAEs as assessed by the investigator that occurred in ≥10% of patients are shown; ¶grouped term.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal; ILD, interstitial lung disease; TRAE, treatment-related adverse event.

Recruitment

Figure 7. Beamion LUNG-1 Study Locations



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