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Zongertinib as first-line treatment in patients with advanced HER2-mutant NSCLC: Beamion LUNG 1

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Background

Zongertinib is an irreversible TKI that selectively inhibits HER2 while sparing wild-type EGFR, thereby limiting associated toxicities. Zongertinib recently received accelerated approval in the United States for previously treated advanced *HER2*-mutant NSCLC, based on phase Ib results from the Beamion LUNG-1 study where it demonstrated clinically meaningful efficacy and a manageable safety profile. In the first-line setting for pts with *HER2*-mutant NSCLC, the standard of care remains chemotherapy ± immunotherapy, with no targeted treatment approved. Here we report the first results in treatment-naïve pts with advanced *HER2*-mutant NSCLC enrolled to Cohort 2 of Beamion LUNG-1 phase Ib.

Methods

Cohort 2 included adult pts with treatment-naïve, advanced/metastatic, non-squamous, *HER2*-mutant NSCLC (TKD mutation), ≥1 measurable non-CNS lesion (RECIST v1.1), and ECOG PS of 0/1; pts received oral zongertinib 120 mg once daily. Pts with stable/asymptomatic brain metastases were eligible. The primary endpoint was objective response (OR, RECIST v1.1). Secondary endpoints included duration of OR (DoR), disease control (DC), and progression-free survival (PFS). All endpoints were assessed by blinded independent central review (BICR).

Results

As of May 8, 2025, 74 pts had received zongertinib (median age: 67 years [range, 35–88], 50% female). The BICR confirmed OR rate was 77% (95% CI: 66–85); 6 (8%) pts had complete response, 51 (69%) had partial response. A further 14 (19%) pts had stable disease, giving a DC rate of 96% (95% CI: 89–99%). The 6-month DoR and PFS rates (KM estimates) were 80% (95% CI: 65–89) and 79% (95% CI: 68–87), respectively; 47% of responding pts remained on treatment at data cut-off. Treatment-related adverse events (TRAEs) were reported in 91% of pts (grade 3 TRAEs in 18% of pts). There were no grade 4/5 TRAEs. The most common TRAEs (all/grade 3) were diarrhea (54%/3%), ALT increased (18%/4%), AST increased (16%/3%), and dysgeusia and nausea (both 16%/0%).

Conclusions

First-line zongertinib elicited strong and clinically meaningful efficacy with a manageable safety profile in treatment-naïve pts with advanced *HER2*-mutant NSCLC, underpinning its ongoing evaluation in the randomized phase III Beamion LUNG-2 study.

Clinical trial identification

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Legal entity responsible for the study

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Disclosure

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