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Abstract CT050: Zongertinib in patients with pretreated *HER2*-mutant advanced NSCLC: Beamion LUNG-1 FREE

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Abstract

Background:

Zongertinib is an irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing EGFR, thereby limiting associated toxicities. Zongertinib was granted Fast Track and Breakthrough Therapy Designations by the FDA for patients (pts) with advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating *HER2* mutations and who have received prior systemic therapy. Beamion LUNG-1 (NCT04886804) is a Phase (Ph) Ia/Ib study evaluating zongertinib in pts with *HER2*-mutant advanced/metastatic NSCLC in Ph Ib. At the primary analysis (May 2024) of Ph Ib Cohort 1, the primary endpoint, confirmed response by blinded independent central review (BICR), was met in pts with pretreated *HER2*-mutant NSCLC within the tyrosine kinase domain (TKD). Here, we report the previously unreported median duration of response (DoR) and median progression-free survival (PFS) for Cohort 1, and first data from Cohorts 3 and 5.

Methods:

In Cohort 1, pts with pretreated *HER2*-mutant NSCLC within the TKD were initially randomized to receive zongertinib 120 mg or 240 mg once-daily; the 120 mg dose was selected at an interim analysis. In exploratory Cohort 3, pts had pretreated *HER2*-mutant NSCLC with TKD or non-TKD mutations. In Cohort 5, pts had *HER2*-mutant NSCLC within the TKD and were pretreated with a HER2-directed antibody-drug conjugate. In Cohorts 3 and 5, pts initially received zongertinib 240 mg. Once the 120 mg dose was selected in Cohort 1, all newly recruited pts received zongertinib 120 mg. Primary endpoint was objective response (best overall response of complete or partial

response; RECIST v1.1) by BICR (Cohorts 1 and 5) and investigator review (Cohort 3). Secondary endpoints included DoR and PFS.

Results:

As of November 29, 2024, 75 pts in Cohort 1, 20 pts with non-TKD mutations in Cohort 3, and 31 pts in Cohort 5 had received zongertinib 120 mg; treatment was ongoing in 33 (44%), 4 (20%), and 13 (42%) pts, respectively. In Cohort 1, the objective response rate (ORR) by BICR was 71% (95% CI: 60-80) and disease control rate (DCR) was 96% (95% CI: 89-99). In Cohort 3, the ORR was 30% (95% CI: 15-52) and DCR was 65% (95% CI: 43-82). In Cohort 5, the ORR was 48% (95% CI: 32-65) and DCR was 97% (95% CI: 84-99). Median (95% CI) DoR and PFS were 14.1 (6.9-not evaluable [NE]) months and 12.4 (8.2-NE) months in Cohort 1 and 5.3 (2.8-NE) months and 6.8 (5.4-NE) months in Cohort 5. DoR and PFS in Cohort 3 were not yet mature. Drug-related adverse events (all/grade [G] ≥3) were reported in 97%/17%, 80%/25%, and 77%/3% of pts in Cohorts 1, 3, and 5, respectively, most commonly diarrhea in all cohorts (mainly G1). There were no cases of drug-related interstitial lung disease (ILD).

Conclusions:

Zongertinib demonstrated significant and clinically meaningful activity with a manageable safety profile in pts with pretreated advanced NSCLC harboring *HER2* mutations.

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