Novel Targeted Therapy Shows Promise for Advanced Lung Cancer With HER2 Mutations

Zongertinib, an experimental oral HER2 inhibitor, shrank tumors in a majority of previously treated patients.

April 30, 2025 By Liz Highleyman

Nearly three quarters of non-small-cell lung cancer (NSCLC) patients with HER2 mutations experienced tumor regression when treated with zongertinib, a novel targeted therapy, according to results from the main cohort of an early study presented at the American Association for Cancer Research annual meeting (AACR 2025) and published in The New England Journal of Medicine.

These findings "suggest that zongertinib may offer a new approach to treating patients with non-small-cell lung cancer with activating HER2 mutations," lead investigator John Heymach, MD, PhD, of MD Anderson Cancer Center, said in a news release. "Notably, more than 70% of patients experienced a tumor response, which is highly meaningful for those with this subtype of lung cancer. If approved by the [Food and Drug Administration], zongertinib would be the first oral targeted treatment option that addresses an unmet need for these patients."

Zongertinib, from Boehringer Ingelheim, is an investigational tyrosine kinase inhibitor that selectively targets HER2 (human epidermal growth factor receptor 2), a protein that plays a role in cell proliferation. Though HER2 is best known as a target for breast cancer treatment, up to 4% of NSCLC tumors are driven by HER2 mutations, which are associated with resistance to standard therapies and poor prognosis.

Currently, the only approved treatment for such patients is Enhertu (trastuzumab deruxtecan), a HER2-directed antibody-drug conjugate administered by IV infusion. Unlike some other HER2 inhibitors, zongertinib does not also interfere with EGFR (epidermal growth factor receptor), which should lessen side effects.

Heymach and colleagues evaluated zongertinib in previously treated people with advanced or metastatic NSCLC with HER2 mutations. The Phase I Beamion LUNG-1 trial (NCT04886804) enrolled participants in the United States, Europe, Asia and Australia. A majority (68%) were women, the median age was 62 years and about two thirds had never smoked. Nearly

40% had cancer that had spread to the brain.

This analysis looked at three cohorts: patients who had tumors with mutations in the tyrosine kinase domain (Cohort 1), people with the same type of mutation who previously received both platinum chemotherapy and a HER2-directed antibody-drug conjugate such as Enhertu (Cohort 5) and people who had tumors with a mutation outside the tyrosine kinase domain (Cohort 3).

People in Cohort 1 were initially randomized to receive zongertinib by mouth at a dose of 120 or 240 milligrams once daily. Patients in Cohorts 3 and 5 initially received the 240 mg dose, but after an interim analysis of data from Cohort 1, newly recruited participants in all cohorts received 120 mg.

In Cohort 1, which included 75 people who received the 120 mg zongertinib dose, 71% had a confirmed objective response, or substantial tumor regression; 7% had a complete response. In this group, the median duration of response was 14.1 months, and the median progression-free survival time was 12.4 months, Heymach reported. What's more, zongertinib showed activity in the brain, with a 41% response rate for the 27 evaluable patients with brain metastasis.

The researchers also found that 48% of the 31 more heavily treatment-experienced patients in Cohort 5 who received the 120 mg zongertinib dose had a confirmed response, as did 30% of the 20 patients with non-tyrosine kinase domain mutations in Cohort 3. In Cohort 5, the median duration of response was 5.3 months, and the median progression-free survival time was 6.8 months; data for Cohort 3 are not yet mature.

Zongertinib was generally safe and well tolerated. Across all three cohorts, about 15% of patients experienced severe (Grade 3 or higher) drug-related adverse events, mostly diarrhea and skin rash. About 3% had adverse events leading to treatment discontinuation. There were no cases of drug-related interstitial lung disease, a potential side effect of Enhertu.

"A 71% response rate is unprecedented in this cancer subtype, and not only is the data strong in showing that this treatment works, but zongertinib has the added convenience of being a once-daily oral therapy," Heymach said in another news release. "When you also consider the improved safety profile compared to less selective inhibitors, this suggests a promising approach for patients in need of new treatments. That's exciting because just a few years ago, these patients had no effective targeted therapies."

Commenting on Heymach's AACR presentation, Charles Rudin, MD, PhD, of Memorial Sloan Kettering Cancer Center, said that next-generation tyrosine kinase inhibitors, like zongertinib, and antibody-drug conjugates are looking better than chemotherapy or chemo-immunotherapy for NSCLC with HER2 mutations.

Given the need for better treatment options for people with previously treated advanced NSCLC with HER2 mutations, the Food and Drug Administration has granted zongertinib a Fast Track Designation, a Breakthrough Therapy Designation and Priority Review status, designed to speed

up approval of medications for diseases with unmet need.

Zongertinib is also being evaluated for first-line treatment of people with unresectable, locally advanced or metastatic NSCLC with HER2 mutations in the Phase III Beamion LUNG-2 trial (NCT06151574), which will compare it to standard-of-care treatment. Zongertinib is also being studied for other solid tumors with HER2 mutations.

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