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A NEW TYROSINE KINASE INHIBITOR ZONGERTINIB (HERNEXEOS®) FOR THE TREATMENT OF HER2-MUTATED NON-SMALL CELL LUNG CANCER

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HER2-activating mutations occur in 2-4% of non-small cell lung cancer (NSCLC) cases, primarily affecting younger patients, women, and non-smokers, with nearly half developing brain metastases. Due to wild-type EGFR inhibition, pan-ERBB tyrosine kinase inhibitors (afatinib, poziotinib) have historically shown poor efficacy and dose-limiting toxicities, resulting in severe rash (80–90%) and diarrhea (15–20%). The HER2-directed antibody-drug combination trastuzumab deruxtecan has a 55% response rate, however it must be administered intravenously and has a black box warning for interstitial lung disease (2–5%). Zongertinib (BI 1810631, Hernexeos®) is a first-in-class oral irreversible tyrosine kinase inhibitor that maximizes anticancer efficacy while maintaining normal skin and gastrointestinal function by achieving about 100-fold selectivity for HER2 over wild-type EGFR.The acrylamide moiety ensures long-term target inhibition by forming a persistent covalent link with cysteine 805 in the HER2 kinase domain. Irreversible binding is crucial, as demonstrated by C805S mutant tests that showed a 34-fold potency loss when covalent binding was inhibited.

Zongertinib showed an objective response rate of 71% in pretreated HER2-mutant NSCLC patients (n=75) in the Phase Ia/Ib Beamion LUNG-1 study (NCT04886804), with a median progression-free survival of 12.4 months and a median duration of response of 14.1 months. The response rate was 48% for patients who had previously had antibody-drug conjugate treatment. 41% of patients with brain metastases showed intracranial response, and 95% showed lesion shrinking, meeting the crucial unmet need of central nervous system involvement in this population.The objective response rate for treatment-naïve patients was 76%, with 11% attaining full radiographic response and 64% of responders sustaining response for at least six months.The safety profile supports the EGFR-sparing design: 1% of patients experienced grade ≥3 diarrhea, 2% had grade ≥3 rash, and there were no reports of interstitial lung disease. This is a significant improvement over antibody-drug conjugates (ILD 2-5% with black box warning) and pan-ERBB inhibitors (severe rash 10-15%, severe diarrhea 15-20%).

Based on these findings, the FDA approved first-line expansion in February 2026 following a remarkable 44-day review under the National Priority Voucher program, which acknowledges game-changing treatments, and accelerated clearance for previously treated patients in August 2025. Beamion LUNG-2 (Phase III confirmatory), Beamion LUNG-3 (adjuvant), and Beamion PANTUMOR-1 (basket trial in HER2-altered breast, gastric, colorectal, biliary tract, urothelial, and gynecologic malignancies) are among the ongoing trials. Zongertinib is a prime example of precision medicine, showing how logical structure-based medication design can get around the efficacy-toxicity constraints of earlier treatments. It creates a new standard of therapy for HER2-mutant NSCLC by delivering high response rates, long-lasting disease control, and intracranial activity with good safety by selective HER2 inhibition with EGFR sparing.