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Zongertinib: A Novel Therapeutic Advance in HER2-Mutant Non-Small Cell Lung Cancer

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Abstract

Non-small cell lung cancer (NSCLC) with HER2 mutations represents a rare oncogenic subtype (2–4% of adenocarcinomas) associated with poor prognosis and high incidence of brain metastases. Treatment options have been limited, with trastuzumab deruxtecan (T-DXd) carrying significant interstitial lung disease (ILD) risk and earlier oral tyrosine kinase inhibitors (TKIs) causing dose-limiting epidermal growth factor receptor (EGFR)-related toxicities. Zongertinib (BI 1810631), a novel, oral, irreversible, and highly selective HER2 TKI, was engineered to spare wild-type EGFR, minimizing off-target toxicity. The phase IB Beamion LUNG-1 trial demonstrated profound efficacy with 71% objective response rate (ORR) in the tyrosine kinase domain cohort and median progression-free survival of 12.4 months. Notably, zongertinib maintained activity in T-DXd-resistant disease (48% ORR) and showed no cases of drug-related ILD. Treatment-related adverse events were predominantly mild (grade 1–2), with only 17% experiencing grade 3 events in the primary cohort. Based on compelling safety and efficacy data, zongertinib received Food and Drug Administration accelerated approval on August 8, 2025, and was designated as preferred subsequent therapy in the National Comprehensive Cancer Network guidelines for advanced HER2-mutant NSCLC, fundamentally transforming the treatment landscape for this patient population.

Keywords

- HER2-mutant non-small cell lung cancer
- medical oncology
- zongertinib

Introduction

Non-small cell lung cancer (NSCLC) remains a leading cause of cancer mortality globally.[1] Activating mutations in the human epidermal growth factor receptor 2 (*HER2*) gene define a distinct and rare oncogenic subtype, having incidence of approximately 2 to 4% of adenocarcinoma (NSCLC).[2] Her-2 positive NSCLC has poorer prognosis and a high incidence of brain metastases.[3–5] The therapeutic strategy is different in Her-2 positive NSCLC as compared to breast and gastrointestinal (GI) cancers. The landscape for previously treated HER2-mutant NSCLC has been inadequate. The only Food and Drug Administration (FDA)-approved targeted therapy, the trastuzumab deruxtecan (T-DXd), offers efficacy but carries a significant risk of severe side effects, including interstitial lung disease (ILD).[6,7]

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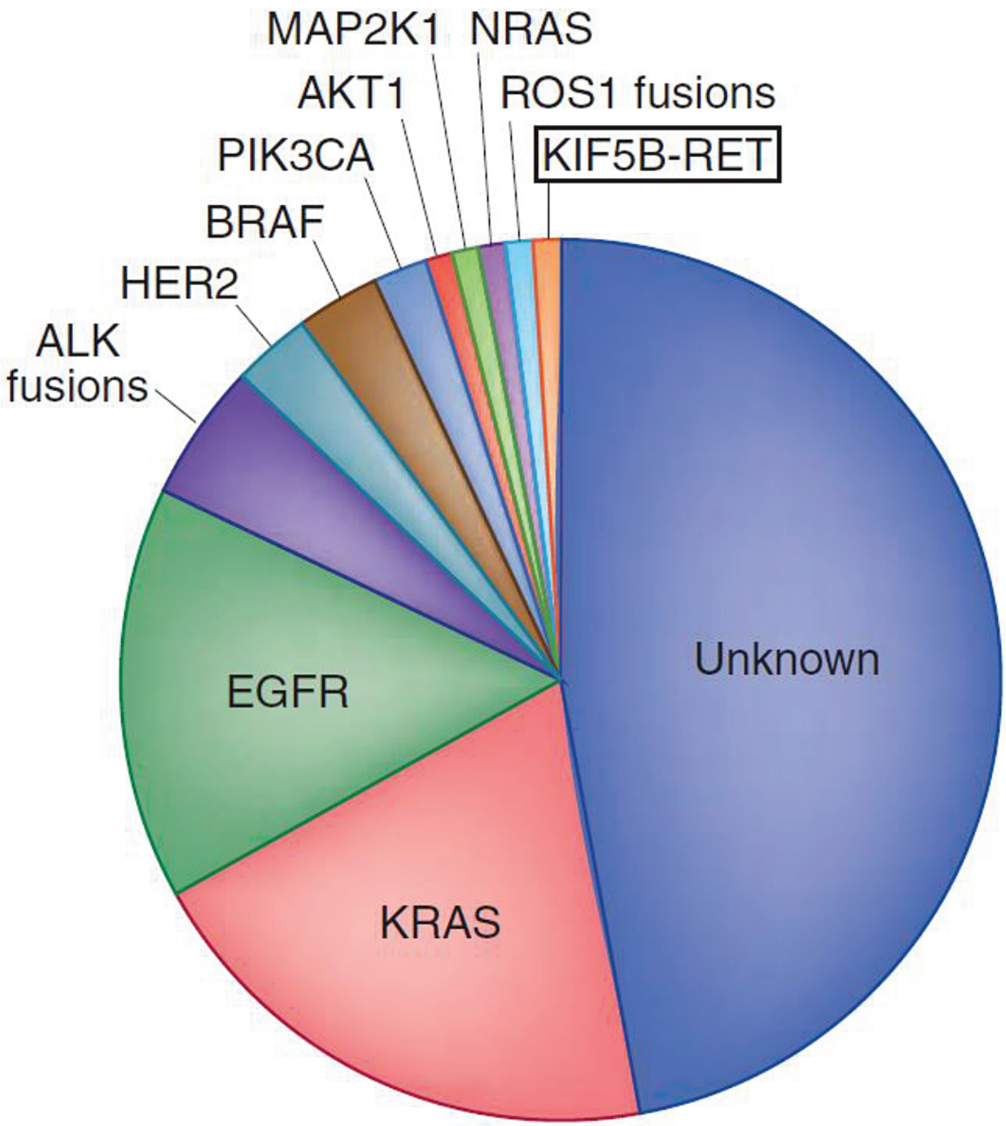

Fig. 1

Earlier attempts with oral pan-HER tyrosine kinase inhibitors (TKIs) such as lapatinib and neratinib has only modest activity and extra dose-limiting toxicities, primarily severe rash and diarrhea, due to unavoidable inhibition of wild-type epidermal growth factor receptor (EGFR).[8,9] Zongertinib (BI 1810631) is introduced as a novel, oral, irreversible, and highly selective HER2 TKI, rationally designed to spare wild-type EGFR action. This engineered selectivity minimizes off-target toxicity. In the pivotal phase IB Beamion LUNG-1 trial, zongertinib demonstrated profound and durable efficacy, achieving a 71% objective response rate (ORR) in the tyrosine kinase domain (TKD) cohort. Crucially, it maintained a manageable safety profile even without any ILD. This favorable efficacy and safety profile, coupled with evidence of systemic response in patients with brain metastases, positions zongertinib as a major therapeutic advance, fundamentally altering the treatment algorithm for advanced HER2-mutant NSCLC.[10]

Regulatory Status and National Comprehensive Cancer Network Incorporation

Zongertinib received ultra-fast approval from the U.S. FDA on August 8, 2025,[11] based on its high safety and efficacy data observed in the Beamion LUNG-1 trial.[12] Soon after U.S. FDA approval, zongertinib was immediately incorporated into the version 8.0 2025 of the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines, securing a preferred subsequent therapy for advanced HER2-mutant NSCLC.[13]

Mechanism of Action

Zongertinib (BI 1810631) is an orally administered, small-molecule compound. Its low molecular weight (535.60 g/mol) is a key feature, suggestive of good oral bioavailability

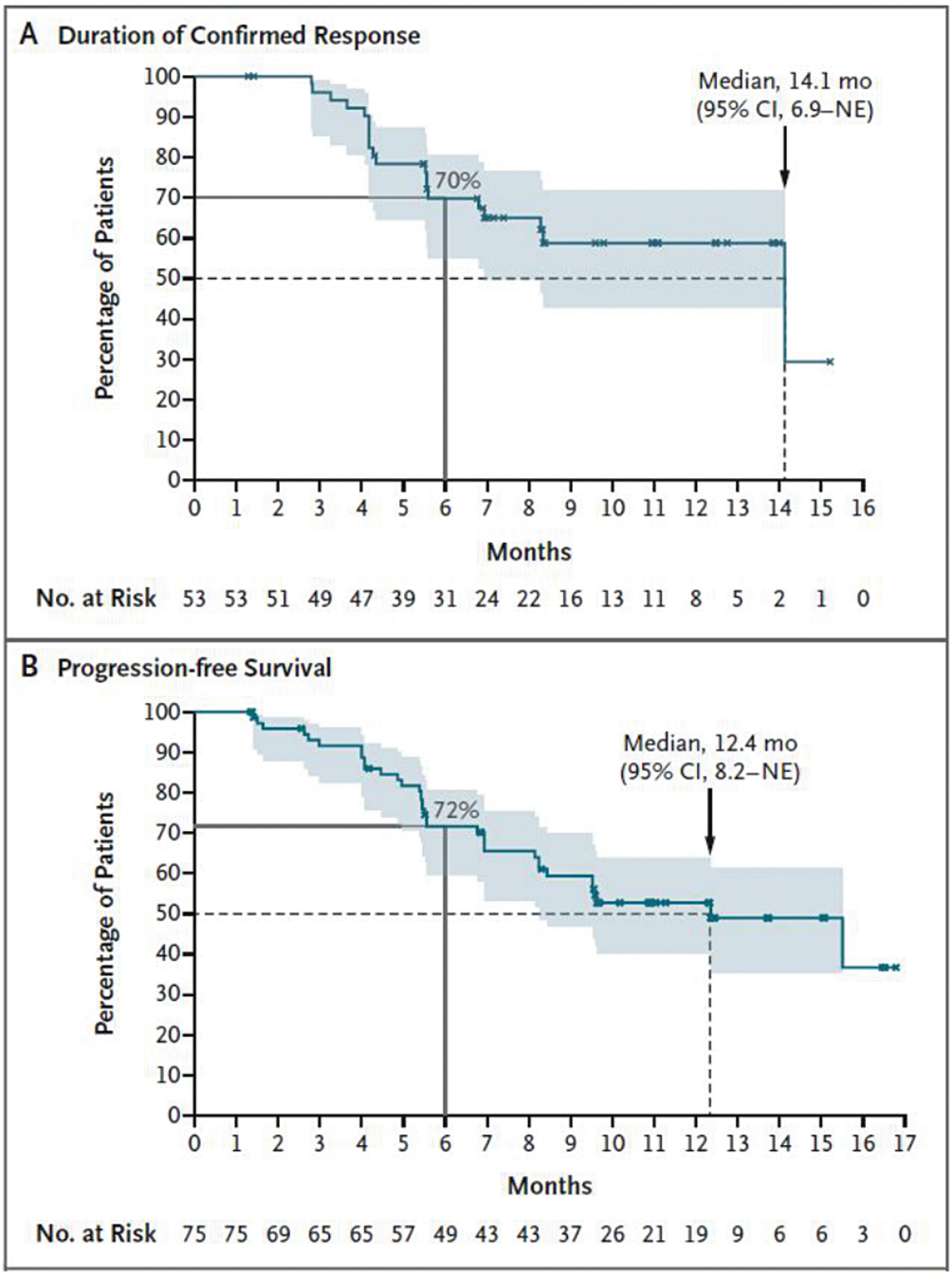

Fig. 2

and potential to cross the blood–brain barrier in HER2-mutant NSCLC.[8]

Zongertinib is defined as a highly potent, irreversible (covalent) HER2 inhibitor. It selectively binds to the TKD of both wild-type and mutated HER2 receptors. The core of zongertinib's pharmacological differentiation lies in its molecular selectivity. It was rationally engineered to potently block HER2 signaling while unequivocally sparing wild-type EGFR. This engineered selectivity is the direct pharmacological solution to the dose-limiting EGFR-related toxicities and TKI-related skin and GI adverse events.[9] A particularly crucial finding was zongertinib's sustained efficacy in HER2-dependent human cancer cells that had already developed resistance to T-DXd. This lack of cross-resistance suggests that zongertinib could serve as a valuable option following progression on T-DXd.[14]

Dosage and Administration

Zongertinib is administered orally.[6] The recommended dose: The standard recommended dose is 120 mg orally once daily with or without food. For patients weighing 90 kg or more, the dose may be increased to 180 mg orally once daily and continue until disease progression or the occurrence of unacceptable toxicity.[10]

Adverse Effect

Zongertinib demonstrated a significantly better tolerability profile compared with previously used oral TKIs. The overall incidence of treatment-related adverse events (TRAEs) across the phase IA population was 82%, with the vast majority being mild (grade 1 or 2). The most common all-grade TRAEs were generally manageable class effects, specifically diarrhea (51%) and rash (16%). Some other grade 1 to 2 toxicities were hepatotoxicity (22%), nausea (15%), dry skin (15%), pruritus (13%), decreased white cell count (13%), anemia (12%), decreased neutrophil count (12%), and nail disorder (11%).[10] Crucially, the rate of high-grade events was low. Grade 3 drug-related events occurred in only 10% of patients in the primary TKD cohort ($N = 75$), and across the phase IA data, grade ¾ events occurred in 10% of patients, with no reported grade 4 or grade 5 TRAEs. The most defining safety characteristic of zongertinib, which provides a key competitive advantage over T-DXd, is the absence of drug-related ILD or pneumonitis. Across the entire Beamion LUNG-1 trial, no cases of drug-related ILD were reported[6] (►**Figs. 1** and **2**).

Future Directions

The most critical ongoing investigation is the phase III Beamion LUNG-2 study.[15] This trial is designed to evaluate zongertinib in the first-line setting for advanced HER2-mutant NSCLC, comparing its efficacy and safety against the current standard of care. Future research efforts are warranted to investigate combination therapies. Preclinical data supporting enhanced activity when zongertinib is combined with T-DXd or KRAS G12C inhibitors[16] provides a strong scientific rationale for developing future clinical trials. This can be evaluated in breast and GI her-2 positive cancers too.

Conclusion

Zongertinib showed strong effectiveness, marked by a 71% ORR and a lasting median progression-free survival of 12.4 months for patients who had prior treatment. Additionally, zongertinib retains considerable effectiveness (48% ORR) even when the disease is resistant to T-DXd. This potency, coupled with a far better safety profile—notably avoiding drug-induced ILD and the ease of taking it orally, drove its accelerated approval and quick uptake as a favored preferred subsequent therapy in the NCCN guidelines. With proven initial activity inside the brain and an ongoing phase III study for initial, first-line use, zongertinib is set to fundamentally change the treatment standard, giving patients with HER2-mutant NSCLC an easy, highly potent, and more tolerable molecular treatment choice.

Conflict of Interest
None declared.

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