Targeting HER2 in advanced non-small cell lung cancer: The emerging role of zongertinib

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Non-small cell lung cancer (NSCLC) remains one of the leading causes of cancer-related mortality worldwide. Among its molecular subtypes, mutations in the *human epidermal growth factor receptor 2* (*HER2*) gene, particularly exon 20 insertions, indicate a distinct oncogenic driver. These alterations are more frequently observed in younger, female, never-smoking patients and are associated with an aggressive clinical course. Despite recognition of HER2 as a therapeutic target, treatment strategies for *HER2*-mutant NSCLC have historically been limited, with earlier HER2-directed approaches yielding only modest efficacy and considerable toxicity. Zongertinib (BI 1810631) is a next-generation, oral, highly selective, irreversible tyrosine kinase inhibitor designed to inhibit *HER2* exon 20 insertions and other activating *HER2* mutations, while sparing epidermal growth factor receptor (EGFR) signaling and thereby minimizing off-target toxicities. Preclinical studies have demonstrated robust antitumor activity in *HER2*-mutant NSCLC models, and early-phase clinical trials have confirmed encouraging efficacy and a favorable safety profile in patients with advanced disease. In recognition of these results, the US Food and Drug Administration granted accelerated approval to zongertinib for the treatment of unresectable or metastatic non-squamous NSCLC harboring *HER2* tyrosine kinase domain-activating mutations, including expansion into the first-line setting. This article summarizes the molecular landscape of *HER2*-mutated NSCLC, the clinical development of zongertinib, and the evidence supporting its use in advanced disease. By providing a focused overview of zongertinib's therapeutic role, it highlights a meaningful advance for a subgroup of patients with NSCLC that has long lacked effective and tolerable targeted options.

Keywords

Antibody–drug conjugates , carcinoma, non-small-cell lung, Erb-B2 receptor tyrosine kinases, *HER2*-mutated non-small cell lung cancer, molecular targeted therapy, precision medicine, tyrosine kinase inhibitors, zongertinib

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Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide.[1] Over the past two decades, the molecular characterization of NSCLC has transformed the therapeutic landscape by enabling the development of targeted therapies that have significantly improved outcomes in subsets of patients.[2] Among the less common but clinically significant molecular alterations in NSCLC are mutations in the *human epidermal growth factor receptor 2* (*HER2*) gene, observed in approximately 2–4% of lung adenocarcinomas.[3–5]

HER2 mutations, particularly exon 20 insertions, represent a distinct oncogenic driver in NSCLC. These alterations are more frequently identified in younger, female, never-smoking patients and confer an aggressive disease course.[4,6] Unlike *HER2* amplification or HER2 overexpression commonly targeted in breast and gastric cancers, *HER2*-mutant NSCLC is driven primarily by activating kinase domain mutations, which historically have proven challenging to target effectively.[5,7,8] Despite the identification of HER2 as a therapeutic target, treatment options for *HER2*-mutant NSCLC have been limited, with modest efficacy and significant toxicity associated with earlier HER2-directed therapies.[9–13] While systemic chemotherapy and immunotherapy have advanced, patients with *HER2*-mutated NSCLC often derive limited benefit from these standard treatments and remain at high risk for early disease progression.[14–16] This underscores the urgent need for novel targeted therapies specifically designed to inhibit *HER2*-mutant oncogenic signaling in NSCLC.

Zongertinib (BI 1810631) is a next-generation, oral, highly selective, irreversible tyrosine kinase inhibitor (TKI) that targets *HER2* exon 20 insertions and other activating mutations and spares epidermal growth factor receptor (EGFR) signaling and thereby reduces off-target toxicities. Preclinical data have demonstrated its potent antitumor activity in *HER2*-mutant NSCLC models, and early-phase clinical trials have shown promising efficacy and a favorable safety profile in patients with advanced disease who have received prior systemic therapy.[17–19] This

article examines the molecular landscape of *HER2*-mutated NSCLC in the context of zongertinib's development and highlights the clinical evidence supporting its use in patients with unresectable or metastatic disease. We also explore zongertinib's potential place in therapy and future directions for optimizing treatment in this challenging molecular subtype. By offering a focused overview of zongertinib's clinical development, this article aims to inform on-going efforts to improve outcomes for patients with *HER2*-mutant NSCLC, which has been a subgroup that has historically lacked effective and tolerable targeted treatment options.

HER2 molecular landscape and historical treatments

HER2, also known as *erb-b2 receptor tyrosine kinase 2 (ERBB2)*, is an oncogene that encodes a receptor tyrosine kinase in the HER/erythroblastic oncogene B (ERBB) family, which also includes EGFR (HER1), HER3, and HER4.[3,20] Each receptor comprises three key structural domains: an extracellular region responsible for ligand binding, a single transmembrane helix anchoring the receptor in the membrane, and an intracellular tyrosine kinase domain (TKD). Unlike other family members, HER2 lacks a known ligand and activates signaling through dimerization, either with other HER receptors or as homodimers when overexpressed, leading to sustained oncogenic signaling.[21] The molecular landscape of HER2 alterations in NSCLC includes three main categories: gene mutations, gene amplifications, and protein overexpression.[22] Importantly, mutations differ fundamentally from *HER2* amplification or protein overexpression seen in breast and gastric cancers, and their presence necessitates a tailored therapeutic approach.[5,7,8]

Molecular subtypes of *HER2* alterations

HER2 mutations represent a distinct oncogenic driver with unique clinical and biological characteristics.[3] The most common *HER2* alterations in NSCLC are in-frame insertions within exon 20 in the TKD, particularly the A775_G776insYVMA variant.[7] These insertions lead to constitutive activation of HER2 signaling, promoting oncogenesis through persistent stimulation of the downstream pathways phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) and mitogen-activated protein kinase (MAPK).[20] Less frequently, point mutations or insertions in other regions of the *HER2* gene may also drive tumor growth, although their sensitivity to HER2-directed therapies can vary.[5,7,23] Understanding the specific functional consequences of these diverse mutations is crucial for guiding therapeutic strategies.[24,25]

Clinically, *HER2*-mutated NSCLC predominantly arises in patients with adenocarcinoma histology and is strongly associated with younger age, female sex, and a never-smoking history.[4,6] Patients tend to exhibit an aggressive course with a higher incidence of brain metastases.[26,27] Reinforcing their role as primary oncogenic drivers, *HER2* mutations are generally mutually exclusive with other actionable alterations such as *EGFR*, *anaplastic lymphoma kinase (ALK)*, or *ROS proto-oncogene 1, receptor tyrosine kinase (ROS1)*.[5,8]

HER2 gene amplification in NSCLC refers to an increased number of *ERBB2* gene copies within tumor cells. Amplification can occur through two distinct mechanisms: as a primary oncogenic driver, particularly in adenocarcinomas of patients with a smoking history, or as an acquired resistance mechanism following targeted therapies such as EGFR TKIs.[28–30] High-level *HER2* amplification has been associated with poor clinical outcomes, including shorter disease-free survival and a greater likelihood of pleural invasion.[31] While *HER2* amplification can lead to overexpression of the HER2 protein, it has not consistently predicted response to HER2-targeted therapies, and the clinical benefit from agents like trastuzumab has been limited in this setting.[32] However, antibody–drug conjugates (ADCs) such as trastuzumab deruxtecan (T-DXd) have shown preliminary activity in select amplified tumors, particularly those with high-level amplification.[28]

HER2 protein overexpression refers to increased HER2 protein levels on the tumor cell surface measured by immunohistochemistry (IHC). In NSCLC, high-level HER2 overexpression (IHC 3+) is relatively uncommon, observed in approximately 2–4% of cases.[31,33] Unlike breast cancer, where HER2 overexpression and *HER2* amplification are tightly correlated and predictive of response to HER2-targeted therapies, these alterations in NSCLC should be separately assessed in clinical practice.[4] Moreover, *HER2* mutations, in particular, represent a unique molecular subset with specific therapeutic vulnerabilities.[3–5,7,8]

In a significant regulatory milestone, based in part on the DESTINY-Lung01 study (A Phase 2, Multicenter, Open-Label, 2-Cohort Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-HER2 Antibody Drug Conjugate (ADC), for HER2-Over-Expressing or -Mutated, Unresectable and/or Metastatic Non-Small Cell Lung Cancer (NSCLC) (DESTINY-Lung01); ClinicalTrials.gov identifier: NCT03505710), the US Food and Drug Administration (FDA) granted accelerated, tumor-agnostic approval in April 2024 to T-DXd for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic therapy and have no satisfactory alternative treatment options.[34,35] This approval reflects the growing recognition of HER2 IHC 3+ as a clinically actionable biomarker across tumor types, including NSCLC.

Diagnostic challenges

Despite their significance, *HER2* mutations have historically been underrecognized due to limited routine testing and a lack of targeted therapies. Accurate and timely identification of *HER2* mutations is critical for patient selection for targeted therapies. *HER2* mutations in NSCLC, most commonly exon 20 insertions, are not reliably detected by IHC or *in situ* hybridization (ISH). These mutations typically occur independently of *HER2* gene amplification or HER2 protein overexpression and are often missed by traditional HER2 testing algorithms used in breast or gastric cancers. Importantly, many *HER2*-mutant tumors demonstrate only low to intermediate HER2 protein expression (IHC 1+ or 2+) and lack amplification, making them undetectable by IHC or ISH alone.[4,5,8,36] Although targeted assays like reverse transcription polymerase chain reaction (RT-PCR) offer high specificity for identifying a *HER2* mutation, they are limited to detecting only well-characterized gene alterations, which may result in missed identification of rarer or novel variants. As such, next-generation sequencing (NGS) is considered the gold standard for accurate identification of *HER2* mutations.[4,37]

HER2 gene amplification may be assessed using ISH techniques, such as fluorescence ISH, which quantify *ERBB2* copy number. However, gene amplification does not always lead to high protein expression, and some amplified tumors may show low IHC scores.[33,38,39] Amplification can also co-occur with other oncogenic drivers, complicating its interpretation. Only NGS reliably identifies *HER2* mutations and amplification, underscoring the need for routine, broad molecular profiling in all patients with advanced NSCLC to guide appropriate use of HER2-targeted therapies.[4,36,37]

Historical treatment approaches and limitations

Conventional chemotherapy and immunotherapy

Immunotherapy has significantly transformed the treatment landscape for advanced and metastatic NSCLC, with immune checkpoint inhibitors

(ICIs) now forming the backbone of first-line therapy for most patients without targetable mutations. The current standard of care for patients with advanced non-squamous NSCLC without driver alterations includes immunotherapy with or without platinum-pemetrexed-based chemotherapy, which has demonstrated improved overall survival (OS) and durable responses in broad, biomarker-unselected populations.[40–43]

However, in the subset of patients with *HER2*-mutant NSCLC, the clinical benefit of immunotherapy is less clear. Multiple retrospective studies have reported lower objective response rates (ORRs) to ICIs in this population, typically ranging from 7% to 27%, with limited durability of response.[15,16,44,45] This reduced efficacy is thought to be due in part to the "cold" tumor microenvironment commonly associated with *HER2*-mutated tumors, which is characterized by low programmed death-ligand 1 (PD-L1) expression, low tumor mutational burden, and minimal immune cell infiltration. These features parallel those seen in *EGFR*-mutated NSCLC, another subgroup known for its poor responsiveness to immunotherapy, and emphasize the need for molecularly guided therapies that directly address the oncogenic driver.[16,45] The addition of chemotherapy to immunotherapy appears to provide at least modest benefit in this setting, with a reported ORR of 37% and median progression-free survival (PFS) of 7.1 months, but these results still fall short of the efficacy typically observed with targeted therapies in other oncogene-driven NSCLC subtypes.[46,47] The development of HER2-directed therapies, including TKIs such as zongertinib and ADCs, is reshaping the treatment paradigm and offering renewed hope for this molecularly defined subgroup.

Monoclonal antibodies

Traditional anti-HER2 monoclonal antibodies, such as trastuzumab, which have revolutionized the treatment of *HER2*-amplified breast and gastric cancers, have demonstrated limited efficacy in *HER2*-mutated NSCLC.[32,48–52] Clinical trials evaluating trastuzumab, either alone or in combination with chemotherapy and pertuzumab, have generally yielded modest response rates but have not significantly improved outcomes compared with chemotherapy alone in patients with NSCLC harboring *HER2* mutations.[53,54] This modest efficacy may be explained by several factors, including the distinct oncogenic mechanism of *HER2* mutations, primarily exon 20 insertions, compared with gene amplification, and the often low levels of HER2 protein expression in mutated NSCLC, which may reduce the binding efficiency of monoclonal antibodies.[4,5,8] Furthermore, the bulky nature of exon 20 insertion mutations can sterically hinder the binding of certain antibodies to the HER2 receptor.[55] These challenges emphasize the need for agents specifically designed to target the unique characteristics of *HER2* mutations in NSCLC.

Antibody–drug conjugates

ADCs represent a significant advancement in HER2-targeted therapy for NSCLC. T-DXd is an ADC composed of a HER2-targeting monoclonal antibody linked to a topoisomerase I inhibitor payload.[56,57] T-DXd has demonstrated substantial efficacy in previously treated patients with *HER2*-mutated NSCLC.[58,59] In the DESTINY-Lung01 trial, T-DXd achieved an ORR of approximately 55%, a median PFS of 8.2 months and a median OS of 17.8 months in this patient population.[60] These findings were subsequently confirmed in the DESTINY-Lung02 study (A Phase 2, Multicenter, Randomized Study of Trastuzumab Deruxtecan in Subjects With *HER2*-mutated Metastatic Non-small Cell Lung Cancer (NSCLC) (DESTINY-LUNG02); ClinicalTrials.gov identifier: NCT04644237), which established T-DXd as a standard of care in this setting, with a recommended starting dose of 5.4 mg/kg administered every 3 weeks.[61]

On August 11, 2022, the FDA granted accelerated approval to T-DXd for adult patients with unresectable or metastatic NSCLC harboring activating *HER2* mutations, as identified by an FDA-approved test and following prior systemic therapy. This approval represented the first FDA-authorized treatment specifically for *HER2*-mutant NSCLC.[62]

While T-DXd is effective, it carries specific toxicities, most notably neutropenia, left ventricular dysfunction, interstitial lung disease (ILD), and pneumonitis. ILD was observed in up to 13% of patients, including fatal cases, necessitating vigilant monitoring and prompt management of pulmonary symptoms.[60,61] Ado-trastuzumab emtansine (T-DM1) has shown modest activity with an ORR of 44%. However, a median duration of response (DoR) of only 4 months has limited the drug's appeal due to its lack of durability.[63] Similar to T-DXd, T-DM1 also carries a risk of pulmonary toxicity. Importantly, sequential use of ADCs with similar mechanisms of action, such as T-DXd and T-DM1, is generally discouraged due to overlapping toxicities and concerns regarding diminished efficacy.[64]

Additional HER2-targeted ADCs are currently in various stages of clinical development. One such agent, trastuzumab rezetecan (SHR-A1811), is an investigational HER2-directed ADC showing promise in *HER2*-mutant NSCLC.[65,66] In the phase II HORIZON-Lung study (Phase I/II Clinical Study of the Safety, Tolerability, Pharmacokinetics, and Efficacy of SHR-A1811 for Injection in Subjects With Advanced Non-small Cell Lung Cancer Who Have HER2 Expression, Amplification, or Mutation; ClinicalTrials.gov identifier: NCT04818333), trastuzumab rezetecan achieved a confirmed ORR of 73% and a median PFS of 11.5 months in previously treated patients. The most common grade 3–4 adverse events included neutropenia, leukopenia, anemia, and thrombocytopenia. ILD was reported in 5% of patients, but no treatment-related deaths occurred.[67] These results support trastuzumab rezetecan's continued clinical development as a potential next-generation ADC for *HER2*-mutant NSCLC.

Pan-HER inhibitors and multi-targeted tyrosine kinase inhibitors

Early attempts to target HER2 in NSCLC involved pan-human epidermal growth factor receptor (pan-HER) inhibitors or multi-targeted TKIs that also inhibit EGFR, such as afatinib, dacomitinib, and neratinib. While these agents demonstrated some preclinical activity against *HER2*-mutated cell lines, their clinical efficacy in patients with NSCLC harboring *HER2* mutations was limited by off-target toxicities and suboptimal potency against specific *HER2* exon 20 insertions. Response rates were generally low, and safety profiles were often challenging due to EGFR-related adverse events.[12,13,68–71]

Newer agents, including poziotinib and pyrotinib, have shown moderate activity in *HER2*-mutant NSCLC, with ORRs up to 36% for pyrotinib and 39% for poziotinib. However, their clinical utility is limited by short durations of response and dose-limiting toxicity (DLT) profiles related to EGFR inhibition, with rash and diarrhea.[9–11,25,72–76] Notably, the FDA denied approval of poziotinib for the treatment of NSCLC with *HER2* exon 20 insertion mutations without additional data from a randomized controlled study, citing concerns over its safety profile, high incidence of adverse events, including rash, diarrhea, and stomatitis, and a lack of meaningful efficacy improvement over existing therapies.[77]

Sevabertinib (BAY 2927088), a reversible mutant *HER2* and *EGFR* TKI, has shown promising activity in *HER2*-mutant NSCLC.[78,79] In the phase I/II SOHO-01 trial (An Open Label, First-in-human Study of BAY 2927088

in Participants With Advanced Non-small Cell Lung Cancer (NSCLC) Harboring an *EGFR* and/or *HER2* Mutation; ClinicalTrials.gov identifier: NCT05099172), sevabertinib achieved an ORR of 64% with a median PFS of 8.3 months in patients naive to HER2-targeted therapy (cohort D; n=81). Among patients previously treated with HER2-directed ADCs, the ORR was 38% with a median PFS of 5.5 months (cohort E; n=55). In patients naive to any systemic anticancer therapy for locally advanced or metastatic disease, sevabertinib produced an ORR of 71% with a median DoR of 11 months (cohort F; n=73). Consistent with dual EGFR inhibition, treatment-related adverse events (TRAEs) included diarrhea, rash, paronychia, and stomatitis. Diarrhea was the most common adverse event, occurring in 84–91% of patients, with grade 3 or higher diarrhea reported in 5–23%. Dose reductions were required in 25–35% of patients, while treatment discontinuation due to drug-related adverse events occurred in approximately 3%. No cases of ILD were reported.[80] These findings support sevabertinib as an effective therapeutic option in *HER2*-mutant NSCLC, although its clinical use may be limited by EGFR-related toxicities. In November 2025, sevabertinib received accelerated approval from the FDA for the treatment of patients with non-squamous NSCLC harboring activating *HER2* TKD mutations following prior systemic therapy.[81]

The limitations of historical HER2-targeted approaches in NSCLC illustrate the need for more selective, potent, and tolerable inhibitors, paving the way for the development of zongertinib.

Zongertinib: mechanism of action and preclinical rationale

Mechanism of action

Zongertinib is a next-generation, oral, irreversible TKI. Unlike earlier-generation HER2-targeted therapies developed for HER2-overexpressing breast and gastric cancers, zongertinib was designed to inhibit HER2 kinase activity in tumors driven by activating mutations, particularly exon 20 insertion variants, which are the predominant oncogenic driver mutations in *HER2*-mutant NSCLC. Zongertinib targets the adenosine triphosphate (ATP)-binding site of HER2, where it forms a covalent bond with cysteine 805, and this covalent interaction is essential for zongertinib's potent ability to inhibit cell proliferation. By selectively targeting *HER2* exon 20 insertions and other activating mutations, zongertinib effectively disrupts oncogenic signaling through the two key drivers of tumor growth in *HER2*-mutant NSCLC, the MAPK and PI3K/AKT pathways.[17]

In contrast to the ADCs, which rely on targeted delivery of cytotoxic agents via antibody-mediated binding to HER2, zongertinib exerts its effect through direct, irreversible inhibition of the HER2 kinase domain.[17,60,63,67] Importantly, zongertinib does not inhibit wild-type EGFR, which is a common source of DLTs in earlier-generation ERBB inhibitors. This EGFR-sparing profile allows for higher therapeutic dosing, improved tolerability and distinguishes zongertinib from agents such as afatinib, neratinib, and poziotinib.[9,12,17,70]

Preclinical development

Preclinical studies have demonstrated that zongertinib exhibits potent and selective activity against a range of *HER2* mutations, including the most prevalent A775_G776insYVMA exon 20 insertion. In cell proliferation assays, zongertinib effectively inhibited the growth of Ba/F3 (a murine interleukin-3 dependent pro-B cell line) models expressing *HER2* wild-type or various *HER2* mutations, as well as human cancer cell lines dependent on *HER2*, including those with *neuregulin 1 (NRG1)* fusions, A775_G776insYVMA exon 20 insertion and other activating mutations, or high HER2 expression. In contrast, significantly higher concentrations were required to inhibit proliferation in *HER2*-independent models, including those reliant on EGFR wild type. Sensitivity across a large panel of human cancer cell lines correlated with HER2 expression levels and mirrored findings from large-scale clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) and RNA interference (RNAi) screens targeting *HER2*.[17]

In vivo, zongertinib monotherapy reduced tumor growth in both cell line-derived and patient-derived xenograft models dependent on A775_G776insYVMA exon 20 insertion or high HER2 expression. Mechanistically, zongertinib downregulated phosphorylated HER2 and suppressed downstream MAPK and PI3K/AKT signaling in a time- and dose-dependent manner. This included reduced levels of phosphorylated extracellular signal-regulated kinase (ERK) and decreased expression of ERK target genes such as *dual-specificity phosphatase 6 (DUSP6), sprouty RTK signaling antagonist 4 (SPRY4), ETS variant transcription factor 4 (ETV4), ETS variant transcription factor 5 (ETV5), and FOS-like antigen 1 (FOSL1)*. Consistent with its biochemical selectivity, much higher doses are required to inhibit EGFR phosphorylation in EGFR wild-type-dependent cells.[17]

Zongertinib demonstrated potent antitumor activity in *HER2*-dependent NSCLC xenograft models resistant to T-DXd. Synergistic effects were also observed when combined with other targeted agents, including Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C inhibitors and the ADCs T-DXd and T-DM1, suggesting the potential for combination-based therapeutic strategies.[17]

These promising preclinical findings provided the rationale for advancing zongertinib into clinical development for patients with advanced *HER2*-mutated NSCLC, particularly those who have progressed on standard systemic therapies. Early-phase trials were launched to assess safety, pharmacokinetics, and antitumor activity in this molecularly selected patient population.

Zongertinib: clinical development

The safety and efficacy of zongertinib have been investigated in the on-going multicenter, multicohort phase Ia–Ib Beamion LUNG-1 study (Beamion LUNG-1: An Open Label, Phase I Dose Escalation Trial, With Dose Confirmation and Expansion, of Zongertinib [BI 1810631] as Monotherapy in Patients With Advanced or Metastatic Solid Tumors With *HER2* Aberrations; ClinicalTrials.gov identifier: NCT04886804) in patients with *HER2*-altered solid tumors.[18,19]

Phase Ia: first-in-human dose escalation study[19]

The phase Ia portion of the Beamion LUNG-1 study was a dose-escalation trial designed to assess the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of zongertinib in patients with advanced, metastatic solid tumors harboring *HER2* alterations. Eligible participants included patients with advanced, unresectable, or metastatic solid tumors harboring confirmed *HER2* aberrations, who were refractory to or ineligible for standard therapies. *HER2* alterations included overexpression (2+ or 3+ by IHC), gene amplification, nonsynonymous somatic mutation, or a gene rearrangement involving *HER2* or *NRG1*. Patients with asymptomatic brain metastasis were eligible for inclusion.

The maximum tolerated dose (MTD) and DLTs were the primary endpoints. The second endpoint was tumor response. Zongertinib was administered in escalating doses using two dosing schedules: twice daily (BID) at 15,

30, 60, 100, or 150 mg, and once daily (QD) at 60, 120, 180, 240, 300, or 360 mg, in 3-week treatment cycles.

As of May 23, 2024, 105 patients were treated, and the MTD was not reached for either the BID or QD dosing regimens. DLTs were infrequent, and only two patients had a DLT during the MTD evaluation period (grade 3 diarrhea and grade 3 thrombocytopenia with 240 mg QD and 360 mg QD, respectively). Other DLTs included grade 2 edema (60 mg BID), grade 2 diarrhea (150 mg BID), grade 3 elevated alanine aminotransferase (ALT) (180 mg QD), grade 3 diarrhea and grade 4 thrombocytopenia (240 mg QD), and additional events at higher doses, including grade 2 ejection fraction decreased, grade 3 thrombocytopenia, and grade 3 elevated ALT and aspartate aminotransferase (AST). Grade 2 acute interstitial pneumonitis was identified after the MTD evaluation period at 360 mg QD.

TRAEs were generally manageable and reported in 82% of patients, with grade ≥3 TRAEs occurring in 10%. The most commonly observed TRAEs included diarrhea (50% overall; 1% grade ≥3), rash (16%; 2%), anemia (10%; 0%), decreased appetite (10%; 1%), and elevated alanine transaminase (10%; 4%).

Based on the overall safety and tolerability profile, 120 mg QD and 240 mg QD were selected as recommended doses for the phase Ib expansion. Preliminary efficacy signals were observed across *HER2*-mutated tumor types. The confirmed investigator-assessed ORR was 30%, with all responses classified as partial responses. The median DoR was 12.7 months, and the median duration of disease control was 8.4 months.

Significantly, patients with NSCLC exhibited strong clinical responses to zongertinib. Among 54 evaluable patients with NSCLC, the confirmed ORR was 35%. Antitumor activity was observed across key subgroups, including patients harboring the A775_G776insYVMA mutation (ORR: 38%) and those previously treated with HER2-directed therapies (ORR: 28%). The median PFS reached 17.2 months for patients with NSCLC receiving zongertinib QD, indicating the potential for durable clinical benefit.

Phase Ib: expansion study in *HER2*-mutant advanced non-small cell lung cancer[18]

In the phase Ib expansion portion of the Beamion LUNG-1 study, zongertinib demonstrated significant and durable antitumor activity with a manageable safety profile in previously treated *HER2*-mutant NSCLC. Three cohorts were analyzed: cohort 1 (*HER2* TKD mutations without prior HER2-directed therapy), cohort 5 (*HER2* TKD mutations with prior ADC therapy), and cohort 3 (non-TKD *HER2* mutations). Subsequently, results from cohort 4 (*HER2* TKD mutation with active brain metastases) and cohort 2 (treatment-naive *HER2* TKD-mutant disease) have been presented at major international conferences.

The trial initially employed a randomized dose-finding approach in cohort 1 by comparing 120 mg versus 240 mg of zongertinib daily. Although both doses yielded similar efficacy, the 120 mg dose was selected for further development due to improved tolerability and fewer treatment interruptions. Subsequent patients in all cohorts received the 120 mg once-daily dose. The primary endpoint was confirmed ORR per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by independent central review (cohorts 1 and 5) or investigator review (cohort 3). Secondary endpoints included DoR, PFS, and safety.

Table 1 summarizes the clinical data from the phase Ib Beamion LUNG-1 trial.[18]

Cohort 1 (*HER2* TKD mutations, n=75 at 120 mg daily): zongertinib demonstrated robust and durable antitumor activity. The confirmed ORR was 71% (95% confidence interval [CI]: 60–80; p<0.001), including 7% complete responses and 64% partial responses. The disease control rate (DCR) was 96%, with a median DoR of 14.1 months and median PFS of 12.4 months. Among 27 patients with evaluable baseline brain metastases, the intracranial ORR per Response Assessment in Neuro-Oncology Brain

Table 1: Summary of zongertinib in *HER2*-mutant non-small cell lung cancer[18]

Category	Cohort 1*	Cohort 5†	Cohort 3‡
ORR	71% (95% CI: 60–80)	48% (95% CI: 32–65)	30% (95% CI: 15–52)
Complete response	7%	3%	0%
Partial response	64%	45%	30%
Disease control rate	96% (95% CI: 89–99)	97% (95% CI: 84–99)	65% (95% CI: 43–82)
Median DoR	14.1 months (95% CI: 6.9–NE)	Not yet mature	Not yet mature
Median PFS	12.4 months (95% CI: 8.2–NE)	Not yet mature	Not yet mature
Intracranial ORR (RANO-BM)	41% (in 27 evaluable with brain metastases)	Not reported	Not reported
Grade ≥3 TRAEs	17%	3%	25%
Most common TRAEs	Diarrhea (56%), rash (33%), increase in ALT (21%) and AST (24%)	Similar with fewer high-grade events	Similar with two episodes of drug-induced liver injury
Drug-related ILD	None	None	None
Treatment discontinuation due to TRAEs	3%	6%	10%
Notable subgroup response	A775_G776insYVMA: 81% P780_Y781insGSP: 75%	Prior T-DXd (n=22): 41% ORR, 5.3-month DoR, 6.8-month PFS	Extracellular (S310F), transmembrane (V659E) responded

**Cohort 1 = patients with TKD mutations (n=75 at 120 mg).*
†Cohort 5 = patients with TKD mutations and prior HER2-directed ADC therapy (n=31 at 120 mg).
‡Cohort 3 = patients with non-TKD mutations (n=20 at 120 mg).
ADC = antibody–drug conjugate; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; DoR = duration of response; HER2 *= human epidermal growth factor receptor 2; ILD = interstitial lung disease; NE = not evaluable; ORR = objective response rate; PFS = progression-free survival; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases; T-DXd = trastuzumab deruxtecan; TKD = tyrosine kinase domain; TRAEs = treatment-related adverse events.*

Metastases (RANO-BM) criteria was 41%. Responses were observed across *HER2* TKD mutation subtypes, with an ORR of 81% for A775_G776insYVMA and 75% for P780_Y781insGSP insertions.

Cohort 5 (*HER2* TKD mutations with prior HER2-directed ADC, n=31 at 120 mg daily): Despite prior HER2-targeted therapy, including T-DXd in 22 patients, zongertinib achieved a confirmed ORR of 48% (95% CI: 32–65). Importantly, the ORR among those previously treated with T-DXd was 41%, with a median DoR of 5.3 months and median PFS of 6.8 months, suggesting a lack of complete cross-resistance and a potential role for sequential HER2 targeting strategies.

Cohort 3 (non-TKD *HER2* mutations, n=20 at 120 mg daily): Among this molecularly heterogeneous group, the confirmed ORR was 30% (95% CI: 15–52), with responses noted across mutation types, including extracellular (S310F) and transmembrane (V659E) domain alterations. These findings support the activity of zongertinib beyond classical TKD alterations; however, additional validation is warranted in larger, biomarker-defined cohorts.

Cohort 2 (*HER2* TKD mutation who had not previously received treatment, n=74 at 120 mg daily): Presented at the European Society for Medical Oncology (ESMO) Congress 2025, zongertinib demonstrated high systemic activity in the first-line setting, with a confirmed ORR of 77% (95% CI: 66–85; p<0.0001), including 8% complete responses and 69% partial responses, and a DCR of 96% (95% CI: 89–99). Responses were rapid and durable, with 6-month DoR and PFS rates of 80% and 79%, respectively, although median DoR and median PFS were not yet mature at the time of reporting.[82]

Cohort 4 (*HER2* TKD mutation with active brain metastases, n=30 at 120 mg daily): Presented at the International Association for the Study of Lung Cancer (IASLC) 2025 World Conference on Lung Cancer, zongertinib showed meaningful intracranial activity in patients with active brain metastases, with an intracranial ORR of 50% by RECIST v1.1 and 43% by RANO-BM. Most patients had received prior systemic therapy (43% with one prior line and 23% with ≥2 prior lines), and 80% had not received prior brain radiotherapy, supporting central nervous system (CNS) activity in a clinically challenging population.[83]

Zongertinib was generally well tolerated across all cohorts. In cohort 1, grade ≥3 TRAEs occurred in 17% of patients, most commonly elevated liver enzymes (ALT 7%, AST 5%). The most frequent TRAEs were diarrhea (56%), rash (33%), and transaminitis, and the majority were grade 1–2. Only 3% of patients discontinued treatment due to adverse events. No cases of drug-related ILD were reported in any cohort. The 240 mg dose, while associated with similar efficacy, resulted in a higher rate of grade ≥3 TRAEs, including diarrhea, and more frequent dose reductions, supporting the selection of the 120 mg dose for future development.

In summary, zongertinib demonstrated high response rates in *HER2* TKD-mutant disease, activity post-T-DXd, preliminary efficacy in non-TKD mutations, potential CNS activity, and a manageable safety profile limiting ILD and significant EGFR-like toxicities.

Clinical considerations and early real-world evidence

Zongertinib has demonstrated promising efficacy and a favorable safety profile in early-phase trials. However, its clinical use also requires careful consideration of potential drug–drug interactions. A phase I drug–drug interaction study in healthy male volunteers showed that co-administration with the strong cytochrome P450 3A (CYP3A) inducer carbamazepine reduced zongertinib exposure by approximately 64% and peak plasma concentration by 44%. These pharmacokinetic changes were accompanied by increased clearance and a shortened half-life, demonstrating zongertinib's susceptibility to CYP3A-mediated metabolism.[84] From a clinical perspective, assessing concomitant medications for CYP3A interaction potential will be essential to optimize treatment efficacy in patients receiving zongertinib.

The first real-world data on zongertinib were reported in six pretreated patients with metastatic *HER2*-mutant NSCLC.[85] Despite prior progression on multiple lines of therapy, including T-DXd (which was discontinued for pneumonitis in two patients), zongertinib achieved an ORR of 83% and a DCR of 100%, with responses including one complete response in a patient with brain metastases. Treatment was well tolerated, with only one grade 1 adverse event (hypertension) and no discontinuations. These findings support zongertinib's potential as an effective and safe option even in patients with reduced performance status, brain metastases, or prior drug-induced pneumonitis.

Discussion: clinical positioning and future directions

The emergence of zongertinib as a targeted therapy for *HER2*-mutant NSCLC marks a major advancement for a historically underserved molecular subset of patients. The phase Ib Beamion LUNG-1 trial demonstrated that zongertinib delivers a compelling combination of efficacy and tolerability in previously treated patients. With a confirmed ORR of 71%, median DoR and PFS over a year, and a low incidence of grade ≥3 toxicities, zongertinib favorably compares with existing HER2-directed therapies, including ADCs such as T-DXd, which are limited by higher rates of ILD and systemic toxicity.[18,34,60]

Zongertinib's oral administration and HER2-selective, EGFR wild-type-sparing design address many of the shortcomings of earlier-generation HER2 inhibitors.[17] Pan-ERBB inhibitors, such as afatinib, poziotinib, and pyrotinib, while mechanistically promising, have yielded only modest efficacy and are frequently poorly tolerated due to EGFR-related off-target effects, such as rash and diarrhea.[9,11,12,73] ADCs, while effective, require intravenous infusion and carry a substantial risk of serious adverse events.[60,63] In contrast, zongertinib offers a more convenient and potentially safer alternative, with a distinct and favorable safety profile.[18]

In recognition of these clinical results, the FDA granted accelerated approval to zongertinib in August 2025 for the treatment of unresectable or metastatic non-squamous NSCLC with *HER2* TKD activating mutations following prior systemic therapy. This marked the first HER2-selective TKI specifically indicated for this patient population. More recently, in February 2026, the FDA also granted accelerated approval to zongertinib as an expanded indication for first-line treatment. The FDA-approved dosing for zongertinib is weight-based: 120 mg orally QD for patients weighing less than 90 kg and 180 mg orally QD for those weighing 90 kg or more. The medication may be taken with or without food and continued until disease progression or unacceptable toxicity occurs.[86,87]

In clinical practice, the therapeutic landscape for *HER2*-mutant NSCLC includes three FDA-approved targeted options: T-DXd, zongertinib, and sevabertinib. Zongertinib is currently the only agent approved for use in the first-line setting and represents a significant shift toward earlier use of HER2-directed therapy. Zongertinib may be considered an important therapeutic option in both first-line and subsequent-line settings for *HER2*-mutant NSCLC, including patients who have

progressed on or cannot tolerate T-DXd. The potential intracranial activity is especially valuable in this population, where brain metastases are a common and clinically challenging complication.[26,27] However, optimal treatment sequencing and the integration of HER2-targeted therapies with chemoimmunotherapy remain unclear and require prospective evaluation. If an ADC is used in earlier lines, transition to a HER2-directed TKI represents a reasonable subsequent strategy. In contrast, there are currently no prospective data to guide sequencing between HER2 TKIs, including the use of zongertinib after sevabertinib or *vice versa*.

Despite encouraging results, several limitations should be considered. The evidence supporting zongertinib is derived from early-phase, single-arm studies, and survival data remain immature. Sample sizes, especially within certain molecular subgroups, including non-TKD mutations, are limited, and cross-trial comparisons with other HER2-directed therapies should be interpreted with caution. In addition, mechanisms of acquired resistance to zongertinib are not yet well characterized, and there are no prospective data to inform optimal sequencing between HER2-targeted agents. There is a need for continued investigation to refine patient selection and therapeutic strategies.

Looking ahead, several areas of development remain critical for optimizing zongertinib's clinical utility. The on-going Beamion LUNG-2 trial (Beamion LUNG 2: A Phase III, Open-label, Randomized, Active-controlled, Multi-centre Trial Evaluating Orally Administered Zongertinib [BI 1810631] Compared With Standard of Care as First-line Treatment in Patients With Unresectable, Locally Advanced or Metastatic Non-squamous Non-small Cell Lung Cancer Harbouring HER2 Tyrosine Kinase Domain Mutations; ClinicalTrials.gov identifier: NCT06151574) is evaluating zongertinib in the first-line setting, comparing it against standard-of-care therapies in treatment-naive *HER2*-mutant NSCLC.[88] Positive results from this study could significantly expand the role of zongertinib and shift the treatment paradigm toward earlier intervention with HER2-targeted therapy.

Beyond its use as monotherapy, future research should explore strategies to overcome or delay acquired resistance. Investigations into resistance mechanisms will be essential. Rational combination approaches, including pairing zongertinib with ICIs, chemotherapy, or ADCs, may improve outcomes and the durability of response. Biomarker development to refine patient selection and identify predictors of response or resistance also remains a key research priority.

Finally, phase III confirmatory data and further real-world evidence will be essential to validate the clinical trial findings and assess zongertinib's impact on quality of life, treatment adherence, healthcare utilization, and cost-effectiveness. These data will play an important role in shaping treatment guidelines, payer coverage, and clinical adoption.

Conclusion

Historically, *HER2*-mutant NSCLC has lacked effective targeted therapies, leaving patients with limited and often suboptimal treatment options after progression on standard chemotherapy and immunotherapy. Zongertinib, a selective, irreversible HER2 TKI, offers a novel and promising therapeutic approach tailored to the unique biology of *HER2* mutations. The results from early-phase clinical trials demonstrate that zongertinib delivers meaningful and durable responses, including activity in patients with central nervous system involvement and in those heavily pretreated with prior systemic therapies. The manageable safety profile, along with its oral administration, distinguishes it from other HER2-directed agents and supports its role as an important treatment option in both first-line and subsequent-line settings. Importantly, the potential integration of zongertinib into routine care reinforces the value of comprehensive molecular profiling in all patients with advanced NSCLC by ensuring that *HER2*-mutant disease is accurately identified and appropriately treated. In conclusion, zongertinib represents a significant step forward in precision oncology for NSCLC and holds the potential to improve outcomes for a molecularly defined subgroup of patients with a traditionally poor prognosis. ❑

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