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Review

Zongertinib in HER2-Mutant Advanced/Metastatic Solid Tumors: A Narrative Review and Future Prospectives

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Abstract

Human epidermal growth factor receptor 2 (HER2) has emerged as a critical therapeutic target in various malignancies, most notably breast and gastric cancers. While significant advances have been made in treating HER2-amplified tumors, therapeutic options for tumors harboring activating HER2 mutations remain comparatively limited. Zongertinib (BI 1810631), a novel, highly selective oral HER2 tyrosine kinase inhibitor (TKI), has demonstrated encouraging activity in HER2-mutant cancers, particularly non-small cell lung cancer (NSCLC). This narrative review examines the molecular rationale, preclinical evidence, and clinical outcomes of zongertinib in HER2-mutant advanced or metastatic solid tumors, with emphasis on NSCLC, and contextualizes its activity across other HER2-altered settings. Early-phase trials such as Beamion LUNG-1 have shown promising outcomes in HER2-mutant NSCLC, with objective response rates (ORRs) exceeding 70% and durable disease control. However, no current data support the efficacy of zongertinib in HER2-wildtype tumors lacking overexpression, amplification, or mutation. HER2-altered disease encompasses biologically distinct entities, including HER2-amplified/overexpressed tumors, HER2-low tumors (immunohistochemistry (IHC) 1+ or 2+ with negative in situ hybridization), and HER2-mutant tumors harboring activating ERBB2 genomic variants. “HER2-indeterminate” refers to tumors with equivocal or discordant HER2 testing results in which genomic profiling may reveal actionable ERBB2 alterations. “HER2-negative” refers specifically to tumors lacking HER2 amplification, overexpression (IHC 0), and activating ERBB2 mutations, and does not include HER2-low or HER2-indeterminate cases. These entities are biologically distinct and may demonstrate differential sensitivity to HER2-directed therapies. Current clinical evidence for zongertinib is strongest in HER2-mutant disease, whereas its role in HER2-low or truly HER2-negative tumors remains investigational. To date, no clinical evidence supports efficacy of zongertinibin tumors lacking HER2 amplification or activating mutation. In conclusion, while zongertinib holds significant promise in the treatment of HER2-mutated cancers, especially NSCLC, its role in HER2-low tumors remains investigational. Further research should prioritize (i) prospective clinical trials enrolling HER2-low or HER2-mutant subgroups, (ii) preclinical studies identifying rational drug combinations to overcome resistance, and (iii) biomarker refinement to distinguish patients most likely to benefit. Such directions can clarify zongertinib’s therapeutic scope across HER2-altered malignancies.

1. Introduction

Human epidermal growth factor receptor 2 is a member of the epidermal growth factor receptor (EGFR) family of transmembrane receptor tyrosine kinases. While physiologically expressed at low levels in adult tissue [1], the human epidermal growth factor receptor 2 (HER2) gene functions as a proto-oncogene, with the protein integral to the pathogenesis of several solid tumors.

The human epidermal growth factor receptor (HER) family plays a crucial role in regulating cell survival, proliferation, and differentiation by activating several important signaling pathways inside the cell. Among its members, HER2 is a ligand-independent receptor whose activation through heterodimerization exerts its oncogenic function, across multiple signaling pathways [2-4]. Aberrant HER2 activity, through overexpression, amplification, or genomic mutations, has been recognised in a variety of solid tumors. Throughout this review, the term “HER2-negative” is used exclusively to describe tumors lacking HER2 amplification, overexpression, and activating ERBB2 mutation, and does not include HER2-low or HER2-indeterminate cases.

HER2 alterations occur across a wide range of malignancies. Approximately 15-30% of invasive breast cancers and 10-30% of gastric cancers exhibit overexpression or amplification [2], while activating HER2 mutations are increasingly recognized in lung, bladder, colorectal, and cervical cancers [3,5]. Across these tumor types, HER2 dysregulation is frequently associated with aggressive behavior and poorer clinical outcomes [6,7].

Thus, therapeutic targeting of HER2 serves as an important avenue of focus in cancer management, with multiple therapeutic strategies targeting distinct domains of the receptor. Each of its three domains can be independently targeted to block HER2 signalling activity, with monoclonal antibodies such as trastuzumab and pertuzumab. These, followed by the introduction of small-molecule tyrosine kinase inhibitors (TKIs) and antibody-drug conjugates (ADCs), have significantly improved outcomes in breast and gastric cancers [8-11]. However, significant limitations persist. Response rates to monotherapy remain limited in many patients, resistance frequently emerges, and toxicities-particularly those associated with non-selective HER-family inhibition-continue to restrict the broader use of many agents [12]. Furthermore, HER2-mutant tumors often respond differently from HER2-amplified cancers, and existing therapies do not consistently achieve durable benefit across all HER2 alteration types [3].

To address existing limitations and unmet clinical needs, select new-generation therapies such as zongertinib are currently in development. Zongertinib is a novel, irreversible, HER2-selective tyrosine kinase inhibitor designed to reduce EGFR related toxicity while retaining potent activity against HER2-mutant and other HER2-altered tumors [12]. Early clinical studies suggest favorable tolerability and promising activity in HER2-mutant non-small cell lung cancer (NSCLC). This review focuses primarily on the therapeutic potential of zongertinib in HER2-mutant advanced or metastatic solid tumors, particularly NSCLC, while contextualizing its activity relative to other HER2 alteration subtypes. While this review primarily focuses on HER2-mutant solid tumors, distinctions among HER2 amplification, HER2-low expression, and HER2-indeterminate classifications are discussed to contextualize diagnostic and therapeutic considerations.

2. Tumorigenesis After HER2 Alterations: Mechanism and Prognosis

Tumorigenesis in HER2-positive cancers most commonly occurs through gene amplification in the intracellular domain of the HER2 gene, resulting in receptor overexpression [13]. HER2 amplification is observed in breast [14], gastric [15], urothelial [3], cervical [16], colorectal, ovarian, endometrial, and esophageal cancers. Overexpressed HER2 proteins are associated with increased dimerization and enhanced downstream signaling. HER2 itself can directly stimulate the Phosphoinositide-3-Kinase/Akt (PI3K/AKT) pathway. The overexpressed protein, via interaction with other transmembrane proteins, can bring about potentiation of signals [17], confer chemotherapy resistance [18], and increase activation of secondary messengers in its downstream signaling pathway [19]. Other mechanisms include interference with cell polarity, disruption of cell cycle checkpoints, and evasion of endocytosis. Estrogen, via the ER-Alpha (estrogen receptor alpha) receptor, can also activate HER2 signaling. This is an important factor in the development of tamoxifen resistance in breast cancer [20].

In addition to amplification, somatic HER2 mutations represent a distinct oncogenic mechanism. While the prevalence of these mutations in cancers is lower than overexpression (approximately 2-4% in NSCLC) [21-23], it is still significant enough to warrant discussion. The most common alterations in NSCLC are exon 20 insertions within the tyrosine kinase domain, including the tyrosine-valine-methionine-alanine (YVMA) insertion [12,21,24], which promote constitutive kinase activation.

Beyond exon 20 insertions, HER2 mutations encompass a heterogeneous spectrum of activating alterations affecting multiple receptor domains, including extracellular domain substitutions (e.g., S310F/Y), transmembrane domain alterations, and additional kinase domain variants. These mutations promote constitutive receptor activation independent of ligand binding or gene amplification, leading to persistent downstream signaling through the PI3K/AKT and Mitogen-activated protein kinase (MAPK) pathways.

Importantly, the distribution and functional impact of HER2 mutations vary across tumor types. In NSCLC, kinase domain exon 20 insertions predominate and are typically mutually exclusive with other major driver mutations such as EGFR or anaplastic lymphoma kinase (ALK) alterations. In contrast, breast cancers more frequently harbor extracellular domain or kinase domain point mutations, often in the absence of HER2 amplification. Colorectal and bladder cancers demonstrate additional heterogeneity, with kinase domain substitutions and rare fusions contributing to oncogenic activation.

Unlike amplification-driven tumors, which rely on receptor overexpression and dimerization-dependent signaling, mutation-driven tumors are characterized by structural activation of the kinase domain. This distinction has therapeutic implications, as mutation-driven tumors may demonstrate differential sensitivity to selective HER2 TKIs compared with antibody-based therapies primarily targeting receptor overexpression.

Conventional HER2 assessment relies primarily on immunohistochemistry (IHC) and in situ hybridization (ISH) to detect protein overexpression and gene amplification. However, these approaches may fail to identify tumors driven by activating ERBB2 mutations in the absence of amplification. For example, HER2-mutant NSCLC frequently lacks HER2 overexpression by IHC, despite harboring oncogenic exon 20 insertions detectable only by next-generation sequencing [21-23]. Similarly, in breast cancer, HER2 mutations may occur in tumors classified as HER2-negative by standard IHC

criteria [25,26]. This diagnostic discordance underscores the limitation of expression-based testing and supports incorporation of genomic profiling to identify mutation-driven disease that may benefit from selective HER2 TKIs.

The term "HER2-indeterminate" has been used to describe tumors in which conventional IHC and ISH testing yield equivocal or discordant results [e.g., IHC 2+ without confirmatory amplification, heterogeneous expression patterns, or low-level copy number gain insufficient for classification as amplified]. These cases may harbor activating ERBB2 mutations or alternative mechanisms of HER2 pathway activation not detectable by standard expression-based assays. Clinically, this category underscores the importance of genomic profiling to clarify therapeutic eligibility and avoid misclassification of potentially targetable disease.

HER2 also plays a variable prognostic role across tumor types. Multiple studies have associated HER2-positive gastric cancers with poorer survival and increased metastatic potential [27-29], although data remain inconsistent in NSCLC [30]. In breast cancer, HER2 overexpression is linked to poor tumor differentiation, increased proliferation, and aggressive spread [14,31]. A study revealed an increased risk of recurrence in HER2-enriched node-negative breast cancers [32], with patients also being more susceptible to brain metastasis [33]. Conflicting evidence exists linking HER2 overexpression in esophageal cancer with poor survival [34,35], whereas in a study of 30 women with high-grade serous papillary endometrial carcinoma, HER2 amplification was a major prognostic factor for poor survival [36]. The biological heterogeneity of HER2 mutations across tumor types underscores the need for mutation-specific therapeutic strategies rather than a uniform HER2-directed approach.

3. Zongertinib: Mechanism of Action

Zongertinib [BI 1810631] is a covalent, irreversible HER2 tyrosine kinase inhibitor [TKI]. It is selective for HER2, thus circumventing the adverse effects (AEs) of pan-HER TKIs through its EGFR-sparing activity [37]. The orally administered agent thus does not affect the rest of the EGFR family (Figure 1). Figure 1 illustrates the proposed mechanism of action and selectivity of zongertinib. It depicts HER2-driven signaling in tumors harboring activating mutations, which result in sustained downstream activation of pathways such as PI3K/AKT, MAPK, and Janus Kinase/Signal Transduction and Activation of Transcription (JAK/STAT). The Figure 1 contrasts older pan-HER TKIs with zongertinib, highlighting its preferential HER2 selectivity and relative sparing of wild-type EGFR. It also demonstrates the binding of zongertinib to the intracellular HER2 tyrosine kinase domain, leading to inhibition of receptor autophosphorylation and suppression of oncogenic signaling.

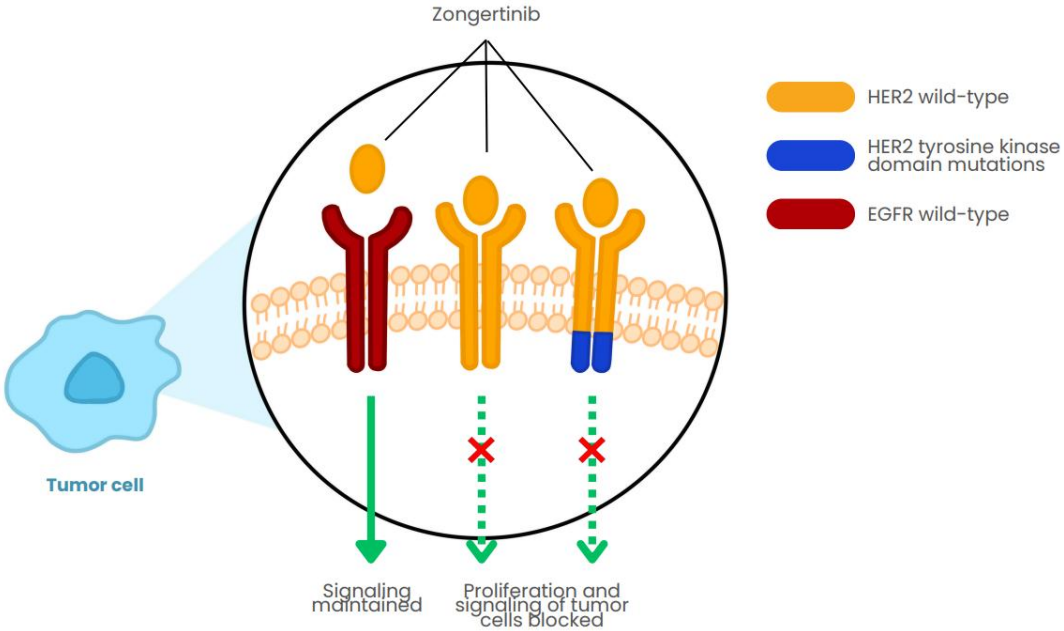

Figure 1. Mechanism of action of zongertinib showing its preferential inhibition of wild-type and mutated HER2 receptors and sparing EGFR.

This selectivity has also been demonstrated in exon 20 mutations, which, as mentioned above, could be valuable in patients with NSCLC with HER2 mutations. A report of six patients with HER2-mutant NSCLC receiving zongertinib from December 2023 to January 2024 outside of clinical trials reported promising results; 100% disease control, with one patient showing a complete response and four showing a partial response to the agent [38].

As the drug is currently being investigated in the Beamion LUNG-1 phase I (NCT04886804) and Beamion LUNG-2 phase III randomized controlled trials (NCT06151574), available information on its interactions is sparse. However, upon incubation with

human hepatocytes, zongertinib undergoes hepatic oxidation via the cytochrome P450 (CYP) 3A4/5 system. This was exhibited by the effect of carbamazepine, a strong CYP3A inducer, which, upon co-administration with zongertinib, reduced its area under the curve (AUC) by 63.5% and *C*max by 43.6% [39]. Zongertinib can also be metabolized by glucuronidation and glutathione conjugation. It weakly interacts with efflux pumps [such as P-glycoprotein and breast-cancer resistance protein.

Given its novel mechanism of action, zongertinib has benefits over older agents administered for HER2-positive cancers. Nonselective ErbB TKIs [erlotinib, gefitinib, and afatinib] can potentially produce cutaneous and gastrointestinal (GI) AEs [40]. The monoclonal antibody conjugate trastuzumab deruxtecan, which is the drug of choice for several HER2-mutant cancers, is also associated with AEs such as neutropenia and interstitial lung disease (ILD), the latter of which can lead to discontinuation by patients and death in some cases [41]. Meanwhile, Beamion LUNG-1 reported no cases of treatment-related ILD in patients receiving zongertinib. Similarly, zongertinib has lower incidence of cutaneous and GI AEs compared to non-selective ErbB [42].

4. Preclinical Evidence

Preclinical evaluation of zongertinib has systematically demonstrated (i) HER2 selectivity over EGFR, (ii) potent activity against HER2-mutant models, (iii) favorable pharmacokinetic properties, and (iv) robust *in vivo* antitumor efficacy.

Proliferation assays using the murine pro-B Ba/F3 cell line demonstrated zongertinib's EGFR-sparing activity and high affinity for HER2. In engineered Ba/F3 cell lines expressing HER2 variants incapable of forming covalent bonds with zongertinib, a marked reduction in the agent's potency was observed, highlighting another important property of BI 1810631 mentioned above.

The agent's potency was further evaluated inHER2-dependent human cancer cell lines, including those harboring activating mutations. Zongertinib demonstrated high activity across these models and significantly downregulated HER2 signaling pathways.

In vitro hepatocyte assays revealed increased plasma protein binding and low clearance rates, along with low solubility and high permeability, the latter two characteristics suggesting the potential for dissolution rate-limited absorption.

In vivo pharmacokinetic studies conducted in mouse, rat, dog, and minipig models showed good oral bioavailability and consistently low clearance across species.. These animal models were then used to determine the possible pharmacokinetic properties of zongertinib in humans, predicting similarly favorable exposure profiles. Exposure-based modeling using xenograft systems further supported dose selection, with 40 mg predicted to achieve tumor growth inhibition in patients.

The mechanism of action was also elucidated in *in vivo* mouse xenograft models, with decreased protein phosphorylation and downstream signaling observed in cells exhibiting ErbB2 gene amplification. Zongertinib administration was also associated with dose-dependent tumor shrinkage in these models [12].

5. Clinical Development and Trials

Zongertinib has progressed through early-phase clinical trials (Table 1), with the previously mentioned Beamion LUNG-1 phase Ia/Ib multicentre, multicohort trial demonstrating encouraging results.

Table 1. Clinical trials of zongertinib in HER2-altered advanced/metastatic solid tumors.

Trial	Phase & Population	Dose	Key Endpoints	Results	Status
Beamion LUNG-1 [NCT04886804]	Phase Ia-HER2-aberrant solid tumors	15-360 mg QD/BID	Safety, MTD, ORR, DCR	ORR 30.2%, DCR 82.9%; NSCLC: ORR 19%, DCR 92.6%, DoR ~12.7 mo	Completed
Beamion LUNG-1 Phase Ib Cohort 1	Previously treated HER2-mutant NSCLC	120 mg QD	ORR, PFS, safety	ORR 71%, DCR ~93%, median PFS ~12.4 mo	Completed
Beamion LUNG-2 [NCT06151574]	Phase III-1st-line HER2-mutant NSCLC	120 mg QD vs. chemo + pembrolizumab	PFS, ORR, OS, safety	Ongoing-Randomized control trial	Recruiting
LUNG-1 NSCLC dosing sub-population	Extension of LUNG-1 NSCLC cohort	QD vs. BID	ORR, DCR, PFS	QD: ORR 35%, DCR 93%, PFS ~17.2 mo	Ongoing
AACR 2025 Update [LUNG-1]	Previously treated HER2-mutant NSCLC	120 mg QD	ORR, PFS, safety	ORR ~71%; favorable safety vs. T-DXd	Published

Note: QD: one a day; BID: twice a day; MTD: maximum tolerated dose; ORR: objective response rate; OS: Overall Survival; DCR: disease control rate; DoR: duration of response; PFS: progression-free survival; NSCLC: non-small cell lung cancer mo months; T-DXd: trastuzumab deruxtecan.

Phase Ia focused on dose escalation across seven institutions in the United States, the Netherlands, China, and Japan. Eligible patients were at least 18 years old with advanced, unresectable, and/or metastatic solid tumors harboring HER2 alterations (overexpression, amplification, somatic mutations, or gene rearrangements) and not responsive to or eligible for standard therapy. They all had an Eastern Cooperative Oncology Group (ECOG) Performance score of 0-1 (that is, fully active or restricted but ambulatory). Patients with asymptomatic brain metastases were also included in the trial.

More than half of the patients had NSCLC, with additional cases of colorectal (14%) and breast cancer (11%). Forty-four percent of these patients had received at least one HER2-directed agent, including trastuzumab, pertuzumab, pyrotinib, trastuzumab deruxtecan (T-DXd), or trastuzumab emtansine (T-DM1). Two dosing regimens were evaluated: Twice-daily administration starting at 15 mg and escalating to 150 mg, and once-daily dosing beginning at 60 mg and escalating to 120, 180, 240, and 300 mg.

The primary endpoint of Phase Ia was maximum tolerated dose (MTD), with complete response (CR) and partial response (PR) as key efficacy outcomes. Phase Ia showed that the MTD for zongertinib was not reached. The objective response rate (ORR) across both regimens was reported at 30% overall, with responses observed in NSCLC, breast, colorectal, cervical, vulvar, GI, ovarian, and biliary tract cancers [43]. Disease control was reported in 93% of patients with mutant NSCLC, with an ORR of 35%. This sub-cohort does exhibit a lower ORR than in the main population tested (as discussed below), but can be attributed to greater pre-treatment exposure compared to the more selective Ib cohort. Differences in dose intensity between BID escalation regimens and the fixed 120 mg QD dosing regimen in Phase Ib might have also contributed to the difference in the ORR seen.

Twenty-four of these patients harbored YVMA mutations; 9 had a confirmed PR, and 13 had stable disease. Six of 27 NSCLC patients with brain metastases achieved an objective response to zongertinib (Table 1). This intracranial activity is clinically meaningful, given the high incidence of brain metastases in HER2-mutant tumors. Similar promising efficacy was observed in patients receiving the once-daily regimen.

A similar ORR (33%) was observed in breast cancer patients; 3 patients had HER2 amplification / overexpression, and 2 had HER2 mutations. The ORR in patients with a history of receiving previous ADCs was 32%, with 92% showing disease control, showing that the drug is just as effective when received post-ADC (e.g., T-DXd).

Treatment-related adverse events (TRAEs) occurred in 82% of patients in Phase Ia. The most common were diarrhea (50%), rash (16%), and anemia (10%). Grade ≥3 TRAEs were observed in 10% of patients and included elevated Alanine Aminotransferase (ALT) / Aspartate Aminotransferase (AST), rash, hypocalcemia, diarrhea, lymphopenia, decreased appetite, thrombocytopenia, hypertension, and nausea. One grade 4 thrombocytopenia event was reported, with no grade 5 TRAEs [43].

Phase Ib of the Beamion LUNG-1 trial focused on the safety and efficacy of zongertinib specifically in HER2-mutant NSCLC. The first of the five cohorts involved in this trial included patients with previously treated HER2-mutant NSCLC, with overall response as the primary endpoint.

In Phase Ib Cohort 1, an ORR of 71% was observed among previously treated patients with HER2-mutant NSCLC [42]. However, this cohort consisted of a relatively limited sample size within a single-arm, non-randomized study design, which may limit cross-trial comparisons and generalizability. Furthermore, patients were molecularly selected and enriched for activating kinase domain mutations, potentially contributing to the high observed response rate. In comparison, the DESTINY-Lung01 trial reported an approximate ORR of 55% with trastuzumab deruxtecan in a similar population [41]. While cross-trial comparisons should be interpreted cautiously, these findings suggest promising activity of zongertinib in mutation-driven NSCLC.

Zongertinib also demonstrated a favorable safety profile. Grade 3 and grade 4 treatment-related adverse events were reported at rates of 15% and 3%, respectively. Therapy was discontinued in four patients due to TRAEs, and 10 patients (7.6%) experienced serious adverse events [42].

The favorable safety profile of zongertinib is likely attributable to its selective HER2 inhibition with relative sparing of wild-type EGFR signaling [12]. Pan-HER TKIs such as afatinib, pyrotinib, and poziotinib are associated with higher rates of dermatologic and GI toxicities, including rash and diarrhea, due to EGFR inhibition [40,44-46]. In contrast, zongertinib demonstrated comparatively lower incidences of grade ≥3 toxicities in early-phase trials [42,43].

Importantly, ILD, a clinically significant adverse event associated with trastuzumab deruxtecan and reported in up to 26% of patients in DESTINY-Lung01 [41], has not been observed as a treatment-related event in Beamion LUNG-1 to date [42,43]. However, given the limited sample sizes and duration of follow-up in early-phase studies, continued pharmacovigilance in larger randomized trials will be essential to fully characterize rare or delayed toxicities.

While zongertinib's kinase selectivity reduces off-target EGFR inhibition, potential class-related toxicities, including hepatic enzyme elevations and GI effects, remain important considerations [43]. Ongoing phase III data will further define its comparative tolerability profile.

Although the most mature clinical evidence for zongertinib derives from HER2-mutant NSCLC, early-phase studies have included patients with other HER2-altered solid tumors. In Phase Ia of Beamion LUNG-1, responses were observed in breast, colorectal, cervical, ovarian, biliary tract, and gastrointestinal cancers harboring HER2 alterations [43]. While patient numbers

within each non-NSCLC subgroup were limited and heterogeneous with respect to alteration subtype and prior treatment exposure, these findings suggest potential tumor-agnostic activity in mutation-driven disease.

In HER2-mutant breast cancer, activating ERBB2 mutations frequently occur in the absence of HER2 amplification and may confer resistance to endocrine therapy or HER2-directed antibodies [25,26]. Preliminary responses to HER2-selective TKIs in this molecular subset support further investigation of mutation-targeted approaches distinct from amplification-based strategies.

Similarly, HER2 alterations in colorectal cancer may emerge as mechanisms of resistance to anti-EGFR therapy, providing biological rationale for selective HER2 inhibition in appropriately selected patients [47]. These data collectively highlight the importance of expanding clinical evaluation beyond NSCLC to define tumor-specific efficacy patterns.

The ongoing phase III Beamion LUNG-2 trial (NCT06151574) is evaluating first-line zongertinib in patients with locally advanced or metastatic HER2-mutant NSCLC. The study compares 120 mg once-daily zongertinib with standard platinum-pemetrexed chemotherapy plus pembrolizumab, with primary endpoints including progression-free survival, ORR, overall survival, patient-reported outcomes, and safety [48].

As previously discussed, zongertinib appears to demonstrate a more favorable safety profile compared with several existing HER2-directed therapies. CIn Phase Ia of Beamion LUNG-1, grade ≥3 treatment-related adverse events (TRAEs) were reported in 10% of patients, compared with 46% grade ≥3 TRAEs observed with T-DXd in the phase II DESTINY-Lung01 trial [41]. ILD, a clinically significant toxicity associated with T-DXd and reported in 26% of patients in DESTINY-Lung01, was not observed as a treatment-related event in Beamion LUNG-1 [42,43].

Pan-HER TKIs have also demonstrated higher toxicity burdens. Pyrotinib was associated with grade ≥3 TRAEs in 20% of patients and required dose reductions in a substantial proportion [44]. Poziotinib demonstrated grade 3 TRAEs in 78.9% of patients, with grade 4 events in four patients and one case of grade 5 pneumonitis [45,46]. Similarly, the HER2-selective TKI BAY 2927088 required dose reduction in 31.8% of patients and treatment discontinuation in 6.8%, with one dyspnea-related death reported [49].

In contrast, zongertinib has demonstrated relatively low rates of serious TRAEs, 10% in Phase Ia and 15% in Phase Ib, and fewer EGFR inhibition-related AEs, likely attributable to its HER2-selective design [12,42,43]. Nevertheless, continued pharmacovigilance in larger phase III datasets will be essential to fully characterize long-term safety and rare toxicities.

Compared with earlier-generation HER2-directed TKIs, zongertinib demonstrates greater kinase selectivity and a more favorable tolerability profile. Poziotinib and pyrotinib, both pan-HER inhibitors, have shown activity in HER2-mutant NSCLC but are associated with higher rates of grade ≥3 rash and diarrhea, often necessitating dose reductions [44-46]. Afatinib has demonstrated limited efficacy in HER2-mutant disease and is similarly constrained by EGFR-related toxicities [40].

In contrast, zongertinib's EGFR-sparing design may explain its lower incidence of dermatologic and gastrointestinal adverse events [12,43]. While trastuzumab deruxtecan has shown substantial efficacy, its risk of ILD remains a clinical concern [41]. Thus, zongertinib may offer a differentiated safety-efficacy balance, although definitive positioning will depend on results from ongoing randomized trials.

6. Resistance Mechanisms and Challenges

Zongertinib has demonstrated promising clinical efficacy, but the emergence of resistance poses a significant challenge to achieving sustainable therapeutic benefits. Primary resistance is often attributed to the development of concomitant oncogenic alterations or the heterogeneity of the tumor. A representative mechanism involves the co-occurrence of TP53 and HER2 mutations, which can interfere with the typical apoptotic function of the drug, thereby compromising its therapeutic efficacy. In addition, the effectiveness of zongertinib is substantially diminished by compensatory signaling pathways, particularly those mediated by alternative receptor tyrosine kinases, which facilitate bypass mechanisms [25,26,50].

In contrast, acquired resistance is predominantly driven by genomic alterations. Resistance to HER2-targeted TKIs may arise through both on-target and off-target mechanisms. Secondary HER2 kinase domain mutations that impair drug binding have been described with other HER2 inhibitors and may represent potential future resistance mechanisms to zongertinib [26]. Additionally, activation of parallel signaling pathways, including MET amplification, HER3 upregulation, PIK3CA mutations, and MAPK pathway reactivation, can restore downstream signaling despite HER2 inhibition [50,51]. Phenotypic transformation to small-cell lung cancer (SCLC)-like states has also been observed in the context of resistance to other targeted therapies and may theoretically occur in HER2-mutant disease [50]. Understanding these mechanisms will be critical to guiding rational combination strategies and sequential therapy design.

Notable mechanisms include the development of HER2 mutations, which greatly impair the efficacy and binding affinity of zongertinib through structural modifications within the kinase domain. Historically, tumours have developed resistance by undergoing phenotypic transformation into SCLC-like states. PI3K/AKT or MAPK signaling can be restored by various factors such as the activation or upregulation of MET, HER3 (ERBB3), or PIK3CA, which induces cellular proliferation despite HER2 inhibition, further contributing to therapeutic resistance [51].

Cross-resistance may contribute to the attenuation of HER2-driven signaling through mechanisms such as receptor habituation or downregulation of HER2 expression. This phenomenon is particularly relevant in patients previously exposed to HER2-targeted therapies, including trastuzumab, T-DXd, or poziotinib [52,53].

Overcoming resistance to zongertinib necessitates a multifaceted therapeutic approach. Combination regimens aimed at counteracting compensatory signaling pathways are under active investigation, with a focus on coadministration of zongertinib alongside MEK or PI3K inhibitors to overcome resistant mutations. Immunotherapy integration is also emerging as a promising avenue. Tumors that carry a greater risk of mutation are increasingly being targeted with immune blockade, particularly via programmed cell death protein 1/ programmed cell death ligand 1 (PD-1/PD-L1) inhibitors. Moreover, biomarker-guided therapy is gaining traction, wherein resistance-associated mutations are identified at an early stage through longitudinal monitoring employing the use of circulating tumor DNA (ctDNA) [50,54,55].

Zongertinib has demonstrated central nervous system (CNS) activity in early phase clinical trials, which could be important for the management of this disease, given the high propensity of HER2 mutant NSCLC to metastasize to the CNS. Further investigations are warranted to assess drug permeability and to elucidate potential resistance mechanisms [38,43].

7. Future Perspectives and Ongoing Research

Resistance to HER2-targeted agents remains a significant challenge in treating patients with HER2-altered tumors [43]. The distinct mechanisms of action of zongertinib and ADCs such as T-DXd or T-DM1 could offer a promising avenue to address and overcome this resistance [12].

Preclinical data have identified promising combination strategies involving zongertinib and other anticancer agents. KRAS-G12C inhibitors such as adagrasib and sotorasib are used in NSCLC harboring KRAS-G12C mutations. Upregulation of ErbB2 signaling has been implicated in resistance to KRAS-G12C inhibition [12]. While KRAS-G12C inhibitors alone demonstrate limited tumor regression, combination with HER2 or EGFR blockade has shown reversal of resistance in preclinical models [47]. In xenograft models expressing KRAS-G12C mutations, combination therapy with zongertinib induced tumor shrinkage and regression [12,56]. These findings suggest that dual targeting of ERBB and KRAS signaling pathways may represent a rational strategy in tumors with co-occurring alterations.

Combination approaches with ADCs have also shown potential. In the NCI-N87 xenograft model, zongertinib combined with T-DXd produced greater tumor growth inhibition than either agent alone. Similar findings were observed with T-DM1 [12]. Zongertinib has additionally demonstrated activity in cell lines resistant to HER2-targeted ADCs, suggesting possible utility in overcoming acquired resistance.

An important unresolved question is the optimal sequencing of zongertinib relative to existing HER2-directed therapies. In HER2-mutant NSCLC, trastuzumab deruxtecan is currently used following prior systemic therapy [41]. Zongertinib may represent an alternative in the post-ADC setting or potentially a preferred earlier-line option pending phase III results. In tumors previously treated with pan-HER TKIs or antibody-based therapies, its distinct mutation-selective mechanism may allow therapeutic benefit despite prior HER2-directed exposure [42,43]. Prospective studies directly comparing sequencing strategies or evaluating crossover outcomes will be essential to define its positioning within advanced treatment algorithms.

HER2 alterations, including mutations, amplifications, overexpression, and fusions (such as SDC4-NRG1 fusion), are prevalent across many solid cancers beyond NSCLC, breast, and gastric adenocarcinomas. Analysis of more than 60,000 real-world tumor samples from various cancer indications revealed HER2 overexpression in many types, including cases with low or diploid ERBB2 gene copy numbers, suggesting that a broader range of patients might benefit from a HER2 selective tyrosine kinase inhibitor, such as zongertinib [12] (Table 2).

Table 2. Current and potential uses of Zongertinib.

Indication	HER2 Alteration Type	Status/Remarks
HER2-Mutant NSCLC [Advanced/Metastatic]	HER2 exon 20 insertions [TKD]	Most advanced; ORR ~71%; Phase III ongoing
HER2-Amplified NSCLC	HER2 amplification	Under investigation; lower response than HER2-mutant
HER2-Mutated Colorectal Cancer	HER2 exon mutations	Preclinical/early exploratory trials
HER2-Mutated Breast Cancer	HER2 TKD mutations	Potential use in T-DXd resistant tumors; not yet established
HER2-Amplified Gastric Cancer	HER2 amplification	Potential indication; no active trials
HER2-Altered Solid Tumors [Basket Trials]	Any activating HER2 alteration	Explored in Phase I Beamion LUNG-1; tumor-agnostic potential
Brain Metastases in HER2-Mutant Cancers	HER2 TKD mutations	Potential CNS efficacy under exploration

Note: TKD: Tyrosine kinase domain; T-DXd: trastuzumab deruxtecan.

While development to date has primarily focused on HER2-mutant NSCLC, ongoing trials reflect a structured expansion strategy. Phase III Beamion LUNG-2 (NCT06151574) is evaluating first-line zongertinib in HER2-mutant NSCLC [48]. The phase II PANTUMOR-1 basket trial (NCT06581432) is assessing tumor-agnostic activity across diverse HER2 alterations. Additionally, Beamion BCGC-1 (NCT06324357) is exploring combination strategies with HER2-targeted ADCs in breast and gastroesophageal cancers [57]. Collectively, these studies will define mutation-specific efficacy, tumor-type expansion potential, and combination feasibility.

Ongoing clinical trials aim to refine biomarker-based patient selection. Determining which specific types of HER2 alterations (e.g., specific mutations, amplification levels, or overexpression levels) predict response to zongertinib remains critical [43]. Effective stratification will require integration of genomic sequencing into routine diagnostic workflows. While IHC and ISH remain standard for detecting HER2 amplification in breast and gastric cancers, next-generation sequencing (NGS) is essential for identifying activating ERBB2 mutations in tumors lacking overexpression [21-23]. Circulating tumor DNA [ctDNA] analysis may further facilitate longitudinal monitoring of resistance-associated mutations [55]. Stratification based on mutation subtype, particularly exon 20 insertions versus extracellular domain substitutions, may refine patient selection and optimize therapeutic responsiveness. Harmonization of molecular testing guidelines across tumor types will be necessary to align clinical trial design with real-world practice.

Data from the ongoing phase II Beamion PANTUMOR-1 basket trial (NCT06581432) could provide crucial clinical insights into the spectrum of zongertinib activity across different tumor types driven by different mechanisms of aberrant HER2 activation, and correlate the response with the specific alteration present (Table 3). Clinical responses were noted in a patient with an SDC4NRG1 fusion, a type of alteration that can activate HER2 signaling, highlighting the potential need to consider biomarkers of HER2 activation that extend beyond ERBB2 gene mutations or amplification/overexpression, potentially including fusions or other mechanisms that lead to HER2 dependence.

The preclinical synergy observed with KRASG12C inhibitors suggests that the co-occurrence of HER2 alterations [which can contribute to ERBB signaling] and KRASG12C mutations may serve as a predictive biomarker for combination therapy with zongertinib and KRAS inhibitors. Increased ERBB signaling has been implicated as a resistance mechanism to KRASG12C inhibitors, providing a biological rationale for this combination biomarker (Table 3).

Table 3. Future research directions and gaps in zongertinib development.

Research Direction / Gap	Description
Biomarker Refinement	Need for identifying predictive biomarkers beyond HER2 mutations to enhance patient selection.
Comparative Efficacy Studies	Head-to-head trials comparing zongertinib with existing HER2-targeted therapies like trastuzumab deruxtecan.
Mechanisms of Resistance	Understanding primary and acquired resistance mechanisms to zongertinib.
Combination Therapies	Exploration of synergy with immune checkpoint inhibitors or other targeted therapies.
Extrapolation to Other Cancers	Evaluating efficacy in non-lung HER2-altered tumors such as breast, colorectal, or gastric cancers.
Real-World Evidence	Post-approval studies in diverse populations to assess long-term outcomes and tolerability.
CNS Activity Evaluation	Investigate CNS penetration and efficacy in patients with brain metastases.

The ongoing clinical development program reflects a structured expansion strategy. Phase III Beamion LUNG-2 (NCT06151574) is evaluating first-line use in HER2-mutant NSCLC [48]. The phase II PANTUMOR-1 basket trial (NCT06581432) is assessing tumor-agnostic activity across diverse HER2 alterations. Additionally, Beamion BCGC-1 (NCT06324357) is exploring combination strategies with HER2-targeted ADCs in breast and gastroesophageal cancers [57]. Collectively, these studies will define mutation-specific efficacy, tumor-type expansion potential, and combination feasibility, shaping the future development trajectory of zongertinib.

8. Conclusion

Older pan-HER TKIs, due to limited selectivity and substantial off-target toxicities, have constrained therapeutic options in HER2-altered solid tumors. Zongertinib's selective HER2 inhibition, demonstrated intracranial activity, and favorable tolerability profile suggest potential advancement within this treatment landscape. Early-phase clinical trials have shown encouraging activity in HER2-mutant NSCLC, with signals of efficacy also observed in other HER2-altered malignancies, including breast and gastric cancers. Across phase I studies, zongertinib has demonstrated consistent target inhibition, durable responses, high disease control rates, and a manageable safety profile, including in heavily pretreated patients and those with brain metastases.

Importantly, to date, no clinical evidence supports the efficacy of zongertinib in tumors lacking HER2 amplification, overexpression, or activating mutation, and its use in truly HER2-negative disease should remain investigational pending further biomarker-driven studies. Current clinical evidence supports its use specifically in HER2-mutant disease, with no validated role in truly HER2-negative tumors. Its specificity and precision in targeting HER2 mutations, including exon 20 insertions, without inhibiting Wild-type epidermal growth factor receptor (WTEGFR), define its clinical relevance and enable a reduction in treatment-limiting toxicities typical of earlier TKIs. Its clinical versatility and scope in modern targeted oncology are further highlighted by its ability to overcome resistance to existing HER2-directed therapies and its potential for synergy when combined with ADCs and KRAS-G12C inhibitors.

Importantly, early-phase data reveal a clear divergence in efficacy between HER2-mutant and HER2-amplified disease, highlighting that these alterations are biologically distinct entities rather than variations along a single spectrum. The markedly higher activity in HER2-mutant NSCLC underscores the need for mutation-specific biomarker refinement and teaches us that future HER2-directed therapy must be tailored to alteration subtype rather than grouped broadly under “HER2-positive” disease.

Future research should prioritize several key areas. First, results from the ongoing phase III Beamion LUNG-2 trial will determine whether zongertinib can be established as first-line therapy in HER2-mutant NSCLC. Second, mutation-subtype-specific analyses are needed to determine whether efficacy differs among exon 20 insertions, extracellular domain mutations, and other ERBB2 variants. Third, prospective trials evaluating rational combination strategies, such as co-targeting KRAS-G12C, MET, or PI3K pathways, may help overcome adaptive resistance mechanisms.

Additionally, expanded basket trials enrolling diverse HER2-mutant solid tumors will clarify the extent of tumor-agnostic applicability. Integration of genomic sequencing and ctDNA-based monitoring into clinical trial design will further refine biomarker-guided treatment strategies. Collectively, these efforts will define the optimal positioning of zongertinib within the evolving HER2-directed therapeutic landscape.

Abbreviations

ADCs: Antibody-drug conjugates

AEs: Adverse effects

ALK: Anaplastic lymphoma kinase

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

AUC: Area under the curve

CNS: Central nervous system

CR: Complete response

ctDNA: Circulating tumor DNA

CYP: Cytochrome P450

CYP3A: Cytochrome P450 3A

DCR: Disease control rate

ECOG: Eastern cooperative oncology group

EGFR: Epidermal growth factor receptor

ER-Alpha: Estrogen receptor alpha

ERBB2: Erythroblastic oncogene B gene

GI: Gastrointestinal

HER2: Human epidermal growth factor receptor 2

IHC: Immunohistochemistry

ILD: Interstitial lung disease

ISH: In situ hybridization

JAK/STAT: Janus Kinase/Signal Transduction and Activation of Transcription

MAPK: Mitogen-activated protein kinase

MTD: Maximum tolerated dose

NGS: Next-generation sequencing

NSCLC: Non-small cell lung cancers

ORR: Objective response rate

PD-1/PD-L1: Programmed cell death protein 1/ programmed cell death ligand 1

PFS: Progression-free survival

PI3K/AKT: Phosphoinositide-3-Kinase/Akt

PR: Partial response

SCLC: Small-cell lung cancer

T-DM1: Trastuzumab emtansine

T-DXd: Trastuzumab deruxtecan

TKI: Tyrosine Kinase inhibitor

TRAEs: Treatment-related adverse events

WTEGFR: Wild-type epidermal growth factor receptor

YVMA: Tyrosine-valine-methionine-alanine

Declaration

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

No datasets were generated or analysed during the current study.

Competing Interests

The authors declare no competing interests.

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Authors' Contributions

All authors have made significant contributions to the preparation of this work and were responsible for reviewing and editing. Faiza Fatima contributed to conceptualization, abstract writing, table preparation, methodology, and supervision. Maryum Ahmed was involved in writing the original draft [introduction], literature review, and data interpretation. Muhammad Taimur Ahmed contributed to writing-original draft [HER2 alterations, mechanism of action, preclinical evidence, clinical development, and comparisons with existing therapies], reviewing and editing, and project administration. Zachariya Aftab contributed to writing-original draft [resistance mechanisms and challenges], data interpretation, and literature search. Mariam Akmal was responsible for writing the original draft [future perspectives and conclusion], figure preparation, and visualization. Aeliya Mirza contributed to reviewing, editing, and quality assurance. Further assistance in reviewing and editing, and quality assurance was provided by Zachariya Aftab and Ansa Ali.

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Generative AI Statement

The authors declare that no generative artificial intelligence technologies were used when preparing this manuscript.

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