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Title: An Update on Therapeutic Strategies for HER2-Mutated Non-Small Cell Lung Cancer

Authors: Masashi Ishihara[1], Shigeru Tanzawa[1], Takeshi Honda[1], Yasuko Ichikawa[1], Kiyotaka Watanabe[1], Nobuhiko Seki[1]

[1]Division of Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan.

Correspondence: Nobuhiko Seki

Division of Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan.

e-mail: nseki@med.teikyo-u.ac.jp

Clinical Question Box

What is the optimal treatment for HER2-mutant NSCLC: ADCs or TKIs?

Trastuzumab deruxtecan remains the preferred treatment for previously treated HER2-mutant NSCLC, supported by strong efficacy in the DESTINY-Lung trials. Trastuzumab rezetecan has also shown promising activity, and several next-generation ADCs are under investigation. Although earlier pan-HER TKIs provided limited benefit, newer mutation-selective TKIs such as zongertinib have demonstrated improved efficacy and tolerability, earning FDA approval alongside trastuzumab deruxtecan. While ADCs currently dominate the treatment landscape, emerging TKIs and combination approaches are expected to further refine personalized therapy for HER2-altered NSCLC.

Abstract

HER2 alterations define a distinct molecular subtype of non-small cell lung cancer (NSCLC), accounting for approximately 2–4% of cases and historically associated with poor responses to conventional chemotherapy and immunotherapy. Recent advances have transformed treatment strategies, with antibody-drug conjugates (ADCs) and next-generation tyrosine kinase inhibitors (TKIs) emerging as key therapeutic options. Among ADCs, trastuzumab deruxtecan demonstrates the most robust efficacy, achieving objective response rates (ORRs) of 34–58% and durable responses lasting up to 16.8 months across the DESTINY-Lung trials. Trastuzumab rezetecan shows comparable promise, while novel ADCs such as disitamab vedotin, MRG002, SYD985, and ARX788 are currently under investigation. On the TKI front, early pan-HER inhibitors offered modest benefits, whereas selective agents like poziotinib, pyrotinib, and particularly zongertinib have shown marked improvements, with ORRs reaching up to 71% and favorable safety profiles. Ongoing trials are exploring optimal sequencing, genotype-guided patient selection, and combination strategies integrating ADCs, TKIs, immunotherapy, and chemotherapy. These developments herald a shift toward personalized, biomarker-driven therapy poised to improve outcomes for patients with HER2-altered NSCLC.

Keywords: HER2 alterations; non-small cell lung cancer; antibody-drug conjugates; tyrosine kinase inhibitors; targeted therapy

Non-Small Cell Lung Cancer (NSCLC)

Lung cancer remains the most commonly diagnosed cancer globally and is the leading cause of cancer-related mortality, with approximately 2.2 million new cases and 1.8 million deaths reported in 2020.[1] In 2022, Europe registered roughly 4.47 million new cancer cases, corresponding to an age-standardized incidence rate of 280 per 100,000 and a lifetime risk of about 27.9% before age 75.[2] NSCLC constitutes around 85% of all lung cancer diagnoses worldwide.[3] A recent real-world analysis of 15,659 U.S. patients with metastatic NSCLC lacking actionable mutations who received first-line treatment between 2020 and 2023 revealed a substantial financial burden. The most common treatment regimens were immune checkpoint inhibitor (ICI) combined with platinum-based chemotherapy (47%), chemotherapy alone (26%), and ICI monotherapy (20%), with a median treatment duration of 4.2 months. Mean healthcare costs reached $32,215 per patient per month (PPPM), peaking for ICI plus chemotherapy regimens ($34,741–$38,454 PPPM), highlighting the urgent need for more effective and cost-efficient therapies.[4] Patients with unresectable Stage III epidermal growth factor receptor (EGFR)-mutant NSCLC incur healthcare costs exceeding $28,000 PPPM, primarily attributed to NSCLC management.[5]

Historically, treatment for metastatic NSCLC relied heavily on systemic chemotherapy, which targets rapidly dividing cells to alleviate symptoms, enhance quality of life, and, in some cases, extend survival.[6] Advances in molecular oncology since the early 2000s have led to the development of targeted therapies designed to disrupt specific molecular mechanisms in cancer cells while sparing normal tissues.[7] Many of these therapies are oral small-molecule kinase inhibitors, although some are administered

intravenously as monoclonal antibodies or other biologics.[8] A deeper understanding of the molecular underpinnings of NSCLC, particularly the roles of oncogenic driver mutations such as EGFR mutations, Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations, and rearrangements involving anaplastic lymphoma kinase (ALK) or c ros oncogene 1 (ROS1), has transformed treatment paradigms.[9] These insights have spurred efforts to identify additional biomarkers and molecular targets to further personalize therapy.[10] Despite these advances, tumor genotyping remains underutilized in advanced NSCLC, especially among patients with adenocarcinoma, highlighting the need for greater awareness of actionable genetic alterations.

In recent years, healthcare systems have implemented various strategies to improve molecular characterization in metastatic NSCLC. Institutions have introduced reflex molecular testing protocols, in which pathologists automatically initiate biomarker testing at the time of diagnosis.[11,12] This approach reduces delays and increases the detection of actionable alterations. Standardized precision oncology workflows involving coordination among oncologists, pathologists, and molecular laboratories have also been developed.[13] These efforts optimize tissue acquisition, testing efficiency, and the use of results in treatment decisions. Together with advances in next-generation sequencing (NGS) technologies, these initiatives have improved access to precision diagnostics and expanded the use of targeted therapies for patients with metastatic NSCLC.

HER2 Alterations

The human epidermal growth factor receptor / erythroblastic leukemia viral oncogene B (HER / ErbB) receptor family, comprising EGFR (HER1), HER2 (ErbB2), HER3, and HER4, regulates essential cellular processes such as growth, differentiation, and survival (Figure 1).[14] Unlike other family members, HER2 lacks a direct ligand and activates downstream signaling pathways, including mitogen-activated protein kinase (MAPK) and hosphatidylinositol 3-kinase / protein kinase B (PI3K-AKT), primarily through heterodimerization with EGFR or HER3.[15] HER2 alterations in NSCLC manifest as activating mutations, most commonly exon 20 insertions, as well as gene amplification and protein overexpression.[16] HER2 amplification involves an increase in the number of HER2 gene copies, leading to protein overexpression on the cell surface and hyperactivation of downstream signaling pathways, which promote uncontrolled cell proliferation and survival. These mutations are more prevalent in female patients, never-smokers, and individuals with adenocarcinoma histology.[17] HER2 amplification and overexpression are observed in 1–3% and 10–15% of NSCLC cases, respectively, with overexpression rates rising to 30% in lung adenocarcinomas.[18]

Importantly, a subset of tumors exhibits both HER2 mutation and gene amplification, suggesting a potential synergistic mechanism driving oncogenesis. These dual alterations may lead to enhanced HER2 signaling, increased receptor dimerization, and stronger activation of downstream pathways, contributing to therapeutic resistance and aggressive disease behavior.[19] Co-existing HER2 mutations and amplifications have been reported in various tumor types, including NSCLC and breast cancer, and are associated with differential responses to targeted therapies.[20] Their identification

underscores the need for comprehensive molecular profiling using NGS to guide optimal treatment selection. HER2 mutations represent a rare but clinically significant molecular subset of NSCLC, occurring in ~2–4% of cases and up to ~5.1% in EGFR / KRAS / ALK-negative adenocarcinomas.[21] In Chinese cohorts (2019–2024), NGS detected HER2 mutations in 3.8–5.6% of cases, demonstrating higher sensitivity than PCR-based methods.[22]

HER2 testing in NSCLC relies on complementary laboratory methods. NGS on tissue DNA is the most comprehensive and guideline-recommended first-line approach, accurately detecting HER2 point mutations and exon 20 insertions with near-perfect sensitivity and specificity (Table 1). NGS using circulating tumor DNA (ctDNA) from plasma, also called liquid biopsy, offers a non-invasive alternative for rapid or serial testing, though its sensitivity is lower (around 70–80%) and a negative result should be followed up with tissue testing when possible. Targeted polymerase chain reaction (PCR) assays, including amplification-refractory mutation system (ARMS), competitive allele-specific TaqMan PCR (castPCR), and droplet digital PCR (ddPCR), are extremely sensitive and specific for known HER2 hotspot variants but may miss rare or novel alterations, making them best suited for focused screening rather than comprehensive profiling. Fluorescence in situ hybridization (FISH) remains the reference method for detecting ERBB2 gene amplification (copy-number gain) and is useful when amplification affects treatment decisions or to confirm NGS findings. Immunohistochemistry (IHC) assesses HER2 protein overexpression but correlates poorly with ERBB2 genomic alterations, serving as a complementary test for evaluating protein expression rather than detecting mutations or insertions.

Interest in mutation-driven HER2 NSCLC has grown due to its limited response to conventional therapies and the development of targeted treatment options. NSCLC characterized by HER2 mutations or overexpression defines a distinct and aggressive molecular subtype that has historically been resistant to chemotherapy and immunotherapy.[16] The advent of antibody-drug conjugates (ADCs) has transformed treatment. By combining HER2-targeted antibodies with cytotoxic payloads, ADCs enable selective tumor cell killing and exert a bystander effect, demonstrating promising efficacy, durable responses, and manageable safety profiles in heavily pretreated patients.[23] HER2-directed tyrosine kinase inhibitors (TKIs) have historically shown limited efficacy due to structural challenges posed by exon 20 insertions and HER2's unique kinase conformation.[24] However, next-generation, mutation-selective TKIs now demonstrate encouraging activity in both treatment-naïve and previously treated patients, marking a paradigm shift in the management of HER2-altered NSCLC.

ADCs

Trastuzumab Deruxtecan (T-DXd)

T-DXd has emerged as the most extensively studied HER2-targeted ADC, showing consistent and robust activity across multiple clinical trials (Table 2). In the DESTINY-Lung01 Phase II study, which enrolled patients with HER2-overexpressing or HER2-mutant unresectable or metastatic NSCLC exhibiting immunohistochemistry (IHC) scores of 2+ or 3+, T-DXd achieved an objective response rate (ORR) of 34% (14/41) and a disease control rate (DCR) of 78% (32/41), with a median duration of response (DOR) of 6.2 months, progression-free survival (PFS) of 6.7 months, and overall survival (OS) of 11.2 months.[25] In the DESTINY-Lung02 Phase II study, which specifically targeted previously treated HER2-mutant metastatic NSCLC, the agent demonstrated even greater efficacy, achieving an ORR of 49% (50/102) and a DCR of 93%, with a median DOR of 16.8 months and OS of 19.5 months.[26] Similarly, the DESTINY-Lung03 Phase II basket trial, focusing on HER2-overexpressing non-squamous NSCLC, reported an ORR of 44% (16/36), a median DOR of 12.2 months, and an OS of 14.7 months.[27] Data from the DESTINY-Lung05 Phase II trial, conducted in a Chinese cohort with HER2 exon 19 or 20 mutations, revealed an even higher ORR of 58% (42/72), a DCR of 92%, and a median PFS of 10.8 months.[28]

Building on these results, ongoing trials are evaluating T-DXd in earlier treatment settings and broader patient populations. The pivotal DESTINY-Lung04 Phase III trial (NCT04644237) is comparing first-line T-DXd with platinum–pemetrexed chemotherapy, with or without pembrolizumab, in patients with unresectable or metastatic HER2-mutant nonsquamous NSCLC.[29] Additional studies, such as DESTINY-Lung06, are exploring its

role in HER2-expressing tumors with lower levels of HER2 and in combination with ICI.[30] These trials aim to establish T-DXd not only as the standard treatment in previously treated settings but also potentially as a first-line option.

Trastuzumab Emtansine (T-DM1)

T-DM1, an earlier-generation HER2-directed ADC, has shown meaningful, though comparatively modest, activity. In a Phase II basket study (NCT02675829) enrolling patients with Stage IV or recurrent HER2-mutant NSCLC harboring exon 20 insertions, T-DM1 achieved an ORR of 44% (8/18) and a DCR of 83%, with a median PFS of five months.[31] Similarly, the Japanese Phase II trial JapicCTI-194620 evaluated T-DM1 in previously treated patients with adenocarcinoma harboring exon 20 insertions and reported an ORR of 38% (8/21), a DCR of 52%, a median PFS of 2.8 months, and an OS of 8.1 months.[32] Despite these promising findings, T-DM1's clinical utility is limited by a shorter DOR and lower efficacy compared with T-DXd. Consequently, its role is evolving, primarily as an alternative in regions where T-DXd is unavailable or as part of combinatorial strategies currently under investigation.

Trastuzumab Rezetecan

Trastuzumab rezetecan represents a next-generation HER2-directed ADC with encouraging clinical outcomes. In the Phase I–II study (NCT04818333), pretreated patients with HER2-altered advanced NSCLC, including those harboring exon 20 insertions and over-expression, achieved an ORR of 42% (18/43) and an impressive DCR of 95%, with a median DOR of 13.7 months and PFS of 8.4 months.[33] More recent results from the HORIZON-Lung Phase II trial, published in 2025, demonstrated even greater

efficacy: an ORR of 73% (69/94), a DCR of 99%, and a median PFS of 11.5 months.[34] These findings position trastuzumab rezetecan as a potential alternative or complement to T-DXd, especially in HER2-mutant NSCLC. Expansion cohorts within the HORIZON-Lung program are currently investigating its role in earlier lines of therapy and combination regimens, while global Phase III studies are being planned to confirm these promising outcomes.

Emerging HER2-Targeted ADCs

In addition to the agents listed in Table 2, several novel HER2-directed ADCs are rapidly advancing through clinical development. Disitamab vedotin (RC48) is currently being evaluated in the DV-005 Phase II trial for HER2-expressing NSCLC and is also under investigation in combination with agents such as bevacizumab and ICIs to enhance therapeutic synergy.[35] MRG002, a trastuzumab–vedotin-based ADC, is in Phase II evaluation (NCT05141786) for patients with HER2-mutant unresectable or metastatic NSCLC.[36] Other innovative ADCs include SYD985 (trastuzumab duocarmazine), which utilizes a duocarmazine payload to enhance DNA damage, and ARX788, a site-specific conjugated ADC designed to improve the therapeutic index and reduce off-target toxicity.[37,38] Early-phase studies of these agents are ongoing globally and are expected to diversify the ADC landscape for HER2-altered NSCLC.

ADCs have transformed the treatment landscape for HER2-altered NSCLC. T-DXd demonstrates the strongest and most durable efficacy, establishing it as the preferred option for previously treated patients, with ongoing trials exploring its use in first-line settings. Trastuzumab rezetecan shows promising activity and may complement or potentially rival T-DXd, pending results from Phase III trials. Meanwhile, T-DM1 remains

relevant in select cases but has largely been surpassed by newer ADCs. Next-generation ADCs, including disitamab vedotin, MRG002, SYD985, and ARX788, aim to improve potency, safety, and combination strategies. Ongoing studies will clarify optimal sequencing, HER2 status-based patient selection, and personalized treatment approaches. Front-line trials like DESTINY-Lung04 may establish T-DXd as the standard therapy. Promising agents (rezetecan, RC48) and combination regimens with TKIs or immunotherapy are under evaluation. Priorities include genotype-guided therapy, improved understanding of resistance mechanisms, dose optimization, and broader global access, alongside expanding research beyond exon 20 mutations to include HER2 amplification and overexpression.

Serious *Adverse Events (SAEs)*

HER2-targeted ADCs have significantly improved clinical outcomes, but their safety profiles require ongoing and careful evaluation. In clinical trials for NSCLC, SAEs were common. They occurred in about 50–100% of patients treated with T-DXd, 6–24% with T-DM1, and up to 100% in early-phase studies of Trastuzumab Rezetecan (Table 2). These findings highlight the need for close safety monitoring and individualized toxicity management. Interstitial lung disease (ILD) or pneumonitis is a major concern and can be life-threatening. It has been reported in up to 10–15% of patients receiving T-DXd, with grade ≥3 events seen in a smaller proportion.[39] Although overt cardiotoxicity is uncommon with T-DXd, regular cardiac evaluation is recommended.[40] T-DM1 demonstrates a more predictable and generally manageable safety profile, with reported serious adverse events including hepatotoxicity, more frequent declines in left ventricular ejection fraction, and, rarely, ILD, relative to T-DXd.[41] Effective use of HER2-targeted ADCs requires

243 proactive monitoring. Regular blood counts, liver function testing, and prompt assessment
244 of new or worsening respiratory symptoms are essential. Coordination among oncologists,
245 pulmonologists, and cardiologists supports early intervention, dose modification, or
246 treatment interruption to preserve efficacy and reduce toxicity.

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TKIs

Afatinib

Afatinib, an irreversible pan-HER inhibitor, was among the earliest TKIs tested in HER2-mutant NSCLC. In a Phase II basket trial conducted by De Greve et al., seven patients with Stage IIIB/IV HER2-mutant NSCLC were treated; however, no objective responses were observed (Table 3). Despite this, a DCR of 71% was reported, with a median PFS of 17 weeks.[42] Similarly, in a Phase II study by Peters et al. evaluating afatinib in 28 patients with Stage IV NSCLC harboring A775_G776insYVMA exon 20 insertions, only 3 of 16 evaluable patients (19%) achieved a partial response, while the majority exhibited stable disease.[43] Dziadziuszko et al. evaluated 13 patients, reporting an ORR of 7.7%.[44] Collectively, afatinib demonstrated modest efficacy and limited durability of response, which restricts its use in modern clinical practice.

Dacomitinib

Dacomitinib, another irreversible pan-HER inhibitor, was evaluated in a Phase II trial conducted by Kris et al., which enrolled 26 patients with HER2-mutant advanced or metastatic NSCLC. The ORR was 12% (3/26), with a median PFS of three months and OS of nine months. Six patients (23%) experienced SAEs of more than Grade 2, underscoring the safety limitations of this agent.[45] Given its modest efficacy and relatively unfavorable toxicity profile, dacomitinib has largely fallen out of favor compared to newer, mutation-specific HER2 TKIs.

Neratinib

Neratinib, an irreversible pan-HER inhibitor, has demonstrated limited clinical benefit in HER2-mutant NSCLC. In a Phase II basket trial led by Hyman et al., only 2 of 26 patients (4%) achieved a partial response, and the DCR was 42%, with a median PFS of 5.5 months.[46] Similarly, the PUMA-NER-4201 study by Le et al. reported no objective responses among 17 enrolled patients with exon 20 insertions, although 35% achieved stable disease, with a median PFS of three months.[47] Due to these disappointing results, neratinib development in NSCLC has largely stalled; however, ongoing studies are exploring combination strategies to overcome resistance mechanisms.

Poziotinib

Poziotinib, an oral, irreversible pan-HER inhibitor, represents one of the first TKIs to demonstrate meaningful clinical activity against HER2 exon 20 insertions. In a Phase II study by Robichaux et al., poziotinib achieved an ORR of 42% (5/12) and a DCR of 83%, with a median PFS of 5.6 months.[48] These encouraging findings were confirmed in the ZENITH20 multicohort Phase II trial. In Cohort 2, which included 90 patients with previously treated HER2-mutant advanced NSCLC, poziotinib demonstrated an ORR of 35% (26/74) and a DCR of 82%, with a median DOR of 5.1 months and a median PFS of 5.5 months.[49] Similarly, Cohort 4 enrolled 80 previously treated HER2-mutant patients and reported an ORR of 39% (31/80) and a DCR of 73%, with a median PFS of 5.6 months.[50] However, poziotinib's clinical use has been limited by frequent Grade ≥3 toxicities and high rates of SAEs (reported in up to 75% of patients), prompting further optimization of dosing strategies.

Pyrotinib

Pyrotinib, an irreversible pan-HER TKI developed in China, has shown robust efficacy in HER2-mutant NSCLC, particularly in cases with exon 20 insertions. In an early Phase I/II trial conducted by Wang et al., pyrotinib achieved an ORR of 53% (8/15) and a DCR of 73%, with a median PFS of 6.4 months and OS of 12.9 months.[51] Subsequent Phase II data from Zhou et al., involving 60 patients with exon 20 insertions, confirmed an ORR of 30% and a DCR of 85%, with a median PFS of 6.9 months and OS of 14.4 months. Importantly, pyrotinib demonstrated a more manageable safety profile compared to poziotinib, with lower rates of severe adverse events (~20%).[52] Ongoing studies are evaluating pyrotinib in earlier lines of therapy and in combination regimens with ICIs and chemotherapy, positioning it as a promising treatment option for HER2-mutant NSCLC, particularly within Asian populations.

Tarloxotinib

Tarloxotinib is a novel hypoxia-activated pan-HER TKI designed to selectively release its active metabolite within hypoxic tumor microenvironments, potentially reducing systemic toxicity. In the RAIN-701 study, 11 patients with previously treated HER2-mutant advanced lung cancer were enrolled. Among the nine evaluable patients, two partial responses (22%) were observed, and the DCR was 67%.[53] While these findings are preliminary, tarloxotinib remains an intriguing investigational agent that requires further clinical validation.

Zongertinib

Zongertinib represents a next-generation, highly selective HER2 TKI optimized for activity against exon 20 insertions while minimizing off-target effects. In the Phase I a/b

trial presented by Heymach et al. in 2025, 75 patients with advanced or metastatic HER2-mutant NSCLC, predominantly harboring A775_G776insYVMA insertions, were treated. Remarkably, zongertinib achieved an ORR of 71% (53/75) and a DCR of 96%, with a median DOR of 9.7 months and PFS of 10.9 months. Severe adverse events occurred in 17% of patients, indicating a favorable safety profile relative to earlier-generation TKIs.[54] These promising data suggest that zongertinib may represent the most effective HER2-directed TKI to date, and ongoing Phase II/III studies are expected to further define its role in clinical practice.

Discussion

The development of HER2-targeted TKIs has progressed from nonselective pan-HER inhibitors with modest efficacy, such as afatinib, dacomitinib, and neratinib, to next-generation, mutation-selective agents that demonstrate significantly improved response rates and tolerability, including poziotinib, pyrotinib, and zongertinib.[55] Among these, zongertinib currently exhibits the most compelling efficacy data and the most favorable safety profile, positioning it as a potential best-in-class TKI. Future strategies will focus on optimizing patient selection, refining HER2 mutational profiling to distinguish exon-specific sensitivities, and investigating combination regimens that integrate TKIs with ADCs, ICIs, and chemotherapy. As clinical data mature, personalized treatment algorithms will increasingly leverage both targeted TKIs and ADCs to improve outcomes for patients with HER2-altered NSCLC.

The therapeutic landscape for HER2-altered NSCLC has evolved dramatically over the past decade. Early-generation TKIs, such as afatinib, dacomitinib, and neratinib, provided limited benefits, with modest response rates and short PFS. In contrast, the development of ADCs and next-generation, mutation-selective TKIs has transformed treatment strategies, offering substantially improved efficacy and tolerability. ADCs currently lead the field, with T-DXd demonstrating strong clinical activity in the DESTINY-Lung trials and establishing itself as the preferred treatment for previously treated HER2-mutant NSCLC. Earlier TKIs showed limited efficacy, but newer agents designed to overcome HER2 exon 20 steric hindrance, including poziotinib, pyrotinib, and zongertinib, have shown notable improvements. Among these, zongertinib is emerging as a potential

best-in-class TKI, with efficacy approaching that of ADCs like T-DXd, which has been approved by the FDA (Table S1).

Although ADCs such as T-DXd often induce more durable and profound responses compared with TKIs, the development of resistance remains inevitable. Resistance to HER2-targeted therapies in HER2-altered NSCLC arises from multiple, often overlapping mechanisms (Table 4). Structural alterations of the HER2 receptor, including secondary mutations, truncations, or heterogeneous expression, can impair drug binding and reduce treatment efficacy. Tumor cells may activate alternative or bypass signalling pathways, such as EGFR, HER3, MET, or FGFR, to sustain growth despite HER2 inhibition. Acquired downstream mutations in genes like PIK3CA or KRAS can further drive resistance through persistent activation of the PI3K/AKT or MAPK pathways.[56-58] Immune-mediated resistance may occur through reduced antibody-dependent cellular cytotoxicity or increased immunosuppression in the tumor microenvironment (TEM). In addition, impaired drug internalization, increased efflux, or altered lysosomal processing can decrease the cytotoxic payload delivery of antibody–drug conjugates.[59] Phenotypic plasticity, including epithelial–mesenchymal transition (EMT), enables tumor cells to become less dependent on HER2 signalling, while intratumoral heterogeneity and clonal evolution promote the emergence of resistant subclones.[60] Together, these mechanisms highlight the complexity of HER2 resistance and underscore the need for dynamic molecular monitoring and combination strategies to overcome therapeutic failure.

Notably, cross-resistance between ADCs and TKIs appears to be incomplete, suggesting a rationale for sequential or combinatorial therapeutic strategies. For example, patients who progress on T-DXd may still derive benefit from subsequent TKI therapy, or

vice versa, depending on the dominant molecular resistance mechanisms identified at progression. Emerging agents, including trastuzumab rezetecan and the novel HER2-selective TKI zongertinib, have demonstrated prolonged durations of response and favorable safety profiles in early-phase trials, comparable to or exceeding those of T-DXd.[34,61] These findings underscore the importance of molecular re-profiling at progression and rational sequencing of HER2-targeted therapies to overcome resistance and optimize long-term disease control. Safety considerations play an important role in treatment selection. ADCs and TKIs both continue to evolve, with newer generations aiming to improve efficacy and tolerability. Recent advances, particularly with agents such as pyrotinib and zongertinib, highlight the progress being made toward safer and more effective HER2-targeted therapies for mutation-selective patient populations.

Ongoing research aims to personalize HER2-targeted therapy and optimize treatment sequencing. The DESTINY-Lung04 Phase III trial is evaluating T-DXd as a potential first-line standard, while emerging ADCs such as disitamab vedotin, MRG002, SYD985, and ARX788 show promise for improved efficacy and safety. Meanwhile, next-generation TKIs like zongertinib and pyrotinib are undergoing late-phase evaluation, including trials combining TKIs with ICIs and chemotherapy to enhance response depth and durability. Combination approaches involving ADCs plus TKIs or ADCs plus immunotherapy are also under exploration to maximize tumor control and delay resistance. Moreover, genotype-guided treatment strategies that distinguish HER2 exon 20 insertions from HER2 overexpression/amplification will refine patient selection and therapeutic decision-making.

Conclusion

Therapeutic strategies for HER2-altered NSCLC are rapidly advancing. T-DXd remains the current standard of care, demonstrating strong and durable efficacy. Meanwhile, trastuzumab rezetecan and other emerging ADCs show comparable promise. Next-generation TKIs, particularly zongertinib and pyrotinib, offer improved efficacy and safety profiles compared to earlier agents. Future treatments will rely on personalized, biomarker-driven approaches that integrate optimized sequencing and combination strategies to enhance outcomes and overcome resistance.

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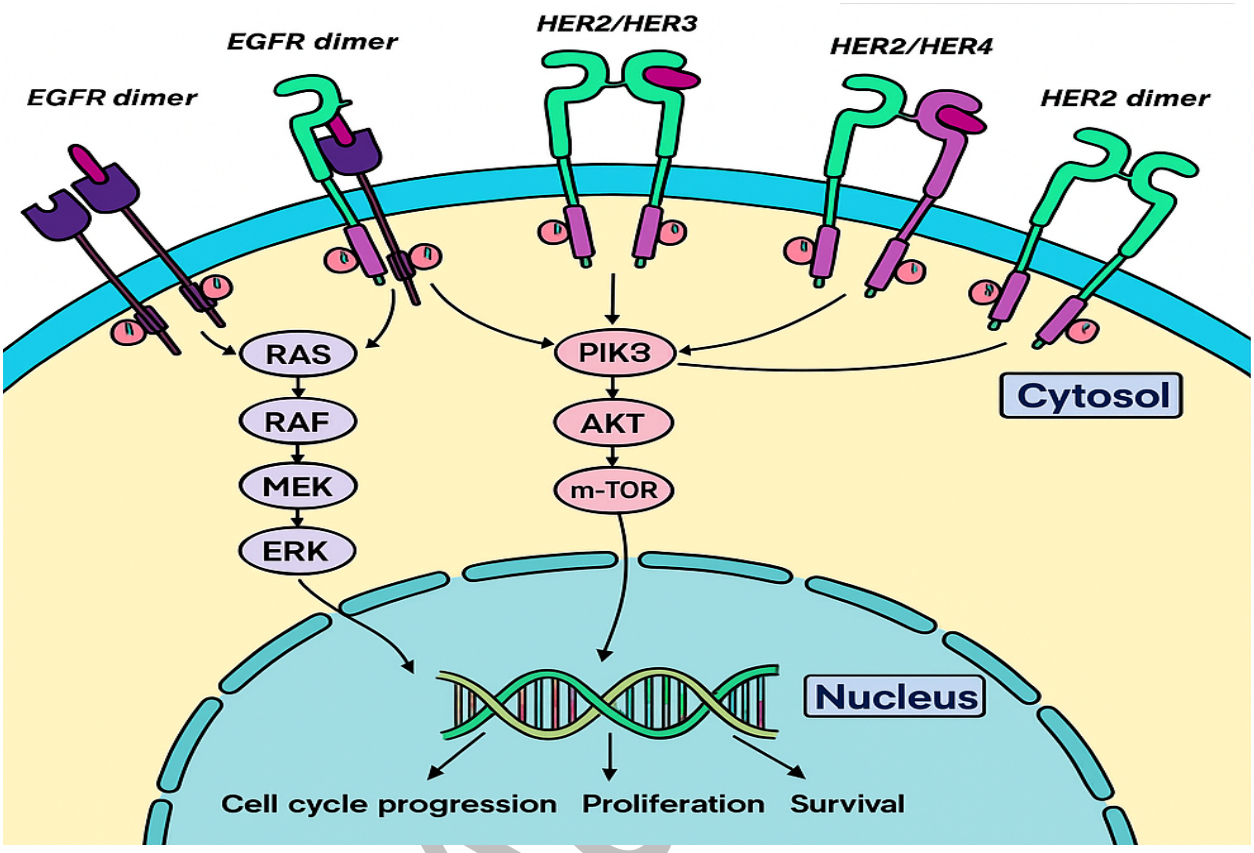
624 Figure 1 Downstream signaling pathway of the HER2 receptor



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627 Table 1: HER2 Testing Methods in NSCLC

Assay	Best for detecting	Analytical performance	Sample type	Practical notes
NGS (DNA, tissue)	HER2 point mutations & exon 20 insertions; can infer amplification	SNVs/indels ≥5% VAF: ~99–100% sensitivity & specificity in validated panels; amplification detection improving with depth	FFPE tissue / biopsy	Most comprehensive test for HER2 alterations; guideline-recommended first-line genomic test
NGS (ctDNA, liquid biopsy)	Same alterations as tissue; limited by tumor DNA shedding	Sensitivity ~70–80% vs tissue; specificity ~99%	Plasma (ctDNA)	Useful when tissue is unavailable or for rapid/serial monitoring; negative result → reflex to tissue
Targeted PCR (ARMS, castPCR, ddPCR)	Known HER2 hotspots (some exon 20 insertions)	Very high sensitivity (down to ~0.1% VAF); excellent specificity but limited coverage	Tissue; some assays validated for plasma	Fast, inexpensive for known variants; may miss rare/novel insertions → NGS preferred for full profiling
FISH (ERBB2 amplification)	Gene amplification (copy-number gain)	High sensitivity & specificity; considered reference for amplification	FFPE tissue; occasionally cytology	Detects amplification only (not mutations); used when amplification affects management or to confirm NGS results
IHC (HER2 protein)	Protein overexpression (3+)	Variable correlation with HER2 mutations; concordance low (~14% overlap)	FFPE tissue	Not a mutation test; used to assess overexpression alongside genomic testing per guidelines

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Table 2 Development of HER2–Targeted ADCs in NSCLC

Author	Agents	Study	Criteria	Main HER2 mutation	Cases	ORR	DCR	DOR (m)	PFS (m)	OS (m)	SAEs
Smit et al. 2024[25]	Trastuzumab Deruxtecan	DESTINY-Lung01 (P2)[a]	HER2-overexpressing or HER2 mutant unresectable or metastatic NSCLC	IHC 2+, 3+	41	14/41 (34%)	32/41 (78%)	6.2	6.7	11.2	41/41 (100%)
Goto et al. 2023[26]		DESTINY-Lung02 (P2)[a]	Previously treated HER2-mutant metastatic NSCLC	Single-nucleotide variants and exon 20 insertions	102	50/102 (49%)	95/102 (93%)	16.8	-	19.5	63/101 (62%)
Planchard et al. 2024[27]		DESTINY-Lung03 part 1(P2 basket)	HER2-overexpressing unresectable, locally advanced, or metastatic nonsquamous NSCLC	IHC 2+, 3+	36	16/36 (44%)	-	12.2	8.2	14.7	-
Cheng et al. 2024[28]		DESTINY-Lung05 (P2)	Previously treated metastatic nonsquamous NSCLC with HER2 mutations (Chinese population)	HER2 exon 19 or 20 mutation	72	42/72 (58%)	66/72 (92%)	-	10.8	-	37/72 (51%)
Li et al. 2018[31]	Trastuzumab Emtansine	NCT02675829 (P2 basket)	Stage IV or recurrent HER2-mutant lung cancer	Exon 20 insertion	18	8/18 (44%)	15/18 (83%)	-	5	-	1/18 (6%)
Iwama et al. 2021[32]		JapicCTI-194620 (P2)	Previously treated adenocarcinoma lung cancer with HER2 mutations	Exon 20 insertion (A775_G776insYVMA)	22	8/21 (38%)	11/21 (52%)	-	2.8	8.1	5/21 (24%)
Li et al. 2024[33]	Trastuzumab Rezetecan	NCT04818333 (P1-2)[b]	Pretreated HER2-altered advanced non-small cell lung cancer	Exon 20 insertion (A775_G776insYVMA)	43	18/43 (42%)	41/43 (95%)	13.7	8.4	-	
Li et al. 2025[34]		HORIZON-Lung (P2)	HER2-overexpressing or HER2 mutant unresectable or metastatic NSCLC	Exon 20 insertion (A775_G776insYVMA)	94	69/94 (73%)	93/94 (99%)	-	11.5	-	94/94 (100%)

a: data of 5.4 mg/lg only; b: data of 4.8 mg/lg only

Table 3: Development of HER2–Targeted TKIs in NSCLC

Author	Agent	Study	Cases	Eligibility	Main HER2 mutation	ORR	DCR	DOR	PFS	OS	SAEs
De Greve et al. 2015[42]	Afatinib	P2 basket	7	Stage IIIB/IV NSCLC with HER2 mutation	-	0/7	5/7 (71%)	-	17 w	-	-
Peters et al. 2018[43]		P2	28	Stage IV NSCLC with HER2 mutation	A775_G776insYVMA	3/16 (19%)	11/16 (69%)	-	-	-	-
Dziadziuszko et al. 2019[44]		P2	13	Advanced NSCLC with HER2 exon 20 mutations	A775_G776insYVMA	1/13 (7.7%)	7/13 (53.8%)	-	15.9 w	56 w	3/13 (23%)
Kris et al. 2015[45]	Dacomitinib	P2	26	HER2-mutant advanced or metastatic NSCLC	A775_G776insYVMA	3/26 (12%)	-	-	3 m	9 m	6/23 (23%)
Hyman et al. 2018[46]	Neratinib	P2 basket	26	HER2-mutant advanced or metastatic NSCLC	-	2/26 (4%)	11/26 (42%)	-	5.5 m	-	-
Le et al. 2021[47]		PUMA-NER-4201	17	HER2-mutant advanced or metastatic NSCLC	Exon 20 insertion	0/17 (0%)	6/17 (35%)	-	3 m	10 m	-
Robichaux et al. 2020[48]	Poziotinib	P2	12	HER2-mutant previously treated advanced or metastatic NSCLC	Y772dupYVMA	5/12 (42%)	10/12 (83%)	-	5.6 m	-	8/12 (75%)
Le et al. 2022[49]		ZENITH20 Cohort 2	90	HER2-mutant previously treated advanced or metastatic NSCLC	Exon 20 insertion (Y772_A775dupYVMA)	26/74 (35%)	61/74 (82%)	5.1 m	5.5 m	-	75 (83%)
Cornelissen et al.[50]		ZENITH20 Cohort 4	80	HER2-mutant previously treated advanced or metastatic NSCLC	Exon 20 insertion (Y772_A775dupYVMA)	31/80 (39%)	58/80 (73%)	5.7 m	5.6 m	-	60/80 (75%)
Wang et al. 2019[51]	Pyrotinib	P1-2	15	HER2-mutant previously treated advanced or metastatic NSCLC	A775_G776insYVMA	8/15 (53%)	11/15 (73%)	-	6.4 m	12.9 m	None
Zhou et al. 2020[52]		P2	60	HER2-mutant previously treated advanced ALC	Exon 20 insertion	18/60 (30%)	51/60 (85%)	-	6.9 m	14.4 m	12/60 (20%)
Liu et al. 2020[53]	Tarloxotinib	RAIN-701	11	HER2-mutant previously treated advanced ALC	-	2/9 (22%)	6/9 (67%)	-	-	-	-
Heymach et al. 2025[54]	Zongertinib	P1a-1b	75	Advanced or metastatic HER2-mutant NSCLC	A775_G776insYVMA	53/75 (71%)	72/75 (96%)	9.7 m	10.9 m	N.S.	13/75 (17%)

Table 4. Mechanisms of Resistance to HER2-Targeted Therapy in HER2-Altered NSCLC

Mechanism	Description / Key Findings	Therapeutic Implications
Downstream pathway mutations	Acquired PIK3CA or KRAS mutations activate downstream signalling independent of HER2.	Genetic profiling at progression to tailor next-line therapy; dual blockade of HER2 and PI3K/AKT.
Activation of bypass pathways	Upregulation of EGFR, HER3, MET, IGF1R, or FGFR pathways sustains downstream signalling despite HER2 inhibition.	Combination approaches with PI3K, mTOR, or MEK inhibitors may overcome resistance.
HER2 structural alterations	Secondary mutations or truncated HER2 forms reduce antibody binding or drug efficacy. Loss or heterogeneity of HER2 expression may lead to incomplete target inhibition.	Re-biopsy to reassess HER2 status; consider switching from antibody-based to TKI therapy if HER2 expression decreases.
Impaired immune-mediated effects	Reduced ADCC or increased immune suppression in the TME	Combine HER2-targeted therapy with immune checkpoint inhibitors or TME-modulating agents.
Drug internalization or efflux changes	Reduced endocytosis of HER2–ADC complexes, increased drug efflux, or altered lysosomal trafficking.	Use ADCs with alternative linkers/payloads or combine with endosomal modulators.
Phenotypic plasticity / EMT	Tumor cells undergo EMT or dedifferentiation, decreasing HER2 dependency.	Consider combining HER2 therapy with EMT or stemness pathway inhibitors.
Tumor heterogeneity and clonal evolution	Mixed HER2 expression and coexistence of multiple driver mutations lead to selection of resistant clones.	Serial genomic monitoring to detect emerging resistance clones and guide therapy.