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Advances in HER2-Targeted Tumor Therapy: Molecular Mechanisms, Treatment Strategies and Clinical Challenges

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Abstract. Human epidermal growth factor receptor 2 (HER2) is a vital oncotherapeutic target across multiple solid tumors, covering breast, gastric/gastroesophageal junction, non-small cell lung, colorectal, biliary, urothelial, cervical, endometrial, salivary gland, and ovarian cancers, as well as esophageal adenocarcinoma. Clarifying HER2-mediated oncogenic signaling and identifying validated treatment strategies are critical for standardized clinical practice and innovative drug discovery. This review begins with HER2 structural features and downstream oncogenic signaling, then summarizes therapeutic frameworks for HER2-positive cancers, including conventional regimens, single targeted agents, and combination therapies. Three major clinical obstacles—drug resistance, treatment-related toxicities and tumor heterogeneity—are analyzed alongside corresponding solutions, followed by prospects in novel drug development, precision medicine and multidisciplinary cooperation. Current clinical data show that single-agent therapies possess modest antitumor activity; chemo-targeted combinations partially enhance efficacy yet are hindered by resistance and heterogeneity. Further innovations in precision medicine are urgently needed to enable personalized management. This work systematically reviews pan-cancer HER2-related oncogenic mechanisms and the full spectrum of targeted regimens offering mechanistic and clinical references for precision therapy and new drug research of HER2-positive solid tumors.

Keywords: HER2+, molecular mechanisms, targeted therapy, drug resistance, tumor heterogeneity

1. Introduction

The HER2 proto-oncogene has a long research history. As early as 1987, Professor Dennis Slamon and his team detected ERBB2 gene aberrations in breast cancer and confirmed that HER2 overexpression strongly correlated with worse breast cancer prognosis [1]. Subsequently, trastuzumab was approved by the FDA in 1998 based on clinical trial data submitted by Professor Slamon, making it the first HER-targeted therapeutic agent to receive marketing authorization. The manuscript containing the relevant trial data was formally published in 2001 [2]. To date, the portfolio of HER2-targeted agents has expanded substantially, encompassing various categories such as monoclonal antibodies, bispecific antibodies, tyrosine kinase inhibitors (TKIs), antibody-drug conjugates (ADCs) and cell therapies. Their indications have also expanded beyond breast cancer to

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include multiple solid tumors, such as gastric cancer, non-small cell lung cancer, colorectal cancer, and biliary tract cancer [3, 4].

Anti-HER2 therapy has progressed rapidly, driven by continuous development of new agents and expanding tumor indications. Existing reviews partially summarize relevant advances, yet few systematically integrate molecular mechanisms, therapeutic strategies and clinical hurdles amid updated anti-HER2 drugs, deepening resistance research and broadening pan-tumor applications. This systematic review retrieved HER2-related studies published 1978–2026 from PubMed, Web of Science and Wanfang Data to synthesize evidence on HER2-mediated oncogenic mechanisms, treatment regimens and clinical challenges.

2. Overview and molecular mechanisms of the HER2-positive target

2.1. Definition and structure of the HER2-positive target

Human epidermal growth factor receptor 2 (HER2), also known as ERBB2 or NEU, belongs to the EGFR/ErbB family and is essentially a receptor tyrosine kinase located on the cell membrane. The ERBB2 proto-oncogene encoding HER2 maps to chromosomal region q12-q21.32 on the long arm of chromosome 17. Under physiological conditions, it regulates cell growth, proliferation and differentiation [4, 5]. Structurally, HER2 is a transmembrane glycoprotein consisting of three functional domains: the extracellular domain, the transmembrane region, and the intracellular tyrosine kinase domain. The extracellular domain serves as the binding site for monoclonal antibodies. Trastuzumab and pertuzumab recognize and bind to distinct epitopes within the HER2 extracellular domain. The intracellular tyrosine kinase domain, which is the target of tyrosine kinase inhibitors (TKIs), possesses catalytic kinase activity [6, 7].

2.2. Activation mechanism of the HER2 signaling pathway

HER2-driven signaling depends on receptor homodimerization or heterodimerization with EGFR/HER3/HER4. Dimerization triggers intracellular tyrosine kinase transphosphorylation, which activates C-terminal tyrosine residues to recruit downstream signaling mediators. The HER2/HER3 heterodimer bears the strongest oncogenic signaling activity and dominates HER2-positive tumors. As an essential binding partner of overexpressed HER2, the HER2/HER3 complex robustly stimulates the PI3K/AKT/mTOR cascade, which is the core pathway sustaining tumor cell survival and proliferation [4, 8, 9].

HER2 transduces downstream signals through four core signaling cascades:

(1) Mitogen-activated protein kinase (MAPK) pathway, which principally modulates cell proliferation and differentiation;

(2) Phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway, which orchestrates cell survival, metabolism and protein synthesis;

(3) Protein kinase C (PKC) pathway, which participates in the regulation of cell proliferation and differentiation;

(4) Signal transducer and activator of transcription (STAT) pathway, which mediates transcriptional regulation of target genes.

Notably, the MAPK and PI3K/AKT cascades act as master signaling axes governing tumor cell viability and proliferation, and constitute the predominant pathways underlying acquired resistance to anti-HER2 targeted therapeutics [10, 11].

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2.3. Roles of the HER2-positive target in tumorigenesis and tumor progression

HER2 aberrations are mainly classified into three molecular subtypes: gene amplification, activating mutations, and ligand-mediated aberrant activation. Gene amplification and subsequent protein overexpression represent the most prevalent forms, occurring in approximately 15%–30% of breast cancers and 4.4%–53.4% of gastric/gastroesophageal junction carcinomas. Such alterations have also been identified in a broad spectrum of solid malignancies, including colorectal cancer, biliary tract cancer, non-small cell lung cancer, endometrial cancer, ovarian cancer, bladder cancer, and salivary gland carcinoma. HER2 overexpression is generally positively correlated with poor clinical prognosis [4, 7, 12].

HER2-activating mutations are relatively rare, predominantly reside within the kinase domain, and occur independently of gene amplification, which augments intrinsic HER2 kinase activity. Such alterations are most frequently identified in non-small cell lung cancer, with exon 20 insertions being the predominant subtype, and represent a key therapeutic target for HER2-directed treatment in lung malignancies [13]. Comparable alterations have also been documented in breast, gastric and colorectal cancers, predominantly manifesting as missense mutations, whose precise clinical implications remain under further investigation [6]. In addition, a tiny subset of malignancies exhibit aberrant HER2 pathway activation via ligand-mediated mechanisms. For instance, NRG1 gene fusions lead to persistent membrane expression of neuregulin fusion proteins, which drive constitutive activation of HER2/HER3 signaling.

3. Therapeutic strategies for HER2-positive malignancies

3.1. Conventional therapeutic modalities

3.1.1. Surgical resection

Surgical resection is the primary curative modality for early-stage HER2-positive solid tumors. For operable cases, standard procedures include breast-conserving surgery or total mastectomy for breast cancer, minimally invasive endoscopic resection or subtotal gastrectomy for gastric/gastroesophageal junction carcinoma, and video-assisted thoracoscopic surgery (VATS) lobectomy with systematic mediastinal lymph node dissection for HER2-positive non-small cell lung cancer. The optimal surgical strategy should be determined based on tumor size, location, and patient preference [14, 15]. For locally advanced or high-burden HER2-positive tumors, neoadjuvant therapy (preoperative chemotherapy plus anti-HER2 targeted agents) followed by resection is the recommended paradigm. Surgery alone eradicates only localized lesions; given the high inherent invasiveness and metastatic risk of this molecular subtype, all operable patients require perioperative chemo-targeted combination therapy, as monotherapy is associated with an extremely high recurrence risk. Curative resection is not indicated for metastatic advanced disease [16].

3.1.2. Chemotherapy

Cytotoxic chemotherapy constitutes the backbone of treatment for HER2-positive malignancies and served as the primary systemic therapy for advanced patients prior to the advent of targeted agents. To date, chemotherapy is frequently combined with anti-HER2 therapeutics to augment therapeutic efficacy. For patients with HER2-positive gastric/gastroesophageal junction carcinoma (G/GEJC),

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cisplatin plus capecitabine or 5-fluorouracil represented the standard first-line chemotherapy regimen for advanced disease before the approval of trastuzumab [4]. For patients with advanced HER2-mutant non-small cell lung cancer, trastuzumab deruxtecan (T-DXd) serves as the standard later-line regimen, supported by the most robust clinical evidence and a superior objective response rate. Pan-HER TKIs such as poziotinib and pyrotinib are available only as alternative monotherapies following disease progression after ADC treatment [4, 17]. For HER2-positive breast cancer, cytotoxic chemotherapy regimens commonly consist of anthracyclines, taxanes and other cytotoxic agents [16].

3.1.3. Radiotherapy

Radiotherapy represents an indispensable local therapeutic modality for HER2-positive malignancies, which is mainly administered as postoperative adjuvant treatment, curative-intent therapy for unresectable locally advanced tumors, and palliative care for metastatic patients. For breast cancer, adjuvant postoperative radiotherapy is the standard of care following breast-conserving surgery and markedly diminishes the risk of local recurrence. Radiotherapy plays a pivotal role in managing brain metastases derived from HER2-positive tumors; whole-brain radiotherapy achieves a symptomatic relief rate of up to 70%, using conventional fractionation schedules of 30 Gy in 10 fractions or 20 Gy in 5 fractions [18].

3.2. Targeted therapy

Based on molecular structures and mechanisms of action, currently available anti-HER2 targeted agents are categorized into three major classes: anti-HER2 monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and antibody-drug conjugates (ADCs). These three classes differ substantially in signaling pathways modulated, eligible patient populations, and resistance mechanisms, collectively forming the comprehensive therapeutic framework for HER2-positive malignancies [6]. Representative anti-HER2 monoclonal antibodies include trastuzumab and pertuzumab. Trastuzumab binds to domain IV of the extracellular region of HER2, directly hindering HER2 homodimerization, thereby suppressing ligand-induced intracellular kinase phosphorylation and blocking proliferative signaling cascades. By contrast, pertuzumab targets extracellular domain II of HER2 and directly interferes with HER2–HER3 heterodimerization, fundamentally inhibiting the HER2/HER3 signaling axis that confers the strongest oncogenic activity. Dual anti-HER2 blockade with the combination of trastuzumab and pertuzumab simultaneously abrogates both homodimer and heterodimer formation, markedly elevating objective response rates and reducing recurrence risk. Anti-HER2 monoclonal antibodies are indicated for the treatment of HER2-positive breast cancer and HER2-positive gastric/gastroesophageal junction adenocarcinoma [19].

HER-targeted tyrosine kinase inhibitors (TKIs) are oral small molecules that competitively bind the intracellular ATP pocket of HER receptors, suppressing kinase phosphorylation and blocking the core PI3K/AKT and RAS/ERK oncogenic cascades.HER-TKIs fall into four mechanistic subgroups: reversible pan-HER agents (e.g., lapatinib) inhibit EGFR and HER2 catalytic activity; irreversible pan-HER agents (neratinib, pyrotinib) disrupt HER2-HSP90 chaperone interaction, triggering HER2 ubiquitination and proteasomal degradation; HER2-selective tucatinib features minimal off-target toxicity and blood–brain barrier penetration via its lipophilic structure; next-generation mutation-selective zongertinib targets mutant HER2 kinase domains without interfering with wild-type EGFR. When combined with monoclonal antibodies or antibody-drug conjugates, TKIs exert synergistic antitumor activity through dual upstream-downstream pathway blockade and are clinically indicated

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for HER2-positive breast, cervical, and biliary tract cancers [20]. Anti-HER2 antibody-drug conjugates (ADCs) consist of three core components: anti-HER2 monoclonal antibody, linker, and cytotoxic payload. After receptor-mediated endocytosis into lysosomes, cytotoxic moieties are released to trigger tumor cell apoptosis, with trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) as the leading representative agents.

T-DM1carries the microtubule inhibitor DM1 via a non-cleavable thioether linker, with a membrane-impermeable payload that selectively eliminates HER2-high tumor cells. In contrast, T-DXd adopts a cleavable tetrapeptide linker that liberates a lipophilic topoisomerase inhibitor, conferring robust bystander cytotoxicity against neighboring HER2-low or HER2-negative tumor cells. This property addresses intratumoral heterogeneity, benefiting both HER2-positive and HER2-low populations. Both ADCs retain trastuzumab's intrinsic antitumor activities (HER2 signaling blockade and antibody-dependent cellular cytotoxicity) and are indicated for HER2-positive breast, non-small cell lung, and gastric/gastroesophageal junction adenocarcinomas [3].

4. Challenges facing targeted therapy for HER2-positive malignancies

4.1. Drug resistance

Acquired resistance to anti-HER2 targeted therapy falls into two major categories: target-derived resistance and bypass pathway dysregulation. Target-level mechanisms include downregulated membrane HER2 expression, drug-binding epitope masking, ERBB2 kinase domain mutations, and intratumoral HER2 heterogeneity with coexisting high- and low-expression tumor clones. Bypass resistance involves PI3K/MAPK hyperactivation driven by PTEN loss or PIK3CA/RAS mutations, compensatory receptor kinase amplification, cell cycle/DNA repair aberrations, epithelial–mesenchymal transition, metabolic reprogramming, and immunosuppressive microenvironment remodeling, collectively driving therapeutic escape [4, 21].

4.2. Adverse reactions

Anti-HER2 monoclonal antibodies exhibit a well-documented risk of clinically significant cardiotoxicity. Suppression of cardiomyocyte HER2 signaling reduces left ventricular ejection fraction (LVEF), which may progress to congestive heart failure in severe cases. Fever, chills and dyspnea are common during the first infusion. Baseline evaluations (medical history, physical examination, electrocardiography, echocardiographic LVEF measurement) are mandatory before treatment initiation, and cardiac function should be monitored every 3 months; asymptomatic cardiac dysfunction requires intensified surveillance (e.g., every 6–8 weeks) [14]. Prophylactic glucocorticoids substantially mitigate infusion-related reactions, though these agents may trigger mild gastrointestinal adverse effects including nausea and diarrhea [22, 23]. Diarrhea is the most prevalent shared adverse event of HER-TKIs, with a high overall incidence for pan-HER inhibitors (lapatinib, neratinib, pyrotinib) and occasional grade 3 severity. Uncomplicated diarrhea is managed conservatively with dietary/lifestyle adjustments, oral rehydration and loperamide; for complicated diarrhea, anti-HER2 TKIs and concomitant chemotherapy must be discontinued immediately, followed by inpatient multidisciplinary assessment with close monitoring of vital signs and laboratory parameters [24]. Dermatological toxicity (acneiform rash, hand-foot skin reaction) is the second most frequent event, with particularly high rash incidence associated with poziotinib. Elevated liver function tests, stomatitis and cardiovascular adverse events are also common, and

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combination with chemotherapy exacerbates hematologic toxicity, fatigue, nausea and vomiting [4, 25].

Anti-HER2 antibody-drug conjugates (ADCs) differ markedly in toxicity profiles. T-DM1 mainly causes thrombocytopenia and transaminase elevation, with low rates of severe myelosuppression and minimal interstitial lung disease risk. T-DXd yields far more severe hematologic adverse effects, with grade 3 neutropenia and anemia occurring frequently; its dose-dependent interstitial pneumonitis carries life-threatening potential, while its membrane-permeable cytotoxic payload triggers mild-to-moderate systemic symptoms including nausea, fatigue, and alopecia. For T-DXd, prophylactic G-CSF is recommended for patients with prior neutropenia. Treatment can be restarted at the original dose after grade 3 neutropenia resolution, while one-level dose reduction is required after grade 4 recovery [26]. Disitamab vedotin (RC48) presents a characteristic toxicity spectrum dominated by peripheral sensory neuropathy and multiple cytopenias. Other novel ADCs such as ZW49 and SHR-A1811 are associated with ocular surface injury and mild myelosuppression. Infusion-related reactions are commonly observed across all ADC subtypes, mostly grade 1–2, and the majority of patients can tolerate treatment after symptomatic intervention [4].

4.3. Tumor heterogeneity

4.3.1. Impacts of tumor heterogeneity on HER2-targeted therapy

Intratumoral HER2 expression heterogeneity is a core intrinsic driver of diminished anti-HER2 targeted efficacy and therapeutic failure. Individual lesions harbor coexisting HER2-high, -low and -negative subclones with divergent proliferative and invasive potentials. Conventional agents (trastuzumab, T-DM1) selectively eradicate HER2-positive cells, whereas HER2-negative subclones persist and ultimately drive disease progression. Retesting of clinical specimens demonstrates a marked downregulation of HER2 expression and progressively worsening heterogeneity in recurrent gastric, biliary, and other solid tumors during sustained trastuzumab treatment [27, 28]. In addition, T-DM1 exerts cytotoxic effects dependent on cellular internalization and lacks transcellular bystander activity. Against heterogeneous tumors, it only targets HER2-positive regions, resulting in limited overall antitumor activity. Even for the same therapeutic agent, its efficacy is directly determined by the spatial distribution of HER2 expression within lesions [29].

4.3.2. Strategies for the treatment of heterogeneous tumors

Second-generation ADCs represented by T-DXd and ARX788 are equipped with cleavable linkers and membrane-permeable payloads, serving as the core strategy to overcome HER2 intratumoral heterogeneity. Fluorescence imaging in xenograft models has verified that the antibody moiety of T-DXd is retained exclusively within HER2-positive cells, while the liberated DXd toxin can freely diffuse into adjacent HER2-negative tumor regions to achieve cross-subclone cytotoxicity [29]. In addition, multi-site sequential tissue biopsy and dynamic ctDNA monitoring via liquid biopsy enable detection of temporal shifts in intratumoral HER2 expression, allowing early prediction of the risk of progressive heterogeneity [30]. Meanwhile, multi-target combination regimens for synergistic tumor control represent another promising approach against heterogeneous malignancies. Combinatorial administration of ADCs with immune checkpoint inhibitors, PI3K inhibitors and other bypass pathway suppressors achieves coordinated suppression of tumor proliferation through multiple signaling cascades, thereby improving therapeutic efficacy [31].

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5. Conclusion

This review systematically summarizes advances in HER2-positive solid tumors. Starting from HER2 structure and its downstream oncogenic signaling, it delineates pathogenic subtypes including ERBB2 amplification and kinase mutations, and confirms that HER2/HER3 heterodimer-mediated sustained activation of PI3K and MAPK pathways is the core driver of tumor proliferation, which underpins the development of all current anti-HER2 targeted agents.

For clinical management, surgery, radiotherapy and chemotherapy are fundamental curative options for early-stage lesions. Three targeted agent classes—monoclonal antibodies, TKIs, and ADCs—form the precision treatment backbone , each with distinct binding epitopes and cytotoxic mechanisms; they are used as monotherapy or combinations based on tumor histology, HER2 expression and prior treatment. Novel modalities such as bispecific antibodies and cellular therapies are under clinical investigation.

Accumulating clinical trial data reveal three major persistent challenges in HER2-targeted therapy. First, multifaceted resistance mechanisms—including loss of HER2 expression, secondary kinase mutations, compensatory activation of MET/PI3K or other bypass pathways, epithelial-mesenchymal transition and metabolic reprogramming—collectively cause therapeutic failure. Second, intratumoral HER2 heterogeneity drives tumor recurrence, as conventional agents fail to eradicate HER2-negative subclones. Third, efficacy varies markedly across solid tumor types: monoclonal antibodies work only in highly ERBB2-amplified tumors; TKIs show superior activity in ERBB2-mutant lung cancer; next-generation ADCs cover amplification, mutations and low HER2 expression, supporting stratified treatment strategies.

This review has three main limitations. First, it focuses on high-prevalence HER2-altered tumors (breast, gastroesophageal and lung cancers), with limited evidence for rare HER2-mutated malignancies such as salivary gland and endometrial tumors. Second, it primarily summarizes large phase II/III registration trials, with inadequate integration of preclinical studies and phase I exploratory trials. Third, economic evaluations of therapeutic regimens are not included, limiting their reference value for clinical medication decisions in primary care settings.

Future HER2-targeted therapy research will advance in four core directions. First, ADCs and bispecific antibodies will be structurally optimized to reduce severe toxicities such as cardiopulmonary injury and interstitial lung disease. Second, widespread liquid biopsy and spatial sequencing will enable real-time dynamic monitoring for early prediction of resistance and tumor heterogeneity. Third, novel synergistic regimens (e.g., ADCs plus immunotherapy or bypass pathway inhibitors) will be further explored and validated. Fourth, individualized stratified treatment models will be established based on genetic profiles, tumor heterogeneity and organ function. These advances are expected to overcome resistance and recurrence bottlenecks, and ultimately improve survival and quality of life for patients with various HER2-altered solid tumors.

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