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Chinese guidelines for HER2-targeted therapy in gastric and gastroesophageal junction adenocarcinoma (2025 Edition)

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Abstract

Gastric and gastroesophageal junction adenocarcinoma (GC/GEJC) poses a substantial clinical burden in China. This updated guideline introduces a refined human epidermal growth factor receptor 2 (HER2) classification system (high, intermediate, low, absent) to redefine patient stratification for targeted therapy. It integrates cutting-edge evidence on standardized detection—including immunohistochemistry, in situ hybridization, and liquid biopsy—to overcome spatial-temporal heterogeneity. Recent progress in the use of HER2-targeted agents, including monoclonal antibodies, antibody–drug conjugates, tyrosine kinase inhibitors, and bispecific antibodies, is systematically reviewed and presented to inform evidence-based clinical practice. These updates aim to optimize personalized HER2-targeted therapy and improve outcomes in GC/GEJC patients.

Keywords HER2, Gastric cancer, Guideline, Diagnosis, Treatment

Introduction

Background

China bears one of the highest global burdens of gastric and gastroesophageal junction adenocarcinoma (hereafter collectively referred to as “gastric cancer”), with the majority of patients diagnosed at an advanced stage. Systemic therapy remains the cornerstone of treatment for advanced disease. Despite available interventions, the overall prognosis remains poor, with a median overall survival (OS) of approximately 12 months in patients with advanced gastric cancer [1]. Effective systemic treatment is therefore essential to improving clinical outcomes. Among targeted approaches, therapy directed against human epidermal growth factor receptor 2 (HER2) has become a major area of focus. Recent advances, particularly the combination of HER2-targeted therapy with immunotherapy and the development of

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Table 1 Summary of recommendations

No	Clinical scenario	Recommendation	Level of evidence	Strength of recommendation
Detection of HER2 in gastric cancer				
1	Specimen preparation	Standardized protocols for specimen collection, preservation, and fixation are critical to ensure the accuracy and reliability of HER2 testing in gastric cancer	High	Strong
2	Evaluation of HER2 protein expression	IHC should be employed as the standard method for evaluating HER2 protein expression in gastric cancer. Testing should adhere to standardized protocols, and pathology reports must specify HER2 scores as IHC 0, 1+, 2+, or 3+	High	Strong
3	Detection of HER2 gene amplification	ISH is the definitive method for determining HER2 gene amplification and must be executed according to SOPs to ensure accuracy and reproducibility. In cases with IHC 2+, FISH testing is mandatory to clarify HER2 status	High	Strong
4	Detection of HER2 gene mutations and fusions	In patients with gastric cancer for whom tissue biopsy is not feasible, HER2 amplification may be assessed using ctDNA obtained via liquid biopsy. NGS may be considered for the comprehensive detection of HER2 variants in both tissue and ctDNA specimens	Low	Weak
5-a	Management of HER2 heterogeneity	Given the heterogeneity of HER2 expression in gastric cancer, diagnostic precision can be improved through multi-site biopsy, assessment of multiple paraffin blocks	Low	Strong
5-b		Re-biopsy is not mandatory after progression. Whenever feasible, re-biopsy may be considered to reassess recurrent or metastatic lesions to guide the consideration of second-line HER2-targeted therapy	Low	Weak
HER2-targeted therapies in gastric cancer				
6	First-line therapy	For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ and PD-L1 CPS < 1, trastuzumab plus chemotherapy is recommended as first-line therapy	High	Strong
7		For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ and PD-L1 CPS ≥ 1, the addition of pembrolizumab to trastuzumab and chemotherapy is recommended as first-line treatment	High	Strong
8		For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ and high PD-L1 expression who are unable to tolerate chemotherapy, treatment with trastuzumab in combination with a PD-1 inhibitor may be considered	Low	Weak
9	Second-line therapy	Trastuzumab is not routinely recommended for continuation beyond progression in advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ who have experienced disease progression after trastuzumab-containing first-line therapy, due to limited demonstrated benefit	Moderate	Strong
10		For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ who have not previously received trastuzumab, second-line therapy with trastuzumab in combination with paclitaxel is recommended	Moderate	Strong
11		For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ who have previously received treatment, second-line therapy with T-DXd is recommended	High	Strong
12-a	Third-line or Later-line therapy	Disitamab vedotin is recommended as third-line or later-line therapy for advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+	Moderate	Strong
12-b		Disitamab vedotin is recommended as third-line or later-line therapy for advanced gastric cancer patients with HER2 IHC 2+/FISH–	Moderate	Strong
13-a		T-DXd is recommended as third-line or later-line therapy for advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+	Moderate	Strong
13-b		T-DXd is recommended as third-line or later-line therapy for advanced gastric cancer patients with HER2 IHC 2+/FISH–	Low	Strong
14	Maintenance therapy	For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ who received first-line therapy with trastuzumab plus chemotherapy, maintenance therapy with trastuzumab monotherapy is recommended	Moderate	Strong
15		For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ who have received first-line treatment comprising trastuzumab, chemotherapy, and pembrolizumab, maintenance therapy with trastuzumab and pembrolizumab in combination with single-agent chemotherapy may be considered	Low	Weak
16	Resistance to HER2-therapy	For patients with resistance to HER2-targeted therapies, participation in clinical trials is recommended	Moderate	Strong

Table 1 (continued)

No	Clinical scenario	Recommendation	Level of evidence	Strength of recommendation
17	Perioperative therapy	In locally advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+, participation in clinical trials of HER2-targeted therapy is encouraged in the perioperative setting (including both neoadjuvant and adjuvant phases)	Moderate	Strong
18	Conversion therapy	In advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+, HER2-targeted therapy may be considered for conversion therapy. The timing of surgical intervention should be guided by multidisciplinary assessment of tumor response, patient performance status, and surgical eligibility	Low	Weak

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; SOP, standard operating procedure; CPS, combined positive score; T-DXd, Trastuzumab Deruxtecan

novel compounds, have significantly broadened the therapeutic landscape. Monoclonal antibodies have shown robust efficacy in tumors with HER2-high expression (immunohistochemistry [IHC] 3+ or IHC 2+ with fluorescence in situ hybridization [FISH]+). More recently, antibody–drug conjugates (ADCs) have demonstrated clinical activity across a wider spectrum of HER2 expression, including IHC 2+/FISH- and IHC 1+ tumors [2]. For example, in the RC48-C008 trial, disitamab vedotin (RC48) provided clinical benefit in patients with HER2 IHC 2+ or 3+ gastric cancer, including those with IHC 2+ tumors regardless of in situ hybridization (ISH) status [3]. Similarly, the DESTINY-Gastric01 trial evaluated trastuzumab deruxtecan (T-DXd) in patients with HER2 IHC 2+/ISH- and IHC 1+ tumors, reporting therapeutic benefit in these subgroups [4]. These findings from RC48-C008 and DESTINY-Gastric01 trials challenge the traditional definition of HER2-positive disease and suggest a broader therapeutic window for HER2-targeted ADCs.

In response to these evolving data, and under the leadership of the CSCO Expert Committee on Gastric Cancer, the CSCO Expert Committee on Tumor Pathology, the Precision Therapy Committee of the Chinese Anti-Cancer Association, and the Beijing Anti-Cancer Association Gastric Cancer Committee, this updated guideline, Chinese Guidelines for HER2-Targeted Therapy in Gastric and Gastroesophageal Junction Adenocarcinoma (2025 Edition), has been developed. The aim is to provide clinicians with evidence-based and practice-informed recommendations that reflect current advancements in the field.

The recommendations presented herein are graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [5]. The GRADE system comprises two components (see Table S1 and Table S2). The first evaluates the quality of evidence based on risk of bias, inconsistency, indirectness, imprecision, and potential publication bias, and categorizes evidence as high, moderate, low, or very low in quality [6]. The second component assigns the strength of recommendations, which is determined by weighing

the balance between benefit and risk of interventions, the quality of supporting evidence, patients’ values and preferences, and resource considerations. Recommendations are designated as either strong or weak [7]. A total of 18 recommendations presented herein are summarized in Table 1.

Revised classification of HER2 status in gastric cancer

Based on the clinical data presented in Table 2, this guideline introduces an updated classification of HER2 status in gastric cancer. HER2 expression is now stratified into four categories (subsequent mentions of HER2-high/intermediate/low/absent-expression in this text follow the definition): HER2-high expression (IHC 3+ or IHC 2+/FISH+), HER2-intermediate expression (IHC 2+/FISH-), HER2-low expression (IHC 1+), and HER2-absent expression (IHC 0). Notably, in the ToGA trial, patients with IHC 3+ or IHC 2+/FISH+, traditionally designated as HER2-positive, are classified under the new term “HER2-high expression.” The reclassification reflects evolving therapeutic developments and aims to refine patient stratification for HER2-targeted therapies.

Nakayama et al. evaluated the clinicopathological features of 734 patients with advanced gastric cancer and reported a stepwise increase in the prevalence of intestinal-type histology and liver metastases from HER2-absent to HER2-low, HER2-intermediate, and HER2-high expression groups [8]. Conversely, the incidence of peritoneal metastases declined across these categories.

Each HER2 subgroup is associated with distinct pathological and clinical characteristics. HER2-high expression tumors comprise approximately 12.8% to 23.2% of gastric cancers. These tumors are predominantly of the intestinal type (exceeding 50%), are more likely to metastasize to the liver, and are less frequently associated with peritoneal dissemination. Tumor mutational burden is comparable to that observed in HER2-intermediate, HER2-low, and HER2-absent expression groups, and overall prognosis is relatively favorable. HER2-intermediate expression and HER2-low expression tumors account for approximately 21% to 24% of cases. Although the full clinicopathological characteristics of these subgroups remain to

Table 2 Revised classification of HER2 status in gastric cancer: definitions, prevalence, clinicopathological features, and representative clinical evidence

Classification	Prevalence	Clinicopathological features	Key clinical evidence
IHC 3+ or IHC 2+/FISH+	12.8–23.2%	> 50% intestinal-type histology; frequent liver metastases; relatively low incidence of peritoneal dissemination; associated with favorable prognosis	• In the ToGA trial, trastuzumab plus chemotherapy yielded a mOS of 13.8 months • The KEYNOTE-811 study reported an mOS of 20 months and a mPFS of 10 months with pembrolizumab plus trastuzumab and chemotherapy • In the DESTINY-Gastric01 trial, T-DXd achieved an mOS of 12.5 months and an ICR confirmed ORR of 51.3% • The RC48-C008 study demonstrated that disitamab vedotin resulted in an mOS of 7.9 months and an mPFS of 4.1 months
IHC 2+/FISH-	5.4%	Predominantly diffuse-type histology (55.8%); intermediate rates of liver and peritoneal metastases; immune micro-environment demonstrates heightened inflammatory activity; prognosis poorer than HER2-high and comparable to HER2-low expression disease	• In DESTINY-Gastric01 (n = 19), T-DXd achieved an ICR confirmed ORR of 26.3%, with an mPFS of 4.4 months and an mOS of 7.8 months • In RC48-C008 (n = 6), disitamab vedotin showed an ICR confirmed ORR of 16.7%, mPFS of 5.5 months, and mOS of 5.8 months
IHC 1+	18.6%		• In DESTINY-Gastric01 (n = 21), T-DXd yielded an ICR confirmed ORR of 9.5%, an mPFS of 2.8 months, and an mOS of 8.5 months • Additional clinical trial data are pending
IHC 0	56.0–61.6%	Lowest frequency of intestinal-type histology; high incidence of peritoneal metastases; rare liver metastases; immune microenvironment similar to HER2-intermediate and HER2-low expression disease; poor prognosis	• In the Chinese subgroup of CheckMate-649 (CPS ≥ 5), nivolumab plus chemotherapy resulted in an mOS of 15.3 months and an mPFS of 8.5 months • In the SPOTLIGHT trial, zolbetuximab combined with chemotherapy achieved an mOS of 18.23 months and an mPFS of 10.61 months

CPS, combined positive score; FISH, fluorescence in situ hybridization; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan

*HER2-high expression corresponds to HER2-positive status as defined by the ToGA trial criteria

**Interpretation and scoring of HER2 status in gastric cancer, using immunohistochemistry (IHC) and in situ hybridization (ISH), should remain consistent with standards set forth by the Chinese Society of Clinical Oncology (CSCO) and the College of American Pathologists (CAP). This update pertains solely to nomenclature and reflects recent advances in the management of gastric cancer, with the goal of optimizing patient stratification for precision HER2-targeted therapies

be elucidated, emerging evidence suggests that their rates of diffuse-type histology, liver metastasis, and peritoneal metastasis fall between those of HER2-high expression and HER2-absent expression [8–11]. Emerging ADC data suggest that HER2-intermediate and HER2-low GC/GEJC may not be therapeutically equivalent. In the DESTINY-Gastric01 exploratory cohort of T-DXd, we initially observed that the IHC2+/FISH– and the IHC 1+ population had different therapeutic effects. The confirmed ORR was numerically higher in IHC 2+/FISH– than in IHC 1+ disease (26.3% vs 9.5%), with a similar gradient in median PFS (4.4 vs 2.8 months), supporting the continuity of the target density-dependent ADC sensitivity, indicating that the treatment for IHC 1+ and IHC 2+ needs to be differentiated rather than simply classified as HER2-negative treatment [12].

HER2 alterations in gastric cancer and their clinical significance

HER2 alterations in gastric cancer primarily include HER2 protein overexpression, HER2 gene amplification, and HER2 gene mutations.

HER2 protein expression in gastric cancer

In normal gastric mucosal glandular cells, HER2 protein expression is minimal and typically undetectable by IHC. In contrast, malignant gastric epithelial cells

exhibit variable degrees of HER2 overexpression. The reported prevalence of HER2 expression in gastric cancer has historically varied considerably due to inconsistencies in IHC reagents, scoring systems, and interpretive criteria [13–15]. The ToGA trial not only initiated the era of HER2-targeted therapy in gastric cancer but also established the first standardized IHC-based protocol for assessing HER2 expression. Among 3665 tumor samples analyzed in the trial, the distribution of IHC scores was as follows: 0 in 58.2% of cases, 1+ in 18.6%, 2+ in 11.8%, and 3+ in 11.4% [16]. A retrospective study conducted at four representative clinical centers in China examined 726 gastric cancer specimens and found IHC scores of 0, 1+, 2+, and 3+ in 59.0%, 19.3%, 11.6%, and 10.2% of cases, respectively; the HER2-high expression rate was 13% (91 of 726 cases) [17]. Similarly, the HER-EAGLE study, a large-scale epidemiologic analysis of HER2 expression in Chinese patients with gastric cancer, reported IHC scores of 0/1+, 2+, and 3+ in 78.6%, 12.7%, and 8.7% of cases, respectively, with an overall HER2-high expression rate of 12.0% [18]. HER2 protein expression is strongly correlated with histological subtype and tumor location. HER2-high expression is significantly more common in intestinal-type adenocarcinomas (31.8%) compared with diffuse-type tumors (6.1%). Additionally, HER2-high expression is observed at particularly high rates, up to 32.2%, in gastroesophageal junction adenocarcinomas

[16]. Small-sample studies have reported HER2 overexpression in approximately 17.1% of alpha-fetoprotein (AFP)-producing gastric cancers [19]. These findings suggest that HER2 assessment is especially critical in patients with intestinal-type histology, gastroesophageal junction involvement, or AFP-producing tumors. Quantification of HER2 protein expression is central to the selection of patients for HER2-targeted therapies.

HER2 gene amplification in gastric cancer

Amplification of the HER2 gene leads to overexpression of the HER2 protein. FISH remains the standard method for detecting HER2 gene amplification and is particularly essential for clarifying HER2 status in cases with IHC 2+ to confirm HER2-high expression.

HER2 gene mutations in gastric cancer

At present, the function and therapeutic potential of HER2 gene mutations in gastric cancer have not been systematically elucidated [20–23]. The frequency of these mutations is relatively low, ranging from 3% to 7.7% [22, 24–27]. Importantly, HER2 mutations typically occur independently of gene amplification and are nearly always associated with negative IHC staining. Analysis of public genomic databases ($n = 1,566$) indicates that HER2 mutations exhibit a heterogeneous distribution, with mutational hotspots localized to the kinase domain (exons 18–21, 37.3%), the extracellular domain (33.5%), and the juxtamembrane domain (20.5%). Among these, the p.Arg678Gln substitution (also referred to as G678Q) in the juxtamembrane region is the most frequently observed hotspot in advanced gastric cancer, accounting for 20.5% of reported mutations. This is followed by S310F/Y mutations within the extracellular domain (19.2%). Sensitivity to HER2-targeted therapies is strongly influenced by the specific mutation, with only activating mutations representing viable therapeutic targets. HER2-mutant gastric cancers are clinically and pathologically distinct from those with HER2 amplification. These tumors are predominantly diagnosed at TNM stage IV (14 of 16 cases, 87.5%), are poorly differentiated (15 of 18 cases, 83.3%), and are most commonly of the diffuse-type histology (14 of 18, 77.8%). Notably, all tumors demonstrated an absence of HER2 expression by IHC (18 of 18, 100%), while the majority exhibited PD-L1 expression (10 of 13, 76.9%) [28].

Other less common alterations include HER2 gene fusions, though current data are limited to preclinical and mechanistic studies. These fusions often lead to HER2 amplification and overexpression. Identified fusion partners include *ZNF207*, *MDK*, and *NOS2*. However, not all HER2 fusion variants are predictive of response to HER2-targeted therapies.

Prognostic values of HER2 status in gastric cancer

The prognostic significance of HER2 status in gastric cancer remains a subject of ongoing debate. Several studies suggest that HER2 overexpression or gene amplification is associated with poorer outcomes and may serve as an adverse prognostic indicator independent of age, sex, or tumor stage [29–31]. A meta-analysis including 42 studies and 12,749 patients found that in 71% of the included reports, HER2 overexpression or amplification correlated with reduced survival and/or unfavorable clinicopathologic features, such as serosal invasion, lymph node metastasis, advanced disease stage, or distant metastasis [32]. Conversely, a retrospective study involving 1,006 Japanese patients with gastric cancer found no association between HER2 overexpression and disease-specific survival or recurrence-free survival [33]. Similarly, a Chinese study reported no statistically significant difference in 3-year OS between patients with HER2-high expression and those with HER2-absent expression. Multivariate analysis further indicated that HER2 status was not an independent prognostic factor. However, HER2 overexpression or amplification was significantly associated with tumor differentiation and patient sex, but not with lymph node metastasis or tumor stage [17].

Application of liquid biopsy

Liquid biopsy encompasses the qualitative and/or quantitative assessment of circulating tumor cells (CTCs), circulating tumor microemboli (CTM), cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), and exosomes [34, 35]. In gastric cancer, clinical application of liquid biopsy is currently centered on detecting HER2 gene amplification in advanced disease. By circumventing the spatial and temporal heterogeneity inherent to tumor tissue, liquid biopsy provides a valuable tool for identifying patients likely to benefit from HER2-targeted therapies, monitoring treatment efficacy in real time, and predicting recurrence and prognosis [36–38]. In patients with advanced gastric cancer, detection of somatic copy number alterations (SCNAs) in the HER2 gene through preoperative ctDNA analysis has demonstrated high concordance with HER2 overexpression and amplification status assessed by IHC and FISH in tumor samples [34, 38–41]. This approach facilitates accurate patient stratification and dynamic monitoring of response to HER2-targeted therapies [40–42]. The Japanese HERALD/EPOC1806 trial evaluated the efficacy of T-DXd in patients with advanced solid tumors harboring HER2 amplification detected via cfDNA. Among the 62 patients enrolled, the confirmed objective response rate (ORR) was 56.5% by investigator assessment, with a median progression-free survival (PFS) of 7.0 months [43]. In clinical scenarios where timely procurement of tumor tissue is not feasible, liquid biopsy may serve as a

reliable alternative or adjunctive method for determining HER2 status in gastric cancer [44]. Of note, a proportion of patients with HER2-high expression gastric cancer fail to respond to HER2-targeted therapies, a phenomenon attributed to both intrinsic and acquired resistance mechanisms driven by molecular heterogeneity within the tumor. Genomic profiling of ctDNA may offer insights into these resistance pathways [38]. In addition to informing therapeutic decisions and resistance mechanisms, liquid biopsy enables real-time assessment of treatment response. In a study by Liu et al. [45], patients with advanced gastric cancer who exhibited low baseline CTC counts or a reduction in CTCs following the first cycle of chemotherapy experienced significantly greater benefit from palliative chemotherapy. Furthermore, patients with low CTC counts demonstrated longer median PFS and OS compared with those with higher CTC burdens. ctDNA can help address spatial heterogeneity, but key limitations should be acknowledged: (i) false-negative results occur with low tumor fraction (low shedding, low-volume disease, or on-treatment sampling), and *ERBB2* copy-number is vulnerable to low ctDNA content; (ii) analytical performance (limit of detection, pipelines, and amplification thresholds) varies across assays/platforms, limiting comparability, and (iii) *ERBB2* amplification in plasma may represent a high-shedding metastatic subclone rather than dominant biology across all lesions [46–48]. Besides, a negative ctDNA result does not exclude HER2 amplification. Whenever feasible, tissue testing remains the preferred method [48].

Detection of HER2 alterations in gastric cancer

A proposed algorithm for the HER2 detection of gastric cancer is shown in Fig. 1.

Specimen preparation and considerations

Accurate HER2 testing requires a series of critical steps, including specimen acquisition, pre-analytical processing, molecular or IHC analysis, and post-analytical interpretation. Close collaboration between clinical and pathology laboratories is essential to ensure the quality and integrity of both tissue and liquid biopsy specimens.

Specimen types

Tissue specimens suitable for HER2 testing include biopsies obtained via fine-needle aspiration, forceps, or surgical excision, provided they contain sufficient tumor material. When tissue samples are unavailable or inaccessible, liquid biopsy specimens may be used for molecular testing in appropriately equipped laboratories with validated protocols.

Tissue fixation

Formalin-fixed, paraffin-embedded (FFPE) tissue should be preserved in 3.7% neutral buffered formalin. The fixative volume must be ≥ 10 times the tissue volume, and fixation should last 8–48 h. Surgical specimens should be fixed within one hour of excision, ideally within 30 min. Specimens obtained by endoscopic mucosal resection or surgery should be fully extended and pinned to a board. For surgical resections, an incision should be made along the serosal surface opposite the tumor to expose the lesion adequately prior to fixation.

Liquid biopsy sample preparation

Standardized handling of blood specimens is critical to ensure reliable liquid biopsy results. Key recommendations include: 1) use dedicated ctDNA blood collection tubes, as specified for proper sample preservation; 2) process samples promptly—whole blood should be sent to the laboratory immediately, with plasma separated without delay to prevent nucleic acid degradation, followed by freezing at -80°C to avoid repeated freeze–thaw cycles; 3) for molecular residual disease monitoring after curative surgery, samples should ideally be collected within one week post-operation. For advanced disease, serial sampling is valuable, such as obtaining a pre-treatment baseline, monitoring dynamics during therapy to assess early response, and collecting samples at clinical or radiographic progression to identify mechanisms of resistance.

Recommendation 1: Standardized protocols for specimen collection, preservation, and fixation are critical to ensure the accuracy and reliability of HER2 testing in gastric cancer.

Level of evidence: High quality.

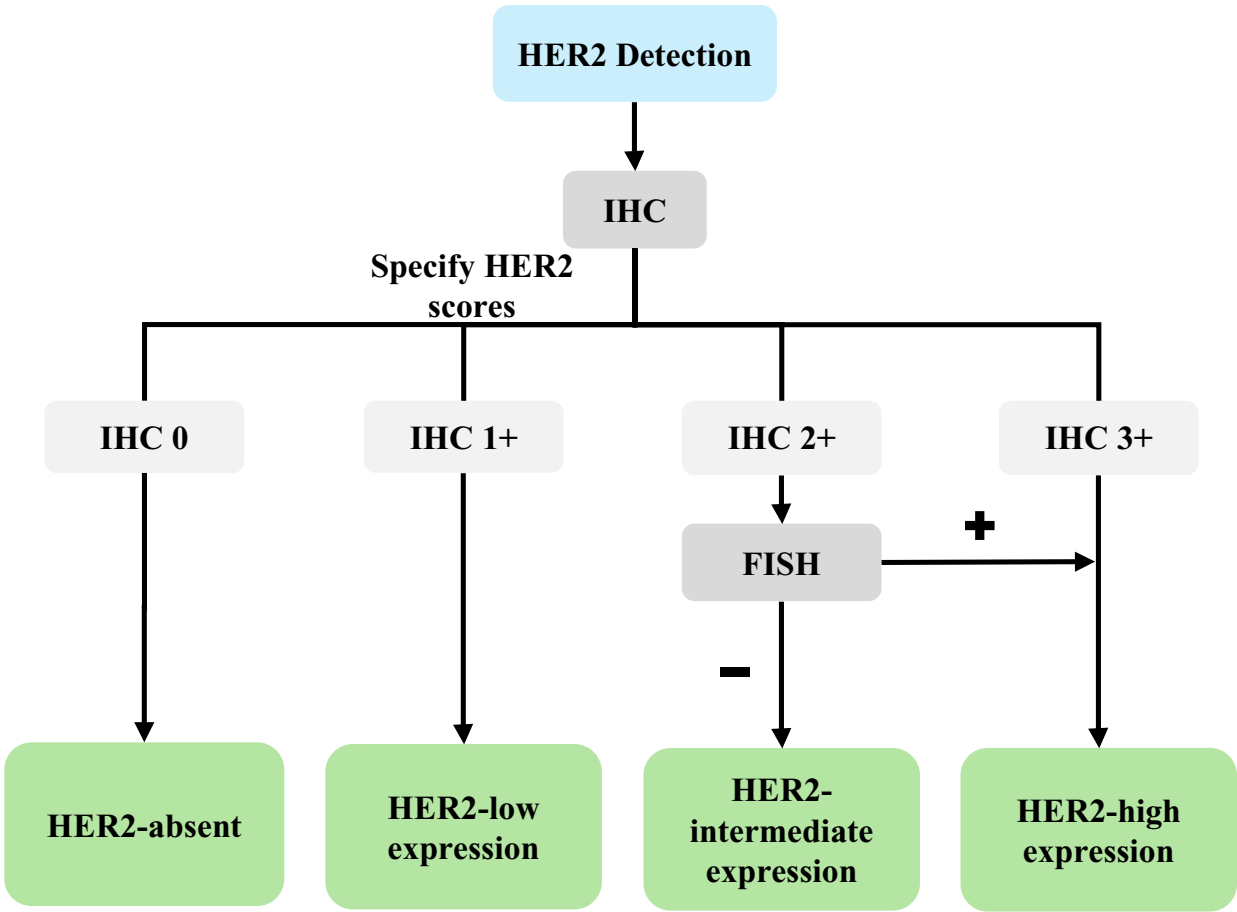
Strength of recommendation: Strong.

Forms of HER2 alterations, detection methods, and interpretation standards

Evaluation of HER2 protein expression

Methods IHC remains the primary method for evaluating HER2 protein expression. Depending on laboratory capabilities, staining may be performed manually, semi-automatically, or fully automatically. Among these, fully automated platforms provide the greatest consistency across assay batches.

Laboratory requirements Testing should be conducted in laboratories equipped with the requisite instrumentation and space. Personnel must be proficient in core techniques such as specimen processing, antibody selection,



When tissue biopsy is not feasible, HER2 detection may be assessed using ctDNA obtained via liquid biopsy. NGS is considered for the comprehensive detection of HER2 variants in both tissue and ctDNA specimens. Given the heterogeneity of HER2 expression in gastric cancer, diagnostic precision can be improved through multi-site biopsy, multiple paraffin blocks, dynamic and metastatic testing.

Fig. 1 HER2 detection algorithm of gastric cancer. Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization

and antigen retrieval. Laboratories must implement and maintain validated SOPs and participate in both internal and external quality assurance programs. Technical staff must be appropriately certified and trained.

Antibody selection It is recommended that laboratories use diagnostic kits approved by the National Medical Products Administration (NMPA) of China.

Controls Each IHC slide should include appropriate positive controls. A gradient control, comprising validated

gastric cancer tissues with known IHC scores of 0, 1+, 2+, and 3+, is preferred to support consistent scoring.

Interpretation and scoring Scoring criteria differ between biopsy samples and surgically resected specimens (see Table S3). Given the intratumoral heterogeneity characteristic of HER2 expression in gastric cancer, the entire slide must be examined systematically. Specific staining is defined as membranous localization, characterized by complete, basolateral, or lateral membrane staining. Cytoplasmic or nuclear staining should be considered

nonspecific. Pathology reports must clearly document the HER2 IHC score and distinguish between IHC 0 and 1+. Optical magnification assists in accurate scoring: IHC 3+ is generally recognizable under low magnification, with distinct membranous staining; IHC 2+ is best visualized at 10× to 20× magnification, showing clear but less intense membrane staining; IHC 1+ typically requires 40× magnification for confirmation [49] (see Figure S1). In exceptional cases, such as when strong staining is observed in fewer than 10% of tumor cells, not meeting the threshold for IHC 3+, but accompanied by HER2 amplification on FISH, interpretation should be reviewed by a gastric cancer multidisciplinary team [49].

Recommendation 2: IHC should be employed as the standard method for evaluating HER2 protein expression in gastric cancer. Testing should adhere to standardized protocols, and pathology reports must specify HER2 scores as IHC 0, 1+, 2+, or 3+.

Level of evidence: High quality.

Strength of recommendation: Strong.

Detection of HER2 gene amplification

Methods FISH remains the standard method for evaluating HER2 gene amplification. Laboratories equipped with advanced infrastructure may also utilize dual-color silver-enhanced in situ hybridization as an automated alternative.

Laboratory requirements Testing should be conducted in laboratories that are fully equipped with the requisite instrumentation and space. Personnel must be proficient in all procedural steps, including specimen preparation, pre-treatment, enzymatic digestion, hybridization, post-hybridization washing, and signal quantification. A robust SOP must be in place and validated through stringent internal and external quality control measures. All technical staff must be appropriately credentialed and have received formal training in HER2 testing methods.

Probe selection Only diagnostic reagents approved by the NMPA should be used.

Controls External positive and negative controls should consist of gastric cancer tissues with known HER2 amplification status. Internal controls within the same slide should include non-neoplastic gastric mucosal epithelial cells, lymphocytes, or stromal cells.

Interpretation The region with the highest HER2 signal density should be selected for analysis. HER2 and CEP17

signals should be enumerated in at least 20 consecutive tumor nuclei. The HER2/CEP17 ratio is used to determine amplification status. A ratio ≥ 2.2 is diagnostic of HER2 gene amplification. In cases with clustered or aggregated HER2 signals or where the ratio exceeds 20, amplification can be confirmed without further calculation. A ratio < 1.8 is considered indicative of no amplification. For ratios between 1.8 and 2.2, an additional 20 tumor nuclei should be assessed, or signal enumeration should be repeated by a second qualified pathologist. A final ratio ≥ 2.0 is classified as amplified; < 2.0 as not amplified. Cases exhibiting an average of ≥ 3 CEP17 signals per nucleus meet criteria for chromosome 17 polysomy and should be reported as such. Test reports must also include the average HER2 and CEP17 signal counts per cell. Any specimen failing to meet established quality control criteria must be re-evaluated [13].

Recommendation 3: ISH is the definitive method for determining HER2 gene amplification and must be executed according to SOPs to ensure accuracy and reproducibility. In cases with IHC 2+, FISH testing is mandatory to clarify HER2 status.

Level of evidence: High quality.

Strength of recommendation: Strong.

Detection of HER2 gene mutations and fusions, and the application of liquid biopsy specimens

Indications While HER2 protein expression and gene amplification are routinely assessed to guide HER2-targeted therapy, emerging evidence indicates that mutations in the HER2 gene itself, as well as in downstream or bypass signaling pathways [50], and gene fusions involving HER2 [51], may modulate treatment efficacy. In patients with advanced HER2-high expression gastric cancer who demonstrate suboptimal response or develop acquired resistance to HER2-targeted therapies, molecular profiling for HER2 mutations and gene fusions should be considered.

Methods Next-generation sequencing (NGS) is the preferred approach for detecting HER2 mutations and alterations in ctDNA. Digital polymerase chain reaction is also commonly utilized for quantifying HER2 amplification in ctDNA. For the detection of HER2 gene fusions, transcriptome sequencing (RNA-seq) is recommended to characterize structural variants.

Laboratory requirements and interpretation NGS-based testing must be conducted in accredited laboratories with validated platforms and stringent quality control

systems. Personnel should be thoroughly trained and certified in molecular diagnostics. Currently, no NMPA-approved assay specifically covers HER2 mutations or fusions; thus, assay performance validation, methodological standardization, and careful clinical interpretation of sequencing data are essential for accurate diagnosis and therapeutic decision-making.

Recommendation 4: In patients with gastric cancer for whom tissue biopsy is not feasible, HER2 amplification may be assessed using ctDNA obtained via liquid biopsy. NGS may be considered for the comprehensive detection of HER2 variants in both tissue and ctDNA specimens.

Level of evidence: Low quality.

Strength of recommendation: Weak.

HER2 heterogeneity and the role of re-biopsy in gastric cancer

Gastric cancer demonstrates pronounced biological heterogeneity, which can result in discordant HER2 test results across different tumor regions or disease stages. This variability may substantially impact the clinical application and therapeutic efficacy of HER2-targeted therapies.

Patterns of heterogeneity

HER2 heterogeneity in gastric cancer is manifested in three principal forms: intratumoral, spatial, and temporal. Intratumoral heterogeneity refers to variation in HER2 expression within tumor tissues. HER2 expression is significantly more frequent in well-differentiated tumors and those classified as intestinal-type according to the Lauren classification, compared with poorly differentiated or diffuse/mixed-type tumors [52, 53]. Spatial heterogeneity denotes differences in HER2 expression across various biopsy sites within the primary tumor or between primary and metastatic lesions. Such variability can influence treatment selection [13, 16, 54, 55]. In the Korean GASTHER1 study, 5.7% of patients with HER2-absent expression primary tumors exhibited HER2 expression in recurrent or metastatic sites. The likelihood of HER2 expression differed by metastatic location, with a rate of 17.2% in liver lesions versus 3.4% in other sites ($p = 0.012$) [56]. Temporal heterogeneity reflects dynamic alterations in HER2 status during the clinical course of the disease, particularly in response to HER2-targeted therapies [55].

Strategies to mitigate the impact of heterogeneity

When heterogeneity in HER2 expression is observed on IHC analysis, this finding should be documented in the

pathology report, accompanied by a recommendation to perform FISH for definitive HER2 status assessment.

Biopsy specimens Multi-site sampling reduces sampling bias due to tumor heterogeneity [57–59]. Endoscopic biopsy should ideally include at least six tissue fragments, with 6 to 8 samples recommended.

Surgical specimens Tissue blocks rich in intestinal-type tumor morphology should be selected for HER2 testing. In larger tumors, analysis of additional paraffin blocks may improve detection rates.

Reassessment after HER2-targeted therapy Treatment with trastuzumab may alter HER2 expression in both primary and metastatic sites of HER2-high expression gastric cancer. Upon disease progression or evolution, re-biopsy should be conducted to re-evaluate HER2 status [60, 61]. Prior studies have demonstrated that some tumors initially classified as HER2-high expression may transition to HER2-absent expression after first-line trastuzumab-based therapy. Such shifts may inform eligibility for second-line HER2-targeted therapies and underscore the need for re-evaluation prior to further therapeutic intervention [62].

Recommendation 5-a: Given the heterogeneity of HER2 expression in gastric cancer, diagnostic precision can be improved through multi-site biopsy, assessment of multiple paraffin blocks.

Level of evidence: Low quality.

Strength of recommendation: Strong.

Recommendation 5-b: Re-biopsy is not mandatory after progression. Whenever feasible, re-biopsy may be considered to reassess recurrent or metastatic lesions to guide the consideration of second-line HER2-targeted therapy.

Level of evidence: Low quality.

Strength of recommendation: Weak.

HER2-targeted agents in gastric cancer

Therapeutic strategies targeting HER2 in gastric cancer include monoclonal antibodies, ADCs, tyrosine kinase inhibitors (TKIs), and bispecific antibodies [63–66].

Monoclonal antibodies bind specifically to the extracellular domain of HER2, thereby preventing receptor dimerization and eliciting antibody-dependent cellular cytotoxicity (ADCC). Trastuzumab was the first monoclonal antibody approved for the treatment of HER2-high expression gastric cancer and remains widely used in

clinical practice [65]. Other agents, such as pertuzumab and margetuximab, were discontinued due to suboptimal efficacy or strategic redirection of development programs.

ADCs enable targeted delivery of cytotoxic agents to HER2-expressing tumor cells, thereby enhancing treatment specificity and potency [4, 67–75]. T-DXd (DS-8201), characterized by a high drug-to-antibody ratio (DAR 7.7) and a potent bystander effect, has demonstrated robust antitumor activity in HER2-high expression gastric cancer and has been approved in China. Disitamab vedotin, which operates via a similar mechanism, has likewise shown promising efficacy. In contrast, trastuzumab emtansine (T-DM1) features a lower DAR, reduced payload uniformity, and lacks a bystander effect, factors that may limit its activity in tumors with pronounced intratumoral heterogeneity; clinical development of this agent was therefore discontinued.

TKIs are small-molecule inhibitors that target the intracellular ATP-binding site of HER2 and other ErbB family kinases, thereby suppressing downstream signaling (e.g., MAPK/ERK and PI3K/AKT) independent of antibody accessibility to the extracellular domain [76]. In the phase II trial, the combination regimen containing Tucatinib demonstrates promising clinical potential, particularly when optimizing paclitaxel dosing, and may offer a new therapeutic option for patients with HER2-positive gastroesophageal cancer [77]. The utility of pyrotinib remains under investigation [78].

Bispecific (often biparatopic) anti-HER2 antibodies are engineered to engage two distinct, non-overlapping HER2 epitopes (frequently corresponding to the canonical trastuzumab- and pertuzumab-associated regions), thereby increasing functional avidity and enabling receptor crosslinking/clustering [79]. Representative agents under active development in HER2-expressing gastric cancer include anbenitamab and zanidatamab, which exemplify this dual-epitope/biparatopic strategy and are frequently positioned in combination regimens with chemotherapy and/or immune checkpoint blockade to maximize depth and durability of anti-tumor response [80, 81] (see Table S4). Multiple additional trials are ongoing in HER2-expressing gastric cancer (see Table S5). The specific clinical application of these HER2-targeted agents in GC will be elaborated below.

HER2-targeted therapies for recurrent or metastatic gastric cancer

A proposed algorithm for the HER2-targeted therapies of advanced and metastatic gastric cancer is shown in Fig. 2. HER2-targeted therapies for recurrent or metastatic gastric cancer are summarized in Table S6. The survival and response outcomes of HER2-targeted therapies across

different treatment settings in advanced gastric cancer are summarized in Table 3.

First-line therapy

Systemic therapy remains the cornerstone of treatment for unresectable or metastatic HER2-high expression gastric cancer. In the ToGA trial, patients with advanced gastric cancer demonstrating HER2 IHC 3+ or FISH+ were randomized to receive fluorouracil or capecitabine plus cisplatin, in combination with either trastuzumab or placebo. The addition of trastuzumab significantly improved clinical outcomes, including the ORR (47% vs. 35%, $p=0.0017$), median PFS (6.7 vs. 5.5 months, $p=0.0002$), and median OS (13.8 vs. 11.1 months, $p=0.0046$), leading to its approval as first-line therapy for HER2-high expression gastric cancer [13]. Subsequent phase II studies have investigated various trastuzumab plus chemotherapy combinations in HER2-high expression gastric cancer. In a prospective trial, the combination of trastuzumab, docetaxel, and capecitabine achieved an ORR of 67.8%, with a median PFS of 8.1 months and a median OS of 20.9 months [82]. The EVIDENCE study, a multicenter observational analysis involving 1,556 patients across 85 institutions in China, reported that trastuzumab-based regimens significantly prolonged OS (median 22.3 months) and PFS (median 8.2 months). Notably, the XELOX regimen combined with trastuzumab yielded the most favorable outcomes, with a median OS of 34.6 months [83]. These findings collectively support the efficacy and safety of trastuzumab in combination with multiple chemotherapy backbones for HER2-high expression gastric cancer.

The HELOISE trial compared standard-dose trastuzumab (loading dose 8 mg/kg, then 6 mg/kg every three weeks) with a higher-dose regimen (loading dose 8 mg/kg, then 10 mg/kg every three weeks) in patients with HER2-high expression gastric cancer. The study showed no additional survival benefit with the higher dose, thereby reaffirming the standard dosing schedule as optimal for first-line treatment [84].

KEYNOTE-811, a global, multicenter, randomized phase III trial, evaluated the addition of pembrolizumab to trastuzumab and chemotherapy in patients with advanced HER2-high expression gastric cancer. Pembrolizumab significantly improved outcomes compared to trastuzumab plus chemotherapy alone, extending median OS (20.0 vs. 16.8 months; hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.67–0.94), median PFS (10.0 vs. 8.1 months; HR, 0.73; 95% CI, 0.61–0.87), and ORR (72.6% vs. 60.1%). Among patients with PD-L1 combined positive score (CPS) ≥ 1 , the pembrolizumab combination further improved median OS (20.1 vs. 15.7 months; HR, 0.79; 95% CI, 0.66–0.95) and median PFS (10.9 vs. 7.3 months; HR, 0.71; 95% CI, 0.59–0.86), with an ORR

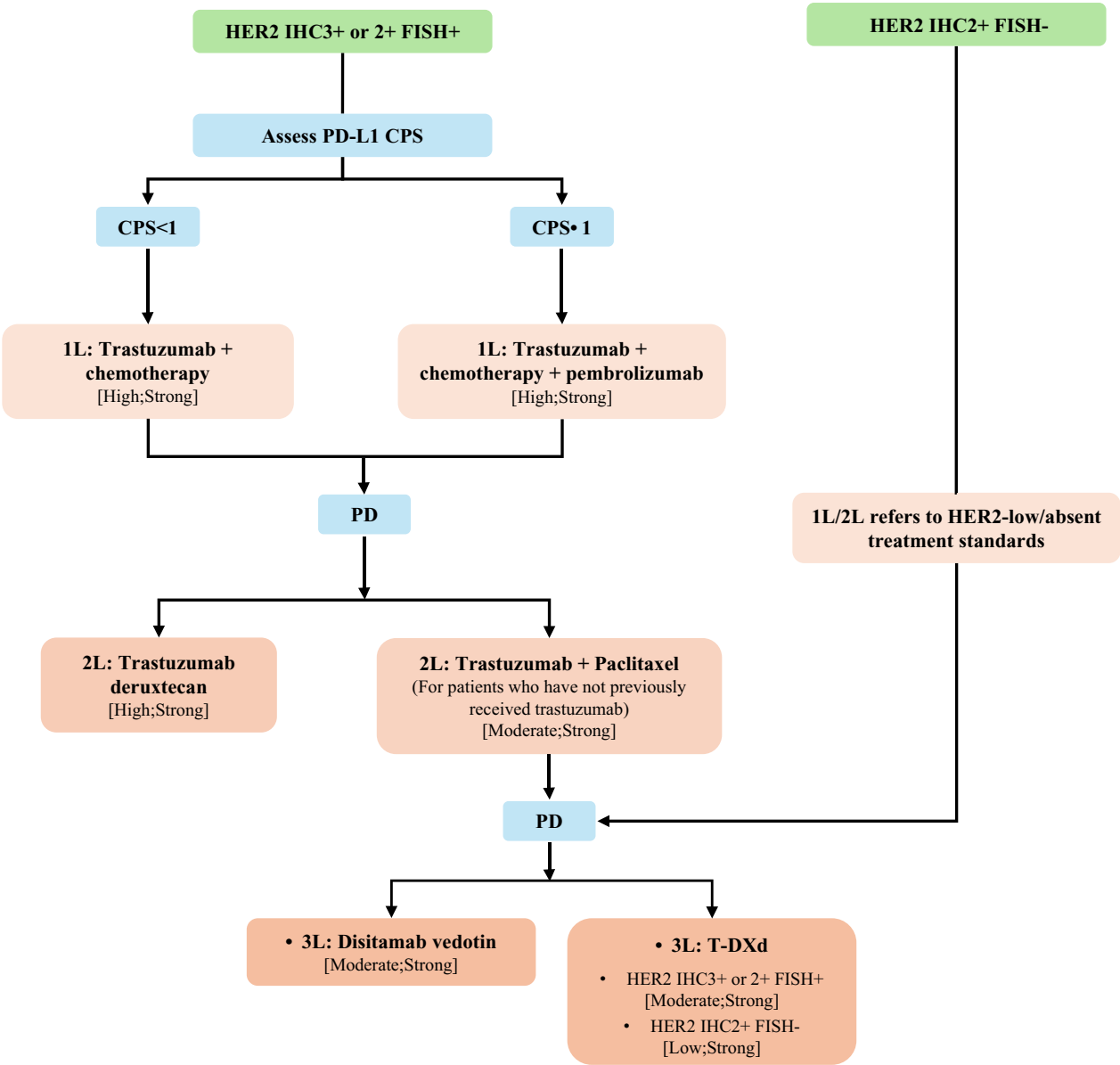


Fig. 2 Treatment algorithm of HER2 IHC3+ or IHC2+/FISH+ and IHC2+/FISH- advanced/metastatic gastric cancer. Abbreviations: HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1; CPS, combined positive score; PD, progressive disease; 1L, first-line therapy; 2L, second-line therapy; ≥ 3L, third-line or later-line therapy

of 73.2% compared to 58.4% [85]. However, no survival benefit was observed in the PD-L1 CPS < 1 subgroup. In fact, a numerically inferior OS was noted in the pembrolizumab arm (18.2 vs. 20.4 months; HR, 1.10; 95% CI, 0.72–1.68), with no meaningful difference in PFS (9.5 vs. 9.5 months; HR, 0.99; 95% CI, 0.62–1.56). Based on these findings, in June 2024, the NMPA approved pembrolizumab in combination with trastuzumab and chemotherapy as a first-line treatment for patients with unresectable or metastatic HER2-high expression gastric or gastroesophageal junction adenocarcinoma with PD-L1 CPS ≥ 1.

The global, randomized phase III HERIZON-GEA-01 trial presented at the 2025 ASCO meeting demonstrated that in previously untreated patients with HER2-positive locally advanced unresectable or metastatic gastroesophageal adenocarcinoma, the median PFS was 12.4 months with zanidatamab + tislelizumab + chemotherapy, 12.4 months with zanidatamab + chemotherapy, and 8.1 months with trastuzumab + chemotherapy; the corresponding hazard ratios were 0.63 (95% CI 0.51–0.78; $P < 0.0001$) and 0.65 (95% CI 0.52–0.81; $P < 0.0001$) for the two zanidatamab-containing regimens. The median OS was 26.4, 24.4, and 19.2 months, respectively; the

Table 3 Summary of studies evaluating HER2-targeted therapy in advanced gastric cancer

Treatment setting	Study	Treatment regimen	Median OS (months)	Median PFS (months)	ORR (%)
First-line therapy	ToGA	Trastuzumab + chemotherapy vs. chemotherapy	13.8 vs. 11.1	6.7 vs. 5.5	47 vs. 35
	Prospective study	Trastuzumab + docetaxel + capecitabine	20.9	8.1	67.8
	EVIDENCE	Trastuzumab + chemotherapy	22.3	8.2	51.7
	KEYNOTE-811	Trastuzumab + chemotherapy + pembrolizumab vs. trastuzumab + chemotherapy	20.0 vs. 16.8	10.0 vs. 8.1	72 vs. 60
First-line maintenance	Retrospective study	No maintenance vs. trastuzumab maintenance	16.9 vs. 19.0	9.9 vs. 13.2	-
	Observational study	Trastuzumab vs. trastuzumab + chemotherapy maintenance	16.5 vs. 20.0 (p=0.169)	7.9 vs. 11.0 (p=0.892)	-
	AGEO	Trastuzumab vs. trastuzumab + chemotherapy maintenance	17.0 vs. 15.2 (p=0.40)	3.7 vs. 5.1 (p=0.60)	-
Second-line therapy	RAINBOW	Ramucirumab + Paclitaxel vs. paclitaxel	9.6 vs. 7.4	4.4 vs. 2.86	28 vs. 16
	DESTINY-Gastric04	T-DXd vs. Ramucirumab + paclitaxel	14.7 vs. 11.4	6.7 vs. 5.6	44 vs. 29(confirmed ORR)
	DESTINY-Gastric02	T-DXd	12.1	5.6	42(confirmed ORR)
	HER-RAM	Trastuzumab + ramucirumab + paclitaxel	13.6	7.1	54(confirmed ORR)
Third-line and beyond	DESTINY-Gastric01	T-DXd vs. chemotherapy	12.5 vs. 8.4	5.6 vs. 3.5	51 vs. 14(confirmed ORR)
	DESTINY-Gastric06	T-DXd	11.1	5.7	28.8(confirmed ORR)
	RC48-C008	Disitamab vedotin	7.9	4.1	24.8
Post-progression use	MD Anderson	Trastuzumab	11.0	5.0	-
	T-ACT	Paclitaxel vs Trastuzumab + Paclitaxel	10.0 vs. 10.2	3.2 vs. 3.7	-
	JFMC45-1102	Trastuzumab + chemotherapy	16.8	5.1	37(confirmed ORR)

OS, overall survival; PFS, progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan

corresponding hazard ratios were 0.72 (95% CI 0.57–0.90; $P=0.0043$) and 0.80 (95% CI 0.64–1.01; $P=0.0564$). In patients with measurable disease, the confirmed ORR was 70.7%, 69.6%, and 65.7%, respectively. Zanidatamab is expected to become a new standard for first-line treatment, although it has not yet received approved for application in China [81].

In MSKCC study, a two-phase induction regimen was evaluated as first-line therapy for patients with advanced HER2-high expression gastric cancer. During the initial cycle, patients received pembrolizumab and trastuzumab; chemotherapy was introduced starting from the second cycle. Notably, tumor reduction was observed in 48% of patients (12 of 25) within three weeks of receiving pembrolizumab and trastuzumab, with two patients achieving partial responses [86]. These findings offer preliminary evidence for patients who are not candidates for chemotherapy.

Recommendation 6: For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ and PD-L1 CPS < 1, trastuzumab plus chemotherapy is recommended as first-line therapy.

Level of evidence: High quality.

Strength of recommendation: Strong.

Recommendation 7: For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ and PD-L1 CPS ≥ 1, the addition of pembrolizumab to trastuzumab and chemotherapy is recommended as first-line treatment.

Level of evidence: High quality.

Strength of recommendation: Strong.

Recommendation 8: For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ and high PD-L1 expression who are unable to tolerate chemotherapy, treatment with trastuzumab in combination with a PD-1 inhibitor may be considered.

Level of evidence: Low quality.

Strength of recommendation: Weak.

Second-line therapy

The current standard of care for second-line treatment of advanced gastric cancer predominantly comprises chemotherapy, either alone or in combination with anti-angiogenic agents. However, effective HER2-targeted therapies in this setting remain inadequately defined, and no consensus standard has been established. The continuation of trastuzumab beyond progression in patients with HER2-high expression gastric cancer who

have previously received trastuzumab-containing first-line therapy, remains a matter of ongoing debate, lacking robust evidence from high-level clinical trials. A small-sample retrospective analysis from MD Anderson Cancer Center assessed 43 patients who following progression on trastuzumab plus chemotherapy, continued trastuzumab in combination with an alternative chemotherapy. The median PFS and OS were 5.0 months and 11.0 months, respectively [87]. Similarly, the phase II T-ACT trial (WJOG7112G) conducted in Japan examined paclitaxel with or without trastuzumab in 99 patients with HER2-high expression gastric cancer after progression on first-line treatment. Median PFS was 3.2 months with paclitaxel alone and 3.7 months with the combination; median OS was 10.0 months and 10.2 months, respectively, differences that were not statistically significant [88]. In a subset analysis of the T-ACT trial, HER2 status was reassessed using fresh tumor biopsy samples from 16 patients after progression. Loss of HER2 overexpression was observed in 69% of cases, implicating HER2 loss as a potential mechanism of resistance to trastuzumab. These findings reinforce the limited clinical benefit of continuing trastuzumab beyond progression.

In patients with HER2-high expression gastric cancer who were not treated with trastuzumab in the first-line setting, second-line HER2-targeted therapy may retain clinical value. In the Japanese multicenter, single-arm phase II JFMC45-1102 trial, trastuzumab combined with paclitaxel in trastuzumab-naïve patients achieved an investigator-confirmed ORR of 37.0%, a median PFS of 5.1 months, and a median OS of 16.8 months. Treatment was generally well tolerated [89]. These results support the use of trastuzumab in the second-line setting for patients who have not previously received HER2-targeted therapy.

Recommendation 9: Trastuzumab is not routinely recommended for continuation beyond progression in advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ who have experienced disease progression after trastuzumab-containing first-line therapy, due to limited demonstrated benefit.

Level of evidence: Moderate quality.

Strength of recommendation: Strong.

Recommendation 10: For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ who have not previously received trastuzumab, second-line therapy with trastuzumab in combination with paclitaxel is recommended.

Level of evidence: Moderate quality.

Strength of recommendation: Strong.

Several small-sample studies suggest that combination regimens incorporating HER2-targeted therapies may offer clinical benefit. In the investigator-initiated HER-RAM study conducted in Korea, a triplet regimen of trastuzumab, ramucirumab, and paclitaxel was evaluated in 50 patients with advanced gastric cancer previously treated with trastuzumab. The confirmed ORR was 54% assessed by investigator, median PFS was 7.1 months, and median OS was 13.6 months [90]. In the phase I RC48-C013 trial conducted in China, 30 patients with HER2-expressing advanced gastric cancer received disitamab vedotin in combination with the PD-1 inhibitor toripalimab as second-line or later-line therapy. The investigator-confirmed ORR was 43%, and the median PFS was 6.2 months, though most participants had not been previously treated with PD-1/PD-L1 inhibitors [91].

HER2-targeted ADCs have demonstrated encouraging efficacy in the second-line treatment of advanced gastric cancer. T-DXd has been approved in the United States, European Union, and other regions for patients with HER2-high expression gastric cancer who have progressed following first-line therapy. The DESTINY-Gastric02 trial [92] evaluated the efficacy and safety of T-DXd in a Western cohort of patients with biopsy-confirmed HER2-high expression gastric or gastroesophageal junction adenocarcinoma who had previously received trastuzumab-based first-line treatment. Among the 79 participants, the median OS was 12.1 months, median PFS was 5.6 months, and the investigator-confirmed ORR was 41.8%.

DESTINY-Gastric04, the first global phase III randomized controlled trial to evaluate a second-line treatment for advanced gastric cancer, compared T-DXd monotherapy directly with the standard regimen of ramucirumab plus paclitaxel. The results demonstrated a statistically significant and clinically meaningful improvement in OS with T-DXd [93]. The trial enrolled 494 patients with unresectable or metastatic HER2-high GC/GEJC whose disease had progressed during or after a prior trastuzumab-based regimen. The median OS was 14.7 months (95% CI, 12.1 to 16.6) in the T-DXd group, compared with 11.4 months (95% CI, 9.9 to 15.5) in the ramucirumab plus paclitaxel group, yielding a HR for death of 0.70, representing a 30% reduction in mortality risk. Median PFS was 6.7 months versus 5.6 months, respectively (HR, 0.74). The investigator-confirmed ORR was higher with T-DXd than with ramucirumab plus paclitaxel (44.3% [95% CI, 37.8 to 50.9] vs. 29.1% [95% CI, 23.4 to 35.3]). The median duration of response (DoR) was also prolonged with T-DXd: 7.4 months (95% CI, 5.7 to 10.1) compared to 5.3 months (95% CI, 4.1 to 5.7). The safety profile of T-DXd was consistent with findings from prior clinical trials in gastric cancer. The incidence of

treatment-related serious adverse events and grade 3 or higher treatment-related adverse events was comparable between the two groups. The findings from DESTINY-Gastric04 provide compelling evidence supporting the use of T-DXd as a second-line treatment in patients with HER2-high expression advanced gastric cancer, addressing a significant unmet need by introducing an effective HER2-targeted therapy into this setting. T-DXd has formally received approval from the NMPA for monotherapy in adults with locally advanced or metastatic HER2-high GC/GEJC.

Recommendation 11: For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ who have previously received treatment, second-line therapy with T-DXd is recommended.

Level of evidence: High quality.

Strength of recommendation: Strong.

Third-line and later-line therapy

Therapeutic options for patients with advanced HER2-high expression gastric cancer remain limited in the third-line setting. Apatinib has demonstrated a median OS of 6.5 months with an ORR of only 2.8% [94], while nivolumab has shown a median OS of 5.3 months and a confirmed ORR of 11.2% [95]. In contrast, ADCs have emerged as a promising therapeutic class for patients with HER2-high or HER2-intermediate expression who have progressed after at least two prior lines of therapy.

The RC48-C008 study was a single-arm, phase II trial conducted in China, enrolling 125 patients with advanced gastric cancer and HER2 expression (IHC 2+ or 3+ without FISH testing) who had received two or more previous systemic regimens. Among them, 52.8% had received 2 prior lines and 47.2% had received ≥ 3 lines; 57.6% had prior trastuzumab exposure and 85.6% had received taxane-based chemotherapy. Patients with previous treatment with T-DM1 or other ADCs were excluded. Treatment with disitamab vedotin achieved an ORR of 24.8%, with a median PFS of 4.1 months and a median OS of 7.9 months. Subgroup analyses showed ORRs of 23.0% in patients with HER2 IHC 2+ (irrespective of FISH status), and 26.6% in those with IHC 3+. Besides, subgroup analyses showed ICR confirmed ORRs of 16.7% in patients with HER2 IHC 2+ with FISH- and 26.3% in those with HER2 IHC 3+ or IHC 2+ with FISH+ [3]. Disitamab vedotin has been approved in China for advanced gastric cancer in patients with HER2 IHC 3+, IHC 2+/FISH+ or IHC 2+ FISH- who have received at least two prior systemic regimens.

Recommendation 12-a: Disitamab vedotin is recommended as third-line or later-line therapy for advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+.

Level of evidence: Moderate quality.

Strength of recommendation: Strong.

Recommendation 12-b: Disitamab vedotin is recommended as third-line or later-line therapy for advanced gastric cancer patients with HER2 IHC 2+/FISH-.

Level of evidence: Moderate quality.

Strength of recommendation: Strong.

The DESTINY-Gastric01 trial was a multicenter, randomized phase II study enrolling patients from Japan and South Korea with advanced HER2-high expression gastric cancer who had progressed after at least two prior treatment regimens. Participants were randomized to receive either T-DXd (6.4 mg/kg) or investigator's choice of chemotherapy (irinotecan or paclitaxel) [4]. Final results demonstrated a median OS of 12.5 months in the T-DXd group compared to 8.4 months in the chemotherapy group ($p=0.01$). The ORRs were 51.3% versus 14.3%, median PFS was 5.6 versus 3.5 months, and the median DoR was 12.5 versus 3.9 months, respectively. DESTINY-Gastric06, a bridging phase II trial designed to support regulatory approval in China, enrolled 73 patients with advanced HER2-high expression gastric cancer [96]. In patients who had previously received multiple HER2-targeted therapies, T-DXd achieved a median OS of 11.1 months [97]. Based on these findings, T-DXd was approved in China in August 2024 for the treatment of locally advanced or metastatic HER2-high expression gastric or gastroesophageal junction adenocarcinoma after at least two prior systemic regimens. In an exploratory cohort of the DESTINY-Gastric01 study, 19 patients with HER2 IHC 2+/ISH- tumors were evaluated. The ICR-confirmed ORR was 26.3% (95% CI, 9.1–51.2%), with a median DoR was 7.6 months, the disease control rate (DCR) was 89.5%, median OS was 7.8 months, and median PFS was 4.4 months. As an exploratory study, it does not power for definitive conclusions. Further research with a larger sample size is needed in the future.

Recommendation 13-a: T-DXd is recommended as third-line or later-line therapy for advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+.

Level of evidence: Moderate quality.

Strength of recommendation: Strong.

Recommendation 13-b: T-DXd is recommended as third-line or later-line therapy for advanced gastric cancer patients with HER2 IHC 2+/FISH–.

Level of evidence: Low quality.

Strength of recommendation: Strong.

HER2-targeted therapy in special clinical scenarios

HER2-targeted maintenance therapy in gastric cancer

Evidence guiding maintenance therapy in advanced gastric cancer remains limited, with no high-level recommendations currently available. In clinical practice, maintenance strategies are often employed after response or stable disease is achieved through a defined course of chemotherapy, with the goal of prolonging tumor control and enhancing quality of life.

In the ToGA trial, chemotherapy was limited to a maximum of six cycles, while trastuzumab monotherapy continued until disease progression or the emergence of unacceptable toxicity [13]. Similarly, a prospective observational study from China demonstrated no statistically significant differences in PFS or OS between patients receiving maintenance therapy with trastuzumab monotherapy and those receiving trastuzumab in combination with chemotherapy (median PFS: 7.9 vs. 11.0 months; HR, 1.06; $p=0.892$; median OS: 16.5 vs. 20.0 months; HR, 0.71; $p=0.169$) [98]. A retrospective analysis of 139 patients reported that among 109 responders to six cycles of first-line trastuzumab plus chemotherapy, continued trastuzumab maintenance therapy significantly prolonged both PFS (13.2 vs. 9.9 months; $p=0.002$) and OS (19.0 vs. 16.9 months; $p=0.021$) compared to discontinuation. In another study involving patients with advanced HER2-high expression gastroesophageal adenocarcinoma, maintenance therapy with trastuzumab alone was compared to trastuzumab plus a fluoropyrimidine. The median PFS was 5.1 months (95% CI, 4.2–7.7) versus 3.7 months (95% CI, 3.7–7.5), and median OS was 15.2 months (95% CI, 10.9–19.1) versus 17.0 months (95% CI, 15.5–21.6), respectively, with no statistically significant differences observed (PFS: $p=0.60$; OS: $p=0.40$) [99]. Regarding the choice of maintenance regimen, a small-sample retrospective study found that the number of capecitabine cycles administered in combination with trastuzumab had no significant impact on OS in patients receiving maintenance therapy using trastuzumab with or without capecitabine [100]. Collectively, these findings suggest that continuation of trastuzumab monotherapy following first-line trastuzumab plus chemotherapy may provide clinical benefit, while the addition of chemotherapy during the maintenance phase does not appear to offer further survival advantage.

Recommendation 14: For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ who received first-line therapy with trastuzumab plus chemotherapy, maintenance therapy with trastuzumab monotherapy is recommended.

Level of evidence: Moderate quality.

Strength of recommendation: Strong.

In the MSKCC study, patients with advanced HER2-high expression gastric cancer received pembrolizumab and trastuzumab during the first treatment cycle, with chemotherapy introduced in the second cycle. Given the cumulative toxicity associated with platinum agents, discontinuation of platinum-based chemotherapy was permitted at the discretion of the treating physician based on tolerability. Maintenance therapy was subsequently continued with pembrolizumab, trastuzumab, and/or capecitabine. Similarly, in the KEYNOTE-811 trial, platinum-based chemotherapy was administered for a maximum of 6 to 8 cycles. Following the completion of up to 35 cycles of pembrolizumab, patients were eligible for maintenance treatment with trastuzumab in combination with capecitabine, fluorouracil, or S-1 monotherapy for up to one year [101]. However, the optimal maintenance strategy following the KEYNOTE-811 regimen remains undefined and requires further investigation in prospective clinical studies.

Recommendation 15: For advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+ who have received first-line treatment comprising trastuzumab, chemotherapy, and pembrolizumab, maintenance therapy with trastuzumab and pembrolizumab in combination with single-agent chemotherapy may be considered.

Level of evidence: Low quality.

Strength of recommendation: Weak.

Management of resistance to HER2-targeted therapy in gastric cancer

Resistance to HER2-targeted therapies in gastric cancer arises through multiple, often overlapping mechanisms. These include intratumoral heterogeneity of HER2 expression, loss of HER2 gene amplification, emergence of secondary mutations, activation of HER2 heterodimers, alterations in downstream signaling pathways, and dysregulation of the tumor immune microenvironment [38, 102, 103]. Compared with breast cancer, HER2 expression in gastric cancer is markedly more heterogeneous, frequently displaying variable staining intensity. Furthermore, discordance in HER2 status between primary and metastatic lesions is common and may impair

therapeutic efficacy. During trastuzumab-based therapy, a subset of patients may convert to HER2-absent status upon re-biopsy. Analyses using liquid biopsy and NGS of tumor specimens have identified secondary HER2 mutations, activation of downstream signaling cascades, and bypass pathway activation, all of which may contribute to resistance. As trastuzumab exerts its effects partly through ADCC, impaired Fcγ receptor recognition or defective antigen presentation by immune cells may also attenuate clinical response. To date, no prospective clinical trials have specifically addressed resistance to trastuzumab in gastric cancer. However, emerging data suggest that later-line therapies, particularly HER2-targeted ADCs and small-molecule TKIs, may offer clinical benefit in patients with acquired resistance.

Notably, some patients with confirmed HER2-high expression by pathology exhibit limited responses to HER2-targeted therapy. Several factors may account for this, including: (1) diffuse-type histology as defined by the Lauren classification [13]; (2) a low HER2/CEP17 ratio [104]; and (3) the presence of HER2 mutations or fusions, or activation of alternate signaling pathways involving PTEN, MET, or HER3 [38]. Given the considerable intratumoral heterogeneity in gastric cancer, discrepancies between ctDNA-based detection of HER2 amplification and FISH-negative results from endoscopic biopsy specimens are not uncommon. Integrating ctDNA and tissue-based testing may improve diagnostic sensitivity for identifying HER2-high expression disease [44, 105].

Recommendation 16: For patients with resistance to HER2-targeted therapies, participation in clinical trials is recommended.

Level of evidence: Moderate quality.

Strength of recommendation: Strong.

HER2-targeted perioperative and conversion therapy in locally advanced gastric cancer

Surgical resection remains the only potentially curative therapy for patients with locally advanced gastric cancer. However, the substantial risk of postoperative local recurrence and distant metastasis renders surgery alone inadequate in most cases. Consequently, perioperative therapy has become the standard of care. Several phase II trials have investigated HER2-targeted therapies in the perioperative setting among patients with HER2-high expression gastric cancer. In the neoadjuvant setting, combinations of trastuzumab with chemotherapy, targeted agents, or immunotherapy have yielded pathologic complete response (pCR) rates ranging from 9.6% to 50%, and R0 resection rates between 85.9% and 100%

(Table 4). Following the success of immunotherapy in first-line treatment of advanced gastric cancer, their integration into the perioperative setting is under active investigation. In the ML42058 trial, the addition of trastuzumab and atezolizumab to chemotherapy significantly improved the pCR rate (38.1% vs. 14.3%) [106]. These results highlight the potential of combination regimens incorporating HER2-targeted therapy and immunotherapy to enhance short-term outcomes, including pCR and R0 resection rates, in patients with HER2-high expression gastric cancer [106–114]. Nonetheless, the effect of these strategies on long-term survival remains uncertain, and confirmation through high-level evidence is required.

Evidence supporting adjuvant HER2-targeted therapy in gastric cancer is relatively sparse. The Turkish TOXAG trial [115] enrolled 34 patients with stage IB–IIIC HER2-high expression gastric cancer who underwent D2 gastrectomy and received sequential chemoradiotherapy with trastuzumab plus XELOX. The 12- and 24-month disease-free survival (DFS) rates were 65.7% and 55.0%, respectively, while OS rates were 75.0% and 58.0%. In a single-center retrospective study from China, involving 208 patients with stage II–III locally advanced HER2-high expression gastric cancer, adjuvant trastuzumab plus chemotherapy significantly improved 3-year OS (87.6% vs. 69.6%) and 5-year OS (81.4% vs. 58.8%) compared with chemotherapy alone [111]. These findings suggest a potential role for HER2-targeted adjuvant therapy in delaying disease progression, although robust confirmatory evidence is lacking. Moreover, the relative efficacy of neoadjuvant versus adjuvant HER2-targeted therapies in the perioperative management of HER2-high expression gastric cancer remains a matter of ongoing debate. Participation in well-designed clinical trials is essential to define the optimal therapeutic approach.

Recommendation 17: In locally advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH, participation in clinical trials of HER2-targeted therapy is encouraged in the perioperative setting (including both neoadjuvant and adjuvant phases).

Level of evidence: Moderate quality.

Strength of recommendation: Strong.

Conversion therapy is systemic therapy for initially technically/oncologically unresectable or metastatic gastric/GEJ cancer, followed by curative-intent surgery aiming for R0 resection in patients who achieve a meaningful and durable response [116]. The Japanese Gastric Cancer Treatment Guidelines (2021) weakly recommend conversion surgery only when the response is maintained and R0 is achievable, and suggest considering surgery after

Table 4 Summary of studies evaluating neoadjuvant, adjuvant, and conversion therapies in HER2-high expression gastric cancer

Treatment setting	Study	Treatment regimen	Patient	pCR rate (%)	R0 resection rate (%)	OS
Neoadjuvant	NEOHX	Trastuzumab plus XELOX	HER2-high expression GC/GEJC	9.6	90	Median OS, 79.9 months
	HER-FLOT	Trastuzumab plus FLOT	HER2-high expression GC/GEJC	21.4	92.9	3-year OS rate, 82.1%
	PETRARCA AIO	Trastuzumab plus FLOT and pertuzumab vs. FLOT	HER2-high expression GC/GEJC	35	93	24-month OS rate, 84%
	Trigger	Trastuzumab plus S-1 and cisplatin vs. S-1 and cisplatin	HER2-high expression GC/GEJC with extensive nodal disease	50	92	Not reported
	Chinese retrospective study	Trastuzumab plus chemotherapy vs chemotherapy	HER2-high expression GC	-	-	3-year OS, 87.6% vs. 69.6%; 5-year OS, 81.4% vs. 58.8%
	RTOG-1010	Trastuzumab plus chemoradiotherapy vs. chemoradiotherapy	HER2-high expression GC	27	98	Median OS, 38.5 vs. 38.9 months
	INNOVATION	Trastuzumab plus pertuzumab and chemotherapy vs. trastuzumab ± chemotherapy	HER2-high expression GC/GEJC	6.3 vs. 15.1 vs. 3.8	85.9 vs. 90.3 vs. 83.9	3-year OS: 62.2% vs. 72.2% vs. 73.3%
	ML42058	Trastuzumab plus atezolizumab and XELOX vs. trastuzumab plus XELOX	HER2-high expression GC/GEJC	38.1	-	Not reported
	IIT study	Trastuzumab plus chemotherapy	HER2-high expression GC/GEJC	42.9	100	12-month OS, 93.3%; 18-month OS, 86.7%
Adjuvant	TOXAG	XELOX plus radiotherapy and trastuzumab	HER2-high expression GC/GEJC	-	88.2	Not reported
	Chinese retrospective study	Chemotherapy plus trastuzumab vs. chemotherapy alone	HER2-high expression stage II-III GC	-	-	3-year OS, 87.6% vs. 69.6%
Conversion	Mitsui et al	S-1 plus chemotherapy plus trastuzumab	HER2-high expression GC	-	100	Not reported
	Arigami et al	Trastuzumab plus chemotherapy	HER2-high expression GC	36.4	100	5-year OS, 68.6%

GC, gastric cancer; GEJC, gastroesophageal junction cancer; XELOX, capecitabine plus oxaliplatin; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; pCR, pathologic complete response; OS, overall survival

induction for selected oligometastases (e.g., solitary liver metastasis or limited para-aortic nodal disease) [117]. Currently, robust, high-level evidence specific to conversion therapy in advanced HER2-high expression gastric cancer is lacking. Existing clinical strategies are largely derived from first-line HER2-targeted therapies used in metastatic settings. In a study by Mitsui et al., the combination of trastuzumab with DCS (docetaxel, cisplatin, and S-1) was evaluated in 16 patients with unresectable metastatic HER2-high expression gastric cancer [118]. The ORR was 93.8%, with 9 patients (56.3%) achieving resectability and all undergoing R0 resection. Similarly, Arigami et al. retrospectively analyzed outcomes in 33 patients with advanced HER2-high expression gastric cancer who received trastuzumab plus chemotherapy [119]. Of these, 12 patients (36.4%) underwent conversion surgery, also with a 100% R0 resection rate. Importantly, the 5-year OS rate was markedly improved in patients who underwent conversion therapy followed by surgery compared with those who received chemotherapy alone (68.6% vs. 5.6%). Despite these promising findings, conversion therapy for

advanced gastric cancer remains investigational. Most data to date derives from small-scale, retrospective studies, highlighting the need for prospective, randomized controlled trials to establish definitive clinical benefit. For unresectable locally advanced HER2-positive gastric cancer, chemotherapy combined with HER2-targeted therapy is indeed the standard first-line systemic therapy. Conversion therapy should undergo rigorous evaluation by a multidisciplinary team (MDT), as there is currently no established standard.

Recommendation 18: In advanced gastric cancer patients with HER2 IHC 3+ or IHC 2+/FISH+, HER2-targeted therapy may be considered for conversion therapy. The timing of surgical intervention should be guided by multidisciplinary assessment of tumor response, patient performance status, and surgical eligibility.

Level of evidence: Low quality.

Strength of recommendation: Weak.

Safety considerations in HER2-targeted therapy

Cardiac toxicity

Trastuzumab can cause asymptomatic LVEF decline and, less commonly, clinical heart failure; in a clinical-practice gastric cancer cohort, an asymptomatic LVEF drop meeting cardiotoxicity criteria occurred in 7.1% of trastuzumab-treated patients [120]. Baseline LVEF assessment (e.g., echocardiography) and surveillance during therapy are recommended in major cardio-oncology guidance and reflected in regulatory labeling [121]. Operationally, the FDA label advises withholding trastuzumab for $\geq 16\%$ absolute LVEF decline from baseline, or LVEF below normal with $\geq 10\%$ absolute decline, resuming if recovery occurs within 4–8 weeks, and permanently discontinuing for persistent decline or repeated suspensions [122].

Interstitial lung disease (ILD)/pneumonitis

Drug-related pulmonary toxicity from ADCs most commonly manifests as ILD/pneumonitis, which may be asymptomatic early but can present with new/worsening cough, dyspnea, fever, hypoxemia, and new inflammatory CT findings (e.g., ground-glass opacities) [123]. ILD/pneumonitis is a clinically adverse event in DESTINY-Gastric04 trial, independently adjudicated drug-related ILD/pneumonitis occurred in 13.9% (grade 1: 2.9%; grade 2: 10.7%; grade 3: 0.4%; no grade 4/5) [93]. In DESTINY-Gastric06 trial, adjudicated drug-related ILD/pneumonitis occurred in 3.2% (grade 1, $n=2$; grade 2, $n=1$) [96]. Baseline: document pulmonary history/symptoms and risk factors (e.g., prior ILD/pneumonitis or thoracic radiotherapy), educate patients to report new cough/dyspnea/fever promptly, and consider baseline CT and resting SpO₂ ($\pm$ PFTs for higher-risk patients). If ILD/pneumonitis is suspected, immediately hold trastuzumab deruxtecan, obtain prompt chest CT, and exclude infection/other causes with early pulmonology/MDT input. Grade 1 (asymptomatic): withhold until resolved to grade 0; consider prednisolone ≥ 0.5 mg/kg/day, monitor symptoms and pulse oximetry closely, and consider follow-up imaging in 1–2 weeks [123]. Grade 2 (symptomatic): permanently discontinue trastuzumab deruxtecan; start systemic corticosteroids (e.g., ≥ 1 mg/kg/day) for at least 14 days, followed by a gradual taper for ≥ 4 weeks [123]. Grade 3–4: permanently discontinue; hospitalize and initiate IV high-dose methylprednisolone (e.g., 500–1,000 mg/day for 3 days), then transition to ≥ 1 mg/kg/day prednisone-equivalent with a slow taper; reassess alternative etiologies and escalate care if no improvement [124]. Empiric antibiotics may be considered when infection cannot be confidently excluded. For detailed, practice-oriented algorithms (screening, dose modification, steroid taper), refer to the 2024 trastuzumab deruxtecan clinical management and adverse event expert consensus [125].

Neuropathy and common toxicities

Peripheral sensory neuropathy (hypoesthesia/numbness/tingling) is a recognized toxicity of disitamab vedotin [126]. In the RC48-C008 trial, patients with HER2-overexpression GC/GEJC who were under at least second-line therapy were eligible and received RC48 2.5 mg/kg alone every 2 weeks. The results showed that hypoesthesia occurred in 32.8% of patients, including 3.2% grade 3–5 [3]. Grade 1: continue disitamab vedotin therapy with close assessment each cycle [126]. Grade 2: hold treatment and provide symptomatic care; resume at 2.0 mg/kg once symptoms improve to grade 0–1 (or baseline) [126]. Grade 3: hold and treat symptoms; for first occurrence, restart at 1.5 mg/kg after recovery, and discontinue for recurrence or if not recoverable for re-dosing within 28 days [126].

Conclusion

The HER2 gene plays a critical role in the pathogenesis and progression of gastric cancer. In patients with advanced HER2-high or HER2-intermediate expression disease, HER2-targeted therapies now represent a cornerstone of management. Over the past several years, this field has seen notable advances, including the refinement and standardization of HER2 testing methods, the establishment of diagnostic criteria, and the accumulation of both clinical trial data and real-world evidence. These developments, coupled with the approval of novel agents and expanded indications, have laid a stronger foundation for the precise identification of candidates for HER2-targeted therapies and have facilitated timely updates to the Chinese guidelines for gastric cancer. Despite these advances, important challenges remain in the diagnosis and management of HER2-high, HER2-intermediate, and HER2-low expression gastric cancers, particularly in the context of limited high-level evidence. Key areas requiring further investigation include the clinical application of ctDNA for diagnostic and therapeutic purposes, the role of HER2-targeted therapies in early-stage disease, treatment strategies involving ADCs in tumors with HER2-intermediate or HER2-low expression, mechanisms of resistance to HER2-targeted therapies and approaches to overcome them, as well as the management of treatment-related adverse events. Addressing these gaps will necessitate continued clinical investigation, interdisciplinary collaboration, and the integration of emerging data into practice. Multidisciplinary cooperation and open cross-specialty dialogue are essential to advancing the standard of care and optimizing outcomes for patients receiving HER2-targeted therapies.

Abbreviations

ADCC	Antibody-dependent cellular cytotoxicity
ADCs	Antibody-drug conjugates
cfDNA	Cell-free DNA

CPS	Combined positive score
CTCs	Circulating tumor cells
ctDNA	Circulating tumor DNA
CTMs	Circulating tumor microemboli
DFS	Disease-free survival
FFPE	Formalin-fixed, paraffin-embedded
GC/GEJC	Gastric and gastroesophageal junction adenocarcinoma
GRADE	Grading of recommendations assessment; development and evaluation
HER2	Human epidermal growth factor receptor 2
NGS	Next-generation sequencing
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
pCR	Pathologic complete response
SCNAs	Somatic copy number alterations
SOPs	Standard operating procedures
T-DXd	Trastuzumab deruxatecan
ILD	Interstitial lung disease

Supplementary Information

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Additional file 1.

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Author contributions

Xiaotian Zhang, Yakun Wang, Muyan Cai, Fenghua Wang, Tong Xie, Ruihua Xu, Jin Li, Hong Bu and Lin Shen contributed to the study conception and design. All authors collected the data and performed the data analysis. All authors contributed to the interpretation of the data and the completion of figures and tables. All authors contributed to the drafting of the article and final approval of the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

Declaration of interests Xiaotian Zhang reports receiving speaker fees from Daiichi Sankyo, AstraZeneca, Bristol Myers Squibb, MSD, BeiGene, Qilu, Hengrui, and Henlius. Fenghua Wang reports receiving speaker fees from Daiichi Sankyo, Bristol Myers Squibb, MSD, Astellas, and BeiGene, and consulting fees from Hengrui. Ruihua Xue reports receiving speaker fees from Daiichi Sankyo, Bristol Myers Squibb, Roche, Merck Serono, Hutchison,

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