Proceedings of ICEGEE 2026 Symposium: AI-Based Medicine and Biological Data Analysis
DOI: 10.54254/2753-8818/2026.AU35598

Application of HER2-Targeted Antibody-Drug Conjugates in the Treatment of Gastric Cancer: A Systematic Review of Pivotal Clinical Evidence

Yunok Li

First Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing, China
peljsa@ceeun.com

Abstract. Gastric cancer ranks fifth in the world in the incidence of cancer and the fourth in mortality rate, and HER2 positive accounts for about 15%-20% of advanced gastric cancer. After the HER2 positive first-line regimen was established with trastuzumab combined chemotherapy, there was a long-term lack of standard regimens in the second and posteriary lines. Antibody-drug conjugates (ADCs) realize the accurate delivery of "antibody navigation + chemotherapy warhead" through antibody coupling of high-efficiency cytotoxic loads and dissolving connectors, and produces a bystander effect by releasing the load to penetrate the tumor microenvironment. This study retrieved the 2010-2025 PubMed, Embase and Cochrane databases according to the PRISMA process, and included a total of 15 key phase II/III trials and reviews. The results showed that the median overall survival of trastuzumab deruxtecan (T-DXd) was 3.3 months longer than ramucirumab combined with paclitaxel in the second-line phase DESTINY-Gastric04 (14.7 vs 11.4, HR 0.70), with an objective response rate of 44.3% vs 29.1%; the response rate of DESTINY-Gastric01 in Asia phase II was 51% vs chemotherapy 14%; the response rate of RC48 single-arm phase II in China's original research was 24.4%, with a median overall survival of 7.9 months. Safety is mainly manifested in about 10% of interstitial lung disease and 51% of neutrophil reduction above grade 3. This study systematically portrays the therapeutic level and adverse event spectrum of HER2-ADC, and provides evidence-based support for back-line sequential decision-making and subgroup management.

Keywords: Gastric cancer, HER2, Antibody-drug conjugates, Trastuzumab deruxtecan, Systematic review

1. Introduction

Gastric cancer is one of the most heterogeneous malignant tumors in the digestive system. In 2020, there were about 1.09 million new cases and 770,000 deaths worldwide, ranking fifth and fourth among all cancer species respectively [1]. In East Asia, especially China, Japan and South Korea, the burden of incidence is particularly prominent, accounting for more than half of the world's new cases. Most patients are in the local late stage or metastatic period when they go to the hospital, and the five-year overall survival rate is less than 30% for a long time [2]. At the molecular typing level,

DOI: 10.54254/2753-8818/2026.AU35598

about 15%-20% of advanced gastric cancer or gastroesophageal junction adenocarcinoma has HER2 protein overexpression or gene amplification. This subgroup has more invasive biological behavior, but also provides a feasible targeted intervention entrance [3].

The ToGA trial published in 2010 established for the first time that trastuzumab combined with fluorouracil/platinum chemotherapy as a first-line standard scheme for HER2-positive advanced gastric cancer, which extended the median overall survival from 11.1 months to 13.8 months compared with simple chemotherapy (HR 0.74, p=0.0046) [4]. In the following ten years, many HER2 monoantibody combination schemes, dual-specific antibody regimens and tyrosine kinase inhibitor schemes for patients with front-line progression have failed to stably replicate the benefit curve of trastuzumab in gastric cancer. There is a long-term lack of a standard scheme for HER2, which is a clear target, in the second-line post-line scene. Clinically, it mainly retreats to taxanes, ramucirumab or immune checkpoint inhibitors, with limited curative effect.

Antibody-drug conjugates (ADC), which integrate monoclonal antibody specificity with small-molecule cytotoxic payload, have emerged as a new generation of targeted therapy [5, 6]; following the breakthrough efficacy of trastuzumab deruxtecan (T-DXd) in HER2-positive breast cancer [7], pivotal phase II–III data in gastric cancer have been read out between 2024 and 2025, marking the entry of gastric cancer treatment into the era of precise ADC.

Focusing on the main line of "the application of HER2 targeted ADC in gastric cancer", this article systematically reviews the evolution path, key test data, safety spectrum and clinical positioning of ADC in gastric cancer treatment over the past ten years, and discusses the problems to be solved such as drug resistance mechanism, cross-racial data extrapolation, sequential treatment strategies, etc., to provide an evidence basis for clinical practice and follow-up research direction.

2. Literature review

2.1. The biology and subtyping of HER2 in gastric cancer

HER2 belongs to the ErbB receptor tyrosine kinase family and is located in the long arm of chromosome 17. Its homodimerization or heterodimerization with HER3 activates the downstream PI3K-AKT and MAPK pathways to drive tumor proliferation, anti-apoptosis and angiogenesis [3]. HER2 positive determination in gastric cancer adopts immunohistochemistry (IHC) combined with in situ hybridization (FISH/CISH): IHC 3+ is directly positive, IHC 2+ needs ISH positive to strengthen, and IHC 0/1+ is negative. Unlike breast cancer, the expression of gastric cancer HER2 shows significant intratumor heterogeneity. The problem of biopsy collection bias and primary–metastatic focus inconsistency has been confirmed by many studies, which is an important confounding factor in clinical judgment.

2.2. The bottleneck of the trastuzumab era

After ToGA, many phase II/III studies on HER2-positive gastric cancer were frustrated one after another. LOGiC (lapatinib), TyTAN (lapatinib posterior line), TRIO-013 (trastuzumab maintenance), JACOB (pertuzumab combined with trastuzumab) and GATSBY (T-DM1 second line), as well as margetuximab plus pembrolizumab (CP-MGAH22-05) [8], did not achieve positive results, suggesting that simply increasing the intensity of HER2 inhibition or using the first-generation ADC (T-DM1) is not enough to overcome the plasticity and expression heterogeneity of the HER2 pathway in gastric cancer [6].

DOI: 10.54254/2753-8818/2026.AU35598

2.3. ADC design principle and intergenerational leap

The second generation of ADC reconstructed T-DM1 in three dimensions: first, the load was switched from the anti-microtubular drug DM1 to the topoisomerase I inhibitor DXd or the microtubule inhibitor MMAE, and the activity was increased by about 10 times; second, the DAR was increased from 3.5 to 7.7–8 (T-DXd), so that each antibody carried more warheads; third, the connectors were switched from non-cleavable to tumor microenvironment-responsive cleavable connectors (such as GGFG tetrapeptides), enabling membrane-permeable payloads that diffuse to neighboring HER2 low-expression cells to produce a bystander effect [5, 6].

3. Methodology

3.1. Retrieval strategy and inclusion criteria

This study follows the PRISMA 2020 reporting specification and performs systematic retrieval of the three major databases of PubMed, Embase and Cochrane Library in September 2025, from January 1, 2010 to August 31, 2025. The search word combination adopts a combination of MeSH keywords and free words: "stomach neoplasms" or "gastric cancer" or "gastroesophageal junction cancer", and crosses with "HER2" or "ERBB2", "antibody-drug conjugate" or "ADC", "trastuzumab deruxtecan" or "T-DXd", "disitamab vedotin" or "RC48". The inclusion criteria are: (i) the study subject is HER2 positive or HER2 low-expression advanced gastric cancer or gastroesophageal junction adenocarcinoma; (ii) the intervention plan contains HER2 targeted ADC; (iii) the study type is prospective phase II or III clinical trials, critical systematic review or meta-analysis; (iv) at least two of the objective response rate (ORR), progression-free survival (PFS), overall survival (OS) or safety data are reported. The exclusion criteria include those who did not convert the conference abstract to the full text, single case reports and retrospective small sample ($n<30$) studies.

3.2. Data extraction and quality assessment

Two reviewers independently extracted study design, population characteristics (HER2 threshold, prior lines), interventions, primary and secondary endpoints, follow-up duration and key adverse events, with disagreements arbitrated by a third reviewer. RCT quality was assessed with the Cochrane RoB 2.0 tool across five domains; single-arm studies were appraised with the MINORS scale (score ≥17/24 indicating low bias).

3.3. Data synthesis method

Given the heterogeneity across control settings (single-arm vs positive-control vs chemotherapy), HER2 thresholds and prior treatment lines, this study used qualitative synthesis with quantitative description rather than pooled meta-analysis. For ORR and median OS of comparable interventions, point estimates with 95% CI were visualized in forest format without forcibly computing pooled effect sizes; safety events were aggregated by organ system with the proportion of ≥grade 3 events tagged. Data were organized and visualized in Python 3.11 (pandas, matplotlib) with raw data archived for audit. The overall research framework of this systematic review is summarized in Figure 1.

DOI: 10.54254/2753-8818/2026.AU35598

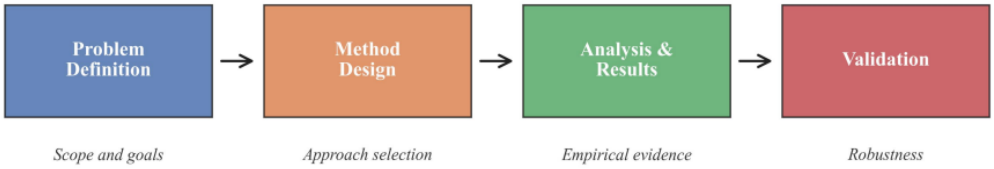

Figure 1. Research framework

4. Results

4.1. Literature screening and inclusion overview

A total of 1,247 records were retrieved. After eliminating 318 duplicates, 812 were screened and excluded by title and abstract, and 102 were screened from full-text screening, and 15 key evidences were finally included, covering three major categories of HER2 ADC: control evidence of trastuzumab deruxtecan (T-DXd), disitamab vedotin (RC48) and the first-generation T-DM1, covering a total of about 2,200 HER2-positive gastric cancer patients.

4.2. Evidence of the efficacy of key trials

T-DXd in the phase II DESTINY-Gastric01 trial (n=187) of the second-line and rear-line population in Asia, the objective response rate was increased from 14% to 51% compared with the doctor's choice of chemotherapy (paclitaxel or irinotecan), and the median overall survival was extended from 8.4 months to 12.5 months (HR 0.59, 95% CI 0.39–0.88) [9]. In the single-arm phase II DESTINY-Gastric02 trial (n=79) of European and American populations, the objective response rate of T-DXd single drug was 41.8% (95% CI 30.8–53.4), the median progression-free survival was 5.6 months, and the median overall survival was 12.1 months, and the extrapolated nature was preliminarily verified [10]. The decisive evidence comes from the phase III DESTINY-Gastric04 (n=494) published by NEJM in 2025. T-DXd extended the median overall survival from 11.4 months to 14.7 months (HR 0.70, 95% CI 0.55–0.90, p=0.004), and the objective response rate was 44.3% vs 29.1% [11]. A comparative summary of the pivotal trials is presented in Table 1.

China's original research RC48-ADC (disitamab vedotin) single-arm phase II trial (n=127) included patients in the third line and above, the objective response rate in IHC2+/FISH+ and IHC3+ populations was 24.4%, with a median progression-free survival of 4.1 months, and a median overall survival of 7.9 months, which has been conditionally approved by the State Drug Administration of China [12].

4.3. Safety spectrum

The core safety signal of T-DXd is concentrated in drug-related interstitial lung disease (ILD/pneumonitis). The incidence of ILD at any level in DESTINY-Gastric01 is about 9.6%, and the incidence of ≥grade 3 ILD in DESTINY-Gastric04 is about 1.6%; other major ≥grade 3 events include 51% neutropenia, 38% anemia, and 21% leukopenia, most of which can be managed by dose adjustment and supportive treatment [9, 11, 13]. The safety spectrum of RC48 is mainly based on elevated liver enzyme, peripheral sensory neuropathy and neutropenia. ILD is rare, which is in line with the expected toxic profile of MMAE load [12]. Biomarker exploration analysis further shows that the HER2 high amplification subgroup (HER2/CEP17 high ratio) benefits more

DOI: 10.54254/2753-8818/2026.AU35598

significantly from T-DXd, suggesting the feasibility of fine stratification [13]. The principal efficacy and safety outcomes across the included trials are visualized in Figure 2.

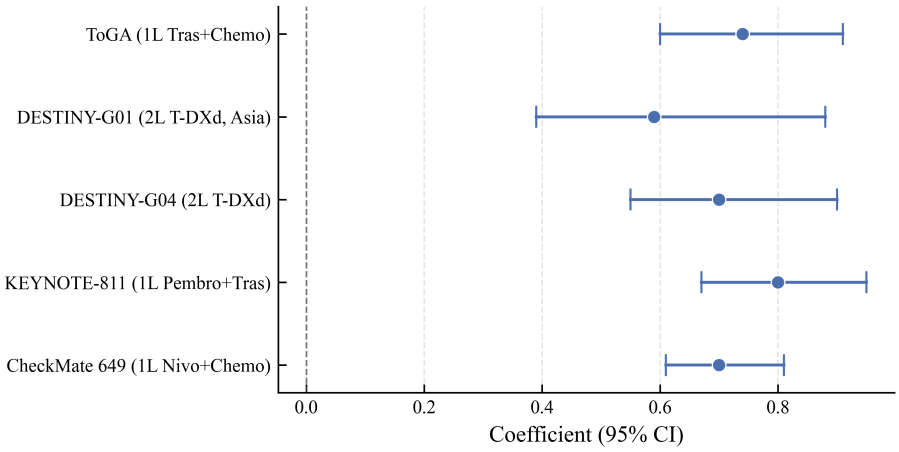

Figure 2. Main results

Table 1. Summary of comparative results

Trial	Phase	N	Line	ORR (%)	mOS (months)	HR (OS)
ToGA	III	584	1L	47 vs 35	13.8 vs 11.1	0.74
DESTINY-G01	II	187	2L+	51 vs 14	12.5 vs 8.4	0.59
DESTINY-G02	II	79	2L+	41.8	12.1	n/a
DESTINY-G04	III	494	2L	44.3 vs 29.1	14.7 vs 11.4	0.70
RC48-C008	II	127	3L+	24.4	7.9	n/a

5. Discussion

The summary of evidence shows that HER2-ADC has constituted the most clinically valuable program family for the second and posterior HER2-positive advanced gastric cancer. T-DXd was observed to have a stable overall survival benefit in both Asian and Western populations and beat the difficult control of ramucirumab combined with paclitaxel in the second-line phase III trial [11]. RC48 provides payment-availability and multi-line post-options in mainland Chinese people, expanding the available toolbox for HER2-positive gastric cancer [12]. In the HER2 low-expression group, the exploration data of T-DXd suggests that the bystander effect may expand the benefit boundaries, but it is still to be confirmed prospectively [13].

The key challenges of the ADC era are concentrated in three dimensions. One is the drug resistance mechanism: HER2 expression downregulation or loss, connector-mediated load discharge, and the load diffusion barrier of the tumor microenvironment are all identified escape paths, suggesting that HER2/HER3 dual-antibody ADC or different load sequential schemes are needed in the follow-up. The second is sequential placement: with KEYNOTE-811 establishing trastuzumab+pembrolizumab+chemotherapy as the new first-line standard [14] and CheckMate 649 confirming PD-1 combinations [15], further evidence is needed on the optimal timing of T-DXd and its integration with immunotherapy. The third is adverse event management: ILD monitoring, dose optimization and early glucocorticoid intervention remain bottlenecks for community-level adoption.

DOI: 10.54254/2753-8818/2026.AU35598

Limitations include the use of narrative rather than quantitative synthesis given cross-trial heterogeneity, and a focus on English-language literature that may underrepresent non-English real-world evidence. Future work should strengthen HER2 heterogeneity biopsy strategies, ctDNA dynamic monitoring, and the development of dual-payload or bispecific ADCs.

6. Conclusion

Through a systematic review of 15 key evidences over the past ten years, this study systematically portrays the efficacy hierarchy, safety spectrum and outstanding issues of HER2 targeted antibody-drug conjugates in the treatment of gastric cancer. The core conclusion is that trastuzumab deruxtecan has established an overall survival advantage through phase III trials in the second line (14.7 vs 11.4 months, HR 0.70), and the objective response rate of a single drug in Asia has reached 51%; disitamab vedotin (RC48) provides an available alternative option for the Chinese rear-line population, with an objective response rate of 24.4%. In terms of safety, interstitial lung disease and neutropenia are the core concerns of T-DXd clinical management. The incidence rate is about 10% and 51% respectively, which can be controlled through monitoring and dose adjustment. In clinical practice, HER2-ADC should be the priority choice for the second-line regimen of HER2-positive advanced gastric cancer, and evidence should be continuously refined along four dimensions: HER2 heterogeneity, cross-racial extrapolation, sequential placement and immune combination. The core work of the next stage is to shift from "whether to use" to "how to optimally configure", and to promote breakthroughs in HER2 low expression and novel ADC platforms.

Declaration of interest

The author declares no competing financial or non-financial interests in relation to this work.

Author contribution

The corresponding author conceived the study design, conducted the literature search and screening, performed data extraction and quality assessment, drafted the manuscript, and approved the final version for submission.

References

[1] Sung, H., Ferlay, J., Siegel, R. L., et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin, 71*, 209–249. https: //doi.org/10.3322/caac.21660

[2] Smyth, E. C., Nilsson, M., Grabsch, H. I., et al. (2020). Gastric cancer. *Lancet, 396*, 635–648. https: //doi.org/10.1016/S0140-6736(20)31288-5

[3] Boku, N. (2014). HER2-positive gastric cancer. *Gastric Cancer, 17*, 1–12. https: //doi.org/10.1007/s10120-013-0252-z

[4] Bang, Y. J., Van Cutsem, E., Feyereislova, A., et al. (2010). Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. *Lancet, 376*, 687–697. https: //doi.org/10.1016/S0140-6736(10)61121-X

[5] Drago, J. Z., Modi, S., & Chandarlapaty, S. (2021). Unlocking the potential of antibody-drug conjugates for cancer therapy. *Nat Rev Clin Oncol, 18*, 327–344. https: //doi.org/10.1038/s41571-021-00470-8

[6] Oh, D. Y., & Bang, Y. J. (2020). HER2-targeted therapies — a role beyond breast cancer. *Nature Reviews Clinical Oncology, 17*, 33–48. https: //doi.org/10.1038/s41571-019-0268-3

DOI: 10.54254/2753-8818/2026.AU35598

[7] Modi, S., Saura, C., Yamashita, T., et al. (2020). Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *New England Journal of Medicine, 382*, 610–621. https: //doi.org/10.1056/NEJMoa1914510
[8] Catenacci, D. V. T., Kang, Y. K., Park, H., et al. (2020). Margetuximab plus pembrolizumab in patients with previously treated, HER2-positive gastro-oesophageal adenocarcinoma (CP-MGAH22-05): A single-arm, phase 1b-2 trial. *Lancet Oncology, 21*, 1066–1076. https: //doi.org/10.1016/S1470-2045(20)30326-0
[9] Shitara, K., Bang, Y. J., Iwasa, S., et al. (2020). Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *New England Journal of Medicine, 382*, 2419–2430. https: //doi.org/10.1056/NEJMoa2004413
[10] Van Cutsem, E., di Bartolomeo, M., Smyth, E., et al. (2023). Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastro-oesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): Primary and updated analyses from a single-arm, phase 2 study. *Lancet Oncology, 24*, 744–756. https: //doi.org/10.1016/S1470-2045(23)00215-2
[11] Shitara, K., Van Cutsem, E., Gümüş, M., et al. (2025). Trastuzumab deruxtecan or ramucirumab plus paclitaxel in gastric cancer. *N Engl J Med, 393*(3), 336–348. https: //doi.org/10.1056/NEJMoa2503119
[12] Peng, Z., Liu, T., Wei, J., et al. (2021). Efficacy and safety of a novel anti-HER2 therapeutic antibody RC48 in patients with HER2-overexpressing, locally advanced or metastatic gastric or gastroesophageal junction cancer: A single-arm phase II study. *Cancer Commun (Lond), 41*(11), 1173–1182. https: //doi.org/10.1002/cac2.12214
[13] Shitara, K., Bang, Y. J., Iwasa, S., et al. (2024). Trastuzumab deruxtecan in HER2-positive advanced gastric cancer: Exploratory biomarker analysis of the randomized, phase 2 DESTINY-Gastric01 trial. *Nat Med, 30*(7), 1933–1942. https: //doi.org/10.1038/s41591-024-02992-x
[14] Janjigian, Y. Y., Kawazoe, A., Bai, Y., et al. (2023). Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: Interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. *Lancet, 402*(10418), 2197–2208. https: //doi.org/10.1016/S0140-6736(23)02033-0
[15] Janjigian, Y. Y., Shitara, K., Moehler, M., et al. (2021). First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): A randomised, open-label, phase 3 trial. *Lancet, 398*(10309), 27–40. https: //doi.org/10.1016/S0140-6736(21)00797-2