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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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MODERN MANAGEMENT OF HER2-POSITIVE GASTRIC CANCER: CLINICAL INSIGHTS AND EVIDENCE FROM TRIALS

Piotr Sobkiewicz *(Corresponding Author, Email: piotr1999.sob@gmail.com)*
MD, Lower Silesian Oncology, Pulmonology and Hematology Center, pl. Ludwika Hirszfelda 12, 53-413 Wroclaw, Poland
ORCID ID: 0009-0007-6610-440X

Martyna Grodzińska
MD, Lower Silesian Oncology, Pulmonology and Hematology Center, pl. Ludwika Hirszfelda 12, 53-413 Wroclaw, Poland
ORCID ID: 0009-0004-1001-6484

Karol Poplicha
MD, State Medical Institute of the Ministry of the Interior and Administration (MSWiA), Wołoska 137, 02-507 Warsaw, Poland
ORCID ID: 0009-0005-3835-9777

Maria Ufniarska
MD, Saint Adalbert Hospital in Gdańsk, aleja Jana Pawła II 50, 80-462 Gdańsk, Poland
ORCID ID: 0009-0008-5927-4811

Aleksandra Piech
MD, Clinical Provincial Hospital No. 2 in Rzeszów, Lwowska 60, 35-301 Rzeszów, Poland
ORCID ID: 0009-0001-4485-2200

Tomasz Ufniarski
MD, University Clinical Center in Gdańsk, 7 Dębinki Street, 80-952 Gdańsk, Poland
ORCID ID: 0009-0008-6555-3403

Justyna Moszkowicz
MD, Clinical Provincial Hospital No. 2 in Rzeszów, Lwowska 60, 35-301 Rzeszów, Poland
ORCID ID: 0009-0009-2582-6187

Karolina Pasierb
MD, The University Hospital in Krakow, Jakubowskiego 2, 30-668 Kraków, Poland
ORCID ID: 0009-0006-5806-3508

Patrycja Kardasz
MD, Saint Adalbert Hospital in Gdańsk, aleja Jana Pawła II 50, 80-462 Gdańsk, Poland
ORCID ID: 0009-0006-8137-9789

Bartłomiej Siuzdak
MD, Clinical Provincial Hospital No. 2 in Rzeszów, Lwowska 60, 35-301 Rzeszów, Poland
ORCID ID: 0009-0003-8691-6617

Marta Jutrzenka
MD, Praga Hospital of the Transfiguration (Szpital Praski p.w. Przemienienia Pańskiego Sp. Z o.o.), Aleja Solidarności 67, 03-401 Warszawa, Poland
ORCID ID: 0000-0001-7266-1586

Patrycja Ucieklak
MD, District Hospital in Zawiercie, ul. Miodowa 14, 42-400 Zawiercie, Poland
ORCID ID: 0009-0002-3681-1051

Jarosław Ucieklak
MD, District Hospital in Zawiercie, ul. Miodowa 14, 42-400 Zawiercie, Poland
ORCID ID: 0009-0002-2702-4953

ABSTRACT

Introduction: Gastric cancer (GC) remains a major global health issue, ranking among the leading causes of cancer-related deaths worldwide. Despite improvements in diagnostic methods, many patients are still diagnosed at an advanced stage. The discovery of HER2 overexpression in approximately 15–20% of GC cases introduced targeted therapy into clinical practice. The ToGA trial established trastuzumab combined with chemotherapy as the first-line treatment for HER2-positive advanced GC, significantly improving survival.
Aim of the study: This review summarizes current knowledge about the epidemiology, clinical staging, and treatment strategies for advanced gastric cancer, with particular focus on HER2-positive tumors. It also outlines the evolution of HER2-targeted therapies and discusses novel agents and clinical trials that may shape future management.
Material and methods: The review was based on data collected from PubMed and Google Scholar using key terms: gastric cancer, HER2-positive, chemotherapy, targeted therapy, immunotherapy, clinical trials, ToGA, T-DXd, ZW25, KN026.
Conclusion: GC is a complex and heterogeneous disease that requires accurate staging and individualized treatment strategies. While traditional chemotherapy remains the foundation of care, the incorporation of targeted therapies and immune checkpoint inhibitors has changed the treatment landscape. HER2 remains a critical biomarker, with newer agents such as trastuzumab deruxtecan, zanidatamab, and KN026 showing promising results. Continued molecular profiling and participation in clinical trials are essential for improving outcomes in HER2-positive GC patients.

KEYWORDS

Gastric Cancer, HER2, Trastuzumab, Targeted Therapy, Chemotherapy, Trastuzumab Deruxtecan, Zanidatamab, KN026

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Introduction

Gastric cancer (GC) remains a significant global health burden, ranking as the fifth most common malignancy and the fourth leading cause of cancer-related death worldwide [1,2]. Its incidence varies geographically, being highest in Eastern Asia and Eastern Europe, while lower rates are seen in Northern Europe, North America, and Africa [2]. Despite improvements in early detection in some regions, many patients are still diagnosed at advanced stages, leading to poor prognosis and limited treatment options [3]. Systemic chemotherapy has been the main treatment for metastatic gastric cancer (mGC), but with limited efficacy and a median overall survival of approximately 12 months [3].

A major advancement in GC treatment was the identification of Human Epidermal Growth Factor Receptor 2 (HER2) as a therapeutic target, present in about 15-20% of gastric and gastroesophageal junction cancers. This led to the landmark ToGA trial, which demonstrated that adding trastuzumab, a monoclonal antibody targeting HER2, to standard chemotherapy significantly improved survival in HER2-positive advanced GC patients [4]. As a result, trastuzumab became the first approved targeted therapy for this subgroup, transforming treatment paradigms [4].

For nearly a decade after ToGA, progress in HER2-targeted therapies remained stagnant. Recently, however, new HER2-directed agents such as trastuzumab deruxtecan (T-DXd) have shown promising clinical results [5]. Additionally, the emergence of immune checkpoint inhibitors, notably anti-PD-1 antibodies, has improved survival in certain GC patient subsets, including those with MSI-H/dMMR tumors [5]. These developments emphasize the growing role of molecular profiling in guiding individualized treatment.

This review highlights the development of HER2-targeted therapies in gastric cancer, focusing on the pivotal role of trastuzumab and the ToGA trial, while discussing emerging therapies and future directions in managing HER2-positive disease.

Methodology

This narrative review synthesizes current evidence on the epidemiology, clinical staging, and therapeutic strategies for HER2-positive gastric cancer, with a focus on the role of trastuzumab and emerging HER2-targeted therapies. The review was conducted in accordance with the PRISMA 2020 guidelines. A structured literature search was performed in PubMed and Google Scholar databases, covering the years 2010–2025, using combinations of terms such as *"gastric cancer," "HER2-positive," "chemotherapy," "trastuzumab," "targeted therapy," "immunotherapy," "clinical trials," "ToGA," "trastuzumab deruxtecan (T-DXd)," "zanidatamab (ZW25),"* and *"KN026."* Boolean operators and database-specific syntax were applied to refine the search.

Eligibility criteria were restricted to peer-reviewed, full-text articles published in English, with priority given to systematic reviews, meta-analyses, randomized controlled trials (RCTs), and pivotal clinical trials. Additional studies were identified through reference and citation tracking.

A total of studies was selected based on relevance, methodological rigor, and contribution to the thematic scope of the review. Data were manually extracted and thematically categorized into domains such as chemotherapy backbones, HER2-targeted therapy, immunotherapy integration, and novel antibody-drug conjugates. Emphasis was placed on clinical outcomes including overall survival, progression-free survival, response rates, safety profiles, and treatment sequencing strategies

Results

Staging of gastric cancer (GC) plays a crucial role in selecting appropriate treatment and assessing prognosis. Currently, the TNM system developed by the American Joint Committee on Cancer (AJCC) is widely used. In the latest, 8th edition, several significant modifications have been introduced compared to previous versions [6,7]. First and foremost, the N3 group has been subdivided into N3a (7–15 involved nodes) and N3b (>15 nodes), which better reflects prognosis. Definitions of gastroesophageal junction (GEJ) tumors have also been clarified, indicating which should be classified according to esophageal and which according to gastric staging. Additionally, differences in pathological and clinical assessment depending on the type of treatment applied have been incorporated [6,7].

Accurate staging is possible through various imaging techniques, such as endoscopic ultrasonography (EUS), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET-CT), and diagnostic laparoscopy. EUS is particularly effective in early stages, while PET-CT and laparoscopy are useful in detecting distant metastases, especially to the peritoneal cavity [6,10].

In clinical practice, verification of tumor resectability is essential. Tumors considered resectable include cases without invasion of critical adjacent structures (T1–T4a), absence of distant metastases (M0), and limited lymph node involvement (N0–N3b). Tumors deemed unresectable involve extensive invasion of the pancreas, major vessels, peritoneal metastases, or presence of distant metastases (M1) [6,8].

In the TNM classification, gastric cancer stage is defined based on depth of invasion into the gastric wall, number of involved lymph nodes, and presence of distant metastases. Stage 0 (carcinoma in situ) indicates presence of atypical cells limited to the mucosa. Stage I includes early forms of cancer confined to mucosal and muscular layers with limited lymph node involvement. Stage II indicates further progression, with deeper wall invasion and increasing number of involved lymph nodes. Stage III is characterized by deep invasion of the gastric wall, extensive lymph node involvement, and potential invasion of adjacent organs. Stage IV is defined by presence of distant metastases involving the liver, lungs, peritoneum, and distant lymph nodes [9].

Only after such staging can treatment be properly planned—whether the patient should proceed directly to surgery, receive neoadjuvant therapy first, or require palliative care [8].

Molecular diagnostics are playing an increasingly important role in planning therapeutic strategies. The assessment of biomarkers such as microsatellite instability (MSI), HER2 overexpression, and Epstein-Barr virus (EBV) presence provides additional prognostic and predictive information, allowing for more precise selection of targeted therapies [6,10].

Tabel 1. Stages of gastric cancer and clinical description

Stage	Clinical description
0 (carcinoma in situ)	Atypical cells confined to the mucosa, without invasion of deeper layers.
IA	Invasion into mucosa or submucosa, no lymph node involvement.
IB	Invasion into submucosa with 1–2 lymph nodes involved or invasion into muscularis propria without lymph node involvement.
IIA	Invasion of the gastric wall with 3–6 lymph nodes involved, or invasion into subserosa without lymph node involvement.
IIB	Involvement of 7–15 lymph nodes or invasion into serosa.
IIIA	Deep wall invasion, involvement of 7–15 lymph nodes, possible invasion of adjacent structures.
IIIB	Advanced serosal involvement and numerous lymph nodes involved.
IIIC	Wall invasion with more than 16 lymph nodes involved and/or multi-organ invasion.
IV	Presence of distant metastases (liver, lungs, peritoneum, distant lymph nodes).

Treatment

Chemotherapy of GC

Chemotherapy plays a crucial role in the treatment of advanced gastric cancer. Systemic therapy primarily uses cytotoxic agents such as fluoropyrimidines, platinum compounds, taxanes, and irinotecan [11]. The most commonly employed first-line strategy is the combination of a fluoropyrimidine (fluorouracil, capecitabine, or S-1) with platinum compounds. Oxaliplatin demonstrates comparable efficacy to cisplatin and often has a better tolerability profile [11,12].

The phase III SOX-GC trial showed that the SOX regimen (S-1 plus oxaliplatin) led to improved survival outcomes compared with the traditional SP regimen (S-1 plus cisplatin) in patients with diffuse or mixed-type gastric cancer [12]. For patients for whom full-dose chemotherapy would be too toxic (due to age or reduced performance status), the phase III GO2 study demonstrated that reducing the dose of a doublet regimen to 60% of the standard allowed preservation of efficacy with improved tolerability [13].

In second-line therapy following first-line failure, taxanes (paclitaxel, docetaxel) and irinotecan are widely used. The phase III ABSOLUTE study conducted in Japan demonstrated that weekly administration of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) was non-inferior in efficacy compared to traditional solvent-based paclitaxel, with a more favorable safety profile [12].

In third-line treatment, the oral cytotoxic agent trifluridine-tipiracil (TAS-102) has been employed. The phase III TAGS trial showed that TAS-102 significantly prolonged overall survival compared with placebo [15]. These findings reinforce TAS-102 as an effective option in subsequent lines of therapy for advanced gastric cancer [13].

Molecular Biomarkers of Immunotherapy in GC

In recent years, growing understanding of the molecular basis of gastric cancer (GC) has led to the increasing use of targeted therapies tailored to the biological features of the tumor. Several key signaling pathways have been identified as playing important roles in the development and progression of the disease. These include alterations involving the TP53 gene, activation of PI3K, immune mechanisms regulated by checkpoints, and pathways associated with cell adhesion. Particular significance has been attributed to systems related to the EGFR/HER2 receptor family and angiogenesis controlled by VEGF and its receptors. The EGFR (HER1), HER2, HER3, and HER4 proteins belong to receptor tyrosine kinases that, upon activation, initiate signaling cascades promoting oncogenic transformation. Their overexpression is often associated with more aggressive disease and poorer prognosis. Agents targeting these receptors, such as cetuximab, panitumumab,

and the novel anti-EGFR antibody GC1118, have demonstrated activity in inhibiting tumor cell growth and migration [14].

Despite FDA approval of several molecularly targeted therapies and immunomodulatory drugs, the precise role of these signaling pathways and their interactions with environmental risk factors remain incompletely understood [15]. Given the high complexity of tumor biology, single therapeutic targets may not yield the desired clinical outcomes. To date, most attention has been devoted to therapies targeting HER2, which have shown efficacy in a subset of patients [1].

HER- 2 positive

HER2-positive GC accounts for approximately 15–20% of all cases. Diagnosis is based on an immunohistochemistry (IHC) score of 3+ or 2+ combined with confirmation of gene amplification via fluorescence in situ hybridization (FISH). Confirmation is necessary due to the heterogeneity of HER2 expression in gastric cancer. Studies have shown significant variability in HER2 levels both within tumors and between primary and metastatic sites, which may lead to misclassification for targeted therapy. Additionally, some patients lose HER2 expression after trastuzumab treatment, limiting further therapeutic efficacy. Therefore, reassessment of HER2 status upon disease progression is recommended [17,18].

The groundbreaking phase III ToGA trial demonstrated that combining trastuzumab with chemotherapy provided therapeutic benefits and is now the standard first-line treatment in advanced HER2-positive gastric cancer [16]. Trastuzumab is a humanized monoclonal antibody binding domain 4 of the HER2 receptor extracellular fragment, thereby blocking intracellular signaling activation and inhibiting tumor cell proliferation. Trastuzumab is administered with cisplatin, capecitabine, or 5-fluorouracil (5-FU). The most common adverse effects are heart failure (up to 4.1%), infusion-related reactions such as fever and chills (40–50%), nausea (21%), and rash (7%).

Margetuximab is a next-generation monoclonal antibody against HER2 designed with Fc fragment modification, allowing more effective binding to activating FcγRIIIa (CD16A) receptor regardless of polymorphism. This enhances recruitment of NK cells, macrophages, and monocytes, resulting in stronger antibody-dependent cellular cytotoxicity (ADCC), making this drug a promising option particularly in patients with limited response to trastuzumab [19].

Zanidatamab (ZW25) is a next-generation bispecific monoclonal antibody simultaneously binding two external HER2 receptor domains (II and IV), enabling more effective blockade of proliferative signaling in tumor cells. Early phase I and II clinical trials showed good tolerability and high antitumor activity, including in patients previously treated with anti-HER2 therapy. Ongoing advanced phase III HERIZON-GEA-01 trials are evaluating zanidatamab with chemotherapy ± tislelizumab in first-line treatment of metastatic HER2-positive gastric and gastroesophageal junction adenocarcinoma. While final results are pending, current data indicate a potentially promising clinical profile [20].

KN026 is an innovative bispecific antibody binding two different HER2 receptor epitopes—those targeted by trastuzumab (ECD IV) and pertuzumab (ECD II)—enabling simultaneous mimicry of both therapies. Phase II clinical trials showed an objective response rate (ORR) of 56% in patients with metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma. Currently, phase II/III trial KN026-001 is evaluating survival benefit of adding KN026 to standard chemotherapy after progression on trastuzumab, which could introduce a new effective strategy for patients resistant to existing therapies [21].

Trastuzumab deruxtecan (T-DXd) is a modern form of targeted therapy in the form of an antibody-drug conjugate demonstrating high efficacy in treating advanced HER2-overexpressing gastric cancer. The drug's mechanism involves linking an anti-HER2 antibody with a topoisomerase I inhibitor via a specialized peptide linker, allowing selective release of the cytotoxic agent within the tumor. A characteristic feature of T-DXd is the so-called bystander effect, enabling the elimination of cancer cells with low or absent HER2 expression, representing a significant advantage over earlier agents such as T-DM1 [23].

In the DESTINY-Gastric01 clinical trial conducted in Asia, T-DXd treatment was associated with significant improvement in response rate and overall survival compared to standard chemotherapy in patients whose prior trastuzumab-based therapies had failed. The efficacy of this approach was also confirmed in the DESTINY-Gastric02 trial involving patients from Western countries. In this analysis, T-DXd used as second-line treatment yielded favorable results in disease control and progression-free survival [22].

Moreover, exploratory analyses indicate potential application of the drug in patients with so-called low HER2 expression, which may significantly expand the population benefiting from therapy. Currently, ongoing phase III trials (DESTINY-Gastric03 and Gastric04) aim to further assess T-DXd efficacy in first- and second-line treatment. Existing data suggest this drug could play an important role in transforming treatment paradigms for HER2-positive gastrointestinal cancers in the future [24].

Summary

Gastric cancer (GC) remains a significant global health challenge, ranking among the five most common cancers and four leading causes of cancer-related mortality. Due to frequent diagnosis at advanced stages, patient prognosis is generally poor. Accurate staging is crucial in guiding therapeutic decisions. For advanced GC, chemotherapy based on fluoropyrimidines and platinum compounds forms the cornerstone of treatment. Upon progression, taxanes, irinotecan, or trifluridine-tipiracil are commonly used. Molecular diagnostics, including assessment of HER2, MSI, and EBV status, are playing an increasingly important role, enabling selection of targeted therapies and immunotherapies.

Approximately 15–20% of GC cases exhibit HER2 overexpression. The landmark ToGA trial demonstrated therapeutic benefit of combining trastuzumab with chemotherapy, establishing a new standard of care for HER2-positive GC. Newer HER2-targeted agents, such as trastuzumab deruxtecan (T-DXd), are now being developed, demonstrating activity even in populations with low HER2 levels. DESTINY-Gastric studies confirm the efficacy of T-DXd, making it a promising therapeutic option in subsequent lines of treatment.

Author's contribution:

The authors confirm contribution to the paper as follows:
Conceptualization: Piotr Sobkiewicz
Methodology: Piotr Sobkiewicz, Martyna Grodzińska, Karol Poplicha, Aleksandra Piech
Software: Piotr Sobkiewicz and Marta Jutrzenka
Check: Piotr Sobkiewicz, Maria Ufniarska, Justyna Moszkowicz
Formal analysis: Piotr Sobkiewicz and Aleksandra Piech
Investigation: Tomasz Ufniarski and Piotr Sobkiewicz
Resources: Piotr Sobkiewicz
Data curation: Maria Ufniarska, Aleksandra Piech, Piotr Sobkiewicz and Martyna Grodzińska
Writing - rough preparation: Bartłomiej Siuzdak, Karol Poplicha, Maria Ufniarska
Writing - review and editing: Aleksandra Piech, Patrycja Kardasz, Karolina Pasierb, Jarosław Uciaklak
Visualization: Marta Jutrzenka
Supervision: Piotr Sobkiewicz
Project administration: Martyna Grodzińska

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REFERENCES

1. Luo D, Liu Y, Lu Z, Huang L. Targeted therapy and immunotherapy for gastric cancer: rational strategies, novel advancements, challenges, and future perspectives. Mol Med. 2025 Feb 8;31(1):52. doi:10.1186/s10020-025-01075-y. PMID: 39923010
2. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, Vogel A, Smyth EC; ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022 Oct;33(10):1005–1020. doi:10.1016/j.annonc.2022.07.004. PMID: 35914639
3. Ajani JA, D'Amico TA, Almhanna K, et al. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(2):167–192. PMID: 35130502
4. Bang YJ, Van Cutsem E, Feyereislova A, et al. 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. 2010;376(9742):687–697. doi:10.1016/S0140-6736(10)61121-X. PMID: 20728210

5. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382(25):2419–2430. doi:10.1056/NEJMoa2004413. PMID: 32469182
6. López-Sala P, et al. Gastric adenocarcinoma: A review of the TNM classification system. Radiologia. 2022;64(2):123–134. doi:10.1016/j.rxeng.2022.01.003. PMID: 36842787
7. Kim TH, et al. Revisiting the 8th AJCC system for gastric cancer: current issues and future perspectives. J Gastric Cancer. 2022;22(1):1–10. doi:10.5230/jgc.2022.22.e2. PMID: 35386808
8. Giandola T, Rinzivillo M, Panzuto F, Capurso G. Imaging in gastric cancer: current practice and future perspectives. Diagnostics (Basel). 2023;13(7):1276. doi:10.3390/diagnostics13071276. PMID: 37046494
9. https://www.cancer.gov/types/stomach/stages
10. Shitara K, Matsuo K, Mizota A, Kondo C, Nomura M, Takahari D, Yokota T, Ura T, Ito S, Sawaki A, Tajika M, Kawai H, Muro K. Association of fluoropyrimidines, platinum agents, taxanes, and irinotecan in any line of chemotherapy with survival in patients with advanced gastric cancer. Gastric Cancer. 2011 Jun;14(2):155-60. doi: 10.1007/s10120-011-0019-3. Epub 2011 Feb 23. PMID: 21340668.
11. Kang BW, Kim JG, Kwon OK, Chung HY, Yu W. Non-platinum-based chemotherapy for treatment of advanced gastric cancer: 5-fluorouracil, taxanes, and irinotecan. World J Gastroenterol. 2014 May 14;20(18):5396-402. doi: 10.3748/wjg.v20.i18.5396. PMID: 24833869; PMCID: PMC4017054.
12. Hall PS, Swinson D, Cairns DA, Waters JS, Petty R, Allmark C, Ruddock S, Falk S, Wadsley J, Roy R, Tillett T, Nicoll J, Cummins S, Mano J, Grumett S, Stokes Z, Kamposioras KV, Chatterjee A, Garcia A, Waddell T, Guptal K, Maisey N, Khan M, Dent J, Lord S, Crossley A, Katona E, Marshall H, Grabsch HI, Velikova G, Ow PL, Handforth C, Howard H, Seymour MT; GO2 Trial Investigators. Efficacy of Reduced-Intensity Chemotherapy With Oxaliplatin and Capecitabine on Quality of Life and Cancer Control Among Older and Frail Patients With Advanced Gastroesophageal Cancer: The GO2 Phase 3 Randomized Clinical Trial. JAMA Oncol. 2021 Jun 1;7(6):869-877. doi: 10.1001/jamaoncol.2021.0848. Erratum in: JAMA Oncol. 2021 Aug 1;7(8):1249. doi: 10.1001/jamaoncol.2021.2796. PMID: 33983395; PMCID: PMC8120440.
13. Shitara K, Takashima A, Fujitani K, Koeda K, Hara H, Nakayama N, Hironaka S, Nishikawa K, Makari Y, Amagai K, Ueda S, Yoshida K, Shimodaira H, Nishina T, Tsuda M, Kurokawa Y, Tamura T, Sasaki Y, Morita S, Koizumi W. Nab-paclitaxel versus solvent-based paclitaxel in patients with previously treated advanced gastric cancer (ABSOLUTE): an open-label, randomised, non-inferiority, phase 3 trial. Lancet Gastroenterol Hepatol. 2017 Apr;2(4):277-287. doi: 10.1016/S2468-1253(16)30219-9. Epub 2017 Jan 19. PMID: 28404157.
14. Shitara K, Doi T, Dvorkin M, Mansoor W, Arkenau HT, Prokharau A, Alsina M, Ghidini M, Faustino C, Gorbunova V, Zhavrid E, Nishikawa K, Hosokawa A, Yalçın Ş, Fujitani K, Beretta GD, Cutsem EV, Winkler RE, Makris L, Ilson DH, Tabernero J. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2018 Nov;19(11):1437-1448. doi: 10.1016/S1470-2045(18)30739-3. Epub 2018 Oct 21. Erratum in: Lancet Oncol. 2018 Dec;19(12):e668. doi: 10.1016/S1470-2045(18)30843-X. PMID: 30355453.
15. Zeng Z, Zhu Q. Progress and prospects of biomarker-based targeted therapy and immune checkpoint inhibitors in advanced gastric cancer. Front Oncol. 2024 Jun 14;14:1382183. doi: 10.3389/fonc.2024.1382183. PMID: 38947886; PMCID: PMC11211377.
16. Lei ZN, Teng QX, Tian Q, Chen W, Xie Y, Wu K, Zeng Q, Zeng L, Pan Y, Chen ZS, He Y. Signaling pathways and therapeutic interventions in gastric cancer. Signal Transduct Target Ther. 2022 Oct 8;7(1):358. doi: 10.1038/s41392-022-01190-w. PMID: 36209270; PMCID: PMC9547882.
17. Moehler M, Oh DY, Kato K, Arkenau T, Tabernero J, Lee KW, Rha SY, Hirano H, Spigel D, Yamaguchi K, Wyrwicz L, Disel U, Pazo-Cid RA, Fornaro L, Xu Y, Sheng T, Yang S, Kadva A, Cruz-Correa M, Xu RH. First-Line Tislelizumab Plus Chemotherapy for Advanced Gastric Cancer with Programmed Death-Ligand 1 Expression ≥ 1%: A Retrospective Analysis of RATIONALE-305. Adv Ther. 2025 May;42(5):2248-2268. doi: 10.1007/s12325-025-03133-7. Epub 2025 Mar 13. PMID: 40075025; PMCID: PMC12006226.
18. Zhang H, Wang Y, Wang Y, Wu D, Lin E, Xia Q. Intratumoral and intertumoral heterogeneity of HER2 immunohistochemical expression in gastric cancer. Pathol Res Pract. 2020 Nov;216(11):153229. doi: 10.1016/j.prp.2020.153229. Epub 2020 Sep 21. PMID: 33010699.
19. Lee HE, Park KU, Yoo SB, Nam SK, Park DJ, Kim HH, Lee HS. Clinical significance of intratumoral HER2 heterogeneity in gastric cancer. Eur J Cancer. 2013 Apr;49(6):1448-57. doi: 10.1016/j.ejca.2012.10.018. Epub 2012 Nov 9. PMID: 23146959.
20. Zhou Y, Wang X, Chen Y. Margetuximab: An active alternative for later-line therapy in patients with HER2-positive advanced breast cancer. MedComm (2020). 2023 Jul 4;4(4):e322. doi: 10.1002/mco2.322. PMID: 37409110; PMCID: PMC10318489.
21. Elimova E, Ajani J, Burris H, Denlinger CS, Iqbal S, Kang YK, Kim JH, Lee KW, Lin B, Mehta R, Oh DY, Rha SY, Seol YM, Yang L, Ozog MA, Garfin PM, Ku G. Zanidatamab plus chemotherapy as first-line treatment for patients with HER2-positive advanced gastro-oesophageal adenocarcinoma: primary results of a multicentre, single-arm, phase 2 study. Lancet Oncol. 2025 May 30:S1470-2045(25)00287-6. doi: 10.1016/S1470-2045(25)00287-6. Epub ahead of print. PMID: 40473445.

22. Liu D, Gong J, Li J, Qi C, Niu Z, Liu B, Peng Z, Luo S, Wang X, Wang Y, Zhao R, Chen L, Deng T, Li Z, Chen L, Fang M, Yang H, Lu L, Zhang Y, Kang F, Xu T, Zhang X, Shen L. Efficacy and safety of KN026, a bispecific anti-HER2 antibody, in combination with KN046, an anti-CTLA4/PD-L1 antibody, in patients with advanced HER2-positive nonbreast cancer: a combined analysis of a phase Ib and a phase II study. Signal Transduct Target Ther. 2025 Mar 19;10(1):104. doi: 10.1038/s41392-025-02195-x. PMID: 40108113; PMCID: PMC11923254.
23. Van Cutsem E, di Bartolomeo M, Smyth E, Chau I, Park H, Siena S, Lonardi S, Wainberg ZA, Ajani J, Chao J, Janjigian Y, Qin A, Singh J, Barlaskar F, Kawaguchi Y, Ku G. Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal 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 Oncol. 2023 Jul;24(7):744-756. doi: 10.1016/S1470-2045(23)00215-2. Epub 2023 Jun 14. PMID: 37329891; PMCID: PMC11298287.
24. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, Chung HC, Kawakami H, Yabusaki H, Lee J, Saito K, Kawaguchi Y, Kamio T, Kojima A, Sugihara M, Yamaguchi K; DESTINY-Gastric01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med. 2020 Jun 18;382(25):2419-2430. doi: 10.1056/NEJMoa2004413. Epub 2020 May 29. PMID: 32469182.
25. Kawakami H, Nakanishi K, Makiyama A, Konishi H, Morita S, Narita Y, Sugimoto N, Minashi K, Imano M, Inamoto R, Kodera Y, Kume H, Yamaguchi K, Hashimoto W, Muro K; EN-DEAVOR Study Group. Real-world effectiveness and safety of trastuzumab-deruxtecan in Japanese patients with HER2-positive advanced gastric cancer (EN-DEAVOR study). Gastric Cancer. 2025 Jan;28(1):51-61. doi: 10.1007/s10120-024-01555-w. Epub 2024 Oct 10. Erratum in: Gastric Cancer. 2025 Jan;28(1):62. doi: 10.1007/s10120-024-01570-x. PMID: 39387986; PMCID: PMC11706843.