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Review Article

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Emerging Targets for Systemic Treatment of Gastric Cancer: HER2 and Beyond

In-Ho Kim [1,2,3]

[1]Division of Medical Oncology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Department of Gastric Cancer Centre, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[3]Cancer Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

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Correspondence to
In-Ho Kim
Division of Medical Oncology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea.
Email: ihkmd@catholic.ac.kr

ORCID iDs
In-Ho Kim
https://orcid.org/0000-0002-0351-2074

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ABSTRACT

In recent years, remarkable progress has been made in the molecular profiling of gastric cancer. This progress has led to the development of various molecular classifications to uncover subtype-specific dependencies that can be targeted for therapeutic interventions. Human epidermal growth factor receptor 2 (HER2) is a crucial biomarker for advanced gastric cancer. The recent promising results of novel approaches, including combination therapies or newer potent agents such as antibody-drug conjugates, have once again brought attention to anti-HER2 targeted treatments. In HER2-negative diseases, the combination of cytotoxic chemotherapy and programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) inhibitors has become the established standard of care in first-line settings. In the context of gastric cancer, potential biomarkers such as PD-L1 expression, Epstein-Barr virus, microsatellite instability, and tumor mutational burden are being considered for immunotherapy. Recently, promising results have been reported in studies on anti-Claudin18.2 and fibroblast growth factor receptor 2 treatments. Currently, many ongoing trials are aimed at identifying potential targets using novel approaches. Further investigations will be conducted to enhance the progress of these therapies, addressing challenges such as primary and acquired resistance, tumor heterogeneity, and clonal evolution. We believe that these efforts will improve patient prognoses. Herein, we discuss the current evidence of potential targets for systemic treatment, clinical considerations, and future perspectives.

Keywords: Gastric cancer; Molecular targeted therapy; Immunotherapy

INTRODUCTION

Gastric cancer is the fifth most prevalent cancer and the fourth leading cause of cancer-related deaths worldwide, representing 5.6% new cancer cases reported in 2020 and 7.7% cancer-related mortality [1]. The incidence of gastric cancer is high in males, with the highest rates observed in Eastern and Central Asia as well as Latin America [2]. Gastric cancers can be categorized based on their primary locations in the stomach. While most cases occur in the distal stomach (non-cardia), approximately 20% gastric cancers arise in the cardia, which is the part of the stomach adjacent to the gastroesophageal junction (GEJ) [3].

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The etiology of gastric cancer remains unknown, although chronic gastritis may be responsible for the cellular changes that lead to malignant transformation [4]. Both anatomical subsites (cardia and non-cardia) share common risk factors such as salt-preserved or smoked foods, alcohol, and smoking [5]. However, they also have distinct etiologies. Cardia gastric cancer is associated with obesity and gastroesophageal reflux disease (GERD), whereas 90% non-cardia cancers can be attributed to *Helicobacter pylori* infection [6]. The global incidence of gastric cancer has steadily declined due to preventive strategies, treatment of *H. pylori* infection, and diet or lifestyle modifications. However, the incidence of proximal gastric and GEJ cancers has increased, which can be attributed to factors such as obesity and inadequately managed GERD [7].

Traditionally, gastric cancer has been classified based on histopathological and morphological features. The histological classification according to Lauren's criteria, has been widely used to categorize gastric cancer into intestinal (approximately 50%), diffuse (30%), and indeterminate (20%) types [8]. The diffuse-type tends to occur in young patients and females, while intestinal-type gastric cancer typically occurs in elderly patients and males [9-11].

However, histological classification is inadequate for identifying actionable molecular targets. To address this limitation, extensive molecular profiling has led to the development of various molecular-based classifications to uncover subtype-specific dependencies that can be targeted for therapeutic interventions. The Cancer Genome Atlas (TCGA) suggests a molecular classification that categorizes gastric cancer into 4 subtypes: Epstein-Barr virus (EBV)-associated (10%), microsatellite instability (MSI, 20%), chromosomal instability (CIN, 50%), and genomically stable (GS, 20%) [12]. Based on the findings of this study, a relationship was observed between the type of CIN and intestinal histology as well as between the type of GS and diffuse histology. A previous study using gene expression data from TCGA cohort revealed that the EBV and GS subtypes had the best and the worst prognosis, respectively [13]. This study also reported that the CIN and GS subtypes benefitted the most and the least from adjuvant chemotherapy, respectively. Another study suggested that CIN gastric cancer frequently exhibits amplification of genes encoding receptor tyrosine kinases (RTKs), such as epidermal growth factor receptor (EGFR), fibroblast growth factor receptor 2 (FGFR2), human epidermal growth factor receptor 2 (HER2), and mesenchymal–epithelial transcription factor (MET) [14]. Another study conducted by the Asian Cancer Research Group proposed a molecular classification system that categorized gastric cancer into 4 subtypes: microsatellite stable (MSS)/TP53−, MSS/TP53+, MSI, and MSS/EMT [15]. The findings of this study indicate that the MSS/EMT subtype tends to occur at a younger age, with majority (>80%) of patients in this subtype being diagnosed with diffuse-type gastric cancer at stages 3 or 4. In contrast, the MSI subtype primarily occurs in the antrum (75%) and is associated with the intestinal subtype (>60%) and stages 1 or 2 (>50%). Additionally, EBV infection is more frequent in the MSS/TP53+ group compared to that in the other groups.

With a clear understanding of the molecular profile of gastric cancer, extensive research has been conducted to identify novel targets. This led to the success of the Trastuzumab for Gastric Cancer (ToGA) trial for HER2-positive gastric cancer [16]. Subsequently, numerous clinical trials focusing on molecularly driven treatment approaches have been conducted, although most have yielded disappointing results. However, recent studies have reported promising results with the development of new potent agents that are being investigated in clinical trials with more detailed biomarker selection and statistical analyses. In addition to HER2, programmed cell death ligand 1 (PD-L1) has become a biomarker for programmed

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cell death 1 (PD-1)/PD-L1 inhibitors, and EBV/MSI/tumor mutational burden (TMB) is a widely accepted predictive biomarker for immune checkpoint inhibitors (ICIs). In addition to immunotherapy, emerging treatments targeting Claudin18.2 (CLDN18.2) and FGFR2 have shown promising results in clinical trials. Furthermore, new anti-HER2 treatments have shown encouraging outcomes.

This review focuses on the current and emerging biomarkers for the systemic treatment of gastric cancer, highlighting important aspects relevant to clinical utility.

HER2: BEYOND TRASTUZUMAB

HER2, also known as Neu or ErbB2, is a member of the EGFR family, which is located on chromosome 17 (17q21) in humans and encodes the transmembrane glycoprotein p185 [17]. The HER family comprises 4 subtypes: EGFR (also known as HER1), HER2, HER3, and HER4. HER protein activation through ligand-induced homo- or heterodimerization initiates a downstream phosphorylation signaling cascade that leads to cellular growth, proliferation, and differentiation [18]. Various alterations in HER2, such as overexpression, amplification, and other mutations, have been observed in several solid tumors [19]. In gastric cancer, HER2 overexpression is observed in approximately 10-20% of overall, 30% of intestinal type, 15% of mixed type, and around 5% of diffuse type tumors and more commonly reported (30%) in proximal tumor [20]. The signet ring type is typically negative for HER2. Two previous meta-analyses have suggested that HER2 expression is associated with male sex, differentiated tumors, intestinal type, and lymph node metastasis [21,22]. The correlation between HER2 and PD-L1 expression is unclear, given the inconsistent results reported in previous studies [23-26]. The presence of MSI-high was less frequent in HER2-positive tumors than that in HER2-negative tumors [27,28]. And the prognostic value of HER2 remains controversial [21,29-31].

HER2 status should be assessed before initiating systemic therapy and, if possible, re-evaluated for recurrent and metastatic lesions [32]. Immunohistochemistry (IHC) score of 3+ indicates a positive result for HER2 overexpression, whereas a score of 0–1+ indicates a negative result. An IHC score of 2+ is considered equivocal and should be followed by in situ hybridization (ISH). The region with the highest IHC intensity should be selected for ISH and stained for HER2 and chromosome enumeration probe (CEP) 17. The criterion for HER2 amplification is a HER2:CEP17 ratio of ≥2. If CEP17 polysomy is present and the ratio is <2, an average HER2 signal >6 is interpreted as a positive result. Currently, HER2-positive status is usually defined as an IHC score of 3+ or 2+ with positive ISH results [33].

Trastuzumab, the first successful targeted agent against HER2, has demonstrated clinical benefits in the treatment of advanced gastric cancer. The ToGA trial (NCT01041404), a phase 3 randomized controlled trial, compared trastuzumab with chemotherapy (cisplatin/fluorouracil [FP] or capecitabine [XP]) and chemotherapy alone [16]. The results showed a median overall survival (OS) of 13.8 months in the trastuzumab with chemotherapy group compared to 11.1 months in the chemotherapy alone group (hazard ratio [HR] 0.74, 95% confidence interval [CI], 0.60-0.91) [16]. In a pre-planned exploratory analysis, trastuzumab with chemotherapy significantly improved OS compared to chemotherapy alone in patients with HER2 IHC 3+ or 2+ and FISH-positive (median: 16.0 vs. 11.8 months). However, phase 3 trials investigating other HER2 targeted therapies, such as pertuzumab, lapatinib, and

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trastuzumab emtansine (T-DM1), have failed to demonstrate clinical benefits in advanced gastric cancer [34-37]. This discrepancy may be mainly attributed to intra- and inter-tumoral heterogeneity in HER2 expression and amplification in gastric cancer [38]. Previous studies have shown that approximately 30%–60% patients with HER2-positive gastric cancer exhibit intra-tumoral heterogeneity in HER2 overexpression and gene amplification, which is a crucial predictor of trastuzumab-based chemotherapy [39,40]. Furthermore, other studies have reported inter-tumoral and intra-tumoral heterogeneity in 30% and 50% cases, respectively [41]. To address these challenges, there are several recommendations for HER2 testing [42,43] and some studies have suggested that the diagnosis of HER2 positivity in gastric cancer necessitates the acquisition of minimum 4 biopsy specimens and HER2 IHC test should be conducted on both biopsy/resection specimens and primary/metastatic sites [44,45]. In addition to the presence of HER2 heterogeneity, previous reports have suggested HER2 downregulation following progression to trastuzumab, as well as diverse intra-tumoral variations in molecular characteristics [46,47]. Several studies have indicated that approximately 30%–60% patients experiencing disease progression after treatment with trastuzumab-based therapies present HER2 downregulation [48-50]. And the resistance to anti-HER2 treatment can be attributed to the modification of the HER2 downstream signaling pathway, such as the RAS-PI3K signaling pathway, as well as the simultaneous amplification of EGFR, MET, and CCNE1 [51-53]. Consequently, reassessing HER2 status and other molecular alterations following anti-HER2 treatment in subsequent clinical trials, particularly in second- or subsequent-line settings, may be crucial. Fortunately, several emerging strategies targeting anti-HER2, including antibody-drug conjugates (ADCs) and newly engineered agents that have demonstrated promising activity, have aimed to address these challenges.

Trastuzumab deruxtecan (T-DXd), a particularly promising ADC, consists of a humanized anti-HER2 antibody, an enzymatically cleavable peptide linker, and an exatecan-derivative topoisomerase I inhibitor (DXd) [54]. Trastuzumab deruxtecan exhibits a higher drug-to-antibody ratio than other ADCs, with a maximum of 8 DXd molecules per antibody. These molecules are stabilized in the plasma by a unique tetrapeptide linker and can be selectively cleaved by enzymes that are upregulated in tumor cells, enabling targeted local delivery of the payload [55]. Furthermore, the membrane-permeable payloads diffuse into neighboring cells, thereby addressing tumor heterogeneity through a “bystander” effect [56]. The safety and preliminary efficacy of trastuzumab deruxtecan were investigated in a phase 1 study on HER2-expressing advanced solid tumors [57]. Among the 44 patients with HER2-positive gastric cancer included in this study, objective response rates (ORRs) of 43.2% and manageable safety profiles were reported. In the DESTINY-Gastric01 trial (NCT03329690), a phase 2 study comparing trastuzumab deruxtecan to chemotherapy in heavily treated patients (3rd line or higher) with HER2-positive advanced gastric cancer, trastuzumab deruxtecan demonstrated superior efficacy compared to chemotherapy [58]. In the primary cohort of patients with HER2-high positive disease (IHC 3+ or 2+/ISH-positive), the trastuzumab deruxtecan arm showed an ORR of 51%, compared to 14% in the chemotherapy arm. The OS was significantly longer with trastuzumab deruxtecan than that with chemotherapy, with a median of 12.5 versus 8.4 months, respectively (HR, 0.59; 95% CI, 0.39–0.88). Notable toxicities observed were myelosuppression and interstitial lung disease. In the exploratory cohort of patients with HER2-low positive disease (IHC 2+/ISH-negative or IHC 1+), the ORR were 26.3% and 9.5% in the IHC 2+/ISH-negative and IHC 1+ groups, respectively. These findings suggest that trastuzumab deruxtecan has potential activity against HER2-low positive gastric cancer. The effectiveness of trastuzumab deruxtecan as a second-line

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treatment for HER2-positive advanced gastric cancer in patients from the USA and Europe was evaluated in DESTINY-Gastric02 (NCT04014075), a single-arm, phase 2 study [59]. The study revealed that 42% patients achieved an objective response, with 5% experiencing a complete response (CR). The most common severe treatment-related adverse event (TRAEs) observed was myelosuppression, and two patients (3%) experienced treatment-related deaths due to interstitial lung disease or pneumonitis. Based on these findings, the FDA approved trastuzumab deruxtecan for the treatment of patients with HER2-positive gastric cancer who had previously received a trastuzumab-based regimen. Currently, the ongoing randomized phase 3 trial, DESTINY-Gastric04 (NCT04704934), is comparing the efficacy and safety of trastuzumab deruxtecan to the combination of ramucirumab and paclitaxel in the second-line treatment of patients with HER2-positive gastric cancer [60]. Disitamab vedotin (RC48-ADC), which also targets HER2, consists of a monoclonal antibody, disitamab, conjugated to the cytotoxic agent monomethyl auristatin E (MMAE) via a cleavable linker [61]. Disitamab specifically targets different epitopes of the HER2 receptor and has a higher molecular affinity for HER2 than trastuzumab [62]. The linker used was valine-citrulline, which is stable but can be cleaved by cathepsins in lysosomes after disitamab vedotin is endocytosed, resulting in MMAE release and the subsequent killing of HER2-overexpressing cancer cells [63]. RC48-C008, a single-arm phase 2 study (NCT03556345), was conducted to assess the efficacy and safety of disitamab vedotin in heavily treated patients with HER2-overexpressing gastric cancer who had received at least two prior systemic treatments [64]. Among 125 patients, the ORR was 24.8%. The median progression free survival (PFS) and OS were 4.1 and 7.9 months, respectively. The most commonly reported TRAEs are leukopenia, fatigue, and alopecia. Currently, a randomized phase 3 study (NCT04714190), RC48-C007, is ongoing, comparing disitamab vedotin to the physician-selected standard treatment in patients with advanced gastric cancer with HER2 overexpression who have had progression or intolerance after at least two systemic treatments. Currently, several newer ADCs targeting HER2 are being developed in many clinical trials.

In addition to ADCs, trials on novel anti-HER2 antibodies are ongoing. Zanidatamab (ZW25) is a humanized bispecific antibody that targets the juxtamembrane extracellular and dimerization domains of HER2, similar to trastuzumab and pertuzumab, respectively [65]. Zanidatamab has a unique binding mechanism, allowing it to bind to both low and high levels of HER2 expression and induce unique clustering and internalization of the HER2 receptor [66]. A phase 2 trial (NCT03929666) has recently reported the safety and efficacy of zanidatamab in combination with chemotherapy as a first-line treatment for HER2-expressing advanced gastric cancer [67]. Among the 46 patients, zanidatamab with chemotherapy resulted in an ORR of 79% and a disease control rate (DCR) of 92%. The 18- and 12-month OS rates in 42 patients were 84% and 88%, respectively. Currently, an ongoing phase 3 randomized clinical trial, HERIZON-GEA-01 (NCT05152147), investigates first-line zanidatamab in combination with chemotherapy with or without tislelizumab in patients with HER2-expressing advanced gastric cancer. Margetuximab (MGAH22) is a chimeric monoclonal antibody that targets HER2 and has similar specificity and affinity to trastuzumab. It has an engineered Fc domain that enhances binding to both alleles of human CD16A, resulting in enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) against HER2-positive tumors, including those with low HER2 expression, independent of the FcrR variant in the effector cells [68]. CP-MGAH22–05 (NCT02689284) is a single-arm, open-label, phase 1b–2 dose-escalation, and cohort expansion study that evaluated margetuximab plus pembrolizumab in 95 previously-treated patients with HER2-positive, PD-L1-unselected advanced gastric cancer [69]. In the dose-escalation phase, no dose-limiting

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toxicities were observed and the most common grade 3 or higher TRAEs were anemia and infusion-related reactions. No treatment-related deaths occurred. Among the 92 patients evaluated, the ORR was 18.5%. Based on these results, the FDA granted margetuximab an orphan drug designation for treating patients with advanced gastric cancer. Currently, an ongoing randomized phase 2/3 trial, MAHOGANY (NCT04082364), investigates the use of margetuximab in combination with an ICI, with or without chemotherapy, in treatment-naïve patients with HER2-positive advanced gastric cancer [70].

Several studies on small-molecule inhibitors are ongoing. Tucatinib, an oral RTK inhibitor, is being studied for its high selectivity for the kinase domain of HER2, while having a minimal impact on EGFR inhibition [71]. Currently, clinical trials of tucatinib in combination with trastuzumab and chemotherapy are ongoing as first- and second-line treatments for advanced gastric cancer [72,73]. Additionally, other agents, such as afatinib and pyrotinib, are under investigation.

Evaluation of combination therapies involving anti-HER2 treatment and other agents is currently underway, and a combination strategy involving ICIs holds great promise. Trastuzumab may induce PD-L1 upregulation, suggesting a potential resistance mechanism [74]; therefore, investigating the potential synergistic effects of anti-HER2 treatment and PD-1/PD-L1 inhibitors is deemed valuable. The KEYNOTE-811 study (NCT03615326), a randomized phase 3 trial, assessed the use of pembrolizumab or placebo in combination with trastuzumab and chemotherapy (FP or capecitabine/oxaliplatin [XELOX]) as a first-line treatment for advanced HER2-positive gastric cancer [75]. Notably, 85% patients in both pembrolizumab and placebo groups had a PD-L1 combined positive score (CPS) ≥1. At the third interim analysis, with a median follow-up of 38.4 months in the pembrolizumab group and 38.6 months in the placebo group, the median PFS was 10.0 months compared to 8.1 months (HR, 0.73; 95% CI, 0.61–0.87). In the subgroup analysis based on PD-L1 status (CPS ≥1 or <1), PFS was longer in the pembrolizumab group compared to the placebo group for patients with PD-L1 CPS ≥1 (median: 10.9 vs. 7.3 months; HR, 0.71; 95% CI, 0.59–0.86), but there was no significant difference in the population with a PD-L1 CPS <1 (median: 9.5 vs. 9.5 months; HR, 1.03; 95% CI, 0.65–1.64). The ORR was higher in the pembrolizumab group than that in the placebo group (72.6 vs. 59.8%). The median OS was 20.0 and 16.8 months in the pembrolizumab and placebo groups, respectively (HR, 0.84; 95% CI, 0.70–1.01). These results did not meet the predetermined criteria for significance and the final analysis will be continued. Grade 3 or higher TRAE occurred in 58% and 51% patients in the pembrolizumab group and placebo groups, respectively, with no new safety concerns observed. Recently, the ESMO guideline recommended the pembrolizumab, trastuzumab and chemotherapy as the first-line treatment in patients with HER2-positive and PD-L1 CPS ≥1. At present, several trials of ICI in combination with several other anti-HER2 agents, such as T-DXd, ZW25, and margetuxumab, are ongoing for HER2-positive gastric cancer treatment.

Anti-angiogenic treatment may play a role in combination with anti-HER2 treatment in HER2-positive gastric cancer. Anti-angiogenic treatment plays a significant role in the systemic treatment of advanced gastric cancer. According to the RAINBOW and REGARD trials, ramucirumab, a monoclonal antibody targeting the extracellular domain of vascular endothelial growth factor receptor 2 (VEGFR2), is the standard of care in combination with paclitaxel or monotherapy as a second-line treatment [76,77]. However, the results of other trials involving anti-angiogenic agents, either alone or in combination with cytotoxic chemotherapy, have been disappointing [78-81]. Angiogenesis plays a crucial

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role in anti-HER2 resistance, including the interplay between angiogenesis and the HER2 signaling pathways [82-84]. A previous study evaluating the combination of bevacizumab, trastuzumab, and chemotherapy demonstrated notable efficacy and safety [85]. The recent HER-RAM trial (NCT04888663), which investigated the combination of trastuzumab, ramucirumab, and paclitaxel as second-line treatment in patients who progressed after first-line trastuzumab-based treatment for HER2-positive gastric cancer, showed promising results [86]. The ORR and DCR were 54% and 96%, respectively, with a median PFS of 7.1 months and an of OS 13.6 months. Interestingly, loss of HER2 expression was observed in 34.8% patients after first-line trastuzumab-based treatment, and no clear association between HER2 expression and outcome was found. These approaches may provide valuable insights for overcoming HER2 downregulation after anti-HER2 treatment.

Additionally, several treatment strategies such as anti-HER2 chimeric antigen receptor-T (CAR-T) therapy and vaccines, newer ADCs, and combination therapies are emerging. Future results should be noted.

IMMUNOTHERAPY

Immunotherapy has completely changed the trends in cancer treatment over the past decade. Among the various immunotherapies, ICIs, such as PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 inhibitors, have been extensively studied and have now become the standard treatment for many types of cancer. Numerous studies have been conducted to identify predictive biomarkers for ICIs. MSI-high/mismatch repair deficiency (MMRd) and EBV positivity are recognized as biomarkers in gastric cancer, while TMB-high is considered a tumor-agnostic biomarker for ICIs. In recent large-scaled phase 3 trials, PD-L1 expression was proposed as a biomarker for PD-1/PD-L1 inhibitors in gastric cancer [87,88].

The presence of MSI-high was observed in 10%–20% patients with gastric cancer [12]. A previous meta-analysis has indicated that MSI-high is associated with female, advanced age, intestinal Laurén histological type, gastric body/antrum location, early stage, lower rates of nodal metastasis, and a better prognosis [89]. Previous studies have reported that PD-L1 expression is more frequently observed in MSI-high tumors than in MSS tumors [90,91]. Several studies have shown high concordance between MSI-high detected by PCR or next-generation sequencing (NGS) and MMRd detected by IHC [92-94], although discordant results between these testing methods remain a challenging issue. It is well established that there is a significant overlap between MSI-high and TMB-high tumors [95].

TMB was initially identified through whole-exome sequencing, but because of its technical complexity and high cost, comprehensive gene panels using NGS have been used as substitutes in clinical settings [96]. TMB-high is considered a tumor-agnostic biomarker for immunotherapy [97], and a previous retrospective pooled analysis of 12 trials reported that TMB-high is associated with a significant improvement in pembrolizumab efficacy [98]. Moreover, a recent explorative analysis [99] from the KEYNOTE-062 trial [100] showed that TMB-high is significantly associated with clinical outcomes in patients treated with pembrolizumab and pembrolizumab with chemotherapy (ORR, PFS, and OS; all $P<0.05$), but not with chemotherapy. However, the detection methods and cutoff values for TMB are different across numerous studies and tumor types, making standardization of TMB identification a challenging issue [96]. Previous studies have indicated that the role of TMB

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as a biomarker for ICI is uncertain, particularly when tumors with MSI-high are excluded [101,102]. A previous study indicated that TMB-high in 8.3% gastric cancer cases. However, when excluding those with MSI-high, TMB-high is observed in only 1.7% cases [103].

EBV-associated gastric cancer exhibits a distinct CpG island methylator phenotype that differs from MSI-high tumors and frequently harbors mutations in PIK3CA and ARID1A, as well as JAK2 amplification [12,104,105]. EBV-associated gastric cancer is observed in approximately 10% patients [12,106]. Generally, EBV status is determined using EBV-encoded RNA ISH [107]. Previous studies have proposed that the clinical presentation of EBV-associated gastric cancer is more common in men, occurs at a relatively younger age, primarily affects the gastric cardia/body, and exhibits submucosal invasion with a low lymph node metastasis rate [108]. EBV-associated and MSI-high gastric cancers are mutually exclusive [109,110]. Furthermore, EBV-associated gastric cancer is characterized by high PD-L1 expression and immune cell infiltration within the tumor [12,111]. A previous study reported a 100% (6/6) ORR for pembrolizumab in patients with EBV-associated gastric cancer [112]. Another study demonstrated that 8 patients with EBV-associated gastric cancer with measurable lesions achieved 100% DCR following ICI treatment.

PD-L1 expression has been extensively studied in many cancers, including gastric cancer. Studies have reported that PD-L1 expression is elevated in approximately 30%–60% gastric cancer cases [87,88,113]. IHC was primarily used to detect PD-L1 expression. However, assessing PD-L1 status poses several challenges, such as using different antibodies for ICIs (such as 28-8, 22C3, and SP263 assays), scoring methods (such as CPS, tumor positive score [TPS], and tumor area positivity [TAP]), and determining the cut-off value. PD-L1 expression is more likely to be elevated in EBV-positive and MSI-high gastric cancers because of increased inflammation and immune cell infiltration [114]. However, the correlation between PD-L1 expression and gastric cancer remains unclear [115-118].

Immunotherapy was first investigated as PD-1/PD-L1 inhibitor monotherapy in patients with advanced gastric cancer. Several studies have compared PD-1/PD-L1 inhibitors with other chemotherapies [113,119] or the best supportive care [120,121] for previously treated patients. Maintenance of PD-L1 inhibitor monotherapy has been assessed in a first-line setting [122]. Nevertheless, trials on PD-1/PD-L1 inhibitor monotherapy have demonstrated only minimal efficacy or lack evidence of clinical benefit. These findings prompted a combination treatment approach for patients who have not previously received systemic treatment.

The CheckMate 649 trial (NCT02872116), the first successful combination of a PD-1 inhibitor and chemotherapy, assessed the clinical benefit of first-line nivolumab in combination with chemotherapy (XELOX or fluorouracil/leucovorin/oxaliplatin [FOLFOX]) in patients with HER2-negative advanced gastric cancer [87]. The primary endpoints for comparing nivolumab plus chemotherapy vs. chemotherapy alone were OS or PFS in patients with a tumor PD-L1 CPS ≥5. The combination of nivolumab and chemotherapy demonstrated significant improvements in OS (median: 14.4 vs. 11.1 months; HR, 0.71; 98.4% CI, 0.59–0.86) and PFS (median: 7.7 vs. 6.0 months; HR, 0.68; 98% CI, 0.56–0.81) in patients with a tumor PD-L1 CPS ≥5. The KEYNOTE-859 trial (NCT03675737) evaluated the efficacy and safety of chemotherapy (FP or XELOX) with pembrolizumab or placebo in patients with HER2-negative advanced gastric cancer [88]. The primary endpoint was OS in the intention-to-treat (ITT), PD-L1 CPS ≥1, and PD-L1 CPS ≥10 populations. Median OS was longer in the pembrolizumab group than that in the placebo group in the ITT (median:

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12.9 vs. 11.5 months; HR, 0.78; 95% CI, 0.70–0.87), PD-L1 CPS ≥1 (13.0 vs. 11.4 months; HR, 0.74; 95% CI, 0.65–0.84), and PD-L1 CPS ≥10 (15.7 vs. 11.8 months; HR, 0.65; 95% CI, 0.53–0.79) populations. These two studies did not identify any new safety concerns. Although the CheckMate 649 and KEYNOTE-859 trials shared similar designs, they have subtle distinctions. The CheckMate 649 trial assessed the primary endpoint in a PD-L1 CPS ≥5 population, while the KEYNOTE-859 trial evaluated the primary endpoint in the ITT, PD-L1 CPS ≥1, and CPS ≥10 populations. PD-L1 IHC was performed using the 28-8 and 22C3 pharmDx assays in the CheckMate 649 and KEYNOTE-859 trials, respectively. Additionally, the chemotherapy backbones used were oxaliplatin in the CheckMate 649 trial and cisplatin or oxaliplatin in the KEYNOTE-859 trial. In clinical practice, clinicians should consider these differences when making decisions regarding patient selection and treatment regimens.

The clinical benefits of combining PD-1 inhibitors with chemotherapy in patients with low PD-L1 expression are intriguing. For patients with a PD-L1 CPS <1 in CheckMate 649 trial, the unstratified HR for OS and PFS when comparing nivolumab with chemotherapy vs. chemotherapy alone were 0.92 (95% CI, 0.70–1.23) and 0.93 (95% CI, 0.69–1.26), respectively. Similarly, the unstratified HR for OS and PFS when comparing nivolumab with chemotherapy vs. chemotherapy alone were 0.94 (95% CI, 0.78–1.13) and 0.93 (95% CI, 0.76–1.12) for patients with a PD-L1 CPS <5, respectively. Also, in KEYNOTE-859 trials, post-hoc analysis for OS of participants with a PD-L1 CPS <1 and 10, HR for OS when comparing pembrolizumab with chemotherapy vs. chemotherapy alone were 0.92 (95% CI, 0.73–1.17) and 0.86 (95% CI, 0.75–0.98), respectively. A recent pooled analysis of CheckMate-649 [87], KEYNOTE-062 [100], and KEYNOTE-590 (only adenocarcinoma was included) [123] suggested a lack of benefit in the addition of PD-1 inhibitors to chemotherapy in low PD-L1–expressing gastric or esophageal adenocarcinoma [124].

Subgroup analysis based on MSI status was conducted in both the CheckMate 649 and KEYNOTE-859 trials. As anticipated, the clinical benefits in terms of OS were more pronounced for nivolumab in the MSI-high group (unstratified HR, 0.37; 95% CI, 0.16–0.87) compared to that in the MSS group (HR, 0.80; 95% CI, 0.71–0.91) in the CheckMate 649 trial. Similarly, the KEYNOTE-859 trial also demonstrated a more pronounced clinical benefit in terms of OS for pembrolizumab in the MSI-high group (HR, 0.34; 95% CI, 0.18–0.66) compared to the MSS group (HR, 0.79; 95% CI, 0.70–0.89).

In addition to the CheckMate 649 and KEYNOTE-859 trials, several ongoing trials are investigating the use of first-line PD-1/PD-L1 inhibitors with chemotherapy in patients with HER2-negative gastric cancers and promising results have been reported recently [125,126]. Furthermore, there are several ongoing trials exploring the combination of PD-1/PD-L1 inhibitors with other ICI and/or target agents for HER2, VEGF, and other pathways [70,75,127-130].

Several trials have been conducted on immunotherapy for advanced gastric cancer in the perioperative setting. In the adjuvant strategy, ATTRACTION-5 (NCT03006705), a double-blind, randomized, phase 3 study conducted in East Asia, investigated adjuvant chemotherapy with nivolumab or placebo in patients with pathological stage 3 gastric cancer who had undergone D2 or more extended gastrectomy [131]. Unfortunately, the primary endpoint, relapse free survival (RFS) was not met (HR, 0.90; 95.72% CI, 0.69–1.18), with the 3-year RFS rates of 68.4% in the nivolumab with chemotherapy arm and 65.3% in the placebo with chemotherapy arm. In the neoadjuvant setting, two large-scaled phase 3 trials are ongoing. KEYNOTE-585 (NCT03221426) evaluated neoadjuvant/adjuvant chemotherapy

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(fluorouracil/leucovorin/oxaliplatin/docetaxel [FLOT] or FP) with pembrolizumab or placebo, followed by pembrolizumab or placebo in locally advanced resectable gastric cancer [132]. This study showed that pembrolizumab treatment significantly improved the pathological CR rate (13.0% vs. 2.4%), with no significant improvement in event-free survival (EFS), compared to the placebo arm. The MATTERHORN trial (NCT04592913) investigated neoadjuvant/adjuvant chemotherapy (FLOT) with durvalumab or placebo followed by adjuvant durvalumab or placebo in locally advanced, resectable gastric cancer [133]. The addition of durvalumab to perioperative FLOT statistically significantly improved the pathological CR rates (19.2% vs. 7.2%). This study is ongoing to determine the primary endpoint of EFS.

CLAUDIN18.2 (CLDN18.2)

CLDNs, crucial components of tight junctions, are transmembrane proteins with extracellular loops, which are potential targets for diagnosis and treatment [134]. Currently, the CLDN family has 27 identified members, and cancer cells exhibit a specific claudin expression pattern based on tumor cell origin [135]. CLDN18 isoform 2 (CLDN18.2) is a highly selective marker protein expressed exclusively in differentiated gastric mucosal membrane epithelial cells, but not routinely in normal tissues outside the gastric mucosa [136]. When gastric epithelial tissue undergoes malignant transformation, cell polarity disruption results in CLDN18.2 epitope expression on the cell surface. Consequently, CLDN18.2 exhibits high, selective, and stable expression in certain tumor tissues [137]. Therefore, CLDN18.2 is considered a potential target for the systemic treatment of gastric cancer.

Several studies have reported a correlation between CLDN18.2 expression and clinicopathological features of gastric cancer. Previous studies have indicated that CLDN18.2 expression is not associated with age, sex, tumor location, stage, or prognosis [138,139]. Some studies have suggested a correlation between CLDN18.2 expression and diffuse gastric cancer [138,140]. Interestingly, some studies have suggested that CLDN18.2 is frequently expressed in EBV-associated gastric cancer [140-142]. A recent study examined CLDN18.2 status in 408 patients with gastric cancer and identified CLDN18.2-positive (moderate-to-strong expression in ≥75% tumor cells) in 24% patients with almost equal distribution among various molecular subtypes, including MMR, EBV, HER2, and PD-L1 CPS subgroups [143]. This study also reported that the CLDN18.2-positive subtype is associated with Borrmann type 4, KRAS amplification, low CD16, and high CD68 expression. Additionally, this study found no significant differences in OS, PFS, or ORR of chemotherapy based on CLDN18.2 positivity. Another study investigated CLDN18.2 expression in 300 patients with gastric cancer and reported a CLDN18.2 positivity rate of 45% (moderate-to-strong expression in ≥40% tumor cells) [144]. This report also indicated that approximately 20% patients with CLDN18.2-positive gastric cancer had a PD-L1 CPS ≥5. Currently, the clinical implications of CLDN18.2 expression in gastric cancer have not been clearly elucidated yet. Additionally, the existing findings are limited due to the use of inconsistent detection methods, scoring systems, and optimal cut-offs, highlighting the need for method standardization of CLDN18.2 expression. Therefore, further studies are warranted.

Currently, the major therapeutic strategies for targeting CLDN18.2 include engineered monoclonal antibodies, bispecific antibodies, ADCs, and CAR-T cells. First, zolbetuximab (IMAB362) is a first-in-development chimeric immunoglobulin G1 monoclonal antibody

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that specifically binds to CLDN18.2 on the cell surface and mediates cell death through ADCC and complement-dependent cytotoxicity [145]. The FAST study, a phase 2 randomized trial (NCT01630083), investigated the combination of zolbetuximab and chemotherapy (epirubicin/oxaliplatin/capecitabine) compared to chemotherapy alone in 252 patients with advanced CLDN18.2-positive gastric cancer [146]. CLDN18.2 positivity was defined as moderate to strong expression in ≥40% tumor cells. The study demonstrated significant improvements in both PFS (HR, 0.44; 95% CI, 0.29–0.67) and OS (HR, 0.55; 95% CI, 0.39–0.77) with the addition of zolbetuximab to chemotherapy compared to chemotherapy alone. The PFS benefit was particularly notable in patients with moderate-to-strong CLDN18.2 expression in ≥70% tumor cells (HR, 0.38; 95% CI, 0.23–0.62). The combination of zolbetuximab and chemotherapy was generally well-tolerated, with manageable adverse events, including nausea, vomiting, neutropenia, and anemia. Following the promising outcomes of the phase 2 study, 2 phase 3 trials were conducted to further investigate the efficacy and safety of zolbetuximab. The SPOTLIGHT trial (NCT03504397) is a global, randomized, placebo-controlled, double-blind study that examined first-line zolbetuximab or placebo in combination with chemotherapy (FOLFOX) in patients with CLDN18.2-positive, HER2-negative advanced gastric cancer [147]. CLDN18.2 positivity was defined as moderate-to-strong expression in ≥75% tumor cells and observed in 38% of all screened patients and 42% of HER2-negative patients. Out of 565 patients with CLDN18.2-positive tumors, those treated with zolbetuximab and chemotherapy showed a significant improvement in PFS (median: 10.6 vs. 8.7 months; HR, 0.75; 95% CI, 0.60–0.94) and OS (median: 18.2 vs. 15.5 months; HR, 0.75; 95% CI, 0.60–0.94) compared to those treated with placebo and chemotherapy. The most common grade 3 or higher TRAEs were nausea, vomiting, and decreased appetite. No new safety concerns have been identified. The GLOW trial (NCT03653507) is a global, double-blind, phase 3 study that investigated the use of zolbetuximab or placebo in combination with chemotherapy (XELOX) as the first-line treatment for CLDN18.2-positive (moderate-to-strong expression in ≥75% tumor cells) and HER2-negative advanced gastric cancer [148]. In this study, CLDN18.2-positive tumors were observed in 38% of all screened patients and 43% of HER2-negative patients. This study also met the primary endpoint of PFS (median: 8.21 vs. 6.80 months; HR, 0.69; 95% CI, 0.54–0.87) and key secondary endpoint of OS (median: 14.4 vs. 12.2 months; HR, 0.77; 95% CI, 0.62–0.97). The safety profile of zolbetuximab in this trial was consistent with those of 2 previous studies. Interestingly, although zolbetuximab showed a survival benefit in 2 phase 3 trials, the response rate did not improve significantly (ORR, 48 vs. 48% in SPOTLIGHT; 43 vs. 40% in GLOW). This suggests that the combination of zolbetuximab and chemotherapy may have a greater effect on disease stabilization than that on tumor shrinkage. However, further research is needed to confirm this. Currently, a multi-cohort phase 2 ILUSTRO study (NCT03505320) is ongoing to assess the efficacy and safety of zolbetuximab in combination with either chemotherapy or pembrolizumab in patients with CLDN18.2-positive advanced gastric cancer [149].

In addition to zolbetuximab, several ongoing trials have evaluated various novel CLDN18.2-targeting agents, including monoclonal antibodies (TST001 and ZL-1211), bispecific antibodies (Q-1802 and AMG 910), ADCs (LM-302 and CMG901), and CAR-T therapies (CT-041 and LY011), in advanced gastric cancer. Recently, a phase 1 study (NCT03874897) that investigated a CLDN18.2-specific CAR-T cell treatment known as CT-041 demonstrated a promising ORR of 57.1% in previously treated patients with gastric cancer [150]. Most of these trials were in the early phase, and future results are necessary.

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FGFR2

The human fibroblast growth factor (FGF) family consists of 22 ligands that exert their effects via 4 highly conserved transmembrane tyrosine kinase receptors (FGFR1, FGFR2, FGFR3, and FGFR4) [151]. Activation of the FGFR signaling pathway induces various cellular pathways, including the RAS–RAF–MEK–ERK, PIK3CA–AKT–mTOR, and JAK pathways, which can affect angiogenesis, mitogenesis, differentiation, proliferation, tissue homeostasis, and invasion processes [152]. FGFR mutations, fusions, and amplifications have been reported in several cancers [153]. Previous studies have shown that FGFR alterations are observed in 5%–15% gastric cancer cases, with FGFR2 amplification being the most common alteration, accounting for approximately 10% gastric cancer cases [154-156]. Previous studies have indicated a strong correlation between FGFR2 amplification and IHC staining for FGFR2 isoform IIb (FGFR2b) [157]. Additionally, previous studies have suggested that FGFR2 and HER2 amplifications are mutually exclusive; FGFR2 amplification is often observed in MSS tumors and associated with low PD-L1 expression [158,159]. A previous meta-analysis suggested that FGFR2 overexpression results in a deep invasion, high rate of lymph node metastasis, advanced cancer stages, and poor prognosis [160].

In a recent study, promising results were observed with bemarituzumab, a recombinant humanized monoclonal antibody targeting the extracellular domain of FGFR2b in gastric cancer. The FIGHT trial (NCT03694522), a randomized, double-blind, placebo-controlled phase 2 trial, evaluated the efficacy of bemarituzumab in combination with chemotherapy (FOLFOX) compared to a placebo in patients with HER2-negative and FGFR2b-positive advanced gastric cancer [161]. Patients were selected based on FGFR2b overexpression in tumor IHC and FGFR2 amplification in plasma circulating tumor DNA (ctDNA). The study demonstrated a median PFS of 9.5 months in the bemarituzumab group compared to 7.4 months in the placebo group (HR, 0.68; 95% CI, 0.44–1.04). Moreover, the median OS was 19.2 months for the bemarituzumab group and 13.5 months for the placebo group (HR, 0.60; 95% CI, 0.38–0.94). These promising results initiated 2 ongoing randomized phase 3 trials investigating the efficacy of bemarituzumab [162,163].

In the past, the first generation RTK inhibitors were the initially evaluated as the targeting FGFR pathway treatment in gastric cancer. However, these agents demonstrated limited effectiveness owing to their lack of selectivity for kinases, and most clinical trials did not demonstrate any significant clinical benefits, but rather showed several toxicities [164]. Thus, novel TKIs that specifically and selectively inhibit the FGFR signaling pathway have been developed, along with a careful clinical trial design incorporating biomarker tests. Remarkably, these novel agents have exhibited promising outcomes in other types of cancer such as cholangiocarcinoma and urothelial carcinoma [165-168]. Several trials investigating second-generation TKIs, including infigratinib, derazantinib, erdafitinib, and futbatinib, are currently underway for the treatment of gastric cancer.

Finally, we summarize the characteristics of current molecular biomarkers for systemic treatment and the results of pivotal clinical trials in advanced gastric cancer (**Tables 1** and **2**).

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Table 1. Summary of the characteristics of current molecular biomarker for systemic treatment in gastric cancer

Variables	Prevalence	Methods	Clinical characteristics
HER2	10%–20%	IHC, ISH	· More frequent in proximal location. · Associated with male, differentiated tumor, intestinal type and lymph node metastasis. · Inconclusive for the correlation with PD-L1 expression and prognosis.
PD-L1	30%–60%	IHC	· Elevated in gastric cancer with EBV-positive and MSI-high tumor. · Inconclusive for the correlation with the prognosis. · Different methods and scoring according to agents: e.g., Nivolumab: 28-8 pharmDx, CPS≥5; Pembrolizumab: 22C3 pharmDx, CPS≥1 or 10.
MSI-high	5%–20%	PCR, NGS, IHC	· Associated with female, older age, intestinal Lauren histological type, gastric body/antrum location, early stage, lower rates of nodal metastasis, and better prognosis. · A high concordance between MSI-high detected by PCR or NGS and MMRd detected by IHC. · Overlap with TMB-high.
EBV	10%	ISH	· Associated with men, relatively younger age, gastric cardia/body, invasion into the submucosa with a low rate of lymph node metastasis and better prognosis. · High levels of PD-L1 expression and infiltration of immune cells within the tumor.
TMB-high	5%–10%	WES, NGS	· Considered a tumor-agnostic biomarker for immunotherapy, but inconclusive when excluding MSI-high tumor. · Inconclusive for the optimal cut-off. · Overlap with MSI-high.
CLDN18.2	20%–40%	IHC	· Not associated with age, gender, tumor location, stage, and prognosis. · Almost equally distributed among various molecular subtypes including MMR, EBV, HER2, PD-L1 CPS subgroup.
FGFR2	5%–15%	IHC, ISH, NGS	· FGFR2 amplification is the most common alteration in gastric cancer. · Strong correlation between FGFR2 amplification and IHC staining for FGFR2 isoform IIb (FGFR2b). · FGFR2 and HER2 amplifications are mutually exclusive. · Associated with MSS tumors and low levels of PD-L1 expression. · Associated with deep invasion, high rate of lymph node metastasis, advanced stage, and poor prognosis.

HER2 = human epidermal growth factor 2; IHC = immunohistochemistry; ISH = in situ hybridization; PD-L1 = programmed cell death ligand-1; EBV = Epstein–Barr virus; MSI = microsatellite instability; CPS = combined positive score; PCR = polymerase chain reaction; NGS = next-generation sequencing; MMRd = mismatch repair deficiency; TMB = tumor mutational burden; WES = whole-exome sequencing; CLDN18.2 = claudin 18.2; MMR = mismatch repair; FGFR2 = fibroblast growth factor receptor 2; MSS = microsatellite stable.

OTHER TARGETS

In addition to the aforementioned targets, several potential targets, including EGFR [169-171], VEGF/VEGFR2 [78,79], hepatocyte growth factor receptor/MET [172-174], mTOR [175], and poly ADP-ribose polymerase (PARP) [176] have been extensively investigated. However, these results were limited to advanced gastric cancer. These results can be interpreted based by several hypotheses. Many previous trials have been conducted without selecting specific patients. For example, the GOLD trial that examined the effectiveness of olaparib included all patients without screening for BRCA1/2 or other homologous recombinant deficiency statuses [176]. As well known, recent studies on various other cancers have shown that the efficacy of PARP inhibitors varies depending on the presence of BRCA1/2 mutations or other homologous recombination deficiency alterations, leading to successful results through careful study design and biomarker-driven patient selection [177,178]. Similarly, extensive validation of PD-L1 expression using various measures, such as CPS/TPS/TAP and different cut-off points, has been carried out in multiple cancers [179,180], and it is evident that extensive validation experience and careful screening of patients have significantly influenced recent successful results. In addition, it is worth considering whether the investigated agents were truly potent. For example, everolimus, examined in the GRANITE-1 trial [175], has some indications for other cancers, but its effect is not remarkable. Thus, the ability of first-generation targeted agents, including everolimus, to effectively overcome the aggressiveness of gastric cancer is uncertain.

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Table 2. Summary of the recent pivotal trials for systemic treatment in gastric cancer

Variables	KEYNOTE-811 [75]	DESTINY-Gastric01 [58]	CheckMate 649 [87]	KEYNOTE-859 [88]	RATIONALE-305 [125]	SPOTLIGHT [147]	GLOW [148]	FIGHT [161]
Number of patients	698	187	1,581	1,579	997	565	507	153
Population	HER2-positive	HER2-positive	HER2-negative	HER2-negative	HER2-negative	HER2-negative/ CLDN18.2-positive	HER2-negative/ CLDN18.2-positive	HER2-negative/ FGFR2-positive
Phase	3	2	3	3	3	3	3	2
Treatment line	1st line	3rd line or higher	1st line	1st line	1st line	1st line	1st line	1st line
Primary endpoint	OS and PFS in ITT	ORR in ITT	OS or PFS in PD-L1 CPS ≥5	OS in ITT, PD-L1 CPS ≥1, and CPS ≥10	OS in PD-L1 TAP ≥5 and ITT	PFS in ITT	PFS in ITT	PFS in ITT
Experimental arm	Pembrolizumab +trastuzumab +chemotherapy	T-DXd	Nivolumab +chemotherapy	Pembrolizumab +chemotherapy	Tislelizumab +chemotherapy	Zolbetuximab +chemotherapy	Zolbetuximab +chemotherapy	Bemarituzumab +chemotherapy
Control arm	Placebo +trastuzumab +chemotherapy	Chemotherapy (physician's choice)	Chemotherapy	Placebo +chemotherapy	Placebo +chemotherapy	Placebo +chemotherapy	Placebo +chemotherapy	Placebo +chemotherapy
Prevalence by biomarker cut-off (%)	HER2 3+: 78% HER2 2+/ISH +: 21% PD-L1 CPS ≥85%	HER2 3+: 77% HER2 2+/ISH+: 23%	PD-L1 CPS ≥5: 60%	PD-L1 CPS ≥1: 78% PD-L1 CPS ≥10: 35%	PD-L1 TAP ≥5%: 45%	CLDN18.2 ≥75%: 38% in all screened and 100% in ITT	CLDN18.2 ≥75: 38% in all screened and 100% in ITT	FGFR2b overexpression/ FGFR2 amplification: 30% in all screened and 100% in ITT
Median OS (months): experimental vs. control	ITT: 20.0 vs. 16.8	ITT: 12.5 vs. 8.4	PD-L1 CPS ≥5: 14.4 vs. 11.1	ITT: 12.9 vs. 11.5 PD-L1 CPS ≥1: 13.0 vs. 11.4 PD-L1 CPS ≥10: 15.7 vs. 11.8	ITT: 15.0 vs. 12.9 PD-L1 TAP ≥5%: 16.4 vs. 12.8	ITT: 18.2 vs. 15.5	ITT: 14.1 vs. 12.2	ITT: 19.2 vs. 13.5
HR (CI)	HR 0.84 (95% CI 0.70–1.01)	HR 0.59 (95% CI 0.39–0.88)	HR 0.71 (98.4% CI 0.59–0.86)	ITT: HR 0.78 (95% CI 0.70–0.87) PD-L1 CPS ≥1: HR 0.78 (95% CI 0.70–0.87) PD-L1 CPS ≥10: HR 0.65 (95% CI 0.53–0.79)	ITT: HR 0.80 (95% CI 0.70–0.92) PD-L1 TAP ≥5: HR 0.71 (95% CI 0.58–0.86)	HR 0.75 (95% CI 0.60–0.94)	HR 0.77 (95% CI 0.62–0.97)	HR 0.60 (95% CI 0.38–0.94)
Median PFS (months): experimental vs. control	ITT: 10.0 vs. 8.1	ITT: 5.6 vs. 3.5	PD-L1 CPS ≥5: 7.7 vs. 6.0	ITT: 6.9 vs. 5.6 PD-L1 CPS ≥1: 6.9 vs. 5.6 PD-L1 CPS ≥10: 8.1 vs. 5.6	ITT: 6.9 vs. 6.2 PD-L1 TAP ≥5%: 8.6 vs. 7.2	ITT: 10.6 vs. 8.7	ITT: 8.2 vs. 6.8	ITT: 9.5 vs. 7.4
HR (95% CI)	HR 0.73 (95% CI 0.61–0.87)	HR 0.47 (95% CI 0.31–0.71)	HR 0.68 (98% CI 0.56–0.81)	ITT: HR 0.76 (95% CI 0.67–0.85) PD-L1 CPS ≥1: HR 0.72 (95% CI 0.63–0.82) PD-L1 CPS ≥10: HR 0.62 (95% CI 0.51–0.76)	ITT: HR 0.78 (95% CI 0.67–0.90) PD-L1 TAP ≥5%: HR 0.67 (95% CI 0.55–0.83)	HR 0.75 (95% CI 0.60–0.94)	HR 0.69 (95% CI 0.54–0.87)	HR 0.68 (95% CI 0.44–1.04)
ORR (%): experimental vs. control	ITT: 73 vs. 60	ITT: 51 vs. 14	PD-L1 CPS ≥5: 60 vs. 45	ITT: 51 vs. 42 PD-L1 CPS ≥1: 52 vs. 43 PD-L1 CPS ≥10: 61 vs. 43	ITT: 47 vs. 41 PD-L1 TAP ≥5%: 50 vs. 43	ITT: 48 vs. 48	ITT: 43 vs. 40	ITT: 47 vs. 33
Grade 3 or higher TRAE (%)	ITT: 58 vs. 51	ITT: 86 vs. 57	ITT: 59 vs. 44	ITT: 60 vs. 51	Safety population: 54 vs 50	ITT: 87 vs. 78	ITT: 73 vs. 70	ITT: 83 vs. 74

HER2 = human epidermal growth factor 2; CLDN18.2 = claudin 18.2; FGFR2 = fibroblast growth factor receptors 2; OS = overall survival; PFS = progression free survival; ITT = intention to treatment; ORR = objective response rate; PD-L1 = programmed cell death ligand-1; CPS = combined positive score; TAP = tumor area positivity; T-DXd = trastuzumab deruxtecan; ISH = in situ hybridization; HR = hazard ratio; 95% CI = 95% confidence interval; TRAE = treatment related adverse event.

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Currently, newly engineered or novel mechanistic agents, such as ADC, are being developed that exhibit superior mechanical properties compared to previous agents. Several ongoing trials have explored the potential use of these novel agents. Furthermore, the presence of tumor heterogeneity, appropriate backbone of combination therapy, specific disease characteristics such as carcinomatosis peritonei, variations in ethnicity, and differences in treatment patterns between regions (such as Asian and Western countries) can all contribute to the unsatisfactory outcomes observed in previous clinical trials. Therefore, future studies should consider these factors.

FUTURE PERSPECTIVE

Gastric cancer is widely recognized as a highly heterogeneous cancer that poses a significant challenge to the development of targeted treatments. Tumor heterogeneity can be detected both within individual tumors (intra-tumoral heterogeneity) and among primary and/or metastatic tumors (inter-tumoral heterogeneity), in which clonal subpopulations with distinct phenotypic and genetic characteristics coexist. Moreover, this heterogeneity may evolve over treatment course [181,182]. Recognizing that oncogenic alterations are rarely found in all individuals of a specific subtype (such as EBV, MSI-high, CIN, and GS) is crucial, highlighting the significance of intra-subtype heterogeneity [183]. Additionally, it is crucial to acknowledge that patient characterized by a common biomarker, such as HER2 amplification and/or overexpression, can still exhibit diverse underlying tumor characteristics. For example, a previous study reported significant heterogeneity in the presence of RAS/PI3K mutations in patients with HER2-positive gastric cancer [184]. Specifically, trastuzumab-based treatment showed less benefit in patients with HER2-positive gastric cancer with concurrent alterations in the RAS/PI3K pathway. To overcome tumor heterogeneity, liquid biopsy is a non-invasive technique that is currently undergoing extensive investigation. Liquid biopsy can detect microresidual cancers, comprehensively analyze the genomic landscape of tumors, potentially revealing therapeutic targets, and monitor the genomic landscape of tumors over a period to detect treatment failure or the emergence of treatment-resistant tumor subclones [185]. Actually, the FIGHT study demonstrated that subgroup analyses measuring FGFR2 amplification through ctDNA consistently revealed significant improvements in both PFS and OS in patients treated with bemarituzumab [161]. Despite the promising advantages of liquid biopsy, its widespread application in clinical settings for gastric cancer is hindered by several factors including the absence of new liquid biopsy markers, low specificity and sensitivity, lack of standardized procedures and data analysis methods, and high costs [186]. Several studies are currently being conducted on liquid biopsy in the context of gastric cancer, and future results are essential for its potential clinical application.

In addition to the new techniques and methods, a strategy that can be employed in clinical practice is the use of multiple biopsies. Molecular characterization of a single biopsy sample from the tumor tissue is unlikely to accurately reflect the entire tumor or disease entity, which can result in potential misclassification. Therefore, performing multiple biopsies during endoscopic procedures and conducting multiple biomarker tests on separate biopsy tissues can be considered part of this strategy. Additionally, serial biopsy may be a viable option for gastric cancer owing to the non-invasive nature of endoscopy and possibility of repeated biopsies. In the DESTINY-Gastric04 trial, patients are being screened using repeated biopsies and their HER2 results were evaluated [60].

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Although our review mainly focuses on molecular targets, the importance of supportive care is crucial in achieving successful treatment. Patients with gastric cancer often face gastrointestinal obstruction and experience poor nutritional status, which can make them less tolerant to systemic treatment than patients with other types of cancer, such as breast cancer. In line with this point of view, a previous randomized phase 3 GO2 trial (ISRCTN44687907) demonstrated that reduced-intensity chemotherapy offers a favorable patient experience without significantly compromising disease control, making it a viable option for elderly and/or frail patients [187]. Another example is the ongoing randomized phase 3 trial (NCT05226169) in South Korea, which is currently evaluating the efficacy and safety of intravenous ferric carboxymaltose in patients with advanced gastric cancer and iron deficiency anemia who are undergoing palliative systemic treatment. We firmly believe that implementing these approaches can enhance the effectiveness of systemic treatment and improve the prognosis of patients with advanced gastric cancer.

CONCLUSION

In recent years, the molecular characterization of gastric cancer has significantly advanced in recent years. These advancements have led to the development of targeted therapies and immunotherapies, which have shown improved patient prognosis compared to traditional cytotoxic chemotherapy. HER2 remains a crucial biomarker for advanced gastric cancer, and the recent promising results using novel agents have once again brought attention to anti-HER2 targeted treatments. Immunotherapy, particularly PD-1/PD-L1 inhibitors, in combination with cytotoxic chemotherapy, has become the standard of care. PD-L1, EBV, MSI-high, and TMB are potential biomarkers for immunotherapy in gastric cancer; however, further research is needed. Additionally, immunotherapy is expected to play a central role in the backbone of combination treatments, and further studies are required to identify synergistic and predictive biomarkers. Recent studies have shown promising results with anti-CLDN 18.2 and FGFR2 treatments; therefore, further validation of biomarkers is necessary. Furthermore, identifying novel and previously unsatisfactory targets is crucial. These potential targets can be advanced through diverse therapeutic approaches, including ADC, recently engineered agents, and CAR-T cells. Further studies will be conducted to enhance the development of these therapies, addressing challenges such as primary and acquired resistance, tumor heterogeneity, and clonal evolution. Finally, careful management of patients with advanced gastric cancer, considering the aggressive nature of the disease and the vulnerability of patients, along with the implementation of the best supportive care, will improve patient outcomes.

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