Review

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Pembrolizumab in combination with trastuzumab for treatment of HER2-positive advanced gastric or gastro-esophageal junction cancer

Zaheer Qureshi, MD[a], Abdur Jamil, MD[b], Eeshal Fatima, MBBS[e], Faryal Altaf, MD[d], Rimsha Siddique, MBBS[c], Shivendra Shah, MBBS[f,*]

Introduction: Gastric cancer remains a challenging malignancy with a high global mortality rate. Recent advances in targeted therapy and immunotherapy have shown promise in improving patient outcomes. This paper reviews the impact of incorporating targeted agents such as trastuzumab and immunotherapeutic agents like pembrolizumab into standard chemotherapy regimens for gastric cancer treatment.

Methods: A comprehensive analysis was conducted on pivotal clinical trials, including KEYNOTE-590, KEYNOTE-811, and ToGA, focusing on their methodologies, patient populations, treatment regimens, and outcome measures. The review also explored emerging research avenues in precision medicine, particularly genomic sequencing and biomarker identification.

Aim: To assess the efficacy and survival benefits of adding trastuzumab and pembrolizumab to standard chemotherapy in the treatment of gastric cancer and to outline future directions in gastric cancer research.

Results: Including trastuzumab and pembrolizumab in treatment regimens for human epidermal growth factor receptor 2 (HER2)-positive and PD-L1-expressing gastric cancers significantly improved progression-free and overall survival rates compared to chemotherapy alone. These findings highlight the potential of personalized therapy in enhancing treatment outcomes. Furthermore, ongoing research into the gastric cancer microenvironment and the role of the microbiome suggests novel targets for future therapeutic interventions.

Conclusion: The integration of targeted and immunotherapeutic agents with traditional chemotherapy represents a pivotal shift in gastric cancer treatment, moving towards more personalized and effective regimens.

Keywords: gastric cancer, gastro-esophageal junction, pembrolizumab, trastuzumab

Introduction

Despite a gradual decrease in occurrence, gastric cancer, commonly referred to as cancer of the stomach, continues to be a prevalent and very lethal form of neoplasm worldwide[1]. The stomach, positioned in the gastrointestinal tract between the esophagus and small intestine, releases enzymes and gastric acid to facilitate the process of food digestion[2]. Additionally, it releases the intrinsic factor essential for absorbing vitamin B12[2]. The stomach is covered with a mucous membrane that consists of columnar epithelial cells and glands. These cells are susceptible to inflammation, particularly gastritis, which can result in peptic ulcers and, ultimately, cancer of the stomach[1].

Approximately one million instances of stomach cancer are diagnosed annually worldwide. Stomach cancer ranks as the fifth most frequently diagnosed cancer globally and the seventh most widespread[1,3]. The overall lifetime risk of having stomach cancer is 1.87% for males and 0.79% for females globally, from birth to age 74. Male individuals exhibit a higher incidence of gastric cancer[3]. Males in developed countries have a 2.2 times higher likelihood of being diagnosed with stomach cancer compared to females. In less economically developed nations, the ratio stands at 1.83. Gastric cancer has the most significant prevalence of all cancers for males in 5 nations globally. No country has the highest incidence of diagnosed cancer among females[1].

Stomach cancers are more commonly detected in developed countries[3,4]. Among nations with a high-middle Human Development Index (HDI), the average incidence rate for males is 20 per 100 000. In contrast, among countries with a low-middle

[a]The Frank H. Netter M.D. School of Medicine at Quinnipiac University, Bridgeport, CT, [b]Department of Medicine, Samaritan Medical Centre, Watertown, NY, [c]Independent Research Associate, Watertown, [d]Department of Internal Medicine, Icahn School of Medicine at Mount Sinai/BronxCare Health System, New York, NY, USA, [e]Department of Medicine, Services Institute of Medical Sciences, Lahore, Pakistan and [f]Department of Medicine, Nepalgunj Medical College, Chisapani, Nepal

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*Corresponding author. Address: Department of Medicine, Nepalgunj Medical College, Chisapani, 00977, Nepal. Tel: +1 (917) 502 0891. E-mail: shivendra67@gmail.com (S. Shah).

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HDI, the average rate is 6.6 per 100 000[1,3,4]. Until the mid-1990s, gastric cancer was the leading cause of cancer-related deaths worldwide. Gastric cancer causes 783 000 fatalities annually, ranking it as the third most lethal cancer in males globally[3]. Gastric cancer accounts for 8.3% of all cancer fatalities. The overall lifetime risk of mortality due to stomach cancer is 1.36% for males and 0.57% for females, spanning from birth to the age of 74[1].

HIGHLIGHTS

- Approximately one million instances of stomach cancer are diagnosed annually worldwide. Stomach cancer ranks as the fifth most frequently diagnosed cancer globally and the seventh most widespread.
- Two main therapy choices for gastric tumors, based on their molecular characteristics, are ramucirumab and trastuzumab.
- Blocking the PD1 pathway with antibodies like pembrolizumab restores T-cell activity and enhances anti-tumor immunity.
- The KEYNOTE-811 trial's findings highlight the efficacy of pembrolizumab in combination with trastuzumab and chemotherapy as a first-line treatment for metastatic human epidermal growth factor receptor 2 (HER2)-positive gastro-esophageal cancer.
- With advancements in genomic sequencing and biomarker identification, upcoming studies aim to tailor therapies more effectively to individual patient profiles, enhancing efficacy while minimizing toxicity. Immuno-oncology remains at the forefront, with novel checkpoint inhibitors, immune modulators, and combination strategies being explored to amplify anti-tumor responses.

Review

Methods

A systematic literature search informed this narrative review in PubMed, Scopus, Google Scholar, ISI, Embase, Science Direct, and Cochrane databases that identified articles reporting. On "Pembrolizumab" and "Trastuzumab" affecting "HER2-Positive Gastric and Gastro-Esophageal Junction Cancer" to search for studies in electronic databases. The initial search was carried out on 10 March 2024. Titles and abstracts were screened for relevant articles. The reference lists of all included citations were hand-searched to identify other additional studies. After removing duplicates, only original English language articles of any study design were considered to inform the results of this review as relevant to the review objectives. Subsequently, selected articles were categorized into sections to summarize pertinent information.

Types of gastric cancer

The Lauren classification of gastric cancer was established in 1965 and is currently the most used classification compared to other existing categories[5]. The Lauren division identifies two distinct histological subtypes of gastric cancer: intestinal and diffuse[5]. Later, an additional subtype called indeterminate was established to describe less common histology. Signet ring cell carcinoma is classified as the diffuse subtype. Various investigations have demonstrated that the intestinal form is the most prevalent, followed by the diffuse type and concluding with the indeterminate kind[5,6]. Intestinal carcinoma is distinguished by the presence of discernible glands and strong adhesion among the tumor cells. The diffuse subtype consists of loosely cohesive cells that diffusely infiltrate the stomach wall, with minimal or no development of glands. The cells often have a compact, spherical shape characterized by signet ring cell development[6]. The presence of the intestinal subtype is linked to the development of intestinal metaplasia in the gastric mucosa and the prevalence of H. pylori infection. Furthermore, research has shown that the diffuse gastric cancer subtype is more prevalent among females and younger patients. Additionally, this type of gastric cancer arises from the normal gastric mucosa[6].

The 2010 WHO classification is considered the most comprehensive among all categorization systems[7]. In addition to stomach adenocarcinomas, the WHO classification also includes descriptions of other forms of gastric malignancies that have reduced occurrence[7]. Gastric adenocarcinoma is a kind of cancer that can be further classified by subgroups such as tubular, mucinous, papillary, and mixed carcinoma[8]. These subgroups share similarities with the indeterminate type defined by the Lauren classification system. The poorly cohesive carcinoma subtype includes the signet ring cell carcinoma[6,8]. The remaining stomach adenocarcinomas categorized as uncommon are characterized mainly by their poor clinical significance. According to the WHO classification, the most prevalent subtype of gastric cancer is tubular adenocarcinoma, followed by the papillary and mucinous kinds[6–8]. Signet ring cell carcinoma accounts for around 10% of gastric cancers and is characterized by signet ring cells in more than 50% of the tumors[8,9].

Signs and symptoms of gastric cancer

Gastric cancer symptoms are typically vague and often result in diagnosis during a late stage. This is mainly because the stomach and the abdominal cavity are spacious and flexible, allowing for expansion[10]. Patients without cancer frequently experience typical symptoms such as vague gastrointestinal pain, episodic nausea, vomiting, and anorexia, which can also be early signs of the disease. Unless they persist or progress over time, patients and physicians frequently do not initially regard them seriously[10].

Most patients in the United States exhibit symptoms of an advanced stage at presentation[11]. The predominant symptoms observed in gastric malignancies include generalized weight loss, chronic abdomen pain, difficulty swallowing, vomiting blood, loss of appetite, sickness, premature feeling of fullness, and indigestion[11]. Patients with locally advanced or metastatic disease typically experience pronounced abdominal discomfort, possible accumulation of fluid in the abdomen (ascites), weight loss, exhaustion, and exhibit visceral metastases on scans. They may also develop gastric-outlet obstruction[11].

A frequently observed result of the physical examination is the presence of a detectable abdominal mass, which suggests that the disease has progressed significantly. The patient may also exhibit indications of the dissemination of cancer cells through the lymphatic system, such as the presence of Virchow's node (enlarged lymph node in the left supraclavicular area), Sister Mary Joseph node (nodule at the umbilicus), and Irish node (enlarged lymph

node in the left axillary region)[11,12]. Metastasis directly to the peritoneum can manifest as Krukenberg's tumor, which is a mass in the ovary; Blumer's shelf, which is a mass in the cul-de-sac; ascites, which is the presence of cancer cells in the peritoneal fluid; and hepatomegaly, which is an enlargement of the liver due to widespread disease[10,11].

Paraneoplastic manifestations associated with gastric cancer can include dermatological conditions such as diffuse seborrheic keratosis or acanthosis nigricans, hematological conditions like microangiopathic hemolytic anemia and hypercoagulable state (known as Trousseau's syndrome), renal conditions like membranous nephropathy, and autoimmune conditions like polyarteritis nodosa. These clinical findings are rare and not specific to gastric cancer[10–12].

Risk factors of gastric cancer

Gastric cancer has multifactorial etiologies, including genetic predispositions and environmental factors[4]. Genetic mutations such as the GSTM1-null phenotype and CDH1 gene mutations increase the risk of developing hereditary diffuse gastric cancer (HDGC), which can also lead to lobular breast cancer, prostate cancer, and colorectal cancer[4,13]. Other genetic factors like IL-17 and IL-10 polymorphisms, especially in Asian populations, and conditions such as Lynch syndrome and familial adenomatous polyposis (FAP) contribute to a heightened risk of gastric cancer[13].

Despite these genetic predispositions, environmental factors are crucial, with Helicobacter pylori infection being the primary risk factor[13,14]. This bacterium's discovery emphasized its role in peptic ulcer disease and its link to gastric cancer, particularly the non-cardia subtype. The interaction between genetics and environmental factors like diet, smoking, alcohol consumption, and chemical exposure underscores the complex etiology of gastric cancer[13,14].

Lifestyle factors such as obesity and conditions like pernicious anemia and gastro-esophageal reflux disease (GERD) further modulate risk. The impact of gastric surgery, radiation exposure, Epstein-Barr virus (EBV) infection, socioeconomic status, blood group, sex, and race/ethnicity on gastric cancer incidence highlights the disease's multifaceted nature. Overall, the intricate interplay between genetic susceptibility and environmental exposures shapes the risk and incidence of gastric cancer across populations[4,13,14].

Traditional therapy for gastric cancer

Surgical intervention is pivotal in gastric cancer (GC) treatment, especially effective when the tumor is most responsive to chemotherapy[15,16]. Recent advancements such as endoscopic resection and minimally invasive techniques like laparoscopic and robotic-assisted surgeries have revolutionized GC treatment, offering benefits like reduced postoperative complications[1]). Endoscopic mucosal resection and endoscopic submucosal dissection are preferred for early, differentiated types of GC without ulceration, showing favorable long-term outcomes[15,16]. Comprehensive surgical resection remains a cornerstone, particularly with lymphadenectomy D2 for curative intent. Adjuvant chemotherapy, notably with fluorouracil-based regimens, has significantly improved survival rates post-surgery, with newer trials suggesting the benefits of perioperative chemotherapy and targeted agents like pembrolizumab in specific settings[17]. Neoadjuvant chemotherapy has also emerged as a critical component in managing resectable and locally advanced GC, improving survival outcomes compared to surgery alone[15–17].

Prognosis of gastric cancer

The size of the tumor determines the prognosis of gastric cancer and involves both the involvement of nearby lymph nodes and the spread of the tumor beyond the walls of the stomach.

More than half of patients with localized distal gastric cancer can be cured, but early-stage disease represents only 10–20% of all identified cases in the United States[18]. The remaining patients with gastric cancer exhibit metastatic illness in either nearby or faraway locations. The 5-year survival rate for individuals with disseminated illness is close to nil, while patients with distant, resectable localized disease had a survival rate of about 50%[4,11]. The 5-year survival rate for patients with proximal gastric cancer, even when the illness appears to be confined to a specific area, is just 10–15%. Although therapy for people with diffuse gastric cancer can provide relief from symptoms and some extension of life, long-lasting periods of improvement are rare[10,18].

Targeted therapy for gastric cancer

Two main therapy choices for gastric tumors, based on their molecular characteristics, are ramucirumab and trastuzumab. Ramucirumab targets VEGFR2, whereas trastuzumab targets human epidermal growth factor receptor 2 (HER2)[18,19]. Gastric cancer frequently exhibits heterogeneity in the HER2 genotype and phenotype, which could contribute to inaccuracies in testing[19]. Phase II trials investigated the combination of trastuzumab and chemotherapy (cisplatin, capecitabine) compared to chemotherapy alone in patients with advanced gastric cancer who have HER2 + tumors[20]. The results emphasized that trastuzumab is the most suitable treatment option for highly HER2 + tumors[20,21]. Additional research has indicated that lapatinib, when used as a sole targeted treatment, has limited effectiveness against gastric cancer. This could be attributed to the absence of antibody-dependent cell-mediated cytotoxicity (ADCC) in the small molecule therapeutic approach[22]. Pertuzumab is an additional monoclonal antibody that specifically targets the interaction between HER2 and other members of the EGFR family, hence inhibiting HER2 heterodimerization[23].

Approximately 5% of gastric tumors exhibit amplification of the epidermal growth factor receptor (EGFR), which is associated with a poor prognosis. Studies have demonstrated a direct relationship between the overexpression of EGFR and the responsiveness to cetuximab treatment[23]. A phase II trial investigating the combination of cetuximab with oxaliplatin/leucovorin/5-fluorouracil demonstrated a correlation between a more significant EGFR copy number and improved overall survival[24].

Tumor growth is reliant on the presence of blood vessels. Tumors develop new blood vessels to get nutrients from the host, facilitating the tumor's capacity to spread to distant locations[25]. The activity of the vascular endothelial growth factor (VEGF) pathway is closely associated with angiogenesis, metastasis, and vascular development in the majority of solid tumors[25,26]. Comprehending this pathway is crucial for advancing medications that aim at VEGF, such as neutralizing antibodies that target VEGF or its receptor (VEGFR) and targeted TKIs against VEGFR[25].

Bevacizumab is a synthetic antibody derived from human genes and has been modified to target and block the action of VEGF, a protein involved in the growth of blood vessels[27]. Bevacizumab binds to vascular endothelial growth factor (VEGF) to prevent the activation of vascular endothelial growth factor receptor (VEGFR), hence suppressing the formation of blood vessels that supply tumors (tumor angiogenesis)[27–29]. Shah *et al*.[28] conducted a study to evaluate the efficacy of combining bevacizumab and irinotecan with cisplatin for treating advanced gastric cancer. Out of a total of 47 patients with untreated metastatic stomach or gastro-esophageal junction cancer, the rate of effectiveness was 65%, and the median survival duration was 12.3 months. The conclusive histology findings demonstrated a remission rate of 75%[28].

Sunitinib is a specific type of medication called a tyrosine kinase inhibitor. It targets a protein called VEGFR and blocks its activity[30]. It also inhibits the activity of other proteins, such as Raf, platelet-derived growth factor-beta receptor, fibroblast growth factor receptor, and c-KIT, which are involved in many cellular pathways[30,31]. Sorafenib is a highly effective inhibitor of Raf and other receptor tyrosine kinase inhibitors in advanced gastric cancer. Sun *et al*.[31] found that sorafenib effectively suppressed the development and angiogenesis of gastric cancer xenografts. In a study including 44 patients with advanced gastric cancer, the combination of sorafenib with either cisplatin or docetaxel as a second-line treatment resulted in a median progression-free survival (PFS) of 5.8 months and a median overall survival (OS) of 13.6 months[31].

The signaling pathway dependent on VEGF/VEGFR2 plays a crucial role in tumor angiogenesis[32]. Research has observed a correlation between the status and serum levels of VEGF and advanced stage and poor prognosis in cases of GC[32]. The REGARD research assessed the efficacy of ramucirumab. This monoclonal antibody targets VEGFR2 as a second-line treatment for patients with unresectable, advanced gastro-esophageal cancers who had seen disease progression after the first chemotherapy[24]. The efficacy of this antibody, in conjunction with paclitaxel, was evaluated in phase III research (RAINBOW) as a second-line treatment for patients with metastatic gastric cancer who experienced disease progression after the first chemotherapy[33]. The paclitaxel plus ramucirumab group significantly improved overall survival compared to the placebo group[33].

Approximately 10% of gastric cancers exhibit overexpression of the fibroblast growth factor 2 receptor tyrosine kinase (FGFR2), and its amplification is associated with lymphatic invasion and an unfavorable prognosis[34]. Ongoing clinical trials are being conducted to treat patients with FGFR2 amplification with inhibitors, such as dovitinib or AZD4547[35]. The PI3K/AKT/mTOR pathway is frequently activated in GC malignancies. A phase III clinical trial examined the efficacy of the mTOR inhibitor (everolimus) in patients with advanced gastric cancer. The findings revealed no enhancement in the overall survival rate[36]. Furthermore, a phase II trial of MK-2206, a substance that inhibits AKT, yielded no favorable outcomes[37].

Role of HER2 inhibitor

The increased expression of the HER2 gene and an increased level of the HER2 protein is present in 15–20% of individuals diagnosed with gastric cancer[38]. The level of HER2 overexpression and amplification differs depending on the location of the carcinoma, with greater expression observed in the gastro-esophageal and proximal regions compared to the distal areas of the stomach[38]. In addition, there appears to be a correlation between HER2 overexpression and amplification and the Lauren histological classification. Specifically, more significant amounts of HER2 are observed in the intestinal phenotype than in the diffuse and mixed types[38,39]. The predictive features of HER2 overexpression and amplification remain a subject of discussion, but a substantial body of research suggests HER2 is associated with a bad prognosis[39]. The efficacy of HER2-targeted therapy in gastric cancer was proven in the ToGA study, where patients with advanced gastric and gastro-esophageal junction adenocarcinoma who tested positive for HER2 were randomly assigned to receive either 5-FU/capecitabine and cisplatin alone or in combination with trastuzumab[40]. Patient survival significantly increased when treated with a combination of trastuzumab and chemotherapy. Individuals with a significant overabundance of the HER2 protein (IHC3 +) experienced notable advantages from the therapy, resulting in a median overall survival of 17.9 months[40]. Due to the favorable outcomes shown in the ToGA study, it has become standard practice to screen patients with advanced stomach or gastro-esophageal junction adenocarcinoma for the presence of HER2[40,41]. The ToGA trial is considered a significant milestone in treating gastric cancer. It has led to the development of several new HER2-targeted compounds, including pertuzumab, ado-trastuzumab emtansine, lapatinib, afatinib, and dacomitinib. These compounds are currently being tested in phase II and III clinical trials[39–41].

Mechanism of action of pembrolizumab and trastuzumab

Immune checkpoints like CTLA4 and PD1 are crucial in regulating T-cell function and maintaining self-tolerance by inhibiting T-cell activation[42]. CTLA4, expressed on T-cells, competitively binds to CD80 and CD86 on antigen-presenting cells (APCs), reducing CD28-mediated co-stimulation and thereby T-cell activation[42]. PD1, a receptor found on activated lymphocytes, interacts with its ligands PDL1 and PDL2, expressed in various cells, including tumor cells[43]. The engagement of PD1 with PDL1 or PDL2 delivers an inhibitory signal to T-cells, reducing T-cell activity and contributing to tumor immune evasion[43]. PDL1 expression on cancer cells can be intrinsic, due to genetic aberrations, and adaptive, in response to factors like interferon γ in the tumor microenvironment[42,43]. This expression allows tumors to evade immune detection by inhibiting cytotoxic T-cell function[42].

Blocking the PD1 pathway with antibodies like pembrolizumab restores T-cell activity and enhances anti-tumor immunity[44]. Pembrolizumab, a humanized monoclonal antibody targeting PD1, does not activate complement or Fc receptors, minimizing cytotoxic activity[45]. Its pharmacokinetics reveal a dose-proportional increase in concentration, with adjustments for body weight to ensure consistent exposure. Clinically, pembrolizumab has been evaluated in various cancers, demonstrating its potential to improve patient outcomes by reactivating the immune response against tumors[44,45].

Trastuzumab, targeting HER2, marks a pivotal shift towards biologic therapy in HER2-positive gastric cancer, reflecting its overexpression in 10–25% of cases[46]. This overexpression is associated with poor prognosis, especially in intestinal-type

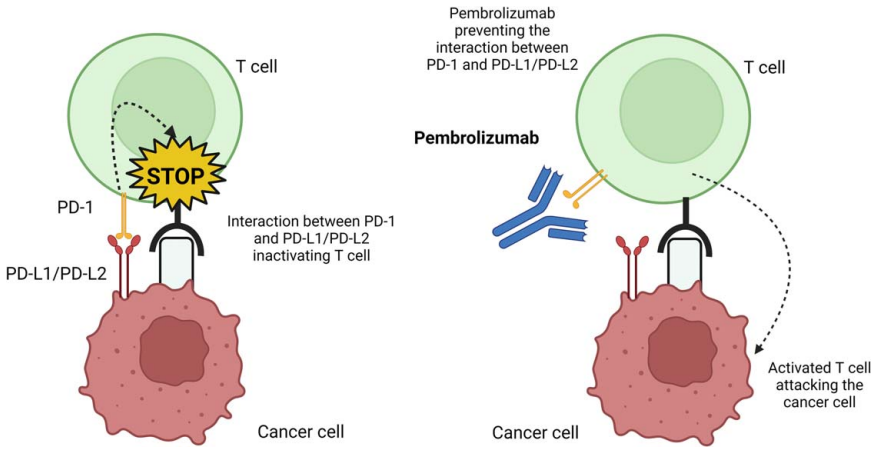

Figure 1. Mechanism of action of Pembrolizumab.

cancers. Trastuzumab, a humanized monoclonal antibody, inhibits HER2-amplified tumor cell lines by blocking the receptor and its downstream signaling pathways, leading to growth arrest and potentially enhancing cell-mediated cytotoxicity[46,47]. Critical studies, like the ToGA trial, have evaluated trastuzumab's addition to chemotherapy, showing its potential to improve outcomes in HER2-positive GC patients, underscoring the importance of targeted therapies in managing advanced gastric cancer[48]. Figure 1 and Figure 2 demonstrate the mechanism of action of Pembrolizumab and Trastuzumab.

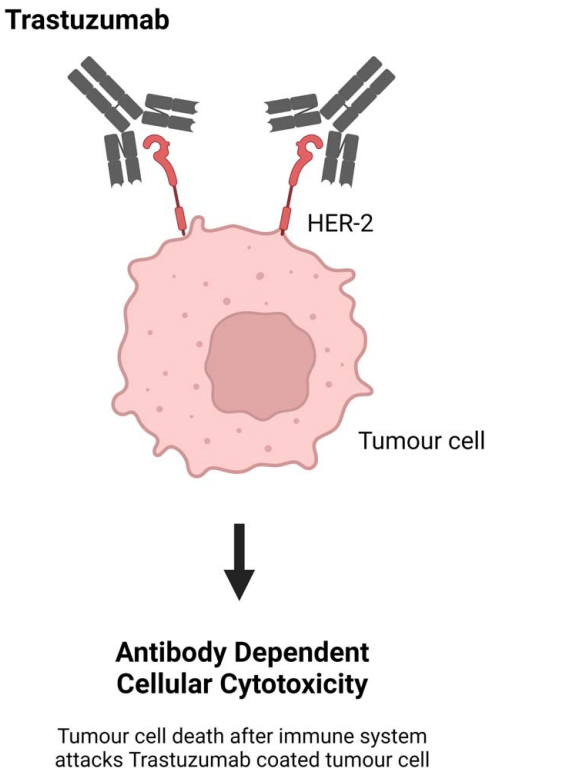

Figure 2. Mechanism of action of Trastuzumab. HER2, human epidermal growth factor receptor 2.

Critical analysis of ToGA trial

The ToGA trial stands as a landmark study in the field of gastric cancer, focusing on the efficacy and safety of adding trastuzumab, a monoclonal antibody targeting the HER2 receptor, to standard chemotherapy in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer. Conducted across 122 centers in 24 countries, this international, phase 3, open-label, randomized controlled trial enrolled 594 patients into two groups: one receiving trastuzumab plus chemotherapy ($n = 298$) and the other receiving chemotherapy alone ($n = 296$). The trial's primary endpoint was overall survival, with progression-free survival, tumor response rate, and safety measures as secondary endpoints[49].

The results demonstrated a clear benefit of incorporating trastuzumab into the treatment regimen. Patients treated with trastuzumab plus chemotherapy experienced a significant extension in median overall survival to 13.8 months, compared to 11.1 months for those receiving chemotherapy alone, marking a 26% reduction in the risk of death [hazard ratio (HR) 0.74, 95% CI 0.60–0.91; $P = 0.0046$] and adding trastuzumab improved progression-free survival, with a median of 6.7 months versus 5.5 months in the chemotherapy-alone group (HR 0.71, 95% CI 0.59–0.85; $P = 0.0002$). The overall tumor response rate was also higher in the trastuzumab combination group at 47%, compared to 35% in those receiving only chemotherapy[40].

Regarding safety, the trial revealed that adding trastuzumab did not significantly increase the incidence of adverse events. The most reported adverse effects across both treatment arms were nausea, vomiting, and neutropenia, with grade 3 or 4 adverse events occurring in 68% of patients in both groups. Importantly, cardiac adverse events were observed at similar rates in both the trastuzumab plus chemotherapy group and the chemotherapy-alone group (6%), suggesting no significant increase in cardiotoxicity due to trastuzumab[40].

The ToGA trial's findings have profound implications for managing HER2-positive advanced gastric or gastro-esophageal junction cancer. By demonstrating a significant improvement in overall survival without substantially increasing toxicity, the study supports the addition of trastuzumab to standard chemotherapy as a new standard of care for this patient population. The results underscore the importance of HER2 as a therapeutic

target in gastric cancer and mark a significant advancement in the treatment of a disease that has historically been associated with a poor prognosis[40].

Critical analysis of KEYNOTE-590 trial

The KEYNOTE-590 study, a phase 3, randomized, placebo-controlled trial, was pivotal in advancing the treatment landscape for patients with previously untreated advanced esophageal cancer, including Siewert type 1 gastro-esophageal junction cancer. Conducted across 26 countries in 168 medical centers, the trial enrolled 749 patients who were randomized to receive either pembrolizumab plus chemotherapy ($n = 373$) or placebo plus chemotherapy ($n = 376$), aiming to evaluate the efficacy and safety of the combination compared to chemotherapy alone[48]. The trial's results were noteworthy, particularly in enhancing OS and PFS across several patient subgroups. For instance, in the subset with esophageal squamous cell carcinoma and a PD-L1 combined positive score (CPS) of 10 or more, the addition of pembrolizumab led to a median OS of 13.9 months, significantly longer than the 8.8 months observed in the placebo group, marking a 43% reduction in the risk of death[48]. This trend of improved survival was consistent across all randomized patients, with those receiving pembrolizumab achieving a median OS of 12.4 months compared to 9.8 months in the placebo cohort[48].

Furthermore, the study highlighted a superior PFS in the pembrolizumab group. The median PFS reached 6.3 months versus 5.8 months in those receiving placebo, alongside a higher overall tumor response rate, indicating the combination's potent anti-tumor activity[48]. Despite these efficacy benefits, the safety profile of pembrolizumab plus chemotherapy remained manageable and aligned with expectations based on the known adverse effects of the components. Treatment-related adverse events of grade 3 or higher were slightly more prevalent in the pembrolizumab group (72%) compared to the placebo group (68%), with common adverse effects including nausea, decreased appetite, anemia, and fatigue[48].

In conclusion, the KEYNOTE-590 trial's findings substantiate pembrolizumab in combination with chemotherapy as a significant advancement in the first-line treatment of advanced esophageal cancer, irrespective of PD-L1 expression status. By offering substantial improvements in survival outcomes without considerably increasing toxicity, this combination therapy emerges as a new standard of care, providing a promising treatment option for patients with a historically poor prognosis, thereby potentially improving survival rates and quality of life for this challenging patient population[48].

Critical analysis of KEYNOTE-811 trial

The KEYNOTE-811 trial, a phase 3 study, offers significant insights into the treatment of HER2-positive gastro-esophageal cancer, specifically assessing the impact of adding pembrolizumab to standard trastuzumab and chemotherapy (fluoropyrimidine and platinum-based therapy). Conducted across 168 medical centers in 20 countries, this trial randomized 698 patients to either pembrolizumab ($n = 350$) or placebo ($n = 348$), alongside chemotherapy and trastuzumab, aiming to evaluate the regimen's efficacy in terms of PFS and OS, as well as its safety profile[49].

In the second interim analysis, with a median follow-up of 28.3 months for the pembrolizumab group and 28.5 months for the placebo group, the trial demonstrated a notable improvement in median PFS for patients receiving pembrolizumab (10.0 months) compared to those in the placebo group (8.1 months), achieving a HR of 0.72 ($P = 0.0002$). This indicates a 28% reduction in the risk of disease progression or death for patients treated with pembrolizumab[49].

However, while the median OS at this analysis showed an extension in the pembrolizumab group (20.0 months) versus the placebo group (16.9 months), the result did not reach prespecified criteria for statistical significance (HR 0.87, $P = 0.084$), suggesting the need for continued follow-up[49].

The safety analysis revealed that grade 3 or worse treatment-related adverse events were slightly more common in the pembrolizumab group (58%) compared to the placebo group (51%). Treatment-related deaths occurred in a small number of patients in both groups (1% in the pembrolizumab group and less than 1% in the placebo group). The most frequent treatment-related adverse events of any grade included diarrhea, nausea, and anemia, with comparable incidence rates between the two groups[49].

The KEYNOTE-811 trial's findings underscore the efficacy of pembrolizumab in combination with trastuzumab and chemotherapy as a first-line treatment for metastatic HER2-positive gastro-esophageal cancer, particularly in patients with PD-L1 combined positive score of 1 or more. The significant improvement in progression-free survival highlights pembrolizumab's potential in enhancing treatment outcomes. Although the improvement in overall survival did not meet the criteria for significance in this interim analysis, the ongoing follow-up for the final analysis may provide further insights. This study reinforces the role of immunotherapy combined with targeted therapy and chemotherapy in managing advanced HER2-positive gastro-esophageal cancers, offering a promising therapeutic strategy for this challenging condition[49].

A summary of recent clinical trials of this therapy in gastric cancer is shown in Table 1.

Other combinations available

Trastuzumab + Fluoropyrimidine and platinum-based chemotherapy

This is a standard first-line treatment for HER2-positive advanced gastric cancer[50]. The most common regimen combines trastuzumab with a fluoropyrimidine (such as capecitabine or 5-fluorouracil) and a platinum compound (such as cisplatin or oxaliplatin)[50,51]. The ToGA trial, which established this combination, showed significantly improved survival rates in patients treated with trastuzumab and chemotherapy compared to chemotherapy alone[51].

Trastuzumab + Ramucirumab

This combination targets the HER2 protein and the VEGFR2 pathway, which is involved in angiogenesis. While primarily researched in clinical trial settings, preliminary data suggest that combining these two targeted therapies could benefit tumor growth and improve survival[52].

Trastuzumab + Pertuzumab

Although more commonly used in breast cancer, the combination of trastuzumab and pertuzumab (another monoclonal antibody targeting a different epitope of the HER2 receptor) is being

Table 1

Recent clinical trials of pembrolizumab and trastuzumab in gastric cancer

Trial	No. patients	Progression-free survival	Overall survival	Adverse effects
KEYNOTE-590	Not specified	6.3 months (pembrolizumab group) vs. 5.8 months (placebo group)	Not specified	Grade 3 or higher: 72% (pembrolizumab group) vs. 68% (placebo group)
KEYNOTE-811	698	10.0 months (pembrolizumab group) vs. 8.1 months (placebo group)	20.0 months (pembrolizumab group) vs. 16.9 months (placebo group) at the second interim analysis	Grade 3 or worse: 58% (pembrolizumab group) vs. 51% (placebo group)
ToGA Trial	594 patients, dividing them into two groups: one receiving trastuzumab plus chemotherapy ($n = 298$) and the other receiving chemotherapy alone ($n = 296$)	6.7 months (trastuzumab group) vs. 5.5 months (chemotherapy-alone group)	Improvement with trastuzumab; 11.1 months (chemotherapy alone), HR 0.74 (0.60–0.91; $P = 0.0046$)	Grade 3 or 4: 68% of patients in both groups. Cardiac adverse events were observed at similar rates in both the trastuzumab plus chemotherapy group and the chemotherapy-alone group (6%)

HR, hazard ratio.

investigated in gastric cancer[53]. This dual HER2 blockade has shown promising results in breast cancer and is expected to enhance the therapeutic effects in gastric cancer by preventing HER2 signaling more comprehensively[53].

Trastuzumab Deruxtecan (T-DXd)

A newer agent, trastuzumab deruxtecan, is an antibody-drug conjugate that combines trastuzumab with a cytotoxic drug, allowing direct delivery of chemotherapy to HER2-expressing cells[54]. This has shown promising activity in patients with previously treated HER2-positive gastric cancer[54].

These combinations are typically considered based on the patient's previous treatments, overall health, and specific characteristics of the cancer. Clinical trials continually update the landscape of available treatments, indicating a dynamic and evolving approach to managing HER2-positive gastric cancers.

Limitations and challenges

The ToGA trial focused on patients with high HER2 expression, potentially limiting its applicability to the broader population of gastric cancer patients who may have lower or heterogeneous expression levels. Outcomes and responses varied significantly across different regions, which may affect the generalizability of the findings. While statistically significant, the survival benefits were relatively modest, indicating a need for more effective treatment combinations or strategies[55].

As an early phase trial, KEYNOTE-511 may face challenges in biomarker identification and validation that could impact the stratification and interpretation of efficacy results. The addition of immunotherapy with pembrolizumab increases the complexity of managing side effects, particularly immune-related adverse events, which require diligent monitoring and management[55].

The KEYNOTE-811 Trial has its share of limitations and challenges. The combination of pembrolizumab with trastuzumab and chemotherapy introduces complexities related to dosing schedules, drug interactions, and increased potential for adverse reactions. As with many advanced cancer trials, selecting and retaining a homogeneous patient population is challenging, potentially leading to variability in treatment outcomes. Determining the most appropriate endpoints and translating these into real-world benefits remains a significant challenge, particularly in trials involving multiple therapeutic agents[56].

All three trials mentioned above have limitations in biomarker identification. Identifying and validating predictive biomarkers for treatment response is crucial but remains challenging. These trials must integrate robust biomarker programs to select patients more likely to benefit from the treatment. Issues such as non-randomization in some study arms, potential biases in patient selection, and short follow-up periods can limit the strength of the conclusions drawn from these trials[54–56].

Risk of misdiagnosis

The diagnosis and treatment of gastric or gastro-esophageal junction cancer in older patients come with unique challenges, primarily due to the higher prevalence of comorbid chronic diseases in this age group. Older patients often have multiple health issues, such as gastrointestinal disorders (like GERD or ulcers), which can mimic or obscure the symptoms of gastric cancers[57]. Symptoms like abdominal pain, nausea, or weight

loss might be misattributed to these more common conditions in elderly patients. Conditions like dementia or decreased cognitive function can make accurate history-taking and symptom reporting more complex, complicating the diagnostic process[58]. Older patients might have various benign conditions such as calcifications or arteriosclerotic changes that could complicate the interpretation of imaging studies like computed tomography (CT) scans or endoscopies used to diagnose gastric cancer[59].

Age-related changes in tissue density and the presence of other pathologies can make biopsy samples harder to interpret. Inflammation from other diseases might be mistaken for cancer or vice versa. Cardiovascular diseases are common in older adults and can significantly impact the type of anesthesia and surgery options available for treating gastric cancer[59]. For instance, a patient with severe cardiovascular disease might not be a candidate for extensive surgery due to the risk of cardiac complications. Older patients have a higher risk of having multiple primary malignancies, complicating treatment plans and prognosis estimations[59,60]. A thorough geriatric assessment to evaluate an elderly patient's functional status, comorbidities, cognition, nutritional status, and social support is crucial to effectively tailor the diagnostic and treatment processes. Coordination between gastroenterologists, surgeons, oncologists, radiologists, and geriatric specialists can help make a comprehensive evaluation and treatment plan. Considering less invasive or less aggressive treatment options might be appropriate for some elderly patients to balance quality of life with treatment efficacy.

Economic implications

Incorporating high-cost therapies into standard treatment regimens for gastric cancer presents significant economic implications, particularly given the global variance in healthcare systems. Advanced therapies like targeted biologics and immunotherapies, while potentially improving survival rates and quality of life, are often prohibitively expensive[60,61]. This can strain public health budgets, especially in low- and middle-income countries with limited healthcare funding. The financial burden of these treatments may lead to disparities in access, with patients in wealthier nations more likely to benefit from the latest advancements than those in developing countries. Additionally, the high cost of these treatments can impact insurance premiums and out-of-pocket expenses, potentially limiting accessibility even in more developed healthcare systems[61]. Policymakers and healthcare providers must balance the benefits of these advanced therapies with their cost-effectiveness. Strategies such as price negotiations, generic drug options, and tiered pricing models can help mitigate these economic challenges and broaden access to these critical treatments.

Role of microbiome

The human microbiome, particularly the diverse communities of bacteria residing in the stomach, plays a significant role in the pathogenesis and progression of gastric and gastro-esophageal junction cancer. Beyond Helicobacter pylori, recent research suggests that the broader gastric microbiome might also influence cancer risk. Variations in microbial composition and diversity can affect the mucosal immune response, disrupt epithelial barrier functions, and modulate the production of carcinogenic compounds. These microbial interactions can contribute to the etiology of gastric cancers by influencing metabolic pathways, immune responses, and the local production of carcinogens or anti-carcinogenic compounds[62].

Additionally, the interaction between dietary factors and the microbiome is an area of growing interest, as diet can significantly alter microbial populations and their metabolic activities, which may impact cancer risk. The potential therapeutic implications include using probiotics, prebiotics, or antibiotics to modify the microbiome and possibly reduce the risk of cancer or enhance the efficacy of cancer treatments[62].

Future trials in gastric cancer

Future trials and research in gastric cancer are poised to revolutionize the treatment landscape further, focusing on unraveling the molecular complexity of the disease and harnessing the potential of precision medicine. With advancements in genomic sequencing and biomarker identification, upcoming studies aim to tailor therapies more effectively to individual patient profiles, enhancing efficacy while minimizing toxicity. Immuno-oncology remains at the forefront, with novel checkpoint inhibitors, immune modulators, and combination strategies being explored to amplify anti-tumor responses. Additionally, integrating targeted therapies against new molecular targets beyond HER2, such as CLDN18.2, MET, and EGFR, offers promise for subsets of patients with specific genetic aberrations[63]. Research is also expanding into the microbiome's role in gastric carcinogenesis and response to therapy, potentially opening avenues for microbiome-modulating treatments. Furthermore, developing vaccine-based therapies and oncolytic viruses represents an innovative approach to stimulating the immune system against gastric cancer cells[64]. As we progress, the emphasis on personalized and combination therapies, supported by robust biomarker-driven clinical trials, is expected to yield significant improvements in outcomes for patients with gastric cancer, transitioning towards more individualized, effective, and less toxic treatment modalities.

Conclusion

In conclusion, pembrolizumab combined with trastuzumab represents a significant step forward in the treatment of HER2-positive advanced gastric or gastro-esophageal junction cancer. It underscores the importance of continued innovation and research in targeted therapies that can provide more effective and less toxic treatment options. This treatment modality offers a targeted approach by leveraging the synergistic effects of pembrolizumab, an immune checkpoint inhibitor that enhances T-cell function, and trastuzumab, a monoclonal antibody that antagonizes explicitly the HER2 receptor, which is overexpressed in certain gastric cancers. The evidence gathered and analyzed from multiple clinical trials and observational studies suggests that this combination therapy enhances the overall survival and progression-free survival rates and maintains a manageable safety profile. Notably, the treatment has shown efficacy in a patient population that is often challenging to treat due to the aggressive nature of HER2-positive advanced gastric cancers. Moreover, the therapy has been associated with improved quality of life indicators, emphasizing its role in palliative care settings alongside its efficacy in extending life. This dual benefit is crucial for patients who often face significant symptomatic burdens due to their

disease. While the results are encouraging, the variability in response among different demographic and genetic subgroups calls for further research to optimize treatment protocols and personalize therapy based on individual patient profiles. Future studies should aim to refine patient selection criteria, explore combinatory strategies with other therapeutic agents, and ultimately guide the development of clinical guidelines that can maximize patient outcomes in this challenging oncological context.

Ethical approval

Our study was a narrative review and therefore, did not involve patients. Thus, ethical approval from the ethics committee was not applicable.

Consent

Our study was a narrative review and therefore, did not involve patients. Thus, taking consent was not applicable.

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Author contribution

Z.Q.: data curation, conceptualization, methodology, supervision; A.J.: writing—original draft; writing—reviewing and editing; E.F.: writing—original draft; writing—reviewing and editing; F.A.: writing—reviewing and editing, supervision; R.S.: writing—original draft; S.S.: writing—original draft.

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The authors declare no conflict of interest.

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References

[1] Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Gastroenterol Rev/Przegląd Gastroenterologiczny 2019;14:26–38.

[2] Hsu M, Safadi AO, Lui F. Physiology, stomach, statpearls, treasure Island (FL): StatPearls Publishing; 2024 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK535425/

[3] Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[4] Machlowska J, Baj J, Sitarz M, *et al*. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci 2020;21:4012.

[5] Hu B, El Hajj N, Sittler S, *et al*. Gastric cancer: classification, histology and application of molecular pathology. J Gastrointest Oncol 2012;3:251.

[6] Sarbia M, Becker KF, Höfler H. Pathology of upper gastrointestinal malignancies. In Seminars in oncology. WB Saunders; 2004;31(No. 4):465–475.

[7] Fléjou JF. WHO Classification of digestive tumors: the fourth edition. In Ann Pathol 2011;31(No. 5 Suppl):S27–31.

[8] Werner M, Becker KF, Keller G, *et al*. Gastric adenocarcinoma: pathomorphology and molecular pathology. J Cancer Res Clin Oncol 2001;127:207–16.

[9] Chon HJ, Hyung WJ, Kim C, *et al*. Differential prognostic implications of gastric signet ring cell carcinoma: stage adjusted analysis from a single high-volume center in Asia. Ann Surg 2017;265:946–53.

[10] Holland JF. Holland-Frei cancer medicine 8. PMPH-USA; 2010. [cited 2024 Mar 13].

[11] Maconi G, Manes G, Porro GB. Role of symptoms in diagnosis and outcome of gastric cancer. World J Gastroenterol WJG 2008;14:1149.

[12] Axon A. Symptoms and diagnosis of gastric cancer at early curable stage. Best Pract Res Clin Gastroenterol 2006;20:697–708.

[13] Marghalani AM, Salman TO, Faqeeh FJ, *et al*. Gastric carcinoma: insights into risk factors, methods of diagnosis, possible lines of management, and the role of primary care. J Family Med Prim Care 2020;9:2659–63.

[14] Yusefi AR, Lankarani KB, Bastani P, *et al*. Risk factors for gastric cancer: a systematic review. Asian Pacific J Cancer Prevent APJCP 2018;19:591.

[15] Orditura M, Galizia G, Sforza V, *et al*. Treatment of gastric cancer. World J Gastroenterol WJG 2014;20:1635.

[16] Cai J, Wei D, Gao CF, *et al*. A prospective randomized study comparing open versus laparoscopy-assisted D2 radical gastrectomy in advanced gastric cancer. Dig Surg 2012;28:331–7.

[17] Ko KJ, Shim JH, Yoo HM, *et al*. The clinical value of non-curative resection followed by chemotherapy for incurable gastric cancer. World J Surg 2012;36:1800–5.

[18] Basaran H, Koca T, Cerkesli AK, *et al*. Treatment outcomes and survival study of gastric cancer patients: a retrospective analysis in an endemic region. Asian Pacific J Cancer Prevent 2015;16:2055–60.

[19] De Vita F, Borg C, Farina G, *et al*. Ramucirumab and paclitaxel in patients with gastric cancer and prior trastuzumab: subgroup analysis from RAINBOW study. Future Oncol. 2019;15:2723–31.

[20] Shitara K, Yatabe Y, Matsuo K, *et al*. Prognosis of patients with advanced gastric cancer by HER2 status and trastuzumab treatment. Gastric Cancer 2013;16:261–7.

[21] Kadowaki S, Masuishi T, Eto T, *et al*. Depth of response predicts the clinical outcome of advanced HER2-positive gastric cancer to trastuzumab-based first-line chemotherapy. Cancer Chemother Pharmacol 2017;80:807–13.

[22] Hecht JR, Bang YJ, Qin SK, *et al*. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2–positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC—a randomized phase III trial. J Clin Oncol 2016;34:443–51.

[23] Tabernero J, Hoff PM, Shen L, *et al*. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol 2018;19:1372–84.

[24] Lordick F, Luber B, Lorenzen S, *et al*. Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Br J Cancer 2010;102:500–5.

[25] Hsu JT, Chen TD, Chuang HC, *et al*. Vascular endothelial growth factor expression is an independent poor prognostic factor for human epidermal growth factor receptor 2 positive gastric cancer. J Surg Res 2017;208:40–50.

[26] Lin Y, Zhai E, Liao B, *et al*. Autocrine VEGF signaling promotes cell proliferation through a PLC-dependent pathway and modulates Apatinib treatment efficacy in gastric cancer. Oncotarget 2017;8:11990.
[27] Lv Y, Song L, Chang L, *et al*. Bevacizumab followed by chemotherapy is potential therapy for gastric cancer. J BU ON Off J Balkan Union Oncol 2016;21:1466–70.
[28] Shah MA, Ilson DH, D'Adamo DO, *et al*. Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol 2006;24:5201–6.
[29] Ohtsu A, Shah MA, Van Cutsem E, *et al*. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011;29:3968–76.
[30] Moehler M, Mueller A, Hartmann JT, *et al*. An open-label, multicentre biomarker-oriented AIO phase II trial of sunitinib for patients with chemo-refractory advanced gastric cancer. Eur J Cancer 2011;47: 1511–20.
[31] Sun W, Powell M, O'Dwyer PJ, *et al*. Phase II study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203. J Clin Oncol 2010;28:2947.
[32] Macedo F, Ladeira K, Longatto-Filho A, *et al*. Gastric cancer and angiogenesis: Is VEGF a useful biomarker to assess progression and remission? J Gastric Cancer 2017;17:1–10.
[33] Wilke H, Muro K, Van Cutsem E, *et al*. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224–35.
[34] Su X, Zhan P, Gavine PR, *et al*. FGFR2 amplification has prognostic significance in gastric cancer: results from a large international multicentre study. Br J Cancer 2014;110:967–75.
[35] Inokuchi M, Fujimori Y, Otsuki S, *et al*. Therapeutic targeting of fibroblast growth factor receptors in gastric cancer. Gastroenterol Res Pract 2015;2015:796380.
[36] Ohtsu A, Ajani JA, Bai YX, *et al*. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J Clin Oncol 2013;31:3935.
[37] Ramanathan RK, McDonough SL, Kennecke HF, *et al*. Phase 2 study of MK-2206, an allosteric inhibitor of AKT, as second-line therapy for advanced gastric and gastroesophageal junction cancer: A SWOG cooperative group trial (S 1005). Cancer 2015;121:2193–7.
[38] Rüschoff J, Hanna W, Bilous M, *et al*. HER2 testing in gastric cancer: a practical approach. Mod Pathol 2012;25:637–50.
[39] Fornaro L, Lucchesi M, Caparello C, *et al*. Anti-HER agents in gastric cancer: from bench to bedside. Nat Rev Gastroenterol Hepatol 2011;8:369–83.
[40] 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; 376:687–97.
[41] Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes—a systematic review. Int J Cancer 2012;130:2845–56.
[42] Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell 2015;27: 450–61.
[43] Keir ME, Butte MJ, Freeman GJ, *et al*. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.
[44] Wahid M, Akhter N, Jawed A, *et al*. Pembrolizumab's non-cross resistance mechanism of action successfully overthrown ipilimumab. Crit Rev Oncol Hematol 2017;111:1–6.
[45] Nguyen CM, Jacob SE. Pembrolizumab. J Dermatol Nurses' Assoc 2017; 9:95–7.
[46] Gunturu KS, Woo Y, Beaubier N, *et al*. Gastric cancer and trastuzumab: first biologic therapy in gastric cancer. Ther Adv Med Oncol 2013;5:143.
[47] Liu J, Pan C, Guo L, *et al*. A new mechanism of trastuzumab resistance in gastric cancer: MACC1 promotes the Warburg effect via activation of the PI3K/AKT signaling pathway. J Hematol Oncol 2016;9:1–5.
[48] Sun JM, Shen L, Shah MA, *et al*. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021;398:759–71.
[49] Janjigian YY, Kawazoe A, Bai Y, *et al*. 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 2023;402:2197–208.
[50] Catenacci DVT, Chung HC, Shen L, *et al*. Safety and efficacy of HER2 blockade by trastuzumab-based chemotherapy-containing combination strategies in HER2 + gastroesophageal adenocarcinoma. ESMO Open 2022;7:100360.
[51] 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, randomized controlled trial [published correction appears in Lancet. 2010 Oct 16;376(9749):1302]. Lancet 2010;376:687–97.
[52] Kim CG, Jung M, Kim HS, *et al*. Trastuzumab Combined with ramucirumab and paclitaxel in patients with previously treated human epidermal growth factor receptor 2-positive advanced gastric or gastroesophageal junction cancer. J Clin Oncol 2023;41:4394–405. doi:10.1200/JCO.22.0212
[53] Swain SM, Miles D, Kim SB, *et al*. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomized, placebo-controlled, phase 3 study. Lancet Oncol 2020;21:519–30.
[54] Modi S, Jacot W, Yamashita T, *et al*. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 2022; 387:9–20.
[55] Sun JM, Shen L, Shah MA, *et al*. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomized, placebo-controlled, phase 3 study [published correction appears in Lancet. 2021 Nov 20;398 (10314):1874]. Lancet 2021;398:759–71.
[56] Janjigian YY, Kawazoe A, Yañez P, *et al*. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Nature 2021;600:727–30.
[57] Chait MM. Gastroesophageal reflux disease: important considerations for the older patients. World J Gastrointest Endosc 2010;2:388–96.
[58] Committee on Diagnostic Error in Health Care; Board on Health Care Services; Institute of Medicine; The National Academies of Sciences, Engineering, and Medicine. Improving Diagnosis in Health Care. Balogh EP, Miller BT, Ball JR, editors. Washington (DC): National Academies Press (US); 2015. PMID: 26803862.
[59] Kawaguchi Y, Akaike H, Shoda K, *et al*. Is surgery the best treatment for elderly gastric cancer patients? World J Gastrointest Surg 2021;13: 1351–60.
[60] Powell AG, Wheat JR, Eley C, *et al*. Economic cost-utility analysis of stage-directed gastric cancer treatment. BJS Open 2021;5:zrab129.
[61] Mahar AL, El-Sedfy A, Brar SS, *et al*. Are we lacking economic evaluations in gastric cancer treatment? Pharmacoeconomics 2015;33:83–7.
[62] Nova E, Gómez-Martinez S, González-Soltero R. The influence of dietary factors on the gut microbiota. Microorganisms 2022;10:1368.
[63] Pihlak R, Fong C, Starling N. Targeted therapies and developing precision medicine in gastric cancer. Cancers 2023;15:3248.
[64] Sahin U, Derhovanessian E, Miller M, *et al*. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature 2017;547:222–6.