Advances in Systemic Therapy for Gastric Cancer

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KEYWORDS

• Gastric cancer • Targeted therapy • Immunotherapy • Cytotoxic chemotherapy

KEY POINTS

- Multiple randomized controlled trials have shown benefit with adjuvant and perioperative chemotherapy with or without radiation therapy in resected stage I to III gastric adenocarcinoma.
- Several standard-of-care options exist for resectable disease, and practices vary depending on region.
- Standard-of-care treatment options for metastatic gastric cancer is guided by performance status, and multiple 2- and 3-drug regimens, with or without immunotherapy, have shown efficacy.
- In human epidermal growth factor 2–overexpressing metastatic gastric cancer, trastuzumab combined with chemotherapy is considered the standard of care.
- Several second- and third-line treatment options have recently been approved, including the vascular endothelial growth factor antibody, ramucirumab, with or without paclitaxel, as well TAS-102.
- Immunotherapy has been approved in the second- and third-line settings for select patients.

INTRODUCTION

Although the global incidence of gastric cancer is declining, it continues to represent a major health problem and leading cause of cancer-related mortality. Many cases are diagnosed late, with unresectable or metastatic disease. For the approximately 50% of patients diagnosed with early stage disease, characterized by disease localized to the stomach or surrounding lymph nodes, systemic chemotherapy, with or without radiotherapy, has proved to improve outcomes in select patients undergoing surgery.[1]

The prognosis remains poor for those patients diagnosed with metastatic or unresectable gastric cancer, with standard-of-care therapies having a modest impact on

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patient survival and quality of life. Currently, the median survival ranges from 4 months with best supportive care (BSC), to 12 months with traditional cytotoxic chemotherapy.[2,3] Over the past few decades, improved understanding of the molecular pathogenesis and biology of cancer has led to the development of novel targeted therapeutic strategies that have led to improvements in survival in select settings. These targeted therapies are currently available as monoclonal antibodies (mAbs) and small molecule inhibitors, most of which are tyrosine kinase inhibitors (TKIs). As a result, current systemic treatments for metastatic gastric cancer consists of combination cytotoxic chemotherapy, with targeted therapies such as trastuzumab and ramucirumab being incorporated in combination with cytotoxic chemotherapy in first- and second-line treatment, respectively, in select settings.[4,5] Furthermore, the discovery of immune checkpoint inhibition in the past decade has been considered a major medical and scientific breakthrough in the treatment of cancer; however, trials examining the use of immunotherapy either as a monotherapy or in combination with cytotoxic chemotherapy in gastric cancers have only led to limited approval in the second-line setting, after failure of initial therapy, with relatively low response rates ranging between 5% and 30%.[6,7] The aim of this chapter is to summarize the currently studied and approved treatments for gastric cancer and to briefly highlight some of the most promising future treatments currently under investigation.

RESECTABLE DISEASE

Patients with early disease (ie, those with in situ or T1a tumors) can often be cured with either endoscopic or surgical resection alone. However, in patients with more advanced disease, those with invasion into or beyond the muscularis propria (≥T2 lesions) or those with regional lymph node involvement, recurrence rates are significantly higher. For these patients, chemotherapy with or without radiotherapy plays an important role in reducing recurrence and has been integrated into standard of care treatment approaches. **Table 1** summarizes several landmark trials that investigated systemic and radiotherapies for the treatment of resectable gastric cancer.

The first study to demonstrate benefit with adjuvant therapy was the US Southwest Oncology Group/Intergroup study (SWOG 9008/INT-0116) reported in 2001. This phase III trial randomized 556 patients with adenocarcinoma of the stomach or gastroesophageal junction (GEJ) to receive surgery followed by adjuvant chemoradiotherapy or surgery alone. Patients who received chemoradiotherapy were administered adjuvant fluorouracil with leucovorin, followed by chemoradiotherapy with 45 Gy of radiation with fluorouracil with leucovorin as a radiosensitizer, and radiation, followed by fluorouracil with leucovorin. The addition of adjuvant chemoradiotherapy led to an improvement in median overall survival (mOS) (36 vs 27 months; hazard ratio [HR] 1.35; CI 95% 1.09 to 1.66; $P = .005$).[1] Although this was a practice changing trial, a major criticism of this study was the low rate of D2 lymph node dissections performed during surgery. Approximately 90% of patients underwent either a D0 or D1 lymph node dissection, suggesting that adjuvant treatment primarily benefits those patients receiving a less extensive lymph node dissection.[16] A retrospective analysis of the Dutch Gastric Cancer Group Trial (DGCT) in which patients were randomly assigned to undergo either a D1 or D2 dissection followed by chemoradiotherapy have led further support to this notion. The investigators found that adjuvant chemoradiotherapy significantly benefited those patients who received a D1 dissection but had a more limited impact on those who received a D2 dissection.[17]

The phase III CLASSIC trial sought to investigate the potential role for postoperative chemotherapy in patients who underwent a curative D2 gastrectomy. In this study,

Table 1
Landmark trials in the treatment of resectable gastric cancer

Author (Date), Study Name	Treatment Regimen	Total Patients	DFS, HR, *P*-value	mOS, HR, *P*-value
MacDonald et al,[1] 2001, SWOG 9008/INT-0116	Adjuvant chemoradiotherapy (fluorouracil) vs surgery alone	556	48% vs 31%, HR 1.52, $P < .001$	36 vs 27 mo, HR 1.35, $P = .005$
Noh et al,[8] 2014, CLASSIC	Adjuvant chemotherapy (capecitabine + oxaliplatin) vs surgery alone	1035	74% vs 59%, HR 0.58, $P < .0001$	78% vs 69%, HR 0.66
Lee et al,[9] 2012, ARTIST	Adjuvant chemotherapy (XP) vs chemoradiotherapy	458	78.2% vs 74.2%, $P = .862$	NR
Park et al,[10] 2019, ARTIST II	Adjuvant chemotherapy vs chemoradiotherapy in D2 node positive disease	538	78% vs 73%, $P = .667$	NR
Cunningham et al, [11] 2006, MAGIC	Perioperative chemotherapy (ECF) vs surgery alone	506	NR HR 0.66, $P < .001$	36% vs 23%, HR 0.75, $P = .009$
Ychou et al,[12] 2011, FNCLCC/FFCD	Perioperative chemotherapy (CF) vs surgery alone	224	34% vs 19%, HR 0.65, 0 = 0.003	38% vs 24%, HR 0.69, $P = .02$
Alderson et al,[13] 2017, UK MRCOE05	Neoadjuvant chemotherapy ECX vs CF	897	14.4 vs 11.6, HR 0.86, $P = .051$	26.1 vs 23.4, $P = .19$
Cats et al,[14] 2018, CRITICS	Perioperative chemotherapy (ECX) vs neoadjuvant chemotherapy + adjuvant chemoradiotherapy	788	NR	43 vs 37 mo, HR 1.01, $P = .90$
Al-Batran et al,[15] 2019, FLOT4-AIO	Perioperative ECX/ECF vs FLOT	716	30 vs 18 mo, HR 0.75, $P < .001$	50 vs 35 mo, HR 0.77, $P = .012$

Abbreviation: NR, not reported.

1035 patients were randomized to receive adjuvant capecitabine and oxaliplatin for 6 months versus observation following surgery. The addition of adjuvant chemotherapy led to a significant improvement in 3-year disease-free survival (DFS; 74% vs 59%; HR 0.58; 95% CI 0.47–0.72; $P < .0001$) and 5-year overall survival (OS; 78% vs 69%; HR 0.66; 95% CI 0.51–0.85). Notably, 56% of patients in the adjuvant chemotherapy arm experienced grade 3 or 4 toxicities primarily in the form of nausea, neutropenia, and decreased appetite.[8]

Multiple studies have also attempted to determine the benefits of radiation therapy when added to adjuvant chemotherapy in patients who achieve a D2 resection. The ARTIST trial randomized 458 patients who had undergone a curative D2 gastrectomy to receive either adjuvant chemotherapy or adjuvant chemoradiotherapy. Patients received 6 cycles of adjuvant capecitabine and cisplatin (XP) versus 2 cycles of XP followed by radiation therapy, then an additional 2 cycles of XP. Interestingly, the addition of radiation therapy did not lead to improvement in 3-year DFS (78.2% vs 74.2%; $P = .862$) or OS. However, a subgroup analysis revealed that in those patients with lymph node positive who received adjuvant chemoradiotherapy there was a 3-year DFS benefit (77.5% vs 72.3%; $P = .0365$).[9] This prompted the subsequent ARTIST II trial, which further examined the role of adjuvant chemoradiotherapy in 538 patients who had undergone curative D2 gastrectomy and were found to have lymph node positive disease. Ultimately, there was no difference in 3-year DFS between adjuvant chemotherapy versus adjuvant chemoradiotherapy (78% vs 73%, respectively; $P = .667$) in this population.[10]

The MAGIC trial investigated the role of perioperative chemotherapy versus surgery alone in 503 patients with potentially resectable gastric adenocarcinoma. Perioperative chemotherapy consisted of 3 cycles of epirubicin, cisplatin, and fluorouracil (ECF) given both before and after resection. The addition of perioperative ECF led to an improvement in 5-year mOS (36% vs 23%; HR 0.75; CI 95% 0.60–0.93; $P = .009$) but was associated with significant toxicities, with 58% of patients being unable to complete all 6 treatments. Of the patients who completed preoperative treatments, 34% were unable to complete postoperative treatments due to disease progression, patient choice, toxicity, or operative complications.[11] In light of these findings, much of the benefit observed on this trial has been attributed to the neoadjuvant treatment received. Given the high rate of toxicity with perioperative chemotherapy in the MAGIC trial, the French FNCLCC/FFCD trial examined the use of perioperative chemotherapy with cisplatin and fluorouracil (CF) versus surgery alone. This study also demonstrated a statistically significant improvement in 5-year mOS (38% vs 24%; HR 0.69; CI 95% 0.50–0.95; $P = .02$), similar to that noted in the MAGIC trial with ECF. Furthermore, the incidence of grade 3 and 4 toxicity was lower, occurring in 38% of patients.[12] Given the improved toxicity profile with a similar survival benefit, the UK Medical Research Council OE05 trial compared the neoadjuvant use of epirubicin, cisplatin, and capecitabine (ECX) with CF. This phase III trial demonstrated a similar mOS (26.1 vs 23.4 months, respectively; $P = .19$) with a lower rate of treatment completion in the ECX arm (81% vs 96%).[13] The CRITICS trial sought to investigate the addition of radiotherapy to perioperative epirubicin, capecitabine, and cisplatin or oxaliplatin (ECX or EOX) in patients with resectable gastric or GEJ adenocarcinoma. In this phase III trial, 788 patients received 3 cycles of preoperative and postoperative ECX/EOX. In the chemoradiotherapy arm, patients also received 3 cycles of preoperative and postoperative ECX/EOX with the addition of postoperative radiotherapy. Ultimately, there was no difference in mOS with perioperative chemoradiotherapy compared with chemotherapy alone (37 vs 43 months, respectively; HR 1.01; 95% CI 0.84–1.22; $P = .90$).[14] This has become widely adopted as the

perioperative treatment regimen of choice and has been adopted into major guidelines throughout the United States.

Recently, the phase II/III FLOT4-AIO trial examined an alternative regimen, a combination of fluorouracil with leucovorin plus oxaliplatin and docetaxel (FLOT), as perioperative therapy. In this trial, 716 patients with locally advanced, resectable gastric or GEJ adenocarcinoma were randomized to receive 3 cycles of preoperative and postoperative ECF/ECX or 4 cycles of preoperative and postoperative FLOT. This regimen demonstrated an improved mOS (50 vs 35 months; HR 0.77; 95% CI 0.63–0.94; $P = .012$) and progression-free survival (PFS) (30 vs 18 months; HR 0.75; 95% CI 0.62–0.91; $P < .001$) with a 27% toxicity rate in both arms.[15]

The role of chemotherapy with or without radiation in patients with resectable disease continues to evolve, and this is reflected in differing global treatment practices. Perioperative chemotherapy is becoming widely adopted in the United States and Europe, adjuvant chemoradiotherapy is still used in much of the United states, and adjuvant chemotherapy alone is often favored in Asia.

ADVANCED DISEASE

First-Line Treatment

Cytotoxic chemotherapy has demonstrated modest activity against gastric cancer: anthracyclines (eg, doxorubicin, epirubicin), fluoropyrimidines (eg, fluorouracil, capecitabine, S-1), platinums (eg, cisplatin, oxaliplatin), taxanes (eg, paclitaxel, docetaxel), and topoisomerase inhibitors (eg, irinotecan). These agents have all shown activity when used as a monotherapy. For example, the objective response rates (ORR) with fluoropyrimidines lies between 20% and 40%,[3,18] compared with an ORR of approximately 20% with either taxanes ORR 20% or irinotecan use.[19,20] Furthermore, a Cochrane review showed an improved mOS with combination chemotherapy when compared with single-agent fluorouracil (8.3 vs 6.7 months).[3]

In patients with human epidermal growth factor 2 (HER2)-negative, metastatic gastric adenocarcinoma, deemed fit for multiagent chemotherapy, the current standard of care consists of either 2- or 3-drug regimens. **Table 2** summarizes the landmark trials for first-line treatment of metastatic gastric cancer. The first multiagent chemotherapy was established in 1980, based on the findings of a randomized trial in which 62 patients with advanced gastric cancer were treated with fluorouracil, doxorubicin, and mitomycin (FAM) and resulted in a partial response rate of 42% and an mOS of 5.5 months.[26] In 1991, a randomized phase III trial compared FAM with fluorouracil, doxorubicin, and methotrexate (FAMTX) and demonstrated an improvement in both mOS (9.7 vs 6.7 months; $P < .004$) and an ORR of (41% versus 9%; $P < .001$). Impressively, 6% of patients in the FAMTX arm demonstrated a complete response (CR) compared with 0% in the FAM arm.[21] FAMTX remained the standard front-line regimen until the late 1990s when the ECF demonstrated superiority in the phase III randomized controlled trial. In this trial 274 patients with advanced gastroesophageal cancer were randomized to ECF or FAMTX. ECF demonstrated both an improved ORR (45% vs 21%; $P = .0002$) and mOS (8.9 vs 5.7 months; $P = .0009$).[22] Surprisingly, mOS of FAMTX in this trial was substantially lower as compared with prior studies, and these results remain controversial to this day. Furthermore, the added benefit of epirubicin, which adds substantial toxicity, has been questions, similar to its use in resectable disease.

In 2006, the V325 study group compared the efficacy of a 2- versus 3-drug combination in a multinational phase II/III trial. In total, 445 patients with metastatic or locally recurrent gastric or GEJ adenocarcinoma were randomized to receive either

Table 2
Landmark trials in first-line treatment of metastatic gastric cancer

Author (Date), Study Name	Treatment Regimen	Total Patients	ORR/CR	mPFS (mo) HR, *P*-value	mOS (mo), HR, *P*-value
MacDonald, et al,[26] 1980	Fluorouracil, doxorubicin, & mitomycin (FAM)	62	42%/NR	NR	5.5
Wils, et al,[21] 1991	Fluorouracil, doxorubicin, & methotrexate (FAMTX) vs FAM	160	41%/6% 9%/0%	NR	9.7 vs 6.7
Webb, et al,[22] 1997	Epirubicin, cisplatin, & fluorouracil (ECF) vs FAMTX	219	45%/6% 21%/2%	FFS: 7.4 vs 3.4 $P = .00006$	8.9 vs 5.7, $P = .0009$
Van Cutsem, et al,[23] 2006, V325	Cisplatin & fluorouracil (CF) vs docetaxel, cisplatin, & fluorouracil (DCF)	270	37%/2% 25%/1%	TTP: 5.6 vs 3.7 HR 1.47, $P < .001$	8.2 vs 9.6, HR 1.29, $P = .02$
Shah et al,[24] 2015	DCF + granulocyte stimulating factor (G-CSF) vs modified DCF (mDCF)	85	33%/NR 49%/NR	6.5 vs 9.7 $P = .2$	12.6 vs 18.8, $P = .007$
Cunningham, et al,[25] 2008, REAL2	Epirubicin, cisplatin, & fluorouracil (ECF) vs Epirubicin, cisplatin, & capecitabine (ECX) Epirubicin, oxaliplatin, & fluorouracil (EOF) Epirubicin, oxaliplatin, & capecitabine (EOX)	1002	41%/4% 46%/4% 42%/3% 48%/4%	6.2 vs 6.7 vs 6.5 vs 7.0[a]	9.9 vs 9.9 vs 9.3 vs 11.2[a]
Bang, et al,[5] 2010, ToGA[b]	Fluoropyrimidine, cisplatin, & trastuzumab vs fluoropyrimidine, cisplatin, & placebo	594	47%/5% 35%/2%	6.7 vs 5.5 HR 0.71, $P = .0002$	13.8 vs 11.1 HR 0.74, $P = .0046$

Abbreviation: NR, not reported.
[a] Noninferior
[b] HER2-positive only.

docetaxel, cisplatin, and fluorouracil (DCF) or CF. In this trial, DCF demonstrated an improved mOS (9.2 vs 8.6 months; $P = .02$), ORR (37% vs 25%; $P = .01$), and time to progression (TTP) (5.6 vs 3.7 months; $P < .001$). Furthermore, the addition of docetaxel led to an increased rate of grade 3 and 4 toxicities, particularly neutropenia (29% vs 12%) when compared with CF.[23] Given the increased rate of neutropenia, a subsequent phase III study examined the use of granulocyte colony-stimulating factor (G-CSF) with DCF support versus modified DCF (mDCF), which consisted of a shorter continuous infusion of fluorouracil along with dose-reduced docetaxel and cisplatin. Modified DCF demonstrated an improved toxicity profile when compared with DCF plus G-CSF (22% vs 52% hospitalized) and a markedly improved mOS (18.8 vs 12.6 months; $P = .007$).[24]

In 2008, the results of the randomized phase III REAL2 trial was published. This study evaluated the interchangeability of 2 fluoropyrimidines, fluorouracil and capecitabine, and 2 platinums, cisplatin and oxaliplatin, in the treatment of advanced gastroesophageal cancer. Using a two-by-two design, the investigators evaluated 4 regimens: ECF; ECX; epirubicin, oxaliplatin, fluorouracil; and EOX. The 4 regimens were ultimately found to have noninferior ORR (41% vs 47% vs 42% vs 48%, respectively), PFS (6.2 vs 6.7 vs 6.5 vs 7.0 months, respectively), and mOS (9.9 vs 9.9 vs 9.3 vs 11.2 months, respectively).[25] The investigators concluded that capecitabine and oxaliplatin was as effective as fluorouracil and cisplatin. Notably, in current clinical practice the toxicity profile of epirubicin has limited its use to younger patients with excellent performance status.

S-1 is an oral fluoropyrimidine composed of tegafur (a prodrug of fluorouracil), gimercil (a dihydropyrimidine dehydrogenase inhibitor, which prolongs the half-life of fluorouracil), and oteracil potassium (an inhibitor of phosphorylation of intestinal fluorouracil, which increases gastrointestinal tolerability). It is approved for use in several Asian counties but has yet to be granted approval in the United States. This approval was based on the SPIRITS trial in which cisplatin plus S-1 (CS) was compared with S-1 monotherapy. CS demonstrated an improved mOS (13.0 vs 11 months; $P = .04$) and median PFS (mPFS) (6.0 vs 4.0 months; $P < .0001$).[27]

HER2 is a transmembrane protein of the ErbB family. Dimerization leads to the activation of downstream signaling pathways that ultimately drives cell-cycle progression, cell proliferation, and resistance to apoptosis.[28] As in breast cancer, *HER2* gene amplification is common and estimated to be present in up to 30% of gastric cancer cases.[29] Trastuzumab is an anti-HER2 mAb that represents one of the few successful targeted therapies for metastatic gastric cancer. The ToGA trial was the first randomized controlled trial to show benefit of trastuzumab and led to its approval in combination with chemotherapy for front-line use in the HER2-positive, metastatic gastric and GEJ adenocarcinoma.[5] HER2-positive disease in this trial was defined as 3+ positivity on immunohistochemistry or a HER2:CEP17 ratio of 2 or greater by fluorescence in situ hybridization. This landmark study randomized 584 patients to receive trastuzumab with a fluoropyrimidine and cisplatin versus placebo plus fluoropyrimidine with cisplatin and demonstrated an improved mPFS (6.7 vs 5.5 months; HR 0.71; 95% CI 0.59–0.85; $P = .0002$) and mOS (13.8 vs 11.1 months; HR 0.74; 95% CI 0.60–0.91; $P = .0046$). The addition of trastuzumab also demonstrated an improved duration of response (6.9 vs 4.8 months; HR 0.53; 95% CI 0.40–0.73; $P < .0001$), ORR (47% vs 35%; $P = .0017$), and TTP (7.1 vs 5.6 months; HR 0.70; 95% CI 0.58–0.85; $P = .0003$). The overall rates of all grades or only grade 3 to 4 toxicities were not significantly different between the 2 arms.[5]

In April 2021, nivolumab was approved for use in combination with chemotherapy for metastatic gastric cancer and esophageal adenocarcinoma. As is described later

in this chapter, the CHECKMATE-649 trial demonstrated a statistically significant improvement in PFS and OS with the combination of chemotherapy and immunotherapy over chemotherapy alone and is now redefining the standard of care.

Subsequent Lines of Treatment

In the second-line setting and beyond, cytotoxic chemotherapy has had a modest impact on mOS. Ramucirumab, an mAb targeting vascular endothelial growth factors (VEGF), has been examined in the front- and second-line setting. In the phase III RAINFALL trial, 645 patients with HER2-negative, metastatic gastric or GEJ adenocarcinoma were randomized to receive ramucirumab plus a fluoropyrimidine and cisplatin or placebo plus a fluoropyrimidine and cisplatin. When added to chemotherapy in the front-line setting, ramucirumab did not significantly improve mOS (11.7 vs 10.7 months, respectively; $P = .6757$), and only marginally improved mPFS (5.7 vs 5.4 months; $P = .0106$).[30] However, in the second-line setting, ramucirumab has demonstrated benefit both as a single agent and in combination with chemotherapy. The phase III REGARD trial compared the use of ramucirumab monotherapy versus BSC in the second-line setting for patients with metastatic gastric or GEJ adenocarcinoma. Ramucirumab monotherapy led to an improvement in mOS (5.2 vs 3.8 months; HR 0.78; 95% CI 0.60–0.99; $P = .047$) and mPFS (6.7 vs 5.3 months; HR 0.80; 95% CI 0.68–0.93; $P = .037$).[31] More recently, the landmark RAINBOW trial randomized patients who had progressed on or within 4 months of first-line chemotherapy (fluoropyrimidine-platinum with or without an anthracycline) to receive either ramucirumab plus paclitaxel or placebo plus paclitaxel. Ramucirumab plus paclitaxel demonstrated an improvement in mOS (9.6 vs 7.4 months; HR 0.81, 95% CI 0.68–0.96; $P = .0169$), leading to the approval of ramucirumab plus paclitaxel in the second-line setting, and this is currently a preferred second-line regimen for patients with metastatic gastric cancer.[4]

Multiple trials have also investigated single-agent chemotherapy in the second-line setting, demonstrating improvements in both quality of life and survival. In 2011, a randomized study compared irinotecan with BSC in the second-line setting and demonstrated a modest improvement in mOS (4.0 vs 2.4 months; HR 0.48, 95% CI 0.25–0.92; $P = .012$).[32] Another phase III study comparing salvage chemotherapy with either docetaxel or irinotecan with BSC in the second-line setting also demonstrated a modest improvement in mOS (5.3 vs 3.8 months, respectively; HR 0.657, 95% CI 0.485–0.891; $P = .007$) with salvage chemotherapy.[33] COUGAR-02, an open-labeled phase III study, compared docetaxel with BSC in the second-line setting in patients with esophageal, gastric, or GEJ adenocarcinoma that had progressed on or within 6 months of treatment with a fluoropyrimidine-platinum regimen. This open-labeled phase III study demonstrated that docetaxel led to an improved mOS (5.2 vs 3.6 months; HR 0.67, 95% CI 0.49–0.92; $P = .01$).[34] Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) was compared with solvent-bound paclitaxel in the phase III ABSOLUTE trial. In this study, nab-paclitaxel was administered either weekly or every 3 weeks compared with solvent-bound paclitaxel, which was administered weekly. This trial demonstrated noninferiority between the weekly nab-paclitaxel and solvent-bound paclitaxel in terms of mOS (11.1 vs 10.9 months; HR 0.97, 97.5% CI 0.76–1.23; noninferiority margin 1.25; one-sided $P = .0085$). However, when nab-paclitaxel was administered every 3 weeks and compared with the weekly solvent-bound paclitaxel, nab-paclitaxel failed to meet the noninferiority threshold (10.3 vs 10.9 months; HR 1.06, 97.5% CI 0.87–1.31; one-sided $P = .062$).[35] Together, these trials demonstrate benefit with single-agent chemotherapy in the second-line setting providing clinicians with several options.

Recently, TAS-102, a combination of trifluridine (FTD), a thymidine analogue, and tipiracil (TPI), thymidine phosphorylase inhibitor, has been examined in patients with metastatic gastric and GEJ cancer. The TAGS trial evaluated this agent in patients with or without prior gastrectomy, who had progressed on at least 2 previous lines of chemotherapy. A total of 507 patients were randomized 2:1 to receive TAS-102 or BSC. FTD/TPI demonstrated an improved mOS (6.0 vs 3.4 months; HR 0.57, CI 95% 0.41–0.79) and mPFS (2.2 vs 1.8 months; HR 0.48, 95% CI 0.35–0.65) in the population who had undergone prior gastrectomy and an improved mOS (5.6 vs 3.8 months; HR 0.80, CI 95% 0.60–1.06) and mPFS (1.9 vs 1.8 months; HR 0.65, 95% CI 0.49–0.85) in patients without a prior gastrectomy.[36] These data led to the approval of TAS-102 as a third-line therapy for patients with metastatic gastroesophageal cancer.

Immunotherapy for Gastric Cancer

Several novel classes of agents have also shown promise in advanced gastric cancer. Immune checkpoint inhibitors (ICIs) are among those that have been most developed and have recently been approved in the second- and third-line settings. Response rates are variable and select patient populations derive more benefit, for example, those with microsatellite instability (MSI-H) or deficient mismatch repair (dMMR), and therefore careful selection is necessary.[37]

Pembrolizumab is the most extensively studied ICI in gastric cancer and is the only agent approved for use in the second-line setting, in MSI-H or dMMR disease, and in the third-line setting, for programmed death ligand 1 (PD-L1)-positive disease. In 2017, pembrolizumab gained approval for use in the third-line setting based on the findings of KEYNOTE-059. This phase II trial enrolled 259 patients and administered pembrolizumab every 3 weeks until disease progression and demonstrated an ORR of 11.6% with 2.3% achieving a CR. Furthermore, inpatients whose tumors that were PD-L1 positive had an ORR of 15.5% compared with 6.4% in those with PD-L1–negative tumors. In tumors that were MSI, the ORR was 57% compared with 9% in MSS tumors.[6]

Subsequently, KEYNOTE-062 sought to examine the use of pembrolizumab monotherapy versus cisplatin plus a fluoropyrimidine with or without pembrolizumab in 763 patients with HER-2–negative, advanced or metastatic gastric or GEJ cancer whose tumors expressed PD-L1 (defined as Combined Positive Score [CPS] $\geq$ 1). When chemotherapy alone was compared with pembrolizumab monotherapy, there was noninferior mOS (10.6 vs 11.1 months; HR 0.91, 95% CI 0.69–1.18; noninferiority margin 1.2) although there was a lower ORR (14.5% vs 36.8%). When examining the use of pembrolizumab monotherapy in patients whose tumors strongly expressed PD-L1 (CPS $\geq$ 10), there was significant improvement in mOS (17.4 vs 10.8 months; HR 0.69, 95% CI 0.49–0.97). Unfortunately, the addition of pembrolizumab to chemotherapy did not lead to an improved mOS (12.5 vs 11.1 months; HR 0.85, 95% CI 0.70–1.03) or mPFS (6.9 vs 6.4 months; HR 0.84, 95% CI 0.70–1.02).[38]

Additional cohorts from KEYNOTE-059 have examined the use of pembrolizumab monotherapy or in combination with chemotherapy (fluoropyrimidine and cisplatin) in the front-line setting for advanced gastric and GEJ cancers. Patients who received pembrolizumab monotherapy were required to have PD-L1–positive disease (CPS $\geq$ 1) and demonstrated an ORR of 25.8% with 6.5% achieving a CR and mPFS of 3.3 month. In the patients who received pembrolizumab in combination with chemotherapy, PD-L1 expression was not a requirement, although 64% of patients had PD-L1 expression. In this arm, ORR was 60%, with 4% demonstrating a CR and mPFS of 6.6 months.[39–41]

More recently, based on the results of the CHECKMATE-649 trial, the combination of nivolumab and chemotherapy has been approved for use in patients with unresectable advanced metastatic gastric or gastroesophageal cancer. In this global phase III study, a total of 1,581 patients with untreated, unresectable advanced or metastatic gastric, GEJ or esophageal cancer were randomized to receive nivolumab with chemotherapy versus nivolumab plus ipilimumab versus chemotherapy alone. In patients with a CPS > 5, the addition of nivolumab to chemotherapy led to improvement in mOS (14.4 vs 11.1 months; HR 0.71; 98.4% CI 0.59-0.86; p<0.0001) and mPFS (7.7 vs 6.0 months; HR 0.68; 98% CI 0.56-0.81; p<0.0001). Notably, benefits with combination therapy were also statistically significant for the PD-L1 CPS $\geq$ 1 population (HR = 0.77; P = .0001) and for all randomly assigned patients (HR = 0.80; P = .0002). Fewer than 5% of patients experienced grade 3 or 4 toxicities, and there were no grade 5 events.[42]

In Asia, nivolumab is approved for monotherapy use based on the results of ATTRACTION-2, which examined 493 patients with unresectable advanced or recurrent gastric or GEJ cancer who progressed after 2 or more previous chemotherapy regimens. Patients from Japan, South Korea, and Taiwan were randomized to nivolumab monotherapy or BSC and demonstrated an improved mOS (5.26 vs 4.14 months; HR 0.63, 95% CI 0.51–0.78; *P* < .0001) and mPFS (1.61 vs 1.45 months; HR 0.60, *P* < .0001).[7] CheckMate-032 examined the use of nivolumab combined with ipilimumab, an anticytotoxic T-lymphocyte–associated protein 4 antibody, in the second-line setting any beyond in patients with locally advanced or metastatic esophageal, gastric, or GEJ cancers regardless of PD-L1 or MSI status. In this phase I/II study, 160 patients were randomized to nivolumab, 3 mg/kg, monotherapy (NIVO3); nivolumab, 1 mg/kg, plus ipilimumab, 3 mg/kg, (NIVO1 + IPI3); and nivolumab, 3 mg/kg, plus ipilimumab, 1 mg/kg, (NIVO3 + IPI1). This trial demonstrated an ORR of 12% versus 24% versus 8%, respectively; mPFS of 1.4 versus 1.4 versus 1.6 months, respectively; and mOS of 6.2 versus 6.9 versus 4.8 months, respectively. Treatment-related grade 3 and 4 toxicities were 17% versus 47% versus 27%, respectively. As would be expected, there were higher rates of toxicity in the arms with combination immunotherapy and particularly higher in the NIVO1 + IPI3 arm.[43] The results of this phase I/II study has led to subsequent larger phase II and III studies investigating nivolumab's role in front-line use either as a monotherapy or in combination with cytotoxic chemotherapy, other immunotherapies, or targeted therapies.

In Europe, avelumab, an mAb targeting PD-L1, is approved as a monotherapy for unresectable or metastatic gastric cancer based on the phase Ib JAVELIN study, which examined its use in patients who had progressed after one or more lines of fluoropyrimidine-platinum chemotherapy. Overall, avelumab demonstrated an ORR of 10%; however, in patient tumors with PD-L1 expression (defined as CPS $\geq$ 1), ORR was improved to 27.3% with an mOS of 9.1 months and 7.5% grade 3 or 4 toxicities.[44] JAVELIN Gastric 100 evaluated avelumab's role in maintenance therapy after first-line chemotherapy versus continued first-line chemotherapy. This phase III trial failed to demonstrate any improvement of mOS (10.4 vs 10.9 months; HR 0.91, 95% CI 0.74–1.11; *P* = .1779).[45] JAVELIN Gastric 300 is currently evaluating avelumab's role in the third-line setting, comparing it with either paclitaxel or irinotecan monotherapy. Preliminary results suggest no improvement in mOS (4.6 vs 5.0 months; HR 1.1, 95% CI 0.9–1.4; *P* = .81) or mPFS (1.4 vs 2.7 months; HR 1.73, 95% CI 1.4–2.2; *P* > .99) with avelumab.[46]

Response rates to immunotherapy in the treatment of gastric cancer have been modest; however, higher responses are observed in patients whose tumors express PD-L1, are MSI-H, or dMMR. As a result, there has been limited approval of ICIs in the

Table 3
Landmark trials in subsequent lines of treatment for metastatic gastric cancer

Author (Date), Study Name	Treatment Regimen	Total Patients	ORR/CR	mPFS (mo) HR, *P*-value	mOS (mo) HR, *P*-value
Fuchs, et al,[31] 2014, REGARD	Ramucirumab & best supportive care vs placebo & best supportive care	355	3%/<1% 3%/0%	2.1 vs 1.3 HR 0.483, $P < .0001$	5.2 vs 3.8 HR 0.776, $P = .47$
Wilke, et al,[4] 2019, RAINBOW	Ramucirumab & paclitaxel vs placebo & paclitaxel	665	28%/<1% 16%/<1%	4.4 vs 2.9 HR 0.635, $P < .0001$	9.6 vs 7.4 HR 0.807, $P = .017$
Fuchs et al,[6] 2018, KEYNOTE-059	Pembrolizumab	259	11.6%/2.3%	2.0	5.6
Kang et al,[7] 2017, ATTRACTION-2	Nivolumab vs placebo	493	11.2%/0% 0%/0%	1.61 v 1.45 HR 0.60, $P < .0001$	5.26 vs 4.14 HR 0.63, $P < .0001$
Doi et al,[44] 2019, JAVELIN	Avelumab	40	10%/2.5%	2.4	9.1

Abbreviation: NR, not reported.

second-line setting or beyond: pembrolizumab (United States),[6] nivolumab (Asia),[7] and avelumab (Europe).[44] Furthermore, these modest results have resulted in studies combining immunotherapy with other modalities to improve outcomes. **Table 3** summarizes the landmark trials for subsequent lines of treatment of metastatic gastric cancer.

Ongoing Studies for Advanced Gastric Cancer

Currently, there are multiple ongoing trials testing novel agents as well as various combination therapies. Success with trastuzumab in HER2-positive disease has prompted further study with trastuzumab deruxtecan, an antibody-drug conjugate combining trastuzumab with deruxtecan, a topoisomerase I inhibitor. The phase II DESTINY-Gastric01 trial randomized patients with previously treated, advanced gastric cancer to trastuzumab deruxtecan or the physician's choice of cytotoxic chemotherapy and demonstrated an improved ORR (51% vs 14%, $P < .001$) and mOS (12.5 vs 8.4 months; HR 0.59; 95% CI 0.39–0.88; $P = .01$).[47] Given these promising results, DESTINY-Gastric02 is evaluating its use in the second-line setting in patients who have received front-line trastuzumab.[48]

With the introduction of immunotherapy onto the treatment landscape, there has been interest in combining immunotherapy with a trastuzumab-chemotherapy backbone. A recent phase II trial examined the addition of pembrolizumab to trastuzumab and fluoropyrimidine/platinum-based chemotherapy in 37 patients with metastatic esophageal, gastric, or GEJ cancer regardless of PD-L1 expression. Notably, 26 of 37 patients (70%) were progression free at 6 months.[49] These promising data have prompted the ongoing, phase III trial, KEYNOTE-811.[50]

Regorafenib is a small molecular TKI with several targets including VEGF. It has been evaluated in the INTEGRATE trial for use in patients with metastatic gastric or GEJ adenocarcinoma who progressed on one or more lines of chemotherapy. In this phase II trial, regorafenib led to an improvement in mPFS (2.6 vs 0.9 months; HR 0.40; 95% CI 0.28–0.59; $P < .001$) with a trend toward improved mOS (5.8 vs 4.5 months; HR 0.74; $P = .147$).[51] INTEGRATE II is the follow-up phase III trial that is currently examining regorafenib in the refractory setting.[52] Regorafenib has been examined in combination with immunotherapy. The phase Ib REGONIVO trial combined regorafenib with nivolumab in 50 patients with metastatic gastric or colorectal cancer who had received at least 2 lines of prior therapy. In the gastric cancer cohort, the mPFS was 5.6 months (95% CI 2.7–10.4 months) and mOS was 12.3 months (95% CI 5.3-not reached) with few treatment-related adverse effects such as rash (12%), proteinuria, (12%) and palmar-plantar erythrodysesthesia (10%).[53] Similar to the RAINBOW trial, regorafenib is currently being examined in the second-line setting in combination with paclitaxel in the phase Ib REPEAT trial.[54]

Claudins are a family of proteins found in gastric mucosa that are involved with tight cell junctions, controlling the movement of molecules between cells. Isoform 2 of claudin-18 (CLDN18.2) is expressed in 50% to 70% of gastric tumors and is thought to be critical for tumor growth and development.[55] Zolbetuximab is a promising anti-CLDN18.2 mAb that is currently being evaluated for use in metastatic gastric cancer. In the phase II FAST trial, patients with advanced or recurrent, HER2-negative CLDN18.2 expressing tumors (defined as >2+ staining with anti-CLDN18 antibodies) were randomized to receive EOX with or without zolbetuximab. The addition of the anti-CLDN18.2 mAb led to an improved mOS (13.0 vs 8.4 months; HR 0.56, 95% CI 0.40–0.67; $P = .0008$) and mPFS (7.5 vs 5.3 months; HR 0.44, 95% CI 0.29–0.67; $P < .0005$).[56] These results prompted the ongoing phase III SPOTLIGHT trial, which randomizes patients with HER2-negative, advanced or metastatic, CLDN18.2-expressing gastroesophageal cancer to FOLFOX with or without zolbetuximab.[57]

SUMMARY

In resectable, localized gastric cancer, randomized trials have demonstrated that adjuvant and perioperative systemic chemotherapy, with or without radiotherapy, improves patient outcomes. Although controversies regarding choice of regimen, timing of therapy, perioperatively versus adjuvant, and whether or not to incorporate radiotherapy remain, there is strong evidence that surgery alone is insufficient, especially in those cases of locally advanced disease. Currently, there are multiple standard-of-care treatment options including fluoropyrimidine/platinum doublet therapies and, for those with strong performance status, a triplicate therapy with FLOT should be considered.[15]

In metastatic disease, traditional cytotoxic chemotherapy has led to modest improvements in patient outcomes. In the front-line setting for HER2-negative, metastatic gastric cancer, standard chemotherapy regimens consist of a combination of a fluoropyrimidine/platinum doublet with the addition of a third chemotherapeutic agent for patients who are medically eligible with good performance status. In HER2-positive disease, trastuzumab is added to a fluoropyrimidine-platinum doublet, which is the standard first-line treatment.[5] In PD-L1 positive disease, nivolumab is added to a fluoropyrimidine-platinum doublet. In the second-line setting, ramucirumab with paclitaxel is a recommended regimen; however, in patients with PD-L1 expressing tumors, pembrolizumab is a reasonable alternative for select patients.[4,6] Currently, several promising targeted therapies and immunotherapies are being investigated and will likely further improve outcomes for patients in the near future.

DISCLOSURE

The authors have nothing to disclose.

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