The Treatment Landscape for Gastroesophageal Adenocarcinomas

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Abstract: The treatment landscape for gastroesophageal adenocarcinomas has significantly changed over the last year. The addition of nivolumab to first-line chemotherapy has led to survival benefit in patients who have metastatic gastroesophageal adenocarcinoma with a programmed death ligand 1 combined positive score of 5 or greater. Similarly, in patients with metastatic human epidermal growth factor receptor 2 (HER2)–positive gastroesophageal adenocarcinoma, the addition of pembrolizumab to chemotherapy and trastuzumab has significantly improved efficacy. Furthermore, a phase 2 study revealed that trastuzumab deruxtecan, a new antibody-drug conjugate, significantly improved survival in comparison with chemotherapy among patients with HER2-positive gastric cancer in the refractory setting, and it produced a signal of efficacy in the second-line setting. Chemoimmunotherapy combinations are now considered the standard of care for a significant number of patients with gastroesophageal adenocarcinomas.

Keywords
Esophageal cancer, gastric cancer, gastroesophageal adenocarcinoma, nivolumab, pembrolizumab, trastuzumab deruxtecan

Background

Gastroesophageal cancers are an important cause of morbidity and mortality worldwide.[1] Although less common in the United States than in Asia, gastroesophageal cancers accounted for more than 26,000 deaths in the United States in 2021.[2] Gastroesophageal cancers can be divided into adenocarcinomas and squamous cell carcinomas. In addition, they may be classified as gastric cancer (GC), esophageal cancer (EC), and gastroesophageal junction (GEJ) cancer. GC and GEJ cancer are typically adenocarcinomas. EC can be squamous cell carcinoma or adenocarcinoma.

The standard of care for unresectable locally advanced or metastatic gastroesophageal adenocarcinoma has long been systemic chemotherapy, which improves survival and quality of life.[3] However, the median overall survival (mOS) of patients with gastroesophageal adenocarcinoma is less than a year, except for the 15% to 20% of patients with human epidermal growth factor receptor 2 (HER2) overexpression, in whom median survival is improved by the addition of trastuzumab to the chemotherapy combination.[4] Over the past year, multiple studies have been presented and subsequently changed the standard of care for patients with both *HER2*-amplified

Table 1. Phase 3 Studies Evaluating Immune Checkpoint Inhibitors for Advanced Adenocarcinoma of the Upper Gastrointestinal Tract in the First-line Setting

Study Name	Population (%)	Comparator Regimens (n)	Primary Endpoint(s)	Results, mo	Statistical Significance	Comments
KEYNOTE-062, 2020	Gastric (67.4), GEJ (32), PD-L1 CPS ≥1, HER2-negative	(1) Pembrolizumab (256) vs placebo plus cisplatin/5-FU (250) (2) Pembrolizumab plus cisplatin/5-FU or capecitabine (257) vs placebo plus cisplatin/5-FU (250)	OS in (a) PD-L1 CPS ≥1 (b) PD-L1 CPS ≥10 PFS in (c) PD-L1 CPS ≥1	(1a) 10.6 vs 11.1 (1b) 17.4 vs 10.8 (1c) 2.0 vs 6.4 (2a) 12.2 vs 11.1 (2b) 12.3 vs 10.8 (2c) 6.9 vs 6.4	(1a) HR 0.91, 99.2% CI 0.69-1.18, noninferiority margin 1.2 (1b) HR 0.69, 95% CI 0.49-0.97 (1c) HR 1.66, 95% CI 1.37-2.01 (2a) HR 0.85, 95% CI 0.70-1.03, *P*=.05 (2b) HR 0.85, 95% CI 0.62-1.17, *P*=.16 (2c) HR 0.84, 95% CI 0.70-1.02, *P*=.04	
CheckMate 649	Gastric (70), GEJ (17), EAC (13), HER2-negative	Nivolumab plus CAPOX or FOLFOX (789) vs chemotherapy alone (792)	(a) OS in PD-L1 CPS ≥5 (b) PFS in PD-L1 CPS ≥5	(a) 14.1 vs 11.1 (b) 7.7 vs 6.05	(a) HR 0.71, 98.4% CI 0.59-0.86, *P*<.0001 (b) HR 0.68, 98% CI 0.56-0.81, *P*<.0001	
ATTRACTION-4	Gastric, GEJ, HER2-negative	Nivolumab plus SOX or CAPOX (362) vs chemotherapy alone (362)	(a) OS (b) PFS	(a) 17.5 vs 17.2 (b) 10.5 vs 8.3	(a) HR 0.90, 95% CI 0.75-1.08, *P*=.257 (b) HR 0.68, 98.51% CI 0.51-0.90, *P*=.0007	Asian patients
ORIENT-16	Gastric, GEJ, HER2-negative	Sintilimab plus CAPOX (327) vs placebo + CAPOX	(a) OS in CPS ≥5 (b) OS in all randomized patients	(a) 18.4 vs 12.9 (b) 15.2 vs 12.3	(a) HR 0.66, 95% CI 0.505-0.864, *P*=.0023 (b) HR 0.766, 95% CI 0.626-0.936, *P*=.0090	All Chinese patients
KEYNOTE-590	Esophageal cancers (squamous and adenocarcinoma), Siewert type I GEJ adenocarcinoma	Pembrolizumab plus chemotherapy vs chemotherapy alone	OS in (a) PD-L1 CPS ≥10 (b) All patients (c) ESCC and PD-L1 CPS ≥10 (d) ESCC PFS in (e) ESCC (f) PD-L1 CPS ≥10 (g) All patients	(a) 13.9 vs 8.8 (b) 12.4 vs 9.8 (c) 13.5 vs 9.4 (d) 12.6 vs 9.8 (e) 6.3 vs 5.8 (f) 7.5 vs 5.5 (g) 6.3 vs 5.8	(a) HR 0.57, 95% CI 0.43-0.75, *P*<.0001 (b) HR 0.73, 95% CI 0.62-0.86, *P*<.0001 (c) HR 0.62, 95% CI 0.49-0.78, *P*<.0001 (d) HR 0.72, 95% CI 0.60-0.88, *P*=.0006 (e) HR 0.65, 95% CI 0.54-0.78, *P*<.0001 (f) HR 0.51, 95% CI 0.41-0.65, *P*<.0001 (g) HR 0.65, 95% CI 0.55-0.76, *P*<.0001	Most patients with squamous cell carcinoma

CAPOX, capecitabine plus oxaliplatin; CPS, combined positive score; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; FOLFOX, 5-fluorouracil/leucovorin plus oxaliplatin; 5-FU, 5-fluorouracil; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mo, month(s); mOS, median overall survival; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; SOX, S-1 plus oxaliplatin.

and HER2-negative gastroesophageal adenocarcinoma.

This review highlights some of the recently presented data and reviews the landscape of treatment in patients with gastroesophageal adenocarcinoma.

HER2-Negative Disease

First-line Treatment

Until recently, first-line treatment for advanced or metastatic gastroesophageal adenocarcinoma had been a platinum/fluoropyrimidine doublet, most commonly oxaliplatin combined with capecitabine (CAPOX) or 5-fluorouracil (5-FU; FOLFOX). Given the signal of benefit for adding pembrolizumab (Keytruda, Merck) to chemotherapy in the phase 2 KEYNOTE-059 study,[5] KEYNOTE-062 investigated the addition of pembrolizumab further in a phase 3 design.[6] The study examined the efficacy of pembrolizumab in the first-line treatment of metastatic programmed death ligand 1 (PD-L1)–positive GC or GEJ adenocarcinoma (Table 1). The study randomly assigned patients to pembrolizumab monotherapy (n=256), pembrolizumab plus chemotherapy (cisplatin+5-FU; n=257), or placebo plus chemotherapy (n=250) in a complex statistical design that had important ramifications for the final results. Pembrolizumab monotherapy was found to be noninferior to chemotherapy in PD-L1–positive (combined positive score [CPS] ≥1) tumors (mOS, 10.6 vs 11.1 months, respectively; hazard ratio [HR], 0.91; 99.2% CI, 0.69-1.18; noninferiority margin, 1.2). In patients with a CPS of 10 or greater, pembrolizumab showed a statistically nonsignificant improvement in OS vs chemotherapy (mOS, 17.4 vs 10.8 months, respectively; HR, 0.69; 95% CI, 0.49-0.97). However, in both groups (CPS ≥1 and CPS ≥10), pembrolizumab monotherapy was associated with significantly lower response rates, shorter progression-free survival (PFS), and no improvement in quality of life, making this regimen less attractive in gastroesophageal adenocarcinoma. Similarly, a trend toward improvement in OS was observed with the addition of pembrolizumab to chemotherapy vs chemotherapy alone in patients with a CPS of at least 1 and those with a CPS of at least 10, but the difference did not reach statistical significance. This regimen is being further investigated in KEYNOTE-859, which is examining the efficacy of adding pembrolizumab to chemotherapy in locally advanced unresectable gastric or GEJ adenocarcinoma (NCT03675737).

The addition of pembrolizumab to chemotherapy in esophageal/GEJ cancers was also investigated in the phase 3 KEYNOTE-590 study.[7] In this study, patients with untreated advanced esophageal (squamous or adenocarcinoma) or Siewert type I GEJ adenocarcinoma were randomly assigned to pembrolizumab plus chemotherapy (5-FU+cisplatin) or chemotherapy alone. Most patients had esophageal squamous cell carcinoma (73%); only 11% had GEJ Siewert 1 adenocarcinoma. The study showed OS benefit in patients with esophageal squamous cell carcinoma and a PD-L1 CPS of 10 or greater (mOS, 13.9 vs 8.8 months; HR, 0.57; 95% CI, 0.43- 0.75) and in all patients with squamous cell carcinoma (mOS, 12.6 vs 9.8 months; HR, 0.72; 95% CI, 0.60-0.88). This benefit in squamous cell carcinoma was driven by the patients with a PD-L1 CPS of 10 or greater, as no benefit was seen in those with a PD-L1 CPS of less than 10; mOS was 10.5 months in the immunotherapy arm vs 11.1 months in the chemotherapy arm (HR, 0.99; 95% CI, 0.74-1.32). In addition, no benefit was seen in the adenocarcinoma population regardless of the PD-L1 status. Despite these negative results in the adenocarcinoma population, the US Food and Drug Administration (FDA) approved the addition of pembrolizumab to chemotherapy in esophageal or Siewert type I GEJ carcinomas regardless of histology type or PD-L1 status.[8]

The discouraging results of KEYNOTE-062 for adenocarcinoma were followed by the exciting results of the CheckMate 649 study in late 2020.[9] This was a global randomized phase 3 study that included patients with previously untreated advanced or metastatic HER2-negative gastric, GEJ, or esophageal adenocarcinoma. Patients were randomized in 1:1:1 ratio to 1 of 3 arms: nivolumab (Opdivo, Bristol Myers Squibb) plus chemotherapy (FOLFOX or CAPOX; n=789), chemotherapy alone (n=792), or nivolumab and ipilimumab (Yervoy, Bristol Myers Squibb). The results of the first 2 arms were presented and published. The study included patients regardless of their PD-L1 status. Most patients had gastric cancer (70%), with a PD-L1 CPS of 5 or greater (60%). The trial met its primary endpoint for nivolumab/chemotherapy compared with chemotherapy alone (mOS, 14.4 vs 11.1 months, respectively; HR, 0.71; 98.4% CI, 0.59- 0.86) in the population with a PD-L1 CPS of 5 or greater. Additional analysis showed statistically significant benefit in all comers regardless of the PD-L1 status (mOS, 13.8 vs 11.6 months; HR, 0.79; 95% CI, 0.71-0.88). However, this benefit was driven by the population with a PD-L1 CPS of 5 or greater (60% of all patients), as no benefit was seen in those with a PD-L1 CPS of less than 5 (HR, 0.94; 95% CI, 0.78-1.13).[9] On the basis of these results, the FDA approved nivolumab in combination with chemotherapy for advanced or metastatic gastric, GEJ, or esophageal adenocarcinoma.[10]

First results of the third arm comparing nivolumab and ipilimumab vs chemotherapy were recently presented.[11] After a follow-up of 35.7 months, the study failed to show OS superiority of nivolumab and ipilimumab (the immunotherapy arm) in comparison with chemotherapy

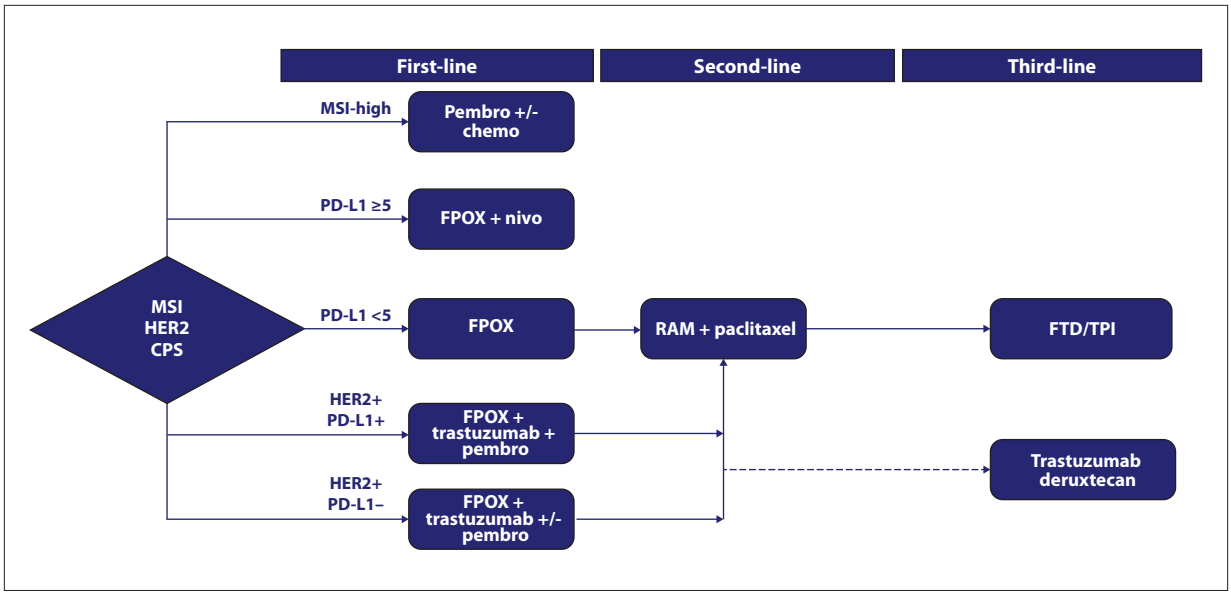

Figure. Suggested treatment algorithm in advanced/metastatic gastroesophageal adenocarcinoma.

CPS, combined positive score; FTD/TPI, trifluridine/tipiracil; FPOX, fluoropyrimidine and oxaliplatin; HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; nivo, nivolumab; PD-L1, programmed death ligand 1; pembro, pembrolizumab; RAM, ramucirumab.

alone, even in the population with a CPS of 5 or greater, with an mOS of 11.2 months in the immunotherapy arm vs 11.1 months in the chemotherapy arm (HR, 0.89; 95% CI, 0.71-1.10).[11]

The role of nivolumab was also investigated in the phase 2/3 ATTRACTION-4 trial, which looked at its efficacy when added to chemotherapy in metastatic gastric or GEJ adenocarcinoma.[12] The study randomly assigned patients to nivolumab plus chemotherapy (n=362) or chemotherapy alone (n=362). The study met its primary endpoint, with an improvement in median progression-free survival (mPFS) from 8.3 months in the chemotherapy arm to 10.5 in the chemotherapy-plus-nivolumab arm (HR, 0.68; 98.51% CI, 0.51-0.91). However, at the final analysis, the difference between mOS in the 2 arms was not statistically significant, with an mOS of 17.5 months in the immunotherapy arm vs 17.2 months in the chemotherapy arm (HR, 0.90; 95% CI, 0.75-1.08). More patients were receiving second-line treatment in ATTRACTION-4 than in CheckMate 649 (66% vs 27%, respectively), including immune checkpoint inhibitors (38% vs 8%). Whether this difference in the subsequent line of therapy explains the discrepant results is unclear, as the benefit seen in the CheckMate study was also noted in the Asian population.

A similar benefit was seen recently with sintilimab, another PD-1 inhibitor, in the randomized phase 3 trial ORIENT-16 trial,[13] which compared sintilimab plus CAPOX vs CAPOX alone. ORIENT-16 included previously untreated Chinese patients with metastatic gastric or GEJ adenocarcinoma, of whom almost 60% had a PD-L1 CPS of 5 or greater and most of whom were PD-L1–positive (84%). The study met its primary endpoint, with an improvement in mOS from 12.9 months in the chemotherapy arm to 18.4 months in the combination arm among those with a CPS of 5 or greater (HR, 0.66; 95% CI, 0.505-0.864). A similar benefit was seen in the overall population, with an mOS of 15.2 months in the immunotherapy arm vs 12.3 months in the chemotherapy arm (HR, 0.766; 95% CI, 0.626-0.936). It is unclear whether this benefit in the overall population was driven by the benefit seen in the population with a PD-L1 CPS of 5 or greater, as the results in the population with a PD-L1 CPS of less than 5 were not presented.

Overall, the addition of immunotherapy to chemotherapy in the frontline setting has significantly improved outcomes in patients with metastatic gastric/GEJ adenocarcinoma (Figure). On the basis of these data, we currently add nivolumab to chemotherapy for patients with a PD-L1 CPS of 5 or greater. This practice is consistent with the National Comprehensive Cancer Network (NCCN) recommendation (category 1). For patients with a PD-L1 CPS of less than 5, we consider chemotherapy alone as standard of care, given the lack of benefit of adding immunotherapy in this population and its potential toxicities (category 2B; NCCN guidelines).[14]

Second-line Treatment

The standard of care for patients with metastatic gastric/GEJ adenocarcinoma in the second-line setting is still paclitaxel and ramucirumab (Cyramza, Lilly), on the basis of results of the RAINBOW trial.[15] Given that many patients have underlying neuropathy due to prior platinum exposure, the use of paclitaxel in this setting remains challenging. Therefore, attempts are currently being made to study alternative, neuropathy-free regimens. The RAMIRIS phase 2 study randomly assigned patients with gastroesophageal adenocarcinoma that had progressed on a prior fluoropyrimidine/platinum-containing regimen to either 5-FU and irinotecan (FOLFIRI) plus ramucirumab (arm A) or paclitaxel plus ramucirumab (arm B).[16] The study did not show a superiority of arm A over arm B, but the 2 arms were comparable for mOS (6.8 vs 7.6 months; HR, 0.72; *P*=.12). A trend towards benefit was seen in the patients with prior docetaxel use in arm A in comparison with those in arm B (mOS, 7.5 vs 6.4 months; HR, 0.71; *P*=.25). Given the promising results, a phase 3 study is currently ongoing to evaluate the combination further (NCT03081143).

The combination of trifluridine and tipiracil (Lonsurf, Taiho Oncology) plus ramucirumab has also been recently investigated in a phase 2 trial from Japan.[17] In this single-arm study, 2 cohorts of patients undergoing second-line (cohort A) and third-line (cohort B) treatment for gastric or GEJ adenocarcinoma received the combination. The primary endpoint was the rate of disease control, which was 85% in cohort A and 77% in cohort B. The mPFS was 5.9 months in cohort A and 5.3 months in cohort B. These results are comparable with the activity of paclitaxel/ramucirumab in the Japanese cohort of the RAINBOW study, which produced a disease control rate of 94% and mPFS of 5.6 months.[18] The study also highlighted in a prespecified exploratory analysis the interesting activity of the combination of trifluridine and tipiracil plus ramucirumab in patients with anti–programed death 1 (anti–PD-1) exposure. In cohort A, the overall response rate (ORR) was 29% (95% CI, 4%-71%) in immunotherapy-experienced patients vs 4% (95% CI, 0%-20%) in immunotherapy-naive patients, and mPFS was 6.1 months (95% CI, 4.1 months to not reached) vs 5.3 months (95% CI, 3.6-7.9). A similar pattern was noted in the later-line cohort, with ORRs of 33% (95% CI, 12%-62%) vs 0% (95% CI, 0%-21%). These results are important to investigate further, especially as more patients are expected to receive anti–PD-1 treatment in the first-line setting. A randomized phase 2 trial (NCT04660760) comparing trifluridine/tipiracil plus ramucirumab with paclitaxel plus ramucirumab is currently enrolling patients in the United States and will delineate the activity of this combination further.

Since the negative results of KEYNOTE-061, which showed no benefit for pembrolizumab vs chemotherapy, immunotherapy currently has no role in the second-line setting in patients with gastric or GEJ adenocarcinoma in the United States. Therefore, paclitaxel plus ramucirumab is still considered the standard of care (Figure). Although outcomes with FOLFIRI plus ramucirumab were comparable to those with paclitaxel plus ramucirumab, it is important to note that the phase 2 RAMIRIS study was negative for superiority. Further results of the phase 3 RAMIRIS study are awaited before this combination can be considered as a standard-of-care option.

Subsequent Lines of Therapy

The combination of trifluridine and tipiracil is considered the standard of care for patients with gastric or GEJ adenocarcinoma after progression on 2 lines of therapy, on the basis of the TAGS trial.[19] This phase study randomly assigned patients to trifluridine and tipiracil or best supportive care. The mOS was 5.7 vs 3.6 months (HR, 0.69; 95% CI, 0.56-0.85). With these results, the FDA approved the combination in 2019 for this patient population.[20]

Pembrolizumab was previously approved (accelerated approval) for the treatment of PD-L1–positive gastric or GEJ adenocarcinoma in the third-line setting, on the basis of phase 2 KEYNOTE-059 study.[5] However, given the negative KEYNOTE-061 and KEYNOTE-062 studies, the Oncologic Drugs Advisory Committee voted against continued approval of pembrolizumab in this setting in April 2021. Subsequently, the combination was voluntarily withdrawn from the market for this indication.

HER2-Positive Disease

For years, the combination of trastuzumab plus chemotherapy has been the standard of care in the first-line setting for patients with advanced HER2-positive gastric/GEJ adenocarcinoma on the basis of the ToGA study, which showed an OS benefit.[4] Since then, multiple studies have failed to improve on this combination in the first- and second-line settings (Table 2).[21-24] Most recently, however, results from 2 studies—KEYNOTE-811 and DESTINY-Gastric01—have affected the standard of care in this population.

First-line Treatment

KEYNOTE-811 is an ongoing phase 3 study evaluating the addition of pembrolizumab (vs placebo) to chemotherapy and trastuzumab in patients with HER2-positive gastric/GEJ adenocarcinoma, with dual primary endpoints of PFS and OS.[25] An interim analysis of the ORR in 264 patients (planned total of 692) showed

Table 2. Phase 3 Studies Evaluating Systemic Therapies in HER2-Overexpressing Advanced Gastric/Gastroesophageal Adenocarcinoma

Study Name	Year Published	Population (%), Line of Treatment	Comparator Regimens (n)	Primary Endpoint	Results	Comments
ToGA	2010	Gastric (80), GEJ (20), first line	Trastuzumab plus chemotherapy (capecitabine plus cisplatin or 5-fluorouracil plus cisplatin; 298) vs chemotherapy alone (296)	OS	13.8 vs 11.1 mo, HR 0.74, 95% CI 0.60-0.91, *P*=.0046	
KEYNOTE -811	2021	Gastric, GEJ, first line	Pembrolizumab plus trastuzumab plus CAPOX/FP (133) vs placebo plus trastuzumab plus CAPOX/FP (131)	(a) OS (ongoing) (b) PFS (ongoing)	ORR, 74.4% vs 51.9%, *P*=.00006	Efficacy results presented at ASCO 2021
HELOISE	2017	Gastric, GEJ, first line	Standard-of-care trastuzumab plus chemotherapy (124) vs higher-dose trastuzumab plus chemotherapy (124)	OS	12.5 vs 10.6 mo, HR 1.24, 95% CI 0.86-1.78, *P*=.24	
TyTAN	2014	Gastric, second line	Lapatinib plus paclitaxel (132) vs paclitaxel alone (129)	OS	11 vs 8.9 mo, HR 0.84, 95% CI 0.64-1.11, *P*=.10	Study in Asian patients
GATSBY	2017	Gastric, GEJ, second line	Trastuzumab emtansine (228) vs paclitaxel or docetaxel (117)	OS	7.9 vs 8.6 mo, HR 1.15, 95% CI 0.87-1.51, *P*=.86	
LOGIC	2015	Gastric, first line	CAPOX plus lapatinib (249) vs CAPOX (238)	OS	12.2 vs 10.5 mo, HR 0.91, 95% CI 0.73-1.12, *P*=.34	
JACOB	2018	Gastric, GEJ, first line	Pertuzumab plus trastuzumab and chemotherapy (388) vs trastuzumab and chemotherapy (cisplatin plus capecitabine or 5-fluorouracil; 392)	OS	17.5 vs 14.2 mo, HR 0.84, 95% CI 0.71-1.00, *P*=.057	

ASCO, American Society of Clinical Oncology; CAPOX, capecitabine plus oxaliplatin; FP, 5-fluorouracil plus platinum; GEJ, gastroesophageal junction; HR, hazard ratio; mo, month(s); ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

a significant improvement in ORR in the pembrolizumab group (74.4%) compared with the placebo group (51.9%). Similarly, a complete response was achieved in 11% of patients in the pembrolizumab group vs 3% in the placebo group, with an overall tolerable safety profile. These results led to the accelerated FDA approval of pembrolizumab in combination with trastuzumab and chemotherapy in the first-line treatment of patients with unresectable locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma.[26] Further results for OS and PFS, as well as subgroup analysis, are awaited. Although the study accrued patients regardless of the PD-L1 status, most (88%) patients had a PD-L1 CPS of 1 or greater, which is higher than what was observed in the INTEGA study.[27] The role of immunotherapy in HER2-positive gastroesophageal adenocarcinoma was also evaluated in INTEGA (AIO STO 0217), a phase 2 trial that randomly assigned patients who had previously untreated metastatic, HER2-positive gastroesophageal adenocarcinoma to trastuzumab plus nivolumab with either ipilimumab (arm A) or FOLFOX (arm B). The primary endpoint was improvement in the 12-month OS rate from the 55% in the ToGA study to 70% in each arm. A total of 88 patients from Germany were enrolled, of whom 67% were PD-L1–positive according to CPS. The study met its primary endpoint of 12-month OS in arm B (70%) but not in arm A (57%). In arm B, the ORR was 56% in the intention-to-treat population, 63% in the

population with a CPS of 1 or greater, and 67% in the population with a CPS of 5 or greater, findings suggestive of increased activity with PD-L1 enrichment.

Subsequent Lines of Therapy

After multiple failed studies of treatment beyond the first line in HER2-positive gastric/GEJ adenocarcinomas (Table 2), promising results from DESTINY-Gastric01(NCT03329690) for the activity of trastuzumab deruxtecan (T-DXd; Enhertu, Daiichi-Sankyo/AstraZeneca), a monoclonal anti-HER2 antibody bound to a cytotoxic topoisomerase I inhibitor, were recently presented. In this phase 2 trial conducted in Asia, patients with HER2-positive gastric/GEJ adenocarcinoma who had received at least 2 previous regimens that included a fluoropyrimidine, a platinum agent, and trastuzumab[28] were randomly assigned to T-DXd or the treating physician's choice of irinotecan or paclitaxel. The primary endpoint was ORR. The study showed a significant improvement in ORR with the experimental treatment, from 14% in the chemotherapy arm to 51% in the T-DXd arm. Additionally, mOS improved from 8.4 to 12.5 months (HR, 0.59; 95% CI, 0.39- 0.88). Compared with chemotherapy, T-DXd was associated with more cases of grade 3 or higher fatigue and cytopenia. In addition, a higher proportion of patients in the T-DXd group than in the chemotherapy group discontinued therapy (15% vs 6%). Drug-related interstitial lung disease or pneumonitis, mostly grade 1 or 2, developed in a total of 12 patients (10%) in the T-DXd group. It is important to note that the median time to first onset of these events was almost 3 months (84.5 days). On the basis of these results, the FDA granted approval to T-DXd for patients with HER2-positive gastric/GEJ adenocarcinoma after progression on at least 2 prior regimens, including trastuzumab and chemotherapy containing a fluoropyrimidine and platinum.[29] Whereas DESTINY-Gastric01 was conducted primarily in Asian patients whose disease had progressed on 2 lines of therapy, the phase 2 DESTINY-Gastric02 trial included patients from Europe and United States with metastatic gastric or GEJ adenocarcinoma after progression on a trastuzumab-containing regimen. HER2 status was centrally confirmed on a biopsy specimen obtained after progression.[30] The study enrolled a total of 79 patients and had a median follow-up of 5.7 months. The ORR was 30%, which is lower than that seen in DESTINY-Gastric01, which mainly included Asian patients in the refractory (third-line and beyond) setting. The disease control rate was 87%, and mPFS was 5.5 months. Toxicities were similar to those seen in the Asian population; the most common were nausea, vomiting, and fatigue. Drug-related interstitial lung disease or pneumonitis developed in 6 patients (7.6%). Although most of these were grade 1 or 2, a grade 5 event developed in 1 patient.

Other studies in the HER2 space are ongoing, and results are awaited. For example, margetuximab (Margenza, MacroGenics), a newer anti-HER2 monoclonal antibody, recently showed promising activity when combined with the anti–PD-1 inhibitor retifanlimab in treatment-naive patients with metastatic gastric/GEJ adenocarcinoma.[31] Part 1 of the study in cohort A was reported and included 40 patients with non–microsatellite instability (MSI)-high disease. After a median follow-up of 7.6 months, the ORR was 52.5%, and the disease control rate was 72.5%. The median duration of response was 10.3 months. Grade 3 or 4 adverse events occurred in 41.9% of the patients. The most common treatment-related adverse events were fatigue (21%), infusion-related reaction (19%), and diarrhea (16%). A total of 3 patients discontinued the combination because of immune-related adverse events. Enrollment in cohort A will continue in part 2 of the study.

Similarly, tucatinib (Tukysa, Seagen), a highly selective HER2-directed tyrosine kinase inhibitor, is being investigated in the MOUNTAINEER-02 study.[32] This phase 2/3 study is evaluating tucatinib and trastuzumab in combination with paclitaxel and ramucirumab, the second-line standard of care, in patients with advanced or metastatic HER2-positive gastroesophageal cancer. HER2 status is determined at baseline with a blood-based next-generation sequencing assay and tissue-based testing.

MSI-High Disease

Both pembrolizumab and dostarlimab (Jemperli, GlaxoSmithKline) have FDA approval for adult and pediatric patients with MSI-high metastatic solid tumors that have progressed following prior treatment and who have no satisfactory alternative options.[33,34] The activity of pembrolizumab in gastric/GEJ adenocarcinoma has been reported in multiple studies. In a post hoc analysis of 3 KEYNOTE studies in gastric/GEJ cancers, patients who received pembrolizumab as monotherapy or combined with chemotherapy showed significant responses; antitumor activity with this regimen was durable in comparison with the durability achieved with chemotherapy alone in MSI-high populations, regardless of the line of therapy.[35] For example, in the first-line KEYNOTE-062 study, the ORR was 57.1% in the pembrolizumab arm, 64.7% in the pembrolizumab plus chemotherapy arm, and 36.8% in the chemotherapy arm.[35] The 2-year OS rates were 71%, 65%, and 26%, respectively. Similarly, the ORR was 46% in the pembrolizumab arm and 16.7% in the chemotherapy arm in the second-line KEYNOTE-061 study. These results illustrate the importance of assessing

the MSI status of patients with gastric/GEJ adenocarcinoma and the value of using checkpoint inhibitors over chemotherapy in this setting.

Conclusion

The results of the recently published phase 3 trials of the addition of checkpoint inhibitors in the treatment of gastric/GEJ adenocarcinomas represent a shift in the treatment landscape and a new standard of care for these patients. Future ongoing studies and longer follow-up will provide further information on novel agents and guide our treatment decisions according to the patient population that is deriving the most benefit.

Disclosures

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