Review Article

How to use anti-PD-1 therapy in gastric cancer: the approach in the United States

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Abstract: Gastric cancer is a leading global cause of cancer-related mortality. In the past, survival achieved in metastatic disease with chemotherapy was less than 1 year. The advent of immune checkpoint inhibitors has changed the treatment of gastric cancer. With demonstration of single agent activity for anti-programmed cell death protein 1 (anti-PD-1) agents in gastric cancer with a particularly high degree of activity in microsatellite instability (MSI) high cancers, global clinical trials added nivolumab and pembrolizumab to first line chemotherapy. Improvements in progression free survival, overall survival and increased response rates led to regulatory approval of these agents in the U.S. The benefit in survival seems limited, however, to patients with programmed cell death ligand 1 (PD-L1) positive or MSI high cancers. Adjuvant therapy with nivolumab improved disease-free survival after chemoradiotherapy and surgery in esophageal and gastroesophageal junction adenocarcinoma in patients with residual disease resected at surgery, and is a new care standard. Results of ongoing trials adding immune checkpoint inhibitors to perioperative chemotherapy in gastric cancer are anxiously awaited. In locally advanced MSI high gastric cancer, immune checkpoint inhibitor therapy is being explored as preoperative therapy given the demonstration of a high degree of pathologic complete response to these agents. Some trials may offer patients nonoperative management if a complete response is achieved.

Keywords: Gastric cancer; nivolumab; pembrolizumab; programmed cell death ligand 1 (PD-L1); microsatellite instability high (MSI-high)

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Introduction

Gastric cancer is a global health problem accounting for the 4th leading cause of cancer related mortality (1). In the U.S., gastric cancer is relatively uncommon and is not subject to screening or early detection programs. This review covers the current utilization of immune checkpoint inhibitor therapies in the U.S. Recent studies have advanced immune checkpoint inhibitor therapy to first line treatment of metastatic gastric cancer in the U.S. Nivolumab is now approved for first line use in gastric, gastroesophageal junction (GEJ), and esophageal adenocarcinoma (2). Pembrolizumab is approved for first line treatment in esophageal and GEJ adenocarcinoma (3), and in the first line treatment of human epidermal growth factor receptor 2 (HER2) positive esophagogastric adenocarcinoma (4). In the adjuvant setting, nivolumab is approved after chemoradiotherapy and surgery in esophageal and GEJ adenocarcinomas if residual disease is found and resected at surgery (5). Substantial activity has been observed for immune checkpoint inhibitors in gastric cancers with microsatellite instability (MSI) high, both in metastatic and locally advanced disease (6,7). Global trials continue to advance other immune checkpoint inhibitors to the forefront of first line therapy. Results from trials of adjuvant and neoadjuvant use of immune checkpoint inhibitors in gastric cancer are anxiously awaited.

Table 1 First line use of immune checkpoint inhibitors

Study	Primary site	Patients	Regimen	Survival	Response
CheckMate-649	Gastric/GEJ adenocarcinoma	955†	Nivolumab + FOLFOX *vs.* FOLFOX	14.4 *vs.* 11.1 months†	60% *vs.* 45%†
		1,581‡		13.6 *vs.* 11.6 months‡	
KEYNOTE-590	Esophageal/GEJ adenocarcinoma and squamous cancer	383§	Pembrolizumab+ chemotherapy *vs.* placebo + chemotherapy	13.5 *vs.* 9.4 months§	45.0% *vs.* 29.3%‡
		749‡		12.4 *vs.* 9.8 months‡	
ATTRACTION-4	Gastric/GEJ adenocarcinoma	724‡	Nivolumab + chemotherapy *vs.* placebo + chemotherapy	17.5 *vs.* 17.2 months‡	57% *vs.* 48%‡
KEYNOTE-859	Gastric/GEJ adenocarcinoma	1,579‡	Pembrolizumab + chemotherapy *vs.* placebo + chemotherapy	12.9 *vs.* 11.5 months‡	51.3% *vs.* 42.0%‡
KEYNOTE-062	Gastric/GEJ adenocarcinoma	507¶	Pembrolizumab + chemotherapy *vs.* placebo + chemotherapy	12.5 *vs.* 11.1 months	48.6% *vs.* 37.2%
		506¶	Pembrolizumab *vs.* chemotherapy	10.6 *vs.* 11.1 months	14.8% *vs.* 37.2%
JAVELIN-100	Gastric/GEJ cancer	805‡	Avelumab *vs.* chemotherapy maintenance	10.4 *vs.* 10.9 months	13.3% *vs.* 14.4%
KEYNOTE-811	Gastric/GEJ cancer	698*		20.0 *vs.* 16.8 months	72.6% *vs.* 59.8%

†, CPS ≥5%; ‡, all patients; §, CPS ≥10%; ¶, CPS ≥1%; *, all patients. GEJ, gastroesophageal junction; CPS, combined positive score.

First line trials of checkpoint inhibitors

A series of positive phase 3 trials combining immune checkpoint inhibitors with first line fluorinated pyrimidine platinum-based chemotherapy in advanced gastric, GEJ, and esophageal adenocarcinoma have changed the standard of care in the U.S. These are outlined in *Table 1*. In HER2 negative patients, CheckMate-649 and ATRACTION-4 combined nivolumab with chemotherapy, KEYNOTE-062, 590, and 859 combined pembrolizumab with chemotherapy, and KEYNOTE-811 treated HER2 positive patients with pembrolizumab, trastuzumab, and chemotherapy.

Nivolumab was added to first line mFOLFOX6 or capecitabine/oxaliplatin on CheckMate-649, an open label trial employing either 240 mg of nivolumab every 2 weeks combined with mFOLFOX6, or 360 mg every 3 weeks combined with capecitabine and oxaliplatin (2). Expression of programmed cell death ligand 1 (PD-L1) was assayed by the 28-8 antibody, and both tumor expression [tumor proportion score (TPS)], and a combined score of the tumor, macrophages, and lymphocytes [combined positive score (CPS)], were measured. Of the 1,581 patients randomized to receive chemotherapy alone or chemotherapy plus nivolumab, there was equal usage of the two chemotherapy regimens, 70% had gastric primaries and 30% had primaries in the esophagus or GEJ, and 22% had prior surgery. TPS ≥1% was seen in only 16% of patients, but 60% had CPS ≥5%. In patients with CPS ≥5%, the dual primary endpoints of progression-free survival (PFS) and overall survival (OS) were improved with the addition of nivolumab to chemotherapy: PFS 6.0 *vs.* 7.7 months [hazards ratio (HR) =0.68, P<0.0001] and OS 11.1 *vs.* 14.4 months (HR =0.71, P<0.001). OS was improved in all patients (HR =0.80) and in patients with CPS ≥1% (HR =0.77). However, in patients with CPS ≤1% and ≤5%, there was no clear OS benefit (HR =0.92 and 0.94, respectively). In the primary analysis population of CPS ≥5% response rate was improved with nivolumab (45% to 60%), and duration of response was improved (7.0 to 9.5 months). Incremental response rate improvements were seen regardless of CPS in patients receiving nivolumab.

Based on the positive results of CheckMate-649, the U.S. FDA granted regulatory approval for nivolumab combined with first line chemotherapy in esophagogastric adenocarcinoma irrespective of PD-L1 score. However, guidelines for use of nivolumab promoted by the National Comprehensive Cancer Network (NCCN) and the American Society for Clinical Oncology (ASCO) have

endorsed usage of nivolumab as first line treatment only in patients with CPS ≥5% (8,9). ASCO guidelines state that for patients with CPS ≥1% and <5% usage of nivolumab should be decided on an individual case basis. For patients with CPS 0% use of nivolumab was not recommended. NCCN guidelines list nivolumab usage in patients with CPS <5% and ≥1% as supported by level 2b evidence, indicating that a lower level of evidence supports usage in these patients, as appropriate, but at the discretion of the treating physician.

The combination of nivolumab and chemotherapy appeared safe and tolerable, although rates of grade 3 and 4 treatment related adverse events were higher with nivolumab (59%) compared to chemotherapy alone (44%).

A third treatment arm on CheckMate-649 treating 234 patients, compared a non-chemotherapy regimen of nivolumab 1 mg/kg and ipilimumab 3 mg/kg cycled every 3 weeks, to chemotherapy (10). Accrual to this arm was closed due to a high rate of adverse events. The non-chemotherapy containing combination was not superior to chemotherapy alone in OS (11.2 *vs.* 11.6 months, HR =0.89, P=0.2302). Neither PFS nor response rate was improved for nivolumab/ipilimumab compared to chemotherapy alone, although the response duration for was longer with immunotherapy (13.2 *vs.* 6.9 months). This combination will not move forward in the treatment of metastatic disease.

An additional trial from Asia, ATTRACTION-4, a double-blind placebo-controlled phase 3 trial, provides supportive evidence for improvements in PFS and antitumor response for the addition of nivolumab to first line chemotherapy in gastric cancer (11). In 724 patients, nivolumab 360 mg or placebo was combined with S-1 or capecitabine and oxaliplatin. PD-L1 expression was measured by immunohistochemical staining with the 28-8 antibody. The primary endpoint of improved PFS was achieved with nivolumab over placebo (10.5 *vs.* 8.3 months; HR =0.68; P<0.0007). Both a higher rate of response (57.5% *vs.* 47.8%) and duration of response (12.9 *vs.* 8.7 months) were observed. Despite these benefits, there was no improvement in OS with treatment with nivolumab (17.2–17.5 months, HR =0.90, P=0.26). The time to improvement and the time to deterioration of quality of life were superior with the combination of nivolumab and chemotherapy.

On this trial only tumor positivity for PD-L1 (TPS) was reported, and 85% were TPS <1%. CPS, which is more inclusive and includes staining for lymphocytes and macrophages, was not reported on this trial, and it is likely a substantial number of the TPS negative patients would have tested CPS positive. No survival benefit was seen for either the TPS positive or negative patients, however.

There is no clear explanation for the failure of nivolumab to improve survival outcome on this trial. A relatively high number of patients on the chemotherapy alone arm (27%) received later line therapy with nivolumab, which could have potentially undercut a survival benefit. Also, on this trial a higher proportion of patients received any form of second or later line therapy (66%) compared to patients treated on CheckMate-649 (39%), which also may have impacted on OS. Despite the absence of a survival benefit, nivolumab is approved to combine with first line chemotherapy in gastric cancer in Japan irrespective of PD-L1 expression.

Although the initial reported trial of pembrolizumab added to first line chemotherapy, KEYNOTE-062, was negative for either progression free or OS benefits, two subsequent trials of first line pembrolizumab, KEYNOTE-590 and 589, have yielded positive results. KEYNOTE-062 treated 763 patients on an open label, phase 3 trial using either capecitabine or continuous infusion 5-FU combined with cisplatin, with or without the addition of pembrolizumab 200 mg given every 3 weeks; a third treatment arm treated patients with single agent pembrolizumab 200 mg every 3 weeks (12). PD-L1 was tested using the 22C3 antibody and only patients testing PD-L1 positive at CPS 1% or higher were enrolled. The majority had gastric primaries (62%) and received capecitabine/cisplatin (69%) and 37% had CPS ≥10%. Superior OS could not be demonstrated for pembrolizumab added to chemotherapy over chemotherapy alone in all patients treated (12.5 *vs.* 11.1 months, HR =0.85, P=0.05) or in patients having a CPS ≥10% (12.3 *vs.* 10.8 months; HR =0.85; P=0.16). Superiority in PFS for the addition of pembrolizumab to chemotherapy also could not be demonstrated compared to chemotherapy alone (6.9 *vs.* 6.4 months, HR =0.84, P=0.04). Pembrolizumab added to chemotherapy led to a numerically higher response rate compared to chemotherapy alone (49% *vs.* 37%).

In comparing treatment with pembrolizumab alone to chemotherapy on KEYNOTE-062, pembrolizumab was non inferior to chemotherapy for survival (10.6 *vs.* 11.1 months), but PFS was inferior (2.6 *vs.* 6.5 months), and patients treated with pembrolizumab had a higher initial death rate. First line pembrolizumab monotherapy will not move forward in the treatment of metastatic gastric cancer.

Positive results for pembrolizumab added to first line

chemotherapy in esophagogastric cancer were subsequently reported on the KEYNOTE-590 and 859 trials. KEYNOTE-590, a placebo controlled randomized trial treated esophageal and GEJ adenocarcinoma and squamous cell cancers with a 5-day infusion of 5-FU with cisplatin given every 3 weeks, with or without pembrolizumab (13). The majority of patients treated had squamous cancers (73%) and testing of PD-L1 by 22C3 indicated a relatively high proportion of patients who were CPS ≥10% (51%) with comparable rates for squamous cancers (52%) compared to adenocarcinoma (48%). Multiple primary endpoints were assessed including outcome in all squamous cancers, in squamous cancers with CPS ≥10%, in all patients with CPS ≥10%, and in all patients. In all patients, OS was improved with the addition of pembrolizumab to chemotherapy (12.4 *vs.* 9.8 months, HR =0.73) and in all patients with CPS ≥10% (13.9 *vs.* 8.8 months, HR =0.57), with a greater benefit in all patients with CPS ≥10% compared to <10% (HR =0.62 *vs.* 0.86). A survival benefit was seen in adenocarcinoma (11.6 *vs.* 9.9 months, HR =0.74). PFS was improved in all patients (6.3 *vs.* 5.8 months, HR =0.65) and in patients CPS ≥10% (7.5 *vs.* 5.5 months, HR =0.51). In all patients treated, response was improved with pembrolizumab from 29% to 45%. Grade 3 or higher treatment related adverse event rates were similar with (72%) or without pembrolizumab (68%), and immune related adverse events were manageable. Based on these positive results, pembrolizumab combined with chemotherapy was approved in the U.S. to treat adenocarcinoma and squamous cancer of the esophagus and GEJ irrespective of PD-L1 status. Similar to the guidelines for nivolumab restriction based on PD-L1 status, ASCO guidelines recommend usage of pembrolizumab combined with chemotherapy in patients with adenocarcinoma with CPS ≥10%, with treatment of patients with CPS between 1 and 10 to be decided on an individual case basis. NCCN guidelines list usage of pembrolizumab in these patients as level 2b evidence, with a lower level of evidence but clinically appropriate as determined by the treating physician.

A second positive trial in gastric adenocarcinoma was recently reported in abstract form on the KEYNOTE-859 trial (14). Over 1,500 patients with cancers of the stomach (78%) or GEJ (22%) were treated with either 5-day infusion 5-FU/cisplatin (14%) or capecitabine/oxaliplatin (86%) every 3 weeks combined with pembrolizumab or placebo. The majority (78%) tested positive by 22C3 for PD-L1 ≥1% and 35% tested ≥10%. The primary endpoint of OS was improved in all patients treated with pembrolizumab compared to placebo (12.9 *vs.* 11.5 months, HR =0.78, P<0.001), with greater benefits for patients CPS ≥1% (HR =0.73 compared to <1% (HR =0.92) and for CPS ≥10% (HR =0.64). PFS was improved in all patients with pembrolizumab from 5.6 to 6.9 months (HR =0.76, P<0.0001). Response rate was improved from 42% to 51% with pembrolizumab as was response duration (5.7 to 8.0 months). Rates of grade 3 or higher treatment related serious adverse events were slightly higher with pembrolizumab (59%) compared to placebo (51%) and immune related adverse events were manageable. Regulatory review of these results is pending.

Based on these practice changing trials, nivolumab is now approved in the first line treatment of advanced esophagogastric adenocarcinoma and pembrolizumab is approved in the first line treatment of esophageal and GEJ adenocarcinoma, with restrictions on use based on PD-L1 CPS. The utility of PD-L1 CPS as a predictive biomarker of survival benefit for treatment with immune checkpoint inhibitor therapy was recently published in a pooled trial analysis (15). The report evaluated over 11,000 patients treated on 17 randomized controlled clinical trials, including 9 first line studies, with nearly 6,100 patients having adenocarcinoma. Not surprisingly MSI high status had the highest correlation with a survival benefit from therapy. A high CPS scored defined as CPS ≥10% achieved a pooled HR for OS of 0.74 compared to 0.87 for CPS <10% in adenocarcinoma.

The addition of pembrolizumab to first line chemotherapy in HER2 positive esophagogastric adenocarcinoma leading to approval of its use was evaluated in the KEYNOTE-811 trial (4). On this placebo controlled randomized trial, patients with HER2 positive esophagogastric adenocarcinoma were assigned to treatment with a 5-day infusion of 5-FU and cisplatin or capecitabine oxaliplatin every 3 weeks combined with trastuzumab with or without pembrolizumab. A planned early interim analysis of response rate was performed in the first 234 patients treated. The majority were stomach primaries (70%), and the vast majority were PD-L1 positive ≥1% by 22C3 at 87%, and 80% tested HER2 positive IHC 3+. Pembrolizumab improved the response rate from 52% to 74% (P=0.00006). Similar rates of grade 3 or higher serious adverse events were seen with (57.1%) or without pembrolizumab (57.1%). Approval for adding pembrolizumab to first line chemotherapy in HER2 positive esophagogastric cancer was achieved in the U.S. based on these strikingly positive results.

Follow up including interim analyses of progression free and overall survival in all 698 patients treated on KEYNOTE-811 has now been published (16). The response advantage was maintained for the addition of pembrolizumab to trastuzumab and chemotherapy over trastuzumab and chemotherapy alone (72.6% *vs.* 59.8%). At a third interim analysis, PFS was superior for pembrolizumab added to treatment (10.1 *vs.* 8.1 months, HR =0.73) with the benefit limited to patients CPS >1% (10.9 *vs.* 7.3 months, HR =0.71). There was no benefit in patients CPS <1% (9.5 *vs.* 9.5 months, HR =1.03). At the second interim analysis overall survival trended superior for pembrolizumab compared to placebo (20.0 *vs.* 16.9 months) but this was not statistically superior (HR =0.87, P=0.84). A trend toward inferior OS was seen in patients with CPS <1% for pembrolizumab compared to placebo (16.1 *vs.* 22.3 months, HR =1.61). This led to modification of FDA guidelines to limit the addition of pembrolizumab to trastuzumab and chemotherapy in patients testing CPS >1%.

A salient negative trial evaluated the potential use of maintenance therapy with an immune checkpoint inhibitor after initial treatment with chemotherapy, JAVELIN Gastric 100 (17). Patients with GEJ or gastric adenocarcinoma who achieved a response or stable disease after initial treatment with capecitabine or 5-FU plus oxaliplatin, were assigned to continuation of chemotherapy or to treatment with the anti PD-L1 agent avelumab. The trial randomized 499 patients mainly with stomach primaries (71%). PD-L1 was scored by tumor positivity and most (77%) were TPS <1%. For the primary endpoint of OS, Avelumab failed to achieve superiority over chemotherapy (10.4 *vs.* 10.9 months, HR =0.91, one-sided P=0.1779) or in PFS (3.2 *vs.* 4.4 months, HR =1.04).

Other promising anti PD-1 agents combined with chemotherapy have emerged on the global stage from trials largely conducted in Asia in gastric cancer. These include positive results reported for sintilimab combined with chemotherapy on the ORIENT-16 trial (18), and Tislelizumab combined with chemotherapy on the RATIONALE 306 trial (19).

MSI high gastric cancer

Gastric cancers with either mutations in DNA mismatch repair proteins, or loss of expression of DNA mismatch repair proteins, have detectable MSI and a high tumor mutational burden. This clinically significant subset of gastric cancers accounts for roughly 7% of cases as reported in recent phase II and III clinical trials (2,12). Mismatch repair protein mutations in MLH1, MSH2, MSH5, and PMS2 can be germline as seen in Lynch syndrome, or loss of expression can be sporadic by epigenetic silencing of the promoter for MLH-1. The lack of ability to repair mismatched nucleotides during DNA replication leads to both MSI and an increase in tumor mutational burden. Mutant proteins in the cancer represent neoantigens that may enhance stimulation of an immune response. Immunohistochemistry can rapidly test for loss of DNA mismatch repair proteins, and MSI can be tested by polymerase chain reaction assay or by next generation sequencing looking for MSI or mutations in DNA mismatch repair genes.

It was clear from early clinical trials of immune checkpoint inhibitors across the spectrum of MSI high cancers that substantial and durable activity was seen for these agents, including gastric cancer. Tumor agnostic approval for the use of nivolumab, pembrolizumab, and dostarlimab has been achieved for MSI high gastric cancer, although current NCCN guidelines recommend utilization as single agents after progression of disease on prior chemotherapy (20). In phase III trials evaluating outcome in the subset of gastric cancer patients testing MSI high, immune checkpoint inhibitor therapy by itself and combined with chemotherapy is consistently and markedly superior to chemotherapy alone. In the KEYNOTE-062 trial, 6.6% of patients were MSI high (12). OS for pembrolizumab alone (HR =0.29) or combined with chemotherapy (HR =0.37) was markedly superior to chemotherapy alone. The median OS was not reached on the pembrolizumab arms, and with no dependence of treatment effect on CPS status. On CheckMate-649, MSI high cancers achieved substantial survival superiority when treated with nivolumab plus chemotherapy *vs.* chemotherapy alone (HR =0.33) (2). NCCN guidelines will likely be revised to support first line use of immune checkpoint inhibitors alone or in combination with chemotherapy irrespective of CPS status.

In locally advanced MSI high esophagogastric cancer, data are emerging for a high degree of efficacy for immune checkpoint inhibitor therapy as neoadjuvant treatment, as reported in the recent French NEONIPGA trial (7). Patients with MSI locally advanced esophagogastric cancer were treated on a phase II trial with 3 months of ipilimumab combined with nivolumab, followed by surgical resection, followed by 9 months of adjuvant nivolumab. Of 32 patients treated, 3 patients did not go on to surgery and all achieved durable clinical complete responses to up

Table 2 Immune checkpoint inhibitors in second or later line therapy

Study	Primary site	Patients	Regimen	Survival	Response
KEYNOTE-059	Gastric/GEJ adenocarcinoma	259[†]	Pembrolizumab	5.6 months[†]	15.5%[‡], 11.6%[†], 6.4%[§]
KEYNOTE-061	Gastric/GEJ adenocarcinoma	395[‡]	Pembrolizumab *vs.* paclitaxel	9.1 *vs.* 8.3 months[‡]	16% *vs.* 14%[‡]
ATTRACTION-2	Gastric/GEJ adenocarcinoma	493[†]	Nivolumab *vs.* placebo	5.3 *vs.* 4.1 months[†]	11.2% *vs.* 0%[†]
JAVELIN-300	Gastric/GEJ adenocarcinoma	371[†]	Avelumab *vs.* paclitaxel or irinotecan	4.6 *vs.* 5.0 months[†]	2.2% *vs.* 4.3%[†]
KEYNOTE-181	Esophageal/GEJ adenocarcinoma	227	Pembrolizumab *vs.* paclitaxel or docetaxel or irinotecan	HR =1.12	Not stated

[†], all patients; [‡], CPS >1%; [§], CPS =0%. GEJ, gastroesophageal junction; HR, hazard ratio; CPS, combined positive score.

front immunotherapy. Of the 29 patients going to surgery, 59% achieved a pathologic complete response and another 21% had a near pathologic complete response. At the study reporting, 97% of patients treated were alive and free of disease.

These provocative results have engendered future trials of neoadjuvant immune checkpoint inhibitor therapy either alone or combined with chemotherapy. These trials will likely consider the possibility of surgery avoidance and organ preservation in patients achieving a clinical complete response to therapy.

Second line trials of checkpoint inhibitors in esophagogastric cancer

The second line use if immune checkpoint inhibitors in gastroesophageal adenocarcinoma has failed to show superiority to chemotherapy. These are outlined in *Table 2*. KEYNOTE-061 was an open label randomized phase III trial of comparing pembrolizumab to weekly paclitaxel as second line chemotherapy in GEJ and gastric adenocarcinoma. Of 592 patients treated, PD-L1 CPS tested by 22C3 was ≥1% in 67% and 33% were PD-L1 negative. Pembrolizumab did not achieve superior OS in the CPS positive patients compared to paclitaxel (9.1 *vs.* 8.3 months, HR =0.82, one-sided P=0.0421). In the MSI high patients, median OS was not reached compared to 8.1 months for chemotherapy. PD-L1 negative patients did poorly with a median OS of only 4.8 months. PFS in the PD-L1 positive patients was superior for paclitaxel (4.1 months) compared to pembrolizumab (1.5 months). Rates of response were similar for pembrolizumab (16%) and paclitaxel (14%) in the PD-L1 positive patients. The negative results for KEYNOTE-061 are further confounded by the use of an inferior control arm, paclitaxel monotherapy (21). Ramucirumab plus paclitaxel is a superior second line treatment compared to paclitaxel alone and is the global standard second line therapy, and use of paclitaxel alone on this trial further undercuts any conclusions that can be drawn.

KEYNOTE-181 treated adenocarcinoma of the esophagus and GEJ and squamous cancer in second line therapy (22). The majority of patients treated on this trial had squamous cancers of the esophagus, and any benefit for pembrolizumab was limited to squamous esophageal cancers. This open label randomized phase III trial compared pembrolizumab to physician's choice second line chemotherapy with paclitaxel, docetaxel, or irinotecan. A minority patients treated had adenocarcinoma (37%) and most (65%) had CPS assessed by 22C3 <10%. OS was not improved with pembrolizumab compared to chemotherapy in patients with adenocarcinoma (HR =1.12, favoring chemotherapy) and no benefit in adenocarcinoma patients with CPS ≥10% (HR =0.93). KEYNOTE-181 did lead to approval in the U.S. for pembrolizumab in the second line treatment of esophageal squamous cell cancers testing positive for PD-L1.

Later line trials of checkpoint inhibitors in esophagogastric cancer

Late line trials evaluating the efficacy of immune checkpoint inhibitors have achieved mixed results. These are outlined in *Table 2*. KEYNOTE-059, a large expansion cohort phase II trial, tested pembrolizumab in 259 patients with gastric and GEJ adenocarcinoma refractory to chemotherapy (23). This trial treated gastric (48.3%) and GEJ cancers (51.4%), with 51.7% receiving two prior chemotherapy regimens and 48.3% receiving three or more prior regimens. The trial included HER2 positive patients, and a small minority

(4%) were MSI high. The majority (57%) tested CPS ≥1% positive by 22C3. Responses were seen in 11.6% of patients with a higher response in PD-L1 positive (15.5%) compared to PD-L1 negative patients (6.4%), with a superior response duration in positive *vs.* negative patients (16.3 *vs.* 6.9 months). The response rate in MSI high patients was 57.1%. Based on these results, pembrolizumab was given conditional approval to treat patients with chemotherapy refractory gastric and GEJ cancers testing positive for PD-L1 or MSI high. This approval, however, was rescinded for non MSI high patients given the subsequent negative results for pembrolizumab in adenocarcinoma in KEYNOTE-061, 062, and 181.

Nivolumab achieved regulatory approval for refractory gastric cancer in Japan based on the ATTRACTION-2 trial (24). Nivolumab was compared to placebo in chemotherapy refractory gastric cancer, treating 493 patients. OS for nivolumab was superior (5.26 months) compared to placebo (4.14 month, HR =0.63, P<0.0001), with an improvement in PFS (HR =0.60, P<0.001) and improved response rate (11.2% *vs.* 0%). Survival benefits were seen irrespective of PD-L1 status, which was assessed by TPS using the antibody 28-8. However, PD-L1 status was only available in 39% (192/493) of randomized patients.

Negative results were reported for the anti PD-L1 agent Avelumab compared to chemotherapy in previously treated gastric cancer on the JAVELIN Gastric 300 trial (25). This open label phase III trial treated 371 patients with physicians' choice chemotherapy with paclitaxel or irinotecan or avelumab. PD-L1 assessed by TPS was ≥1% in 26.8%. Avelumab did not achieve superior survival compared to chemotherapy (4.6 *vs.* 5.0 months, HR =1.1, P=0.81), and chemotherapy was favored over avelumab in both PFS and response rate.

Given the approved use of first line immune checkpoint inhibitor therapy in esophagogastric adenocarcinoma, later line use of these agents will likely become increasingly uncommon.

Adjuvant immunotherapy in esophagogastric cancer

The use of immune checkpoint inhibitor therapy first line in advanced esophagogastric cancer has now been extended to encompass adjuvant therapy. CheckMate-577 evaluated in a randomized phase III, double-blind placebo-controlled phase 3 trial the use of 1 year of adjuvant nivolumab in patients who had residual disease resected at surgery after preoperative chemoradiotherapy for esophageal and GEJ adenocarcinoma or squamous-cell cancer (5). The majority of the 794 patients had adenocarcinoma (71%) with stage III disease (65%) and most (60%) had esophageal primaries. TPS scored by 22-8 was positive in 28%. Superior disease-free survival with nivolumab was achieved (22.4 *vs.* 11.0 months, HR =0.69; P<0.0003) with benefits seen in adenocarcinoma (HR =0.74) and squamous cancer (0.61). Although TPS positive and negative patients benefited, a greater DFS benefit was seen in patients with CPS ≥5% patients (HR =0.62) compared to CPS <5% (HR =0.89). Based on these results nivolumab is now approved as an adjuvant therapy in esophageal cancer after chemoradiotherapy and surgery in patients with residual disease resected at surgery. OS data from this trial are still pending.

Results for the addition of immune checkpoint inhibitor therapy to neoadjuvant and adjuvant chemotherapy in gastric cancer are awaited from ongoing trials, including the KEYNOTE-585 trial (NCT03221426) and the Matterhorn trial (NCT04592913). Two studies reported in abstract form indicated higher rates of pathologic response including pathologic complete response in patients receiving an immune checkpoint inhibitor added to preoperative chemotherapy compared to chemotherapy alone. Atezolizumab combined with the FLOT regimen on the randomized phase II DANTE trial achieved a higher rate of pathologic complete response (24%) compared to chemotherapy alone (15%) (26). In a randomized phase II trial from China comparing preoperative chemotherapy with either S-1 or capecitabine plus oxaliplatin with or without toripalimab, a higher rate of pathologic complete response was reported with toripalimab (22%) compared to chemotherapy alone (7%) (27).

Results of the ATTRACTION-5 trial were recently reported in abstract form (28). After D2 resection of pathologic stage III gastric cancer, 755 patients were randomized in a double-blind, placebo controlled randomized trial to received adjuvant chemotherapy with either S-1 or with capecitabine/oxaliplatin, with or without the addition of 1 year of adjuvant nivolumab. Three-year relapse free survival, the primary endpoint, failed to indicate a benefit for adjuvant nivolumab (68.2%) over chemotherapy alone (65.3%, HR =0.90, P=0.4363). Further follow up on this trial, include exploration of potential biomarkers, is pending.

Toxicity of immunotherapy

In trials combining immune checkpoint inhibitor therapy with chemotherapy, toxicities have been manageable with no increase in treatment related deaths from immunotherapy, despite higher rates of grade 3 and 4 treatment related serious adverse events in the range of 10–15% with immunotherapy. On CheckMate-649 toxicity concerns led to premature closure of the nivolumab/ipilimumab treatment arm possibly due to selection of the schedule of nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks used (10). Appreciation and early treatment of immune related adverse events are critical with the near universal use of these agents in earlier line therapy.

Future directions

Now that first line chemotherapy in esophagogastric adenocarcinoma will include use of immune checkpoint inhibitors, this will shape the design of the next generation of clinical trials of novel agents. In addition to CPS, a research priority remains the identification of biomarkers to select patients most likely to benefit from new therapies.

Novel combinations of immune checkpoint inhibitors with other therapies, including angiogenesis inhibitors, PARP inhibitors, and drugs targeting pathways are ongoing. Provocative data were reported combining the tyrosine kinase inhibitor regorafenib with nivolumab (29) and lenvatinib with pembrolizumab with lenvatinib (30), indicating potential significant anti-tumor response. A phase III trial adding Lenvatinib to pembrolizumab and chemotherapy in the first line treatment of esophagogastric adenocarcinoma is ongoing (NCT04662710).

Conclusions

The advent of immune checkpoint inhibitor therapy in the treatment of esophagogastric cancer has improved response, time on treatment, and survival in metastatic disease. In the U.S. nivolumab is approved to combine with chemotherapy in esophagogastric adenocarcinoma, and pembrolizumab is approved to combine with chemotherapy in esophageal and GEJ adenocarcinomas. Although regulatory approval was irrespective of PD-L1 status, survival benefits with the addition of anti PD-1 agents seem limited to patients with CPS 5–10%. Pembrolizumab is now combined with trastuzumab and chemotherapy in the first line treatment of HER2 positive esophagogastric adenocarcinoma based on a marked enhancement in response rate. For MSI high esophagogastric adenocarcinoma, anti PD-1 agents are approved in the treatment of metastatic disease. The high degree of activity irrespective of PD-L1 status argues for earlier or first line use of these agents with or without chemotherapy. In the adjuvant setting, nivolumab is now approved to administer after chemoradiotherapy and surgery in esophageal and GEJ adenocarcinoma with residual disease resected at surgery. The role of these agents in the surgical management of gastric adenocarcinoma remains to be established. Great promise is evident for use of immune checkpoint inhibitor therapy in the neoadjuvant treatment of MSI high esophagogastric adenocarcinomas, with the potential pursuit of nonoperative management in patients achieving a clinical complete response.

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