Immunotherapy in Esophagogastric Cancer

David H. Ilson, MD, PhD
Memorial Sloan Kettering Cancer Center, New York, New York

Corresponding author:
David H. Ilson, MD, PhD
Memorial Sloan Kettering Cancer Center
1275 York Ave
New York, NY 10065
Email: ilsond@mskcc.org
Tel: (646) 888-4183

Abstract: The uses of immune checkpoint inhibitors have now been advanced to include the first-line treatment of esophagogastric cancers. Initially approved for the treatment of chemotherapy-refractory programmed death ligand 1–positive or microsatellite instability (MSI)–high esophagogastric adenocarcinoma, these agents have been shown in earlier-line trials to have an additive benefit with first-line chemotherapy, and superiority to chemotherapy, in MSI-high cancers. Pembrolizumab and nivolumab have received approval for the second-line treatment of esophageal squamous cancer. The addition of nivolumab to first-line chemotherapy in gastric and gastroesophageal junction (GEJ) adenocarcinoma improved survival, progression-free survival, and response, findings that led to regulatory approval. The addition of pembrolizumab to first-line chemotherapy in esophageal and GEJ adenocarcinoma and squamous cancer also improved all outcomes, which led to the approval of pembrolizumab as part of first-line chemotherapy. The addition of pembrolizumab to first-line chemotherapy in human epidermal growth factor receptor 2–positive esophagogastric adenocarcinoma was also recently approved. In addition, the adjuvant use of nivolumab was recently approved in esophageal and GEJ cancer after chemoradiotherapy and surgery in patients with residual disease found at surgery. This article reviews recent advances in the use of immune checkpoint inhibitor therapy in esophagogastric cancers.

Keywords
Adjuvant therapy, esophageal cancer, FOLFOX, gastric cancer, gastroesophageal junction cancer, microsatellite instability, nivolumab, pembrolizumab, PD-L1

Introduction

Gastric cancer is a leading type of cancer globally; it is the fifth most common type of cancer and the fourth most common cause of cancer-related death.[1] When esophageal cancer is factored in, the case fatalities for esophagogastric cancer are second only to those for lung cancer. In the United States and Western Europe, esophagogastric cancer is less common than in the high-incidence areas of East Asia, Eastern Europe, and South America. The management of locally advanced gastric cancer consists of surgery combined with either perioperative chemotherapy,[2] the dominant practice in the West, or postoperative adjuvant chemotherapy, which is used more often in the East.[3-5] The surgical management of esophageal cancer is

combined with preoperative chemotherapy or chemoradiotherapy.[2,6] Until recently, metastatic disease was treated with first-line chemotherapy consisting of a fluorinated pyrimidine and a platinum agent with or without a taxane, which achieved a median survival of less than 1 year. Recent advances, including the inclusion of trastuzumab in the first-line treatment of metastatic human epidermal growth factor receptor 2 (HER2)–positive disease[7] and the inclusion of ramucirumab (Cyramza, Lilly) in second-line treatment,[8] have now been surpassed by the advent of immune checkpoint inhibitor therapy. This review covers recent practice-changing clinical trials that have advanced immunotherapy to the first-line treatment of esophagogastric cancer, and to the adjuvant setting in esophageal cancer.

Biomarkers for the Selection of Immunotherapy

With nearly all targeted therapies, including immunotherapy, not all patients benefit from new treatments, and biomarkers are used to select those most likely to benefit from these agents. Key biomarkers emerging for immunotherapy in esophagogastric cancer include microsatellite instability (MSI) arising from DNA mismatch repair (MMR) protein deficiency, and programmed death ligand 1 (PD-L1) expression. PD-L1 is the ligand that engages the programmed death receptor 1 (PD-1), leading to immune suppression in the tumor microenvironment. In patients with esophagogastric cancers undergoing immune checkpoint inhibitor treatment, testing for a mutation or deficiency in DNA MMR proteins is now mandatory. The most common mechanism of loss of DNA MMR proteins is epigenetic silencing of the promoter for *MLH1*, but germline or somatic mutations can also occur in *MLH1*, *MSH2*, *MSH5*, and *PMS2*. These mechanisms result in an inability to repair mismatched nucleotides during DNA replication, leading to MSI. Thus, a higher tumor mutational burden results in increased neoantigens from mutant proteins, leading to potentially greater stimulation of an immune response. Testing can be by immunohistochemistry to detect a loss of DNA MMR proteins, by polymerase chain reaction assay looking for MSI, or by next-generation sequencing (NGS) looking for mutations in DNA MMR genes. NGS also can sequence a large number of genomic microsatellite sequences in a sample and determine instability through bioinformatic approaches. MSI is detected in 5% to 7% of gastric cancers, as reported in recent large phase 3 trials of advanced disease and recent reports from surgical adjuvant series,[9-11] and in fewer than 1% of esophageal and gastroesophageal junction (GEJ) cancers.[12] PD-L1 testing is now done routinely by immunohistochemistry staining, and rates of positivity in clinical trials are reported as a tumor proportion score (TPS) for tumor cells only or as a combined positivity score (CPS) for the tumor cells, lymphocytes, and macrophages. The CPS is likely a more accurate assessment of PD-L1 expression because the TPS will not indicate positivity in patients with tumor negativity and immune cell positivity. A high tumor mutational burden, recently defined as the detection of 10 or more mutations per megabase by NGS, is emerging as another potential biomarker of immunotherapy benefit.[13] Other potential biomarkers of response to immunotherapy agents include presence of the Epstein-Barr virus, which in tumors can lead to enhanced expression of both PD-L1 and PD-L2,[14] and other germline and somatic mutations that may increase the tumor mutational burden, including mutations in *POLE*.[15]

For the treatment of solid tumors that are MSI-high or DNA MMR protein–deficient, tumor-agnostic approval has been granted to the anti–PD-1 agents pembrolizumab (Keytruda, Merck) and nivolumab (Opdivo, Bristol Myers Squibb). A high degree of response that is durable is seen in most patients, and the initially approved indication for the later-line use of these agents in MSI-high esophagogastric cancers will likely be changed to include earlier-line therapy. The checkpoint inhibitor pembrolizumab was initially approved as treatment for patients who had chemotherapy-refractory esophagogastric cancer with a CPS of at least 1%,[16] and as second-line chemotherapy for patients who had esophageal squamous cancer with a CPS of at least 10%.[17] Nivolumab was approved in Japan as late-line therapy in gastric cancer irrespective of the CPS, and as second-line therapy in esophageal squamous cancer irrespective of the CPS.[18] As will be discussed, first-line trials of these agents combined with chemotherapy have led to regulatory approval of both pembrolizumab and nivolumab regardless of CPS. A high tumor mutational burden was also recently a basis for tumor-agnostic approval of pembrolizumab as a therapeutic option in refractory solid tumors.[19] However, none of the patients treated in the trial had cancer of the esophagus or stomach, and tumor mutational burden has not been validated as a biomarker for immunotherapy in esophagogastric cancer. In the case of some biomarkers being investigated as indicators of benefit from immunotherapy agents, including gene signatures such as interferon-γ,[16] results have been inconsistent.

Later-Line Trials of Checkpoint Inhibitors in Esophagogastric Cancer

With signals of immune checkpoint inhibitor activity noted in early phase 1 and 2 trials, these agents were evaluated

Table 1. Immune Checkpoint Inhibitors in Second- or Later-Line Therapy

Trial	Tumor Type	Pts, No.	Treatment	OS, mo	RR, %
KEYNOTE-059	Gastric/GEJ cancer	259	Pembrolizumab	5.6	15.5 in PD-L1+
ATTRACTION-2	Gastric/GEJ cancer	493	Nivolumab vs placebo	5.3 vs 4.1	11.2 vs 0
JAVELIN Gastric 300	Gastric/GEJ cancer	371	Avelumab vs paclitaxel or irinotecan	4.6 vs 5.0	2.2 vs 4.3
KEYNOTE-061	Gastric/GEJ cancer	395 (PD-L1+)	Pembrolizumab vs paclitaxel	9.1 vs 8.3	16 vs 11
KEYNOTE-181	Esophageal/GEJ adenocarcinoma or squamous cancer	222 (CPS ≥10%)	Pembrolizumab vs paclitaxel, docetaxel, or irinotecan	9.3 vs 6.7*	21.5 vs 6.1
ATTRACTION-3	Esophageal squamous cancer	419	Nivolumab vs paclitaxel or docetaxel	10.9 vs 8.4*	19 vs 22

*Statistically significant.

GEJ, gastroesophageal junction; mo, months; OS, overall survival; pts, patients; PD-L1+, programmed death ligand 1–positive; RR, response rate.

in larger single-arm and randomized phase 3 trials, which are summarized in Table 1. The large phase 2 expansion cohort of the KEYNOTE-059 trial reported results for pembrolizumab in 259 patients with gastric or GEJ adenocarcinoma.[16] This international multicenter trial enrolled equal proportions of patients with gastric (48.3%) and GEJ cancers (51.4%). Half of the patients had received 2 prior regimens (51.7%), and half had received 3 or more prior regimens (48.3%). A total of 24.3% were HER2-positive, 57% had a CPS of at least 1%, and a small minority had MSI-high tumors (4.0% with tissue available for testing). The response rate in all patients, which was the primary endpoint, was 11.6%, and the response rate was superior in PD-L1–positive patients (15.5%) vs PD-L1–negative patients (6.4%). In addition, the response duration was superior in PD-L1–positive patients vs PD-L1–negative patients (16.3 vs 6.9 months). The response rate was 57.1% in MSI-high patients. On the basis of these results, pembrolizumab was approved to treat patients with chemotherapy-refractory gastric or GEJ cancers that were PD-L1–positive or MSI-high.

Supportive evidence for a benefit of immune checkpoint inhibitor therapy in refractory disease came from the ATTRACTION-2 trial, which was conducted in Japan, Korea, and Taiwan.[20] In this double-blind, placebo-controlled, randomized phase 3 trial, 493 patients were treated with nivolumab or placebo. Overall survival (OS) was superior with nivolumab (5.26 months) vs placebo (4.14 months; hazard ratio [HR], 0.63; *P*<.0001), with an improvement in 12-month survival from 10.9% to 26.2% noted with nivolumab. PFS also was superior with nivolumab (1.61 vs 1.45 months; HR, 0.60; *P*<.001), as was response rate (11.2% vs 0%), with a median response duration of 9.53 months. OS benefits were seen across patient subgroups, including an exploratory analysis comparing PD-L1–positive and PD-1–negative patients, with PD-L1 positivity defined as a TPS of at least 1%. On the basis of ATTRACTION-2, nivolumab was approved in Japan to treat chemotherapy-refractory gastric and GEJ cancer irrespective of the patient's PD-L1 status. Outcomes for nivolumab in ATTRACTION-2 and pembrolizumab in KEYNOTE-59 appear similar in refractory disease.

Distinctly negative results were reported in patients with previously treated advanced disease in the JAVELIN Gastric 300 trial.[21] In this open-label phase 3 trial, 371 patients with previously treated gastric or GEJ adenocarcinoma received avelumab (Bavencio, EMD Serono/Pfizer) or physician's choice of chemotherapy with either paclitaxel or irinotecan. PD-L1 positivity, defined as a TPS of at least 1%, was present in 26.8% of the 317 patients tested. Superiority for OS, the primary endpoint, was not achieved with avelumab (4.6 months) vs chemotherapy (5.0 months; HR, 1.1; *P*=.81). PFS and the response rate favored chemotherapy (2.7 months, 4.3%) over avelumab (1.4 months, 2.2%). No difference in survival outcome was observed as a function of PD-L1 status or the chemotherapy administered. The negative results of this trial, in which the control arm received active treatment, contrast with the positive results for nivolumab vs no treatment

and with the phase 2 expansion cohort data for pembrolizumab in chemotherapy-refractory disease.

Second-Line Trials of Checkpoint Inhibitors in Esophagogastric Cancer

Trials of immune checkpoint inhibitors in second-line treatment have yielded mixed results, with positive results leading to regulatory approval limited to esophageal squamous cancer and negative results for gastroesophageal adenocarcinoma. These trials are outlined in Table 1. KEYNOTE-061 was an open-label, randomized phase 3 trial that compared pembrolizumab with weekly paclitaxel as second-line chemotherapy in gastric and GEJ adenocarcinoma.[9] Of the 592 patients treated, 67% had a PD-L1 CPS of at least 1%, 33% had PD-L1–negative cancers, and 69% had gastric primary tumors. The primary endpoint of superior OS in the patients with a CPS of at least 1% was not achieved when pembrolizumab (9.1 months) was compared with paclitaxel (8.3 months; HR, 0.82; 1-sided *P*=.0421); a post hoc analysis suggested a greater treatment effect of pembrolizumab in patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or a CPS of at least 10%. In the patients with MSI-high disease, the median OS was not reached with pembrolizumab vs 8.1 months with paclitaxel. Patients with PD-L1–negative disease did poorly, with a median OS of 4.8 months. PFS in the patients with a CPS of at least 1% favored paclitaxel (4.1 months) over pembrolizumab (1.5 months). In this group, the response rates were similar for pembrolizumab (16%) and paclitaxel (14%), but the responses to pembrolizumab were more durable (median of 18.0 vs 5.2 months). KEYNOTE-061 failed to advance pembrolizumab as a second-line therapy over chemotherapy in gastric and GEJ adenocarcinoma, except for a potentially enhanced benefit in patients with a CPS of at least 10% and superiority over chemotherapy in patients with MSI-high cancers. The negative results of this trial are confounded by the selection of an inferior control: paclitaxel monotherapy. Paclitaxel plus ramucirumab is the global standard for second-line treatment and is superior to paclitaxel as a second-line therapy, and the use of paclitaxel as the control in KEYNOTE-061 undercuts conclusions drawn from this trial.

A trial with mixed results was KEYNOTE-181, which examined the second-line treatment of patients with squamous cancer or adenocarcinoma of the esophagus and GEJ. In this open-label, randomized phase 3 trial, pembrolizumab was compared with physician's choice of chemotherapy (paclitaxel, docetaxel, or irinotecan). Of the 628 patients treated, most had squamous cancers (63.8%) and 35% had a CPS of at least 10%. The primary endpoint population comprised patients with squamous cancers and a CPS of at least 10%. OS was superior in the patients with a CPS of at least 10% (9.3 vs 6.7 months; *P*<.00853). This benefit was limited to patients who had squamous cancer with a CPS of at least 10% vs those with a CPS of less than 10% (HR, 0.64 vs 0.88). HRs for OS for adenocarcinoma approached 1.0 irrespective of PD-L1 status (HR, 0.93-1.12). Response rates in patients with a CPS of at least 10% were higher in those treated with pembrolizumab than in those who received chemotherapy (21.5% vs 6.1%). On the basis of these results, pembrolizumab received regulatory approval as a second-line therapy in patients with esophageal squamous cancer who have a CPS of at least 10%. The negative results for adenocarcinoma reflect the negative results seen in the KEYNOTE-061 trial of gastric/GEJ cancer.

A second positive trial for esophageal squamous cancer, ATTRACTION-3, was an open-label, randomized phase 3 trial that compared nivolumab vs chemotherapy with paclitaxel or docetaxel as second-line treatment.[18] Of the 419 treated patients, 52% were considered PD-L1–positive by TPS, with a score of at least 1%, and a large percentage had previously undergone radiotherapy (70%) or surgery (49%). OS, the primary endpoint, was superior for nivolumab vs chemotherapy (10.9 vs 8.4 months; HR, 0.77; *P*=.019), with a diminished benefit in patients with a TPS of less than 1% (HR, 0.84) vs those with a TPS of at least 1% (HR, 0.69). Response rates (19% vs 22%) and PFS (HR, 1.08) were similar in the 2 treatment arms. On the basis of these results, nivolumab received approval for use as second-line treatment in patients with esophageal squamous cancers irrespective of PD-L1 status.

Practice-Changing First-Line Trials of Checkpoint Inhibitors in Esophagogastric Cancer

Standard-of-care practice has changed, given the recent series of positive phase 3 trials combining immune checkpoint inhibitors with first-line chemotherapy in esophagogastric cancer. Two initially reported negative trials have now been followed by positive trials that have led to the approval of both pembrolizumab and nivolumab in the first-line treatment of esophagogastric cancer. Results of these trials are outlined in Table 2.

KEYNOTE-062 was an open-label, randomized phase 3 trial comparing first-line chemotherapy (capecitabine or infusional 5-fluorouracil [5-FU] plus cisplatin) with or without pembrolizumab, and chemotherapy with pembrolizumab alone, in patients with gastric or GEJ adenocarcinoma and a CPS of at least 1%.[10] Of the 763 patients treated, two-thirds had gastric primary tumors and received capecitabine/cisplatin. Superiority

Table 2. First-Line Use of Immune Checkpoint Inhibitors

Trial	Tumor Type	Pts, No.	Treatment	OS, mo	RR, %
KEYNOTE-062	Gastric/GEJ cancer	763 (CPS ≥1%)	Chemotherapy +/-pembrolizumab Pembrolizumab vs chemotherapy	12.5 vs 11.1 10.6 vs 11.0	48.6% vs 37.2% 14.8% vs 37.2%
JAVELIN Gastric 100	Gastric/GEJ cancer	749	Avelumab vs chemotherapy maintenance	10.4 vs 10.9	13.3% vs 14.4%
CheckMate 649	Gastric/GEJ cancer	925 (CPS ≥5%) 1581 (all patients)	Nivolumab + FOLFOX vs FOLFOX	14.4 vs 11.1 (CPS ≥5%)* 13.6 vs 11.6 (all pts)*	60% vs 45% (CPS ≥5%)
ATTRACTION-4	Gastric/GEJ cancer	724	Nivolumab vs placebo + chemotherapy	17.5 vs 17.2	57.5% vs 47.8%
KEYNOTE-590	Esophageal/GEJ adenocarcinoma and squamous cell cancer	383 (CPS >10%) 740 (all patients)	Pembrolizumab vs placebo + chemotherapy	13.9 vs 8.8 (CPS >10%)* 12.4 vs 9.8 (all pts)*	45.0% vs 29.3% (all patients)
CheckMate 648	Esophageal squamous cell cancer	970 (49% TPS >1%)	Nivolumab + chemotherapy Nivolumab + ipilimumab Chemotherapy	15.4 * 13.7 * 9.1 (TPS >1%)	53% 35% 20% (TPS > 1%)
ESCORT-1	Esophageal squamous cell cancer	596	Camrelizumab vs placebo + chemotherapy	15.3 vs 12.0*	72.1% vs 62.1%

*Statistically significant.

CPS, combined positivity score; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; GEJ, gastroesophageal junction; mo, months; OS, overall survival; pts, patients; RR, response rate; TPS, tumor proportion score.

for a co–primary endpoint of OS with the addition of pembrolizumab to chemotherapy vs chemotherapy alone could not be demonstrated in all patients (12.5 vs 11.1 months; HR, 0.85; *P*=.05) or in patients with a CPS of at least 10% (12.3 vs 10.8 months; HR, 0.85; *P*=.16). In a noninferiority analysis of pembrolizumab vs chemotherapy, allowing an HR of 1.2, pembrolizumab was noninferior to chemotherapy for OS (10.6 vs 11.1 months). In the patients treated with pembrolizumab alone, the initial death rate was higher and the median PFS was worse (median, 2.0 vs 6.4 months) than in those who received chemotherapy alone. In the small percentage of patients with MSI-high cancers who were treated (6.6%), pembrolizumab with or without chemotherapy achieved superior OS compared with chemotherapy alone, independently of CPS. Although pembrolizumab failed to improve OS when added to first-line chemotherapy in this trial, the results for MSI-high cancers argue for the first-line use of pembrolizumab in patients with MSI-high cancers with or without chemotherapy.

The second negative trial, JAVELIN Gastric 100, evaluated maintenance therapy with the anti–PD-L1 agent avelumab vs continuation of chemotherapy in patients who had gastric or GEJ adenocarcinoma and stable disease or a response after first-line induction chemotherapy with 5-FU or capecitabine plus oxaliplatin.[22] Of the 499 randomized patients, most had gastric primary tumors (71%), and most (77%) had a TPS of less than 1%. Avelumab failed to achieve superiority over chemotherapy for the primary endpoint of OS (10.4 vs 10.9 months; HR, 0.91; 1-sided *P*=.1779) or for PFS (3.2 vs 4.4 months; HR, 1.04).

Practice-changing results from 3 positive trials of immune checkpoint inhibitor therapy combined with chemotherapy have now established new standards of care for esophagogastric cancer, with the remarkable achievement of a benchmark OS exceeding 1 year for the first time in this disease.

In the randomized, open-label CheckMate 649 trial, 1581 patients who had gastric or GEJ adenocarcinoma received first-line treatment with capecitabine, oxaliplatin, or FOLFOX (leucovorin, 5-FU, and oxaliplatin) with or without nivolumab.[23] Most (70%) had gastric primary tumors, 30% had cancers of the esophagus and GEJ, and 22% had previously undergone surgery. Co–primary endpoints of OS and PFS were evaluated in the 60% of patients with a CPS of at least 5%. Nivolumab improved OS (14.4 vs 11.1 months; HR, 0.71; *P*<.001) and PFS (7.7 vs 6.0 months; HR, 0.68). Nivolumab also improved OS in the patients with a CPS of at least 1% (HR, 0.77) and in all patients (HR, 0.80). However, OS was not improved in the subgroup of patients with a CPS of less than 1% and the subgroup with a CPS of less than 5% (HR, 0.92 and 0.94, respectively). Response rates improved with the addition of nivolumab in the patients with a CPS of at least 5% (from 45% to 60%), and the duration of response improved from 7.0 to 9.5 months. Response rates also improved across all CPS subgroups treated with nivolumab.

The positive results from this trial led to approval for nivolumab combined with first-line chemotherapy in gastroesophageal adenocarcinoma irrespective of the CPS. Debate and controversy about the use of nivolumab in patients with a CPS of less than 5%, in whom OS was not improved with the addition of nivolumab, are ongoing. A third arm in this trial, in which the patients received a non–chemotherapy-containing treatment (nivolumab at 1 mg/kg and ipilimumab [Yervoy, Bristol Myers Squibb] at 3 mg/kg cycled every 3 weeks), established in a prior phase 2 trial,[24] was closed prematurely owing to toxicity considerations. Results for these patients have not yet been reported.

The ATTRACTION-4 trial, from Asia, provides additional evidence for a benefit of the addition of nivolumab chemotherapy in the first-line setting.[25] In this randomized phase 3 trial of 724 patients with gastric or GEJ adenocarcinoma, nivolumab or placebo was combined with S-1 or capecitabine and oxaliplatin. Nivolumab added to chemotherapy was superior to chemotherapy alone in the primary endpoint of PFS (10.5 vs 8.3 months; HR, 0.68; *P*<.0007) and resulted in a higher response rate (57.5% vs 47.8%) and response duration (12.9 vs 8.7 months). However, OS with nivolumab and OS with placebo were similar (17.5 vs 17.2 months). The absence of a survival benefit may be attributable to the high percentage of patients in the chemotherapy-alone arm who subsequently received a checkpoint inhibitor (27%). In this trial, the effect of CPS status was not addressed.

The second practice-changing trial leading to approval for pembrolizumab in esophageal and GEJ adenocarcinoma and squamous cell cancer was KEYNOTE-590.[26] In this placebo-controlled, double-blind, randomized phase 3 trial, of the 740 patients treated, most (73%) had esophageal squamous cell cancer and were treated in Asia (52%). In comparison with placebo, pembrolizumab achieved superior OS in patients with a CPS of at least 10% (3.9 vs 8.8 months; HR, 0.57), in patients with squamous cell cancer who had a CPS of at least 10% (13.5 vs 9.4 months; HR, 0.62), in all patients with squamous cell cancer (12.6 vs 9.8 months; HR, 0.72), and in all patients treated (12.4 vs 9.8 months; HR, 0.73). Survival benefits were seen in patients with squamous cell cancer (HR, 0.72) and adenocarcinoma (HR, 0.74), but the benefit was smaller in patients with a CPS score of less than 10% (HR, 0.86) than in patients with a CPS of at least 10% (HR, 0.62). In addition, pembrolizumab improved PFS in all subgroups in comparison with placebo. With the addition of pembrolizumab, the response rate was higher (45.0% vs 29.3%) and the response duration was significantly longer (8.3 vs 6.0 months) in all patients treated. On the basis of these results, pembrolizumab is now approved in combination with first-line chemotherapy in esophageal and GEJ squamous cell cancer and adenocarcinoma.

The third trial leading to regulatory approval of first-line checkpoint inhibitor therapy in esophagogastric cancer was KEYNOTE-811.[27] This randomized, placebo-controlled phase 3 trial evaluated trastuzumab chemotherapy with or without pembrolizumab in HER2-positive esophagogastric cancer. In a planned interim analysis of the first 264 patients treated, most were HER2-positive, with an immunohistochemistry score of 3+ (79%-82%) and a CPS of at least 1% (85%-88%). The response rate was significantly higher with pembrolizumab (74.4%) than with placebo (51.9%; *P*=.0001), as was the complete response rate (11% vs 3%). On the basis of these interim results, the combination of pembrolizumab with first-line chemotherapy in HER2-positive esophagogastric cancer was granted accelerated approval.

With these pivotal 3 positive trials, nivolumab added to first-line chemotherapy in gastric and GEJ adenocarcinoma is now the standard of care. Pembrolizumab added to first-line chemotherapy is now standard therapy in esophageal and GEJ adenocarcinoma and squamous cancer. In addition, in HER2-positive esophagogastric adenocarcinoma, pembrolizumab added to trastuzumab and chemotherapy is now standard therapy.

Two additional trials of checkpoint inhibitor therapy in esophageal squamous cancers reported at the 2021 Annual Meeting of the American Society of Clinical Oncology (Virtual) merit comment. CheckMate 648, an open-label phase 3 trial in patients with metastatic squamous cancer of the esophagus, compared 5-FU/cisplatin chemotherapy alone, chemotherapy plus nivolumab, and a nonchemotherapy regimen of nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg.[28] This trial, the largest ever conducted in esophageal squamous cancer, treated 970 patients. Half (49%) had a PD-L1 TPS of at least 1%, which defined the primary endpoint analysis population. Among the patients with a TPS of at least 1%, OS with nivolumab plus chemotherapy was superior to OS with chemotherapy alone (15.4 vs 9.1 months; HR, 0.54; *P*<.0001), and nivolumab/ipilimumab was also superior to chemotherapy (13.7 vs 9.1 months; HR, 0.64; *P*=.001). PFS in the group with a TPS of at least 1% was better with chemotherapy and nivolumab than with chemotherapy alone (HR, 0.65; *P*=.0032) but the values were similar in a comparison of chemotherapy with nivolumab/ipilimumab (HR, 1.02). Response rates were also higher in the group with a TPS of at least 1% in a comparison of nivolumab and chemotherapy with chemotherapy alone (53% vs 20%) and in a comparison of nivolumab/ipilimumab with chemotherapy alone (35% vs 20%). In all patients treated, regardless of TPS, OS with nivolumab plus chemotherapy was superior to OS with chemotherapy alone (13.2 vs 10.7 months; HR, 0.74), and OS with nivolumab/ipilimumab was also superior to OS with chemotherapy alone (12.8 vs 10.7 months; HR, 0.78). The duration of response was longer in the nivolumab arms, with the longest median duration of response observed for nivolumab/ipilimumab (11.8 months in the TPS >1% group and 11.1 months in all patients). In the group with a TPS of less than 1%, however, no survival superiority over chemotherapy was seen for nivolumab plus chemotherapy or for nivolumab/ipilimumab (HR, 0.96 and 0.96, respectively); superiority was seen only in the TPS-positive patients. Future regulatory approval is likely for the addition of nivolumab to first-line chemotherapy and for the nonchemotherapy option of nivolumab/ipilimumab in esophageal squamous cancer.

A second trial in squamous cancer of the esophagus has been reported from China. ESCORT-1, a double-blind, placebo-controlled, randomized phase 3 trial of the anti–PD-1 antibody camrelizumab,[29] evaluated cisplatin and paclitaxel chemotherapy with and without the addition of camrelizumab in 596 patients, of whom 56% were PD-L1–positive (>1%). OS was longer with the addition of camrelizumab to chemotherapy than with chemotherapy alone (15.3 vs 12.0 months; HR, 0.70; *P*=.0010), as was PFS (6.9 vs 5.6 months; HR, 0.56; *P*<.0001). Survival was superior in both PD-L1–negative (HR, 0.79) and PD-L1–positive patients (HR, 0.59), and the response rate was higher with camrelizumab (72.1% vs 62.1%). The addition of camrelizumab to first-line chemotherapy in esophageal squamous cell cancer will likely be approved in China.

Adjuvant Immunotherapy in Esophagogastric Cancer

The advancement of immune checkpoint inhibitors to first-line therapy in advanced esophagogastric cancer has now been extended to adjuvant therapy. CheckMate 577, a randomized, double-blind, placebo-controlled phase 3 trial, evaluated the use of adjuvant nivolumab in patients who, after preoperative chemoradiotherapy for esophageal and GEJ adenocarcinoma or squamous cell cancer, were found to have residual disease at surgery.[30] Patients were randomized in a 2:1 ratio to receive 1 year of nivolumab or placebo. Of the 794 patients, 71% had adenocarcinoma, 65% had stage III disease, 60% had esophageal primary tumors, and 72% had a TPS of less than 1%. Nivolumab showed a significant advantage over placebo in the primary endpoint of disease-free survival (22.4 vs 11.0 months; HR, 0.69; *P*<.0003). Benefits were found regardless of histology (0.61-0.75), PD-L1/TPS status (HR, 0.73-0.75), and nodal status (HR, 0.67-0.74). A disease-free survival benefit was observed in patients treated less than 10 weeks after surgery (HR, 0.84) or longer than 10 weeks after surgery (HR, 0.66). The disease-free survival benefit was greater in patients with a PD-L1 CPS of at least 5% (HR, 0.62) than in those who had a CPS of less than 5% (HR, 0.89). Given these positive results, adjuvant nivolumab was approved for patients with esophageal or GEJ adenocarcinoma or squamous cancer undergoing chemoradiotherapy and surgery in whom residual disease has been resected at surgery. This groundbreaking trial has identified an adjuvant treatment that is beneficial after chemoradiotherapy and surgery in patients with esophageal or GEJ cancers and has established a new standard of care for adjuvant therapy. Although OS data are still pending, a doubling of disease-free survival will almost certainly translate into an OS benefit.

Toxicity of Immunotherapy

No new safety signals were generated across the spectrum of randomized trials of immune checkpoint inhibitor therapy in esophagogastric cancers. In trials comparing immune checkpoint inhibitor therapy with chemotherapy, the number of grade 3 and 4 treatment-related

adverse events was generally lower with immune checkpoint inhibitor therapy. Serious immune-related adverse events were predictable and generally manageable. In trials combining immune checkpoint inhibitor therapy with chemotherapy, although rates of grade 3 and 4 treatment-related serious adverse events were higher (on the order of 10%-15%), no increase in treatment-related deaths occurred, and toxicities were felt to be manageable. Several trials reported quality-of-life data. In KEYNOTE-590, the deterioration in quality-of-life measures was slower with the addition of pembrolizumab to chemotherapy than with chemotherapy alone.[31] In the adjuvant CheckMate 577 trial, the quality of life of patients who received 1 year of adjuvant nivolumab was similar to that of patients treated with placebo, suggesting no detriment to quality of life with adjuvant therapy.[30] In CheckMate 577, only 5% of patients were taken off therapy owing to a treatment-related adverse event. The toxicity concerns in CheckMate 649 that led to closure of the nivolumab/ipilimumab treatment arm did not develop in CheckMate 648, in which the schedule used, nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg every 3 weeks, was perhaps better tolerated.[28] Recognition and early treatment of immune-related adverse events are key in the era of the now-likely universal use of these agents in earlier-line therapy.[32]

Future Directions

The new standards of care for the first-line use of immune checkpoint inhibitors will influence the design of the next generation of clinical trials of novel agents. Given that the CPS may influence the benefit of these agents in clinical practice, it is now even more urgent to identify biomarkers that indicate which patients are most likely to benefit from the new therapies. Novel combinations of immune checkpoint inhibitors with other agents, including anti-angiogenesis agents, poly(ADP-ribose) polymerase (PARP) inhibitors, and drugs targeting other immune-based pathways, are ongoing. Provocative data were recently reported for the combination of the tyrosine kinase inhibitors regorafenib (Stivarga, Bayer HealthCare) and nivolumab,[33] and the combination of pembrolizumab plus lenvatinib (Lenvima, Eisai),[34] in phase 1 and 2 trials. Further study of these and other combinations will likely continue to move the field forward. Agents attempting to exploit immune recruitment mechanisms while targeting established pathways are also in active development. Margetuximab (Margenza, MacroGenics),[35] a monoclonal antibody targeting HER2 that may potentiate antibody-dependent cellular toxicity, and zolbetuximab,[36] which targets the gap junction protein claudin 18.2 and may also potentiate antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, are now in phase 2 and 3 clinical trials (NCT04082364, NCT03504397, NCT03653507).

Given the benefit of adjuvant nivolumab after combined-modality chemoradiotherapy in esophageal cancer, investigations of whether such a benefit of immune checkpoint inhibitors will be seen in patients with gastroesophageal cancer undergoing perioperative chemotherapy without radiotherapy are now underway (NCT03221426, NCT04592913, NCT03006705, NCT03443856). The evaluation of biomarkers that may be used to identify the patients most likely to benefit from adjuvant treatment with immune checkpoint inhibitors will remain a high research priority.

Disclosure

Dr Ilson has served on advisory boards for Merck, Roche, AstraZeneca, and Bristol Myers Squibb.

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