Systemic therapy for esophagogastric cancer: immune checkpoint inhibition

Tomas G. Lyons, Geoffrey Y. Ku

Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, USA

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Correspondence to: Geoffrey Ku, MD. Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 300 E. 66th Street, Rm 1035, New York, NY 10065, USA. Email: kug@mskcc.org.

Abstract: The poor prognosis for patients with esophagogastric cancers (EGC) requires the development of newer more effective therapies to further improve the treatment outcomes for this disease. Immunotherapy is a novel treatment strategy that is dramatically changing the treatment landscape for several types of cancers. Cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death (PD)-1/PD-ligand are essential immune checkpoint inhibitors that suppress T cell activation. Targeting of these immune checkpoints with monoclonal antibodies has shown clinical efficacy in several solid tumors which has led to their approval and use in routine clinical practice. In EGC early phase evaluation of immune checkpoint inhibitors has yielded encouraging results with multiple phase 3 studies currently ongoing. In this review, the biological rationale for the use of immune checkpoint inhibitors in cancer will briefly be described and the accumulating data concerning their use in EGC will be presented.

Keywords: Esophageal cancer; gastroesophageal cancer; gastric cancer; immunotherapy; cytotoxic T lymphocyte antigen-4 (CTLA-4); programmed death (PD)-1; PD-ligand 1 (PD-L1)

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Introduction

In the United States, esophagogastric cancers (EGC) are an uncommon but aggressive disease. In 2016, an estimated 26,370 patients will be diagnosed with gastric cancer, with an estimated 10,370 deaths. While esophageal cancer cases will number 16,940, with an estimated 15,690 deaths during the same time period (1). Approximately 50% of patients diagnosed with EGC present with overt metastatic disease and chemotherapy is the mainstay of palliation in this setting. The majority of patients will develop chemotherapy resistance, and treatment options beyond first or second line are limited in this disease. With the exception of trastuzumab with first-line chemotherapy for Her2-positive disease (2) and ramucirumab as monotherapy (3) or with paclitaxel chemotherapy (4) in the second-line setting, results of clinical trials utilizing targeted agents have not resulted in efficacious therapeutic options for patients.

Recent years have seen the treatment landscape for many cancers changed dramatically with the development of immune-directed therapies, specifically immune checkpoint inhibitors. There has been growing excitement amongst oncologists and patients alike for the use of checkpoint inhibition in EGC. The first checkpoint inhibitor drug to be approved by the U.S. Food and Drug Administration (FDA) in 2011 was the anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) antibody ipilimumab in advanced melanoma (5,6). Since then, antagonists of the programmed death (PD)-1/PD-ligand 1 (PD-L1) pathway have undergo extensive evaluation in multiple other solid tumors, with FDA approval of immune checkpoint inhibitors in melanoma, non-small cell lung cancer (NSCLC), urothelial carcinoma, renal cell carcinoma, squamous cell carcinoma of the head and neck, Merkel cell carcinoma and Hodgkins lymphoma. In EGC early phase evaluation of immune

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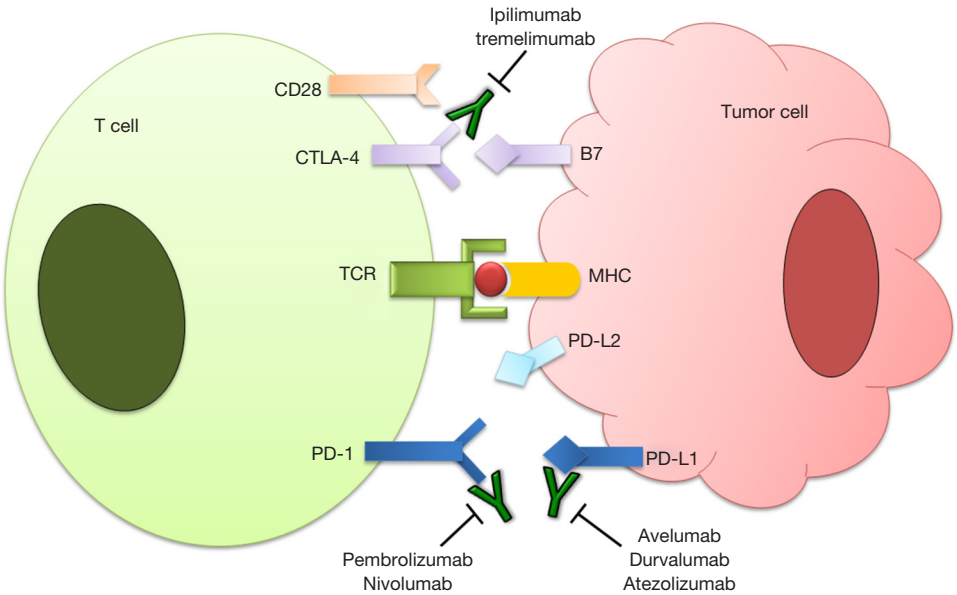

Figure 1 CTLA-4 and PD-1 checkpoint molecules at the T cell-tumor interface. TCR, T cell receptor; MHC, major histocompatibility complex; CTLA-4, cytotoxic T lymphocyte antigen-4; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand; PD-L2, PD-2 ligand.

checkpoint inhibitors has yielded encouraging results, culminating in ongoing phase III studies.

In this review, the biological rationale for the use of immune checkpoint inhibitors in cancer will briefly be described and the accumulating data concerning their use in EGC will be presented.

CTLA-4 and the PD-1/PD-L1/2 pathway in cancer

CTLA-4 is a protein that has high homology with CD28, which is known to be a co-stimulatory molecule expressed on T cells necessary to provide the secondary signal for T cell activation (7). As seen in *Figure 1*, CTLA-4 also binds their cognate ligands, the B7 molecules (which are found on APCs), but with much higher affinity. However, unlike CD28, CTLA-4 expression is induced only when a T cell becomes activated. It then competes with CD28 for binding to the B7 molecules but leads to down-regulation and eventual abrogation of the immune response.

PD-1 is another negative immune checkpoint molecule, as shown in *Figure 1* (8). PD-1 has two ligands, PD-L1 and L2. PD-L2 is mostly expressed on APCs, while PD-L1 is expressed on numerous tissues, including immune and tumor cells. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells (9). Unlike CTLA-4, which is thought to be necessary for T cell activation, the PD-1/PD-L1/2 pathway is thought to protect cells from T cell attack (10).

CTLA-4 checkpoint inhibitors in EGC

Immune checkpoint inhibition with anti-CTLA-4 antibodies has been explored in the treatment of EGC. The two anti-CTLA-4 antibodies that have been evaluated are ipilimumab and tremelimumab.

Tremelimumab

The first immune checkpoint inhibitor to be studied in EGC is tremelimumab. In a phase II study, Ralph *et al*. evaluated tremelimumab 15 mg/kg every 90 days in 18 patients with advanced esophageal, gastroesophageal junction (GEJ) or gastric adenocarcinoma; 15 had received prior 1st-line chemotherapy and 3 had received 2nd-line treatment (11). One patient achieved a partial response (PR, 6%) that was ongoing at 33 months of follow-up while 4 other patients achieved stable disease (SD, 22%). Although median time to progression (TTP) and overall survival (OS) were relatively disappointing (2.83 and 4.83 months respectively), 1/3 of patients were alive at 12 months. It

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Table 1 Results of PD-1 or anti-PD-L1 antibody studies in esophagogastric cancer

Drug	Trial	Phase	Line of therapy	Patients	ORR	mPFS (months)	mOS (months)	1-year OS (%)
Pembrolizumab	KEYNOTE-012 (13)	Ib	≥2	n=39; PD-L1+ n=39	22%	1.9	11.4	42
	KEYNOTE-059 (14) Cohort 1	II	≥2	n=259; PD-L1+ n=148; PD-L1− n=109	11.6%; 15.5%; 6.4%	2.0	5.6	23.4
	KEYNOTE-059 (15) Cohort 2 (pembro + chemo)	II	1st	n=25; PD-L1+ n=16; PD-L1− n=8	60%; 68.8%; 37.5%	6.6	13.8	NS
Nivolumab	Checkmate 032 (16) N 3 mg	I/II	≥2	n=59; PD-L1+ n=16; PD-L1− n=26	12%; 19%; 12%	1.4	6.2	39
	ATTRACTION-2 (17)	III	≥2	n=493	11.2%	1.65	5.32	26.6
Nivolumab + ipilimumab	Checkmate 032 (16) N 1 mg + I 3 mg	I/II	≥2	n=49; PD-L1+ n=10; PD-L1− n=32	24%; 40%; 22%	1.4	6.9	35
	Checkmate 032 (16) N 3 mg + I 1 mg	I/II	≥2	n=52; PD-L1+ n=13; PD-L1− n=30	8%; 23%; 0%	1.6	4.8	24
Avelumab	JAVELIN Solid Tumor (18)	Ib	≥2	N=20; PD-L1+ n=NS; PD-L1− n=NS	15%; 20%; 0%	11.6 weeks; 36 weeks; 11.6 weeks	NS	NS
Durvalumab (19)	NA	I	≥2	n=16	25%	NS	NS	NS

NS, not stated; ORR, overall response rate; mPFS, median progression free survival; mOS, median overall survival; OS, overall survival; N, nivolumab; I, ipilimumab

should be noted that the dose of tremelimumab in this study is now considered sub-therapeutic. In an ongoing study of tremelimumab (with or without the anti-PD-L1 antibody durvalumab), the dose of tremelimumab monotherapy is 10 mg/kg every 4 weeks.

Ipilimumab

Data for ipilimumab were recently reported in abstract form (12). This was for a randomized phase II study in which 114 patients with either a PR or SD to first-line fluoropyrimidine/platinum chemotherapy were randomized to best supportive care (BSC, which mostly consisted of continuation of the fluoropyrimidine) *vs.* ipilimumab. The primary end-point was immune-related progression free survival (irPFS). The study was terminated early after the interim analysis due to the lack of demonstrable clinical activity with ipilimumab. The irPFS was only 2.9 months in patients who received ipilimumab *vs.* 4.9 months for patients who continued on fluoropyrimidine maintenance chemotherapy. The median OS was similar in both groups (12.7 *vs.* 12.1 months). Toxicities were also higher in the ipilimumab *vs.* BSC arm (72% *vs.* 56%) and included pruritus (32%), diarrhea (25%), fatigue (23%) and rash (18%).

PD-1 and PD-L1 checkpoint inhibitors in EGC

There are a number of antibodies targeting the PD-1 and PD-L1 pathway now approved for the treatment of various cancers. Many of these anti-PD-1 and PD-L1 antibodies have been evaluated in EGC, including pembrolizumab, nivolumab, avelumab and durvalumab. The following section along with *Table 1* provides a summary of the clinical trial data involving these PD-1/PD-L1 inhibitors in EGC.

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Pembrolizumab (PD-1 inhibitor)

The KEYNOTE-012 study was a multicenter, nonrandomized, open-label, multicohort phase Ib trial evaluating single-agent pembrolizumab (10 mg/kg every 2 weeks or a 200-mg fixed dose every 3 weeks) that evaluated 39 patients with PD-L1 positive recurrent or metastatic gastric/GEJ adenocarcinoma (13). Based on the cut-off for positivity of ≥1% membranes staining of tumor or peri-tumoral mononuclear inflammatory cells, 40% of tumors were noted to be PD-L1 positive. Nineteen patients were from Asia and the remainder was from the rest of the world. Patients were heavily pre-treated and 2/3 had received ≥2 prior therapies. The confirmed overall response rate (ORR) was 22% for all patients; 4 of these 8 patients had ongoing responses at the time of data analysis and the median duration of response (DOR) was 40 weeks. Median progression free survival (PFS) was 1.9 months and median OS was 11.4 months; the 6- and 12-month OS rates were 66% and 42% respectively.

In the similarly designed KEYNOTE 028 study, 23 patients with PD-L1 positive esophageal cancer were treated, 17 with squamous cell cancer (SCC) and 5 with adenocarcinoma (20,21). The PD-L1 positivity rate in the screened patients was 41%, virtually identical to the rate in GEJ/gastric adenocarcinoma. This was again a heavily pre-treated group, with 87% of patients receiving ≥2 prior therapies. Seven of 23 patients (30%) had a PR, with five of the PRs ongoing at the time of data analysis. The DOR was 40.0 weeks. Six- and 12-month PFS were 30.4% and 21.7% respectively.

The KEYNOTE-059 study is an open-label, multicohort phase II study of patients with advanced gastric/GEJ adenocarcinoma (14). Patients in cohort 1 had received ≥2 prior lines of therapy and HER2/neu positive disease was permitted if the patient had received prior trastuzumab-based therapy. Single agent pembrolizumab was administered at 200 mg every 3 weeks. Patients in cohort 2 had received no prior therapy for advanced disease and were administered pembrolizumab 200 mg plus 800 mg/m^2 of 5-fluorouracil (5-FU; or 1,000 mg/m^2 of capecitabine in Japan) plus 80 mg/m^2 of cisplatin every 3 weeks for six cycles, followed by pembrolizumab plus 5-FU/capecitabine maintenance for up to 2 years or until progression. Lastly, patients in cohort 3 were also treatment-naïve, similar to cohort 2 but must have had PD-L1 positive disease.

Results of cohort 1, which enrolled 259 patients were recently presented (14). Overall, 51.7% of patients had received 2 prior lines of therapy, and 29% and 19.3% had received 3 or ≥4 prior lines of therapy respectively. After a median follow-up of 5.8 months, the ORR was 11.6%, with a complete response (CR) rate of 2.3% and a PR rate of 9.3%. The DOR was 8.4 months. Patients with PD-L1 positive tumors (n=148) had an ORR of 15.5%. The ORR was 6.4% in the PD-L1 negative group (n=109). The median DOR in the PD-L1 positive group was 16.3 *vs.* 6.9 months in those with PD-L1 negative disease. Patients treated in the 3rd-line setting had an ORR of 16.4% compared to 6.4% for patients with ≥4 lines of therapy. The PFS for all patients was 2 months with a median OS of 5.6 months and a 12-month OS rate of 23.4%.

These results are encouraging and suggest that pembrolizumab has promising antitumor activity in pretreated advanced gastric/GEJ cancer. Although response rates were higher in patients with PD-L1 positive disease, responses were also seen in PD-L1 negative disease. This finding is consistent with the use of PD-1 inhibitors in other disease types and demonstrates that PD-L1 expression is an imperfect biomarker to predict response.

Preliminary efficacy and safety data from 25 enrolled patients in cohort 2 of the KEYNOTE-059 study have also been presented in abstract form (15). After a median follow-up of 12.2 months, grade 3-4 treatment-related adverse events (TRAEs) occurred in 76% of patients, with no fatal events. ORR was 60% in all patients and was 68.8% in PD-L1 positive patients and 37.5% in PD-L1 negative patients. Median DOR was 4.6 months in all patients, while median PFS and OS were 6.6 and 13.8 months respectively. These early data suggest that combination of pembrolizumab and cisplatin/5-FU chemotherapy has a manageable toxicity profile and encouraging antitumor activity as 1st-line therapy for patients with advanced gastric cancer. It is interesting to note that the ORR in patients with PD-L1 negative tumors was the same as would be expected with a fluoropyrimidine/platinum doublet alone and the benefit of adding an anti-PD-1 antibody to first-line chemotherapy will have to await several ongoing phase III studies (see below).

There are reasons to believe that adding immunotherapy to chemotherapy can be a beneficial strategy. A recently published randomized phase II study of 1st-line pembrolizumab plus carboplatin/pemetrexed in NSCLC showed an improved response with similar toxicity to chemotherapy alone (22). However, survival data are still pending. Based on this study pembrolizumab has received FDA approval in combination with carboplatin/pemetrexed in non-squamous NSCLC. Given these positive results

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in NSCLC, it is hoped that they might be replicated in advanced EGC.

Nivolumab (PD-1 inhibitor)

CheckMate-032 was a phase I/II open-label study of the safety and activity of nivolumab alone or with ipilimumab in advanced and metastatic solid tumors (16). This study enrolled 160 patients with advanced/metastatic gastric or gastroesophageal cancer who had progressed while receiving standard chemotherapy, most of whom (79%) received ≥2 regimens. Patients were randomized to receive 3 mg/kg of nivolumab every 2 weeks (N3), 1 mg/kg of nivolumab plus 3 mg/kg of ipilimumab (N1 plus I3) or 3 mg/kg of nivolumab plus 1 mg/kg of ipilimumab (N3 plus I1) every 3 weeks for four cycles, followed by 3 mg/kg of nivolumab every 2 weeks until disease progression or intolerable toxicity. Updated results concerning the 59 patients enrolled to the N3 cohort were presented in abstract form and suggest similar activity to pembrolizumab (23). The RR was 12%, with a median time-to-response of 1.6 months and DOR of 7.1 months in the responders. Median OS was 6.2 months for the entire group and the 12-month survival rate was 39%. PD-L1 positivity was assessed using a cut-off of ≥1% for IHC positivity. The RRs in patients with PD-L1 positive and negative tumors were 19% and 12% respectively.

Very similar activity was also noted for nivolumab in a Japanese study of 64 patients with esophageal SCC, who had received a median of 3 prior therapies (24). The response rate was 17.2%, including a CR in 1 patient. Median PFS was 1.5 months and median OS was 10.8 months.

The largest study to date evaluating nivolumab in EGC is the ATTRACTION-2 trial (17). This was a multicenter, double-blind, randomized phase III East Asian study of 493 patients who had received >2 prior regimens. Patients were randomized 2:1 to nivolumab *vs.* placebo. The median OS was 5.32 months with nivolumab *vs.* 4.14 months with placebo (HR 0.63, P<0.0001) The 6-month OS rate was 46.4% *vs.* 34.7% and 12-month OS rate was 26.6% *vs.* 10.9% in favor of nivolumab. The overall response rate was 11.2% *vs.* 0%, with a median DOR to nivolumab being 9.53 months. The PFS was 1.65 *vs.* 1.45 months (HR 0.60, P<0.0001). It is expected that nivolumab will receive approval in Asia as salvage therapy for chemotherapy refractory EGC.

If we compare outcomes from the nivolumab ATTRACTION-2 study with cohort 1 of the pembrolizumab KEYNOTE-059, we observe near identical results for OS 5.32 months (ATTRACTION-2) *vs.* 5.6 months (KEYNOTE-059). Similarly, ORR was 11.2% *vs.* 11.9%, 12-month OS 26.6% *vs.* 23.4% and PFS 1.65 *vs.* 2 months respectively. Taken together, these findings confirm that PD-1 inhibition is an effective treatment approach in this disease setting.

Avelumab (PD-L1 inhibitor)

Avelumab has been evaluated in a phase Ib JAVELIN study (18) that enrolled patients with GC/GEJ who had progressed on ≥2 lines of prior therapy (n=20). Patients who had received 1 line of chemotherapy but had not yet progressed (switch-maintenance) were also enrolled (n=55). For patients in the ≥2 lines of prior therapy cohort ORR was 15% (3/20). PD-L1 expression (≥1% cutoff) was evaluable in 12/20 patients in this cohort. Median PFS was 36.0 weeks (95% CI: 6.0–36.0) for PD-L1 positive and 11.6 weeks (95% CI: 2.1–21.9) for PD-L1 negative tumors. Avelumab is currently being evaluated in the 3rd-line setting *vs.* best supportive care (NCT02625263) and as maintenance therapy after primary chemotherapy *vs.* continuation of chemotherapy in the 1st-line setting (NCT02625610).

Durvalumab (PD-L1 inhibitor)

Finally, abstract presentations have also shown responses for the PD-L1 antibody durvalumab in 16 patients with EGC, where 4 patients had a PR (19).

Nivolumab and ipilimumab (combination PD-1/CTLA-4 inhibition)

The only data for combination immune checkpoint blockade in EGC comes from the Checkmate 032 study, which was recently presented in abstract form (23). In addition to the 59 patients treated with nivolumab alone (and discussed above), there were an additional two cohorts that received different doses of nivolumab together with ipilimumab. A total of 49 patients were enrolled to the N1 + I3 cohort and 52 patients enrolled to the N3 + I1 cohort. Baseline characteristics in these other two groups were similar to the nivolumab-only arm. The highest response rate (24%) was reported for patients in the N1 + I3 group. The ORR for the N3 + I1 group was 8%. The N1 + I3 group contained 10 PD-L1 positive tumors with an ORR of 40% *vs.* 22% for PD-L1 negative tumors. Survival data in these relatively small groups

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of patients appeared comparable; 6.2 *vs.* 6.9 *vs.* 4.8 months for N3, N1 + I3 and N3 + I1 cohorts respectively. Grade ≥3 toxicities were highest in the N1 + I3 group (35% *vs.* 5% in the N3 group). The most common G3/4 toxicities seen in this group were diarrhea 10%, ALT increased 14% and AST increased 10%. Nevertheless, this dose has been selected as the basis for a proposed phase III study.

These results have to be interpreted with caution not only because of the small patient numbers but because patients were not randomized to the treatment arms but were instead enrolled sequentially. Unless validated, these findings also raise puzzling questions: why does the addition of ipilimumab 1 mg/kg to nivolumab 3 mg/kg result in a lower ORR *vs.* nivolumab monotherapy? Similarly, why does the combination of N1 + I3 result in a higher ORR *vs.* N3 without any hint of a survival benefit? Overall, this study justifies the ongoing phase III Checkmate 677 study (discussed below) but not the routine use of combination anti-PD-1 and anti-CTLA-4 therapy.

Pembrolizumab and ramucirumab (PD-1 and VEGF inhibition)

Ramucirumab is a monoclonal antibody against VEGFR2, which is approved as a single agent and in combination with paclitaxel for 2nd-line therapy in EGC. A multicohort phase 1a/b study was presented in abstract form by Chau *et al.* and is the first to evaluate the simultaneous targeting of both PD-1 and VEGFR2 in EGC (25). Forty-one patients with advanced gastric or GEJ adenocarcinomas were enrolled to 3 cohorts; previously treated with chemotherapy (cohorts A and B) or chemotherapy-naive (cohort A2). Ramucirumab was administered at 8 mg/kg on Days 1 & 8 (Cohorts A and A2) or 10 mg/kg on Day 1 (Cohort B) with pembrolizumab 200 mg every 3 weeks. Response rate in cohort A and B was 7%. PFS and OS rates at 6 months were 22.4 % and 51.2% respectively. Eighteen patients were enrolled to A2 cohort with a response rate of 17%. Any grade toxicity was 80%, with a grade 3/4 toxicity rate of 24%, most commonly colitis (7%) and hypertension (7%). Again, these small numbers preclude any specific conclusion but the activity noted so far does not seem to indicate any particular advantage to adding ramucirumab to pembrolizumab.

Pembrolizumab in microsatellite unstable (MSI) EGC

Four subtypes of gastric cancer have been identified by the Cancer Genome Atlas (TCGA): Epstein-Barr virus (EBV) positive, MSI, genomically stable (GS) and chromosomal instability (CIN) (26). Of these subtypes, both the EBV and MSI groups may be more responsive to immune checkpoint inhibition.

The MSI subgroup accounts for 22% of gastric cancer patients. Patients' cancers may be MSI through both a somatic or germline mutation. Although the TCGA analysis reported such a relatively high incidence of the MSI subgroup, it is critical to note that this analysis was restricted to patients with operable tumors. In the metastatic setting, the incidence of mismatch repair protein-deficient (dMMR) or MSI tumors is much lower. Our anecdotal experience in over 200 patients suggests a dMMR/MSI incidence of <5%; we have tested tumor samples from >200 patients and only 4 patients were found to be dMMR/MSI (27).

Pembrolizumab has shown activity only in MSI-high colorectal cancer (28). Recent data also suggest significant activity in other mismatch repair-deficient gastrointestinal cancers, including gastric cancer (29). In May 2017, the FDA granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. The approval was based on data from 149 patients with MSI-H or dMMR cancers enrolled across five single-arm clinical trials (30). Ninety patients had colorectal cancer and 59 patients were diagnosed with one of 14 other cancer types, of which 9 patients had EGC. ORR was 39.6% with a DOR of ≥6 months being 78% in the total population. There were 11 CRs and 48 partial responses. Of the 9 EGC patients, ORR was 56% with 5 out of the 9 patients achieving a PR.

To ensure MSI-H patients get access to checkpoint inhibitor therapy, it is prudent to test all patients with EGC for dMMR or MSI status irrespective of a family pedigree that might suggest a germline mutation. It is likely that, as next-generation sequencing becomes part of routine clinical practice, mutational burden will identify patients with MSI-H tumors, who are most likely to benefit from checkpoint inhibitors.

Future directions

Given the promising results from earlier phase studies, numerous phase III studies are ongoing or planned, as noted in *Table 2*. Of note, the KEYNOTE-059 study, which has completed accrual, included a first-line arm in

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Table 2 Ongoing phase II/III studies of immune checkpoint inhibitors in esophagogastric cancer

Drug	Trial identifier	Phase	Neoadjuvant/adjuvant	1st line metastatic	2nd line metastatic	3rd line metastatic	Status
Pembrolizumab	KEYNOTE-059 (NCT02335411)	II	–	Pembro + cisplatin/5-FU or Pembro	–	Pembrolizumab	Completed
	KEYNOTE-062 (NCT02494583)	III	–	Pembro *vs*. Pembro + cisplatin/5-FU *vs*. cisplatin/5-FU	–	–	Ongoing
	KEYNOTE-061 (NCT02370498)	III	–	–	Pembro *vs*. paclitaxel	–	Ongoing
	KEYNOTE-181 (NCT02564263)	III	–	–	Pembro *vs*. taxane or irinotecan	–	Recruiting
	KEYNOTE-180 (NCT02559687)	II	–	–	–	Pembrolizumab	Ongoing
	(NCT02918162)	II	Pembro + platinum/5-FU doublet or triplet for 3 cycles pre-op and 3 cycles post-op, followed by maintenance Pembro for 1 year	–	–	–	Recruiting
	PROCEED (NCT03064490)	II	Pembro + carbo/taxol + radiation, followed by adjuvant Pembro for 3 cycles	–	–	–	Recruiting
	(NCT02954536)	II	–	Pembro + trastuzumab + platinum/5-FU	–	–	Recruiting
Nivolumab	Checkmate 649 (NCT02872116)	III	–	Nivo + Ipi *vs*. Nivo + FOLFOX *vs*. FOLFOX	–	–	Recruiting
	(NCT02569242)	III	–	–	Nivo *vs*. taxane	–	Recruiting
	Checkmate 577 (NCT02743494)	III	Nivo *vs*. placebo as adjuvant therapy for ypTanyNany tumor	–	–	–	Recruiting
Avelumab	JAVELIN 100 (NCT02625610)	III	–	Oxaliplatin/5-FU followed by maintenance avelumab *vs*. maintenance chemotherapy or BSC	–	–	Recruiting
	JAVELIN 300 (NCT02625623)	III	–	–	–	Avelumab + BSC *vs*. taxane or irinotecan + BSC or BSC alone	Ongoing
Durvalumab	(NCT02340975)	Ib/II	–	–	Durvalumab *vs*. tremelimumab *vs*. durvalumab + tremelimumab	Durvalumab + tremelimumab	Recruiting
	(NCT02658214)	Ib	–	Durvalumab + tremelimumab + oxaliplatin/5-FU	–	–	Recruiting

Pembro, pembrolizumab; Nivo, nivolumab; Ipi, ipilimumab; BSC, best supportive care; 5-FU, 5-fluorouracil.

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which patients received pembrolizumab in combination with 5-FU/cisplatin. Preliminary efficacy and safety data have been discussed above (15). This combination is being further tested in the phase III KEYNOTE-062 study (31). This is a study of pembrolizumab as first-line treatment for patients with advanced PD-L1 positive gastric or GEJ adenocarcinoma. Participants will be randomly assigned to one of the three treatment arms: pembrolizumab as monotherapy, or pembrolizumab + cisplatin + 5-FU, or placebo + cisplatin + 5-FU. The results of both of these studies will therefore determine if there is a benefit for combination immune checkpoint blockade and chemotherapy in the first-line therapy of EGC.

In addition to the above 1st-line studies with pembrolizumab, Checkmate 649 is a phase III study which is currently enrolling advanced PD-L1 positive or negative, advanced gastric or GEJ patients and randomizing them to ipilimumab + nivolumab *vs.* nivolumab + oxaliplatin/5-FU (FOLFOX or XELOX) *vs.* oxaliplatin/5-FU alone.

The Checkmate 577 study is evaluating the benefit of adjuvant nivolumab *vs.* placebo in patients with locally advanced esophageal/GEJ tumors (both adenocarcinomas and SCC), who have undergo chemoradiation and surgery but are found to have persistent disease ($ypT_{any}N_{any}$ tumor) (32).

Finally, a phase Ib/II study is evaluating combination immune checkpoint blockade, this time with a PD-L1 inhibitor (durvalumab) and an anti-CTLA-4 antibody (tremelimumab) in the 2nd- and 3rd-line setting (33).

These studies represent only a small fraction of ongoing or planned phase I/II studies that will combine immune checkpoint inhibitors with other immunotherapy drugs, chemotherapy, targeted therapies or locoregional approaches (such as radiation or ablative procedure).

Conclusions

The evaluation of immune checkpoint inhibitors in solid tumors in general but also in EGC has occurred at a breathtaking pace. Two studies, ATTRACTION-2 (nivolumab) and KEYNOTE-059 (pembrolizumab) have now confirmed the activity of an anti-PD-1 antibody in the chemorefractory setting. Results of the many phase III studies are awaited with eager anticipation and it is hoped that they will establish a new treatment paradigm in EGC. These drugs are not without both economic and clinical toxicity, with responses rates in a small albeit significant population of patients. Therefore it is imperative that we attempt to identify patients most likely to benefit from these therapies, through ongoing correlative efforts and the next generation of studies evaluating combinatorial strategies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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