



Esophageal, gastric cancer and immunotherapy: small steps in the right direction?

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Abstract: The treatment of advanced, solid-tumor oncology has been reshaped over the last eight years with the development and FDA approval of several immune checkpoint inhibitors (ICIs) comprised of monoclonal antibodies targeting either PD-1, PD-L1, or CTLA-4 across numerous disease states and indications. Yet, despite their vast expansion of use in both solid-tumor and hematologic malignancies, gastrointestinal cancers have had limited approvals to date. This review article will focus on the use of the currently studied, approved uses and the potential future roles of ICIs in the treatment of cancers of the upper gastrointestinal tract through recent updates on ongoing studies and discussion of phase III studies underway. A single immunotherapy agent, Pembrolizumab, is the only currently approved treatment option in subset of patients with unresectable locally advanced, recurrent, or metastatic esophageal, gastroesophageal, or gastric cancers after failure or intolerance of initial systemic treatments. The only patients who are currently considered for treatment with ICI are those with tumors that are either microsatellite instability-high (MSI-H), DNA mismatch repair deficient (dMMR), or in those with esophageal, GEJ, or gastric adenocarcinomas that have at least one-percent expression of PD-L1 after failing at least two lines of systemic therapy based on early results from the KEYNOTE-059 trial released in 2017, or second-line treatment of locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) with combined positive score (CPS) of 10 or greater based on the combined results from KEYNOTE-180 and KEYNOTE-181 in 2019. However, despite these limited successes thus far, there are numerous ongoing studies evaluating several ICIs for efficacy and safety in esophageal, GEJ, and gastric cancers. These agents are being studied in countless aspects of these malignancies: from neoadjuvant and adjuvant treatment in resectable disease to first-line treatment and beyond in the advanced, unresectable, or metastatic setting. In this article we will review the currently approved agents as well as ongoing clinical trials that will be approaching completion in the next 5 years, potentially altering the landscape of treatment in upper GI malignancies.

Keywords: Immunotherapy; esophageal neoplasms; stomach neoplasms

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Introduction

Esophageal cancer (consisting of both squamous cell carcinoma and adenocarcinoma) is the eighteenth most common malignancy in the US by incidence with 17,650 new cases in 2019, representing 1.0% of all new cancer cases (1). Esophageal cancer accounts for 2.6% of cancer deaths in 2019, with 16,080 succumbing to this disease (1). Nearly 40% of patients present with metastatic disease at diagnosis (1). Rates of new cases and deaths have been falling by nearly 1% annually over the last 10 years (1). While it has a five-year survival of 19.9%, although five-year survival in patients with metastatic disease is 4.8% (1). As of 2016, an estimated 46,477 people were living with esophageal cancer (1).

In the United States, gastric cancer is the fifteenth most common cancer by incidence with 27,510 new cases diagnosed in 2019, representing 1.6% of all new cancers (2). Gastric cancer resulted in 11,140 deaths in 2019, representing 1.8% of cancer deaths (2). Nearly 40% of patients present with metastatic disease at diagnosis (2). Despite a five-year survival of 31.5%, overall, five-year survival in patients with metastatic disease is far less, 5.3% (2). Based on estimates from 2016, approximately 113,054 people were living with gastric cancer in the US (2). Both the rates of new cases and death have declined by 1.5% and 2.1% annually over the last 10 years, respectively (2).

Systemic treatment of advanced, metastatic esophageal, gastroesophageal junction (GEJ), and gastric cancer utilizes a combination of multiple cytotoxic chemotherapeutic agents, although no single, standard of care regimen exists. Combination chemotherapy with a platinum and fluoropyrimidine doublet, such as FOLFOX, CAPOX, cisplatin/5-fluorouracil (5-FU), or cisplatin/capecitabine are common regimens with the addition of Trastuzumab for the treatment of HER2-positive disease (3-7). Other agents like Irinotecan, or taxanes (docetaxel or paclitaxel) can be combined with fluoropyrimidines and/or platinum or ramucicromab, or used as monotherapy for those unfit for combination regimens (8-10).

The use of immune checkpoint inhibitors (ICIs) in the treatment of both hematologic malignancies and solid organ malignancies has been expanding rapidly since the first approval for Ipilimumab in 2011 for the treatment of BRAF-negative metastatic melanoma (11-14). Now, more than 1,000 immunotherapy clinical trials later, we are exploring their uses in countless malignancies in first, second and later-line metastatic disease, as well as in the

adjuvant setting. This review article will focus on the use of the currently studied, approved uses and the future roles of these agents in the treatment of cancers of the esophagus, GEJ, and stomach.

Current role and rationale for immunotherapy in the treatment paradigm of esophageal, GEJ, and gastric cancers

Despite the numerous approvals for immunotherapy in other malignancies, gastrointestinal cancers have had limited approvals to date. Currently, there is no role for immunotherapy in the neoadjuvant or adjuvant settings in resectable disease, or in first-line treatment of unresectable locally advanced, recurrent, or metastatic esophageal, gastroesophageal, or gastric cancers. However, a single immunotherapy agent, pembrolizumab, is considered an approved treatment option in subset of patients in either the second-line, third-line, or later-line settings in unresectable locally advanced, recurrent, or metastatic esophageal, gastroesophageal, or gastric cancers. The two subsets of patients with advanced, unresectable, or metastatic solid tumors, who its use could be considered are patients with tumors demonstrating: (I) microsatellite instability-high (MSI-H) or (II) DNA mismatch repair deficient (dMMR). Additional indications for ICI treatment of esophageal, GEJ, and gastric cancers are esophageal, GEJ, or gastric adenocarcinomas with PD-L1 CPS greater than or equal to 1, or esophageal squamous cell carcinoma (ESCC) with CPS greater than or equal to 10.

Similar to many other GI malignancies, Pembrolizumab gained approval for either MSI-H or dMMR unresectable, or metastatic solid tumors in May 2017 (15,16). This approval came in the wake of a study by Le *et al.* evaluating patients with mismatch repair-deficient malignancies, after this signal was seen in colorectal cancers (15,16). Overall response rates (ORR) was seen in 53% of patients with dMMR malignancies (see *Table 1*) across 12 different tumor types, including esophageal, GEJ, and gastric cancers (16). Mismatch repair deficiencies are seen in ~1% of esophageal and GEJ cancers and nearly 9% of gastric adenocarcinomas (16).

The use of immunotherapy in adenocarcinoma of the GEJ and stomach began with multinational phase Ib KEYNOTE-012 study (NCT01848834) evaluating safety and tolerability of Pembrolizumab in several solid tumor cohorts, including triple-negative breast cancer, urothelial cancer, head and neck cancer, and advanced gastric cancer, with the results of the gastric cancer cohort published

Table 1 Published studies in immunotherapy in esophageal, gastroesophageal junction and gastric cancers

Study name	Year	Medication	Disease	Setting	Phase, study size	Outcomes
ONO-4538-07/ JapicCTI-No. 142422 (17)	2017	Nivolumab	Squamous cell carcinoma, adenosquamous cell carcinoma or adenocarcinoma of esophagus	Advanced, previously treated, any line	Phase II, 65	ORR 17%, CR 2%, DCR 42%, mDOR NR, mPFS 1.5 mo, mOS 10.8 mo, Gr. 3-4 TRAEs 17%, 11% discontinued due to TRAEs
ATTRACTION-2 (18,19) (ONO-4538-12) (NCT02267343)	2017	Nivolumab 3 mg/kg q2w vs. placebo	GEJ or gastric cancer	Unresectable advanced or recurrent, third-line or later	Phase III, 493	OR: 11.2% vs. 0% (P<0.0001)*; DCR: 40.3% vs. 25% (P=0.0036)*; mPFS: 1.61 mo vs. 1.45 mo (P<0.0001)*; mOS: 5.26 mo vs. 4.14 mo (P<0.0001)*; Gr. 3-5 TRAEs: 12% vs. 6%
CheckMate-032 (20,21) (NCT01928394)	2018	Nivolumab 3 mg/kg; nivolumab 1 mg/kg + ipilimumab 3 mg/kg; nivolumab 3 mg/kg + ipilimumab 1 mg/kg	Esophageal, GEJ or gastric adenocarcinoma	Locally advanced or metastatic, second-line or later	Phase I/II, 160; Nivo3, 59; Nivo1 + Ipi3, 49; Nivo3 + Ipi1 52	Nivo3: ORR 7% (19% PD-L1+, 12% PD-L1-, 29% MSI-H, 11% non-MSI-H); DCR 37% (31% PD-L1+, 42% PD-L1-, 71% MSI-H, 28% non-MSI-H); mDOR 14.1 mo; Gr. 3-4 TRAEs 17%; 3% leading to discontinuation. Nivo1 + Ipi3: ORR 20% (40% PD-L1+, 22% PD-L1-, 50% MSI-H, 19% non-MSI-H); DCR 47% (50% PD-L1+, 41% PD-L1-, 50% MSI-H, 43% non-MSI-H); mDOR NR; Gr. 3-4 TRAEs 41%; 20% leading to discontinuation. Nivo3 + Ipi1: ORR 4% (23% PD-L1+, 0% PD-L1-, 50% MSI-H, 5% non-MSI-H); DCR 37% (38% PD-L1+, 33% PD-L1-, 50% MSI-H, 36% non-MSI-H); mDOR NR; Gr. 3-4 TRAEs 27%; 10% leading to discontinuation
KEYNOTE-012 (22)	2016	Pembrolizumab 10 mg/kg q2w for up to 24 months	PD-L1 + gastric or GEJ adenocarcinoma	Recurrent or metastatic, any line	Phase Ib, 39	ORR 24% in Asia, 21% in rest of world; TTR 8 weeks; DOR 40 weeks in Asia, NR in rest of world; mOS 11.4 mos in Asia, NR in rest of world; Gr. 3-5 TRAEs 13%, 10% interrupted treatment, 0.8% stopped treatment
KEYNOTE-016 (15,16)	2017	Pembrolizumab	dMMR deficient solid tumors	Unresectable or metastatic, later-line	Phase II, 86	ORR 53%, CR 21%; DCR 77%; mPFS and mOS NR
KEYNOTE-028 (23,24) (NCT02054806)	2017	Pembrolizumab 10 mg/kg q2w for up to 24 months	PD-L1 + squamous cell or adenocarcinoma of esophagus or GEJ	Locally advanced, or metastatic, any line	Phase Ib, 23	ORR 30%, CR 0%; DCR 39%; mDOR 15 mo; mPFS 1.8 mo; mOS 7.0 mo; Gr. 3-5 TRAEs 17%

Table 1 (continued)

Table 1 (continued)

Study name	Year	Medication	Disease	Setting	Phase, study size	Outcomes
KEYNOTE-059 (25-29) (NCT02335411)	2017	Pembrolizumab 200 mg IV q3w	Advanced gastric or GEJ cancers	Metastatic, third-line or later	Phase II, 259	ORR 11.6%, CR 2.3%; DCR 27.0%; mDOR 8.4 mo; mPFS 2.0 mo; mOS 5.6 mo; Gr. 3-5 TRAEs 17.8%; PD-L1+ ($\geq 1\%$): ORR 15.5%; mDOR 16.3 mo; PD-L1- ($<1\%$): ORR 6.4%; mDOR 6.9 mo
	2019	Pembrolizumab 200 mg IV q3w +/- chemotherapy		Metastatic, first-line	Phase II, cohort 2 (+ chemo), 25 & cohort 3 (monotherapy if PD-L1 CPS ≥ 1), 31	Cohort 2: ORR 60%, CR 4%; DCR 80%; mDOR 4.6 mo; mPFS 6.6 mo; mOS 13.8 mo (11.1 mo PD-L1-, 19.8 mo PD-L1+); Gr. 3-5 TRAEs 80%, 12% discontinuation due to TRAEs; Gr. 3 IRAEs 16%, no discontinuations due to IRAEs. Cohort 3: ORR 25.8%, CR 6.5%; DCR 35.5%; mDOR 9.6 mo; mPFS 3.3 mo; mOS 20.7 mo; Gr. 3-5 TRAEs 22.6%; no discontinuation due to TRAEs; Gr. 3-5 IRAEs 9.7%
KEYNOTE-061 (30,31) (NCT02370498)	2018	Pembrolizumab 200 mg q3w vs. paclitaxel 80 mg/m ² on D1,8,15 of 28-day cycle	Gastric or GEJ adenocarcinomas	Advanced, second-line (after failed platinum and fluoropyrimidine doublet therapy)	Phase III, 592 (395 with CPS ≥ 1)	CPS ≥ 1 ; mOS: 9.1 vs. 8.3 mo (Not significant); mPFS: 1.5 vs. 4.1 mo (Not significant); Gr. 3-5 TRAEs (all enrolled pts): 14% vs. 35%
KEYNOTE-180 (32,33) (NCT02559687)	2018	Pembrolizumab 200 mg IV q3w	Esophageal (squamous cell or adenocarcinoma) cancer or GEJ adenocarcinoma	Advanced, metastatic, third-line or later	Phase II, 121	ORR 9.9%, DCR 30.6%; mDOR NR; mPFS 2.0 mo; mOS 5.8 mo; Gr. 3-5 TRAEs 12.4%; ESCC: ORR 14.3%; PD-L1+: ORR 13.8%

*, statistically significant; Gr., grade.

in 2016 (22). This small study revealed early promising results with ORR of 24% in Asia and 22% in patients from the rest of the world (see *Table 1*) and was generally well tolerated with 13% grade 3 or greater treatment related adverse events (22). Only 10% of patients had to interrupt treatment due to toxicity (22). Due to this signal of efficacy and tolerability shown in KEYNOTE-012, further industry-supported studies evaluating the efficacy of PD-L1 inhibition with Pembrolizumab have been undertaken. KEYNOTE-059 (NCT02335411) is the phase II study in 259 patients with advanced gastric and gastroesophageal adenocarcinoma who had received at least two previous lines of therapy to assess the safety and response rates of pembrolizumab monotherapy (25-27). The study showed promise from a tolerability and activity standpoint (see *Table 1*). ORR was 11.6% and 17.8% of patients experienced grade 3 or higher TRAEs with 0.8% discontinuing treatment as a result of TRAEs (25-27). The duration of response was 8.4 months overall. However, in patients with PD-L1 positive tumors (greater than or equal to 1% expression), the objective response rate and duration of response was much more promising, at 15.5% and 16.3 months (25-27). Due to the promise seen with immune checkpoint inhibition in GEJ and gastric cancers in these early phase studies, the FDA approved Pembrolizumab for treatment of advanced or metastatic gastric, or GEJ, adenocarcinoma with CPS greater than or equal to 1 with disease progression after two lines of systemic therapy in September 2017 (34). Additionally, the phase III, KEYNOTE-061 (NCT02370498) study is underway to further assess the efficacy of Pembrolizumab (30,31). However, despite this signal for potential impact, pembrolizumab failed to significantly improve overall survival or progression free survival in advanced GEJ or gastric cancers compared with single-agent paclitaxel, despite its better tolerability (see *Table 1*) (30,31).

The much anticipated results of the phase III study, KEYNOTE-062, of Pembrolizumab in first-line treatment of advanced or metastatic gastric or GEJ adenocarcinoma were recently presented at the 2019 ASCO Annual Meeting (35,36). KEYNOTE-062 assessed the efficacy and safety of Pembrolizumab with and without chemotherapy to chemotherapy alone in first-line advanced, or metastatic, gastric or GEJ cancers (see *Table 2*). In patients with CPS greater than or equal to 1, Pembrolizumab and chemotherapy did not result in superior mOS (12.5 *vs.* 11.1 mos; HR 0.85, 95% CI: 0.70–1.03) or mPFS (6.9 *vs.* 6.4 mos; HR 0.84, 95% CI: 0.70–1.02) compared to chemotherapy

alone. However, Pembrolizumab monotherapy was found to have non-inferior mOS compared with chemotherapy (10.6 *vs.* 11.1 mos; HR 0.91, 95% CI: 0.69–1.18; non-inferiority margin 1.2) despite lower ORR (14.5% *vs.* 36.8%, respectively) (35,36). However, in patients with strongly positive PD-L1 tumors (CPS \geq 10), pembrolizumab monotherapy resulted in a significant improvement in mOS (17.4 *vs.* 10.8 mos; HR 0.69, 95% CI: 0.49–0.97) compared with chemotherapy (35,36).

KEYNOTE-028 was one of the first studies to investigate the safety and activity of Pembrolizumab in the treatment of esophageal carcinoma (23,24). This phase Ib study investigating several solid tumor types, including a cohort of 23 patients with esophageal cancer, 78% exhibiting squamous cell histology, served as an early signal for both safety and efficacy in PD-L1 expressing esophageal carcinomas. ORR was 30% with 17% of patients experiencing grade 3 or higher TRAEs (see *Table 1*) (23,24). This study was open to any patients with locally advanced, or metastatic esophageal carcinoma, regardless of histologic subtype, who had either failed prior standard therapies or were not candidates for these therapies, with 87% of patients enrolled having received at least 2 lines of prior therapy (23,24). Of note, esophageal cancers exhibit variable rates of PD-L1 depending on the histology of the tumor, with approximately 18% in adenocarcinomas and 44% in squamous cell carcinomas (65,66). Given the potential for a significant population of patients with esophageal cancer who could benefit from immunotherapy, clinical trials were undertaken to assess for safety and efficacy. Next, came KEYNOTE-180 (NCT02559687), that evaluated advanced, metastatic ESCC, esophageal and GEJ adenocarcinomas who had failed at least two prior lines of therapy, regardless of PD-L1 expression status (32,33). The majority of patients enrolled were ESCC (52.1%) and just under half of the patients had PD-L1 positive tumors (47.9%), defined at combined positive score (CPS) greater than or equal to 10%. ORR was just 9.9%, DCR was 30.6% and 12.4% of all patients experiencing grade 3 or higher TRAEs, leading to discontinuation of treatment in 4.1%. Objective response rates were slightly better in subgroups of patients with ESCC (14.3%) and PD-L1-positive tumors (13.8%) (32,33). A recent update of this cohort from KEYNOTE-180 with longer follow-up was presented at 2019 ASCO Annual Meeting, with similar results (discussed in further detail below) (32,57). Furthermore, the results of KEYNOTE-181 (NCT02564263), a phase III study evaluating second-line Pembrolizumab in advanced or metastatic ESCC, EAC, or

Table 2 Recent updates on immunotherapy clinical trials in esophageal, gastroesophageal junction and gastric cancers

Study name/ identifier	Conference/ year	Medication	Disease reported	Setting	Phase, study size reported	Outcomes
JAVELIN Solid Tumor JPN Trial (37,38), NCT01943461	ESMO 2018 Congress	Avelumab 10 mg/kg q2w	Gastric or GEJ cancer	Advanced, second-line or beyond	Phase Ib, 40 (Japanese only)	ORR 10%; DCR 52.5%; mPFS 2.5 mo; mOS 9.1 mo; Gr. 3-4 TRAEs 7.5%. Subgroups: PD-L1+ (CPS \geq 1): ORR 27.3%; PD-L1-: ORR 3.7%
NCT03472365 (39,40)	ASCO Annual Meeting 2019	Carmelizumab (SHR-1210) 200 mg D1 + oxaliplatin 130 mg/m ² D1 + capecitabine 1,000 mg/m ² BID D1-14 + apatinib 375 mg daily on 21-day cycle for 4-6 cycles followed by carmelizumab 200 mg q3w + apatinib 375 mg daily	Gastric or GEJ cancer	Advanced or metastatic, first- line	Phase II, 43 (cohort 1)	ORR 44%; DCR 76.7%; Gr. 3-4 TRAEs 21%
NCT03603756 (41,42)	ASCO Annual Meeting 2019	Carmelizumab (SHR-1210) 200 mg + liposomal paclitaxel 150 mg/m ² + nedaplatin 50 mg/m ² on D1 + apatinib 250 mg D1-14 x6-9 cycles	Esophageal squamous cell carcinoma	Locally advanced unresectable, or metastatic, first-line	Phase II, 26	ORR 73.1%, 0% CR; DCR 96.2%; Gr. 3-4 TRAEs: Neutropenia 51.7%
NCT02639065 (43,44)	ASCO Annual Meeting 2019	Durvalumab 1,500 mg q4w, up to 1 year	Esophageal and GEJ adenocarcinoma	Locally advanced, after neoadjuvant concurrent CRT and R0 resection	Phase II, 24	1-yr RFS 79.2%; 26 mo RFS 67.9%; 1-yr OS 95.5%; 2-yr OS 59.2%
NCT02572687 (45,46)	ASCO Annual Meeting 2019	Durvalumab 750 mg + ramucirumab 8 mg/kg q2w	Gastric and GEJ adenocarcinoma	Locally advanced, unresectable, or metastatic, second-line or later	Phase Ib, 29	Overall: ORR 21%; DCR 55%; mDOR 15.4 mos; mPFS 2.6 mos; mOS 12.4 mos. PD-L1 \geq 25%: ORR 36%; DCR 71%; mPFS 5.5 mos; mOS 14.8 mos. PD-L1 0-24%: ORR 0%; DCR 33%; mPFS 1.5 mos; mOS 5.5 mos
NCT02340975 (47,48)	ASCO Annual Meeting 2018	Durvalumab 20 mg/kg + tremelimumab 1 mg/kg q4w for 4 cycles, followed by durvalumab 10 mg/kg q2w for 12 mos. Durvalumab 10 mg/kg q2w. Tremelimumab 10 mg/kg q4w for 7 doses	Gastric or GEJ adenocarcinoma	Recurrent or metastatic	Phase Ib/II, 94	Durvalumab + tremelimumab: ORR 11.1% in 2 nd Line, 12.0% in 3 rd Line; DCR (8 wks) 44.4% in 2 nd Line, 44.0% in 3 rd Line; mPFS 1.8 mos in 2 nd & 3 rd Line; mOS 9.2 mos in 2 nd Line, 10.6 mos in 3 rd Line; Gr. 3-5 TRAEs 29%, 17% discontinued for TRAEs. Durvalumab: ORR 8.3%; DCR (8 wks) 12.5%; mPFS 1.6 mos; mOS 3.2 mos; Gr. 3-5 TRAEs 17%, 4% discontinued for TRAEs. Tremelimumab: PR 8%; Gr. 3-5 TRAEs 50%, 33% discontinued for TRAEs

Table 2 (continued)

Table 2 (continued)

Study name/ identifier	Conference/ year	Medication	Disease reported	Setting	Phase, study size reported	Outcomes
NCT02517398 (49,50)	ESMO 2018 Congress	M7824 1,200 mg q2w	Esophageal adenocarcinoma	Advanced, post-platinum	Phase I, 30	ORR 20.0%; DCR 33.3%; Gr. 3 TRAEs 23.3%. Subgroups: PD-L1+ (≥1%): ORR 22.2% (31% of pts had PD-L1+ tumors); PD-L1-: ORR 20%
NCT02699515 (51-53)	ESMO 2018 Congress	M7824 1,200 mg q2w	Gastric or GEJ adenocarcinoma	Recurrent, with no further standard therapies	Phase I, 31 (Asia only)	ORR 22.6%; DCR 38.7%; mDOR 10.1 wks; Gr. 3-5 TRAEs 22.5%
ATTRACTION-2 (19,54) (ONO- 4538-12) (NCT02267343)	ESMO 2018 Congress	Nivolumab 3 mg/kg q2w vs. placebo	Esophageal squamous cell carcinoma	Unresectable advanced or recurrent, third- line or later	Phase I, 30 (Asia only)	ORR 20%; DCR 36.7%; Gr. 3-4 TRAEs 20%, 10% discontinued due to TRAE
KEYNOTE-059 (NCT02335411) (27,29)	ASCO Annual Meeting 2019	Pembrolizumab 200 mg q3w	GEJ or gastric cancer	Metastatic, third-line or later	Phase III, 493	mOS 5.3 vs. 4.1 mo (HR 0.62, 0.51-0.76)*
KEYNOTE-062 (35,36) (NCT02494583)	ASCO Annual Meeting 2019	Pembrolizumab 200 mg q3w +/- chemotherapy	Gastric or GEJ cancers	Advanced, metastatic, first- line	Phase II, cohort 2 (+chemo), 25 & cohort 3 (monotherapy if PD-L1 CPS ≥1), 31	Cohort 1: ORR 11.6% (15.5% in PD-L1+, 6.4% in PD-L1-); mDOR 16.1 mo; 1 & 2-yr OS: 24.6% & 12.5%; grade 3-5 TRAEs 18%, 2% discontinuation for TRAEs Cohort 2: ORR 60% (73% in PD-L1+, 37.5% in PD-L1-); mDOR 4.6 mo; 1 & 2-yr OS: 52% & 32%; Gr. 3-5 TRAEs 80%, 12% discontinuation for TRAEs. Cohort 3: ORR 25.8%, mDOR NR; 1 & 2-yr OS: 63.6% & 40.1%; Gr. 3-5 TRAEs 26%, No discontinuation for TRAEs CPS ≥1: mOS 12.5 mo (P+C) vs. 11.1 mo (C) vs. 10.6 (P); -P vs. C = non-inferior; -P+C vs. C=Not significant; mPFS: 6.9 mo (P + C), 6.4 mo (C), 2.0 (P); -P+C vs. C for mPFS = Not significant; ORR: 48.6% (P+C), 36.8% (C), 14.5% (P); Subgroups CPS ≥10: mOS 12.3 mo (P+C) vs. 10.8 mo (C) vs. 17.4 (P); -P vs. C= (HR=0.69)*; -P+C vs. C=Not significant; mPFS: 5.7 mo (P+C), 6.1 mo (C), 2.9 (P); ORR: 52.5% (P+C), 36.7% (C), 25.0% (P)

Table 2 (continued)

Table 2 (continued)

Study name/ identifier	Conference/ year	Medication	Disease reported	Setting	Phase, study size reported	Outcomes
NCT02954536 (55,56)	ASCO Annual Meeting 2019	Pembrolizumab 200 mg q3w + trastuzumab 6 mg/kg (after 8 mg/ kg load) + oxaliplatin 130 mg/m2 q3w + capecitabine 850 mg/m2 2 w on/1 w off	HER2+ (ICH 3+ or FISH+) esophageal, GEJ, or gastric adenocarcinomas	Advanced, first- line	Phase II, 32	ORR 87%; mPFS 11.3 mo; no correlation between PD-L1 status and PFS or OS; Gr. 3–4 irAEs 20%
KEYNOTE-180 (32,57) (NCT02559687)	ASCO Annual Meeting 2019	Pembrolizumab 200 mg q3w	Esophageal (squamous cell or adenocarcinoma) cancer or GEJ adenocarcinoma	Advanced, metastatic, third-line or later	Phase II, 121	ORR 10%; DCR 31%; mDOR NR; mPFS 2.0 mo; mOS 5.8 mo; Gr. 3–5 TRAEs 16% (6% discontinued due to TRAEs). Subgroups: PD- L1+; ORR 14%; PD-L1-; ORR 6%; ESCC: ORR 14%; EAC: ORR 5%
KEYNOTE-181 (58-60) (NCT02564263)	ASCO 2019 GI Cancers Symposium ASCO Annual Meeting 2019	Pembrolizumab 200 mg q3w vs. chemotherapy. CHEMO: paclitaxel, docetaxel, or irinotecan	Esophageal squamous cell carcinoma or adenocarcinoma. Or Siewert type I adenocarcinoma of GEJ	Advanced, metastatic, second-line	Phase III, 628	mOS: 8.2 vs. 7.1 mos (P=0.0095); Gr. 3–5 TRAEs: 18% vs. 41%. Subgroups PD-L1 CPS ≥10: mOS 9.3 vs. 6.7 mos (P=0.0074)*; mPFS 2.6 vs. 3.0 mo; ORR 21.5% vs. 6.1%; -mDOR 9.3 vs. 7.7 mos
NCT02407990 (61,62)	ESMO 2017 Congress	Tislelizumab 2 mg/kg or 5 mg/kg q2w or q3w	Gastric or esophageal cancer	Advanced, recurrent/ refractory, second-line or later	Phase I, 47	PR 6.4%, DCR 32%, no Gr. 3–5 TRAE
NCT03469557 (63,64)	ASCO 2019 GI Cancers Symposium	Tislelizumab 200 mg q3w + cisplatin 80 mg/m2 q3w for up to 6 cycles + 5-FU 800 mg/m2/ day on days 1–5 q3w for up to 6 cycles	Esophageal squamous cell carcinoma	Inoperable, locally advanced, or metastatic, First-line	Phase II, 15 Chinese patients only	Gr. 3–5 TRAEs 60%, 26.7% discontinued due to TRAEs

*, statistically significant; Gr., grade.

adenocarcinoma of GEJ support the use of Pembrolizumab monotherapy. In patients with CPS greater than or equal to 10, Pembrolizumab resulted in superior overall survival compared with second-line chemotherapy (9.3 *vs.* 6.7 mos; HR 0.69, 95% CI: 0.52–0.93), along with lower rates of grade 3–5 TRAEs (18% *vs.* 41%) (58–60). Median OS for ESCC with CPS greater than or equal to 10 was 10.3 months compared with 6.7 months with chemotherapy, 12-month OS was 48% *vs.* 23% respectively (58,59). One important question remaining within this study population is the presence of MSI-H, which may dilute these results. As a result of the findings of KEYNOTE-180 and KEYNOTE-181, Pembrolizumab was granted FDA approval as monotherapy for the treatment of recurrent locally-advanced, or metastatic, ESCC with CPS greater than or equal to 10 with disease progression after one or more systemic treatments on July 30, 2019 (67).

Future directions of immunotherapy in esophageal, GEJ and gastric cancers

Although only pembrolizumab is approved for treatment of upper GI tract malignancies, we are privy to a vast array of early phase trials with several ICIs, in larger groups of patients with a variety of diseases. In the subsections below, we will briefly discuss each immunotherapy agent, the current literature and upcoming, large studies that are underway to further establish their individual roles in the treatment of esophageal, GEJ and gastric cancers. Each of these agents is discussed further in *Tables 1–3*, which outline published studies, recent updates for ongoing clinical trials and upcoming phase II and III clinical trials which are enrolling more than 100 patients but have not published any results to date, respectively.

Atezolizumab

Atezolizumab has found a role in the treatment of several solid tumors, including most notably, extensive small cell lung cancer, and metastatic urothelial carcinoma. However, its role in GI malignancies is much less established. While there are several ongoing small (<100 patients), phase I and II studies that are underway, there has not been any published results for the use of atezolizumab in esophageal, GEJ or gastric cancers. No completed studies small (<100 patients). The largest study underway is the phase II DANTE study (NCT03421288) evaluating the use of peri-operative FLOT *vs.* FLOT and Atezolizumab in locally

advanced, resectable gastric and GEJ adenocarcinoma with expected study completion in February 2025 (68,69).

Avelumab

Avelumab is an anti-PD-L1 monoclonal antibody approved in Europe for gastric cancer since 2017; however, it is currently only approved by the FDA for use in Merkel cell carcinoma in the US. The phase Ib JAVELIN Solid Tumor JPN study evaluated the role of Avelumab in advanced gastric or GEJ cancers after failed first line treatment amongst 40 Japanese patients. It showed limited effectiveness in this setting with ORR of 10% independent of PD-L1 expression with low rates of grade 3–4 TRAEs (7.5%) (37,38). However, subgroup analysis based on PD-L1 expression exhibited higher ORR (27.3%) in patients with CPS scores greater than or equal to 1 (37,38). Despite these findings, no large (>100) patient phase II or III studies are ongoing in the United States.

Camrelizumab (SHR-1210)

Camrelizumab (SHR-1210) is a novel anti-PD-L1 monoclonal antibody whose role in treatment of Hodgkin lymphoma, hepatocellular carcinoma, esophageal, GEJ and gastric cancers is being evaluated by clinical trials. While no large (>100 patient), phase II or III studies are currently underway in the US for these disease states, two small Phase II studies recently reported abstract data at the 2019 ASCO Annual Meeting. The first of these studies is the phase II study (NCT03472365) evaluating camrelizumab in combination with chemotherapy (oxaliplatin and capecitabine) and anti-VEGFR2 therapy (apatinib) in advanced, or metastatic GEJ or gastric cancer in the first-line setting (39,40). This showed early promise with ORR of 44%, DCR of 76.7%, and was generally well tolerated with 21% of patients experiencing grade 3–4 TRAEs (39,40). The second of these phase II studies evaluated the use of first-line Camrelizumab with combination chemotherapy and Apatinib in locally advanced, unresectable, or metastatic, ESCC with robust ORR of 73.1%, DCR of 96.2%. However, this regimen carried with it significant grade 3–4 TRAEs, namely 51.7% neutropenia (41,42). These studies were agnostic of PD-L1 or MSI testing.

Durvalumab

Durvalumab (MEDI4736) is another anti-PD-L1

Table 3 Key ongoing phase II and III clinical trials (>100 patients) for immunotherapy in esophageal, gastroesophageal junction and gastric cancers

Disease	Setting	Phase/planned enrollment	Interventions	Status, Est. completion date	Study name & identifier
Gastric and GEJ adenocarcinoma	Peri-operative, locally advanced, resectable (\geq cT2 and/or N-positive)	Phase II, 295	FLOT vs. FLOT + atezolizumab	February 2025	DANITE, NCT03421288 (68,69)
Gastric and GEJ adenocarcinoma	Untreated, locally advanced, unresectable or metastatic, first-line	Phase II, 250	Relatlimab (BMS-986213) + nivolumab + oxaliplatin-based chemotherapy vs. nivolumab + oxaliplatin-based chemotherapy	July 2023	CA224-060, NCT03662659 (70,71)
Gastric and GEJ adenocarcinoma	Untreated, locally advanced unresectable, or metastatic, first-line	Phase II, 118	mFOLFOX vs. mFOLFOX + nivolumab + ipilimumab	December 2022	Moonlight (AIO-STO-0417), NCT03647969 (72,73)
GEJ or gastric cancer	Untreated, advanced or metastatic, first-line	Phase III, 2,005	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg vs. nivolumab + chemotherapy vs. chemotherapy. CHEMO: FOLFOX or XELOX	October 2022	CheckMate-649 (74), NCT02872116
HER2+ metastatic gastric or GEJ adenocarcinoma	Untreated, unresectable, or metastatic, first-line	Phase III, 732	Trastuzumab + chemotherapy + placebo vs. trastuzumab + chemotherapy + pembrolizumab. CHEMO: FP, CAPOX or SOX	March 2024	KEYNOTE-811, NCT03615326 (75,76)
Gastric or GEJ adenocarcinoma	Untreated, resectable, neoadjuvant + adjuvant	Phase III, 860	Neoadjuvant: chemotherapy + pembrolizumab 200 mg q3w for 3 cycles vs. chemotherapy + placebo for 3 cycles. Adjuvant: pembrolizumab +200 mg q3w + chemotherapy for 3 cycles followed by pembrolizumab 300 mg q3w for 11 cycles vs. placebo q3w + chemotherapy for 3 cycles followed by placebo q3w for 11 cycles. CHEMO: cisplatin 80 mg/m ² , 5-FU 800 mg/m ² D1–5, or capecitabine 1,000 mg/m ² PO BID D1–14	July 2023	KEYNOTE-585 (77,78), NCT03221426
Esophageal adenocarcinoma or squamous cell carcinoma or Siewert type 1 GEJ adenocarcinoma	Locally advanced unresectable, or metastatic, first-line	Phase III, 700	Pembrolizumab + chemotherapy vs. chemotherapy + placebo	August 2021	KEYNOTE-590 (79,80), NCT03189719
Esophageal or GEJ cancer	Resected, adjuvant	Phase III, 760	Nivolumab vs. placebo	October 2024	CheckMate-577 (81), NCT02743494
Esophageal squamous cell carcinoma	Advanced, recurrent or metastatic, first-line	Phase III, 939	Nivolumab + ipilimumab vs. nivolumab + 5-fluorouracil or cisplatin vs. 5-FU or cisplatin	December 2021	CheckMate-648 (82,83), NCT03143153
Esophageal squamous cell carcinoma	Advanced unresectable, or metastatic, second-line	Phase III, 450	Tislelizumab 200 mg q3w vs. chemotherapy. CHEMO: paclitaxel 135–175 mg/m ² IV Q3W or 100 mg/m ² IV weekly for 6 weeks with 1 week of rest (Japan only), docetaxel 75 or 70 mg/m ² IV Q3W, or irinotecan 125 mg/m ² IV Q3W	September 2021	NCT03430843 (84,85)

monoclonal antibody under investigation in upper gastrointestinal malignancies and other solid malignancies. It is not currently used for treatment in any GI malignancy outside of clinical trial. Its only approved uses are in unresectable Stage III non-small cell lung cancer that has not progressed (i.e., maintenance) after concurrent platinum-based chemotherapy and radiation therapy and in locally advanced or metastatic urothelial cancer following progression on platinum-containing chemotherapy or within 12 months of receiving platinum-containing chemotherapy peri-operatively (neoadjuvant or adjuvant). Durvalumab is being investigated in the adjuvant setting as monotherapy, and in combination with another ICI, tremelimumab, or in combination with ramucirumab, a VEGFR2 inhibitor, in advanced gastric and GEJ adenocarcinoma.

The role of durvalumab in locally advanced esophageal and GEJ adenocarcinoma in the adjuvant setting was evaluated in a study out of the Big Ten Consortium with early results presented at the 2019 ASCO Annual Meeting (43,44). The use of durvalumab was evaluated after neoadjuvant, concurrent chemotherapy and radiation and R0 resection in locally advanced disease (43,44). With the addition of durvalumab to standard tri-modality treatment, patients had 1-year relapse-free survival (RFS) of 79.2% and 1-year overall survival of 95.5% with low rates of grade 3 irAEs (12.5%) (43,44). Historically, trimodality therapy resulted in 1-year RFS of 50%. Given the tolerability of durvalumab in the adjuvant setting, and nearly 30% absolute improvement in 1-year RFS, further large studies are needed to assess its safety and efficacy, although none are currently underway in the United States (43,44).

In a phase Ib/II study by Kelly *et al.* (NCT02340975), the use of Durvalumab and Tremelimumab were evaluated in advanced GEJ and gastric adenocarcinomas after failed systemic treatment, alone and in combination (47,48). Of the 94 patients reported in the 2018 ASCO abstract, 58 patients received a combination of durvalumab and tremelimumab (35% with PD-L1 >1%; outcomes in 27 in second-line; 25 in third-line are reported), 24 received durvalumab alone (38% with PD-L1 >1%) in the second-line setting, and 12 patients received tremelimumab alone (50% PD-L1 >1%) in the second-line setting (47,48). The combination of durvalumab and tremelimumab in both the second-line and third-line setting had modest ORR (11.1 and 12.0, respectively) with limited PFS (1.8 months for in both lines) (47,48). Overall survival was more promising in

combination ICI compared with single agent durvalumab (9.2 mos in second-line, 10.6 mos in third-line and 3.2 months in single agent second-line), although combination therapy had higher grade 3–5 TRAEs (29% *vs.* 17%) with higher discontinuation rates due to TRAEs (17% *vs.* 4%) compared with Durvalumab alone (47,48). The final results of this study have not been published to date.

Additionally, the combination of durvalumab and the VEGF2 inhibitor, ramucirumab as part of a basket study included a cohort of patients with advanced gastric or gastroesophageal adenocarcinoma (45,46). ORR was modest (21%) amongst all 29 enrolled patients, which was higher (36%) in the 14 patients with 'high' PD-L1 expression (greater than or equal to 25% of tumor cells and/or immune cells) and negligible in patients with 'low' PD-L1 expression (0%) (45,46). Median PFS (2.6 mos) and median OS (12.4 mos) for all patients was modest, which were both greater in the subgroup with high PD-L1 expression (mPFS 5.5 mos; mOS 14.8 mos) (45,46). Median PFS (1.5 mos) and median OS (5.5 mos) were shorter for the subgroup of patients with 'low' PD-L1 expression (45,46).

M7824

M7824 is a first-in-class bifunctional fusion protein, combining human anti-PD-L1 IgG1 monoclonal antibody with two (2) extracellular domains of TGF-Beta receptor II. This was developed based on basic science research noting that inhibition of TGF-Beta pathway, which promotes tumor immunosuppression. Coupling this with PD-L1 monoclonal antibodies is hoped to enhance the response to PD-L1 inhibition. Two recent phase I studies were presented at ESMO 2018 Congress in advanced esophageal adenocarcinoma after platinum chemotherapy (NCT02517398) and in recurrent gastric or GEJ adenocarcinoma and esophageal squamous cell cancer with no further standard treatment options (NCT02699515) (49-53). These gave signals for efficacy with ORRs in the 20–25% range, DCRs between 30–40%, and with similar rates of grade 3–4 TRAEs as other immunotherapies (20–25%) (49-53). ORRs were similar amongst PD-L1 positive (CPS \geq 1) and negative esophageal adenocarcinomas 22.2% and 20%, respectively (49,50). Additional studies in larger cohorts are needed to assess efficacy and safety, but the signal for efficacy in advanced disease gives hope for the future role of M7824 in the treatment of ESCC, as well as esophageal, GEJ, and gastric adenocarcinomas.

Nivolumab

Nivolumab is the second most studied ICI in esophageal, GEJ, and gastric cancers. However, despite several ongoing clinical trials and a promising phase III results out of Japan, it has not gained FDA approval in the US for any of these diseases. The ONO-4538-07 (JapicCTI-No.142422) phase II study investigating the use of Nivolumab in advanced, previously treated ESCC, Adenosquamous carcinoma and adenocarcinoma of the esophagus was published in 2017 (17). The ORR and grade 3–4 TRAEs were both 17%, with mPFS of 1.5 mos and an 11% discontinuation rate due to TRAEs (see *Table 1*), showing favorable tolerability and a modest signal of efficacy given that 68% of patients had received at least 3 previous chemotherapy regimens (17). Both the ATTRACTION-2 (NCT02267343) and CheckMate-032 (NCT01928394) studies have published results, with ATTRACTION-2 presenting updated results at ESMO 2018 Congress (18–21,54). ATTRACTION-2 is one of the largest published studies in this collection of diseases to date, comparing nivolumab *vs.* placebo in third-line or later treatment of unresectable, advance, or recurrent GEJ or gastric cancer (18,19,54). Compared with best supportive care and placebo, it prolonged median PFS by 0.2 months (1.61 *vs.* 1.45 months, $P < 0.0001$) and median OS by 1 month (5.26 *vs.* 4.14 months, $P < 0.0001$) with good safety profile (grade 3–5 TRAEs: 12% *vs.* 6%) in these heavily pretreated patients (18–21,54). CheckMate-032 then explored combination immune checkpoint inhibition in a multi-cohort phase I/II study in locally advanced or metastatic adenocarcinomas of the esophagus, GEJ or stomach (20,21). In the second-line or later setting, single agent nivolumab showed only modest efficacy, agnostic of PD-L1 or MSI status. However, responses in PD-L1-positive and MSI-H tumors were more robust, with TRAEs similar to other Nivolumab studies. Further combinations of Nivolumab and Ipilimumab were studied with Nivolumab 1 mg/kg and Ipilimumab 3 mg/kg yielding higher ORR/DCR, again with better responses seen in PD-L1-positive or MSI-H disease; however, this came at the price of doubled toxicity rates and a seven-fold increase in discontinuation rates compared with single agent Nivolumab (20,21). As a result of this early promise in pre-treated disease, several large phase II and III studies are ongoing in the US utilizing in the adjuvant setting, as well as first-line, advanced or metastatic disease with combination immunotherapy, immunochemotherapy or immunochemotherapy with other targeted therapies with study completion dates

between December 2021 and October 2024 (70–74,81–83). The studies include the MOONLIGHT, CA224-060, CheckMate-577, CheckMate-648, and CheckMate-649 trials (70–74,81–83).

Pembrolizumab

Pembrolizumab is the most studied ICI in upper GI malignancies, with numerous large studies currently enrolling and scheduled for completion by March 2024. While pembrolizumab was already approved in second-line or later setting as discussed above, several recent updates to phase II and phase III KEYNOTE trials have been presented at major oncology conferences. Additional cohorts from the phase II KEYNOTE-059 (NCT02335411) evaluating Pembrolizumab use in combination with chemotherapy, or as monotherapy, in the first-line setting for advanced gastric/GEJ cancers (27–29). Patients receiving pembrolizumab monotherapy were required to have positive PD-L1 expression, defined as CPS greater than or equal to 1, while the combination therapy arm did not require this, but had 64% of participants with PD-L1 positive tumors (27–29). The combination of cisplatin, 5-FU, and pembrolizumab resulted in a 60% ORR with 4% CR and mPFS of 6.6 months (27–29). ORR for patients receiving pembrolizumab monotherapy was 25.8% with CR of 6.5% and mPFS of 3.3 months (27–29). These studies are discussed in detail below in greater detail (see *Table 2*). One phase II study (NCT02954536) in HER2+ esophageal, GEJ, or gastric adenocarcinoma combining chemotherapy, trastuzumab and pembrolizumab showed promising results, agnostic of PD-L1 status, and with a tolerable side effect profile (55,56). There remains great hope for an increased role of immunotherapy with Pembrolizumab with several large, ongoing phase III studies (see *Table 3*), including KEYNOTE-585 (neoadjuvant chemoimmunotherapy gastric and GEJ adenocarcinoma), KEYNOTE-590 (chemoimmunotherapy in untreated, advanced or metastatic EAC, ESCC or GEJ adenocarcinoma), and KEYNOTE-811 (HER2+ metastatic gastric or GEJ adenocarcinoma) (75–79).

Tislelizumab (BGB A317)

Tislelizumab is an investigational anti-PD-1 monoclonal antibody currently being studied in numerous disease states as monotherapy and in combination with other treatments (*Table 2*). The phase 1 dose escalation/expansion study

(NCT02407990) across numerous advanced solid tumors showed early promising results in recurrent/refractory gastric or esophageal cancers (55 patients) (61,62). While the preliminary results by Desai *et al.* did not show robust ORR (6.4% PR), it did show DCR of 32%, comparable to early studies for ICIs in these previously treated, with the promising absence of any grade 3–5 TRAEs (61,62). At the 2019 ASCO GI Cancers Symposium, Xu *et al.* presented early safety data from the ESCC cohort (15 Chinese patients) of their phase 2 study (NCT03469557) combining tislelizumab with chemotherapy (cisplatin and 5-FU in this cohort) in the first-line setting (63,64). At least sixty-percent (and up to 80%) of patients with inoperable, locally-advanced, or metastatic ESCC (median age 61 years) experienced grade 3–5 TRAEs, with 26.7% (4 patients) discontinuing therapy due to these adverse effects with a median treatment duration of 108 days (63,64). Despite the high percentage of high-grade adverse effects in this small cohort, many of the adverse effects did not result in treatment discontinuation (vomiting was the most common). Efficacy data was not matured at time of the abstract publication (63,64). Beyond the aforementioned phase 2 study, there is an ongoing phase 3 study (NCT03430843) comparing the efficacy and tolerability of second-line tislelizumab against chemotherapy with no results published to date (Table 3) (84,85).

Tremelimumab

Tremelimumab (formerly ticilimumab, CP-675,206) is an anti-CTLA-4 monoclonal antibody without any FDA approvals, but has recently received orphan drug status for mesothelioma. Its role in GEJ and gastric adenocarcinoma is currently under investigation as both monotherapy and in combination with durvalumab (see section on durvalumab above regarding combination immune checkpoint inhibition). However, early results by Kelly *et al.* of a small sample (12 patients) treated with second-line tremelimumab monotherapy showed a very modest response rate (8% PR) and significant toxicities (Gr. 3–4 TRAEs 50%, with 33% discontinuation rate) (47,48). Median PFS and OS were not calculated due to small sample size (47,48). The combination results were more promising with less toxicities (see Table 2).

Conclusions

The treatment of esophageal, GEJ and gastric cancers has

begun to evolve in the era of immunotherapy. While small steps have been made in the treatment paradigm of these diseases, there are many questions left unanswered. The approval of Pembrolizumab in a small subset of patients with: PD-L1-positivity, MSI-H and dMMR deficient tumors after failed, or intolerance to, chemotherapeutic treatment is just the beginning. Despite the successes and promise for an ever-expanding role of immunotherapy, there have also been several key failures. Although it may feel like immunotherapy takes the cliched ‘three steps forward, two steps back’ path to approval in the treatment of upper GI malignancies, these treatments continue to represent progress and hope for what lies ahead. We have a tremendous amount to learn with several large studies in their infancy, we are hopeful that continued progress towards improved therapy with less toxicity is just over the horizon. The use of biomarkers, whether it be MSI, or PD-L1 expression (measured by CPS), in determining the potential for efficacy of immune checkpoint inhibition. Several ongoing studies are investigating other potential biomarkers to aid in improving patient selection to maximize benefit seen with these agents.

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Footnote

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