Review Article

A narrative review of the evolving role of immunotherapy in the management of esophageal and gastric cancer

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Background and Objective: Despite recent advances in the multidisciplinary management of esophagogastric cancer, overall prognosis remains poor. There is a need for improved treatment options, along with predictive biomarkers that improve therapeutic decision-making.

Methods: We conducted an extensive review of immunotherapy articles in the PubMed database between December 2013 and October 2021. Articles in English were included. We included phase 1, 2, and 3 clinical trials for immunotherapy review, and prospective, retrospective, and meta-analyses for biomarker review.

Key Content and Findings: Initial studies of immunotherapy were performed in patients with relapsed refractory metastatic disease and demonstrated a modest survival benefit. Subsequent studies have evaluated the use of these agents in combination with first line chemotherapy for metastatic disease. Finally, recent data indicates that immunotherapy in the adjuvant setting after concurrent chemoradiation and surgery improves disease free survival. Both microsatellite instability high (MSI-H) status and Epstein-Barr virus (EBV) positivity predict response to immunotherapy, but many patients without these biomarkers still benefit. The predictive impact of programmed cell death-ligand 1 (PD-L1) expression and tumor mutational burden (TMB) have been variable, and the optimal cutoff point for these biomarkers remains poorly defined.

Conclusions: While immunotherapy agents have demonstrated clinical benefit and are now incorporated into the current standard of care, novel immunotherapy approaches such as dual immunotherapy combinations, chimeric antigen receptor (CAR) T cells, and tumor vaccines need to be further investigated. As the era of precision medicine beckons, refined biomarkers to predict benefit are needed.

Keywords: Immunotherapy; gastric cancer; esophageal cancer; biomarkers

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Introduction

Esophagogastric cancers, which include esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), gastroesophageal junction (GEJ) adenocarcinoma, and gastric adenocarcinoma (GAC), are collectively one of the leading causes of cancer related deaths worldwide (1). Even though survival rates have improved, prognosis with the use of cytotoxic chemotherapy is still poor, and patients with metastatic disease have a 5-year survival less than 6% (1-3).

This narrative review assesses the rapidly evolving role of immunotherapy in the management of esophagogastric tumors and evaluates the role of biomarkers to predict sensitivity and resistance to immunotherapeutic strategies. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-55/rc).

Table 1 The search strategy summary

Items	Description
Date of search	Between 24th January, 2021 and 16th January, 2022
Databases and other sources searched	PubMed
Search terms used	Immunotherapy, gastric cancer, esophageal cancer, biomarkers, PD-L1, microsatellite instability, EBV, tumor mutational burden, prognostic
Timeframe	Esophageal and gastric cancer immunotherapy articles were between 2nd December, 2017 and 14th October, 2021. Articles related to chemotherapy were between 3rd January, 2008 and 14th October, 2021
Inclusion, and exclusion criteria	Inclusion criteria: only articles written in English were included. Sections involving neoadjuvant, adjuvant, and metastatic disease immunotherapy trials: Phase 1, 2, and 3 clinical trials were included. Biomarker section: prospective observational studies, retrospective analysis, and meta-analysis were reviewed, and included. Exclusion criteria: not applicable
Selection process	Authors AM, HU, and JS conducted the selection of articles. Consensus was reached with discussion among all authors

PD-L1, programmed death-ligand 1; EBV, Epstein-Barr virus.

Methods

To review the role of immunotherapy in esophagogastric cancer, an extensive electronic search was undertaken of articles in PubMed database from 20 December, 2013 until 14 October, 2021 for immunotherapy related articles, and chemotherapy related articles between 3 January 2008, until 14 October 2021. Neoadjuvant, adjuvant, and metastatic disease immunotherapy articles were identified using keywords, "immunotherapy", "gastric cancer", and "esophageal cancer". The studies we reviewed in the neoadjuvant, adjuvant, and metastatic disease immunotherapy section included phase 1 and 2 clinical trials, and phase 3 randomized controlled trials. To review the clinical impact of prognostic and predictive biomarkers in biomarker section, the database was searched using keywords such as "biomarkers", "PD-L1 (programmed cell death-ligand 1)", "microsatellite instability", "EBV (Epstein Barr Virus)", and "tumor mutational burden". We reviewed prospective observational studies, retrospective analyses, and meta-analyses in this section. We used articles written in English only. Entire text of the articles was reviewed and analyzed. We also reviewed National Comprehensive Cancer Network (NCCN) guidelines and recent Food and Drug Administration (FDA) approvals in esophagogastric cancers. Method have been summarized in *Table 1*.

Immunotherapies: mechanism of action

Programmed cell death 1 receptor (PD-1) is a transmembrane receptor expressed on tumor infiltrating lymphocytes. In order to evade immune surveillance, tumors either constitutively or inducibly express the inhibitory transmembrane protein programmed death-ligand 1 (PD-L1). Interaction between PD-L1 and PD-1 inhibits cytotoxic T-cell mediated damage to tumor cells, thereby promoting tumor cell growth (4,5). Monoclonal antibodies that block PD-1 (pembrolizumab, nivolumab, cemiplimab) and PD-L1 (durvalumab, avelumab, atezolizumab) disrupt this interaction and inhibit cell growth. Ipilimumab and tremelimumab target cytotoxic T lymphocyte-associated protein 4 (CTLA-4). CTLA4 is expressed on T cells and binds to antigen presenting cells via CD80 and CD86 receptors. Antibodies that block this binding can also inhibit tumor cell growth (6). In the last decade, the United States FDA and other regulatory agencies have approved various immunotherapy agents that block PD-1, PD-L1, and CTLA-4 for the treatment of various solid tumors and hematologic malignancies.

Neoadjuvant and adjuvant immunotherapy trials

Esophageal cancer (ESCC, EAC, and GEJ adenocarcinoma)

Preclinical data suggests that chemoradiation can upregulate PD-L1 expression and $CD8^+$ cytotoxic T-lymphocytes within the tumor microenvironment (TME) (7). Also, radiation can cause immunologic cell death which releases neoantigens and activates immune response (8). Hence, immunotherapy has the potential to improve outcomes in

Table 2 Neoadjuvant immunotherapy trials in esophageal cancer

Immunotherapy agent	Conventional therapy components	Phase	Clinical trial identifier	Current status
Pembrolizumab (PROCEED)	Chemotherapy-RT	2	NCT03064490	Recruiting
Pembrolizumab (KEYSTONE-002)	Chemotherapy-RT	3	NCT04807673	Recruiting
Toripalimab	Chemotherapy-RT	3	NCT04280822	Recruiting
Nivolumab (FRONTiER)	Chemotherapy (cisplatin, 5-FU +/– docetaxel)	1	NCT03914443	Active, not recruiting
Camrelizumab	Chemotherapy (carboplatin, paclitaxel)	1/2	NCT04506138	Recruiting

patients being treated with curative intent.

Until recently, the standard of care treatment for locally advanced ESCC, EAC, and GEJ adenocarcinoma included neoadjuvant chemoradiation followed by surgery. There was no role for adjuvant therapy following surgery, regardless of whether there was a pathologic complete response or residual disease. Recent practice-changing studies have demonstrated the potential of immunotherapy to improve outcomes in these patients.

For patients with locally advanced esophageal or GEJ cancer who have residual disease following chemoradiation and surgery, adjuvant nivolumab is the new standard of care. In the pivotal phase III Checkmate 577 trial, patients with locally advanced esophageal or GEJ cancer (both squamous cell and adenocarcinoma) who had residual disease following chemoradiation and resection were randomized to 1 year of adjuvant nivolumab (200 mg IV every 2 weeks for 16 weeks followed by 480 mg IV every 4 weeks) versus placebo. Adjuvant nivolumab doubled the median disease-free survival (DFS) compared to placebo [22.4 *vs.* 11.0 months, hazard ratio (HR) =0.69 (96.4% CI: 0.56–0.86), P<0.001]. DFS benefit was seen regardless of histological subtype or PD-L1 expression as measured by combined positive score (CPS) (9). NCCN guidelines now recommend adjuvant nivolumab in patients with locally advanced ESCC, EAC, or GEJ adenocarcinoma who have residual disease following chemoradiation and margin negative resection (10).

Other adjuvant studies are ongoing. An ongoing study is evaluating one year of adjuvant pembrolizumab in patients with locally advanced ESCC treated with neoadjuvant cisplatin-based chemoradiation who have high risk features including close or involved margin, extraneural invasion, and/or pathologically involved lymph nodes (NCT03322267) (11).

Immune checkpoint inhibitors (ICIs) are also being investigated in the neoadjuvant setting. A phase 2 pilot study evaluated neoadjuvant nivolumab given before and with chemoradiation in 16 patients with stage II/III esophageal and GEJ cancer. Pathologic complete response (pCR) was observed in 40% of patients who received surgery (12). Another phase 2 pilot trial assessed the pCR rate of neoadjuvant pembrolizumab, chemoradiation, and surgery, followed by adjuvant pembrolizumab in 28 patients with stage Ib–III ESCC. 46% of patients who underwent surgery had pCR, and the 12-month overall survival (OS) rate was 82% (13). Other trials have reported similar efficacy and tolerability using the ICIs pembrolizumab, camrelizumab, and atezolizumab (14-17). Neoadjuvant immunotherapy trials in esophageal cancer are listed in *Table 2*.

Gastric cancer

In locally advanced resectable gastric cancer, perioperative chemotherapy is the worldwide standard of care. For patients who can tolerate a triplet regimen, FLOT [5-fluouracil (5-FU) with leucovorin (LV), oxaliplatin and docetaxel] is preferred based on data demonstrating superior survival when compared to ECF (epirubicin, cisplatin, and 5-fluorouracil) (18).

Other studies are evaluating the safety and efficacy of immunotherapy combined with perioperative chemotherapy. In China, the anti PD-1 antibody sintilimab was evaluated in combination with neoadjuvant capecitabine plus oxaliplatin (CAPOX) in resectable (T3/4NxM0) gastric and GEJ adenocarcinoma. In 26 patients who had received gastrectomy after neoadjuvant treatment, 6 patients (23.1%) achieved pCR and 14 patients (53.8%) achieved major pathologic response (MPR) (19). Sintilimab combined with FLOT has also been evaluated. In a phase 2 study in 20 patients with resectable (T3/T4 or node positive)

gastric or GEJ adenocarcinoma, 62.5% of evaluable patients achieved MPR, including 3 patients with a pCR (20). Atezolizumab and avelumab are also being studied in combination with FLOT in the DANTE (NCT03421288) and ICONIC (NCT03399071) trials (21,22). Finally, KEYNOTE-585 is an active phase 3 trial that will establish the OS, event-free survival (EFS) and pCR rate of neoadjuvant and adjuvant pembrolizumab plus chemotherapy (cisplatin + 5-FU before and after surgery) versus placebo plus chemotherapy in patients with advanced (T3/T4 or node positive) gastric or GEJ adenocarcinoma (23). Pending results of these studies, the role for immune checkpoint inhibition in the treatment of resectable gastric and GEJ adenocarcinoma may change.

Immunotherapy trials for metastatic disease

First line: human epidermal growth factor receptor 2 (HER2) negative

In patients with HER2 negative esophagogastric cancer, chemotherapy has been the traditional standard of care. The REAL-2 trial established the non-inferiority of capecitabine to 5-FU/LV and oxaliplatin to cisplatin (24). NCCN guidelines favor two drug regimens for most patients due to their favorable tolerability compared to three drug regimens (25), and in the United States 5-FU/leucovorin combined with oxaliplatin (FOLFOX) is preferred. Globally, FOLFOX, CAPOX, and 5-FU plus cisplatin serve as the chemotherapy backbone for ongoing first line studies evaluating immunotherapy.

Results from recent clinical trials have dramatically changed the treatment landscape for esophagogastric cancers such that—in patients with PD-L1 expressing tumors—anti-PD-1 therapy plus chemotherapy is the new standard of care. KEYNOTE-590 was a phase 3, randomized, double-blind placebo-controlled trial comparing cisplatin and 5-FU in combination with pembrolizumab or placebo. The study enrolled 749 patients with previously untreated ESCC or EAC. Median OS (mOS) was superior for patients receiving pembrolizumab plus chemotherapy compared with placebo plus chemotherapy (12.4 *vs.* 9.8 months; HR =0.73; P<0.0001). Objective response rate (ORR) also favored pembrolizumab plus chemotherapy (45% *vs.* 29%). Survival benefit for pembrolizumab plus chemotherapy was particularly impressive in patients with ESCC CPS ≥10 (mOS 13.9 *vs.* 8.8 months; HR =0.57; P<0.0001), ESCC regardless of CPS (mOS 12.6 *vs.* 9.8 months; HR =0.72; P=0.0006), and all patients with CPS ≥10 (mOS 13.5 *vs.* 9.4 months; HR =0.62; P<0.0001) (26). Based on this data, pembrolizumab plus chemotherapy (5-FU + platinum) is now FDA approved for metastatic and/or locally advanced esophageal or gastroesophageal junction tumors not amenable for resection. Of note, this approval is not limited to a specific histological subtype or PD-L1 CPS score.

Nivolumab plus chemotherapy and nivolumab plus ipilimumab have also shown activity in patients with previously untreated, metastatic ESCC. CheckMate-648 was a Phase 3 study that randomized 970 patients with previously untreated, metastatic ESCC to nivolumab plus chemotherapy, nivolumab plus ipilimumab, or chemotherapy alone (1:1:1). Median OS favored nivolumab plus chemotherapy over chemotherapy alone (13.2 *vs.* 10.7 months; HR =0.74; P=0.002) and nivolumab plus ipilimumab over chemotherapy (12.8 *vs.* 10.7 months; HR =0.78; P<0.011). In patients with PD-L1 positive disease (defined as tumor cell PD-L1 CPS ≥1), there was a PFS benefit for nivolumab plus chemotherapy, but not for nivolumab plus ipilimumab. Additionally, in the PD-L1 positive sub-population, ORR was 53% for patients receiving nivolumab plus chemotherapy, 35% for nivolumab plus ipilumumab, and 20% for chemotherapy (27). Based on these results, both nivolumab plus chemotherapy and nivolumab plus ipilimumab are considered effective first-line treatment for ESCC, though the benefit for immunotherapy in patients with PD-L1 negative tumors is questionable. Given the superior response rate and PFS for nivolumab plus chemotherapy, the optimal patient population for the nivolumab plus ipilimumab combination is not well defined.

First line nivolumab plus chemotherapy has also been evaluated in unresectable or metastatic GAC, GEJ adenocarcinoma, or EAC. In the pivotal phase 3 CheckMate 649 study, patients with newly diagnosed unresectable or metastatic GAC, GEJ adenocarcinoma, or EAC were randomized to nivolumab plus chemotherapy (FOLFOX or CAPOX) or chemotherapy alone. In patients with PD-L1 CPS ≥5, survival was significantly prolonged with nivolumab plus chemotherapy compared to chemotherapy alone (14.4 *vs.* 11.1 months; HR =0.71; P<0.0001). Nivolumab plus chemotherapy had a higher PFS as compared to chemotherapy alone (7.7 *vs.* 6.0 months; HR =0.68; P<0.0001). Of note, survival for nivolumab plus chemotherapy was superior to chemotherapy alone in all patients, regardless of CPS, though the magnitude of benefit was smaller in the intention to treat (ITT) population (13.8 *vs.* 11.6 months; HR =0.80; P=0.0002) (28). Based on these

results, the United States FDA has approved nivolumab plus 5-FU and platinum-based chemotherapy for the first line treatment of metastatic GAC, GEJ adenocarcinoma, and EAC.

Of note, not all trials of first line immunotherapy have shown consistent benefit. In KEYNOTE-062, first-line pembrolizumab monotherapy demonstrated non-inferiority in comparison with chemotherapy in patients with PD-L1–positive (defined as CPS ≥1) metastatic gastric/GEJ cancer, but the combination of pembrolizumab and chemotherapy did not show a benefit over chemotherapy alone in patients with PD-L1 positive disease (29). Similarly, ATTRACTION-4 was a phase 3 study conducted in Asia that randomized patients with advanced gastric and GEJ adenocarcinoma to chemotherapy (S-1 plus oxaliplatin or CAPOX) plus nivolumab or placebo. Chemotherapy plus nivolumab improved PFS (10.5 *vs.* 8.3 months; P=0.0007) and ORR (57.5 *vs.* 47.8%; P=0.0088), but there was no improvement in OS (17.5 *vs.* 17.2 months; P=0.257) (30).

Second line: *HER2 negative*

The value of second line anti-PD-1 therapy depends on histology (adenocarcinoma *vs.* squamous cell carcinoma). KEYNOTE-061 evaluated pembrolizumab versus paclitaxel in patients with PD-L1–positive (CPS ≥1) advanced GAC/GEJ cancer who had progressed on first line platinum and fluoropyrimidine chemotherapy. Pembrolizumab did not meet the pre-specified statistical significance threshold for overall survival (9.1 *vs.* 8.3 months; one-sided P=0.04), and PFS favored paclitaxel (HR =1.27; 95% CI, 1.03–1.57) (31).

KEYNOTE-181 was a phase 3 trial that compared single agent pembrolizumab versus standard of care chemotherapy (physician choice of paclitaxel, docetaxel, or irinotecan) in 628 patients with advanced or metastatic ESCC or EAC previously treated with one or more lines of chemotherapy. Sixty three percent (63%) of patients had ESCC. Overall, there was no survival difference between pembrolizumab and chemotherapy (7.1 *vs.* 7.1 months; P=0.06). Survival favored pembrolizumab in patients with ESCC (8.2 *vs.* 7.1 months; P=0.0095) and in patients with PD-L1 CPS ≥10 (10.3 *vs.* 6.7 months; P=0.0074) (32). Based on KEYNOTE-181, the FDA approved pembrolizumab as second line therapy in patients with locally advanced or metastatic ESCC with PD-L1 (CPS ≥10).

Nivolumab has also demonstrated efficacy in patients with refractory ESCC. In the phase 3 ATTRACTION-3 trial, 419 patients with ESCC who had progressed on one line of therapy were randomized to single agent nivolumab versus chemotherapy (investigator's choice of paclitaxel or docetaxel). OS favored nivolumab compared with chemotherapy (10.9 *vs.* 8.4 months; P=0.019). Of note, this benefit was seen in the nivolumab group regardless of PD-L1 CPS score (33). As a result, nivolumab is currently listed in the NCCN guidelines as recommended therapy for patients with metastatic ESCC who have progressed after fluoropyrimidine and platinum-based chemotherapy (10).

Third line: *HER2 negative*

The efficacy of anti-PD-1 therapies was initially established in the refractory setting (34). In the open-label, non-comparative, multi-cohort KEYNOTE-059 trial, patients with gastric or GEJ adenocarcinoma who had progressed on at least 2 prior lines of therapy received single agent pembrolizumab. The primary endpoints were response rate and safety. Among 259 patients enrolled, over half (55%) had tumors expressing PD-L1 (defined as CPS ≥1) and were mismatch repair (MMR) proficient (35). Based on an ORR of 13% (95% CI: 8.2–20.0), pembrolizumab was FDA approved for patients with PD-L1 expressing recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma. However, on the basis of low response rates in KEYNOTE-059, and negative results from KEYNOTE-061 and KEYNOTE-062, the FDA Oncologic Drugs Advisory Committee (ODAC) voted against the continued approval of single agent pembrolizumab after 2 or more lines of therapy (36).

Several additional trials evaluating the use of pembrolizumab and nivolumab in the metastatic setting are summarized in *Table 3*.

HER2 positive disease

Recent evidence supports pembrolizumab plus chemotherapy and trastuzumab for the first line treatment of HER2 positive metastatic gastric and GEJ adenocarcinoma. A non-randomized phase 2 trial evaluated first line pembrolizumab in combination with chemotherapy and trastuzumab. Based on significant clinical activity in 37 patients (ORR 91%, PFS 13 months, and OS 27 months), a Phase III trial (KEYNOTE-811) was launched (37,38). Initial analysis of 264 randomized patients reported improved response rate for patients receiving pembrolizumab plus chemotherapy + trastuzumab versus chemotherapy + trastuzumab alone (ORR: 74.4% *vs.* 51.9%; P<0.001) (38). Based on these results, the US FDA

Table 3 Immunotherapy clinical trials for locally advanced, recurrent or metastatic esophagogastric cancer first line/setting and beyond

Clinical trial	Phase	Line/ setting	Site and histology	Treatment arm(s)	Primary end point	Control[&] arm outcome	Experimental/ immunotherapy arm outcome
KEYNOTE-59 Cohort 2/3	II	First line	GC[@]	Pembro + Chemo (Cis/5-FU or cape)	Cohort 2: safety; cohort 3: ORR and safety	–	PFS: 3.3 months; mOS: 20.7 months
KEYNOTE-62	III	First line	GC	Pembro alone, pembro + chemo, placebo + chemo	OS and PFS for PD-L1 CPS ≥1 or ≥10	mOS: PD-L1 CPS ≥1, Chemo + placebo 11.1 months; PD-L1 CPS ≥10, Chemo + placebo 10.8 months	mOS: PD-L1 CPS ≥1: Pembro =10.6 months, Pem + chemo=12.5 months; PD-L1 CPS ≥10: Pembro 17.4 months (statistically not tested; HR =0.69), Pem + chemo 12.8 months
KEYNOTE-590	III	First line	ESCC, EAC	Pembro + chemo *vs.* chemo	OS and PFS in ESCC, PD-L1 ≥10, and all patients	mOS: all patients: 9.8 months (ORR =29%), ESCC PD-L1 ≥10: 8.8 months, PD-L1 ≥10: 9.4 months	mOS: all patients: 12.4 months (HR =0.73, ORR =45%), ESCC PD-L1 ≥10: 13.9 months (HR =0.57), PD-L1 ≥10: 13.5 months (HR =0.62)
ATTRACTION-4 (ONO-4538-37)	III	First line	GC	Chemo + Nivo (C + N) *vs.* Chemo + placebo (C + P)	OS and PFS	mOS: 17.2 months	mOS: 17.5 months (HR =0.90)
CHECKMATE 649	III	First line	GC, EAC	Chemo + Nivo (C + N) *vs.* Nivo + Ipi *vs.* chemo	OS and PFS in PD-L1 positive (CPS ≥5)	mOS: PD-L1 CPS ≥5: 11.1 months; all patients: 11.6 months	mOS: PD-L1 CPS ≥5: 14.4 months (HR =0.71) all patients: 13.8 months (HR =0.80)
KEYNOTE-12	Ib	Second line*	GC PD-L1 positive	Pembrolizumab	Safety	–	PFS: 1.9 months; OS: 11.4 months
KEYNOTE 61	III	Second line	GC	Pembrolizumab *vs.* paclitaxel	OS and PFS for PD-L1≥1	PD-L1 CPS ≥1: 8.3 months; PD-L1 CPS ≥10: 8 months; MSI-H: 8.1 months; PD-L1 CPS <1: 8.2 months	PD-L1 CPS ≥1: 9.1 months (HR =0.82); PD-L1 CPS ≥10; 10.4 months (HR =0.64); MSI-H: not reached; PD-L1 CPS <1: 4.8 months (HR =1.20)
KEYNOTE 28	Ib	Second line	EAC, ESCC, PD-L1 positive	Pembrolizumab	Safety and ORR	–	PFS: 1.8 months; OS: 7 months
KEYNOTE 180	II	Third line	EAC, ESCC	Pembrolizumab	ORR	–	OS: all patients: 5.8 months
KEYNOTE-181	III	Second Line	EAC, ESCC	Pembrolizumab *vs.* Chemo (pacliatxel/ docetaxel/ irinotecan)	OS in PD-L1 CPS ≥10, ESCC < and all patients	PD-L1 CPS ≥10: 6.7 months, ESCC: 7.1 months, ESCC with PD-L1 CPS ≥10: 6.7 months, all patients: 7.1 months	PD-L1 CPS ≥10: 9.3 months (HR =0.69), ESCC: 8.2 months (HR =0.78), ESCC with PD-L1 CPS ≥10: 10.3 months (HR =0.64), all patients: 7.1 months (HR =0.89)

Table 3 (*continued*)

Table 3 (*continued*)

Clinical trial	Phase	Line/ setting	Site and histology	Treatment arm(s)	Primary end point	Control[&] arm outcome	Experimental/ immunotherapy arm outcome
ATTRACTION-2	III	Third line	GC	Nivolumab *vs.* placebo	OS	OS: Placebo group: 4.14 months, PD-L1 positive[$]: 3.83 months, PD-L1 negative: 4.19 months	OS: Nivolumab group: 5.26 months (HR =0.63), PD-L1 positive[$]: 5.22 months (HR =0.51), PD-L1 negative: 6.05 months (HR =0.72)
ATTRACTION-3	III	Second line	ESCC	Nivolumab *vs.* chemotherapy (paclitaxel/ docetaxel)	OS	OS: 8.4 months	OS: 10.9 months (HR =0.77)

*, 85% patients had received at least 1 line of therapy, 15% were treatment naïve; [#], PD-L1 positivity= PD-L1 CPS ≥10; [@], all gastric cancer trial included patients with gastroesophageal junction adenocarcinoma as well; [$], PD-L1 positivity was defined as staining in 1% or more of tumor cells. Ph, Phase trial; L, Line of therapy; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; Pembro, pembrolizumab; Nivo, nivolumab; Chemo, chemotherapy; RT, radiation therapy; TRAE: Treatment related adverse events; N/A, not available; ORR, objective response rate; DCR, disease control rate; DOR, duration of response; OS, overall survival; PFS, progression free survival; QOL, quality of life; Cis, cisplatin; Cape, capecitabine; Ox, oxaliplatin; DOR, duration of response; TTR, time to response; Ipi, ipilimumab; pts, patients; Pacli, paclitaxel; NR, not reached.

granted accelerated approval to first line pembrolizumab in combination with trastuzumab, 5-FU- and platinum-containing chemotherapy for unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma (39).

Novel anti-HER2 therapies are also being evaluated in combination with anti-PD-1 therapy. Margetuximab is a chimeric Fc-engineered IgG1 kappa anti-HER2 monoclonal antibody. The modified Fc region of margetuximab mediates tumor cell destruction through antibody dependent cell-mediated cytotoxicity, and also potentiates adaptive immunity through anti HER-2 directed T-cell responsiveness (40). A phase 1b/2 trial evaluated pembrolizumab with margetuximab in 92 patients with HER2+ gastroesophageal adenocarcinoma previously treated with at least one line of chemotherapy. The ORR for the combination was 18%, PFS was 2.7 months, and mOS was 12.5 months. PD-L1–positive tumors had an ORR of 33% (41). The phase 2/3 MAHOGANY trial comparing margetuximab plus retifanlimab (anti PD-1 antibody) with or without chemotherapy and margetuximab plus tebotelimab [anti-PD1 and anti-lymphocyte activation gene 3 (LAG3) antibody] with front line chemotherapy is ongoing (NCT04082364) (40).

Biomarkers

PD-L1

PD-L1 expression is a predictive biomarker for immune checkpoint inhibition and can be measured as tumor proportion score (TPS) or combined positive score (CPS). TPS is defined as the number of positive tumor cells divided by the total number of viable tumor cells. CPS, which includes the total number of positive tumor cells, lymphocytes and macrophages, divided by the total number of viable tumor cells, may offer a more complete assessment of the tumor immune microenvironment (42). The effectiveness of PD-L1 expression as a predictive biomarker is controversial. In multiple clinical trials, absence of PD-L1 expression (CPS=0) is associated with minimal immunotherapy benefit. In KEYNOTE-61, patients with PD-L1 CPS 1 or less had inferior survival with pembrolizumab compared to paclitaxel (4.8 *vs.* 8.2 months) (31). Similarly, in KEYNOTE-59, the ORR for pembrolizumab monotherapy was only 6.4% in PD-L1 negative (CPS <1) tumors compared to 15.5% in PD-L1 positive (CPS ≥1) tumors (35). Recent studies demonstrate increasing benefit as CPS increases (with typical cut-offs defined as CPS ≥ 5 or CPS ≥10) (26,28,32). We summarize clinical trial results based on PD-L1 expression in *Table 4* (including data from, ATTRACTION-2, JAVELIN-100, and KEYNOTE-059 trials) (43-45). While the US FDA approved nivolumab and pembrolizumab in combination with chemotherapy in the first line setting for patients with HER2 negative gastroesophageal cancer regardless of CPS, the NCCN guidelines still include PD-L1 expression (as

Table 4 Outcomes from various clinical trials in relation to PD-L1 expression

Clinical trial	Treatment(s), line of treatment, cancer site	PD-L1 positive cutoff	Outcomes in relation to PD-L1 status
KEYNOTE-181	Pembrolizumab *vs.* chemotherapy, esophageal SCC and AC	PD-L1 CPS ≥10	mOS: pembrolizumab 9.3 months, chemotherapy 6.7 months
KEYNOTE-061	Pembrolizumab *vs.* paclitaxel, second line, gastric and GE junction AC	PD-L1 CPS ≥1	mOS: PD-L1 CPS ≥10: pembrolizumab 10.4 months, paclitaxel 8.0 months; PD-L1 <1: pembrolizumab 4.8 months, paclitaxel 8.2 months
KEYNOTE-059	Pembrolizumab monotherapy; third line, gastric and GE junction AC	PD-L1 CPS ≥1	ORR: PD-L1 positive 15.5%, PD-L1 negative 6.4%; mDOR: PD-L1 positive 16.3 months, PD-L1 negative 6.9 months
ATTRACTION-3	Nivolumab *vs.* chemotherapy, second-line, esophageal AC and adenosquamous	PD-L1 staining ≥1% tumor cells	Nivolumab arm mOS: PD-L1 positive 10.9 months, PD-L1 negative 10.9 months
ATTRACTION-2	Nivolumab *vs.* placebo; third line	PD-L1 staining ≥1% tumor cells	mOS with nivolumab: PD-L1 positive 5.22 months, PD-L1 negative 6.05 months
Javelin-100	Induction chemotherapy followed by avelumab *vs.* further chemotherapy, first-line, gastric and GE junction AC	In prespecified analysis, PD-L1 protein expression ≥1% in tumor cells by IHC; post-hoc analysis, PD-L1 CPS ≥1	mOS: prespecified PD-L1 population: avelumab 16.2 months, chemotherapy 17.7 months; post hoc analysis (using CPS): avelumab 14.9 months, chemotherapy 11.6 months

PD-L1, protein programmed death-ligand 1; GE, gastroesophageal; SCC, squamous cell carcinoma; AC, adenocarcinoma; CPS, combined positive score; mOS, median overall survival; mDOR, median duration of response.

measured by CPS) as a recommended biomarker (10,25).

In addition to PD-L1 expression, there are ongoing studies evaluating other biomarkers. Studies done by Morihiro *et al.* and Choi *et al.* have found that PD-L1 expression combined with other variables such as MSI, $CD8^+$ TILs (Tumor Infiltrating Lymphocytes), and $FOXP3^+$ TILs may be more predictive than PD-L1 expression alone (46,47).

Microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR)

MSI-H/dMMR is strongly predictive of immunotherapy benefit, regardless of line of therapy received. The incidence of MSI-H/dMMR differs by histology. MSI-H/dMMR is detected in up to 8% of patients with metastatic gastric cancer, but is rarely seen in ESCC (48). Chao *et al.* reported outcomes from patients with MSI-H gastric and gastroesophageal tumors included in the KEYNOTE-059 (third line), KEYNOTE-061 (second line), and KEYNOTE-062 (first line) trials. Median OS for pembrolizumab was not reached in all three studies, indicative of substantial survival benefit. Median PFS for pembrolizumab was not reached in KEYNOTE-059 and was 17.8 months in KEYNOTE-061. In KEYNOTE-062, median PFS was 11.2 months for pembrolizumab, not reached for pembrolizumab plus chemotherapy, and only 6.6 months for chemotherapy alone. The ORR was 57.1%, and 46.7% for pembrolizumab in KEYNOTE-059, and KEYNOTE-061 respectively. In KEYNOTE-062, the ORR was 57.1% for pembrolizumab, 64.7% for pembrolizumab plus chemotherapy, and only 36.8% for chemotherapy. Early treatment with immunotherapy may be particularly beneficial in this patient population but these analyses are limited by the relative rarity of MSI-H/dMMR disease (49).

Tumor mutational burden (TMB)

TMB is an objective measurement of the number of tumor cell mutations. Tumors with high mutational burden (TMB-H) tend to have a greater number of immunogenic antigens, which is associated with immunotherapy response (50). The US FDA has approved pembrolizumab for solid tumors with TMB ≥10 mutations/megabase (FoundationOne CDx assay). In patients with TMB-H gastric cancer and ESCC, studies have shown variable responses to immunotherapy (51-53). Valero *et al.* reported response to immune checkpoint blockade in TMB-H (≥10 mut/mb) MSS (microsatellite stable) tumors of 16

Table 5 Key FDA approvals and NCCN category 1 recommendations for immunotherapy in esophagogastric tumors

Nivolumab—first line in combination with 5-FU and platinum-based chemotherapy for metastatic, locally advanced HER2 neu negative gastric, GE junction, and esophageal adenocarcinoma
Pembrolizumab—first line in combination with 5-FU and platinum-based chemotherapy for metastatic HER2 neu negative esophageal and GE junction tumors
Pembrolizumab—first line in combination with trastuzumab, and 5-FU/platinum-based chemotherapy in metastatic HER2 neu positive gastric, and GE junction adenocarcinoma
Nivolumab—monotherapy second line (after prior 5-FU and platinum-based chemotherapy) for metastatic esophageal squamous cell cancer
Pembrolizumab—monotherapy second line for metastatic esophageal squamous cell cancer with PD-L1 CPS ≥10
Pembrolizumab—monotherapy third line for metastatic gastric and GE junction adenocarcinoma with PD-L1 CPS ≥1
Pembrolizumab for MSI-H or mismatch repair deficient tumors
Pembrolizumab for TMB-High (>10 mutations/megabase) tumors

FDA, Food and Drug Administration; NCCN, National Comprehensive Cancer Network; 5-FU, 5-fluorouracil; HER2, human epidermal growth factor receptor 2; GE, gastroesophageal; PD-L1, protein programmed death-ligand 1; CPS, combined positive score; MSI-H, microsatellite instability high; TMB, tumor mutational burden.

different tumor types. In the gastric cancer cohort, response rate was 31% in TMB-low and 20% in TMB-H group (54). Further studies are needed to establish optimal TMB cutoffs for individual cancers, including esophagogastric cancers.

Epstein-Barr virus (EBV) positivity

EBV is detected in 8–10% of gastric cancers, and is associated with male gender (55). EBV positivity is associated with *PD-L1* amplification, recurrent *PIK3CA* mutations, and DNA hypermethylation (56). Kim and colleagues reported a phase 2 trial of 61 patients with metastatic GC, including 6 patients who were positive for EBV. All 6 EBV positive patients had partial response (PR) with pembrolizumab (57). Similarly, Xie *et al.* prospectively treated 9 patients who had EBV positive gastric cancer with nivolumab and ipilimumab alone or with chemotherapy (S-1 or capecitabine and platinum). Three patients had a partial response (58). Based on these results, EBV in situ hybridization (ISH) testing should be considered in patients with metastatic gastric cancer.

Discussion

The prognosis for patients with metastatic esophagogastric cancers is poor, with survival typically less than 12 months with the use of conventional chemotherapy alone (59-62). There is tremendous need for novel therapies that both improve survival and maintain quality of life. Immunotherapy was deemed the "Breakthrough of the year" in 2013 by the publication *Science*, and its application to solid tumors has only grown since that time (63). The US FDA has approved first line pembrolizumab in combination with chemotherapy for esophageal or GEJ cancers and nivolumab with chemotherapy for gastric, GEJ adenocarcinoma, and EAC. In HER2 positive metastatic gastric and GEJ adenocarcinoma, pembrolizumab is approved with front line trastuzumab and chemotherapy. Pembrolizumab is also approved as monotherapy in ESCC with PD-L1 CPS ≥10 along with MSI-H, and TMB-high (≥10 mut/mb) gastroesophageal tumors (32,35,64-67). Nivolumab is recognized by the NCCN as a category 1 recommendation in the second line setting for ESCC regardless of PD-L1 status (33). Immune checkpoint inhibitors are generally well tolerated, and medical oncologists have learned to manage treatment related immune adverse events.

For surgically resectable tumors, the use of neoadjuvant and perioperative chemotherapy alone or in combination with radiation therapy have improved survival compared to surgery alone. However, relapse rates are still very high. Hence, several studies utilizing immunotherapy in combination with chemotherapy or chemoradiotherapy in the neoadjuvant, adjuvant, and perioperative setting are ongoing. Based on meaningful disease-free survival benefit, adjuvant nivolumab is recommended for patients with locally advanced esophageal and GE junction tumors who have residual disease following chemoradiation and R0 resection. FDA approvals for immunotherapy agents in esophagogastric tumors are summarized in *Table 5*.

In the era of precision medicine, several studies have evaluated the role of biomarkers such as PD-L1, MSI, TMB, and EBV. The optimal threshold for PD-L1 expression is unknown, and it may be optimally used as a negative selector for immune checkpoint blockade (68-71). The combination of PD-L1 with other biomarkers such as MSI, $CD8^+$ TILs, and $FOXP3^+$ TILs may improve its ability to predict immunotherapy benefit. MSI-H status and EBV positivity may be better predictive biomarkers for response to immunotherapy, however the rate of positivity for these biomarkers is relatively rare.

Novel immunotherapy approaches are being investigated in both gastric and esophageal tumors. These approaches include dual immune checkpoint inhibitor combinations, adoptive T-cell transfer therapies such as chimeric antigen receptor (CAR) T cells, and vaccines. For all novel immunotherapy strategies, it will be critical to find the safest dose and identify biomarkers that predict treatment benefit.

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Footnote

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