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GASTROINTESTINAL CANCERS (J MEYER, SECTION EDITOR)

Role of Immunotherapy in Advanced Gastroesophageal Cancer

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Abstract

Purpose of Review Immunotherapy and tumor microenvironment have been at the forefront of cancer research over the past several decades. Here, we will review the role of immunotherapy in advanced gastroesophageal cancers including targeted antibodies, immunomodulating agents, vaccines, oncolytic virus therapy, and adoptive immunotherapy, and discuss the future direction for immunotherapy in this population.

Recent Findings Targeted antibodies are already standard-of-care. An anti-PD-1 monoclonal antibody is currently FDA approved for second-line treatment of locally advanced or metastatic ESCC, as well as beyond second-line treatment of advanced G/GEJ cancers, and recent data suggests it may be considered in first-line treatment of advanced G/GEJ cancers. Combination therapies such as immunotherapy plus chemotherapy and/or radiotherapy, vaccines, oncolytic viral therapy, and adoptive immunotherapy in varying combinations are currently under active investigation.

Summary Several trials are ongoing and are hoped to reach more efficacious and individualized treatment options in advanced gastroesophageal cancer, where novel treatment options are desperately needed.

Keywords Immunotherapy · Advanced gastric cancer · Advanced esophageal cancer · Advanced gastroesophageal cancer · PD-1 · PD-L1

Introduction

Survival for patients with advanced gastroesophageal cancer is poor, and is responsible for more than a million deaths per year globally [1]. In 2019, gastric cancer represented 1.6% of all cancer cases in the USA (with an estimated 27,510 new cases expected in 2019), with a 5-year relative survival rate of 5.3% for patients with distant disease [2]. Approximately 50% of patients with gastric cancer will be diagnosed with advanced-stage disease, although in some countries such as Japan and South Korea, where screening is routinely performed, early detection is more frequent [3]. The median overall survival (OS) duration of patients with metastatic gastric cancer ranges from 3 months with only supportive care treatment to 16 months in fit patients in clinical trials; thus, there is still an unmet need in oncology to improve the treatment options for these patients [4]. There is considerable overlap between gastric cancer and distal esophageal cancers in their treatment and clinical trial inclusion. In the USA, esophageal cancer represented 1% of all cancer cases with an estimated 17,650 new cases expected in 2019, with a 5-year relative survival rate of 4.8% for patients with distant disease [2, 5]. Approximately 50% of patients diagnosed with esophageal cancer present with unresectable or metastatic disease.

In distant metastatic gastroesophageal cancers, several double-agent or triple-agent chemotherapy regimens have been established as first-line treatment options. There have been multiple large randomized phase III trials using additional targeted therapies which have led to changes in clinical practice such as HER2 antibody, trastuzumab, and vascular endothelial growth factor receptor 2 (VEGFR2) antibody, ramucirumab [6–8]. However, esophageal and gastric cancers have limited treatment options in the locally advanced and metastatic setting; usually resistance to chemotherapy leads to limited efficacy beyond the first- or second-line setting. Chemotherapy results in modest improvements in survival with a median survival for fit patients with advanced disease

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treated on first-line clinical trials of 9–11 months [9, 10]. Unfortunately, chemotherapy treatment aims to stabilize disease progression and improve patients' prognosis but is unable to cure or control the disease long term, making the search for alternative therapeutic options of crucial importance.

In comparison with other common cancers, therapeutic directions in advanced gastroesophageal cancer are still in early phase but rapidly evolving and include biologic and immunologic exploration. The novel molecular classifications proposed by The Cancer Genome Atlas (TCGA) and the Asian Cancer Research Group (ACRG) have fine-tuned our appreciation for multiple gastric cancer subtypes, and have opened the gates to more tailored therapy. Here, we will review the role of immunotherapy in advanced gastroesophageal cancers, including targeted antibodies, immunomodulating agents, vaccines, oncolytic virus therapy, and adoptive immunotherapy, and discuss the future direction for immunotherapy in this population.

Immune Microenvironment in Gastroesophageal Cancer

Immunotherapy is perhaps the most significant breakthrough in the history of cancer treatment, as illustrated by the awarding of the 2018 Nobel Prize in Medicine to immunologists James Allison and Tasuku Honjo. Understanding the unique immune microenvironment of each cancer is crucial to discovering and developing therapeutic options for patients. Prior to our discussion of the current role of immunotherapy in advanced gastroesophageal cancer, we will review our current understanding of the immune microenvironment in this subset of patients.

In order to activate a specific antitumor response from T cells, the major histocompatibility complex (MHC) on antigen presenting cells (APC) must present a cognate peptide to the T cell receptor located on the T cell. This process is orchestrated by interactions between inhibitory and co-stimulatory molecules between T cells and tumor cells such as cytotoxic T lymphocyte-associated protein-4 (CTLA-4), cluster of differentiation-28 (CD-28), and PD-1 and its ligands, PD-L1/PD-L2. [11]. Blockade of these inhibitory receptors, such as CTLA-4 or PD-1, leads to T cell activation. PD-1 is expressed on activated T cells and binds to PD-L1 and PD-L2 on the APC, which results in inhibition of T cell migration, proliferation, and also effector functions including cytokine secretion [12].

We know that there are a number of factors in the TME that can often predict whether a patient is likely to respond to single-agent PD-1 inhibition. These factors include a high tumor antigen load, loss of help by CD4-positive helper cells, and immune-regulatory cytokines and ligands for co-inhibitory proteins expressed by tumor and stromal cells, ultimately leading to a progressive loss of the ability of effector CD8-positive T cells to produce pro-inflammatory cytokines and their capacity to kill cancer cells [13].

The localization of PD-L1 expression within the TME seems to have clinical significance. PD-L1 upregulation occurs in approximately 40% of gastroesophageal cancers; however, key differences are emerging in that, unlike lung cancer or melanoma, there is little PD-L1 expressed on the cancer cells of upper gastrointestinal tumors, but rather expression occurs predominantly on infiltrating myeloid cells at the invasive margin [14, 15]. The localization of PD-L1 expression within the TME may affect its use as a biomarker. The stromal expression rather than membranous expression may be responsible for the somewhat lower responses to single-agent PD-1 inhibitors in gastroesophageal cancer compared with other tumor types [13].

Another observation made in gastroesophageal cancers is that more CD8-positive T cell infiltration occurs at the peritumoral interfaces of tumors that were also PD-L1 positive compared with those that were PD-L1 negative. When CD8-positive T cell densities were divided into low, mid, and high categories, 89% of stroma PD-L1 positive tumors had high CD8-positive T cell densities. This illustrates the relationship between CD8-positive T cells, a source of pro-inflammatory cytokines (e.g., interleukin-2, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and β-chemokines) and expression of PD-L1 in esophagogastric cancer [14, 16].

Interestingly, in EBV$^-$positive gastric cancers (~10%), approximately 50% and 94% PD-L1 positive staining is seen on tumor cells and immune cells, respectively [17, 18]. EBV positive gastric cancers occur predominantly in the gastric fundus or body and are more common among men. Gastric TCGA investigators described a recurrent amplification at 9p24.1, the locus containing *JAK2* but also *CD274* and *PDCD1LG2*, which encode PD-L1 and PD-L2, respectively. These 9p amplifications occurred in 15% of EBV-driven gastric tumors and result in enhanced neoepitope presentation [19]. Therefore, there are ongoing studies evaluating checkpoint inhibitors in EBV-positive gastric cancer [17].

Defective mismatch repair (MMR) genes have also been identified as being predictive of response to PD-1 inhibition because somatic mutations have the potential to encode non-self immunogenic neoantigens [20]. Whole-exome sequencing has demonstrated a mean of 1782 somatic mutations in MMR-deficient tumors (MSI-high) compared with approximately 73 in MMR-proficient tumors (microsatellite stable (MSS)) [20]. Additionally, immunologic evaluation of the immune microenvironment in MMR-deficient tumors demonstrated strong expression of several immune checkpoint ligands, most notably, PD-1/PD-L1, lymphocyte activating gene-3 (LAG-3), indoleamine 2,3-dioxygenase enzyme (IDO), and CTLA-4, which help develop resistance to immunologic attack [21]. MMR deficiency has been identified in

approximately 17–21% of gastric cancers, and data indicate a higher response rate among these patients (on the order of approximately 50%) [15, 22].

Ultimately, as we will review below, the higher the PD-L1 expression, the higher the response rates in gastroesophageal cancers. However, there are also a substantial number of patients with PD-L1-negative tumors who also respond to combination immunotherapy, which highlights the imperative need for future investigations to gain yet more understanding about the complex interactions occurring in the TME including viral infections, mutational burden, MSI status, and other immunomodulating factors.

Targeted Antibodies

Therapeutic monoclonal antibodies represent a validated, passive immunotherapy strategy. Two of the currently approved therapies for treatment of advanced gastroesophageal cancers are monoclonal antibodies targeting HER2 and VEGFR2. For patients with HER2-positive gastroesophageal cancer (~ 20% of patients), the 2010 Trastuzumab for Gastric Cancer (ToGA) trial evaluated trastuzumab in combination with cisplatin and fluoropyrimidine based chemotherapy in the first-line setting [23]. The median OS was 13.8 months (95% confidence interval (CI) 12–16) in those assigned to trastuzumab plus chemotherapy compared with 11.1 months in those assigned to chemotherapy alone (HR 0.74; [95% CI 0.60–0.91]; p = 0.0046), with the greatest margin of benefit seen in those with high levels of HER2 overexpression, and therefore trastuzumab is the standard-of-care treatment in first-line treatment of HER2-positive advanced gastroesophageal cancers.

The VEGFR2 antibody, ramucirumab, has been shown to have comparable efficacy with chemotherapy as a single agent in previously treated patients [8], and in 2014, the OS was significantly longer when ramucirumab was used in combination with paclitaxel (median OS 9.6 months [95% CI 8.5–10.8] vs 7.4 months [95% CI 6.3–8.4], HR 0.807 [95% CI 0.678–0.962]; p = 0.017) [7]. The OS results from these two pivotal clinical trials led to the Food and Drug Administration (FDA) approval of ramucirumab in the second-line setting as a single-agent or in combination with paclitaxel.

The epidermal growth factor receptor (EGFR) has been successfully targeted in wild-type KRAS colorectal metastatic cancer as well as in squamous cell head and neck cancers and metastatic lung cancer. It is overexpressed by 30 to 50% in gastroesophageal tumors; however, the EXPAND trial (cetuximab, an EGFR inhibitor) and the REAL3 trial (panitumumab, an EGFR inhibitor) failed to demonstrate benefit in advanced gastroesophageal tumors [24]. Nimotuzumab, another humanized monoclonal anti-EGFR antibody, did not increase OS or progression-free survival (PFS) in the overall population in a phase II clinical trial for advanced gastric cancer, but those with EGFR overexpression had a substantial benefit, which increased interest in selecting patients by EGFR status for EGFR-targeting therapies [25]. A phase II trial of paclitaxel, cisplatin, and nimotuzumab in first-line setting in unresectable or metastatic esophageal squamous cell carcinoma showed promising results [26], and further trials are underway.

Immunomodulators: Anti-PD-1

Targeting the immune checkpoint pathways of PD-1, PD-L1, and CTLA-4 has led to outstanding success in treatment of melanoma, non-small cell lung cancer, and urothelial cancers. This inspired a series of investigational efforts using these agents in gastroesophageal cancers. The evolution of immunotherapy trials and the subsequent standard-of-care changes based on their results reinforce the importance of continued research in this patient population. In this section, we will review key checkpoint inhibitor trials in advanced gastroesophageal cancers (Table 1). Of note, there is ongoing research evaluating efficacy and safety of implementing immunotherapy during the neoadjuvant and adjuvant setting in combination with chemotherapy and/or radiation therapy, which are beyond the scope of this review. Currently, pembrolizumab, an anti-PD-1 monoclonal antibody, is FDA-approved in the second-line and beyond second-line treatment in a certain subtypes of advanced gastroesophageal cancer. Ongoing trials are further evaluating checkpoint inhibitors as monotherapy or in combination with chemotherapy and/or radiation therapy, as well as in earlier lines of therapy in advanced gastroesophageal cancer.

First-Line Treatment Trials

Front-line data presented in the American Society of Clinical Oncology (ASCO), May 2019, indicate that immunotherapy can be considered in specific patients with advanced gastric (G)/GEJ cancers. In the randomized phase III trial, KEYNOTE-062, patients received one of three treatment options as initial therapy: intravenous pembrolizumab, pembrolizumab plus chemotherapy, or chemotherapy plus placebo. The trial enrolled 763 HER2-negative patients, and all patients had a PD-L1 combined positive score (CPS) ≥ 1; 281 (37% of the enrollees) had a score of ≥ 10 [[27••]]. Of note, PD-L1 expression was evaluated by the FDA-approved test PD-L1 IHC 22C3 pharmDx Kit (Dako), and CPS is determined by the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells evaluated, multiplied by 100 [28]. The trial achieved its primary endpoint, showing that for patients with PD-L1-positive (CPS ≥ 1), HER2-negative, advanced G/GEJ cancer, initial therapy with pembrolizumab resulted in non-inferior OS compared with standard chemotherapy [27••]. Additionally, pembrolizumab showed clinically meaningful

Table 1 Key clinical trials investigating checkpoint inhibitors in advanced gastroesophageal cancer

Treatment line	Name of trial [reference]	Trial phase	Drug(s) tested	Dose	Cancer type	n	Median PFS (m)	ORR (%)	Objective response (CR + PR)	Median OS (m)	1 year OS (%)
First-line	**KEYNOTE-062 [27••]**	Phase III	**Pembrolizumab**	200 mg IV Q3W	advanced G/GEJ	**256**	**2, 2.9^**	**14.8, 25^**	NA	**10.6, 17.4^**	**47, 57^**
			Pembrolizumab + chemo	200 mg IV Q3W + standard doses		**257**	NA	**48.6, 52.5^**	NA	NA	NA
			Chemo + placebo	Standard doses		**250**	**6.4, 6.1^**	**37.2, 37.8^**	NA	**11.1, 10.8^**	**46, 47^**
First-line	KEYNOTE-059 (cohort 2 and 3) [28]	Phase II	**Pembrolizumab (cohort 3)**	200 mg IV Q3W	advanced G/GEJ	**31**	NA	25.8	NA	NA	NA
			Pembrolizumab + chemo (cohort 2)	200 mg IV Q3W + standard doses		25	NA	60	NA	NA	NA
First-line	KEYNOTE-590 [29]	Phase III	Pembrolizumab	200 mg IV Q3W	advanced E/GEJ	~350	NA	NA	NA	NA	NA
			Pembrolizumab + chemo	200 mg IV Q3W + standard doses		~350	NA	NA	NA	NA	NA
Second-line	KEYNOTE-061* [30]	Phase III	**Pembrolizumab**	200 mg IV Q3W	advanced G/GEJ	**196**	**1.5**	NA	NA	**9.1**	NA
			Chemo	Standard doses		**199**	**4.1**	NA	NA	**8.3**	NA
Second-line	KEYNOTE-181❖ [31••]	Phase III	**Pembrolizumab**	200 mg IV Q3W	advanced ESCC	**85^**	**3.2^**	**22^**	NA	**10.3^**	**48^**
			Chemo	Standard doses		**82^**	**2.3^**	**7^**	NA	**6.7^**	**23^**
Second-line	ATTRACTION-3 [32]	Phase III	Nivolumab	240 mg IV Q2W	advanced ESCC	210	1.7	NA	NA	10.9	47
			Chemo	Standard doses		209	3.4	NA	NA	8.4	34
Beyond second-line	KEYNOTE-180❖ [33]	Phase II	**Pembrolizumab**	200 mg IV Q3W	advanced ESCC	**35^**	NA	**20^**	NA	NA	NA
Beyond second-line	KEYNOTE-059❖ (cohort 1) [34••]	Phase II	Pembrolizumab	200 mg IV Q3W	advanced G/GEJ	259	NA	NA	**15.5**, 6.4	**5.8,** 4.9	NA
Beyond second-line	ATTRACTION-2 [35•]	Phase III	Nivolumab	240 mg IV Q2W	advanced G/GEJ	330	NA	NA	NA	5.26	26.2
			Placebo	NA		163	NA	NA	NA	4.14	10.9
Beyond second-line	CHECKMATE-032 [36]	Phase I/II	Nivolumab	3 mg/kg Q2W	advanced G/GEJ	59	NA	NA	12	NA	39
			Nivolumab + Ipilimumab	1 mg/kg + 3 mg/kg Q3W		49	NA	NA	24	NA	35
			Nivolumab + Ipilimumab	3 mg/kg + 1 mg/kg Q3W		52	NA	NA	8	NA	24

^ = CPS ≥ 10

*Study did not show superiority of pembrolizumab to paclitaxel

❖ Led to FDA approval

Bold PD-L1-positive; at least CPS ≥ 1

n, sample size; *PFS*, progression free survival; *ORR*, overall response rate; *CR*, complete response; *PR*, partial response; *OS*, overall survival; *m*, months; *IV*, intravenous; *Q3W*, every 3 weeks; *G*, gastric; *GEJ*, gastroesophageal junction; *NA*; not available; *E*, esophageal; *ESCC*, esophageal squamous cell; carcinoma; *chemo*, chemotherapy; *Q2W*, every 2 weeks; *FDA* Food and Drug Administration

improvement in OS among patients with tumors that had high levels of PD-L1 expression (CPS of ≥ 10); survival with pembrolizumab was superior to chemotherapy (HR = 0.69) with a median OS of 17.4 months for those receiving pembrolizumab compared with 10.8 months for those receiving chemotherapy. The trial evaluated combined treatment with pembrolizumab plus standard chemotherapy but found this regimen did not improve survival relative to chemotherapy alone regardless of CPS score [27••]. The safety profile of pembrolizumab was consistent with prior experiences, with rates of serious side effects lowest among patients treated with pembrolizumab alone.

At the European Society for Medical Oncology (ESMO) Congress, September 2019, KEYNOTE-062 authors presented an exploratory analysis of 50 patients with MSI-high tumors where median OS was not reached (NR) in both pembrolizumab arms; median OS was NR [95% CI, 10.7-NR] in pembrolizumab group vs NR [95% CI, 3.6-NR] in pembrolizumab plus chemotherapy [HR 0.37; 95% CI 0.14–0.97], vs 8.5 months [95% CI, 5.3–20.8] in chemotherapy group [HR 0.29; 95% CI, 0.11–0.81]. PFS was also prolonged in both pembrolizumab arms in patients with MSI-high tumors; median PFS was 11.2 months [95% CI, 1.5-NR] in pembrolizumab group vs NR [95% CI, 3.6-NR) in pembrolizumab plus chemotherapy, vs 6.6 months [95% CI, 4.4–8.3] in chemotherapy group [HR 0.72; 95% CI, 0.31–1.68] [37•]. The objective response rate with pembrolizumab vs chemotherapy was 57.1% vs 36.8%, and 64.7% vs 36.8% with pembrolizumab plus chemotherapy vs chemotherapy, respectively. Grade 3–5 drug-related adverse events occurred in 17% of patients in the pembrolizumab arm vs 73% patients receiving pembrolizumab plus chemotherapy vs 69% of patients on chemotherapy [37•]. In summary, the results of KEYNOTE-062 suggest that pembrolizumab is not inferior to chemotherapy in first-line treatment of patients with advanced G/GEJ cancer and CPS score of ≥ 1, and the greatest benefit was seen in patients with CPS ≥ 10. In addition, it has a substantially improved safety profile compared with that of standard-of-care chemotherapy. There have not been any changes reflecting this data in FDA guidelines as of this time.

Another randomized, double-blinded, placebo-controlled phase III trial, KEYNOTE-590, is designed to evaluate efficacy and safety of pembrolizumab vs placebo plus standard chemotherapy as first-line treatment in participants with locally advanced or metastatic esophageal carcinoma [29]. This trial hopes to further define the role of immunotherapy in advanced esophageal cancer.

Second-Line Treatment Trials

Key trials in second-line therapy in advanced gastroesophageal cancer include KEYNOTE-181, a phase III trial; 628 patients were randomly assigned to receive either pembrolizumab or chemotherapy. For patients with PD-L1 expression with CPS ≥ 10, the median OS was 10.3 months in those receiving pembrolizumab vs 6.3 months for patients receiving chemotherapy, and ORR was 22% and 7%, respectively [31••]. This trial, along with KEYNOTE 180 (Table 1), led to FDA approval of pembrolizumab for second-line treatment in locally advanced or metastatic ESCC with CPS score ≥ 10 in July 2019.

Reported in September 2019, another phase III randomized trial, ATTRACTION-3, evaluated nivolumab vs paclitaxel or docetaxel in patients with advanced ESCC (regardless of PD-L1 expression). The median OS was 10.9 months in the nivolumab group vs 8.4 months in the chemotherapy group (HR = 0.77, $P = 0.019$), 12-month OS was 47% vs 34%, respectively, and median PFS was 1.7 vs 3.4 months [HR = 1.08, 95% confidence interval = 0.87–1.34], respectively. Nivolumab was associated with significant improvement in OS and a favorable safety profile compared with chemotherapy in previously treated patients with advanced ESCC, and might represent a new standard second-line treatment option [32]. There are ongoing trials that include non-Asian patients are investigating nivolumab for advanced G/GEJ cancer in various settings and earlier treatment lines.

Of note, KEYNOTE-061, a phase III, open-label study evaluating pembrolizumab vs chemotherapy for patients with advanced G/GEJ cancer failed to confirm the superiority of pembrolizumab to paclitaxel as a second-line therapy [30].

Beyond Second-Line Treatment Trials

In September 2017, the results of the KEYNOTE-059 trial led to the accelerated FDA approval of pembrolizumab beyond second-line treatment in PD-L1-positive (CPS ≥ 1), advanced G/GEJ cancer. This multicenter, open-label, non-randomized, phase II trial, cohort 1 demonstrated manageable toxic effects and promising antitumor activity with pembrolizumab monotherapy. The objective response rate was higher in patients with PD-L1-positive (CPS ≥ 1) vs PD-L1-negative tumors (23 of 148 [15.5%] vs 7 of 109 [6.4%]), respectively; nonetheless, patients with PD-L1-negative tumors also experienced objective responses, including CR in 3 patients (2.8%). Responses were durable in the overall population, with a longer response duration in patients with PD-L1-positive tumors. [[34••]].

Another notable trial, ATTRACTION-2, a phase III randomized, double-blind, placebo-controlled trial in Japan, South Korea, and Taiwan, evaluated efficacy and safety of nivolumab in patients with advanced G/GEJ cancer. A total of 493 patients received either nivolumab or placebo. The median OS was 5.26 months (95% CI 4.60–6.37) in the nivolumab group and 4.14 months (3.42–4.86) in the placebo group (HR 0.63, 95% CI 0.51–0.78; $p < 0{\cdot}0001$). The 12-month OS rates were 26.2% (95% CI 20.7–32.0) with

nivolumab and 10.9% (95% CI 6.2–17.0) with placebo, and in December 2019, the 2-year updated data showed an ongoing higher OS rate in the nivolumab vs placebo group 10.6% vs 3.2%, respectively. The OS benefit was observed regardless of tumor PD-L1 expression [35•, 38].

Combined immunotherapy was uniquely evaluated in the CHECKMATE-032 study; nivolumab monotherapy vs a combination of nivolumab and the anti-CTLA-4 antibody ipilimumab (different doses; Table 1) in a PD-L1 biomarker unselected advanced G/GEJ cancer. There was a greater benefit in PD-L1-positive vs PD-L1-negative patients in the combination therapy arm. Nivolumab monotherapy and nivolumab plus ipilimumab demonstrated clinically meaningful antitumor activity, durable responses, encouraging long-term OS, and a manageable safety profile, and so phase III studies evaluating use of these in earlier lines of therapy are underway [36].

Immunomodulators: Anti-PD-L1, Anti-CTLA-4

In many clinical scenarios in other cancers, anti-PD-1 and anti-PD-L1 are considered essentially equivalent, however, not compared head-to-head. There have been several anti-PD-L1 therapies under investigation, and, overall, response rates to anti-PD-L1 therapies appear to be lower than to anti-PD-1 for patients with gastric cancer. In a phase 1b study in 2016, patients with G/GEJ adenocarcinoma received avelumab, a humanized anti PD-L1 monoclonal antibody, after progression on prior therapy and as maintenance following first line chemotherapy, and in both settings had a modest response rate, and durability of responses was also demonstrated (5/14 responses were > 40 weeks) [39]. Durvalumab, another anti-PD-L1 monoclonal antibody with demonstrated activity in gastric cancer, is being investigated in ongoing clinical trials in this disease [40].

The CTLA-4 antibodies ipilimumab and tremelimumab have also been assessed in gastroesophageal cancer; however, they have yet to show any significant effect in advanced gastroesophageal cancers. A phase II study assessed the efficacy of ipilimumab as sequential or maintenance treatment immediately after first-line chemotherapy in unresectable or metastatic gastroesophageal cancer compared with best supportive care (BSC), and the interim analysis (IA) did not show an improvement in immune-related progression-free survival (irPFS) with ipilimumab vs BSC was not observed (HR = 1.44 [80% CI: 1.09, 1.91], $p = 0.097$) [41]. Another phase II study evaluating tremelimumab in the second-line treatment of unselected advanced gastroesophageal cancer showed a response rate of 5% in 18 patients, with a sole responder reported to continue on treatment at 32.7 months, a response in excess of expected survival in this setting [42].

Other Immunomodulating Targets

The KEYNOTE-012 trial also investigated the use of a six-gene IFN-γ signature that was previously identified to predict response in melanoma [13]. The six genes included *CXCL9*, *CXCL10*, *IDO1*, *IFNG*, *HLA-DRA*, and *STAT-1,* which were used to calculate an IFN-γ composite score. However, the numbers of enrolled patients were small and so the pre-specified gene signature did not meet significance, but there is a signal and the ongoing KEYNOTE studies will continue to investigate this. Other targets currently under investigation include glucocorticoid-induced tumor necrosis factor receptor-related protein (GITR), OX40, IL-2/IL-2R, and CD137 (also known as 4-1BB); activating these pathways can help prevent immunosuppression and increase the survival or activation of cancer-fighting T cells. Similarly, blocking LAG-3 pathway or IDO enzyme may be able to help prevent suppression of cancer-fighting T cells. Additionally, targeting STAT3, an intracellular signaling protein, or CD40, a co-stimulatory pathway, can help stimulate adaptive immune responses.

GITR is an attractive target for immunotherapy. On the basis of the potent preclinical antitumor activity of agonist anti-GITR antibodies, the first in-human phase I trial of GITR agonism with the anti-GITR antibody TRX518 was reported at ASCO 2019, where the study team is investigating TRX518 with PD-1 pathway blockade in patients with advanced refractory tumors [43, 44].

At the ESMO 2018 Congress, the combination of DKN-01 (humanized monoclonal antibody targeting the Dickkopf-1 protein, and Wnt pathway modulator) and pembrolizumab was presented to demonstrate promising clinical activity with a 23.5% overall response rate (ORR) and 58.8% disease control rate in evaluable G/GEJ cancer patients who have been heavily pretreated and have not had prior anti-PD-1/PD-L1 therapy [45]. The combination has generated durable responses in subgroups less likely to respond to pembrolizumab monotherapy, for example, patients whose tumors are microsatellite stable and/or PD-L1 negative.

The inhibitory immune checkpoint LAG-3 holds considerable potential, with increasing evidence of having remarkable interactions with other immune checkpoints especially PD-1. Anti-LAG-3 antibody not only promotes effector CD8 T cell activity but also inhibits regulatory CD4 T cell-induced suppressive function in the TME. Currently there are ongoing trials (NCT02935634) in advanced gastric cancer with anti-LAG-3 monoclonal antibody relatlimab (BMS-986016) plus nivolumab, as well as other trials with LAG-3-targeted immunotherapy including IMP321 and LAG525 in advanced solid tumors [46, 47].

Vaccines

In this era of immunotherapy and subsequent immune response arousal, vaccines have attracted more interest and are under investigation in gastroesophageal cancers. Vaccines are designed to launch an immune response against tumor-specific or tumor-associated antigens (TAAs). In order to enhance the immune response, antigens are commonly delivered in combination with adjuvants and/or cytokines such as interleukins or granulocyte macrophage colony-stimulating factor (GM-CSF). TAAs including melanoma-associated antigen-3 (MAGE-3) and New York Esophageal Squamous Carcinoma-1 (NY-ESO-1), expressed in gastrointestinal tumors and testis but not in normal tissue, have been increasingly studied in advanced solid tumors including gastroesophageal tumors [48]. The use of NY-ESO-1 vaccines in esophageal cancer patient is known to result in CD4 and CD8 T cell responses and tumor regression [49], and several trials of vaccines, given alone or with other therapies, are currently underway [50].

A vaccine against human leucocyte antigen (HLA)-A24-restricted human vascular endothelial growth factor receptor (VEGFR)1–1084 and VEGFR2–169 in combination with chemotherapy showed a median time to progression of 9.6 months and median OS of 14.2 months [51]. Eighty-two percent of patients displayed immune responses against VEGFR1/2; however, only those with an immunological response to the VEGFR2–169 peptides showed statistically significantly improved survival.

Another clinical trial using HLA-A24-binding peptide vaccines containing a combination of novel cancer-testis antigens and anti-angiogenic peptides (including DEPDC1, URLC10, FoxM1, Kif20A, and VEGFR1) in advanced chemotherapy-refractory gastric cancer was found to be safe and, in the HLA-A24+ group, patients who showed T cell responses specific to antigen peptides had a tendency toward better survival than those who showed no response [52].

Oncolytic Virus Therapy

Researchers are using modified viruses which release more antigens, generating a greater immune response against the tumor, ultimately leading to self-destruction of tumor cells. Phase I studies are actively recruiting to evaluate safety and efficacy, including OH2, a Type 2 herpes simplex virus expressing GM-CSF, as monotherapy or in combination with anti-PD-1 antibody (NCT03866525). Another phase I study (NCT00794131) in advanced solid tumors is investigating GL-ONC1, an oncolytic vaccinia virus, which has shown the ability to preferentially locate, colonize, and destroy tumor cells in preclinical models; results of the study are pending. Another group has evaluated the safety and immunogenicity of a vaccination approach with multimodal oncolytic potential in non-human primates, where primates received a replication-deficient adenoviral prime, boosted by the oncolytic Maraba rhabdovirus (MG1), where both vectors expressed the human (h)MAGE-A3 [53]. The boosting with MG1-MAGEA3 induced an expansion of hMAGE-A3-specific CD4-positive and CD8-positive T cells with the latter peaking at impressive levels and persisting for several months. It was noted that T cells reacting against epitopes fully conserved between simian and human MAGE-A3; humoral immunity was demonstrated by the detection of circulating MAGE-A3 antibodies. Clinical investigations utilizing this program for the treatment of MAGE-A3-positive solid malignancies are underway (NCT02285816, NCT02879760) [53].

Cell Therapy

Investigational studies in which patients' own immune cells are modified to target tumor cells and then reintroduced into the patient, also known as adoptive immunotherapy, are also underway in gastroesophageal cancers. DCs pulsed with tumor cell antigens have produced some initial promising results in gastroesophageal cancers. In one early study, MAGE-A3 peptide-pulsed DCs were able to induce peptide-specific T cell responses and minor tumor regression in some patients, and in another study, tumor regression in one of nine patients treated with HER2(p369)-pulsed DCs was demonstrated [54, 55]. Adoptive immunotherapy with tumor-associated lymphocytes (TALs) in conjunction with chemotherapy has also been studied in a randomized controlled study in patients with advanced gastric cancer, with a median survival of 8.5 months for the control group and 11.4 months for patients treated with adoptive T cell therapy plus chemotherapy ($p = 0.05$). Challenges include that many patients will not develop tumor-specific T cells [56], and that DC therapy efficacy is often short-lived due to removal of DCs by activated CD8-positive lymphocytes; therefore development of adjunctive therapies is needed to further enhance these therapeutic options [57].

Chimeric antigen receptor (CAR) expressing T cells have already been associated with remarkable results in hematologic malignancies, and are now being studied in patients with gastric cancer where they have been genetically modified to recognize antigens including human carcinoembryonic antigen (CEA), erb-b2 receptor tyrosine kinase 2 (ERBB2), and HER2. There are several ongoing phase I studies in HER2 and CEA positive solid tumors including gastroesophageal tumors [58].

Conclusions

Our understanding of the mechanisms underlying immune modulation has exponentially flourished in the last decade, allowing for the development of multiple therapeutic approaches that are revolutionizing the treatment of cancer, with

advanced gastroesophageal cancer still in the early phases of investigations. Targeted antibodies such as trastuzumab and ramucirumab are already part of standard-of-care, with ongoing clinical trials exploring other targeted antibodies. Anti-PD-1 monoclonal antibody, pembrolizumab has been validated in PD-1 positive patients, and is currently FDA approved for second-line treatment of locally advanced or metastatic ESCC with CPS ≥ 10, as well third-line and beyond treatment of advanced G/GEJ cancers with CPS of ≥ 1. Recent data also suggests pembrolizumab is non-inferior to chemotherapy in advanced G/GEJ cancers with CPS≥1, and that pembrolizumab may be considered in first-line treatment of advanced G/GEJ cancers with CPS≥10 and/or are MSI-high. Combination therapies such as dual immunotherapy, immunotherapy plus chemotherapy, and/or radiation therapy are under active investigation and represent the next frontier of studies. Additionally, further therapeutic approaches such as vaccines, oncolytic viral therapy, and adoptive immunotherapy in varying combinations are currently underway in several trials and are hoped to reach more efficacious and individualized treatment options in advanced gastroesophageal cancer, where novel treatment options are desperately needed.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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