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Anti-Tumour Treatment

Evolution of checkpoint inhibitors for the treatment of metastatic gastric cancers: Current status and future perspectives

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ABSTRACT

Background: Standard treatment options for patients with advanced gastric or gastroesophageal junction cancer (GC/GEJC) are associated with limited efficacy and some toxicity. Recently, immunotherapy with antibodies that inhibit the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) interaction has emerged as a new treatment option. This manuscript reviews early-phase and late-phase trials of immunotherapy in advanced GC/GEJC.

Methods: Searches for studies of immunotherapy in GC/GEJC were performed using PubMed, ClinicalTrials.gov, and abstract databases for select annual congresses. Findings were interpreted based on expert opinion.

Results: Monotherapy with anti–PD-1/PD-L1 antibodies, including pembrolizumab, nivolumab, avelumab, durvalumab, and atezolizumab, has shown interesting objective response rates (ORRs; 7–26%) across varying GC/GEJC populations, with ORRs potentially higher in PD-L1 + vs PD-L1 − tumors. Safety profiles compare favorably with chemotherapy, with grade ≥3 treatment-related adverse events occurring in 5–17%. Based on a large phase 2 study, pembrolizumab was approved in the United States for third-line treatment of patients with PD-L1 + GC/GEJC. In a phase 3 trial, third-line or later nivolumab increased overall survival vs placebo in an Asian population, leading to regulatory approval in Japan, although other completed phase 3 trials did not show superiority for pembrolizumab or avelumab monotherapy vs chemotherapy. Other trials in advanced GC/GEJC are assessing various anti–PD-1/PD-L1–based strategies, including administration in first-line and later-line settings and as combination (with chemotherapy or agents targeting other immune checkpoint proteins, eg, CTLA-4, LAG-3, and IDO) or switch-maintenance regimens.

Conclusions: Anti–PD-1/PD-L1 antibodies have shown encouraging clinical activity in advanced GC/GEJC. Results from ongoing phase 3 trials are needed to further evaluate the potential roles of these agents within the continuum of care.

Introduction

Gastric cancer (GC) and gastroesophageal junction cancer (GEJC) are a major global health concern [1]. GC is the fifth most common cancer worldwide and the third leading cause of cancer-related death, with > 700,000 attributed fatalities globally per year, the highest number of which are in Eastern Asia [2]. In countries without active screening programs, GC is mostly diagnosed at an advanced stage due

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to its nonspecific symptoms, which is associated with a poor overall survival (OS) [3,4]. GEJC has historically been considered a distinct disease from GC, although both are genomically very close and have similar recommended treatments for advanced disease [5–8]. There has been a shift in the relative incidence of GC vs GEJC, with GC declining and GEJC increasing, particularly in the Western hemisphere. However, GEJC remains far less common than GC overall. Interpretation of GEJC epidemiology has been complicated historically by a lack of uniform classification [9]. The Cancer Genome Atlas project has identified 4 major genomic subtypes found in both GC and GEJC adenocarcinoma: Epstein-Barr virus (EBV)+, microsatellite instable (MSI), genomically stable, and chromosomally instable [5,6]. In addition, the Asian Cancer Research Group has developed an alternative genomic classification system for GC based on 4 subtypes: MSI, microsatellite stable (MSS)/epithelial-to-mesenchymal transition, MSS/TP53+, and MSS/TP53−; the differential survival durations shown for Asian Cancer Research Group subtypes have been validated in independent cohorts [10].

Cytotoxic chemotherapy is the basis of treatment for most patients with advanced GC/GEJC, with choice of regimen directed by patient performance status, human epidermal growth factor receptor 2 (HER2) expression, and treatment history [7,11–13]. Although various chemotherapy regimens have shown antitumor activity, their toxicity profiles may limit their extended use in a patient population that is often frail and cachectic [11,14]. First-line (1L) chemotherapy for patients with HER2− GC/GEJC varies between countries [7,11,12]; however, combination chemotherapy that includes a fluoropyrimidine and platinum agent is commonly administered and is associated with a median OS of approximately 8–13 months [7]. Fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI) and taxane-based regimens have shown similar OS rates [15,16]. It was recently reported in a press release that a phase 3 trial of ramucirumab (an antiangiogenic agent) vs placebo in combination with cisplatin and capecitabine or 5-FU as 1L treatment for patients with HER2– GC/GEJC met its primary endpoint of progression-free survival (PFS) but failed to improve OS [17]. For the 6–30% of patients with HER2+ GC/GEJC [18], trastuzumab in combination with fluoropyrimidine and platinum-based chemotherapy is the standard of care based on a demonstrated OS benefit (median 14 vs 11 months with chemotherapy alone) [19]. In a separate study, adding pertuzumab to the standard trastuzumab/chemotherapy combination did not prolong OS [20]. Other targeted therapies have so far failed to improve clinical outcomes, as seen in trials of epidermal growth factor receptor antibodies (cetuximab or panitumumab) added to platinum-based chemotherapy vs chemotherapy alone in unselected patients with GC/GEJC [21] or esophagogastric cancer [22], and selective MET receptor ligand inhibitors (rilotumumab or onartuzumab) vs placebo added to chemotherapy in patients with MET+ GC/GEJC [23,24]. Across different regions, various second-line (2L) treatments are administered to patients with advanced GC/GEJC [7,11,12], such as FOLFIRI, irinotecan, and taxane-based regimens [16,25], and ramucirumab with or without paclitaxel [26,27]. In randomized trials in the 2L setting, the median OS for ramucirumab vs placebo was 5.2 vs 3.8 months (hazard ratio [HR], 0.776; $P = 0.047$) and for ramucirumab and paclitaxel vs paclitaxel alone was 9.6 vs 7.4 months (HR, 0.807; $P = 0.017$) [26,27]. However, ramucirumab is associated with rates of grade ≥3 treatment-related adverse events (TRAEs) of approximately 60% when administered as monotherapy and ≥80% in combination with paclitaxel [26,27]. Following recent approvals of anti–programmed death 1 (PD-1) antibodies pembrolizumab, in the United States for programmed death ligand 1 (PD-L1)+ tumors, and nivolumab, in Japan, third-line (3L) treatment has evolved to include immunotherapy regimens [28,29], and patients with adequate performance status may otherwise receive chemotherapy regimens not previously received [25]. Because existing treatments generally do not result in durable antitumor responses in any line and OS remains short, novel strategies with the potential to extend treatment response and benefit a wider range of patients are needed.

Rationale for maintenance therapy in GC/GEJC

Although 1L chemotherapy for advanced GC/GEJC may be administered until disease progression, duration of combination treatment may be limited by toxicity [7,14,30]. Maintenance therapy, ie, continuation of an agent given as part of the 1L induction regimen or sequential treatment with a different agent until progression in patients with nonprogressive disease (switch maintenance), is an established treatment strategy for several advanced tumors, including colorectal cancer, ovarian cancer, and non-small cell lung cancer, based on studies showing significant prolongation of PFS and OS [31–33]. Unlike combination approaches, switch maintenance avoids the potential for additive toxicity with agents administered concurrently and may limit the overall duration of treatment with cytotoxic chemotherapy while enabling potential synergistic activity between agents with different mechanisms of action [31–33].

Small studies have suggested that fluoropyrimidine-based maintenance therapy is feasible in patients with GC/GEJC, although data are limited [34–36]. Trastuzumab and ramucirumab are administered until disease progression [7]; thus, their clinical efficacy benefits in patients with GC/GEJC may be due in part to maintenance treatment [19]. There is ongoing interest in identifying tolerable agents for maintenance therapy with the aim of prolonging the benefits of systemic chemotherapy in a wider population of patients with GC/GEJC, and initial studies of immunotherapy in this setting are discussed later.

Rationale for checkpoint inhibitors in GC/GEJC

The development and progression of tumors are characterized by evasion of immune responses, including tumor escape mediated through immune checkpoint pathways [37–40]. The etiology of GC/GEJC in some patients has been associated with immunosuppressive treatment for organ transplants and viral infections [41,42], suggesting that the immune system plays an important role in tumor control. Furthermore, key immune checkpoint proteins, including cytotoxic T-lymphocyte antigen 4 (CTLA-4), indoleamine 2,3-dioxygenase (IDO), T-cell immunoglobulin and mucin domain-containing protein 3, lymphocyte activation gene 3 protein (LAG-3), and PD-1, are overexpressed on immune cells in patients with GC/GEJC, suggesting a role for tumor-induced T-cell exhaustion in disease progression [43–45]. PD-1 (expressed on immune cells) and its ligand, PD-L1 (expressed on immune and tumor cells), are expressed on up to 50% of GC/GEJC tumors [46,47]; expression has been associated with a worse prognosis [48,49], although occasional studies have found a reverse correlation [43]. By overexpressing PD-L1 directly or inducing PD-L1 expression on immune cells, cancer cells exploit the PD-1/PD-L1 pathway to promote an immunosuppressive environment and allow immune escape and hence tumor growth [50,51]. Antibodies that block checkpoint proteins can restore and enhance antitumor activity of T cells by blocking inhibitory signals (Fig. 1) [52,53]. Furthermore, some GC/GEJC tumors have a high mutational burden, particularly MSI-high tumors [5], creating tumor neoantigens that can be targeted by immune responses. A high tumor mutational burden has been shown to predict durable clinical benefit with anti–PD-1/PD-L1 treatment in various tumors [54,55]. The potential of immunotherapy for advanced GC/GEJC was initially suggested in preliminary studies showing increased immune activation and antitumor responses following treatment with polysaccharide-K, picibanil, and the bacillus Calmette–Guérin vaccine [42]. Furthermore, it is well established that chemotherapy may increase tumor immunogenicity and potentially increase susceptibility to subsequent checkpoint inhibitor therapy [56], which may be highly relevant to the GC/GEJC treatment landscape.

It has been reported that GC tumors exhibit distinct gene expression signatures related to T-cell function in Asian vs non-Asian patients. Specifically, tumors in non-Asian patients showed higher expression of markers associated with T-cell activity, including CTLA-4, CD3,

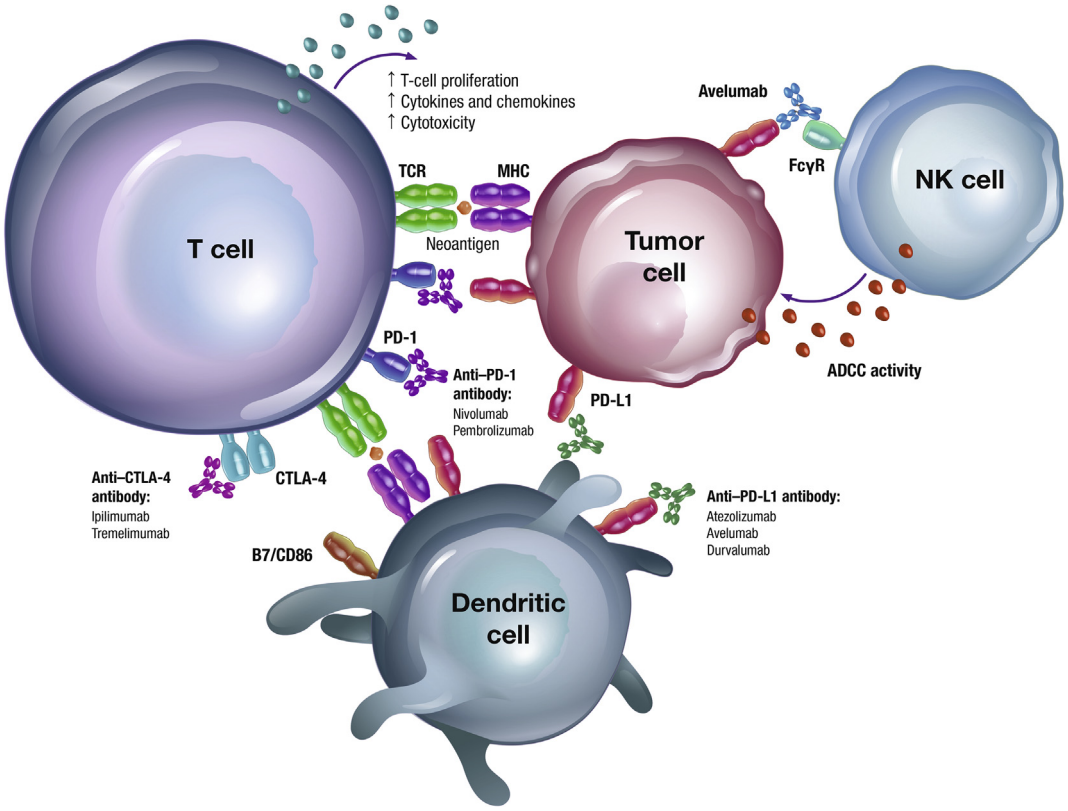

Fig. 1. Overview of immune pathways and actions of checkpoint inhibitors. The role of immune checkpoint inhibitors in restoring antitumor activity. Immune checkpoint proteins are expressed on the surface of T cells that interact with their ligands on antigen-presenting cells (eg, dendritic cells), resulting in tumor immune evasion. Immune checkpoint inhibitors (anti–programmed death 1 [PD-1]/programmed death ligand 1 [PD-L1] and anti–cytotoxic T-lymphocyte–associated antigen 4 [CTLA-4] antibodies) prevent the receptors and ligands from binding and promote T-cell–mediated antitumor responses. A potential role for antibody-dependent cellular cytotoxicity (ADCC) in avelumab's mechanism of action is also depicted. MHC, major histocompatibility complex; NK, natural killer; TCR, T-cell receptor.

CD45R0, and CD8, and lower expression of the immunosuppressive T-regulatory cell marker FOXP3, compared with those in Asian patients [57]. Furthermore, a meta-analysis of data from various cancers found that expression of PD-L1 on tumor-infiltrating immune cells was an indicator of a favorable prognosis in non-Asian patients but not in Asian patients [58]. Thus, evaluation of the effects of immunotherapy in both Asian and non-Asian populations with GC/GEJC is an important consideration.

The remainder of this review focuses on clinical trials of various immune checkpoint inhibitors (Fig. 1) in GC/GEJC, including completed or ongoing trials.

Phase 1 and 2 trials of checkpoint inhibitors as 2L or later treatment after progression on prior chemotherapy

Monotherapy

The first study of a checkpoint inhibitor in GC/GEJC was a small phase 2 trial of tremelimumab (anti–CTLA-4), performed in 18 patients with metastatic gastric or esophageal adenocarcinoma (Table 1). In this study, the objective response rate (ORR) was low (1 of 18 patients [6%]), but the responding patient (with esophageal adenocarcinoma) experienced a durable response and remained on treatment after 32.7 months [59]. The first study of an anti–PD-1 antibody in advanced GC/GEJC was KEYNOTE-012, a phase 1b study of pembrolizumab in 39 patients with recurrent or metastatic PD-L1 + (≥1% tumor cell cutoff; 22C3 assay) GC/GEJC adenocarcinoma; 33 of the 39 patients had received prior therapy for metastatic disease, and 2 additional patients had received adjuvant therapy only [60]. The ORR adjudicated by central review was 22%, based on 8 partial responses, with no significant difference between Asian and non-Asian patients (24% vs 21%, respectively), and the median OS was 11.4 months overall. Grade ≥3 TRAEs occurred in 13% of patients. Following these encouraging results, a large phase 2 trial of pembrolizumab in patients with GC/GEJC, comprising 3 cohorts, was initiated (KEYNOTE-059) [61]. Cohort 1 represents the largest early-phase trial of a checkpoint inhibitor in GC/GEJC, enrolling 259 patients who received pembrolizumab monotherapy as 3L or later treatment [61]. The ORR in this cohort was 12%, with a trend for higher ORR in PD-L1 + vs PD-L1 − tumors (16% vs 6%, respectively; PD-L1 status was based on a combined positive score of ≥1%, ie, PD-L1 + tumor or immune cells; 22C3 assay), and median OS was 5.5 months. Grade ≥3 TRAEs occurred in 18% of patients. Results from this cohort led to the accelerated approval of pembrolizumab by the US Food and Drug Administration (FDA) as 3L treatment for patients with advanced PD-L1 + GC/GEJC [28]. Results from the other 2 cohorts of the KEYNOTE-059 trial are summarized in later sections of this review.

Treatment with nivolumab (anti–PD-1) with or without ipilimumab (anti–CTLA-4) was assessed in 160 pretreated patients with advanced GC/GEJC or adenocarcinoma of the esophagus in the phase 1/2 CheckMate 032 study [62]. Patients were enrolled into 3 subgroups, including 1 that received nivolumab monotherapy (3 mg/kg). In this subgroup, the ORR was 12%, and patients with PD-L1 + vs PD-L1 − tumors (based on a ≥ 1% tumor cell cutoff; 28-8 assay) had a trend for a higher ORR (19% and 12%, respectively), and median OS was 6.2 months. Grade 3/4 TRAEs occurred in 17% of patients. Nivolumab monotherapy is also being assessed in an ongoing open-label phase 1/2 study that is recruiting a subgroup of patients with EBV + advanced GC (NCT02488759).

Data from 2 studies of avelumab, an anti–PD-L1 antibody, in

Table 1
Summary of data from early-phase trials of checkpoint inhibitors including patients with advanced GC/GEJC.

Trial	Phase	Treatment	Patients by tumor type, n	PD-L1 status	Patients by treatment line, n	ORR, %	Median PFS, months (except where stated)	Median OS, months
2L or later therapy								
KEYNOTE-012 (NCT01848834)	1	Pembrolizumab	GC: 39	PD-L1 +	1L: 4 2L + : 35	22	1.9	11.4
JAVELIN Solid Tumor (NCT01772004)	1	Avelumab	GC or GEJC: 62	Unselected	2L + : 62	Overall: 10[a] PD-L1 + : 29[a] PD-L1 − : 7[a]	Overall: 6.0 wks[a] PD-L1 + : 6.3 wks[a] PD-L1 − : 10.4 wks[a]	Not reported
JAVELIN Solid Tumor JPN (NCT01943461)	1	Avelumab	GC or GEJC: 20	Unselected	2L + : 20	15	PD-L1 + : 12.3 wks PD-L1–: 11.1 wks	Not reported
CP1108 (NCT01693562)	1	Durvalumab	Not reported	Unselected	2L + : 28	7	Not reported	Not reported
GO27831 (NCT01375842)	1	Atezolizumab	GC: 6	Unselected	2L + : 6	17	Not reported	Not reported
I4T-MC-JVDF/ KEYNOTE-098 (NCT02443324)	1	Ramucirumab + pembrolizumab	GC: 16 GEJC: 25	Unselected	2L + : 41	7	2.6	6.2
I4T-MC-JVDJ (NCT02572687)	1	Ramucirumab + durvalumab	GC: 19 GEJC: 7	Unselected	2L: 19 3L: 6	15	Not reported	Not reported
CheckMate 032 (NCT01928394)	1/2	N3: nivolumab 3 mg/kg; N1I3: nivolumab 1 mg/kg + ipilimumab 3 mg/kg; N3I1: nivolumab 3 mg/kg + ipilimumab 1 mg/kg	GC, N3: 19 N1I3: 22 N3I1: 18 GEJC, N3: 40 N1I3: 27 N3I1: 34	Unselected	1L, N3: 0 N1I3: 1 N3I1: 0 2L, N3: 10 N1I3: 6 N3I1: 16 3L + , N3: 49 N1I3: 42 N3I1: 36	N3 overall: 12 PD-L1 + : 19 PD-L1 − : 12 N1I3 overall: 24 PD-L1 + :40 PD-L1 − : 22 N3I1 overall: 8 PD-L1 + : 23 PD-L1 − : 0	N3: 1.4 N1I3: 1.4 N3I1: 1.6	N3: 6.2 N1I3: 6.9 N3I1: 4.8
No identifier reported	2	Tremelimumab	GC: 6 GEJC: 6 EC: 6	Unselected	2L: 18	6	2.8	4.8
KEYNOTE-059 cohort 1 (NCT02335411)	2	Pembrolizumab	GC: 124 GEJC: 134	Unselected	3L + : 259	Overall: 12 PD-L1 + : 16 PD-L1 − : 6	2.0	5.5
1L therapy								
I4T-MC-JVDF/ KEYNOTE-098 (NCT02443324)	1	Ramucirumab + pembrolizumab	GC: 18 GEJC: 10	Unselected	1L: 28	14	5.6	Not reported
KEYNOTE-059 cohort 2 (NCT02335411)	2	Pembrolizumab + cisplatin + 5-FU or capecitabine	GC: 20 GEJC: 5	Unselected	1L: 25	60 PD-L1 + : 69 PD-L1 − : 38	6.6	13.8
KEYNOTE-059 cohort 3 (NCT02335411)	2	Pembrolizumab	GC: 19 GEJC: 12	PD-L1 +	1L: 31	26	3.3	20.7
1L maintenance therapy								
JAVELIN Solid Tumor (NCT01772004)	1b	Avelumab	GC or GEJC: 89	Unselected	1L Mn: 89	Overall: 9 PD-L1 + : 9 PD-L1 − : 5	Overall: 12.0 wks PD-L1 + : 17.6 wks PD-L1 − : 11.6 wks	Not reported
CA184-162 (NCT01585987)	2	Ipilimumab vs BSC	GC: 95 GEJC: 19	Unselected	1L Mn, Ipilimumab: 57 BSC: 57	Ipilimumab: 2 BSC: 7	Ipilimumab: 2.7 BSC: 4.9	Ipilimumab: 12.7 BSC: 12.1

1L, first line; 2L, second line; 3L, third line; 5-FU, 5-fluorouracil; BSC, best supportive care; EC, esophageal cancer; GC, gastric cancer; GEJC, gastroesophageal junction cancer; Mn, maintenance; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1.
[a] Unconfirmed.

patients with GC/GEJC, have been reported to date. In the JAVELIN Solid Tumor trial, avelumab was administered to a large phase 1b cohort of patients with locally advanced or metastatic GC/GEJC unselected for PD-L1 expression [63]. A total of 151 patients were enrolled, including a subgroup of 62 patients who received avelumab as 2L or later treatment. In an interim analysis from this subgroup, the unconfirmed ORR was 10%, and clinical activity was seen irrespective of PD-L1 expression status (based on a ≥ 5% tumor cell cutoff; 73-10 assay). Avelumab was associated with an acceptable safety profile, including grade ≥3 TRAEs in 10% of patients. OS data were not mature at the time of reporting [63]. Avelumab has also been studied in a phase 1 expansion cohort of Japanese patients with advanced GC/GEJC that progressed after chemotherapy (JAVELIN Solid Tumor JPN) [64]. In the first 20 patients enrolled, the ORR was 15% based on partial responses in 3 patients, and there was 1 grade 3 TRAE (5%).

Data have been reported following durvalumab (anti–PD-L1)

treatment in 28 patients with previously treated gastroesophageal cancer within a phase 1 trial. The ORR was 7%, and grade ≥3 TRAEs occurred in 17% [65]. Durvalumab is also being evaluated in a phase 1/2 study as monotherapy in patients with advanced GC/GEJC (NCT02340975), but no data have been reported to date. In addition, in a phase 1 study of atezolizumab (anti–PD-L1) in patients with various solid tumors, 1 of 6 patients with GC had a confirmed response [66].

Combination therapy

In addition to assessing nivolumab monotherapy, the phase 1/2 CheckMate 032 study assessed combination therapy with different doses of nivolumab plus ipilimumab (N1I3: nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; N3I1: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg) in pretreated patients with advanced GC/GEJC or adenocarcinoma of the esophagus [62]. In the N1I3 and N3I1 subgroups, ORRs were 24% and 8%, respectively, and similar to those in the monotherapy setting; patients with PD-L1+ vs PD-L1− tumors (≥1% tumor cell cutoff; 28-8 assay) had trends for higher ORRs in both combination groups. The median OS durations in the N1I3 and N3I1 subgroups were 6.9 and 4.8 months, respectively. Grade ≥3 TRAEs occurred in 47% and 27% of patients in the N1I3 and N3I1 subgroups, respectively, and occurred more often compared with nivolumab monotherapy in the same study (17%).

Phase 1 and 2 trials of checkpoint inhibitors as 1L therapy

Monotherapy

In addition to patients with previously treated GC/GEJC, pembrolizumab monotherapy was also investigated as 1L treatment in cohort 3 of the phase 2 KEYNOTE-059 trial [61]. In the 31 patients enrolled, who all had PD-L1+/HER2− tumors, the ORR was 26%, median OS was 20.7 months, and grade ≥3 TRAEs occurred in 23% [61].

Combination therapy

In cohort 2 of KEYNOTE-059, 25 patients with advanced HER2− GC/GEJC received 1L treatment with pembrolizumab in combination with 5-FU/cisplatin chemotherapy [61]. The ORR was 60%, and there was a potential association between PD-L1+ tumors (≥1% combined positive score based on tumor or immune cells; 22C3 assay) and higher ORR (69% and 38% in patients with PD-L1+ vs PD-L1− tumors, respectively). Median OS was 13.8 months. The incidence of grade 3/4 TRAEs was 76%, which was notably higher than that seen with 1L pembrolizumab monotherapy (23%).

Durvalumab is being evaluated in combination with tremelimumab in a phase 1/2 study in patients with advanced GC/GEJC (NCT02658214), although no data have been reported to date.

Phase 1 and 2 trials of checkpoint inhibitors as 1L maintenance treatment

Based on the encouraging antitumor activity and safety profiles of checkpoint inhibitors in GC/GEJC, there has been considerable interest in assessing whether these agents could provide a clinical benefit as maintenance treatment in patients without disease progression after 1L induction chemotherapy. CA184-162 (NCT01585987) was a phase 2 trial comparing the efficacy of maintenance ipilimumab vs best supportive care (BSC) following 1L chemotherapy in 114 patients with unresectable locally advanced/metastatic GC/GEJC [67]. In the BSC arm, 79% of patients received continued fluoropyrimidine chemotherapy. Ipilimumab did not improve efficacy compared with fluoropyrimidine/BSC (median OS, 12.7 vs 12.1 months, respectively), and grade ≥3 TRAEs occurred in 23% with ipilimumab vs 9% with fluoropyrimidine/BSC, respectively [67]. It remains possible that a small proportion of patients may show a long-term OS benefit with longer follow-up, although the mechanism of action of ipilimumab and its toxicity profile may not be ideal for maintenance treatment in GC/GEJC.

The JAVELIN Solid Tumor trial assessed avelumab maintenance treatment in a subgroup of 89 patients with advanced GC/GEJC without disease progression following 1L induction chemotherapy, representing the first study of an anti–PD-1/PD-L1 agent administered as maintenance treatment in any tumor type [63]. In an interim analysis, the unconfirmed ORR was 9%, comparable to the ORR seen in the 2L subgroup (10%; discussed in an earlier section); however, 2% of patients in the maintenance subgroup had complete responses, which were not seen in the 2L subgroup. Median OS was immature at data cutoff. The safety profile of avelumab was similar in both subgroups.

In addition to ongoing studies of durvalumab monotherapy and combination therapy for advanced GC/GEJC, durvalumab is also being evaluated as maintenance therapy in a separate phase 2 study in patients with advanced GC/GEJC (NCT02678182), but no data have been reported to date.

Phase 3 trials

Following the encouraging efficacy and safety seen in early-phase studies, several phase 3 trials have been initiated to assess anti–PD-1/PD-L1 therapies in patients with advanced GC/GEJC (Table S1). These trials differ in terms of eligible patient population, line of therapy, disease status, and treatment strategy being assessed.

Monotherapy

JAVELIN Gastric 100 (NCT02625610) is the only phase 3 trial assessing switch-maintenance treatment with immunotherapy. This study is comparing avelumab vs continuation of leucovorin + 5-FU + oxaliplatin (FOLFOX) or capecitabine + oxaliplatin (XELOX) in patients with advanced GC/GEJC and without disease progression after 1L induction chemotherapy. The hypothesis for this trial is that avelumab may provide durable antitumor activity following immunogenic priming and tumor shrinkage induced by 1L chemotherapy, with the added benefit of avoiding the toxicity burden of additional chemotherapy or combination therapy. The primary endpoints are PFS and OS, and recruitment is now complete.

Two phase 3 trials were designed to compare 2L pembrolizumab monotherapy vs paclitaxel in non-Asian (KEYNOTE-061; NCT02370498) or Asian (KEYNOTE-063; NCT03019588) patients with advanced PD-L1+ GC/GEJC that progressed after 1L platinum/fluoropyrimidine doublet therapy. A recent press release reported that KEYNOTE-061 did not meet its primary endpoints of superior OS and PFS for pembrolizumab vs paclitaxel [68]; data for KEYNOTE-063, which has completed enrollment, are expected in the near future. Two other phase 3 trials were performed to assess later-line treatment with an anti–PD-1/PD-L1 antibody in patients with GC/GEJC. ATTRACTION-02 (ONO-4538-12; NCT02267343) is a completed phase 3 trial of 3L or later nivolumab vs placebo in 493 Asian patients with unresectable advanced or recurrent GC/GEJC that had positive findings [69]. Prior treatment (including in the adjuvant setting) included 2 lines in 20%, 3 lines in 40%, and ≥4 lines in 40%. In the nivolumab vs placebo arm, median OS (primary endpoint) was 5.3 vs 4.1 months (HR = 0.63; $p < 0.0001$), and ORR was 11% vs 0% ($P < 0.0001$). Nivolumab efficacy was seen irrespective of PD-L1 status (based on a ≥ 1% cutoff in tumor cells; 28-8 assay). Grade 3/4 TRAEs occurred in 10% of patients treated with nivolumab compared with 4% in the placebo arm. Based on this trial, the Japanese Ministry of Health, Labour, and Welfare approved nivolumab in September 2017 for the treatment of unresectable advanced or recurrent GC progressed after chemotherapy [29]. JAVELIN Gastric 300 (NCT02625623) is a global

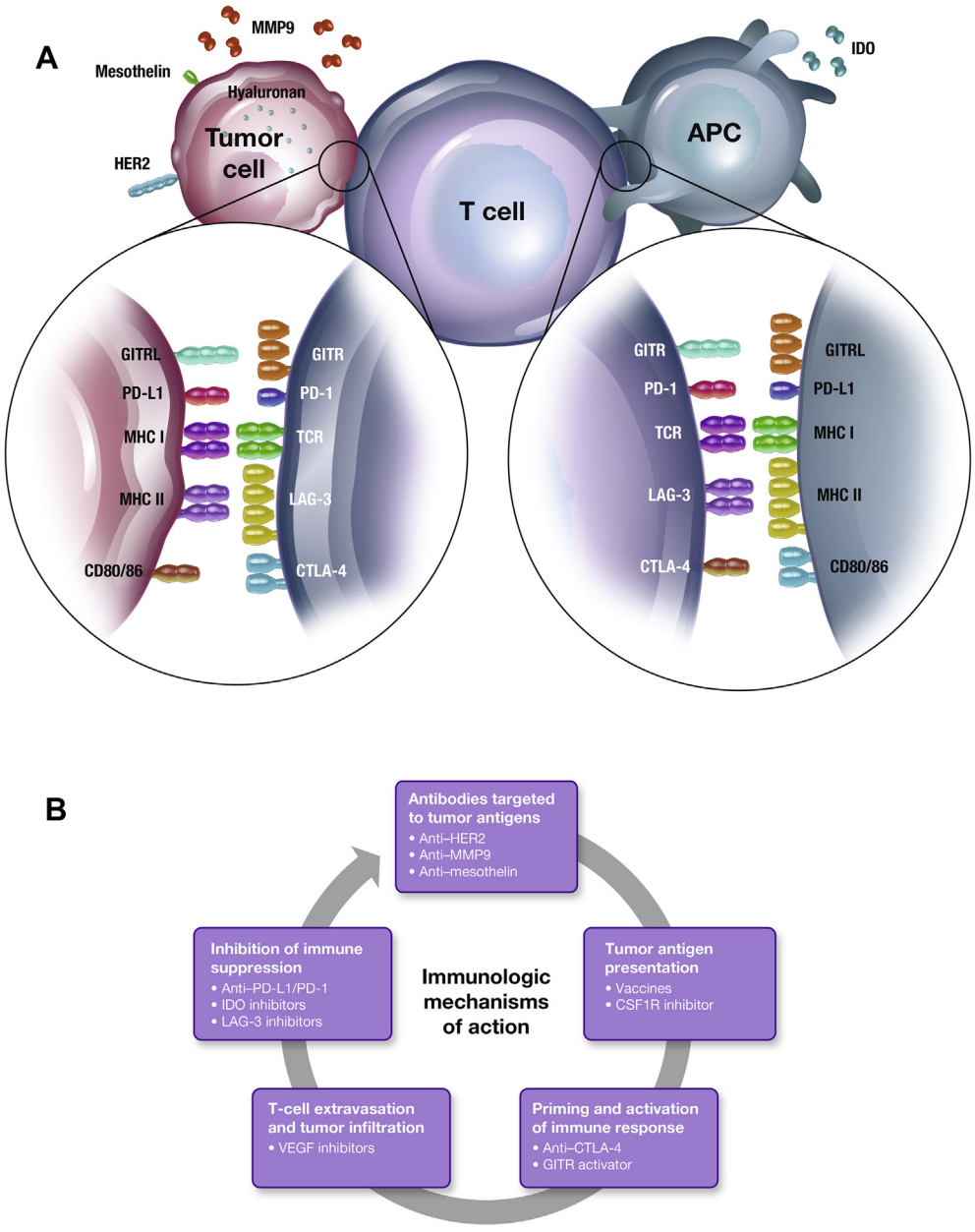

Fig. 2. Overview of potentially synergistic pathways targeted by trials of novel checkpoint inhibitor-based combinations in patients with gastric cancer or gastroesophageal junction cancer. (A) Strategies to activate T cells against tumors may include targeting of both inhibitory and activating immune receptors, resulting in a robust and durable antitumor immune response. (B) Because tumors may limit immune responses through multiple mechanisms, simultaneous targeting of multiple pathways may be required to reinitiate antitumor responses. APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; CSF1R, macrophage colony-stimulating factor 1 receptor; GITR, glucocorticoid-induced tumor necrosis factor receptor (TNFR)-related protein; GITRL, GITR ligand; HER2, human epidermal growth factor 2; IDO, indoleamine 2,3-dioxygenase; LAG-3, lymphocyte activation gene 3 protein; MHC, major histocompatibility complex; MMP9, matrix metallopeptidase-9; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TCR, T-cell receptor; VEGF, vascular endothelial growth factor.

randomized trial of 3L avelumab compared with investigator choice of chemotherapy (either paclitaxel or irinotecan) performed in 371 patients with advanced GC/GEJC progressed or relapsed after 2 prior lines of treatment, unselected for PD-L1 expression and stratified by region (Asia vs non-Asia), with all patients receiving BSC as background therapy. Thus, JAVELIN Gastric 300 differs to ATTRACTION-02 in terms of its choice of control arm (chemotherapy instead of placebo) and patient treatment history (receiving study treatment as 3L treatment only instead of 3L or later). It has been reported in a press release that the trial did not meet its primary endpoint of superior OS for avelumab vs chemotherapy [70]. Although full details for the KEYNOTE-061 and JAVELIN Gastric 300 phase 3 trials are awaited, the reported outcomes suggest that monotherapy with anti–PD-1/PD-L1 agents is not superior to chemotherapy as later-line treatment for advanced GC/GEJC, supporting trials assessing alternative immunotherapy-based treatment options and different settings.

Combination therapy

Ongoing phase 3 trials assessing checkpoint inhibitor–based combination therapy in the 1L setting are KEYNOTE-062 (NCT02494583), a trial of pembrolizumab alone or in combination with cisplatin/5-FU vs cisplatin/5-FU alone in patients with PD-L1 + /HER2 − advanced GC/GEJC, and CheckMate 649 (NCT02872116), a 3-arm trial of nivolumab plus ipilimumab, nivolumab plus investigator choice of chemotherapy (XELOX or FOLFOX), or XELOX/FOLFOX alone in patients with previously untreated advanced or metastatic GC/GEJC. The primary endpoint in both studies is OS in patients with PD-L1 + tumors. Enrollment in KEYNOTE-062 is complete.

In addition, ATTRACTION-04 (ONO-4538-37; NCT02746796) is a phase 2/3 trial evaluating the safety and efficacy of 1L nivolumab plus S-1 (tegafur/gimeracil/oteracil potassium) plus oxaliplatin (SOX) therapy or capecitabine plus oxaliplatin (CAPOX) therapy in Asian patients with unresectable advanced or recurrent GC/GEJC. Interim safety and clinical activity data in 39 patients from part 1 of the study were reported recently [69]. The ORR for patients treated with

nivolumab/SOX and nivolumab/CAPOX was 67% and 71%, respectively. Grade ≥3 TRAEs, most of which were common side effects of chemotherapy, occurred in 52% and 67% of patients, respectively, and there was no difference in activity and safety between the 2 regimens. Part 2 of this study, a randomized comparison of nivolumab vs placebo in combination with SOX/CAPOX, is ongoing, and results are awaited.

Ongoing phase 3 trials in the neoadjuvant/adjuvant setting are ONO-4538-38 (NCT03006705), a trial of nivolumab in combination with S-1 or CAPOX vs S-1 or CAPOX alone in patients with resected GC/GEJC; CheckMate 577 (NCT02743494), a trial of nivolumab vs placebo in patients with esophageal cancer or GEJC after chemoradiotherapy and surgery; and KEYNOTE-585 (NCT03221426), a trial comparing pembrolizumab plus chemotherapy vs chemotherapy alone as neoadjuvant or adjuvant treatment for untreated patients with GC/GEJC.

Trials of novel checkpoint inhibitor-based combinations in GC/GEJC

Immunotherapy-based combinations are an increasing focus within oncology. Combining immunotherapy with a targeted antiangiogenic agent may take advantage of complementary mechanisms of action for the treatment of GC/GEJC [56]. In addition, preclinical studies suggest that vascular endothelial growth factor has immunomodulatory activity that may be blocked by antiangiogenic agents, providing a further rationale for combinations with checkpoint inhibitors [71,72]. In an ongoing phase 1 study of durvalumab plus ramucirumab in patients with various advanced malignancies, the preliminary ORR in patients with unresectable or metastatic GC/GEJC who had received 1–2 prior lines of treatment was 15%, and grade 3 TRAEs occurred in 19% (no grade 4 or 5 TRAEs) [73]. In a phase 1 study of pembrolizumab plus ramucirumab in 69 patients with advanced GC/GEJC receiving 1L or later treatment, ORR in the 1L and 2L or later subgroups was 14% and 7%, and grade ≥3 TRAEs occurred in 39% and 27%, respectively [74]. Thus, these 2 studies suggest no additive activity for ramucirumab combined with a checkpoint inhibitor. Other ongoing trials of checkpoint inhibitors plus antiangiogenic agents include trials of atezolizumab plus bevacizumab with or without chemotherapy (NCT01633970) and nivolumab plus ramucirumab (NCT02999295).

In addition to CTLA-4 and PD-1/PD-L1, other suppressive immune checkpoint proteins include LAG-3 (a lymphocyte surface protein) and IDO (an enzyme that catabolizes tryptophan, creating an immunosuppressive tumor microenvironment), and inhibitors of these proteins may work in synergy with anti–PD-1/PD-L1 antibodies to produce a more robust antitumor immune response (Fig. 2) [75]. Trials examining this strategy in which enrollment of patients with GC is specified in the trial record include nivolumab plus BMS-986016 (anti–LAG-3; NCT01968109) and pembrolizumab plus epacadostat (IDO inhibitor; NCT02178722; NCT03196232), and other similar trials are ongoing in patients with various advanced tumors. In addition, FRACTION-GC (NCT02935634) is assessing nivolumab plus BMS-986016 (LAG-3 inhibitor) or ipilimumab specifically in patients with advanced GC. An alternate strategy to enhance antitumor responses would be to combine a checkpoint inhibitor with an agonist antibody that activates a co-stimulatory receptor expressed on T cells. For example, the combination of INCAGN01876 (anti–glucocorticoid-induced tumor necrosis factor receptor–related protein) and nivolumab with or without ipilimumab (vs ipilimumab alone) is being tested in patients with advanced or metastatic tumors, including a cohort of patients with advanced GC/GEJC (NCT03126110).

Combining checkpoint inhibitors with antibodies targeted to proteins overexpressed on tumors is another rational treatment strategy; for example, combining anti-HER2 antibodies with immunotherapy may enhance antibody-dependent cell-mediated cytotoxicity against tumor cells by natural killer cells [76]. Studies investigating this approach are combining treatment with pembrolizumab and trastuzumab (NCT02901301) or margetuximab (NCT02689284) in patients with HER2+ advanced GC/GEJC or combining nivolumab and andecalixizimab (anti–matrix metallopeptidase-9; NCT02864381). Finally, another trial (NCT03122548) is investigating a combination of pembrolizumab and CRS-207, a live attenuated *Listeria monocytogenes* vaccine genetically engineered to overexpress mesothelin, in patients with advanced GC/GEJC.

Novel biomarkers for checkpoint inhibitors in GC/GEJC

Four major genomic subtypes of GC/GEJC adenocarcinoma have been identified [5], of which the MSI-high subtype (8–37% of cases) has been associated with preferential response to checkpoint inhibitor therapy in various tumors [77]. Similarly, in the KEYNOTE-012 and KEYNOTE-059 (cohort 1) trials, patients with MSI-high GC/GEJC tumors had a higher probability of response to pembrolizumab [60,78]. Pembrolizumab was recently granted accelerated approval by the FDA for treatment of patients with unresectable or metastatic, MSI-high, or mismatch repair–deficient solid tumors that progressed after prior treatment [28].

Other potential biomarkers that have been evaluated to identify patients with GC/GEJC most likely to respond to checkpoint inhibitor therapy have included PD-L1 expression, gene expression signatures, serum soluble factors, T-cell subsets, and tumor mutational burden [79]. The association between PD-L1 expression and response to checkpoint inhibitors has been inconsistent across tumor types and between agents. In early trials in GC/GEJC, a potential trend for higher ORRs associated with PD-L1+ status was reported with different agents, although responses were also noted in PD–L1− tumors (Table 1) [61–64]. The recent US approval of pembrolizumab as 3L or later treatment of advanced GC/GEJC was only in patients with PD-L1+ tumors (≥1% cutoff), based on the higher ORR seen in this subgroup (16% vs 6% for PD-L1−) [28]. The definition of PD-L1+ GC/GEJC is based on a combined positive score, which includes assessment of PD-L1 expression on tumor cells, lymphocytes, and macrophages; this is different than the definition of PD-L1+ non-small cell lung cancer, which is based on assessment of tumor cells only [28]. Given the trends noted in the early KEYNOTE trials, eligibility based on PD-L1+ status is a feature of pembrolizumab phase 3 trials in advanced GC/GEJC. However, as noted above, the phase 3 KEYNOTE-061 trial failed to show superiority for pembrolizumab vs chemotherapy in patients with PD-L1+ tumors [68]. Furthermore, in the phase 3 trial of 3L nivolumab vs placebo in Asian patients (ATTRACTION-02), efficacy benefits were seen irrespective of PD-L1 expression [69].

Gene expression signatures may provide insights into the molecular features associated with response to checkpoint inhibitors. For example, KEYNOTE-012 showed a nonsignificant trend toward longer survival with pembrolizumab treatment for tumors characterized by an interferon γ gene signature ($P = 0.07$) [60]. Cohort 1 of KEYNOTE-059 showed a positive association between a T-cell–inflamed gene expression signature and response to pembrolizumab ($P = 0.014$) [78]. Separate studies have shown the T-cell–inflamed phenotype includes tumors within all GC genomic subtypes [80]. *Helicobacter pylori* and EBV infections induce a T-cell response in gastric tissues and increase PD-L1 expression, suggesting another subset of cancers that may preferentially respond to checkpoint inhibitor therapy [81,82]; however, clinical data to confirm this hypothesis are lacking. Finally, a phase 2 trial has been initiated that will analyze pembrolizumab treatment in relation to gene expression profiling, copy number variations, Lauren classification, EBV/TP53 status, and integrative genomic analysis (NCT02589496); this hypothesis-generating approach will hopefully lead to better understanding of the predictive value of these biomarkers.

Safety profile of checkpoint inhibitors in patients with GC/GEJC

Overall, checkpoint inhibitors are generally better tolerated than chemotherapy regimens administered to patients with GC/GEJC.

Table 2
Treatment-related adverse events associated with checkpoint inhibitors in GC/GEJC.

Treatment	Trial	Any TRAE, %	Grade ≥ 3 TRAEs		Grade ≥ 3 irAEs	
			%	Most common	%	Most common
Monotherapy						
Pembrolizumab (anti–PD-1)	KEYNOTE-012	67	13	Fatigue	5	Pneumonitis, hyperthyroidism
	KEYNOTE-059 (cohort 1)	61	18	Anemia, fatigue, dehydration	5	Colitis, pneumonitis
	KEYNOTE-059 (cohort 3)	77	23	Neutropenia, diffuse uveal melanocytic proliferation, colitis, bile duct obstruction, decreased neutrophils, dehydration, hyponatremia, rash	Grade 3: 7 Grade 5: 3	Grade 3: colitis, rash Grade 5: pneumonitis
Nivolumab (anti–PD-1)	CheckMate 032	69	17	Elevated AST, elevated ALT	Not reported	Not reported
	ATTRACTION-02	Nivolumab: 43 Placebo: 27	Nivolumab: 10 Placebo: 4	Nivolumab: decreased appetite, diarrhea, elevated AST, fatigue Placebo: fatigue, decreased appetite	Not reported	Not reported
Avelumab (anti–PD-L1)	JAVELIN Solid Tumor	59	10	Anemia, asthenia, decreased platelet count, elevated GGT, fatigue	1.3	Colitis, adrenal insufficiency
	JAVELIN Solid Tumor JPN	90	5	Elevated ALT	Not reported	Not reported
Durvalumab (anti–PD-L1)	CP1108	54	17	Not reported	Not reported	Not reported
Tremelimumab	No identifier reported	83	17	Atrial fibrillation, elevated AST, diarrhea	Not reported	Not reported
Ipilimumab	CA184-162	Ipilimumab: 72 BSC: 56	Ipilimumab: 23 BSC: 9	Ipilimumab: diarrhea, fatigue, asthenia, hypothyroidism BSC: palmar-plantar erythrodysesthesia	Not reported	Not reported
Combination therapy						
Pembrolizumab + 5-fluorouracil	KEYNOTE-059 (cohort 2)	100	76	Neutropenia, stomatitis	16	Palmar-plantar erythrodysesthesia
Nivolumab + ipilimumab	CheckMate 032	N1/I3: 84 N3I1: 75	N1/I3: 47 N3I1: 27	N1/I3: diarrhea, elevated ALT, elevated AST N3I1: elevated ALT, diarrhea, elevated AST	Not reported	Not reported
Ramucirumab + durvalumab	I4T-MC-JVDJ	65	19	Hypertension	Not reported	Not reported
Ramucirumab + pembrolizumab	I4T-MC-JVDF/ KEYNOTE-098	1L: 82 2L: 80	1L: 39 2L+: 27	1L: hypertension 2L+: colitis, hypertension	Not reported	Not reported

1L, first line; 2L, second line; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSC, best supportive care; GC, gastric cancer; GEJC, gastroesophageal junction cancer; GGT, γ-glutamyl transferase; irAE, immune-related adverse event; N1I3: nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; N3I1: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TRAE, treatment-related adverse event.

Although direct comparisons have not been performed, the profile of side effects that occur with different anti–PD-1/PD-L1 inhibitors are broadly similar (Table 2) [60–64,69]. The most common TRAEs of any grade across the different agents include fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, and rash. In addition, infusion-related reactions occur in approximately 13% of patients treated with avelumab; these reactions are typically low grade and occur during the first 1 to 2 infusions [63]. The incidence of grade ≥3 TRAEs with anti–PD-1/PD-L1 monotherapy in patients with GC/GEJC ranges from approximately 10% to 20%, with the most common events including fatigue, anemia, and elevated alanine and aspartate aminotransferase levels (Table 2). Checkpoint inhibitor therapy is also associated with immune-related AEs (irAEs) that may affect rheumatic, gastrointestinal, skin, pulmonary, endocrine, neurological, hepatic, cardiac, and renal tissues [83]. In studies of patients with GC/GEJC, the most common grade ≥3 irAEs were pneumonitis and colitis. Compared with the rates of TRAEs with anti–PD-1/PD-L1 monotherapy, higher rates have been associated with anti–CTLA-4 antibodies and combination regimens [84]. Although AEs with checkpoint inhibitors are manageable in most cases through treatment interruption and corticosteroid treatment, long-term sequelae and deaths due to irAEs have been reported in a small proportion of patients [83], highlighting the need for education of healthcare professionals and patients, close monitoring, and multidisciplinary collaboration to effectively manage these AEs.

Conclusions

Treatment of advanced GC/GEJC remains an area of great unmet medical need, and new and effective therapeutic strategies are needed across all lines of therapy. Anti–PD-1/PD-L1 antibodies have shown efficacy and tolerability in patients with GC/GEJC [60–64,67,69,74]. The phase 3 trial of nivolumab vs placebo in Asian patients with ≥2 prior lines of treatment confirmed that checkpoint inhibitors can prolong OS compared with placebo [69], leading to the approval of nivolumab in Japan for this patient population, irrespective of PD-L1 status [29]. Although the results seen with pembrolizumab administered as 3L or later treatment for patients with advanced PD-L1+ GC/GEJC in KEYNOTE-059 led to accelerated approval in the United States [28], subsequent phase 3 data from KEYNOTE-061 and JAVELIN Gastric 300 did not show improved efficacy for pembrolizumab or avelumab compared with chemotherapy [68]. Taken together, these results suggest that chemotherapy is the most relevant comparator for randomized studies assessing 2L or later treatment of advanced GC/GEJC. The optimal strategy for incorporating checkpoint inhibitors in the continuum of care for patients with advanced GC/GEJC is unknown, and a range of other strategies is being assessed in phase 3 trials, including monotherapy, maintenance therapy, and combination therapy in earlier lines. The role of checkpoint inhibitors in the premetastatic setting must also be evaluated, and trials are ongoing. Areas for further study include the development and validation of novel biomarkers to identify

patients most likely to respond to treatment and characterization of outcomes with checkpoint inhibitors in different genomically defined disease subgroups. Future developments are eagerly awaited.

Author contributions

All authors met the criteria for authorship set forth by the International Committee of Medical Journal Editors and were involved in conception, preparation, and approval of the manuscript.

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Disclosures

JT has had an advisory role at and has received honoraria and travel expenses from Merck, Roche, Amgen, Eli Lilly, Sanofi, Celgene, Shire, and Sirtex. MM is a full-time employee at UniMedizin Mainz, Germany, has had an advisory role at Eli Lilly, Onyx, and Roche, has received research funding from Merck, Amgen, BMS, Taiho, Roche, AIO, MSD, and EORTC, and has received honoraria from Falk, Nordic, Amgen, AstraZeneca, mci, Eli Lilly, MSD, Merck, Pfizer, and BMS. NB has received funding from Taiho, Ono, and BMS, and has received honoraria from Ono, BMS, Merck Serono, Yakult, Eli Lilly, and Chugai. SG is a full-time employee at Merck KGaA, Darmstadt, Germany. VC is a full-time employee at EMD Serono Research & Development Institute, Inc, and holds stock in BMS. Y-JB has had an advisory role at AstraZeneca, Novartis, Genentech/Roche, MSD, Pfizer, Bayer, BMS, Eli Lilly, Merck Serono, FivePrime, Taiho, Ono, ADC Therapeutics, Green Cross, and Samyang Biopharm, and has received research funding from AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serono, Bayer, GSK, BMS, Pfizer, Eli Lilly, Boehringer Ingelheim, MacroGenics, Boston Biomedical, FivePrime, CKD, Ono, Otsuka, Taiho, Takeda, BeiGene, Hanmi, Green Cross, Curis, Daiichi Sankyo. EYR, M-HR, and JAA have nothing to disclose.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctrv.2018.04.004.

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