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MINIREVIEWS

Advances in immuno-oncology biomarkers for gastroesophageal cancer: Programmed death ligand 1, microsatellite instability, and beyond

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Abstract

Blockade of the programmed death ligand 1 (PD-L1) and programmed cell death 1 (PD-1) receptor axis represents an effective form of cancer immunotherapy. Preclinical evidence initially suggested that gastric and gastroesophageal junction (GEJ) cancers are potentially immunotherapy-sensitive tumors. Early phase clinical trials have demonstrated promising antitumor activity with PD-1/PD-L1 blockade in advanced or metastatic gastric/GEJ cancer. Microsatellite instability (MSI) and PD-L1 expression have been shown to predict higher response to PD-1 inhibitors as highlighted by the recent approvals of pembrolizumab in treatment-refractory solid tumors with MSI status and the third-line or greater treatment of PD-L1 positive advanced gastric/GEJ cancers. However, predictive and prognostic biomarkers remain an ongoing need. In this review, we detail the preclinical evidence and early tissue biomarker analyses illustrating potential predictive biomarkers to PD-1/PD-L1 blockade in gastric/GEJ cancer. We also review the clinical development of PD-1/PD-L1 inhibitors in gastric/GEJ cancer and

highlight several areas in need of future investigation in order to optimize the efficacy of PD-1/PD-L1 blockade in gastric/GEJ cancer.

Key words: Immunotherapy; Programmed cell death 1; Programmed death ligand 1; Microsatellite instablility; Gastric cancer

Core tip: Programmed death ligand 1 (PD-L1) and microsatellite instability have recently entered into clinical practice as recommended biomarker testing for the use of immune checkpoint inhibitors in gastroesophageal cancer. However, PD-L1 still does not carry the highest sensitivity and specificity with variability in testing reported. Incorporation of PD-L1 expression from the tumor microenvironment with counting of immune cells appears to be the most effective strategy to date. Future efforts focusing on composite biomarkers in ongoing research from combinatorial immuno-oncology strategies are necessary to drive the field forward.

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INTRODUCTION

T-cell activation and tolerance are partly regulated by the B7 family of proteins[1]. B7-H1, a transmembrane protein in the B7 family also known as programmed death ligand 1 (PD-L1), has been shown to negatively regulate T-cell-mediated immune responses when bound by the programmed cell death 1 (PD-1) receptor[1-3]. Deficiency of PD-1 leads to impaired tolerance, as demonstrated by the development of pathologies resembling lupus and graft-versus-host disease in mice with PD-1 gene disruption, and in transgenic mice with the PD-1 null mutation, respectively[4].

Many tumors upregulate PD-L1 expression, which can be enhanced by interferon-gamma signaling[3,5]. PD-L1 expression leads to apoptosis of tumor-reactive T cells and tumor growth[5]. Tumorigenesis and tumor dissemination are also increased, but these effects were reversed when anti-PD-L1 antibody was administered[6]. Therefore, activation of the PD-1/PD-L1 axis was a putative mechanism for tumors to evade host tumor antigen-specific T-cell immunity, leading to the concept of PD-1/PD-L1 blockade as a potential form of cancer immunotherapy[3,5,6]. Initial phase I studies of humanized monoclonal IgG4 antibodies against PD-1 and PD-L1 in patients with advanced solid tumors were soon conducted, demonstrating both tumor shrinkage and extended disease stabilization[7]. This paved the way for the development of the first Food and Drug Administration (FDA)-approved PD-1 inhibitors, pembrolizumab and nivolumab, which achieved durable objective responses in early trials[7-9].

Cancers of the stomach and esophagus are among the 8 major global cancers that account for > 60% of total cases and deaths worldwide[10]. In 2012, an estimated 1.4 million cases of gastroesophageal cancer were reported, resulting in 1.1 million deaths globally. Approximately 2/3 of patients with gastroesophageal cancer develop metastatic disease during the course of their disease and despite sequencing of available active systemic agents, prognosis remains poor in advanced disease with a median overall survival (OS) of 8-10 mo[11]. Despite the rapidly growing number of FDA approvals for PD-1/PD-L1 inhibitors in cancer therapy, the first approval of a PD-1 inhibitor specifically for advanced gastroesophageal cancer occurred on September 22, 2017 with the approval of pembrolizumab[12]. Likewise, the PD-1 inhibitor nivolumab received concurrent regulatory approval in Japan for unresectable advanced or recurrent gastric cancer[13]. Although clinical activity is established, biomarkers to optimize patient selection remain an area of significant need in gastroesophageal cancers.

In this review, we highlight the clinical development of PD-1 inhibitors leading up to the recent approvals of pembrolizumab and nivolumab in advanced gastroesophageal cancer. In particular, we discuss preclinical rationale, early biomarker studies, and results currently available from major phase I-III trials investigating PD-1/PD-L1 inhibitors in advanced or metastatic gastroesophageal cancer.

INITIAL STUDIES INTO THE IMMUNOGENICITY OF GASTROESOPHAGEAL CANCER

Landmark analyses by The Cancer Genome Atlas (TCGA) proposed classifications based on comprehensive genomic profiling for 4 subtypes of gastric cancer: Epstein-Barr virus (EBV)-infection, microsatellite instability (MSI), genomic stability, and chromosomal instability[14]. Similarly, classifications were proposed for 3 molecular subtypes of esophageal squamous cell carcinoma (SCC)[15]. Of particular interest were findings suggestive that a relevant proportion of gastric cancer cases may be inherently receptive to immune checkpoint blockade, given that EBV-positive subtypes representing 9% of cases were characterized by genomic amplification of chromosomal region 9p24.1, the locus of genes encoding PD-L1 and PD-L2, and 21.7% of cases demonstrated MSI[14]. In-silico analyses

from RNA-sequencing data also identified gastric cancers as one of the tumor types associated with immune cytolytic activity[16].

A meta-analysis recently demonstrated that tumor and tumor-infiltrating immune cell PD-L1 expression by immunohistochemistry (IHC) is predictive of response to PD-1/PD-L1 inhibitors [odds ratio (OR) 2.26, 95% confidence interval (CI): 1.85-2.75, $P < 0.001$] among advanced solid tumors studied across 41 trials[17]. However, growing evidence suggests that PD-L1 expression alone as the sole predictor of response to PD-1/PD-L1 blockade may not be sufficient, given the lack of response still observed in some PD-L1-expressing tumors, and response in PD-L1 negative patients[18]. Furthermore, there is increasing focus on immune properties of the tumor microenvironment (TME) including density of CD8+ tumor-infiltrating lymphocytes (TILs), expression of various immune checkpoints, and other immune cell phenotypes that may serve as predictive biomarkers for PD-1/PD-L1 blockade[18-21]. Analyses of PD-L1 expression and the TME in gastroesophageal cancers, however, have been limited and only recently have investigations begun to report findings on these topics.

Many studies have focused on quantifying PD-L1 expression and its clinical significance among gastroesophageal cancers. Among histological types of esophageal cancers, SCCs were observed to have higher PD-L1 expression[22]. In another study, presence of TILs and PD-L2 in esophageal cancers were inversely correlated, in contrast to PD-L1 expression, which had no significant correlation with TILs[23]. PD-L1 positivity, however, was associated with significantly poorer prognosis - especially in more advanced stages - and found to be an independent prognostic factor upon multivariate analysis[23].

PD-L1 is not expressed by normal gastric tissue[24], and either not expressed or weakly expressed by gastric adenomas[24,25]. However, 30%-65% of invasive gastric cancers express PD-L1[25-30], and expression was found to correlate to depth of invasion, lymph node metastasis, distant metastasis, and tumor size[24,26,27,31,32]. EBV-positive gastric cancers had higher rates of PD-L1 expression in tumor and immune cells more often than EBV-negative gastric cancers[29,33-36]. In particular, Derks *et al*[29] found that among EBV-positive gastric cancers from the TCGA dataset, PD-L1 was expressed in immune cells in 94% of the cases, whereas only 50% of the cases had tumor cell expression of PD-L1. Among EBV-negative gastric cancers, only those with MSI were found to express PD-L1 within tumor cells. However, EBV-negative cancers without MSI had inflammatory cell expression of PD-L1 in 35% of the cases, and these inflammatory cells were present only at the invasive margin as opposed to deeply infiltrating the tumor. Interestingly, findings of tumor-infiltrating PD-L1+ inflammatory cells occurred only in cancers with EBV positivity or MSI[29], and among gastric cancers in another study, these were noted to have upregulated immune escape pathway genes[34]. Mismatch repair (MMR) deficiency has also been associated with PD-L1 expression in other series[30,37].

The relationship between other immune checkpoint molecules and PD-1/PD-L1 among gastric cancers has also been an increasing focus of interest. Expression of FOXP3, a transcription factor involved in regulatory T cell (Treg) function and development, correlated to PD-1 expression among patients with stages II and III gastric cancers[38]. Another study found significant correlation between FOXP3+ Tregs and PD-L1 expression, and significantly higher expression of both was found in patients with more advanced clinicopathological stage and lymph node metastasis; patients with higher levels of FOXP3+ Tregs and PD-L1 expression had poorer prognosis[39]. Blood levels of both PD-1 and the molecule T-cell immunoglobulin-3 (Tim-3), which downregulates T helper 1 and cytotoxic cells, were elevated in gastric cancer patients[40]. In addition, PD-1+ and Tim-3+ CD8 T cells produced less IFN-gamma compared to PD-1 negative- and Tim-3-negative cells, suggestive of T-cell dysfunction[40-42]. In a gastric cancer surgical series, post-operative circulating CD4+ and CD8+ T-cells were found to upregulate PD-1 and lymphocyte activation gene 3 (LAG-3), another co-inhibitor of T-cell activation[43]. Gastric cancer tumor cells have also been reported to more commonly express cytotoxic T-lymphocyte antigen 4 (CTLA-4), a major immune checkpoint molecule with known therapeutic strategies, than PD-L1 (86.7% *vs* 44.9%, respectively)[44]. However, gastric cancer TILs expressed more PD-L1 and PD-1 than CTLA-4[44].

Investigation of PD-1/PD-L1 expression among TILs and the TME has also grown. Gastric cancer expression of PD-L1 was associated with TILs that were positive for CD3, CD8, or FOXP3[45]. PD-L1+ gastric cancers tended to have stromal immune cells expressing PD-1 and PD-L1, and those with PD-L1+ immune cells had increased depth of invasion, although PD-L1+ tumor cells had greater prognostic impact than did PD-L1+ immune cells[36]. Although both PD-L1 expression and increased CD3+ TIL density in the TME of gastric cancers were significantly associated with improved 5-year disease-free survival (DFS) and OS, there was no significant correlation between PD-L1 expression and CD3+ TIL density, leading to the hypothesis that tumor production of immunosuppressive proteins may be a mechanism intrinsic to the tumor[46]. Among gastric and GEJ adenocarcinomas, the majority (44%) expressed PD-L1 in the immune stroma, whereas a minority (12%) expressed PD-L1 on tumor cell membranes[47]. Increased density of CD8+ T cells was associated with PD-L1 expression, as well as with worse progression-free and overall survival, suggestive of adaptive immune resistance[47]. In a study of gastric signet-

Table 1 Phase I clinical trials of programmed cell death 1 inhibitors involving advanced gastroesophageal cancer

n	Primary tumor	Doses	Primary endpoint	Results	Ref.
277[1]	NSCLC, melanoma, cutaneous, mucosal, ocular, RCC, clear cell, non-clear cell, other (CRC, gastric, esophageal, HNSCC, sarcoma, ovarian, breast, pancreatic, uterine, pancreaticoduodenal)	Atezolizumab at escalating doses up to 20 mg/kg every 3 wk	Safety, tolerability, DLT, and RP2D	13% grade 3-4 TRAEs: 5 fatigue; 3 each of increased ALT, increased AST, hypoxia; 2 each of asthenia, dyspnea, myalgia, anemia, hyperglycemia, hyponatremia, cardiac tamponade, hypophosphatemia, tumor lysis syndrome; 1 each of nausea, headache, influenza-like illness, pain, vomiting ORR 18% overall; 21% of NSCLC, 26% of melanoma, 13% of RCC, and 13% of other malignancies (CRC, gastric, HNSCC)	[49]
151	Gastric or GEJ	Avelumab (MSB0010718C) 10 mg/kg every 2 wk until progression, toxicity, or withdrawal	Safety, efficacy	9.9% TRAEs grade ≥ 3: fatigue, asthenia, increased GGT, thrombocytopenia, anemia; 1 treat-ment-related death 14 patients with unconfirmed response: 9.7% patients on 2nd line therapy (all PRs), 9.0% patients on 1st-line maintenance (2 CRs, 6 PRs); disease control rate 29% for 2nd line, 57.3% for 1st line maintenance	JAVELIN [50]
39	PD-L1+ Gastric (previously treated)	Pembrolizumab 10 mg/kg every 2 wk for 2 yr or PD	Safety, tolerability, ORR	13% grade 3-4 TRAEs: 2 grade 3 fatigue, 1 each of grade 3 pemphigoid, hypothyroidism, neuropathy, and 1 grade 4 pneumonitis ORR 22% (95%CI: 10-39)	KEYNOTE 012 [51]
23	PD-L1+ SCC or adenocarcinoma of esophagus or GEJ	Pembrolizumab 10 mg/kg every 2 wk up to 2 yr or until PD, intolerable toxicity, or investigator decision	Safety, ORR	17.4% grade 3-4 TRAEs: 2 with decreased lymphocytes, other 2 patients AE was not specified ORR 30.4% (95%CI: 13.2%-52.9%)	KEYNOTE 028 [53]

[1]Note that 175 patients were "efficacy-evaluable". PD: Progressive disease; SD: Stable disease; ORR: Overall response rate; TRAE: Treatment-related adverse effects; DCR: Disease control rate; DLT: Dose limiting toxicities; RP2D: Recommended phase 2 dose.

ring cell carcinoma, a histologic subtype historically associated with poor prognosis, the presence of CD3+ TILs was associated with increased expression of PD-1 and PD-L1, presence of MSI, and an improved OS[48].

PD-L1 BIOMARKER ANALYSES FROM PHASE I TRIALS

Multiple early phase clinical trials of immune checkpoint inhibitors incorporated cohorts of gastroesophageal cancers to establish early signals of anti-tumor activity and exploratory biomarker analyses (Table 1). The anti-PD-L1 antibody atezolizumab was studied in multiple malignancies including gastroesophageal cancer and found to have grade 3-4 TRAEs in 13% of patients as well as an overall response rate[10] of 18%[49]. PD-L1 expression by IHC was determined using an anti-human PD-L1 rabbit monoclonal antibody (clone SP142; Ventana, Tucson, AZ, United States), with the authors scoring both tumor cells and immune cells. Response was significantly associated with the presence of PD-L1 positivity in tumor-infiltrating immune cells (P = 0.007), but not tumor cells (P = 0.079), with better response among patients with greater IHC scores. Among 141 gastric cancer cases included in the trial, 18% demonstrated PD-L1 expression in immune cells, compared with 5% demonstrating PD-L1 expression in tumor cells. Likewise, the JAVELIN phase Ib trial examined the anti-PD-L1 inhibitor avelumab as first-line maintenance or second-line therapy in a gastric and GEJ cancer cohort[50]. The study demonstrated a disease control rate (DCR) of 57.3% and 29.0% in first- and second-line therapy, respectively. Patients receiving

avelumab exhibited increased ORR if harboring PD-L1 positivity of at least 1% tumor cell staining by an IHC assay (Dako, clone 73-10). However, responses were also observed even in cases with PD-L1 expression < 1% albeit at a lower proportion. TRAEs of grade 3 or higher occurred in 9.9%, with one treatment-related death due to hepatic failure.

KEYNOTE 012 was an open-label trial across 13 centers that investigated pembrolizumab for previously treated gastric cancer[51]. Presence of tumor PD-L1 expression was a requirement for enrollment, with 40% of the patients screened demonstrating PD-L1-positive tumors. PD-L1 expression was detected using the 22C3 antibody with a prototype assay using QualTek or Dako platforms. Tumor positivity was based on a cutoff of at least 1% of scorable tumor cells or immune cells exhibiting membrane staining, or the presence of PD-L1-positive mononuclear inflammatory cells existing in the interface between tumor and stromal cells. ORR was 22% (95%CI: 10-39) comprised exclusively of partial responses[52] as no complete responses (CRs) were observed. Median progression-free survival (PFS) was 1.9 mo (95%CI: 1.8-3.5) and median OS was 11.4 mo (95%CI: 5.7-not reached). 44% of patients with a mononuclear inflammatory cell density of 3 had PR, whereas a 0-2 density score corresponded to a PR rate of 15%. Focusing on tumor cell staining, 24% of patients with a tumor score of 0 had a response, compared to 17% of those with a score of at least 1 (Table 1). As such, there did not appear to be an absolute lower cutoff that could reliably exclude the possibility of response. KEYNOTE 028 investigated pembrolizumab in patients with advanced solid malignancy also requiring tumor expression of PD-L1 as detected by IHC in tumor or stroma, including those with SCC or adenocarcinoma of the esophagus or GEJ[53]. Among esophageal cancers screened, 45% met the criteria for PD-L1 expression. For the patients treated, 13.0% attained stable disease[31], and ORR was reported at 30.4%, with a PFS of 30.4% and 21.7% at 6 and 12 mo, respectively (Table 1). Median duration of response (DOR) was 40.0 wk.

PD-L1 BIOMARKER ANALYSES FROM PHASE II TRIALS

Combination immunotherapy with nivolumab, an anti-PD-1 antibody, and ipilimumab, an anti-CTLA-4 antibody, was tested for advanced gastric, esophageal, and GEJ adenocarcinoma in the phase I/II CheckMate 032 trial (Table 2). Patients received nivolumab alone, nivolumab 1 mg/kg with ipilimumab 3 mg/kg (N1+I3), or nivolumab 3mg/kg with ipilimumab 1mg/kg (N3+I1)[54]. Grade 3-4 TRAEs including diarrhea and elevated transaminases were reported more often in the N1+I3 group, which also achieved greater ORR regardless of PD-L1 status. PD-L1 IHC expression was determined by examining solely tumor cell expression with staining by the 28-8 antibody. 39 of 127 assessable cases (31%) exhibited PD-L1 expression ≥ 1%. While ORRs were greater in PD-L1 ≥ 1% tumors (19% nivolumab alone, 40% N1+I3, 23% N3+I1), responses were still demonstrable in PD-L1 < 1% tumors (12% nivolumab alone, 22% N1+I3, 0% N3+I1). Survival outcomes reported to date have not demonstrated clear differences in median OS between the 3 arms, but as a phase II trial the study was not powered to address this difference. PD-L1 ≥ 1% tumors appeared to demonstrate more favorable rates of 12-month OS in the N1+I3 (50%) *vs* nivolumab alone (34%) and N3+I1 (23%) groups. However, with the small numbers of PD-L1 ≥ 1% tumors in each arm (16 nivolumab alone, 10 N1+I3, 13 N3+I1), it remains difficult to conclude if PD-L1 IHC assessment of tumor cells alone is robust enough to enrich for gastroesophageal cancer patients who will benefit from immune checkpoint inhibitors.

KEYNOTE 059 investigated pembrolizumab among 3 cohorts of patients with gastric and GEJ cancer: (Cohort 1) pembrolizumab after at least 2 prior regimens, (Cohort 2) pembrolizumab with cisplatin and 5-fluorouracil or capecitabine as first-line therapy, and (Cohort 3) pembrolizumab as first-line therapy among patients with at least 1% PD-L1 expression as scored by the 22C3 IHC pharmDx assay[55]. PD-L1 positivity was defined in this study as a combined positive score (CPS) ≥ 1 where the number of PD-L1 positive tumor and immune cells (lymphocytes and macrophages) were divided by the total number of tumor cells evaluated and multiplied by 100. Cohort 1 comprised the largest cohort of 259 patients, and found that those with a CPS ≥ 1 (n = 148, 57%) had an ORR 15.5%, comprised of a CR rate of 2.0% and PR rate of 13.5%. Those considered to be PD-L1 negative, i.e. a CPS < 1 (n = 109), had an ORR of 6.4%, and still exhibited CRs at a rate of 2.8% and PR rate of 3.7%[56]. As such, lack of detectable PD-L1 tumor and/or immune cell expression did not completely exclude the possibility of deriving a response, including CR in 2.8%, though likelihood of response appeared higher if PD-L1 expression was detected. PD-L1 CPS-positive patients had a median DOR of 16.3 mo, compared to 6.9 mo in PD-L1 CPS-negative patients. 51.7% had 2 prior therapies, 29.0% had 3 prior therapies, and 19.3% had 4 or more prior therapies. Patients receiving pembrolizumab as third-line therapy had greater response, with a 16.4% ORR and 3.0% CR rate, compared to those receiving fourth-line therapy[56]. PD-L1-negative patients had an ORR of 5.5%, 1.8% CRs, and 3.7% PRs. Overall 16.6% had grade 3-5 TRAEs, leading to therapy discontinuation and death in 2 patients each.

Cohort 2, which received combined frontline chemotherapy with pembrolizumab, demonstrated a median PFS of 6.6 mo and median OS of 13.8 mo

Table 2 Phase II and III clinical trials of programmed cell death 1 inhibitors in advanced gastroesophageal cancer

n (phase)	Experimental arm	Control or reference arm	Primary endpoint	Results	Ref.
160 (I/II)	N1 + I3: Nivolumab 1 mg/kg every 2 wk and ipilimumab 3 mg/kg every 3 wk N3 + I1: Nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 wk Gastric, esophageal, or GEJ cancer	N3: Nivolumab 3 mg/kg every 2 wk	ORR	N3: ORR 12%, PD-L1 ≥ 1% ORR 19%, PD-L1< 1% ORR 12% N1+I3: ORR 24%, PD-L1≥ 1% ORR 40%, PD-L1< 1% ORR 22% N3+I1: ORR 8%, PD-L1 ≥ 1% ORR 23%, PD-L1 < 1% ORR 0%	CheckMate 032 [54]
259 (II)	Cohort 1 (after ≥ 2 lines of therapy): Pembrolizumab 200 mg every 3 wk up to 2 yr, PD, decision to withdraw, or unacceptable toxicity in gastric cancer	N/A	ORR, safety, tolerability	Overall ORR 11.2% (95%CI: 7.6-15.7), CR 1.9% (95%CI: 0.6-4.4), PR 9.3% (95%CI: 6.0-13.5), SD 17% (95%CI: 12.6-22.1), PD 55.6% (95% CI 49.3-61.7) PD-L1+ ORR 15.5% (95% CI 10.1-22.4), PD-L1- ORR 5.5% (95% CI 2.0-11.6)	KEYNOTE 059 [56]
25 (II)	Cohort 2 (1st line): pembrolizumab 200 mg every 3 wk for up to 2 yr, cisplatin (80 mg/m^2 day 1), and 5-FU (800 mg/m^2 D1-5 Q3W) or capecitabine (1000 mg/ m^2 bid)	N/A	Safety, ORR	Cohort 2: ORR 60% (39-79) overall, 73% (45-92) PD-L1+, 38% (9-76) PD-L1-. Median PFS 7 mo	KEYNOTE 059 [55]
31 (II)	Cohort 3 (PD-L1+, 1st line): pembrolizumab 200 mg every 3 wk for up to 2 yr Gastric or GEJ cancer	N/A	Safety, ORR	Cohort 3: ORR 26% (12-45). Median PFS 3 mo	KEYNOTE 059 [55]
41 (II)	Pembrolizumab 10 mg/kg every 2 wk Cohort A: Mismatch repair (MMR)-deficient colorectal cancers (CRC) Cohort C: MMR-deficient non-CRC	Cohort B: MMR-proficient CRC	ORR, PFS	MMR-deficient CRC: ORR 40%, PFS 78%; median PFS and OS not reached MMR-proficient CRC: ORR 0%, PFS 11%; median PFS 2.2 mo, OS 5.0 mo MMR-deficient non-CRC: ORR 71%, PFS 67%	Keynote-016 [58]
86 (II)	Pembrolizumab 10 mg/kg every 2 wk for MMR-deficient cancers (12 tumor types)	N/A	ORR, PFS	Objective radiographic response 53%, CR 21%; median PFS and OS not reached	[59]
493 (III)	Nivolumab 3 mg/kg every 2 wk until unacceptable toxicity or PD in gastric/GEJ cancers	Placebo	OS	Nivolumab: median OS 5.32 mo, 6-mo OS 46.4%, 12-mo OS 26.6%, ORR 11.2%, median PFS 1.61 mo Placebo: median OS 4.14 mo, 6-mo OS 34.7%, 12-mo OS 10.9%, ORR 0%, median PFS 1.45 mo	ATTRACTION-02 [57]

PD: Progressive disease; ORR: Overall response rate; CI: Confidence interval; OS: Overall survival.

among this smaller cohort of 25 patients. PD-L1 CPS-positive patients had an ORR of 69%, compared to 38% for PD-L1 CPS-negative patients. Thus, the latter appeared in line with historical trials of doublet platinum and fluoropyrimidine chemotherapy in advanced gastric cancer. The presence of PD-L1 CPS positivity would suggest that the addition of pembrolizumab can help achieve deeper responses with chemotherapy. However, this should be cautiously interpreted with the limited number of patients analyzed. Cohort 3, which was single-agent pembrolizumab in first-line therapy but selecting for tumors that had PD-L1 CPS ≥ 1, led to a promising ORR of 26%, median PFS of 3.3 mo, and a median OS of 20.7 mo. Grade 3-5 TRAEs occurred in 18% (cohort 1), 76% (cohort 2), and 23% (cohort 3), with cohort 2 not unexpectedly demonstrating more toxicities associated with use of cytotoxic chemotherapy. Findings from cohort 1 of KEYNOTE 059 ultimately led to the accelerated FDA approval of pembrolizumab in third-line and beyond treatment of PD-L1 positive by the CPS criteria advanced or metastatic gastric or GEJ adenocarcinoma in September of 2017[12].

PD-L1 BIOMARKER ANALYSIS FROM PHASE III TRIALS

Nivolumab was investigated in a phase III trial of 493 patients with gastric and GEJ cancer who had advanced or recurrent disease after 2 or more lines of chemotherapy[57]. Patients receiving nivolumab had significantly improved median OS of 5.2 mo, PFS 1.61 mo, and ORR 11.2%, compared to 4.14 mo, 1.45 mo, and 0%, respectively in patients receiving placebo (all $P < 0.0001$). 11.5% of the nivolumab group and 5.5% of the placebo group suffered TRAEs of grade 3 or higher. An exploratory analysis was conducted of PD-L1 biomarker expression using the 28-8 antibody for IHC and defining PD-L1 positivity as staining in ≥ 1% of tumor cells only. Tumor testing was able to be retrospectively conducted on 192 patient samples, with 26 patients (14%) harboring tumors with PD-L1 positivity in ≥ 1% of tumor cells. Median OS appeared improved with nivolumab vs. placebo regardless of PD-L1 positive (5.22 mo *vs* 3.83 mo) or PD-L1 negative (6.05 mo *vs* 4.19 mo) tumor status. As such, definitive conclusions on tumor PD-L1 status influencing the likelihood of benefit from nivolumab therapy could not be drawn with the limited numbers of PD-L1 positive tumors observed. Subsequently, nivolumab garnered regulatory approval in Japan for third-line and beyond therapy for advanced gastric cancer irrespective of PD-L1 biomarker testing.

MSI AS A BIOMARKER IN GASTRIC CANCER

The seminal phase II trial by Le *et al*[58] demonstrated metastatic colorectal cancers (CRCs) which demonstrated deficient DNA mismatch repair (dMMR) and harbored MSI had a higher propensity to respond to pembrolizumab in comparison to CRCs with proficient MMR and were microsatellite stable (MSS). It is now well recognized that dMMR tumors harbor a high mutational burden translating into the production of tumor neoantigens which evade immune response through the upregulation of immune checkpoints[59]. In addition to dMMR and pMMR CRCs, they included a third cohort of dMMR tumors regardless of histology. Both dMMR CRC and non-CRC cohorts demonstrated encouraging ORRs of 40% and 67%, respectively. Le *et al*[60] subsequently expanded the study further to 86 patients inclusive of 12 tumor types with dMMR, which continued to demonstrate a high ORR of 53% and CR rate of 21%, with median PFS and OS not reached at the time of reporting. Gastroesophageal cancers among 5 patients were included as one of the 12 tumor histologies. Three of the 5 patients exhibited CRs, while 2 of 5 had progressive disease to comprise an ORR of 60%. The high and durable ORRs of pembrolizumab in MSI-high (MSI-H) non-CRC tumors also led to efforts to retrospectively identify patients with MSI-H gastroesophageal cancers from the KEYNOTE-012 and KEYNOTE-028 trials. Pooling of these datasets with the study by Le *et al*[60] in addition to the MSI-H cohort of the ongoing KEYNOTE-158 umbrella trial (NCT02628067), subsequently led to the identification of 9 gastric/GEJ adenocarcinoma patients with reportable responses[61]. Among the 9 cases, 5 (56%) demonstrated an objective response, with median DOR ranging from 5.8 mo to 22.1 mo and ongoing at last analysis. These studies eventually culminated in the unprecedented FDA approval of pembrolizumab in treatment-refractory MSI-H solid tumors, regardless of tissue histology[62].

Cohort 1 of the KEYNOTE-059 trial also conducted an analysis for microsatellite instability, and among 174 assessable cases, 7 were MSI-H (4%). Of these 7 MSI-H gastric/GEJ cancers, the ORR was 57.1% (14.3% CR, 42.9% PR), and a disease control rate (DCR) of 71.4% was also achieved[56]. In contrast, the non-MSI-H subset had an ORR of 9.0% (2.4% CRs, 6.6% PRs) and DCR of 22.2%. Given that MSI-H status and PD-L1 positivity tend to occur together, it is likely that all MSI-H patients in this cohort were PD-L1 positive. In assuming that 4/7 of these MSI-H patients would have responded to pembrolizumab (ORR of 57.1%), subtracting these cases from the PD-L1+ cohort only marginally affects the ORR to pembrolizumab in this cohort (13.5% from the original 15.5%). MSI biomarker analysis was also conducted retrospectively in the gastroesophageal cohorts of the Checkmate 032 trial[63]. Among 72 assessable cases, 11 (15%) were considered MSI-H tumors. Seven of the cases belonged in the nivolumab alone cohort, and 2 each in the N1+I3 and N3+I1 cohorts, thus no definitive comparison could be made of responses in MSI-H cases among the 3 treatment arms. Regardless, ORR was 2/7 (29%) with nivolumab alone, 1/2 (50%) with N1+I3, and 1/2 (50%) with N3+I1. Similar to the data from KEYNOTE-059, the DCR with nivolumab alone among MSI-H gastroesophageal tumors was 71%. Among non-MSI-H tumors, the ORR was 11% with nivolumab alone, 19% with N1+I3, and 5% with N3+I1.

In conclusion, MSI is present in a small, but clinically relevant proportion of gastroesophageal cancers. Responses to PD-1 inhibitors appear to be more favorable in this subset from the small numbers of patients reported in the literature to date. However, lack of MSI does not exclude the potential for response, and it is apparent that primary resistance in MSI-H tumors still exists by the reported cases with no evidence of response to immune checkpoint inhibitors.

MOVING BEYOND PD-L1 AND MSI BIOMARKERS

Other potential predictive biomarkers are gaining interest, and advances in determining prognosis with the assistance of immune markers are ongoing. Dai *et al*[64]

studied the prognostic value of multiple methods of immune marker detection in stage I-IV gastric cancers. PD-L1 expression and TIL infiltration were evaluated by IHC; PD-L1 expression was associated with higher TIL density, and TIL density correlated to lower rates of disease progression and improved survival. Increased mRNA levels of multiple immune markers including PD-L1, CTLA-4, FOXP3, and LAG-3, as detected by real-time quantitative polymerase chain reaction were found in patients with better OS. In-situ hybridization demonstrated a correlation between EBV positivity and PD-L1 expression as well as higher TIL infiltration.

Tumor mutational burden (TMB) has also been of interest as a predictive biomarker for immunotherapy strategies in multiple other tumors[49,65,66]. MSI-H tumors with defective dMMR certainly exemplify high TMB with analyses by Llosa *et al*[59] reporting on average 1782 mutations per tumor by whole-exome sequencing in cases of MMR deficiency, compared to 73 in cases with MMR proficiency (P = 0.007). Such findings translated into clinical benefit with an association between greater mutation rates and prolonged PFS with pembrolizumab (P = 0.02). Clinically available targeted next-generation sequencing panels have also reliably captured TMB in gastrointestinal malignancies[67]. Klempner *et al*[67] reported from a large case series of tumors sequenced using the FoundationOne platform (Cambridge, MA, United Kingdom) that high TMB, defined as > 20 mutations/Mb, existed in 3% of 2065 esophageal cases and 5% of 1485 stomach cancers. Ongoing investigation is required to determine whether there is an ideal TMB cutoff that predicts high likelihood of response to immune checkpoint inhibition in gastroesophageal cancer. An early report from Ku *et al*[68] utilizing the Memorial Sloan Kettering IMPACT panel suggested that having ≥ 14 mutations/Mb corresponded to greater benefit from immune checkpoint inhibition (2-year OS rate 15% *vs* 60%, P = 0.094). However, the proportion of patients comprising this high TMB subset was small (6/55 patients), with 4 of the 6 being comprised of dMMR tumors[68]. The frequency of other genomic alterations which lead to hypermutated phenotypes such as *POLE* mutations have also been characterized in gastroesophageal cancers, but appear to comprise an even lower proportion (< 1%) than dMMR[67]. A follow-up report of gastroesophageal cancers sequenced by the IMPACT panel appeared to suggest that a cutoff of > 9.7 mutations/Mb, representing the top quartile of 40 patients treated with immune checkpoint inhibitors, correlated to greater benefit (median OS 16.8 mo *vs* 6.62 mo, P = 0.058)[69]. Interestingly, 2 patients with durable responses lasting > 12 mo had low TMB (1.9 and 3.3 mutations/Mb), with one of the cases being EBV+. As such, the detection of low TMB does not appear to entirely exclude response to immune checkpoint inhibitors. A recent phase I trial in on the anti-PD-1 antibody SHR-1210 in ESCC supported somatic nonsynonymous mutational load (by WES) as a biomarker of predictive benefit with higher TMB associated with benefit (P = 0.048)[70].

With greater understanding of the dynamics of immune signaling necessary for antitumor responses, immune gene expression profiling has also entered into the forefront of biomarker analyses. High throughput assays such as the NanoString platform (Seattle, WA, United States) were applied to the early KEYNOTE-012 gastric dataset in attempts to enrich for tumor biomarkers beyond PD-L1 expression to be predictive of pembrolizumab response[51]. Muro *et al*[71] reported that high scores from a 6-gene interferon γ signature (*STAT1, HLA-DRA, IFNG, IDO1, CXCL9, CXCL10*) correlated to response, but conclusive results were limited by small patient numbers. Likewise, the same 6-gene signature was examined in the KEYNOTE-028 esophageal dataset, and a correlation to pembrolizumab response was also observed with higher scores. Lastly, Fuchs *et al*[56] reported from the larger dataset of cohort 1 from KEYNOTE-059 that a higher score from an 18-gene T-cell inflamed signature (*CCL5, CD27, CD274 (PD-L1), CD276 (B7-H3), CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PDCD1LG2 (PD-L2), PSMB10, STAT1, TIGIT*) was significantly associated with improved response to pembrolizumab (P = 0.014). Thus, immune gene expression profiling in conjunction with PD-L1 IHC scoring may provide greater specificity to predicting response to anti-PD-1 therapy.

Characterization of gastric cancers has become more complex, with the availability of a variety of techniques such as multiplex IHC, in-situ hybridization, and gene expression profiling. These have expanded the field of immune therapy and facilitated the study of relationships between PD-1/PD-L1 and other factors including EBV positivity, MSI, TIL density, and the presence of other immune markers. The rapidly growing recognition of the stool microbiome influencing immunotherapy responses adds additional complexity from environmental factors influencing biomarker analyses[52,72,73]. Further investigation into these variables in advanced gastric/GEJ cancer is duly warranted to assist further development of immunotherapeutic efforts. With currently available therapies in gastric/GEJ cancer, as in other cancers, a composite score incorporating other immune checkpoints, TILs, MSI status, tumor mutational burden, and the immune profile of the TME may represent a more robust predictive biomarker for checkpoint inhibitors rather than PD-L1 expression alone. Furthermore, to optimize the antitumor efficacy of PD-1/PD-L1 inhibitors in gastric cancer, trials have been conducted and are ongoing to examine the potential of PD-1/PD-L1 inhibitors in combination with other therapies. While combination strategies are likely necessary, it may come at a cost of additive toxicity, and as such robust predictive biomarkers will truly allow for personalization of immunotherapeutic approaches.

As observed in all of the trials discussed, the majority of patients do not derive significant benefit and demonstrate primary resistance to currently studied immune checkpoint inhibitors. Identification of patients least likely to respond is equally important to optimal

response biomarker studies. Whether or not high disease burden, low mutational burden, or the IPRES (innate anti-PD-1 resistance) transcriptional signature seen in melanoma can serve as surrogates for resistance (or have a mechanistic role) in gastric and esophageal cancers remains unknown[74-76]. Studies in the non-metastatic setting, many of which are ongoing, may aid in identifying some resistance markers and changes between locoregional and advanced disease[77].

CONCLUSION

Cancer immunotherapeutic approaches with PD-1/PD-L1 inhibitors continue to gain considerable momentum as more disease indications are added. Preclinical and early biomarker studies provided ample evidence that gastric/GEJ cancer is an immune-sensitive tumor. Immune parameters including MSI status, TILs, PD-L1 expression, and the immune profile of the TME are among some, but not all, of the potential predictive biomarkers for checkpoint inhibitors in advanced gastric/GEJ cancer. Early phase clinical trials provided promising signals of antitumor activity of PD-1/PD-L1 blockade to advance into larger studies. Recently, pembrolizumab received FDA approval for the third-line treatment of PD-L1 CPS expressing advanced gastric/GEJ adenocarcinoma. With the CPS criterion, this represents the first biomarker testing incorporating both assaying of tumor cells and the associated immune cells within the TME. Pembrolizumab has also been approved in a tissue-agnostic indication for treatment-refractory solid tumors that are MSI-H. In the small proportion of gastroesophageal cancers harboring this biomarker, encouraging and clinically relevant responses have been reported in the few cases reported to date. Nivolumab likewise has received Japanese approval for third-line treatment in advanced gastric/GEJ adenocarcinoma, though a predictive biomarker has not been linked to this indication. We anticipate composite biomarkers will improve patient selection and potentially individualize treatment, though broader clinical implementation may be slow. The identification of more robust predictive biomarkers and development of combination therapies incorporating immune checkpoint inhibitors represent necessary and ongoing areas of investigation to optimize this class of agents in gastric/GEJ cancer.

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