A Systematic Review and Meta-analysis of PD-1 and PD-L1 Inhibitors Monotherapy in Metastatic Gastric and Gastroesophageal Junction Adenocarcinoma

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Abstract

Immune checkpoint inhibitors are new targeted treatments that harness the body's immune system to attack cancers. Drugs that are most extensively used among checkpoint inhibitors inhibit the PD-L1 or PD-1 (programmed death 1) ligand or receptor pair and are currently approved for many cancer indications. In gastric or gastroesophageal junction adenocarcinomas one inhibitor, pembrolizumab has regulatory approval for PD-L1 positive carcinomas. This meta-analysis investigates available data on the efficacy of PD-L1 or PD-1 inhibitors as a class in gastric or gastroesophageal junction adenocarcinomas. The literature was reviewed to identify clinical studies that included arms with PD-L1 or PD-1 inhibitors as monotherapy in gastric or gastroesophageal junction adenocarcinomas. Relevant patient characteristics, outcomes, and adverse effects were recorded. Summary estimates of response rates (RR) and survival were calculated using a random or fixed effect model, depending on heterogeneity. Six studies with a total of 1068 patients were included in the analysis. The summary RR was 10.63% (95% confidence interval (CI) 5.36–15.89%). The summary disease control rate (DCR) was 28.11% (95% CI 24.60–31.63%). Summary progression-free survival (PFS) was 1.59 months (95% CI 1.24–1.94 months). Summary overall survival (OS) was 5.72 months (95% CI 0–12.19 months). A subset of patients derived long-term benefits as seen in other cancer locations. The adverse effect rate was low and consistent with that in other disease locations. Low efficacy of immune checkpoint inhibitors as a class in gastric or gastroesophageal junction adenocarcinomas is observed in this analysis and stresses the need for effective biomarker use for the identification of most probable responders.

Keywords: Adenocarcinoma, Gastric cancer, Gastroesophageal junction, Immune checkpoint inhibitors.

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Introduction

Gastric and gastroesophageal junction adenocarcinomas represent one of the most common types of cancer and are more common in men than in women.[1] Mortality from stomach cancer remains high and was 4.3 per 100,000 population in men and 2.3 per 100,000 in women in the US between 2011 and 2015. Some populations, such as, African Americans and Hispanics have even higher incidence and mortality rates.[1] With an estimated 469.000 deaths in men and 254.000 deaths in women, gastric cancer rates the third cause of death by cancer in men and fifth in women worldwide.[2]

Immune blockade inhibitors (also called immune checkpoint inhibitors, ICIs) are a new class of targeted anti-neoplastic drugs that block inhibitory receptors of the immune system and activate an immune response to the tumor.[3] Currently, immune inhibitory receptors targeted in the clinic include CTLA-4 (cytotoxic T lymphocyte antigen 4) and PD-1 and its ligand PD-L1. Several other immune inhibitory receptor blockers are in advanced phase clinical studies.[4] Monoclonal antibodies against CTLA-4 or PD-1 receptors and its ligand PD-L1 are approved for use in various malignancies, such as, lung cancer, melanoma, urothelial, renal, and hepatocellular carcinomas as well as Hodgkin's lymphoma.[5–12] One of the immune checkpoint inhibitors, pembrolizumab has also obtained approval in the US for any tumor with microsatellite instability (MSI).[13] Clinical trials leading to approval of ICIs have been impressive in that they have documented long-lasting control of some previously refractory to chemotherapy patients and these drugs have now moved to the first-line metastatic setting in certain cancers. Studies in other cancers have produced less impressive results. Cancers responding to ICIs tend to be those with a higher tumor mutation burden, while non-responsive cancers tend to have a lower mutation burden.[14,15] Besides the mutation burden, other possible predictive markers of response to ICIs include MSI and tumor micro-environment PD-L1 expression (for PD-1 inhibitors). Both these markers, in contrast to tumor burden, are on some occasions embedded in the indication of the drugs.[6,13]

Immune blockade inhibitors have been studied in clinical trials for many common gastrointestinal cancers.[16] Gastric and gastroesophageal junction adenocarcinomas constitute one of the gastrointestinal cancer groups where ICIs have been investigated. Results of these trials have been encouraging in subsets of patients and regulatory approval has been granted by the USFDA to the PD-L1 inhibitor pembrolizumab for gastric gastroesophageal junction adenocarcinomas that express PD-L1.[17] The current investigation

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presents a meta-analysis of trials that included arms with PD-1 or PD-L1 monotherapy to inform on the efficacy of these drugs in gastric and gastroesophageal adenocarcinomas. It will also seek to analyze any data on markers predictive of response arising from these trials.

METHODS

A meta-analysis of all phase II and III studies that included monotherapy arms of PD-1 and PD-L1 inhibitors nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab in metastatic gastric or gastroesophageal adenocarcinoma patients was performed to better understand the efficacy of these drugs with a similar mechanism of action in these cancers. These five checkpoint inhibitors are currently in clinical use for different indications in oncology.

The search of the literature for this meta-analysis was performed in the Medline or PubMed database (www.ncbi.nlm.nih.gov/pubmed), the EMBASE (Excerpta Medica) database, and the Cochrane Central Register of Controlled Trials with the search terms "nivolumab" or "pembrolizumab" or "atezolizumab" or "avelumab" or "durvalumab" and "gastric cancer" or "gastroesophageal cancer". The date of the last search of the databases was November 20, 2019. Studies of any prospective design (except for dose-finding phase I) were included if they were in the English language and if they included treatment arms that received therapy with one of the checkpoint inhibitors as monotherapy. In contrast, articles in other languages, case reports or small (less than 15 patients) non-randomized-case series, pre-clinical studies or reviews and opinion articles were excluded. Also excluded were studies of combination therapies of checkpoint inhibitors with other checkpoint inhibitors, other targeted drugs or chemotherapeutics. References of retrieved articles were searched manually for additional studies of relevance.

Studies retained were scanned for data describing the demographics of the treated population, characteristics of the treated diseases and the efficacy and toxicity of treatment of interest. Population data of patients in the arms treated with one of the five checkpoint inhibitors of interest extracted for the analysis included age of the patients, ECOG performance status, number and type of previous lines of treatment for metastatic disease, and histologic sub-type. Additional data of interest that were searched and recorded when available included positivity for HER2, PD-L1, EBV, presence of MSI, and tumor mutation burden. Efficacy outcomes of interest included RR, DCR, median OS, and median PFS, with their respective 95% CI. Information on overall and grade 3 and 4 toxicity rates were also extracted from included studies. All studies of the meta-analysis were evaluated for the risk of bias with the revised Cochrane risk-of-bias for randomized trials (RoB 2.0) tool.[18]

Descriptive statistics were calculated for all patients' characteristics of interest and outcome measures. Pooled outcomes rates were weighted according to the number of patients in each series. Heterogeneity among the studies was evaluated with Cochran's Q and I^2 tests. The fixed or random-effect model was used if heterogeneity was low or high, respectively.[19] Calculations were performed in Excel (Microsoft Corp.) as previously described with some modifications[20] and re-performed for confirmation of results with Open Meta-analyst, an open-source online software, developed by researchers at Brown University (www.cebm.brown.edu/openmeta/).[21] The two tools produced similar results.

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RESULTS

Literature search disclosed 46 publications on nivolumab, 53 publications on pembrolizumab, 8 publications on atezolizumab, 10 publications on avelumab, and 6 publications on durvalumab in gastric or gastroesophageal adenocarcinoma (Fig. 1). Among these publications, a total of 115 articles were reviews, opinions, or clinical studies that did not include arms with PD-1 or PD-L1 inhibitors as monotherapy and thus were excluded. One study of nivolumab was excluded because it concerned squamous histology.[22] Another small study of 23 patients treated with nivolumab included mostly squamous carcinomas and only five patients with adenocarcinomas and was also excluded.[23] Clinical studies that fulfilled the inclusion criteria included three publications on pembrolizumab,[24–26] two articles on nivolumab,[27,28] and one article with avelumab.[29] No trials concerning gastric or gastroesophageal adenocarcinoma with monotherapy arms of atezolizumab or durvalumab were identified. The six articles included were published between 2016 and 2018 and concerned the monotherapy arm of multi-arm trials ($n = 4$) or single-arm reports ($n = 2$) (Table 1). The six studies included a total of 1068 patients in their PD-L1 or PD-1 inhibitors monotherapy arms that were analyzed for efficacy and toxicity outcomes. Five of the six trials were performed globally and one[28] was performed only in far Eastern countries (Table 1). One study included patients in the second line of treatment,[24] three studies included patients in the second line or higher line of treatment[25,27,29] and two studies included patients in the third line or higher of metastatic treatment.[26,28] The dose of medication in the three pembrolizumab studies was a fixed dose of 200 mg every 3 weeks in two studies and 10 mg/kg every 2 weeks in the third. Both nivolumab studies used a dose of 3 mg/kg every 2 weeks. The avelumab trial used a dose of 10 mg/kg every 2 weeks.

The median age of the patients in the six studies ranged between 59 and 64 years. Most patients (62.3%) had an ECOG PS of 1 and the rest (37.6%) had an ECOG PS of 0 (Table 2). The number of prior lines of therapy in the metastatic setting was 1 in 239 patients (22.4%), 2 lines in 385 patients (36.1%) and 3 or more lines of therapy in 437
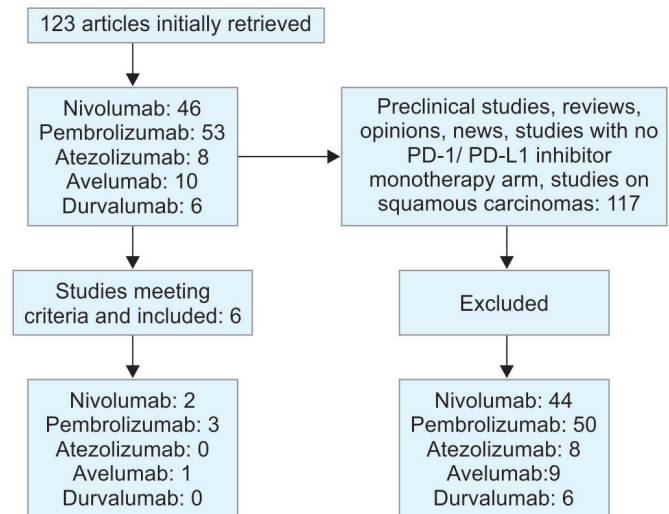

Fig. 1: Flow diagram of the studies evaluated for the meta-analysis and reasons for exclusion

Table 1: The six studies included in the current meta-analysis

First author [Reference]	Study registration number	Year of publication	Country	Total number of patients	Number of patients in analyzed arm	Line of treatment	RR (%)	DCR (%)
Janjigian[27]	NCT01928394	2018	USA, Europe (5 countries)	160	59	≥2nd	11.86	32.2
Shitara[24]	NCT02370498	2018	30 countries	395	196	2nd	15.82	NA
Muro[25]	NCT01848834	2016	USA, Israel, Japan, Korea, Taiwan	39	39	≥2nd	20.51	33.33
Fuchs[26]	NCT02335411	2018	16 countries	259	259	≥3rd	11.58	27.03
Kang[28]	NCT02267343	2017	Japan, Korea, Taiwan	493	330	≥3rd	9.09	32.73
Bang[29]	NCT02625623	2018	Global	371	185	2nd, 3rd	2.16	22.16

Table 2: Characteristics of the included patients from the six studies. Some characteristics were available in only part of the studies. The intestinal histologic type includes variants

	Patients (n = 1068)	%
Age medians (range)	59–64 (24–89)	56 (22–85)
ECOG PS		
0	402	37.6
1	665	62.3
2	1	0.1
Histologic type	n = 970 (4 studies)	
Intestinal	520	53.6
Diffuse/mixed	174	17.9
Unknown/other	276	28.5
Prior lines of chemotherapy		
0	6	0.6
1	239	22.4
2	385	36.1
≥3	437	40.9
Location	n = 737 (5 studies)	
GEJ	309	41.9
Stomach	428	58.1
PD-L1	n = 821	
Positive	461	56.2
Negative	360	43.8
MSI status	n = 199 (some patients from 2 studies)	
MSI-H	14	7.0
MSI-L	185	93.0
HER2 status	n = 331 (2 studies)	
Positive	107	32.3
Negative	224	67.7
Efficacy		
Median OS (months) (95% CI)	5.72	0–12.19
Median PFS (months) (95% CI)	1.59	1.24–1.94
RR% (95% CI)	10.63	5.36–15.89
DCR% (95% CI)	28.11	24.6–31.63

patients (40.9%). Information on the location of the primary tumor was available in 737 patients from 5 studies. The gastroesophageal junction was the location of the primary tumor in 41.9% of those patients and the rest of the stomach in 58.1% of the patients (Table 2).

The majority of the patients (53.6%) had an intestinal histologic type and 17.9% of patients had a diffuse or mixed histologic type. Regarding PD-L1 and HER2 status, the information was available in 821 and 331 patients, respectively. A total of 56.2% of patients were positive for PD-L1 and 32.3% of patients were positive for HER2. Microsatellite status (MSI) was reported in two studies,[24,25] although these data were not available in all patients even in these two studies. Overall 199 patients had data for MSI status and 14 patients (7%) were MSI-H (MSI High). No studies included data on tumor mutation burden or EBV status of the tumors. Similarly, no data were presented in any of the six studies regarding smoking which may be related to the mutation burden of the tumors.

The risk of bias is estimated to be moderate in five of the six studies due to their phase II non-randomized design or randomized open-label design.[24–27,29] These designs could be associated with biases in the domains of intervention assignment and adhesion and of outcomes measurement. One study was double-blind, placebo-controlled.[28] This design has a lower risk of bias.

The analysis of RR from the six studies disclosed a summary RR of 10.63% (95% CI 5.36–15.89%) (Fig. 2). Evaluation of heterogeneity between studies confirmed a high level of heterogeneity with an I^2 value of 87 (Cochran's $Q = 40.23$, x^2 $p < 0.0001$) and thus a random effect model was used for the meta-analysis calculations.

Disease control rate was not available in one study[22] and the remaining five studies that included a total of 872 patients formed the basis of DCR calculation. Analysis for DCR showed that the five studies had low heterogeneity for this outcome with an I^2 value of 1.7 (Cochran's $Q = 5.84$, x^2 $p = 0.21$). As a result, the fixed-effect model was retained. The summary DCR was 28.11% (95% CI 24.60–31.63%) (Fig. 3).

Progression-free survival (PFS) analysis was performed under the random effect model as the level of heterogeneity between studies was high ($I^2 = 98$, Cochran's $Q = 292$, $x^2 p < 0.00001$). Summary PFS was 1.59 months (95% CI 1.24–1.94 months) (Fig. 4).

Finally, the summary OS was 5.72 months (95% CI 0–12.19 months) (Fig. 5). This analysis was also performed under the random effect model as the level of heterogeneity between studies was high ($I^2 = 66$, Cochran's $Q = 14.92$, $x^2 p = 0.01$).

Among the five studies that included both PD-L1 positive and PD-L1 negative patients, two studies reported RR separately for the two PD-L1 groups[26,27] and two other studies reported a median OS separately.[28,29] In one study that reported on RRs, RR in PD-L1-positive patients was 13% and RR in PD-L1-negative patients was 4%.[27] In the other study, RR was 15.5% in PD-L1-positive patients

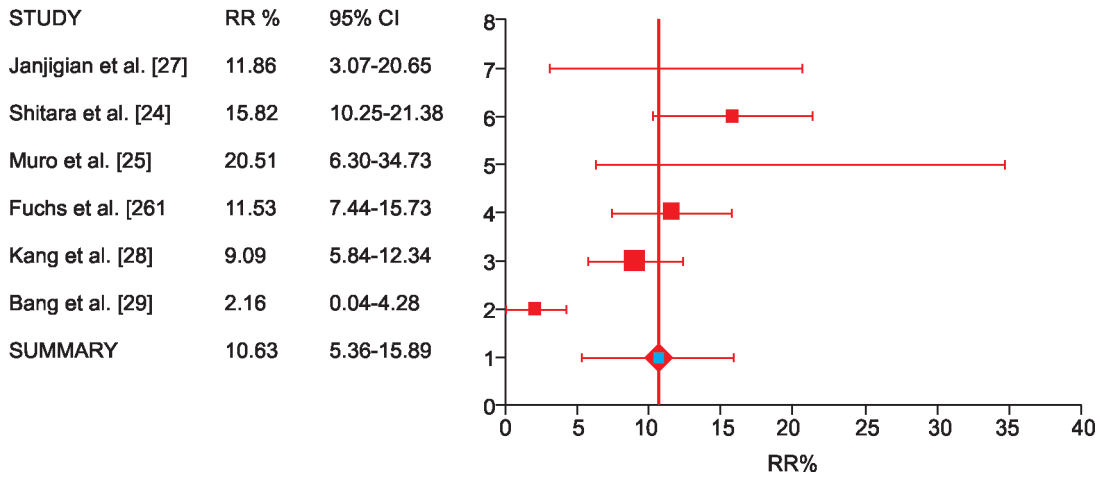| STUDY	RR %	95% CI
Janjigian et al. [27]	11.86	3.07-20.65
Shitara et al. [24]	15.82	10.25-21.38
Muro et al. [25]	20.51	6.30-34.73
Fuchs et al. [261	11.53	7.44-15.73
Kang et al. [28]	9.09	5.84-12.34
Bang et al. [29]	2.16	0.04-4.28
SUMMARY	10.63	5.36-15.89

Fig. 2: Diagram of RR and 95% CI of studies of PD-1 and PD-L1 inhibitors in metastatic gastric and gastroesophageal junction adenocarcinoma. The estimated overall RR was 10.63% (95% CI 5.36–15.89%)
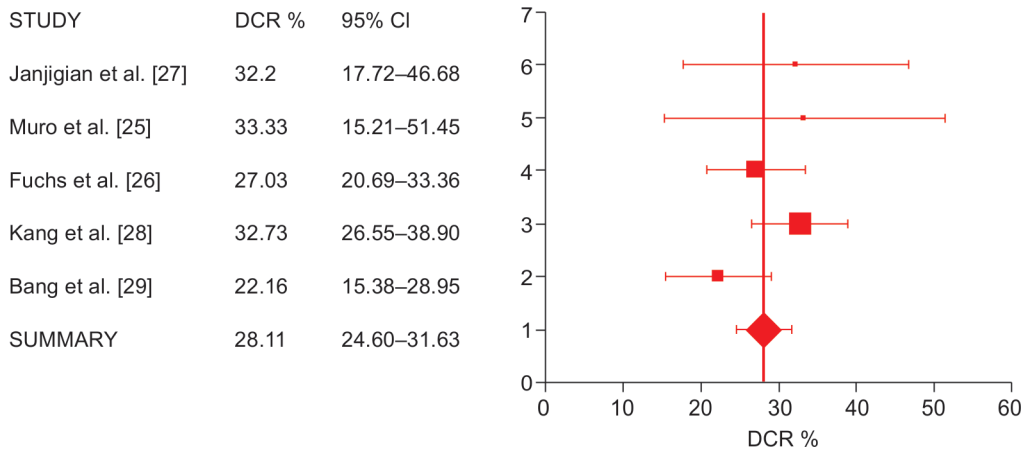
STUDY	DCR %	95% CI
Janjigian et al. [27]	32.2	17.72–46.68
Muro et al. [25]	33.33	15.21–51.45
Fuchs et al. [26]	27.03	20.69–33.36
Kang et al. [28]	32.73	26.55–38.90
Bang et al. [29]	22.16	15.38–28.95
SUMMARY	28.11	24.60–31.63

Fig. 3: Diagram of the meta-analysis of DCR and 95% CI. Five studies were included in this analysis. The overall DCR was 28.11% (95% CI 24.60–31.63%)

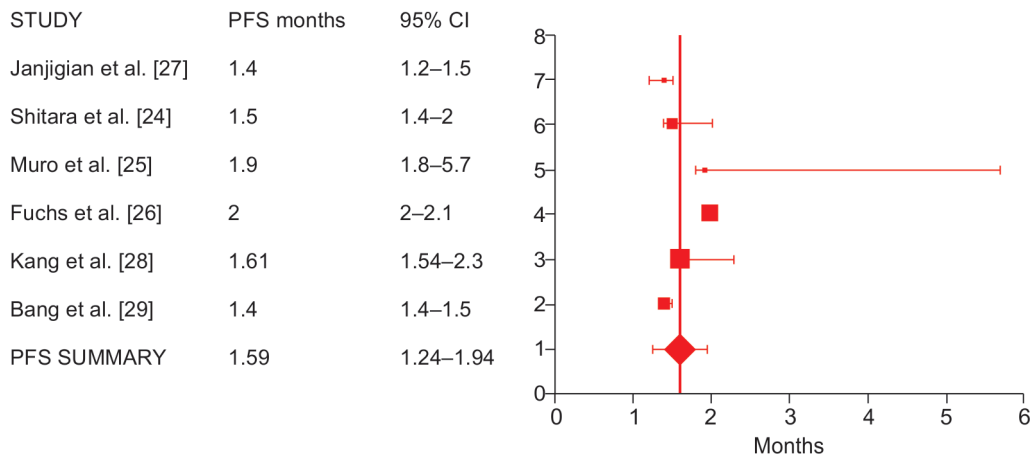| STUDY	PFS months	95% CI
Janjigian et al. [27]	1.4	1.2–1.5
Shitara et al. [24]	1.5	1.4–2
Muro et al. [25]	1.9	1.8–5.7
Fuchs et al. [26]	2	2–2.1
Kang et al. [28]	1.61	1.54–2.3
Bang et al. [29]	1.4	1.4–1.5
PFS SUMMARY	1.59	1.24–1.94

Fig. 4: Diagram of PFS in the six studies that form the basis of the report and summary estimates of PFS. Summary PFS was 1.59 months (95% CI 1.24–1.94 months)
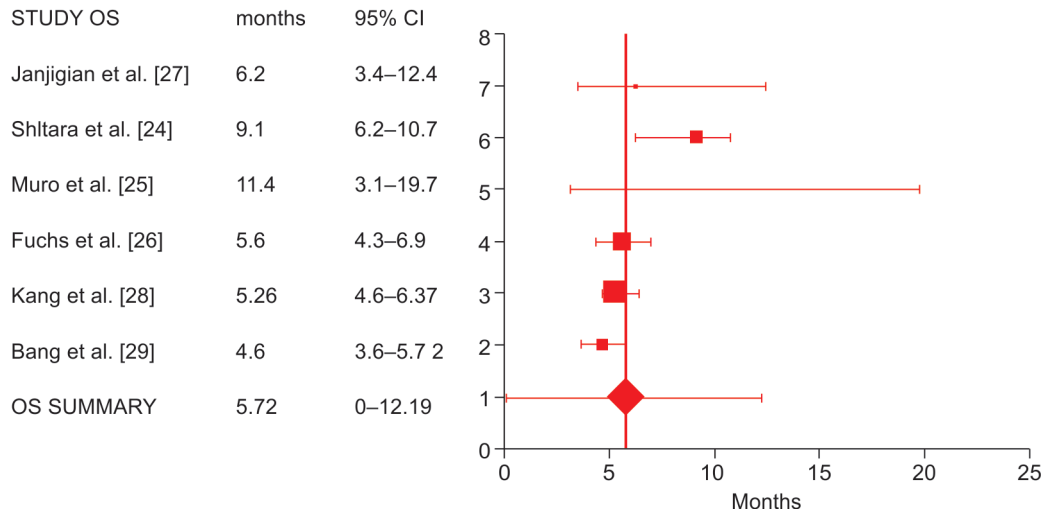
STUDY OS	months	95% CI
Janjigian et al. [27]	6.2	3.4–12.4
Shltara et al. [24]	9.1	6.2–10.7
Muro et al. [25]	11.4	3.1–19.7
Fuchs et al. [26]	5.6	4.3–6.9
Kang et al. [28]	5.26	4.6–6.37
Bang et al. [29]	4.6	3.6–5.7 2
OS SUMMARY	5.72	0–12.19

Fig. 5: Meta-analysis of OS and 95% CI. Summary OS was 5.72 months (95% CI 0–12.19 months)

and 6.4% in PD-L1-negative patients.[26] In contrast, in both studies that reported on the median OS, these were no better in PD-L1 positive patients (median OS 5.22 months and 4 months in PD-L1 positive patients and 6.05 months and 4.6 months in PD-L1 negative patients, respectively).

Response rates of the trial that included only patients at the second line of treatment (15.82%, 95% CI: 10.25–21.38%)[24] was only minimally higher than the RR of the two trials that included only patients at the third or later lines of treatment (11.58%, 95% CI: 7.44–15.73% and 9.09%, 95% CI: 5.84–12.34%, respectively).[26,28] Similarly, PFS was not significantly different (1.5 months in the study with second-line patients, 2 months and 1.61 months in the two studies with a third and higher line of treatment patients). Overall survival was somewhat higher in the second-line study (9.1 months) than in the two studies that included third and higher line patients (5.6 and 5.26 months, respectively) but with overlapping 95% CIs.

Treatment with PD-1 and PD-L1 inhibitors was very well tolerated and the only adverse effects of all grades that were observed in more than 10% of patients were asthenia and pruritus or cutaneous rashes (Table 3). Severe immune-related adverse effects were very rare.

Discussion

Metastatic gastric and gastroesophageal adenocarcinoma remains a lethal disease despite increasing options for treatment.[30] Immunotherapy with PD-L1 and PD-1 inhibitors provides an additional option of treatment. These drugs are monoclonal antibodies that inhibit the interaction of the inhibitory PD-L1 or PD-1 pair and thus allow activation of effector cytotoxic T cells and NK cells to attack tumor cells if appropriate neo-antigens are presented on the tumor cells' surface.[31,32] Tumor types with high mutation loads such as lung cancers and melanoma as well as tumors with MSI independently of the primary site have been found to be most sensitive to PD-L1 or PD-1 inhibition.

In the current report six studies that included arms with patients with metastatic gastric or gastroesophageal adenocarcinomas who were treated with a PD-L1 or PD-1 inhibitor as monotherapy were identified and analyzed. A brief discussion of the design and results of the six studies follows.

Table 3: All-grade and grade 3–4 toxicities observed in the six included studies. Some toxicities were included in the toxicity discussion of some studies but not in others and thus the denominator is less than a total of 1068 patients

Toxicity %	All grades or total number of toxicity information mentioned	All grades (%)	Grade 3–4 or total number of toxicity information available	Grade 3–4 (%)
Asthenia/fatigue	147/1068	13.8	18/1068	1.7
Neutropenia	0	–	0	–
Febrile neutropenia	0	–	0	–
Anemia	29/640	4.5	14/640	2.2
Peripheral neuropathy	4/235	1.7	0	–
Nausea	69/970	7.1	3/970	0.3
Diarrhea	76/1029	7.4	8/1029	0.8
Alopecia	1/381	0.3	–	–
Pruritus/rash	115/883	13.0	2/883	0.2
Immune related				
Hyperthyroidism	12/526	2.3	0	–
Hypothyroidism	59/824	7.2	1/824	0.1
Interstitial lung disease	5/565	0.9	–	–
Colitis	2/526	0.4	–	–
Hypophysitis	3/526	0.6	–	–
Hepatitis/ enzymes elevation	47/574	8.2	21/574	3.6

The first nivolumab study included was a randomized phase II trial with three arms in chemotherapy pretreated patients without selection for PD-L1 status.[27] Besides the nivolumab monotherapy arm, the trial included two arms with combinations

of nivolumab and the CTLA-4 inhibitor ipilimumab in different doses. Objective RR (the primary endpoint) were 12% with nivolumab monotherapy, 24% in the arm that received nivolumab 1 mg/kg and ipilimumab 3 mg/kg and 8% in the arm that received nivolumab 3 mg/kg and ipilimumab 1 mg/kg with overlapping 95% confidence intervals in the three arms. The second nivolumab study included in the current analysis was a randomized phase III trial of nivolumab *vs* a placebo arm in the third or later line of treatment of metastatic gastric and gastroesophageal junction cancer also without selection for PD-L1 status.[28] The 1-year OS was 26.6% in the nivolumab arm *vs* 10.9% with placebo. The study showed a modest but statistically significant median OS increase with nivolumab from 4.14 months in the placebo arm to 5.32 months in the nivolumab arm.

Three studies included in the current analysis concerned pembrolizumab. A phase Ib study allowed patients with both PD-L1-positive and PD-L1-negative metastatic gastric and gastroesophageal junction adenocarcinoma.[25] This study observed partial responses in eight of the 36 (22%) evaluable patients and a median OS of 11.4 months. Importantly, some patients remained on treatment for protracted time periods exceeding 6 months.[25] A second pembrolizumab trial was an extensive phase II study that included 259 patients with gastroesophageal cancer, both PD-L1-positive and PD-L1-negative, who were treated in the third line metastatic setting.[26] Response rate was 11.58% and stable disease was observed in 15.45% of patients, for a CBR of 27.03%. The third pembrolizumab study included in the current analysis was a randomized, open-label, multicenter phase III trial in pretreated patients.[24] It included only PD-L1-positive patients defined as 1% or more positive staining in histologic sections counting both cancer and inflammatory cells. The second arm in this trial received weekly paclitaxel. Although better tolerated, pembrolizumab did not improve PFS or OS compared with paclitaxel.[24]

The anti-PD-L1 antibody avelumab was the subject of investigation in the last included study which was a phase III trial in patients with metastatic gastric or gastroesophageal junction adenocarcinoma irrespective of PD-L1 status in the second or third-line setting.[29] This study compared avelumab with a control arm of physician's choice chemotherapy. Most patients (64.5%) in the control arm received irinotecan and 29% received paclitaxel. The trial showed no improvement in OS or PFS with avelumab *vs* chemotherapy.[29]

The pooled analysis of the six monotherapy arms disclosed a low RR of about 10% and an equally unimpressive DCR of 28.1%. Summary PFS was just above 1.5 months and summary OS was below 6 months. These results confirm a low efficacy of PD-L1 or PD-1 inhibitors in mostly unselected patients with metastatic adenocarcinoma of the stomach and gastroesophageal junction. Similar results have been reported in a phase II study of nivolumab in 64 patients with esophageal squamous cell carcinoma.[22] Objective RR in this study was 17% and DCR was 42%. Despite these mediocre results several points deserve noticing regarding the efficacy of PD-L1 or PD-1 inhibitors in gastric and gastroesophageal junction adenocarcinoma. First as seen in most other cancers there were long-term responses among responders and in fact, long-term responses are not rare. As a result, a significant minority of patients derive long-term benefits. Thus, the challenge becomes to identify biomarkers that would predict the efficacy of these immunotherapeutic drugs. In this direction, the first identified marker that has been

intuitively identified is the expression of the target ligand, PD-L1. The expression of PD-L1 has been tested in other cancers and is successfully used as a biomarker for patient selection for treatment with pembrolizumab in lung cancer.[6] In contrast, it is not required for response in other cancers and other PD-1 or PD-L1 inhibitors. The studies in gastric or gastroesophageal junction adenocarcinomas, besides one study[24], allowed for the inclusion of patients independently from their PD-L1 status. Sub-group analysis of RR in two trials showed a numerically higher rate in PD-L1 positive patients than in PD-L1 negative counterparts (13 *vs* 4% in one trial and 15.5 *vs* 6.4% in the other).[26,27] However, two other trials that reported median OS separately in PD-L1 positive and negative patients disclosed no differences.[28,29] Another prognostic marker for immune blockade inhibitors efficacy is MSI status. A comparatively small number of patients from two studies (total of 174 patients) had a known MSI status. Among those, seven patients were MSI-H and four of them (57.1%) showed a response. In contrast, only 15 out of 167 patients with MSI-L status (9.0%) had a response to treatment. Other prognostic factors for Immune blockade inhibitors efficacy include tumor mutation burden and EBV status.[14,33] Unfortunately, no data on these factors have been reported in any of the six studies. Similarly, no information was provided in any of the studies regarding responses in histologic subtypes (intestinal *vs* diffuse) or HER2-positive *vs* negative tumors.

Line of treatment may affect the observed efficacy of a given therapy in the metastatic setting, as treatments tend to become less efficacious as a given cancer progresses along previous lines of therapy developing the most complex genetic aberrations. Three of the studies of the current meta-analysis included patients across lines of metastatic treatment and thus are not informative regarding this point.[25,27,29] Among the other three trials, one included only second-line patients[24] and two included third or higher-line patients.[26,28] Comparison of survival of patients that received PD-1 or PD-L1 inhibitors in the different lines of therapy shows that PFS was very similar in the second and third or higher lines of treatment but OS was numerically longer in the second line of therapy. Of note, however, the study that included only patients in the second line was also the only one that had PD-L1 positivity as an inclusion criterion.[24]

Adverse effects profile of PD-L1 or PD-1 inhibitors in gastric or gastroesophageal junction adenocarcinomas were entirely consistent with this profile reported in other cancers. A meta-analysis of 31 studies of nivolumab across different cancers, for example, reported a rate of 10.4% for asthenia of all grades, 13% for the rash of all grades, 11.8% for nausea of all grades, and 12.1% for diarrhea of all grades.[34] These were all similar to adverse effects observed in the current meta-analysis (Table 3). Regarding immune-related adverse effects, the same meta-analysis of 31 studies observed hypothyroidism and transaminases elevations as the most common immune-related adverse effects and also very consistent with the current meta-analysis.

Limitations of the present meta-analysis consist mostly of the aforementioned lack of information regarding predictive markers that could enrich for responding patients and guide further development of the drugs. Another limitation could stem from the inclusion of studies with both anti-PD-1 drugs (nivolumab and pembrolizumab) and anti-PD-L1 drugs (avelumab) in the analysis. Despite blocking the same pair of ligand or receptor, the target proteins expression defers in the various cells of the tumor micro-environment and thus therapeutic effects may not

be completely super-imposable. Nevertheless, results with the only study with an anti-PD-L1 agent available and included in the analysis were generally consistent with the results of the remaining five studies of anti-PD-1 drugs. However, one notices that efficacy measures in the avelumab study tended to be the lowest among studies.

The current systematic review and meta-analysis observed low RR and survival outcomes of PD-1 or PD-L1 inhibitors in mostly unselected patients with gastric or gastroesophageal junction adenocarcinomas. Further establishment of this class of drugs in this disease will rely on marker-identified patients with higher response probabilities as well as on synergistic combinations. Predictive markers, such as, MSI status, EBV status, tumor mutation burden, as well as PD-L1 expression already exist and await further refinement for clinical use. As mentioned previously the only current approval of a PD-1 or PD-L1 inhibitor by the FDA in gastric or gastroesophageal junction adenocarcinomas is for pembrolizumab for PD-L1 positive cancers.[17] Improvement of these markers, for example taking into consideration specific mutation signatures with the differing propensity for neo-antigen production, could provide even more predictive power. Further studies results are eagerly awaited.[35,36]

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