

Efficacy and safety of anti-PD-1/PD-L1 agents vs chemotherapy in patients with gastric or gastroesophageal junction cancer: a systematic review and meta-analysis

Bi-Cheng Wang, MD^{a,*}, Zhan-Jie Zhang, MD^a, Chen Fu, MS^b, Chang Wang, MS^c

Abstract

Background: Current therapeutic options have limited efficacy for patients with advanced gastric or gastroesophageal junction cancer. Immune checkpoint inhibition now has been increasingly used in advanced gastric or gastroesophageal junction cancer therapy. To further understand the efficacy and safety of anti-programmed cell death 1 (PD-1) and its ligand 1 (PD-L1) agents is critical for clinical practice. We conducted this systematic review and meta-analysis to assess the benefit and risk of PD-1 and PD-L1 inhibitors.

Methods: The PubMed, EMBASE, Cochrane Library, and Web of Science online databases were searched up to Jun 16, 2019. Primary outcomes were overall survival (OS), progression-free survival (PFS). Second outcomes were objective response rate (ORR), disease control rate (DCR) and adverse events.

Results: Six studies were assessed for inclusion in the final synthesis, of which 5 were eligible for meta-analysis. Compared with chemotherapy, the pooled hazard ratio (HR) for OS and PFS was, respectively, 1.01 (95% confidence interval [CI]: 0.88–1.15, $P = .93$) and 1.58 (95% CI: 1.38–1.81, $P < .001$) after treatment with PD-1/PD-L1 inhibitors. In patients treated with anti-PD-1/PD-L1 agents, the pooled ORR was 9.9% (95% CI: 4.4%–15.5%) and the pooled DCR was 30.8% (95% CI: 21.8%–39.9%). Sub-analysis for treatment related adverse events indicated that fatigue was the most common toxicity in anti-PD-1/PD-L1 therapy (incidence 10.6%, 95% CI: 5.6%–15.6%).

Conclusion: PD-1/PD-L1 inhibitors appear to improve the antitumor activity in advanced gastric or gastroesophageal junction cancer patients. However, single-agent PD-1/PD-L1 inhibitor did not result in a relative improvement in OS and PFS compared with chemotherapy in the treatment of patients with advanced gastric or gastroesophageal junction cancer. Further randomized clinical trials are warranted to confirm our findings.

Abbreviations: CI = confidence interval, DCR = disease control rate, HR = hazard ratio, ORR = objective response rate, OS = overall survival, PD-1 = programmed cell death 1, PD-L1 = programmed death-ligand 1, PFS = progression-free survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, VEGFR2 = vascular endothelial growth factor 2.

Keywords: gastric cancer, gastroesophageal junction cancer, immune checkpoint inhibitor, PD-1, PD-L1

Editor: Undurti N. Das.

The authors have no funding and conflicts of interests to disclose.

^aCancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, ^bDepartment of Dermatology, the First Hospital of Wuhan, Wuhan, China, ^cInstitute of Anatomy, University of Bern, CH-3012 Bern, Switzerland.

* Correspondence: Bi-Cheng Wang, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, China (e-mail: bcsnowell@163.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Wang BC, Zhang ZJ, Fu C, Wang C. Efficacy and safety of anti-PD-1/PD-L1 agents vs chemotherapy in patients with gastric or gastroesophageal junction cancer: a systematic review and meta-analysis. *Medicine* 2019;98:47(e18054).

Received: 22 July 2019 / Received in final form: 16 October 2019 / Accepted: 22 October 2019

<http://dx.doi.org/10.1097/MD.00000000000018054>

Highlights:

1. PD-1/PD-L1 inhibitors showed a similar overall survival outcome in comparison with chemotherapy in the treatment of patients with advanced gastric or gastroesophageal junction cancer.
2. PD-1/PD-L1 inhibitors increased the risk of disease progression relative to chemotherapy in the treatment of patients with advanced gastric or gastroesophageal junction cancer.
3. Anti-PD-1 therapy had higher response rates than anti-PD-L1 therapy for treating advanced gastric or gastroesophageal junction cancer.

1. Introduction

Gastric or gastroesophageal junction cancer is the fifth most common cancer and the third most common cause of cancer mortality worldwide.^[1] Patients with newly diagnosed advanced gastric or gastroesophageal junction cancer have a poor prognosis, with approximately 1-year lifespan. Particularly, patients with recurrent or refractory gastric or gastroesophageal junction cancer have an even worse prognosis.^[2–5]

For advanced gastric or gastroesophageal junction cancer patients, treatment with platinum and fluoropyrimidine is the standard first line therapy, with trastuzumab added for patients with human epidermal growth factor 2 positive tumors.^[6–10] The second line treatment options for patients with disease progression include docetaxel, paclitaxel, or irinotecan and the vascular endothelial growth factor 2 (VEGFR2) monoclonal antibody ramucirumab alone or in combination with paclitaxel.^[11–16] At present, no standard third-line therapy is available for patients whose disease progresses after 2 or more lines of systemic therapy that have been recommended by international treatment guidelines.^[18,9,17,18] Thus, new treatment options for patients with advanced gastric or gastroesophageal junction cancer are urgently needed.

Immune checkpoint inhibitors such as programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors have revolutionized cancer therapy in recent years.^[19,20] Overexpression of PD-L1 has been observed in 65% of gastric cancer,^[21] making blockage of PD-1/PD-L1 signaling pathway a rational target in patients with gastric or gastroesophageal junction cancer. Initial trial results have demonstrated the antitumor activity and safety of immunotherapy in patients with unresectable advanced or recurrent gastric or gastroesophageal junction cancer in single-arm studies or randomized clinical trials using placebo or chemotherapy as the comparator. However, there is no consensus on the role of PD-1/PD-L1 inhibitors in the treatment of advanced gastric or gastroesophageal junction cancer.

We are interested in how treatment with anti-PD-1/PD-L1 agents compares with placebo/chemotherapy for the outcomes and adverse events. Thus, we performed this meta-analysis to integrate the benefit and risk of the PD-1/PD-L1 inhibitors in published clinical trials of gastric or gastroesophageal junction cancer. The results of our analysis should provide useful guidance for future research.

2. Methods

We conducted the meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline (PRISMA).^[22] The data used in the analysis were not original raw data, but were based on the published clinical studies with ethical approvals. Therefore, ethical approval was not necessary.

2.1. Search strategy and study selection

The search was done in the electronic databases PubMed, Cochrane Library, Web of Science, and EMBASE to identify all relevant records until Jun 16, 2019. Additionally, the search terms, including “gastric cancer or gastroesophageal junction cancer or gastric adenocarcinoma or gastroesophageal junction adenocarcinoma”, “pembrolizumab or nivolumab or avelumab or atezolizumab or durvalumab”, and “trial or clinical trial or randomized clinical trial or randomized controlled trial”, were used to identify relevant articles with no restriction on language. The references of relevant published studies and review articles were searched for more eligible trials. The search results were uploaded into EndNote (<http://endnote.com/>) for further review.

2.2. Inclusion and exclusion criteria

Studies eligible for inclusion met all of the following criteria:

- (1) prospective clinical trials in patients with gastric or gastroesophageal junction cancer,

- (2) participants in immunotherapy arm were treated with a single anti-PD-1/PD-L1 agent,
- (3) antitumor activity and safety data were available.

Conference abstracts were excluded due to the increase of heterogeneity. For multiple publications that were identified reporting on the same clinical study, the one with the most complete publication data was eligible. Any discrepancies were resolved by discussion.

2.3. Data extraction

Detailed reviews of full-text articles regarding trial name, study design, drug used, number of patients, PD-L1 status, line of chemotherapy, and survival outcomes were independently performed by Bi-Cheng Wang and Chen Fu. The hazard ratios (HR) of overall survival (OS) and progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and safety data reporting in the studies and supplementary materials were obtained from each eligible trial.

2.4. Statistical analysis

OS and PFS data from randomized controlled trials were assessed by HR and 95% confidence interval (CI). RevMan version 5.3 software (Cochrane Collaboration’s Information Management System) was used to conduct this part meta-analyses. A fixed-effects model was used when the heterogeneity test showed no statistical significance ($P \geq .10$, $I^2 \leq 50\%$). Otherwise, a random-effects model was applied. $P < .05$ was considered statistically significant differences.

Pooled incidences of ORR, DCR, any-grade treatment related adverse events, and grade ≥ 3 treatment related adverse events were done using STATA statistical software (version 14.0). The analyses were conducted in a Random-effects model. Statistical heterogeneity among the studies was tested by the Cochran Q chi-square test and I^2 statistic percentages. Low heterogeneity was defined as $I^2 < 50\%$ or $P < .10$. Publication bias for small-study effects was evaluated by egger test.

3. Results

3.1. Eligible studies and characteristics

Our search of the PubMed, EMBASE, Cochrane Library, and Web of Science databases identified 388 relevant publications. We then excluded 125 records after screening the titles and abstracts. After eligibility assessment, a total of five clinical trials involving were selected for inclusion in the systematic review,^[23–27] comprising three randomized controlled trial and 2 single arm trials (Fig. 1). Patients with advanced gastric or gastroesophageal junction cancer in single anti-PD-1/PD-L1 agent arm were selected for final meta-analysis. The characteristics of the eligible studies were displayed in Table 1. The survival outcomes in the selected studies were presented in Table 2.

3.2. Overall survival (OS)

OS data was available from 2 studies,^[25,27] including 481 patients in the anti-PD-1/PD-L1 group and 482 patients in the chemotherapy group. Forest plots showed that the anti-PD-1/PD-L1 group had a similar risk of death compared to chemotherapy group (hazard ratio [HR]: 1.01, 95% CI: 0.88–1.15, $P = .93$; heterogeneity [H]: $I^2 = 26\%$, $P = .25$) (Fig. 2).

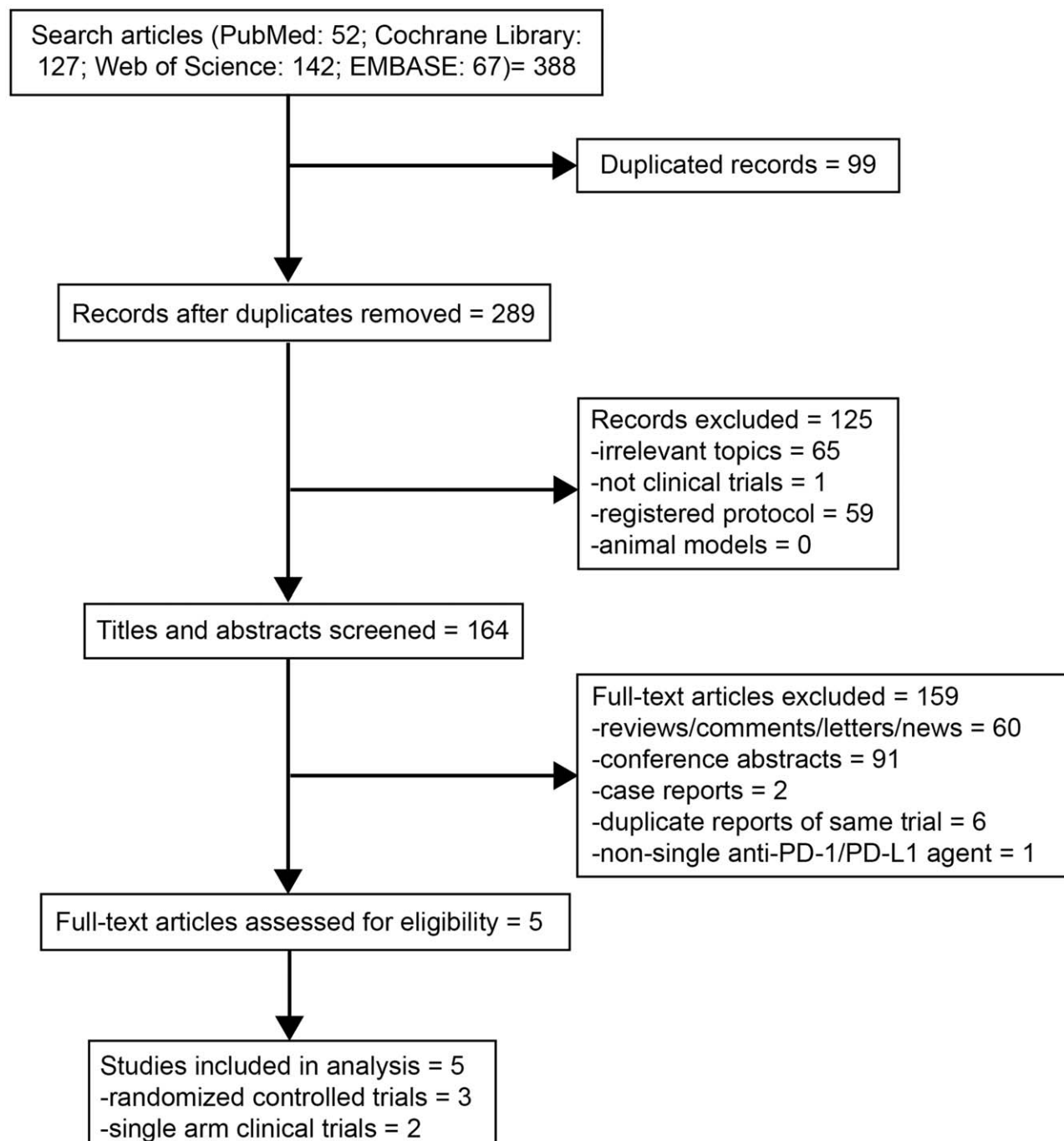


Figure 1. Flow chart of the study identification process.

3.3. Progression-free survival (PFS)

PFS data was extracted from the same 2 studies in the above analysis. Forest plots showed that patients in the anti-PD-1/PD-L1 group had a statistically significant higher risk of disease progression compared to the chemotherapy (HR: 1.58, 95% CI: 1.38–1.81, $P < .001$; H: $I^2 = 12\%$, $P = .29$) (Fig. 3).

3.4. Objective response rate (ORR)

The ORR data of advanced gastric or gastroesophageal junction cancer patients treated with anti-PD-1/PD-L1 agents

were available from 5 studies including 900 patients (Table 3). The pooled ORR was 9.9% (95% CI: 4.4%–15.5%). However, the test of heterogeneity showed that the heterogeneity was high ($I^2 = 88.9\%$, $P < .001$), and egger test indicated that there was a publication bias ($P = .069 < .1$). In the subgroup analysis, the pooled ORR was 11.3% (95% CI: 9.0%–13.7) in anti-PD-1 group, and 2.2% (95% CI: 0.1%–4.3%) in anti-PD-L1 group. These results suggested that PD-1 inhibitors might have a higher ORR than PD-L1 inhibitors in the treatment of advanced gastric or gastroesophageal junction cancer patients.

Table 1
Characteristics of the eligible studies.

Trial	Year	Design	Drug	No. Patients	Male	PD-L1+ patients	Age (mean, range)	Dose	Line
KEYNOTE-012	2016	Phase Ib	Pembrolizumab	39	28 (71.8%)	36 (100%)	63.0 (33–78)	10 mg/kg, q2weeks	0+
KEYNOTE-059	2018	Phase II	Pembrolizumab	259	198 (76.4%)	148 (57.1%)	62.0 (24–89)	200 mg, q3weeks	2+
KEYNOTE-061	2018	Phase III	Pembrolizumab	PEM: 296 PAC: 296	PEM: 202 (68.2%) PAC: 208 (70.3%)	PEM: 196 (66.2%) PAC: 199 (67.2%)	PEM: 62.5 (54–70) PAC: 60.0 (53–68)	200 mg, q3weeks	1+
ATTRACTION-2	2017	Phase III	Nivolumab	NIV: 330 PLA: 163	NIV: 229 (69.4%) PLA: 119 (73.0%)	NIV: 16/130 (12.3%) PLA: 10/62 (16.1%)	NIV: 62.0 (54–69) PLA: 61.0 (53–68)	3 mg/kg, q2weeks	2+
JAVELIN Gastric 300	2018	Phase III	Avelumab	AVE: 185 CHE: 186	AVE: 140 (75.7%) CHE: 127 (68.3%)	AVE: 46 (29.3%) CHE: 39 (24.4%)	AVE: 59.0 (29–86) CHE: 61.0 (18–82)	10 mg/kg, q2weeks	2+

AVE = avelumab, CHE = chemotherapy, Dose = anti-PD-1/PD-L1 agents dose, PAC = paclitaxel, PLA = placebo, PEM = pembrolizumab, NIV = nivolumab.

Table 2
Summary of the outcomes in the selected studies.

Study	Median follow-up (months)	Median duration of response (months)	Median PFS (months)	Median OS (months)
KEYNOTE-012	10.8 (IQR: 3.5–14.0)	1.9 (IQR: 1.6–1.9)	1.9 (95% CI: 1.8–3.5)	11.4 (95% CI: 5.7–NRD)
KEYNOTE-059	5.8 (range: 0.5–21.6)	8.4 (range: >1.6–>17.3)	2.0 (95% CI: 2.0–2.1)	5.6 (95% CI: 4.3–6.9)
KEYNOTE-061	7.9 (IQR: 3.4–14.6)	PEM: 18.0 (95% CI: 8.3–NRD) PAC: 5.2 (95% CI: 3.2–15.3)	PEM: 1.5 (95% CI: 1.4–1.6) PAC: 4.1 (95% CI: 3.2–4.2)	PEM: 6.7 (95% CI: 5.4–8.9) PAC: 8.3 (95% CI: 7.7–8.8)
ATTRACTION-2	NIV: 8.87 (IQR: 6.57–12.37) PLA: 8.59 (IQR: 5.65–11.37)	NIV: 9.53 (95% CI: 6.14–9.82) PLA: NR	NIV: 1.61 (95% CI: 1.54–2.30) PLA: 1.45 (95% CI: 1.45–1.54)	NIV: 5.26 (95% CI: 4.60–6.37) PLA: 4.14 (95% CI: 3.42–4.86)
JAVELIN Gastric 300	AVE: 10.6 (range: 0.1–17.8) CHE: 10.6 (range: 0.0–17.6)	NR	AVE: 1.4 (95% CI: 1.4–1.5) CHE: 2.7 (1.8–2.8)	AVE: 4.6 (95% CI: 3.6–5.7) CHE: 5.0 (4.5–6.3)

AVE = avelumab, CI = confidence interval, CHE = chemotherapy, IQR = interquartile range, NIV = nivolumab, NRD = not reached, NR = not reported, PAC = paclitaxel, PEM = pembrolizumab, PLA = placebo.

Overall survival

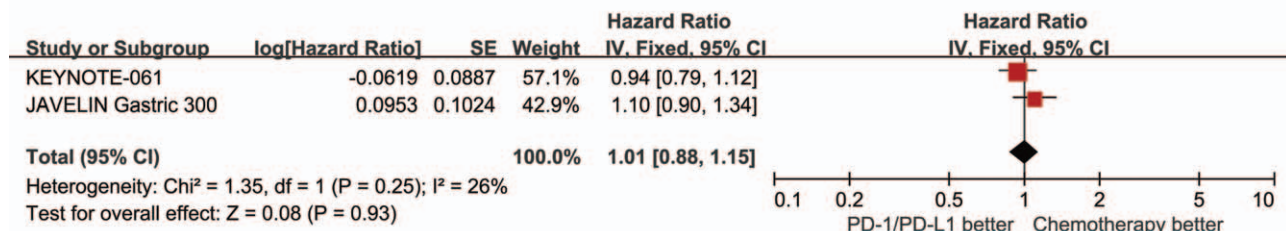


Figure 2. Forest plots of hazard ratios for overall survival in patients with gastric or gastroesophageal junction cancer between PD-1/PD-L1 inhibitor group and chemotherapy group. CI = confidence interval, I² = index of heterogeneity, IV = Inverse Variance statistical method, Fix = Fixed effect analysis model.

Progression-free survival

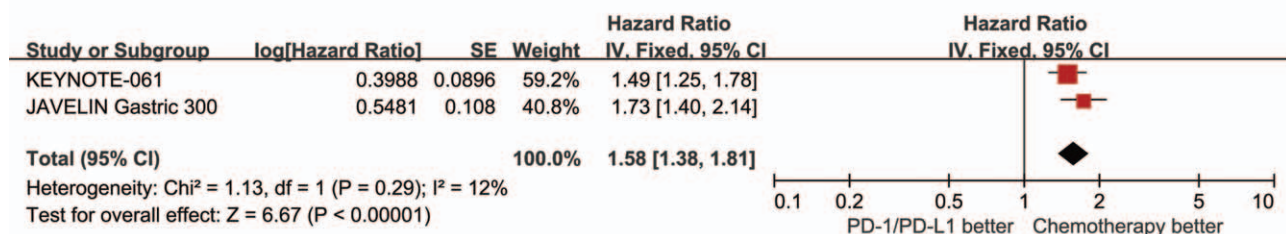


Figure 3. Forest plots of hazard ratios for progression-free survival in patients with gastric or gastroesophageal junction cancer between PD-1/PD-L1 inhibitor group and chemotherapy group.

Study	n	Incidence	95% CI
Anti-PD-1			
KEYNOTE-012	36	22.2%	8.6%–35.8%
KEYNOTE-059	259	11.6%	7.7%–15.5%
KEYNOTE-061	152	9.9%	5.1%–14.6%
ATTRACTION-2	268	11.2%	7.4%–15.0%
Sub-total	715	11.3%	9.0%–13.7%
Sub-H: $I^2=0\%$, $P=.414$			
Anti-PD-L1			
JAVELIN Gastric 300	185	2.2%	0.1%–4.3%
Sub-total	185	2.2%	0.1%–4.3%
Sub-H: -			
Total	900	9.9%	4.4%–15.5%
H: $I^2=88.9\%$, $P<.001$			
Egger test, $P=.069$			

CI=confidence interval, H=heterogeneity, n=number of patients.

3.5. Disease control rate (DCR)

The DCR data of patients treated with anti-PD-1/PD-L1 agents were available from four of 5 studies including 748 patients (Table 4). The pooled DCR was 30.8% (95% CI: 21.8%–39.9%). Although the heterogeneity was high ($I^2=85.1\%$, $P<.001$), no publication bias was observed through egger test ($P=.815>.1$). In anti-PD-1 group, the pooled DCR was 34.1% (95% CI: 23.9%–44.4%), an 11.9% higher rate in comparison with anti-PD-L1 group.

3.6. Treatment related adverse events

Overall, 412 (48.6%) of 847 advanced gastric or gastroesophageal junction cancer patients from 4 studies developed at least 1 any-grade adverse event, and 98 (11.6%) of 847 patients developed at least one adverse event of grade ≥ 3 .

The overall incidence of any-grade treatment related toxicities was 50.8% (95% CI: 43.4%–58.2%). Subgroup analysis showed that the incidence of any-grade treatment related toxicities was similar between anti-PD-1 group and anti-PD-L1 group (52.1% vs 48.9%) (Table 5).

The overall incidence of grade ≥ 3 treatment related toxicities was 11.3% (95% CI: 8.9%–13.7%). In addition, patients in anti-PD-1 group (12.0%, 95% CI: 9.3%–14.8%) had a slightly higher incidence compared with patients in anti-PD-L1 group (9.2%,

Study	n	Incidence	95% CI
Anti-PD-1			
KEYNOTE-012	36	36.1%	20.4%–51.8%
KEYNOTE-059	259	27.0%	21.6%–32.4%
ATTRACTION-2	268	40.3%	34.4%–46.2%
Sub-total	563	34.1%	23.9%–44.4%
Sub-H: $I^2=81.4\%$, $P=.005$			
Anti-PD-L1			
JAVELIN Gastric 300	185	22.2%	16.2%–28.1%
Sub-total	185	22.2%	16.2%–28.1%
Sub-H: -			
Total	748	30.8%	21.8%–39.9%
H: $I^2=85.1\%$, $P<.001$			
Egger test, $P=.815$			

CI=confidence interval, H=heterogeneity, n=number of patients.

Study	n	Incidence	95% CI
Anti-PD-1			
KEYNOTE-012	39	66.7%	51.9%–81.5%
KEYNOTE-061	294	52.7%	47.0%–58.4%
ATTRACTION-2	330	42.7%	37.4%–48.1%
Sub-total	663	52.1%	41.5%–62.8%
Sub-H: $I^2=83.8\%$, $P=.002$			
Anti-PD-L1			
JAVELIN Gastric 300	184	48.9%	41.7%–62.8%
Sub-total	184	48.9%	41.7%–62.8%
Sub-H: -			
Total	847	50.8%	43.4%–58.2%
H: $I^2=75.8\%$, $P=.006$			
Egger test, $P=.259$			

CI=confidence interval, H=heterogeneity, n=number of patients.

95% CI: 5.1%–13.4%) in the subgroup analysis of grade ≥ 3 treatment related adverse events (Table 6).

The most frequent any-grade toxicities were fatigue (10.6%, 95% CI: 5.6%–15.6%), pruritus (9.2%, 95% CI: 6.9%–11.4%), rash (6.9%, 95% CI: 4.2%–9.5%), hypothyroidism (6.4%, 95% CI: 3.1%–9.7%), diarrhea (6.2%, 95% CI: 4.8%–7.7%), decreased appetite (6.0%, 95% CI: 3.8%–8.2%), and nausea (5.5%, 95% CI: 4.1%–6.9%) (Table 7). For grade ≥ 3 treatment related toxicities, anemia (2.5%, 95% CI: 1.2%–3.8%) was most common, followed by fatigue (1.3%, 95% CI: 0.3%–2.2%), decreased appetite (0.9%, 95% CI: 0.2%–1.6%), diarrhea (0.5%, 95% CI: 0.1%–1.0%), and nausea (0.5%, 95% CI: 0.1% to 1.0%) (Table 8).

3.6.1. Publication bias. Owing to the small number of the studies analyzed, publication bias was not assessed for OS and PFS. In the results of egger test, publication bias was only observed in the ORR analysis ($P=.069<.1$), whereas the analyses of DCR ($P=.815>.1$), any-grade adverse events ($P=.259>.1$), and grade ≥ 3 adverse events ($P=.786>.1$) showed no publication bias.

Study	n	Incidence	95% CI
Anti-PD-1			
KEYNOTE-012	39	12.8%	2.3%–23.3%
KEYNOTE-061	294	14.3%	10.3%–18.3%
ATTRACTION-2	330	10.3%	7.0%–13.6%
Sub-total	663	12.0%	9.3%–14.8%
Sub-H: $I^2=13.2\%$, $P=.316$			
Anti-PD-L1			
JAVELIN Gastric 300	184	9.2%	5.1%–13.4%
Sub-total	184	9.2%	5.1%–13.4%
Sub-H: -			
Total	847	11.3%	8.9%–13.7%
H: $I^2=14.4\%$, $P=.320$			
Egger test, $P=.786$			

CI=confidence interval, H=heterogeneity, n=number of patients.

Table 7
Pooled sub-analysis of any-grade adverse events.

AEs	Incidence	95% CI
Fatigue	10.6%	5.6%–15.6%
Pruritus	9.2%	6.9%–11.4%
Rash	6.9%	4.2%–9.5%
Hypothyroidism	6.4%	3.1%–9.7%
Diarrhea	6.2%	4.8%–7.7%
Decreased appetite	6.0%	3.8%–8.2%
Nausea	5.5%	4.1%–6.9%
Anemia	3.4	–0.0%–6.8%
Pneumonia	1.3%	–1.0%–3.7%

AEs = adverse events, CI = confidence interval.

4. Discussion

Findings from our meta-analysis suggested that PD-1/PD-L1 inhibitors did not significantly decrease the relative risk of death compared with chemotherapy in patients with advanced gastric or gastroesophageal junction cancer after at least 1 line of standard chemotherapy. Moreover, anti-PD-1/PD-L1 immunotherapy significantly increased 58% of the risk of disease progression.

Promising activity and manageable safety of anti-PD-1/PD-L1 immunotherapy had already been demonstrated in patients with advanced gastric or gastroesophageal junction cancer. In the single arm clinical trial KEYNOTE-059,^[24] the ORR was 11.6% (95% CI: 8.0%–16.1%) when patients were treated with pembrolizumab, and PD-L1 positive cancer showed a higher ORR relative to PD-L1 negative cancer (15.5% vs 6.4%). Patients treated with pembrolizumab in the previous phase Ib study KEYNOTE-012 had also an expectable overall response rate (22%).^[23] Accordingly, the Food and Drug Administration (FDA) granted accelerated approval for pembrolizumab for the treatment of patients with advanced or recurrent gastric or gastroesophageal junction cancer.^[28] Another anti-PD-1 agent, nivolumab, exhibited a significantly lower risk of death than placebo, and prolonged the median OS from 4.14 months to 5.26 months.^[26] These survival benefits indicated that PD-1 inhibitors might be new treatment options for heavily pretreated advanced gastric or gastroesophageal junction cancer patients. However, the median PFS was less than 2 months, making the physicians and patients hard to choose immunotherapy.

In KEYNOTE-061 studies, the differences were carefully analyzed between pembrolizumab and paclitaxel in patients with previously treated, advanced gastric or gastroesophageal junction cancer.^[25] In the overall population, pembrolizumab group had a shorter median OS (6.7 months vs 8.3 months) and an obviously shorter median PFS (1.5 months vs 4.1 months). Even

Table 8
Pooled sub-analysis of grade ≥ 3 adverse events.

AEs	Incidence	95% CI
Anemia	2.5%	1.2%–3.8%
Fatigue	1.3%	0.3%–2.2%
Decreased appetite	0.9%	0.2%–1.6%
Diarrhea	0.5%	0.1%–1.0%
Nausea	0.5%	–0.1%–1.0%
Pneumonia	0.4%	–0.1%–0.9%
Hypothyroidism	0.4%	–0.3%–1.2%

AEs = adverse events, CI = confidence interval.

in the PD-L1 positive population, the median OS was 9.1 months with pembrolizumab and 8.3 months with paclitaxel. The authors still considered that pembrolizumab did not improve the OS in comparison with paclitaxel. The lack of survival benefits with blockage of PD-1/PD-L1 therapy was consistent with finding from JAVELIN Gastric 300 study.^[27] These suggested that PD-1/PD-L1 antagonists might not be superior to chemotherapy in the treatment of patients with pretreated and advanced gastric or gastroesophageal junction cancer.

In our findings, patients treated with PD-1 inhibitors achieved higher response rates compared with patients received PD-L1 inhibitors therapy in the overall population. When patients were treated with pembrolizumab or nivolumab, the ORRs were ranged from 9.9% to 22.2%. The KEYNOTE-012 demonstrated the highest ORR partly due to the earlier line of immunotherapy that patients received. However, participants in JAVELIN Gastric 300 showed only 2.2% ORR, extremely low response rate relative to other studies. To analyze the difference, we noticed that 16 of 130 (12.3%) patients in nivolumab arm and 10 of 62 (16.1%) patients in placebo arm were detected as elevated expression of PD-L1. Conversely, in post-hoc analysis of KEYNOTE-061, the treatment effects were greater for patients whose tumor had high expression levels of PD-L1 and for patients with microsatellite instability. Thus, we speculated that advanced gastric or gastroesophageal junction cancer patients with overexpressed PD-L1 might be more suitable for anti-PD-1/PD-L1 treatment.

Encouragingly, ATTRACTION-4 study reported that nivolumab combined with S-1 plus oxaliplatin or capecitabine plus oxaliplatin was well tolerated and demonstrated promising efficacy as the first-line therapy for unresectable advanced or recurrent gastric or gastroesophageal junction cancer.^[29] The median OS was over 13.9 months, and the median PFS was 9.7 months. In addition, the ORR was 65.8%, and the DCR was 84.2%. Compared with a single PD-1/PD-L1 inhibitor in our selected studies, immunotherapy in combination with chemotherapy had higher efficacy. The combination treatment strategy might be a better choice for patients with advanced gastric or gastroesophageal junction cancer in the future.

All eligible studies reported a manageable toxicity profile. Nonetheless, from the standpoint of patient counseling, several results of treatment related adverse events should be vigilant. Nearly 50.8% of patients with advanced gastric or gastroesophageal junction cancer treated with anti-PD-1/PD-L1 agents experienced at least one any-grade treatment related adverse event, and 11.3% had at least one grade ≥ 3 adverse event. Although the participants in the clinical trials were heavily pretreated, the incidence of grade ≥ 3 adverse events was low and symptomatic toxicities were observed equally in both anti-PD-1 and anti-PD-L1 groups. The three most common any-grade treatment related adverse events were fatigue (10.6%), pruritus (9.2%), and rash (6.9%). The 3 most common grade ≥ 3 treatment related adverse events were anemia (2.5%), fatigue (1.3%), and decreased appetite (0.9%). These numbers can be critically shared with patients with advanced gastric or gastroesophageal junction cancer before they begin anti-PD-1/PD-L1 therapy. Considering the potential risks, clinical vigilance is warranted for early recognition and intervention to prevent severe complications.

4.1. Limitations

This meta-analysis has several limitations. First, there were 3 randomized controlled trials, but only KEYNOTE-061 and

JAVELIN Gastric 300 studies were included in the comparison analysis, because ATTRACTION-2 was designed as placebo controlled study. The results of further researches, such as KEYNOTE 181 and KEYNOTE 585, are worth awaited. Second, although we had searched three PD-L1 inhibitors, no publications of atezolizumab or durvalumab were eligible for final analysis. Third, publication bias was observed in ORR analysis due to the small size of eligible studies. Despite these limitations, this meta-analysis is a meaningful study of the estimates of the efficacy and safety of PD-1/PD-L1 inhibitors in the treatment for advanced gastric or gastroesophageal junction cancer patients.

5. Conclusions

For patients with advanced gastric or gastroesophageal junction cancer, single anti-PD-1/PD-L1 inhibitor was not superior to chemotherapy. Although not studied via meta-analysis, anti-PD-1/PD-L1 therapy combined with traditional chemotherapy was an effective therapeutic regimen. Because four of 5 studies included in our meta-analysis were open-label or single arm clinical trials, bias cannot be excluded.

Acknowledgment

We thank the members of the Bi-Cheng Wang workgroup for their critical comments and for helping to improve the manuscript.

Author contributions

Conceptualization: Bi-Cheng Wang, Chen Fu.

Data curation: Bi-Cheng Wang, Chen Fu.

Formal analysis: Bi-Cheng Wang, Chen Fu.

Investigation: Bi-Cheng Wang, Chen Fu.

Methodology: Bi-Cheng Wang, Chen Fu.

Project administration: Bi-Cheng Wang, Chen Fu.

Resources: Bi-Cheng Wang, Chen Fu.

Software: Bi-Cheng Wang.

Supervision: Bi-Cheng Wang, Chang Wang.

Validation: Bi-Cheng Wang, Chen Fu.

Visualization: Bi-Cheng Wang, Chen Fu.

Writing – original draft: Bi-Cheng Wang, Zhan-Jie Zhang, Chang Wang.

Writing – review & editing: Bi-Cheng Wang, Zhan-Jie Zhang, Chang Wang.

References

- [1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359–386.
- [2] Noone AM, HN, Krapcho M. SEER cancer statistics review. 1975, 2015.
- [3] Chau I, Chen L-T, Kang Y-K, et al. Nivolumab safety profile in Asian and Western patients with chemotherapy-refractory (CTx-R) advanced gastric/gastroesophageal junction (adv G/GEJ) cancer from the ATTRACTION-2 and CheckMate-032 trials. *Journal of Clinical Oncology* 2018;36:
- [4] Wagner AD, SN, Moehler M. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2017;8:CD004064.
- [5] Digkila A, Wagner AD. Advanced gastric cancer: current treatment landscape and future perspectives. *World J Gastroenterol* 2016;22:2403–14.
- [6] Network NCC. NCCN clinical practice guidelines in oncology. Gastric cancer (version 5 2017) 2017.
- [7] Van Laethem JL, Carneiro F, Ducreux M, et al. The multidisciplinary management of gastro-oesophageal junction tumours: European Society of Digestive Oncology (ESDO): expert discussion and report from the 16th ESMO World Congress on Gastrointestinal Cancer, Barcelona. *Dig Liver Dis* 2016;48:1283–9.
- [8] Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;27(suppl 5):v38–49.
- [9] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017;20:1–9.
- [10] Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet (London, England)* 2010;376:687–97.
- [11] Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014;15:78–86.
- [12] Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer (Oxford, England: 1990)* 2011;47:2306–14.
- [13] Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012;30:1513–8.
- [14] Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol* 2013;31:4438–44.
- [15] Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet (London, England)* 2014;383:31–9.
- [16] Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224–35.
- [17] Ajani JA, D'Amico TA, Almhanna K, et al. Gastric cancer, version 3.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2016;14:1286–312.
- [18] Shen L, Shan YS, Hu HM, et al. Management of gastric cancer in Asia: resource-stratified guidelines. *Lancet Oncol* 2013;14:e535–47.
- [19] Li X, Shao C, Shi Y, et al. Lessons learned from the blockade of immune checkpoints in cancer immunotherapy. *J Hematol Oncol* 2018;11:31.
- [20] Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and anti-CTLA-4 therapies in cancer: mechanisms of action, efficacy, and limitations. *Front Oncol* 2018;8:86.
- [21] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014;513:202–9.
- [22] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med* 2009;3:e123–130.
- [23] Muro K, Chung HC, Shankaran V, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol* 2016;17:717–26.
- [24] Fuchs CS, Doi T, Jang RW. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial (vol 4, e180013, 2018). *Jama Oncol* 2019;5:579.
- [25] Shitara K, Ozguroglu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet (London, England)* 2018;392:123–33.
- [26] Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet (London, England)* 2017;390:2461–71.

- [27] Bang YJ, Ruiz EY, Van Cutsem E, et al. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. *Ann Oncol* 2018;29:2052–60.
- [28] Moriwaki T, Fukuoka S, Taniguchi H, et al. Propensity score analysis of regorafenib versus trifluridine/tipiracil in patients with metastatic colorectal cancer refractory to standard chemotherapy (REGOTAS): A Japanese Society for Cancer of the Colon and Rectum Multicenter Observational Study. *Oncologist* 2018;23:7–15.
- [29] Boku N, Ryu MH, Kato K, et al. Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4). *Ann Oncol* 2019;30:250–8.