Original Article

Efficacy and safety of immune checkpoint inhibitors in gastric cancer: a network meta-analysis of well-designed randomized controlled trials

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Background: Immune checkpoint inhibitors (ICIs) that inhibit the programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) interactions have shown promising prospects as treatment options for advanced gastric cancer (AGC). This manuscript analyzed well designed clinical trials to evaluate the efficacy and safety of immunotherapy in AGC.

Methods: PubMed, Embase, the Cochrane Library, and Medline were searched for randomized controlled trials (RCTs) of AGC treatments that were published before April 2020. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and treatment-related adverse events (TRAEs) were evaluated to determine the efficacy and safety of ICIs. Network meta-analysis was performed using a random-effects model under the Bayesian framework. The ability of each treatment was ranked using the surface under the cumulative ranking (SUCRA) curve.

Results: Our analysis included five studies having seven immunotherapy regimens and 1,730 patients. The network meta-analysis showed that nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks (88.369%) was the regimen most likely to improve PFS. Nivolumab 3 mg/kg every 3 weeks (84.563%) and nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks (84.556%) were similarly best for OS outcome with excellent tolerance. The regimen of avelumab 10 mg/kg every 2 weeks (91.167%) had the lowest TRAEs. All immunotherapies had similar response rates.

Conclusions: We recommend nivolumab 3 mg/kg every 2 weeks or nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks as the preferred regimen due to their high efficacies.

Keywords: Advanced gastric cancer (AGC); chemotherapy; immunotherapy; network meta-analysis

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Introduction

Gastric cancer (GC) has a particularly poor prognosis and a high incidence rate worldwide (1). Of the total cases of GC reported worldwide in 2018, China's cases accounted for >45% of the incidence rate and >50% of the mortality rate. D2 radical surgery is still the most effective treatment for advanced gastric cancer (AGC) (2). Despite remarkable improvements in surgical and comprehensive therapies, recurrence and metastasis are still the main causes of death from AGC.

Treatments aim to stabilize disease progression, improve

patients' prognosis, and reduce recurrence and metastasis rates for AGC. In recent years, the therapeutic strategy for GC has shifted from surgical treatment to comprehensive treatment based on collaboration between members of a multi-disciplinary team (3). With the development of adjuvant/neoadjuvant therapy, as well as progress in targeted therapy and immunotherapy drugs, the 5-year survival rate of GC patients in China has improved (4). First-line chemotherapy, which is usually comprised of platinum and fluoropyrimidine, can extend the overall survival (OS) by approximately 7 months.

For patients with progression of disease on first-line chemotherapy, treatment options include chemotherapy with irinotecan, taxanes (paclitaxel or docetaxel), and trastuzumab for HER-2 (epidermal growth factor receptor 2), or ramucirumab [a monoclonal antibody against vascular endothelial growth factor receptor 2 (VEGFR2)] used either in monotherapy or in combination with paclitaxel (5). However, most AGC patients experience disease progression following these treatments. No guidelines have been recommended for the standard treatment for patients who have failed two or more lines of therapy. Nonetheless, the prognosis for these patients remains poor. Novel therapy options with acceptable safety profiles need to be developed.

Immune checkpoint inhibitors (ICIs) offer promising new treatment options for AGC patients. Inhibiting immune checkpoints can increase T cell activity and enhance antitumor immunity (6). There are currently six FDA-approved ICI immunotherapy options for GC. These include humanized monoclonal antibodies against programmed death 1 (PD-1) (nivolumab, pembrolizumab), programmed death-ligand 1 (PD-L1) (avelumab, atezolizumab, durvalumab), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) (ipilimumab) (7). Several trials investigating the effects of immunomodulating agents and chemotherapies on AGC have been performed and have shown good safety and a positive effect on the survival of patients (8-10). However, due to the limited number of trials, no standard guideline is currently available. Many challenging issues remain, including understanding the specific immunogenicity of gastric carcinoma, selecting the best regimen and the optimal protocol for combining chemotherapy with immunotherapy, optimizing long-term survival with multi-agent cancer immunotherapy combination regimens, and personalizing approaches through composite biomarkers. Furthermore, additional phase III studies on ICIs for metastatic GC have shown discordant results. So far, we failed to find a robust study for patients with AGC that compares the effects of treatment selection in clinical practice.

Traditional meta-analysis uses data only of clinical trials to directly analyze the comparison in the study, but cannot do an indirect analysis between multiple treatment methods among trials with different treatments. Hence, in the present study, we performed a network meta-analysis of well-designed clinical trials to evaluate the impact of ICIs on the outcome of patients with AGC, considering the predictors of efficacy and safety. We present the study in accordance with the Preferred Reporting Items for Systematic Reviews statement for Network Meta-Analyses (PRISMA-NMA) reporting checklist (11) (available at http://dx.doi.org/10.21037/atm-20-6639).

Methods

Literature search

We searched the PubMed, Embase, the Cochrane Library, and Medline databases for intake-related studies that were published between January 1, 2005, and April 11, 2020. The search keywords in the search strategy (provided in detail in Appendix 1) referred to GC, immunotherapy, immune checkpoints (PD-1, PD-L1, and CTLA-4), and specific drug names (ipilimumab, nivolumab, pembrolizumab, sintilimab, camrelizumab, atezolizumab, durvalumab, avelumab, and toripalimab). Two authors (SP and ZZ) independently assessed the process of the literature search and the full texts for eligible inclusions.

Study selection

Publications adopted in this network meta-analysis met the criteria as follows: (I) prospective randomized controlled trials (RCTs); (II) patients were proven to have GC or including gastroesophageal junction (GEJ) cancer; (III) pairwise comparison of treatment modalities, including ICIs; and (IV) inclusion of one or more of the following outcomes: progression-free survival (PFS), OS, objective response rate (ORR), or treatment-related adverse events (TRAEs). Trials that included ICIs in the first-line therapy were excluded. If trials had multiple publications, the latest publication was adopted to provide the longest follow-up.

Data extraction and quality assessment

The following information was extracted from the eligible

studies by two independent authors: first author's name, abbreviation of study, publication year, clinical register, country, sample size, age, intervention regimen, control treatment, and follow-up. PFS was set as the primary outcome of the current analysis; the secondary outcomes were OS and severe TRAEs (grades 3 to 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events). All eligible studies were evaluated for risk of bias using the Cochrane Risk of Bias tool, which assigns three levels of bias across each of seven aspects (12). Disagreements in the above parts were resolved through group discussions.

Statistical analysis

PFS and OS were measured using hazard ratios (HRs) and 95% confidence intervals (CIs), which could reduce the heterogeneity caused by the different follow-ups that were extracted from each adopted study. Odds ratios (ORs) with 95% CIs were also calculated in the analyses for ORR and TRAE outcome. Assessments of efficacy and safety of immunotherapy compared with placebo/chemotherapy were carried out initially by traditional pairwise meta-analysis in RevMan software version 5.3. Statistical heterogeneity was assessed in each comparison using the I^2 statistic and P value. The random-effect model was adopted when I^2>50%, otherwise the fixed-effect model was adopted. Next, the network meta-analyses of two classifications were carried out in a Bayesian framework in OpenBUGS version 3.2.3. One was based on the different drugs and doses; the other was based on the different immune targets. We did not carry out an inconsistency analysis since paired comparisons in the only closed loop was from the same study. Surface under the cumulative ranking (SUCRA) scores were used to rank treatments for each outcome and calculated by R software version 3.5.3. A higher SUCRA score stands for better efficacy (13). All tests were two-sided with an α of 0.05.

Results

Included studies and their characteristics

Five RCTs, which included 1,730 patients, were ultimately incorporated into this network meta-analysis after the systematic literature retrievals (10,14-17). The filtering process is illustrated in the flow diagram (*Figure 1*). Among the five RCTs, patients received seven different treatments: placebo/chemotherapy, nivolumab 3 mg/kg every 2 weeks, avelumab 10 mg/kg every 2 weeks, pembrolizumab 200 mg every 3 weeks, ipilimumab 10 mg/kg every 3 weeks, nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks, and nivolumab 3 mg/kg every 3 weeks plus ipilimumab 1 mg/kg every 3 weeks. The basic information of the five RCTs is summarized in *Table 1*. The earliest of the five studies was published in 2017. The follow-up has ranged from 7.9 to 28 months, with one study not providing detailed follow-up information (17). Moreover, except for the CheckMate 032 trial that sets up three arms but no placebo/chemotherapy, the others were all two arms and compared immunotherapy with placebo or chemotherapy. There was a high degree of consistency among the patients enrolled in the current analysis: before receiving immunotherapy, the patients were over 18 years and had been diagnosed with unresectable, locally advanced or metastatic GC or including GEJ cancer (GEJC); they also had disease progression or intolerance following at least one first-line chemotherapy. The risk of bias assessment for each study according to seven aspects is shown in *Figure 2*.

Traditional pairwise comparison meta-analysis of immunotherapy and placebo/chemotherapy

Due to the limited number of adopted studies, there was only one study of each specific ICI versus placebo/chemotherapy. Therefore, we classified all ICIs as immunotherapy and compared the immunotherapy with placebo/chemotherapy in the traditional pairwise comparison meta-analysis. On account of there being no comparison with placebo/chemotherapy in the CheckMate 032 trial, traditional meta-analysis adopted four of the five RCTs. For survival outcomes, the result of the meta-analysis indicated no statistical difference in PFS or OS between the immunotherapy and placebo/chemotherapy groups (PFS: HR =1.22, 95% CI: 0.75–1.99, P=0.43; OS: HR =0.87, 95% CI: 0.67–1.13, P=0.30) (*Figure 3A,B*). For ORR outcome, the immunotherapy had no obvious advantage in alleviating disease when compared with placebo/chemotherapy (OR =1.00, 95% CI: 0.25–3.97, P=1.00) (*Figure 3C*). Additionally, placebo/chemotherapy was not superior to immunotherapy in terms of severe TRAEs (OR =0.70, 95% CI: 0.21–2.31, P=0.56) (*Figure 3D*). The above results indicate that aside from severe TRAEs, the traditional meta-analysis did not determine a significant advantage of the immunotherapy over placebo/chemotherapy.

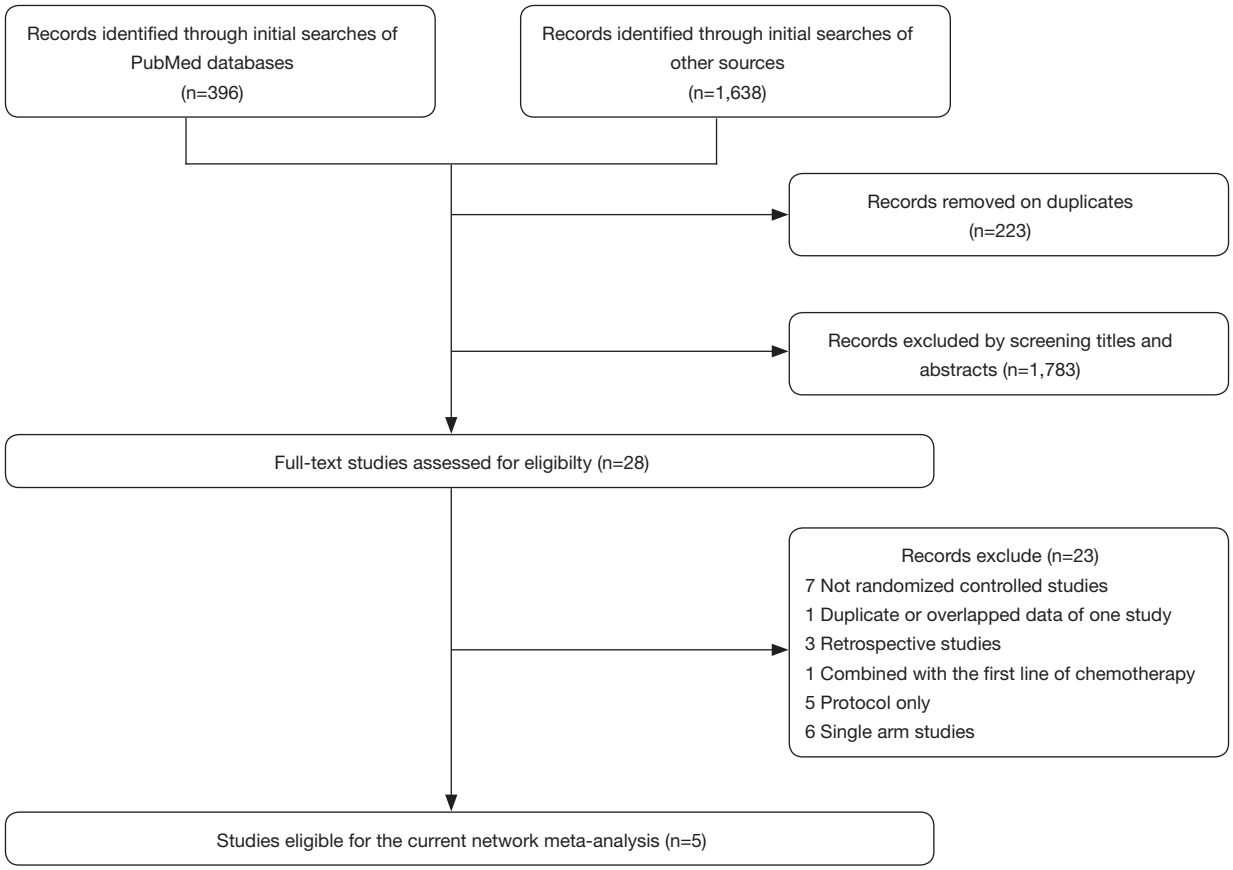


Figure 1 Flow diagram of the study selection of the current meta-analysis.

Network meta-analysis of specific ICIs and placebo/chemotherapy

In the current network meta-analysis, we analyzed six different immunotherapeutic treatments and placebo/chemotherapy (*Figure 4A*) and different combination of immune targets (*Figure 4B*). Due to a large deviation, we did not present the ORR comparisons among different regimens.

For PFS outcome in Figure S1, we observed that nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks (HR =0.60, 95% CI: 0.49–0.74) and nivolumab 3 mg/kg every 2 weeks (HR =0.49, 95% CI: 0.27–0.91) could significantly prolong patients' PFS when compared to placebo/chemotherapy. On the contrary, avelumab 10 mg/kg every 2 weeks (HR =1.57, 95% CI: 1.29–1.91), pembrolizumab 200 mg every 3 weeks (HR =1.49, 95% CI: 1.25–1.77), and ipilimumab 10 mg/kg every 3 weeks (HR =1.62, 95% CI: 1.03–2.55) led to poorer PFS than placebo/chemotherapy. Moreover, as shown in *Figure 5A*, we ranked all treatments. We found that nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks (88.369%) had the highest probability of prolonging PFS, followed by nivolumab 3 mg/kg every 3 weeks plus ipilimumab 1 mg/kg every 3 weeks (81.514%), and nivolumab 3 mg/kg every 2 weeks (77.275%). In terms of OS outcome, only nivolumab 3 mg/kg every 2 weeks (HR =0.62, 95% CI: 0.51–0.76) was observed to be significantly superior to placebo/chemotherapy and also better than avelumab 10 mg/kg every 2 weeks, pembrolizumab 200 mg every 3 weeks, and ipilimumab 10 mg/kg every 3 weeks (Figure S2). Furthermore, nivolumab 3 mg/kg every 2 weeks (84.563%) had the highest probability of prolonging OS, followed by nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks (84.556%) and nivolumab 3 mg/kg every 3 weeks plus ipilimumab 1 mg/kg every 3 weeks (54.519%) (*Figure 5B*). When focusing on severe TRAEs, we analyzed and ranked it from the perspective of not causing severe TRAEs. As shown in Figure S3, it is

Table 1 Characteristics of subjects in eligible studies

Author	Study abbreviation	Year	Register	Country	Sample size	Median age, year	Intervention 1	Intervention 2	Control	Median follow-up, month
Chen LT (14)	ATTRACTION-2	2019	NCT02267343	Multicenter	493	62; 61	Nivolumab 3 mg/kg/2 weeks	–	Placebo	27.3
Janjigian YY (10)	CheckMate 032	2018	NCT01928394	Multicenter	160	53; 58; 60	Nivolumab 1 mg/kg/3 weeks plus ipilimumab 3 mg/kg/3 weeks	Nivolumab 3 mg/kg/3 weeks plus ipilimumab 1 mg/kg/3 weeks	Nivolumab 3 mg/kg/2 weeks	24; 22; 28
Bang YJ (15)	JAVELIN Gastric 300	2018	NCT02625623	Multicenter	371	59; 61	Avelumab 10 mg/kg/2 weeks	–	Physician's choice of chemotherapy	10.6
Shitara K (16)	KEYNOTE-061	2018	NCT02370498	Multicenter	592	63; 60	Pembrolizumab 200 mg/3 weeks	–	Paclitaxel 80 mg/m² intravenously on days 1, 8, and 15 of 4week	7.9
Bang YJ (17)	–	2017	NCT01585987	Multicenter	114	65; 62	Ipilimumab 10 mg/kg/3 weeks	–	Placebo	–

Figure 2 Risk of bias assessment from seven aspects for the adopted studies.

worth noting that placebo/chemotherapy did not show a superior ability to prevent severe TRAEs. Among direct and indirect analyses, avelumab 10 mg/kg every 2 weeks was the only comparison having a significantly higher OR than ipilimumab 10 mg/kg every 3 weeks (HR =36.79, 95% CI: 1.26–1,066.00). It is encouraging that there was no significant difference in the other comparisons. In the rank part, nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks had the lowest probability in preventing severe TRAEs (15.333%), which might be attributed to the combination of ICIs (*Figure 5C*).

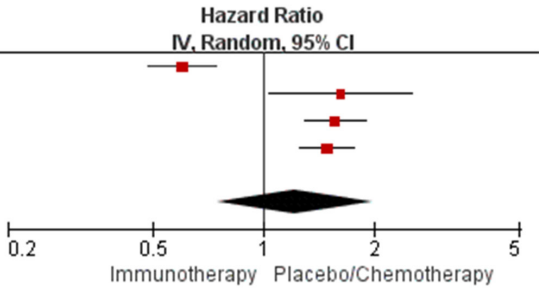
Network meta-analysis of treatments for different immune targets and placebo/chemotherapy

After comparing different ICIs, we intended to compare the therapeutic effects of the immune targets of the drugs (*Figure 4B*).

A **Progression-free survival**

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
ATTRACTION-2	-0.51083	0.108589	25.8%	0.60 [0.48, 0.74]
Bang YJ	0.482426	0.231259	22.0%	1.62 [1.03, 2.55]
JAVELIN Gastric 300	0.451076	0.100118	26.0%	1.57 [1.29, 1.91]
KEYNOTE-061	0.398776	0.088734	26.2%	1.49 [1.25, 1.77]
Total (95% CI)			**100.0%**	**1.22 [0.75, 1.99]**

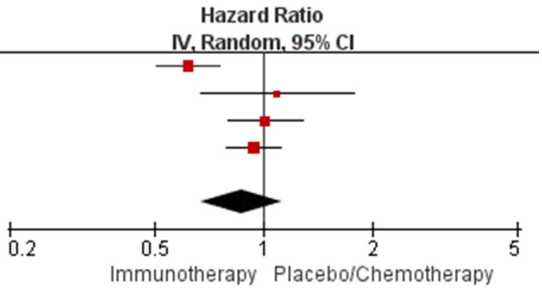
Heterogeneity: Tau² = 0.23; Chi² = 55.58, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.79 (P = 0.43)



B **Overall survival**

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
ATTRACTION-2	-0.47804	0.101762	28.3%	0.62 [0.51, 0.76]
Bang YJ	0.086178	0.247821	15.6%	1.09 [0.67, 1.77]
JAVELIN Gastric 300	0.00995	0.119899	26.6%	1.01 [0.80, 1.28]
KEYNOTE-061	-0.06188	0.089044	29.5%	0.94 [0.79, 1.12]
Total (95% CI)			**100.0%**	**0.87 [0.67, 1.13]**

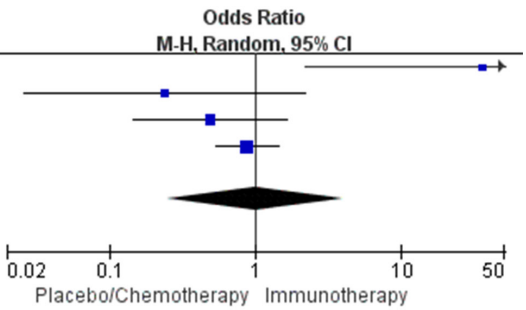
Heterogeneity: Tau² = 0.05; Chi² = 13.96, df = 3 (P = 0.003); I² = 79%
Test for overall effect: Z = 1.03 (P = 0.30)



C **Overall response rate**

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ATTRACTION-2	32	268	0	131	14.8%	36.14 [2.20, 595.03]
Bang YJ	1	57	4	57	19.2%	0.24 [0.03, 2.19]
JAVELIN Gastric 300	4	185	8	186	29.5%	0.49 [0.15, 1.66]
KEYNOTE-061	33	296	37	296	36.5%	0.88 [0.53, 1.45]
Total (95% CI)		**806**		**670**	**100.0%**	**1.00 [0.25, 3.97]**
Total events	70		49			

Heterogeneity: Tau² = 1.29; Chi² = 11.46, df = 3 (P = 0.009); I² = 74%
Test for overall effect: Z = 0.00 (P = 1.00)



D **severe treat-related adverse event**

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ATTRACTION-2	142	330	43	131	26.4%	1.55 [1.01, 2.36]
Bang YJ	13	57	4	57	21.5%	3.91 [1.19, 12.87]
JAVELIN Gastric 300	18	184	69	177	25.7%	0.17 [0.10, 0.30]
KEYNOTE-061	42	294	96	276	26.4%	0.31 [0.21, 0.47]
Total (95% CI)		**865**		**641**	**100.0%**	**0.70 [0.21, 2.31]**
Total events	215		212			

Heterogeneity: Tau² = 1.36; Chi² = 56.68, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.58 (P = 0.56)

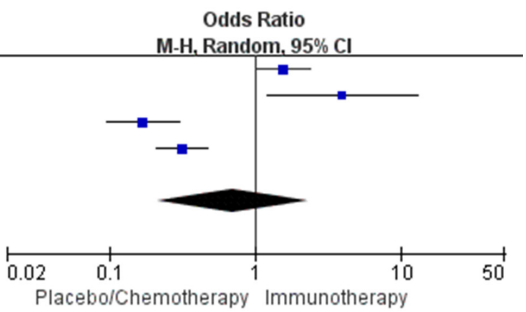


Figure 3 Traditional pairwise comparison meta-analysis between immunotherapy and placebo/chemotherapy: (A) PFS; (B) OS; (C) ORR; (D) severe TRAEs. PFS, progression-free survival; OS, overall survival; ORR, objective response rate; TRAE, treatment-related adverse event.

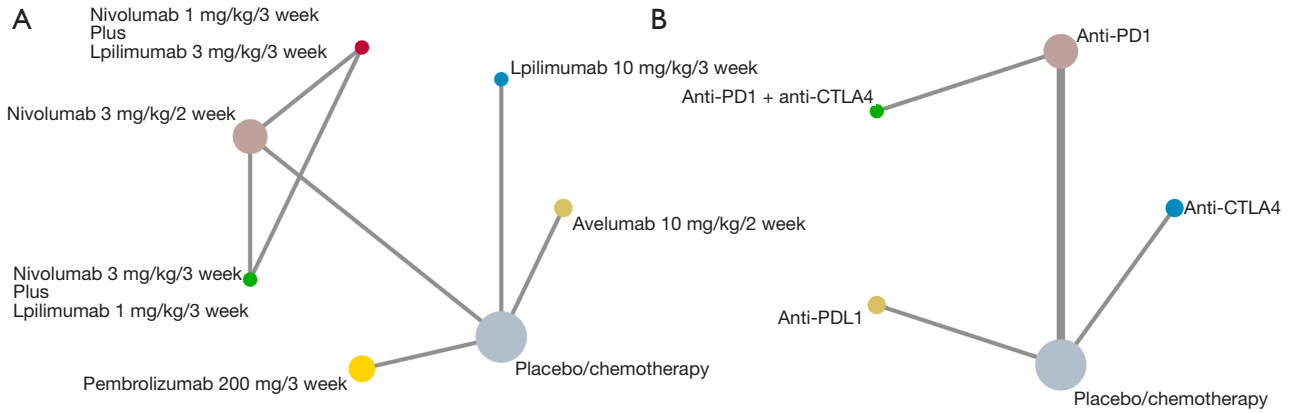


Figure 4 Network plot of comparisons for all interventions adopted in the network meta-analyses: (A) comparison among ICIs and placebo/chemotherapy; (B) comparisons among ICIs' immune targets and placebo/chemotherapy. The size of each node represents the number of eligible patients and the line thickness shows the number of studies for each comparison. ICI, immune checkpoint inhibitor.

Our results showed that no immune target had a significantly superior ability to prolong GC patients' PFS than placebo/chemotherapy (Figure S4). The latter (81.952%) also had the highest probability of prolonging PFS (*Figure 5D*). Moreover, among the four different immune targets, the anti-PD-1 drug (69.962%) and anti-PD-1 plus anti-CTLA-4 drug (69.954%) were more advantageous for prolonging PFS. Differing from PFS, the anti-PD-1 drug (HR =0.78, 95% CI: 0.69–0.89) was found to have significant advantages in prolonging the OS of GC patients when compared with placebo/chemotherapy (Figure S5). The anti-PD-1 drug (87.472%) and anti-PD-1 plus anti-CTLA-4 drug (71.955%) had higher probabilities than placebo/chemotherapy to prolong patients' OS and also were better than the other two immune targets (*Figure 5E*). When comparing severe TRAEs, no significant difference was found among the four immune targets and placebo/chemotherapy (Figure S6). After ranking, we found that the anti-PD-1 drug (64.500%) prevented severe TRAEs better than placebo/chemotherapy, while the anti-PD-1 plus anti-CTLA-4 drug (32.000%) was worse (*Figure 5F*).

Discussion

This is the first network meta-analysis to study the efficacy and safety of ICIs (PD-1, PD-L1, and CTLA-4 antibodies) as second-line or later treatment for AGC. This article has included a total of five relevant RCTs having 1,730 cases until April 11, 2020. Intervention regimens were categorized according to the clinical trials as follows: nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks, nivolumab 3 mg/kg every 3 weeks plus ipilimumab 1 mg/kg every 3 weeks, nivolumab 3 mg/kg every 2 weeks, pembrolizumab 200 mg every 3 weeks, avelumab 10 mg/kg every 2 weeks, and ipilimumab 10 mg/kg every 3 weeks.

In the network analysis, nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks (88.369%) had the best efficacy and was the most likely to improve PFS but met a high and severe TRAE rate. Nivolumab 3 mg/kg every 2 weeks was best for OS outcome (84.563%). The incidence of severe TRAEs of pembrolizumab and avelumab treatment was lower than that of nivolumab and ipilimumab regimens. None of the ICI regimens significantly increased ORR in our traditional pairwise comparison meta-analysis. The ORRs were similar to those in the monotherapy setting, no matter whether the patients had PD-L1+ or PD-L1– tumors. However, in the CheckMate 032 study, combination therapy with different doses of nivolumab plus ipilimumab met higher ORRs in both combination groups than monotherapy (24% and 8%) (18). In the KEYNOTE-059 trial, patients with PD-L1+ *vs.* PD-L1– tumors had trends for higher ORRs (19).

The findings of the traditional meta-analysis suggested that anti-PD-1/PD-L1 treatment compared to chemotherapy improved long-term OS clinical benefit and prolonged the duration of response in pretreated advanced or metastatic GC/GEJC patients (20,21). Anti-PD-1 therapy may have worked better for PD-L1+ patients; however, it was also effective for PD-L1– patients. The traditional meta-analysis could compare only the advantages

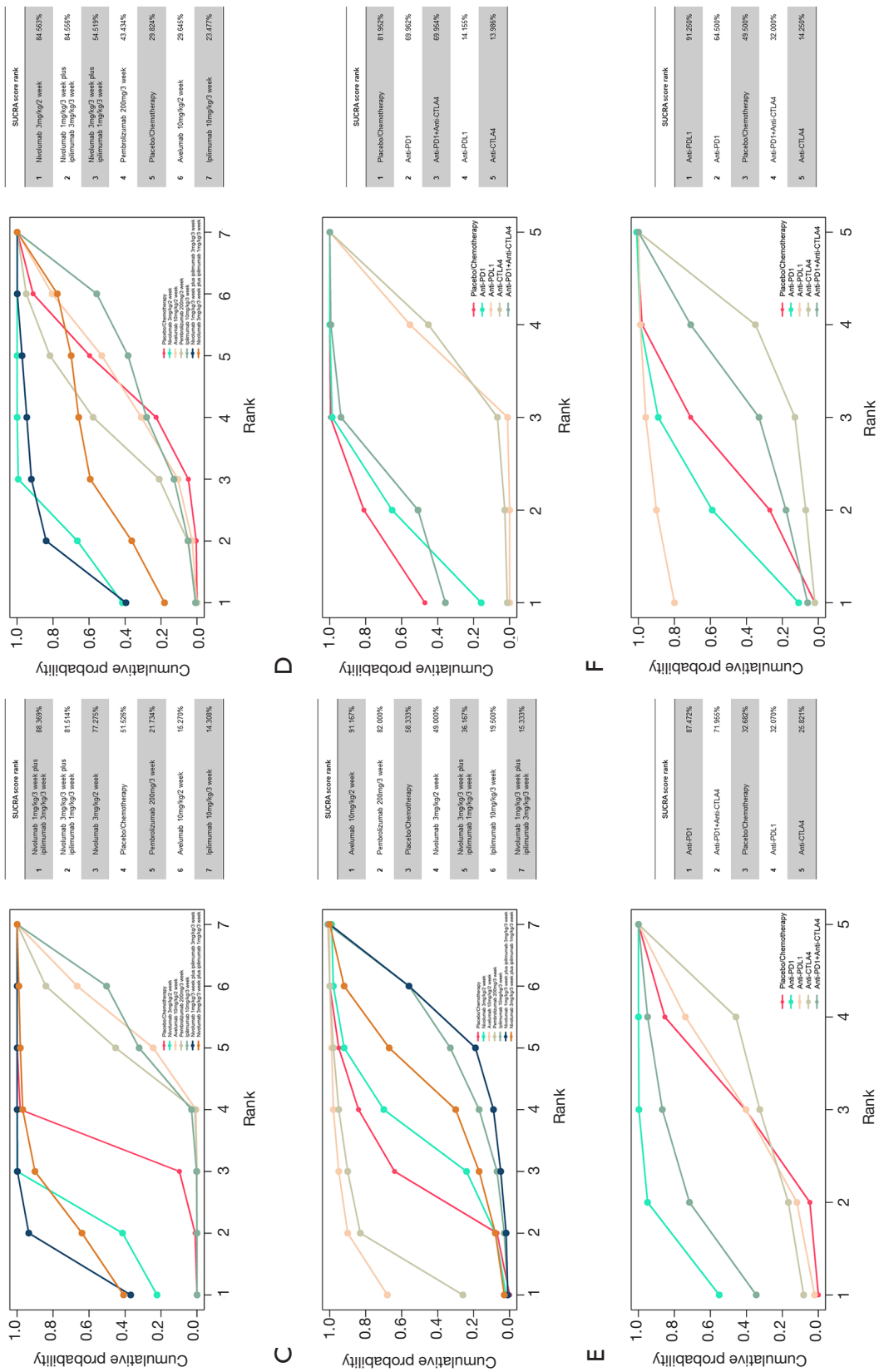


Figure 5 Cumulative probability of each intervention under different rankings for different outcomes and the likelihood of it being the best treatment based on the SUCRA are shown: (A) PFS of ICIs; (B) OS of ICIs; (C) severe TRAEs of ICIs; (D) PFS of immune targets; (E) OS of immune targets; (F) severe TRAEs of immune target. SUCRA, surface under the cumulative ranking; PFS, progression-free survival; ICI, immune checkpoint inhibitor; OS, overall survival; TRAE, treatment-related adverse event.

and disadvantages of immunotherapy with regular chemotherapy or placebo without grouped comparison between the different drugs and regimens (21). Network analysis could determine which specific regimens were relatively effective on PFS, OS, ORR, and TRAEs using direct and indirect comparisons of interventions within RCTs or across multiple treatments. The blinded RCTs included in our study design had high credibility and an improvement over the previous meta-analysis.

The processes that inhibit T cell function are called immune checkpoint pathways. Better immunotherapies for cancer patients could be achieved if the prevention of immune checkpoint signaling could be identified and the antitumor T-cell functions be reactivated by these pathways (22). GC is considered as a cold type of tumor that usually has a low infiltration of CD8+ T cells, as well as immune-suppressive cells (23). However, some studies suggest that the expression of PD-L1 may improve the prognosis of patients by increasing the proportion of CD8+ TIL. PD-L1 is commonly expressed in GC cells in the range of 17.4–49.1% (21,24). That is a delightful prospective of ICIs in AGC. Although these therapies are associated with long-lasting response rates, only a subset of patients derives clinical benefit, which varies according to the tumor type. The research for predicting the response to ICIs is a matter of intense investigation as this may contribute toward maximizing disease control, reducing side effects, and minimizing cost. The approval of ICIs for use in GC has pushed immuno-oncology research in this cancer type. In *Table 1*, we summarize the clinical trials evaluating the safety and efficacy of ICIs in GC.

After pembrolizumab was approved in the United States for PD-L1+ tumors and nivolumab in Japan, third-line (3L) treatment has evolved to include immunotherapy regimens in AGC/GEJC (25). The first study of pembrolizumab, the KEYNOTE-012 study, included 39 patients with recurrent or metastatic PD-L1+ GC/GEJC. The ORR was 22%, the median OS was 11.4 months, and grade ≥3 TRAEs occurred in 13% of the patients (8). Following these results, pembrolizumab was trialed in patients with GC/GEJC (KEYNOTE-059). This study comprised three cohorts. Cohort 1 represented the largest early-phase trial of ICI in GC/GEJC, enrolling 259 patients who received pembrolizumab monotherapy as 3L or later treatment. The ORR was 15.5% with a trend for higher ORR in PD-L1+ *vs.* PD-L1– tumors (16% *vs.* 6%, respectively). The median OS was 16.3 months (9,19). The ATTRACTION-2 study also revealed that nivolumab administration to GC patients was associated with improved OS compared to patients treated with placebo regardless of the PD-L1 status (14,26). However, the current literature data regarding the prognosis has shown controversial results (KEYNOTE-062). Pembrolizumab alone or in combination with cisplatin/5-FU *vs.* cisplatin/5-FU alone in patients with AGC showed that pembrolizumab or chemotherapy brought survival benefit to patients with PD-L1-positive AGC. However, there was no difference in PFS and OS between pembrolizumab plus chemotherapy compared with chemotherapy alone (27). The above illustrates the efficacy of ICI treatment with a certain degree of hysteresis, but it can provide some patients with long-term clinical benefits. Our analysis has shown that anti-PD-1 with or without anti-CTLA-4 treatment, compared with placebo/chemotherapy, improved the OS rate but had no advantage in terms of PFS. The number of high-quality studies is limited. In addition, many of them were single-arm studies, and the number of patients was low. This may amplify inaccuracies. High-quality RCT research is needed for verification.

In addition to assessing monotherapy, combination therapy with different doses of nivolumab plus ipilimumab (N1I3: nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; N3I1: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg) was assessed in patients with AGC in the CheckMate 032 study (10,18). The median OS in the N1I3 and N3I1 subgroups were 6.9 and 4.8 months, respectively. Grade ≥3 TRAEs occurred in 47% and 27%. In cohort 2 of KEYNOTE-059, 25 patients with HER2–AGC received treatment with 1L pembrolizumab in combination with 5-FU/cisplatin chemotherapy. The ORR was 60%, and there was a potential association between PD-L1+ tumors and higher ORR (69% and 38% in patients with PD-L1+ *vs.* PD-L1– tumors, respectively). The median OS was 13.8 months. The incidence of grade 3/4 TRAEs was 76%, which was notably higher than that seen with 1L pembrolizumab monotherapy (23%). Our network meta-analysis proved that while various combinations of ICI treatment achieved promising results in treating AGC, TRAEs occurred more often with combination therapy than with monotherapy in the multiple treatments. This should be given more attention.

Key problems in immunosuppressive therapy need to be solved urgently. At present, the question remains of how to correctly screen the subset of patients that would respond well to ICIs. The indicators of immunosuppressive treatment in the population reported in the literature include mainly PD-1/PD-L1 expression level, microsatellite

instability (MSI) level, and tumor mutation load burden. However, no precise screening standard or guideline has been released. The expression of PD-L1 was high in MSI-H GC; MSI-H may induce innate antitumor immune responses and make tumors more sensitive to immune checkpoint blockades (28,29). Results from the KEYNOTE-061 study showed that pembrolizumab was significantly safer than the standard second-line paclitaxel treatment, and subgroup analysis showed that patients with high PD-L1 expression or MSI-H benefitted from the pembrolizumab treatment (16). Some meta-analyses found that the efficacy of anti-PD-1 therapy in MSI-H patients was significantly better than that of microsatellite stable, which could increase ORR to 3.40 times and disease control rate to 2.26 times (21). In addition, the efficacy of pembrolizumab was also related to circulating tumor DNA (ctDNA). Compared to patients with a low ctDNA mutation load, patients with a high mutation load had higher ORRs (30).

More than half of the patients receiving ICIs developed TRAEs, but the probability of developing grade ≥3 TRAEs was low and the incidence of treatment leading to death was almost zero (15,31,32). Therefore, ICI treatment can be considered as being safe. How to predict and prevent TRAEs from tumor immunotherapy is challenging. The side effects of tumor immunotherapy include mainly fatigue, skin ulcers, immune dermatitis, immune colitis, immune hepatitis, immune thyroiditis, and immune nephritis. Tumor pseudo- and hyper-progression was also recently reported to be one of the important TRAEs of immunotherapy (33). How to simultaneously block proteins involved in immune system regulation (such as TNF, IL-6) can separate the efficacy and toxicity of combined immunotherapy but needs further study.

The merit of the network meta-analysis of this study was that we compared the efficacy and safety of seven therapeutic regimens, including different combinations of four ICIs referring to three immune targets for AGC. In contrast, many clinical trials have directly compared only one or two ICIs with traditional chemotherapy or placebo. Moreover, the trials selected in this network meta-analysis were all RCTs with big samples and had high evidence-based value. Using direct and indirect comparisons of interventions within RCTs or across multiple treatments, it is also the first network meta-analysis to determine which specific regimens are relatively effective on PFS, OS, ORR, and TRAEs. There are also some limitations in this network meta-analysis that should be noted. Firstly, only five RCTs studies were included, which limited the sample size. Due to the limited literature, many indicators might have some heterogeneity. Meanwhile, there is insufficient data on ORR, which leads to results that have low reliability. Further tests should be determined to optimize the result. The lack of standardized agents in chemotherapy or placebos may also affect the reliability and validity of our results. Furthermore, our study only compared the therapeutic value of partial PD-1, PD-L1, and CTLA-4 inhibitors. Atezolizumab and durvalumab were not enrolled in the comparison as we failed to retrieve related RCTs.

Herein, we focused on the therapeutic effects of ICIs on AGC patients and carried out network meta-analysis to compare each ICI and immune target. We found that nivolumab with or without ipilimumab had a significantly better ability than the placebos or traditional chemotherapy to prolong patients' PFS and OS without causing significant severe TRAEs. Furthermore, in immune target analyses, anti-PD-1 with or without anti-CTLA-4 drugs were confirmed as having OS benefit but no PFS benefit. Therefore, according to the regimens adopted in the five RCTs, we recommend nivolumab 3 mg/kg every 2 weeks or nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks as the preferred regimen.

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Footnote

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