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META-ANALYSIS

Efficacy and safety of anti-PD-1/anti-PD-L1 antibody therapy in treatment of advanced gastric cancer or gastroesophageal junction cancer: A meta-analysis

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Abstract

BACKGROUND

Faced with limited and inadequate treatment options for patients with advanced gastric cancer or gastroesophageal junction cancer (GC/GEJC), researchers have turned toward, with the support of promising clinical trials, anti-PD-1/anti-PD-L1 antibody therapy. But there are also different clinical trial results. To better assess its efficacy and safety, we integrated data from 13 eligible studies for a systematic review and meta-analysis.

AIM

To comprehensively evaluate the efficacy and safety of anti-PD-1/anti-PD-L1 antibody therapy in the treatment of advanced GC/GEJC patients.

METHODS

PubMed, Web of Science, Cochrane Library ,and EMBASE databases were searched to identify eligible articles with outcomes including objective response rate (ORR), disease control rate (DCR), overall survival (OS), progression-free survival (PFS), and adverse events (AEs) of anti-PD-1/anti-PD-L1 antibody therapy.

RESULTS

Our study encompassed a total of 13 trials totaling 1618 patients. The outcomes

showed a pooled ORR and DCR of 15% (95% confidence interval [CI]: 14%-18%) and 40% (95%CI: 33%-46%), respectively. The pooled 6-mo OS and PFS were 54% (95%CI: 45%-64%) and 26% (95%CI: 20%-32%), respectively, and the 12-mo OS and PFS were 42% (95%CI: 21%-62%) and 11% (95%CI: 8%-13%), respectively. In addition, the incidence of any-grade AEs and grade ≥ 3 AEs was 64% (95%CI: 54%-73%) and 18% (95%CI: 16%-20%), respectively. Most importantly, PD-L1 positive patients exhibited a higher ORR rate than PD-L1 negative patients (odds ratio = 2.54, 95%CI: 1.56-4.15).

CONCLUSION

Anti-PD-1/anti-PD-L1 antibody therapy has shown promising anti-tumor efficacy with manageable AEs in advanced GC/GEJC patients, with PD-L1 overexpressing patients exhibiting a higher ORR. What is more, the clinical efficacy of anti-PD-1/PD-L1 combined with traditional chemotherapy drugs is even better, although the occurrence of AEs still causes considerate concerns.

Key Words: Gastric cancer; Gastroesophageal junction cancer; Anti-PD-1/anti-PD-L1 antibody therapy; Meta-analysis; Systematic review

Core Tip: Anti-PD-1/anti-PD-L1 antibody therapy, such as nivolumab and pembrolizumab, which has been approved by the FDA for marketing, enhances the body's cellular immune response to anti-tumor effects by regulating T cell function. At present, it has become the first-line treatment for extensive stage small cell lung cancer and other cancers. In recent years, some clinical trials have also shown that anti-PD-1/anti-PD-L1 antibody therapy has a reliable effect in advanced gastric cancer or gastroesophageal junction cancer (GC/GEJC) patients, but there is still controversy. The main purpose of this meta-analysis was to comprehensively evaluate the efficacy and safety of anti-PD-1/anti-PD-L1 antibody therapy in the treatment of advanced GC/GEJC patients.

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INTRODUCTION

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third leading cause of cancer death worldwide[1]. Although GC incidence has been declining globally, there were still 1033701 new GC cases and 782685 death counts in 2018, with overall half occurring in East Asia, especially China[2]. Because GC patients often present nonspecific symptoms, diagnosis occurs predominantly at an advanced stage, where approximately 50% of patients have already developed locally advanced or metastatic tumor, bringing the 5-year survival rate from less than 30%[3,4] down to approximately 15%[5-7].

Currently, the primary treatment option for GC patients is surgery and chemotherapy, with especially poor prognosis and overall survival (OS) rate for patients with advanced GC[8,9]. Current clinical guidelines recommend dual or triple platinum/fluorouracil combinations for human epidermal growth factor receptor 2 (HER-2) negative patients, and trastuzumab in combination with platinum and fluorouracil chemotherapy for HER-2 positive patients as the first-line treatment options, and taxanes, irinotecan, or ramucirumab for patients with performance status (PS) 0-1 as the second-line treatment options[10-12]. Nevertheless, despite these treatments, most patients with advanced gastric cancer or gastroesophageal junction cancer (GC/GEJC) continue to deteriorate after treatment[13,14].

Immune checkpoint inhibitors, such as PD-1 and PD-L1 inhibitors, have become the

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first-line treatment for multiple malignancies[15]. Inhibition of PD-1 and PD-L1 enhances the *in vitro* response of T cells as well as the antitumor activity in preclinical models[16,17]. The phase I studies with anti-PD-1 drugs, such as nivolumab and pembrolizumab, in non-small-cell lung cancer (NSCLC), advanced melanoma, renal cell carcinoma (RCC), and other solid tumor patients have demonstrated very promising response with controlled side effects. Inspired from this results, PD-1 blockers were studied for further trials and showed excellent response in phase III trial patients with advanced melanoma than in those with NSCLC and RCC[18]. Anti-PD-1/anti-PD-L1 antibody therapies exhibiting success in many clinical trials for various types of tumors regardless of pathologic grade with long-lasting responses and tolerable toxicity[18,19]. At present, the United States Food and Drug Administration (FDA) has approved PD-1 pathway inhibitors for cancer treatment including the monoclonal antibodies nivolumab (anti-PD-1; Bristol-Myers Squibb), pembrolizumab (anti-PD-1; Merck), atezolizumab (anti-PD-L1; Genentech/Rothe), avelumab (anti-PD-L1; EMD Serono/Pfizer), and durvalumab (anti-PD-L1; AstraZeneca).

Several studies have shown the prevalent overexpression of PD-L1 in GC patients, and the expression of PD-L1 plays a key role in cancer immune escape and related tumor progression and poor prognosis[20,21]. Reducing the expression of PD-L1 in human gastric cancer cell line SGC-7901 can significantly inhibit cell proliferation and migration and tumor growth in subcutaneously transplanted mouse models[22]. In addition, many clinical studies have initially shown that PD-L1 blockers can significantly inhibit the tumor progression of many advanced cancers such as melanoma, GC, non-small cell lung cancer, ovarian cancer and so on[23,24]. Thus, anti-PD-1/anti-PD-L1 antibody therapy seemed promising as a potential approach for GC/GEJC.

In the meantime, several clinical trials have already evaluated the efficacy of anti-PD-1/anti-PD-L1 antibody therapy in advanced GC/GEJC patients, and the results show that this therapy has good anti-tumor activity and controllable adverse reactions for advanced GC/GEJC patients. However, one study suggested that not all tumors expressing PD-L1 respond to PD-1/PD-L1 inhibitors[16]. And the treatment regimen has not been included in the authoritative clinical practice guidelines, such as EMSO GC diagnosis and treatment guidelines, which means that there is yet no scholarly consensus on the efficacy and safety of PD-1/PD-L1 inhibitors in the treatment of advanced GC/GEJC. To address this need, we meta-analyzed all published clinical studies based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[25].

MATERIALS AND METHODS

Systematic literature search

PubMed, Web of Science, the Cochrane Library, and Embase were searched from inception up to March 5, 2020 using the following MeSHs headings (Gastric Cancer OR Stomach Cancer OR Stomach Neoplasm OR Gastric Neoplasm OR GC OR gastroesophageal OR Gastro Esophageal Junction Cancer OR GEJC) AND (Nivolumab OR MDX-1106 OR ONO-4538 OR BMS-936558 OR Opdivo OR Pembrolizumab OR lambrolizumab OR Keytruda OR MK-3475 OR SCH-900475 OR Atezolizumab OR anti-PDL1 OR MPDL3280A OR Tecentriq OR RG7446 OR Durvalumab OR MEDI4736 OR Imfinzi OR Avelumab OR Bavencio OR MSB0010682 OR MSB0010718C).

Inclusion and exclusion criteria

The literature included in this study must meet all of the following criteria: (1) Prospective clinical trials in patients with advanced GC/GEJC; (2) Patients in the immunotherapy group were treated with anti-PD-1/PD-L1 drugs; and (3) The literature provides relevant anti-tumor activity and safety data [objective response rate (ORR), disease control rate (DCR), OS, progression-free survival (PFS), adverse events (AEs), or grade ≥ 3 AEs].

The exclusion criteria for this study were as follows: (1) Conference abstracts, case reports, comments, editorials, *etc.*; (2) For multiple publications that have been determined to be reported in the same clinical study, the publication with the most complete publication data is qualified; and (3) The literature information was insufficient to extract the required useful data.

Selection of relevant studies

During the preliminary screening process, relevant studies were first independently selected by two authors (Yang L and Dong XZ) of this study. Any disagreements were then resolved through mutual discussion and consultation.

Data extraction

Data were extracted independently by two researchers, including the name of the first author, year of publication, trial name, trial phase, number of participants, interventions, OS, PFS, ORR, DCR, AEs, tumor characteristics, and expression level of PD-L1 (positive expression as > 1% and negative expression as ≤ 1%). Any unavailable data were recorded as "NA".

Quality assessment

Bias risk was assessed using the Cochrane Collaboration's tool[26] in the following domains: Random sequence generation, allocation concealment, blinding of outcome participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each result was classified as low risk, high risk, or unclear risk. Quality assessment was done independently by two researchers with disagreements solved through discussion.

Statistical analysis

To evaluate the efficacy of anti-PD-1/anti-PD-L1 antibody, the overall ORR and DCR as well as the combined OS and PFS rates (both 6 mo and 12 mo) were calculated. To assess its safety, the overall risk of AEs and grade ≥ 3 AEs were calculated. All statistical calculations were performed using Review Manger version 5.3 (Cochrane Collaboration's Information Management System) and STATA version 14.0 (STATA, College Station, TX, United States). Statistical heterogeneity across studies was assessed using the Cochran Q chi-square test and the I^2 index. Whence significant heterogeneity was determined with either $I^2 > 50\%$ or P value < 0.1, the random-effects model was applied[27]. Sensitivity analysis was performed by removing individual studies one by one to test the reliability of the results. Publication bias was determined using Begg's and Egger's methods.

RESULTS

Literature search

The whole process of study selection is shown in Figure 1. Out of the 1220 initially retrieved records, 946 remained after the removal of duplicates. After the screening of titles and abstracts, 709 records were excluded and 237 were reviewed for full text. After further removal of conference reports, reviews, duplicates, and studies without clinical trials, 13 records were defined eligible[28-40].

Study characteristics

The detailed characteristics of the included studies are summarized in Table 1. The 13 eligible studies include six single-arm trials[29,33-35,38,39], five randomized controlled trials (RCTs)[28,30,31,37,40], and two dose-escalation cohort expansion studies[32,36]. A total of 1618 GC/GEJC patients were included, of whom 787 received pembrolizumab, 429 received nivolumab, 375 received avelumab, and 27 received durvalumab. Pembrolizumab was intravenously administered at 200 mg in five trials[29,34,35,39,40] and 10 mg/kg in another[38]. Nivolumab was intravenously administered at 3 mg/kg in two studies[31,36], and 360 mg in another[30]. Avelumab and durvalumab were administered at 10 mg/kg[28,32,33] and 20 mg/kg[37], respectively.

Quality assessment of included studies

The quality assessment was conducted using Review Manger 5.3. Details of risk of bias for each study are presented in Figure 2. Due to the particularity of clinical trials in cancer treatment, the single-arm and dose-escalation trails are inherently considered high-risk in terms of bias. The 13 studies included in this meta-analysis were low-risk in terms of random sequence generation, allocation concealment, incomplete outcome data, and selective reporting. Blinding of outcome assessment and other biases might exist in two and four studies, respectively. Bias (blinding of outcome participants and personnel) was high risk. Generally speaking, the quality assessment of the included studies had a low risk of bias.

Table 1 Characteristics of included studies

Ref.	Trial	Clinical trials.gov, No.	Study design	Phase	Case, experimental *vs* control, (*n*)	Intervention methods	ORR (%)	DCR (%)	12-mo OS (%)	12-mo PFS (%)
Bang *et al*[28] 2018	JAVELIN Gastric 300	NCT02625623	RCT	III	371, 185 *vs* 186	Avelumab 10 mg/kg Q2 W *vs* paclitaxel 80 mg/m^2 or irinotecan 150 mg/m^2 1, 8, 15 d of 4-wk cycles.	2.2	22.2	NA	NA
Bang *et al*[29] 2019	KEYNOTE-059 (cohorts 2 and 3)	NCT02335411	Single-arm	II	31	Pembrolizumab 200 mg on day 1 of 21-d cycles.	25.8	35.5	63.0	NA
Boku *et al*[30] 2019	ATTRACTION-4	NCT02746796	RCT	II	40, 21 *vs* 19	Nivolumab 360 mg Q3 W + SOX or Cape OX.	65.8	84.2	NA	NA
Chen *et al*[31] 2020	ATTRACTION-2	NCT02267343	RCT	III	493, 330 *vs* 163	Nivolumab 3 mg/kg Q2 W *vs* placebo 3 mg/kg Q2 W.	11.9	40.3	87.1	9.3
Chung *et al*[32] 2019	JAVELIN Solid Tumor	NCT01772004	Dose-escalation	I	150	Avelumab 10 mg/kg Q2 W.	6.7	45.3	38.0	12.6
Doi T *et al*[33] 2019	JAVELIN Solid Tumor JPN trial	NCT01943461	Single-arm	I	40	Avelumab 10 mg/kg Q2 W	10.0	52.5	31.0	NA
Fuchs *et al*[34] 2018	KEYNOTE-059 (cohorts 1)	NCT02335411	Single-arm	II	259	Pembrolizumab 200 mg Q3 W.	11.6	27.0	23.4	NA
Herbst *et al*[35] 2019	JVDF	NCT02443324	Single-arm	Ia/b	41	Pembrolizumab 200 mg on day 1 + ramucirumab 10 mg/kg days 1-8.	7.3	51.2	30.8	12.3
Janjigian *et al*[36] 2018	CheckMate-032	NCT01928394	Dose-escalation	I/II	59	Nivolumab 3 mg/kg Q2 W.	12.0	32.0	39.0	8.0
Kelly *et al*[37] 2020	NA	NCT02340975	RCT	Ib/II	27	Durvalumab 20 mg/kg + tremelimumab 1 mg/kg Q4W.	7.4	NA	37.0	NA
Muro *et al*[38] 2016	KEYNOTE-012	NCT01848834	Single-arm	Ib	39	Pembrolizumab 10 mg/ kg Q2 W.	22.0	33.0	42.0	NA
Shah *et al*[39] 2019	KEYNOTE-180	NCT02559687	Single-arm	II	121	Pembrolizumab 200 mg Q3 W.	9.9	30.6	28.0	NA
Shitara *et al*[40] 2018	KEYNOTE-061	NCT02370498	RCT	III	592, 296 *vs* 296	Pembrolizumab 200 mg Q3 W *vs* paclitaxel 80 mg/m^2 1, 8, 15 d of 4-wk cycles	11.1	20.7	40.0	NA

ORR: Objective response rate; DCR: Disease control rate; OS: Overall survival; PFS: Progression-free survival; RCT: Randomized controlled trial; NA: Not available.

ORR

ORR, which is the optimal number of partial responses (PR) or complete responses (CR) divided by the total number of patients receiving treatment, for all 1618 patients was recorded. Overall, the pooled ORR was 15% (95% confidence interval [CI]: 14%-18%, $P < 0.001$), exhibiting significant heterogeneity ($I^2 = 100\%$, $P < 0.001$) (Figure 3). Within subgroup analysis, the pooled ORR for monotherapy was 12% (95%CI: 9%-15%, $P < 0.001$) and 27% (95%CI: -6%-59%, $P < 0.001$) for combined therapy.

DCR

Only 12 trails including 1591 patients reported DCR, which is the sum of patients diagnosed with complete remission, partial remission, or stable disease. The pooled DCR was 40% (95%CI: 33%-46%, $P < 0.001$), exhibiting high heterogeneity ($I^2 = 100\%$, $P < 0.001$) (Figure 4). Compared to patients in the monotherapy group, patients in the

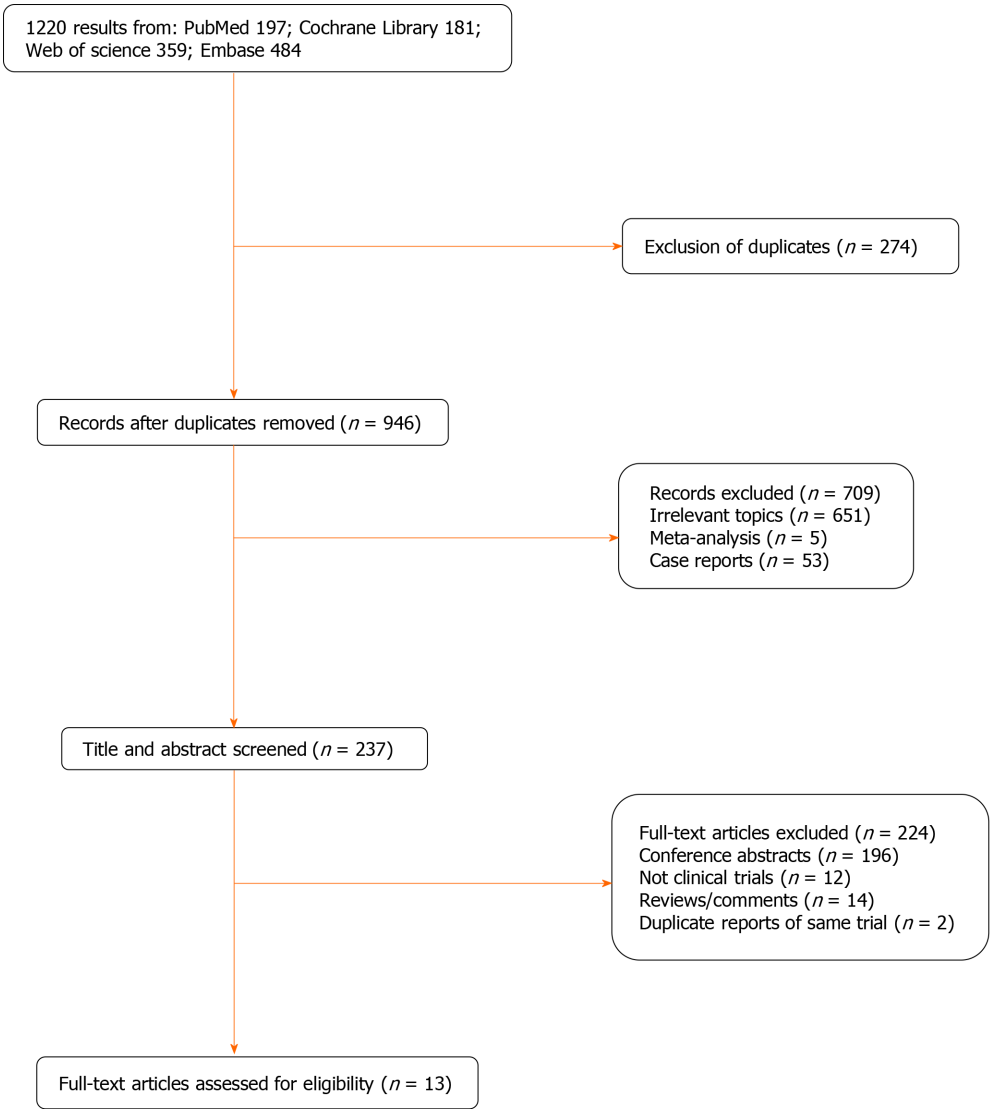


Figure 1 Record selection process.

combination group had a higher DCR (68%, 95%CI: 35%-100% *vs* 34%, 95%CI: 27%-41%).

Survival benefits: OS and PFS

The 6-mo OS of 685 patients in six trials and 6-mo PFS of 708 patients in eight trails were reported. The pooled 6-mo OS and PFS were 54% (95%CI: 45%-64%, $P < 0.001$, Figure 5A) and 26% (95%CI: 20%-32%, $P < 0.001$, Figure 5B), respectively. Furthermore, the 6-mo OS and PFS of patients in the monotherapy group were 46% (95%CI: 45%-48%, $P < 0.001$) and 21% (95%CI: 17%-26%, $P < 0.001$), respectively, significantly lower than the corresponding OS of 72% (95%CI: 27%-116%, $P < 0.001$) and PFS of 34% (95%CI: 3%-72%, $P < 0.001$) of patients in the combination group.

The 12-mo OS and PFS were reported in 11 trials involving 1393 and 4 trials involving 580 patients. The pooled 12-mo OS and PFS were 42% (95%CI: 21%-62%, $P < 0.001$, Figure 5C) and 11% (95%CI: 8%-13%, $P < 0.001$), respectively (Figure 5D). However, contrary to the 6-mo OS and PFS results in the subgroup analysis, the 12-mo OS of patients in the monotherapy group was 43% (95%CI: 21%-66%), significantly higher that (34%; 95%CI: 28%-40%) of patients in the combination group, while the 12-mo PFS (12%, 95%CI: 11%-14%) of patients in the combination group was only slightly higher than that (10%, 95%CI: 7%-13%) of patients in the monotherapy group.

PD-L1 expression and ORR

Of the 1191 patients in nine trials, the ORR was 15% (95%CI: 9%-21%, $P < 0.001$, Figure 6A) for patients with positive (> 1%) PD-L1 expression and 7% (95%CI: 3%-11%, $P = 0.001$, Figure 6B) for patients with negative (≤ 1%) PD-L1 expression. In

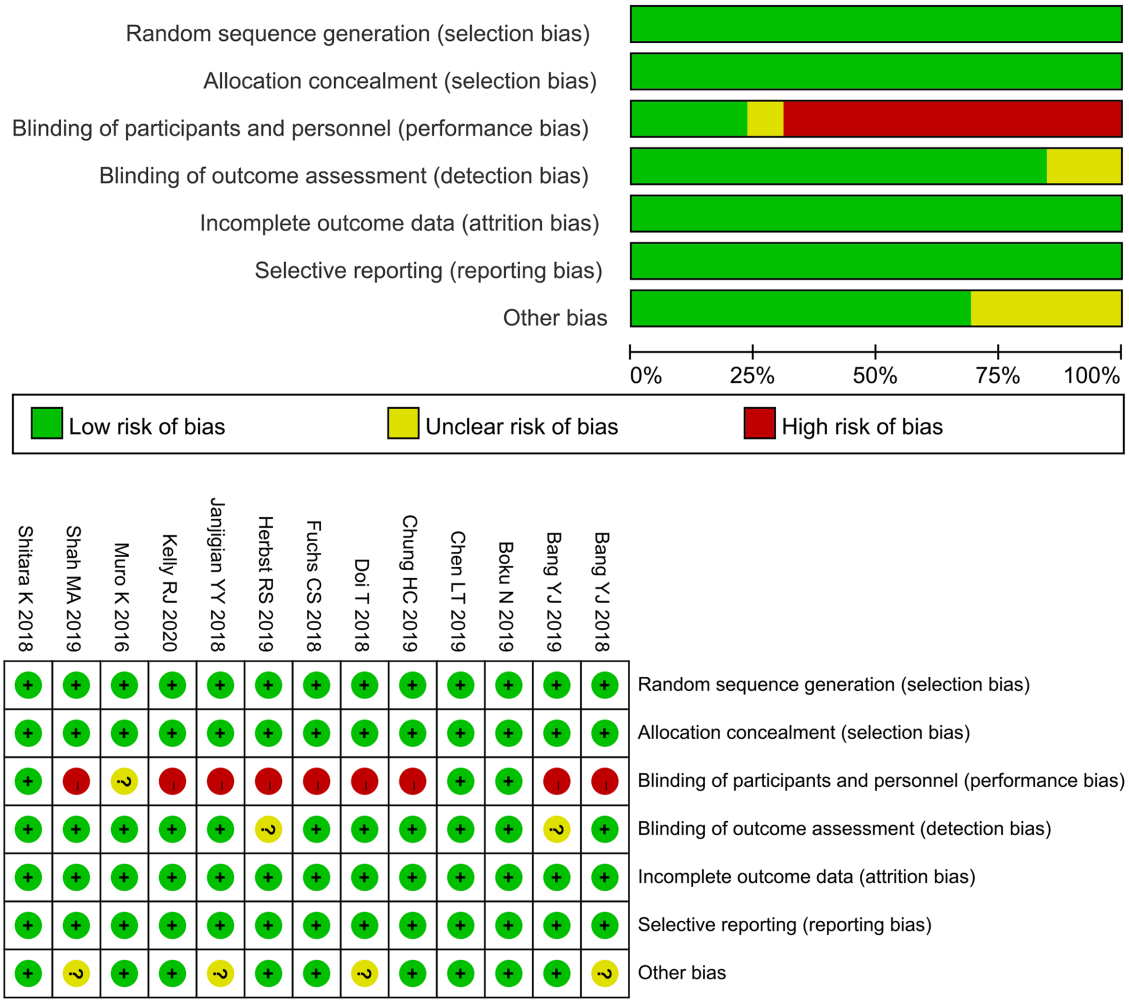


Figure 2 Risk of bias graph and summary.

addition, the pooled OR was 2.54 (95%CI: 1.56-4.15, $P < 0.001$), indicating that the ORR of PD-L1 positive patients was significantly higher than that of negative patients (Figure 7).

AEs related to treatment

Of the 1618 patients included in 13 trials reporting AEs, 869 (53.7%) experienced at least one AE and 237 (14.6%) experienced at least one grade ≥ 3 AE. The overall incidence of any-grade AEs was 64% (95%CI: 54%-73%, $P < 0.001$, Figure 8) with significantly more patients under the combination therapy than under monotherapy (84% *vs* 58%). The total incidence of grade ≥ 3 AEs was 18% (95%CI: 16%-20%, $P < 0.001$). In the monotherapy group, the incidence of grade ≥ 3 AEs was 13% (95%CI: 11%-15%, $P < 0.001$), which was 22% lower than that of the combination therapy group (Figure 9).

The most common any grade AEs was fatigue (15.8%; 95%CI: 11.1%-20.5%), followed by infusion reaction (13.8%; 95%CI: 1.3%-26.3%), pruritus (13.1%; 95%CI: 9.8%-16.4%), decreased appetite (9.6%), nausea (9.4%), abdominal pain (9.3%), diarrhea (8.3%) and pyrexia (8.0%). The most common grade ≥ 3 AEs was abdominal pain (2.8%, 95%CI: -3.4%-9.0%), and the incidence of other common grade ≥ 3 AEs was fairly low (Table 2).

Publication bias and sensitivity analysis

Manual removal of any study for sensitivity analysis found no changes and reverse in the forest plot direction of all the results, indicating that the study results are both reliable and stable. Begg and Egger's tests on publication bias showed only presence of bias in 12-mo OS ($P = 0.015 < 0.05$). No publication bias was found in other outcomes (Table 3).

Table 2 Meta-analysis of common adverse events with anti-PD-1/PD-L1 antibody therapy

Common AE	Any grade (%)	95%CI	Grade ≥ 3 (%)	95%CI
Fatigue	15.8	11.1-20.5	1.2	0.6-1.9
Infusion reaction	13.8	1.3-26.3	0.6	-0.2-1.4
Pruritus	13.1	9.8-16.4	NA	NA
Decreased appetite	9.6	5.7-13.5	0.9	0.2-1.6
Nausea	9.4	4.1-14.6	1.4	-2.5-5.4
Abdominal pain	9.3	-9.5-28.1	2.8	-3.4-9.0
Diarrhea	8.3	4.7-11.8	0.6	0.2-0.9
Pyrexia	8.0	1.3-14.6	NA	NA
Vomiting	7.8	0.1-15.4	NA	NA
Rash	7.3	5.2-9.4	0.9	-0.1-1.8
Arthralgia	6.2	3.4-9.0	NA	NA
Hypothyroidism	4.4	2.0-6.7	0.4	0-0.9
Elevated AST	4.1	2.1-6.2	1.5	-0.6-3.5
Asthenia	3.2	1.3-5.1	0.7	-0.2-1.6
Elevated ALT	2.7	1.2-4.1	0.9	-0.4-2.1
Pneumonitis	2.7	0-5.4	0.5	0-1.0
Elevated lipase	0.9	-0.4-2.2	0.7	-0.2-1.6
Colitis	0.8	0.2-1.4	0.4	0-0.8

AEs: Adverse events; CI: Confidence interval; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NA: Not available.

Table 3 *P* values of Begg and Egger's tests

Test	ORR	DCR	6-mo OS	6-mo PFS	12-mo OS	12-mo PFS	AEs	Grade ≥ 3 AEs
Begg's *P* value	0.669	0.945	0.452	0.902	0.161	0.734	0.583	0.760
Egger's *P* value	0.973	0.890	0.810	0.448	0.015	0.821	0.924	0.992

ORR: Objective response rate; DCR: Disease control rate; OS: Overall survival; PFS: Progression-free survival; AEs: Adverse events.

DISCUSSION

Immunoregulatory therapy has been shown to be effective in the control of advanced cancer. PD-1, a member of the CD28 family, is a receptor expressed on the surface of activated T cells that inhibits their activation and promotes apoptosis[41]. When bound to ligands, PD-1 can activate intracellular signaling pathways and inhibit the activation of immune cells, thereby reducing antibodies and cytokines secreted by immune cells and even depleting immune cells, thus maintaining the homeostasis of the immune system[42]. PD-L1 is the primary ligand of PD-1 and is expressed in certain tumor cells as well as activated B and T cells, dendritic cells, medullary cells, and endothelial cells. The molecule is also expressed in various tumor types and contributes to tumor immune escape[21,41]. The interaction between PD-1 and PD-L1 leads to down-regulation of T cells and their apoptosis and rejection by tumor microenvironment ultimately, which causes cancer cells to evade immune response[43]. Many studies have shown that blocking the interaction between PD-1 and PD-L1 can enhance T cell responses and mediate antitumor activity[44].

Although numerous clinical trials have already confirmed the efficacy of manageable safety of anti-PD-1/PD-L1 therapy in patients with advanced GC/GEJC, so far the FDA has only approved pembrolizumab for advanced GC/GEJC patients[45]. This approval was merely based on KEYNOTE-059, a single-arm clinical

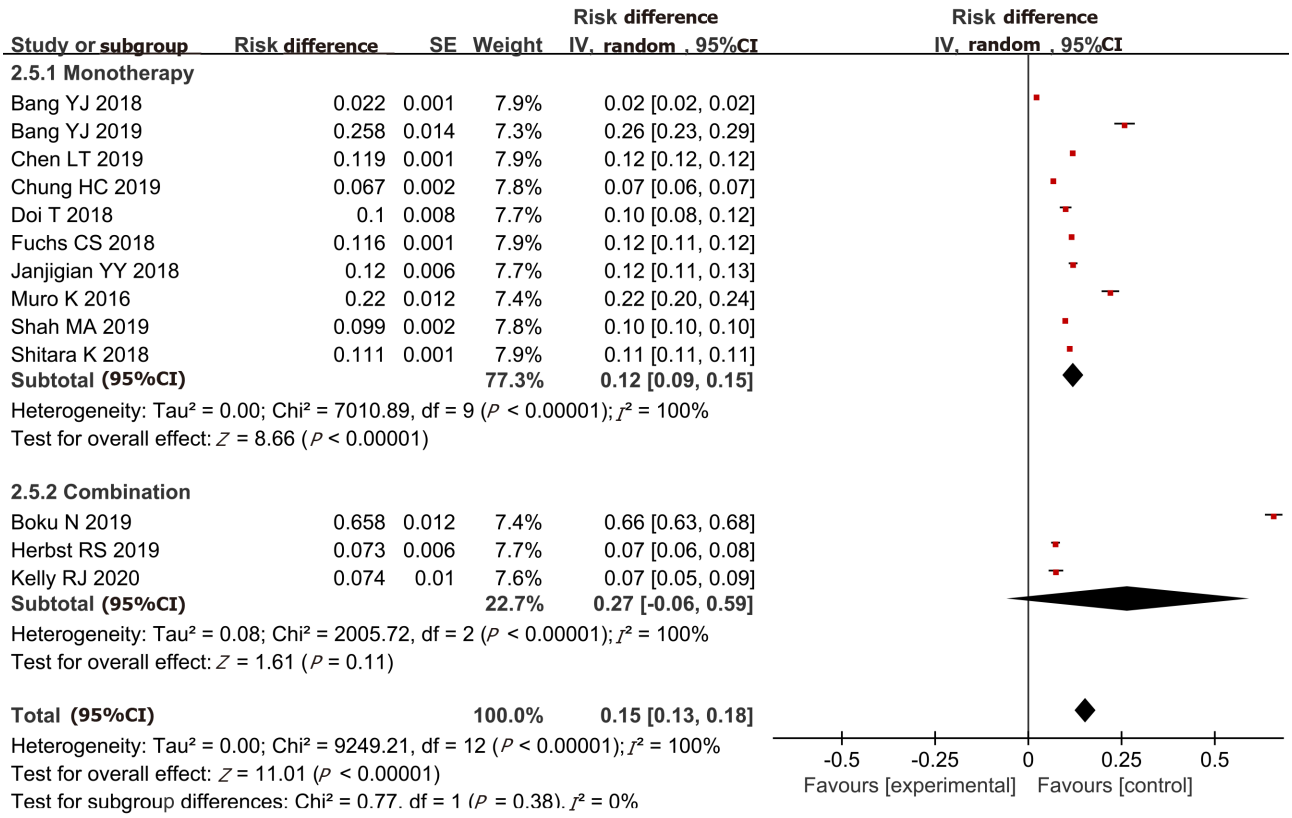


Figure 3 Pooled analysis of objective response rate.

trial, which showed an ORR of 11.6% (95%CI: 0.08-0.161) in Cohort 1, and 25.8% (95%CI: 0.119-0.46) in Cohorts 2 and 3 with a median OS of 20.7 mo (95%CI: 9.2-20.7)[29], 15.5% (95%CI: 10.1%-22.4%) for PD-L1 positive patients and 6.4% (95%CI: 2.6%-12.8%) for PD-L1 negative patients[34].

Contrary to the findings of KEYNOTE-059, KEYNOTE-061, which analyzed the different effects between pembrolizumab and paclitaxel in advanced GC/GEJC patients who had been previously treated[40], and JAVELIN Gastric 300, which compared the efficacy and safety of avelumab and paclitaxel or irinotecan in GC/GEJC patients[28], indicated that anti-PD-1/anti-PD-L1 antibody therapy is not significantly superior, in a significant way, to paclitaxel or irinotecan. ATTRACTION-2, the earliest randomized phase 3 study of an immune checkpoint inhibitor in advanced GC/GEJC patients, showed that nivolumab led to prolonged OS than placebo, and exhibited early and durable responses with a manageable safety profile[31,46]. Additionally, ATTRACTION-4, which studied the safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced or recurrent GC/GEJC, confirmed that nivolumab combined with chemotherapy led to manageable safety as well as clinically relevant antitumor activity with a reported ORR of 65.8%, DCR of 84.2%, and median OS over 13.9 mo.

Although the included clinical trials indicated different conclusions regarding the efficacy and safety of immune checkpoint inhibitors for advanced GC/GEJC patients, when combined, as shown in ORR, DCR, 6-mo OS, 6-mo PFS, 12-mo OS, and 12-mo PFS, it is both effective and manageably safe. A total of 15% of patients exhibited either a complete or a PR, and 40% showed progress in disease control. After treatment, 42% of patients survived for more than 1 year, with 26% exhibiting disease stableness for 6 mo. Moreover, anti-PD-1/anti-PD-Ll antibody therapy also exhibited manageable safety and can, in fact, be tolerated by most patients. The total incidence of any grade AEs was 64%, with signs of fatigue (15.8%), infusion reaction (13.8), and pruritus (13.1%), while that of grade ≥ 3 AEs was 18%, with signs of abdominal pain (2.8%), elevated AST (1.5%), and fatigue (1.2%). Although the immune-related AEs from anti-PD-1/anti-PD-L1 antibody occurred as a consequence of impaired self-tolerance from loss of T-cell inhibition[47], these side effects were generally manageable but can be fatal in some cases. Therefore, doctors should pay close attention to the signs of AE during treatment and take appropriate counter measures. It should be noted that GC/GEJC patients with different PD-L1 levels reacted differently to the anti-PD-1/anti-PD-L1

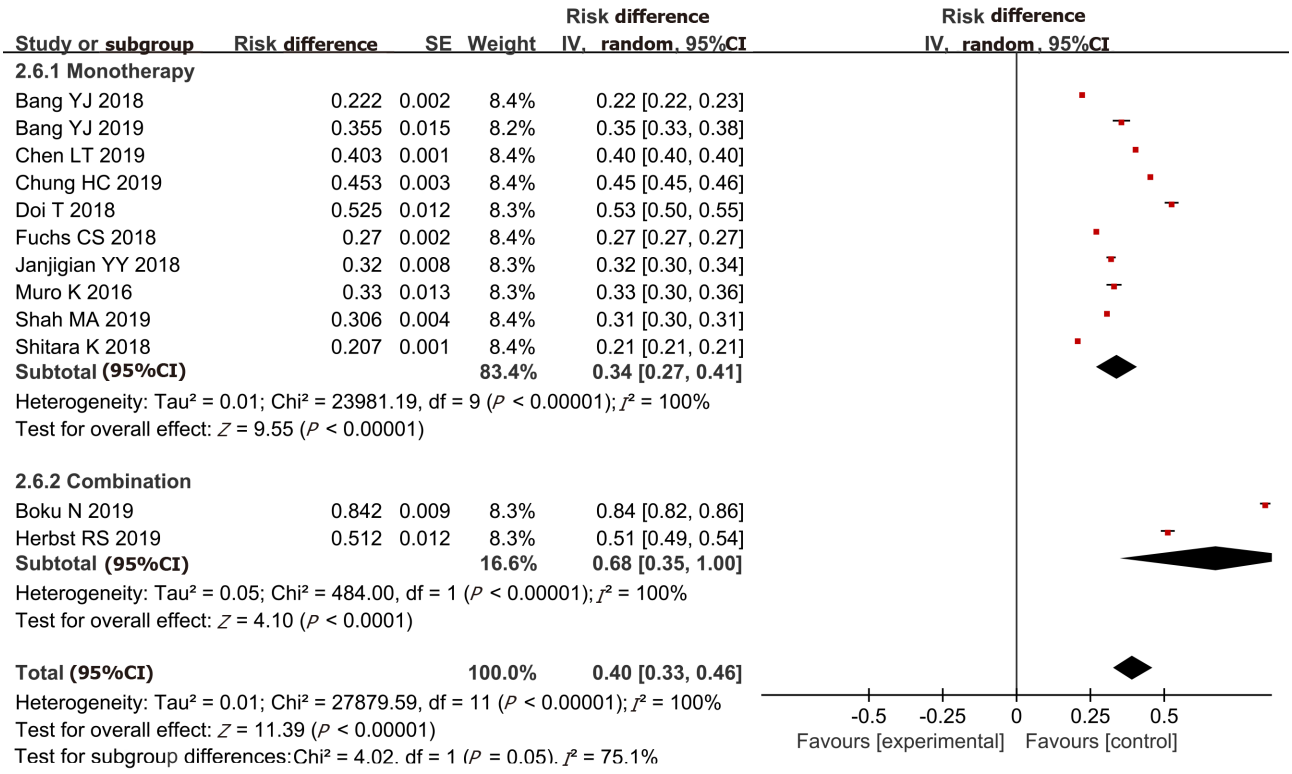


Figure 4 Pooled analysis of disease control rate.

antibody therapy: Patients with PD-L1 overexpression achieved better clinical efficacy, as their ORR was 15% compared with only 7% for PD-L1 negative patients, consistent with a previous study[24].

The Cancer Genome Atlas (TCGA) classifies gastric adenocarcinoma into four molecular subtypes: Epstein-Barr virus positive (EBV$^+$), microsatellite instability-high (MSI-H), genomically stable, or chromosomal instability[23]. MSI-H is associated with high PD-L1 tumor expression, therefore making tumor more sensitive to immunotherapy[48,49]. Consistently, PD-L1 expression has been related to OS[50]. Additionally, a recent meta-analysis also indicated that EBV and MSI subtypes tended to express PD-L1, thus enabling PD-L1 to act as a potential screening predictor for screening for EBV and MSI subtype GC patients.

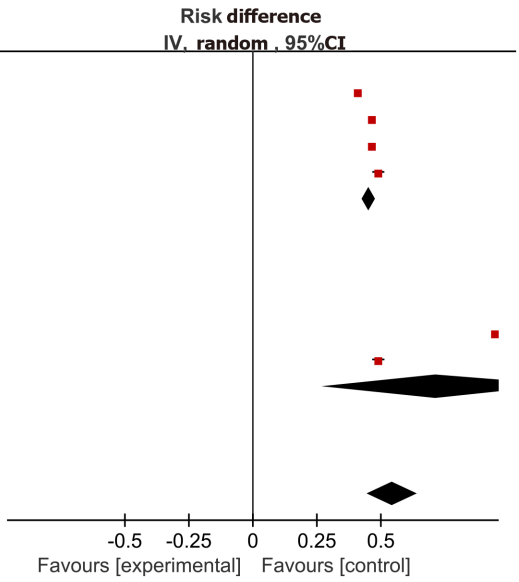
Monotherapy *vs* combination therapy analysis showed that while the ORR (27%), DCR (68%), 6-mo OS (72%), and 6-mo PFS (34%) of the combination therapy group were higher than those of the monotherapy group, the incidence rate of AEs was also higher, with 84% for any grade AEs and 35% for grade ≥ 3 AEs. A study in a melanoma mouse model also showed that the combined use of PD-1 inhibitors and TNF-α inhibitors has a better therapeutic effect than treatment with PD-1 inhibitors alone[51]. Thus, for patients who experienced reduced clinical efficacy, combination therapy may be a more potent option, although doctors should pay more attention to the potential development of AEs as well as the treatment progress of the pre-treated patients.

The efficacy and safety of combinational anti-PD-1/anti-PD-L1 antibody therapy still need to be explored. At present, only four trails were eligible to be included in this study, namely, KEYNOTE-590 (NCT03189719), CheckMate 649 (NCT02872116), KEYNOTE-062 (NCT02494583), and JAVELIN Gastric 100 (NCT02625610), which are all phase 3 clinical trials[30,35,37]. Notably, camrelizumab, a PD-1 inhibitor developed by Jiangsu Hengrui Medicine Co. Ltd., received approval in China in May 2019, although only conditionally for those who have already undergone at least two systemic chemotherapies for either relapsed or refractory classical Hodgkin lymphoma[52]. Additionally, two other phase 3 clinical trials on the efficacy and safety of camrelizumab combined with other chemotherapy drugs, NCT03691090 and NCT03813784, are under way.

To be noted, despite the use of subgroup analysis and random effect model, our study is limited to the inherent heterogeneity of the included studies, in terms of both type and dosage of the drugs although publication bias was not found in most of the

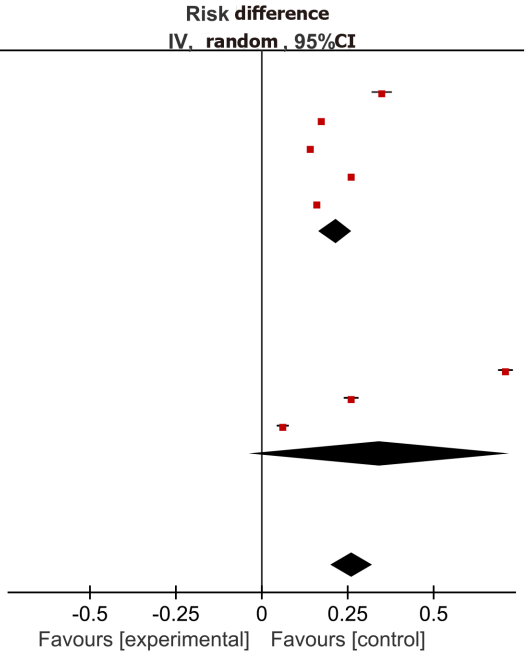
A

Study or subgroup	Risk difference	SE	Weight	Risk difference IV, random, 95%CI
2.2.1 Monotherapy				
Bang YJ 2018	0.41	0.003	16.7%	0.41 [0.40, 0.42]
Fuchs CS 2018	0.465	0.001926	16.7%	0.47 [0.46, 0.47]
Muro K 2016	0.465	0.002	16.7%	0.47 [0.46, 0.47]
Shah MA 2019	0.49	0.012	16.6%	0.49 [0.47, 0.51]
Subtotal (95%CI)			**66.7%**	**0.46 [0.43, 0.48]**
Heterogeneity: Tau² = 0.00; Chi² = 285.16, df = 3 (P < 0.00001); I^2 = 99%				
Test for overall effect: Z = 33.76 (P < 0.00001)				
2.2.2 Combination				
Boku N 2019	0.946	0.006	16.7%	0.95 [0.93, 0.96]
Herbst RS 2019	0.49	0.012193	16.6%	0.49 [0.47, 0.51]
Subtotal (95%CI)			**33.3%**	**0.72 [0.27, 1.16]**
Heterogeneity: Tau² = 0.10; Chi² = 1125.99, df = 1 (P < 0.00001); I^2 = 100%				
Test for overall effect: Z = 3.15 (P = 0.002)				
Total (95%CI)			**100.0%**	**0.54 [0.45, 0.64]**
Heterogeneity: Tau² = 0.01; Chi² = 6685.60, df = 5 (P < 0.00001); I^2 = 100%				
Test for overall effect: Z = 10.94 (P < 0.00001)				
Test for subgroup differences: Chi² = 1.32, df = 1 (P = 0.25), I^2 = 24.0%				



B

Study or subgroup	Risk difference	SE	Weight	Risk difference IV, random, 95%CI
2.1.1 Monotherapy				
Bang YJ 2019	0.349	0.015	12.2%	0.35 [0.32, 0.38]
Chung HC 2019	0.173	0.003	12.6%	0.17 [0.17, 0.18]
Fuchs CS 2018	0.141	0.001	12.6%	0.14 [0.14, 0.14]
Muro K 2016	0.26	0.003	12.6%	0.26 [0.25, 0.27]
Shah MA 2019	0.16	0.003	12.6%	0.16 [0.15, 0.17]
Subtotal (95%CI)			**62.7%**	**0.21 [0.17, 0.26]**
Heterogeneity: Tau² = 0.00; Chi² = 1626.17, df = 4 (P < 0.00001); I^2 = 100%				
Test for overall effect: Z = 8.87 (P < 0.00001)				
2.1.2 Combination				
Boku N 2019	0.709	0.011	12.4%	0.71 [0.69, 0.73]
Herbst RS 2019	0.26	0.011	12.4%	0.26 [0.24, 0.28]
Kelly RJ 2020	0.061	0.009	12.5%	0.06 [0.04, 0.08]
Subtotal (95%CI)			**37.3%**	**0.34 [-0.03, 0.72]**
Heterogeneity: Tau² = 0.11; Chi² = 2100.57, df = 2 (P < 0.00001); I^2 = 100%				
Test for overall effect: Z = 1.78 (P = 0.07)				
Total (95%CI)			**100.0%**	**0.26 [0.20, 0.32]**
Heterogeneity: Tau² = 0.01; Chi² = 4342.64, df = 7 (P < 0.00001); I^2 = 100%				
Test for overall effect: Z = 8.77 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I^2 = 0%				



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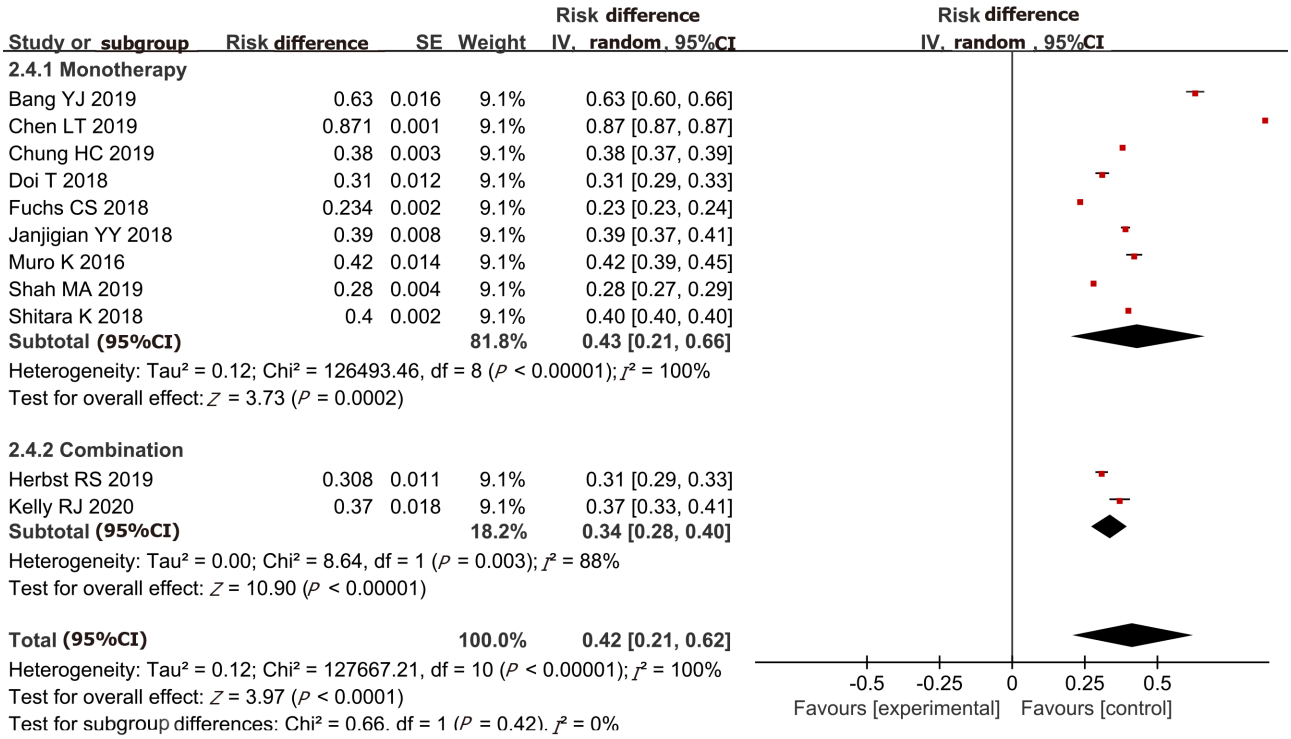

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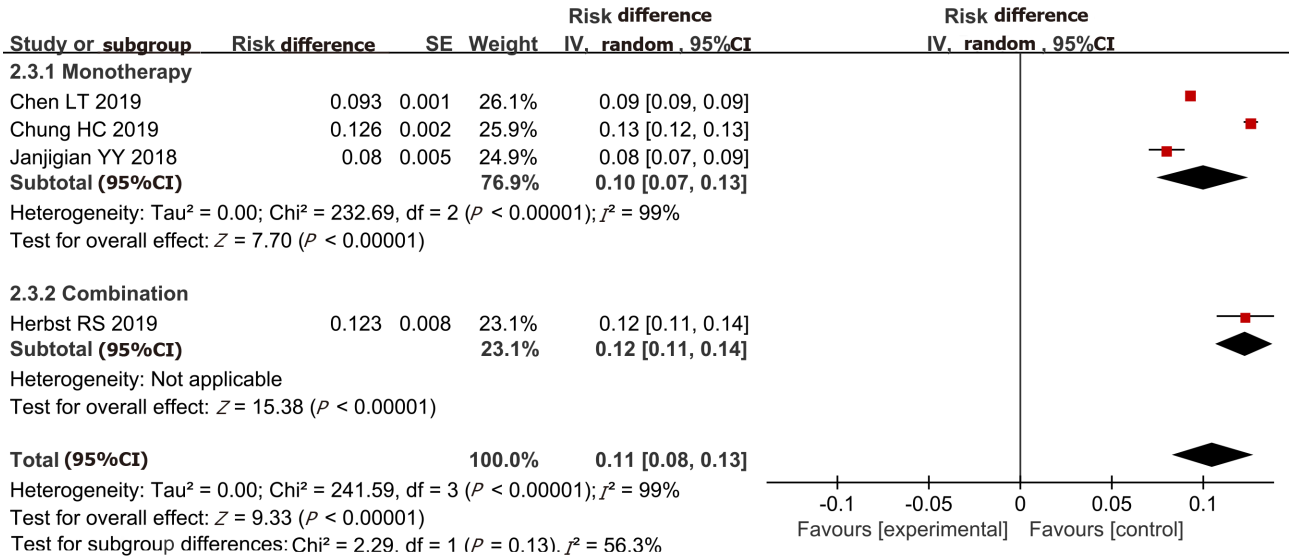


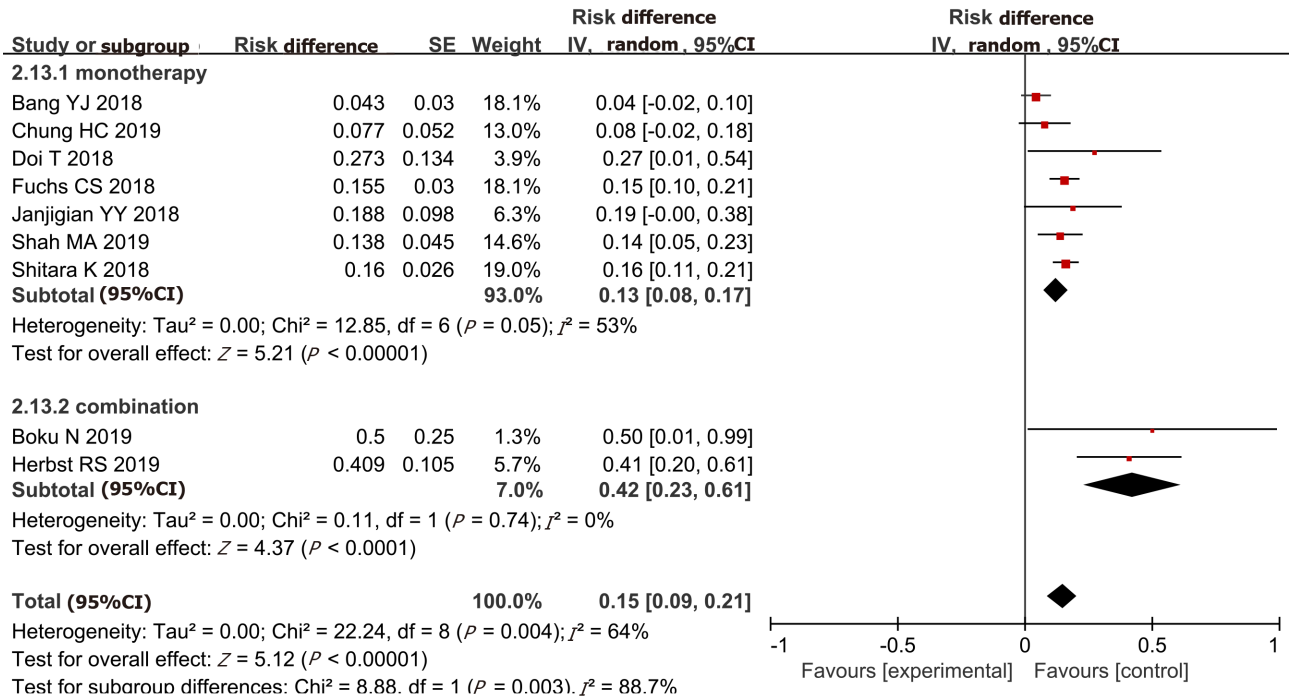
Figure 5 Overall survival and progression-free survival. A: 6-mo overall survival (OS); B: 6-mo progression-free survival (PFS); C: 12-mo OS; D: 12-mo PFS.

studies. Out of the 13 trials, five were RCTs, while the rest were either single-arm trials or dose-escalation trials; this results in potential bias leading to the deviation of the final analysis results.

CONCLUSION

Anti-PD-1/anti-PD-L1 antibody therapy is an effective treatment option with manageable AEs and high ORR for advanced GC/GEJC patients with overexpression

A



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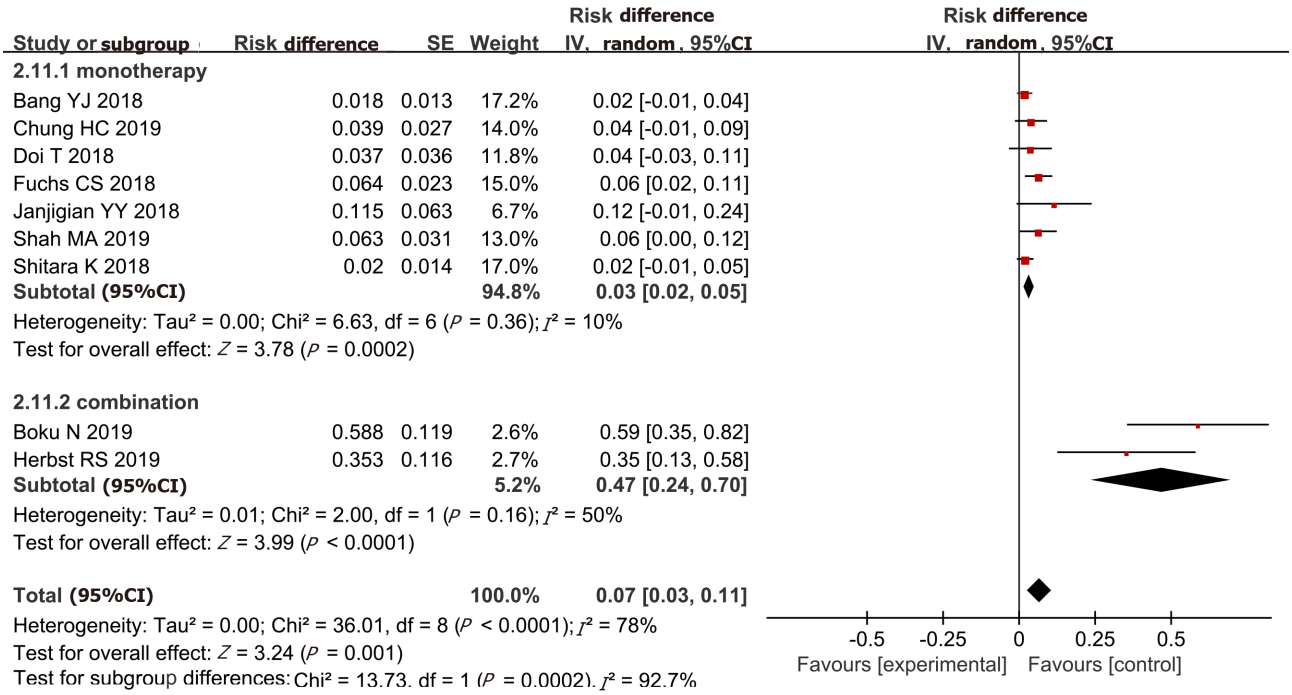

Figure 6 Objective response rate of PD-L1 positive (A) and negative patients (B).

of PD-L1. Furthermore, under the premise of paying close attention to safety of the treatment, it offers even better efficacy in combination with chemotherapy.

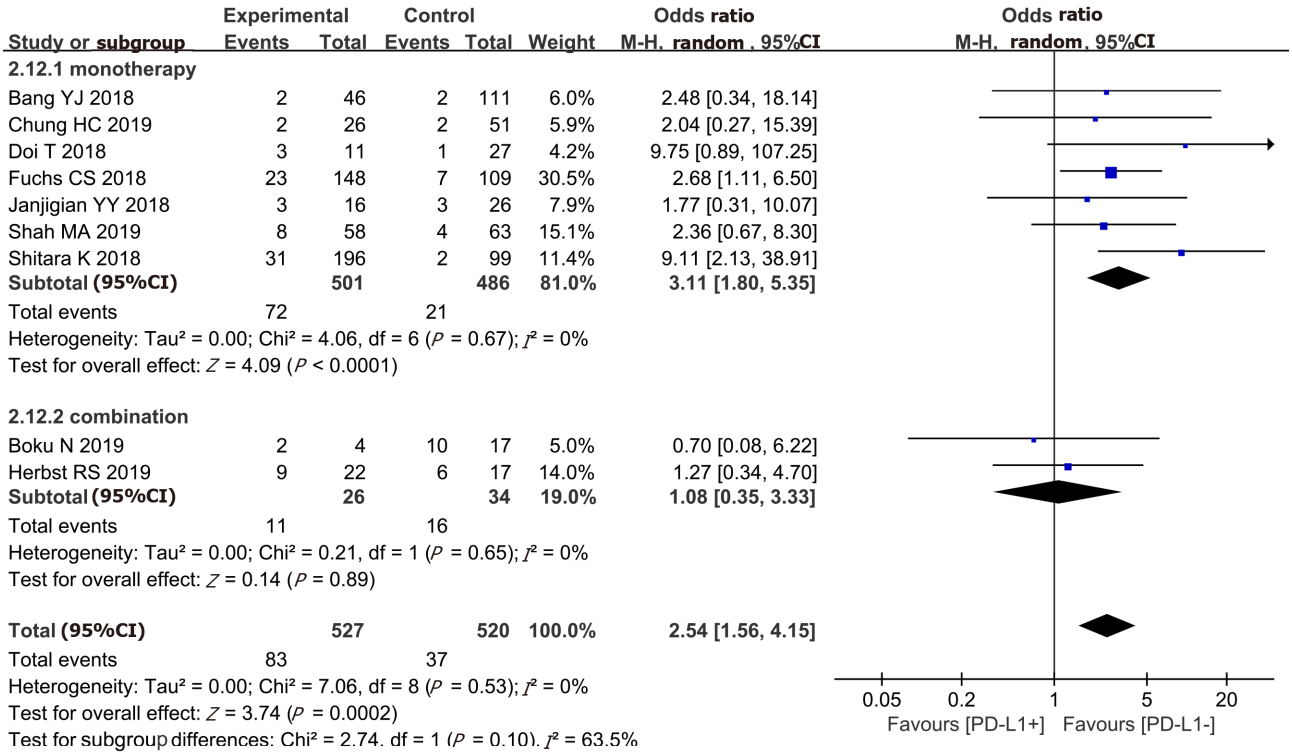

Figure 7 Comparison of objective response rate between PD-L1 positive and negative patients.

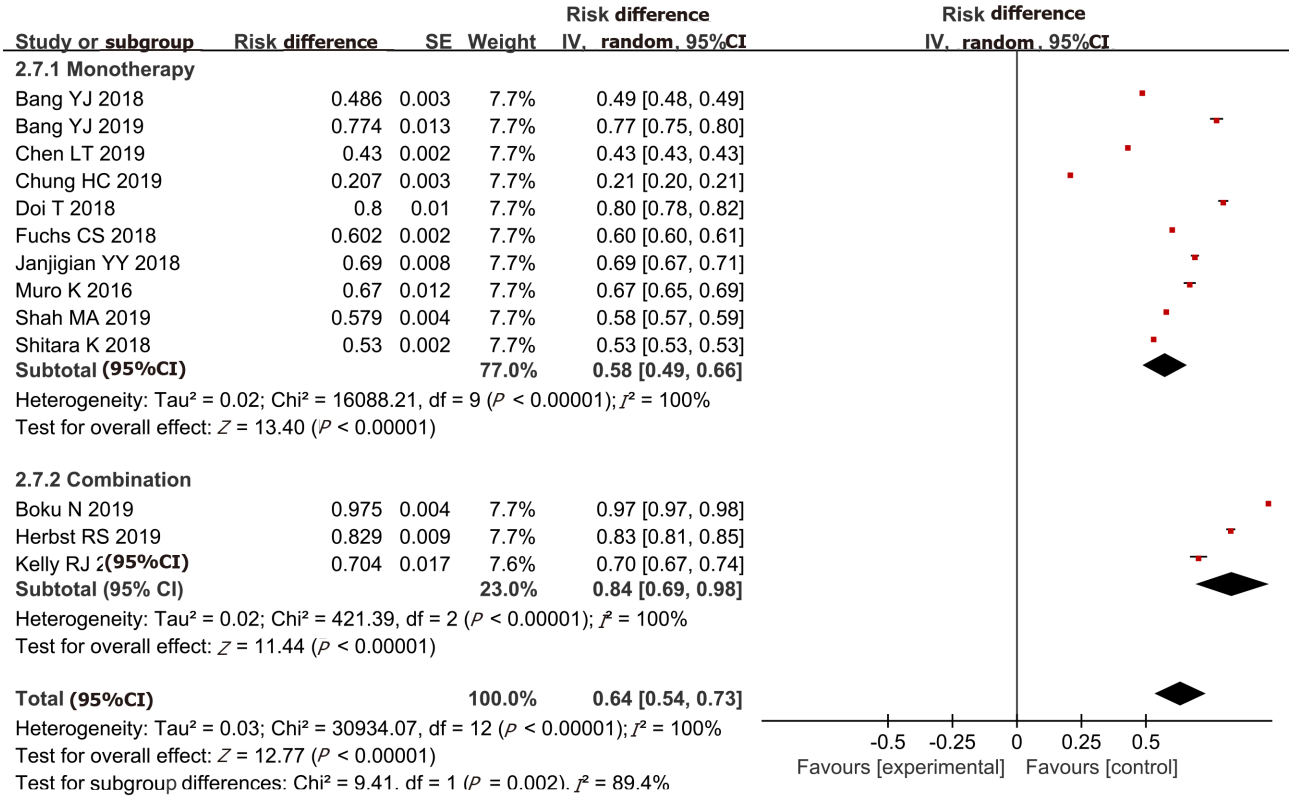

Figure 8 Pooled rate of any grade adverse events.

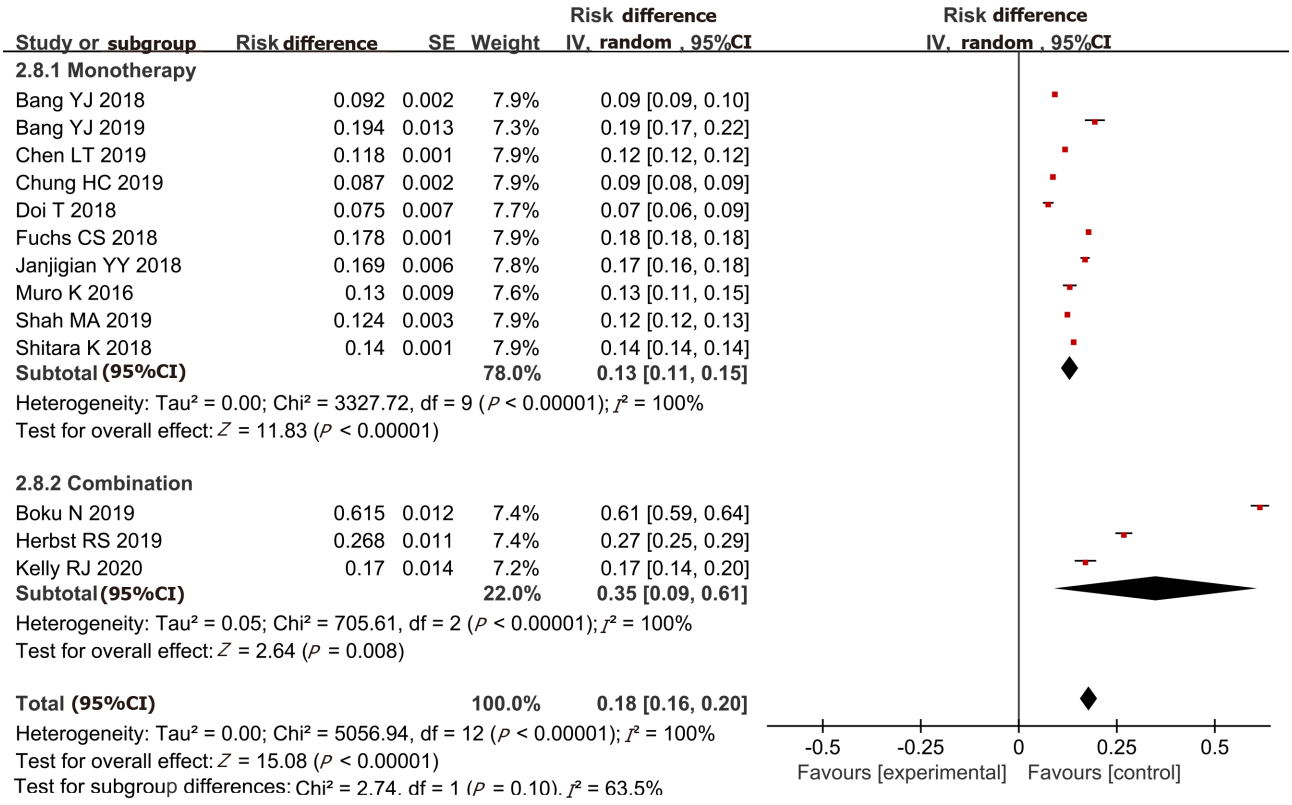

Figure 9 Pooled rate of grade ≥ 3 adverse events.

ARTICLE HIGHLIGHTS

Research background

Many clinical trials have confirmed that advanced gastric cancer or gastroesophageal junction cancer (GC/GEJC) patients can benefit from anti-PD-1/anti-PD-L1 antibody therapy. In addition, Epstein-Barr virus and microsatellite instability subtype gastric cancer patients tend to have high PD-L1 expression. Therefore, anti-PD-1/anti-PD-L1 antibody therapy may become a potential treatment for advanced GC/GEJC patients.

Research motivation

To better assess the efficacy and safety of anti-PD-1/anti-PD-L1 antibody therapy, we integrated data from 13 eligible studies for a systematic review and meta-analysis.

Research objectives

The purpose of this meta-analysis was to clarify the efficacy and safety of anti-PD-1/anti-PD-L1 antibody therapy in advanced GC/GEJC patients.

Research methods

PubMed, Web of Science, Cochrane Library, and EMBASE databases were searched to extract relevant data according to the designed extraction scheme, and conduct statistical analysis using Review Manger 5.3 and STATA 14.0 software. The main outcomes of this study included the objective response rate (ORR), disease control rate (DCR), overall survival (OS), free survival (PFS), and adverse events (AEs).

Research results

Our meta-analysis showed that the combined ORR and DCR were 15% (95%CI: 14%-18%) and 40% (95%CI: 33%-46%), respectively. The combined 6-mo OS and PFS were 54% (95%CI: 45%-64%) and 26% (95%CI: 20%-32%) respectively, and the 12-mo OS and PFS were 42% (95 %CI: 21%-62%) and 11% (95%CI: 8%-13%). In addition, the incidence of any grade AEs and ≥ 3 grade AEs was 64% (95%CI: 54%-73%) and 18% (95%CI: 16%-20%), respectively.

Research conclusions

Anti-PD-1/anti-PD-L1 antibody therapy has good anti-tumor efficacy with manageable AEs in advanced GC/GEJC patients. In addition, under the premise of paying close attention to safety of the treatment, it offers even better efficacy in combination with chemotherapy.

Research perspectives

This meta-analysis demonstrated the efficacy and safety of anti-PD-1/anti-PD-L1 antibody therapy and high ORR for advanced GC/GEJC patients with overexpression of PD-L1. Furthermore, when paying close attention to the safety of treatment, it seems that combination with conventional chemotherapy treatment can achieve better clinical efficacy. This study has some limitations. The future research direction can be to verify the efficacy and safety of anti-PD-1/anti-PD-1 antibody combined with chemotherapy in patients with advanced GC/GEJC.

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