Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

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DOI: 10.17235/reed.2025.11607/2025
Link: PubMed (Epub ahead of print)

Please cite this article as:
Han Zhuo, Yang Haicheng, Wu Tao, Qing Quao, He Xianli, Wang Nan. Evaluating the efficacy of PD-1 or PD-L1 inhibitors in gastric cancer patients. Rev Esp Enferm Dig 2025. doi: 10.17235/reed.2025.11607/2025.

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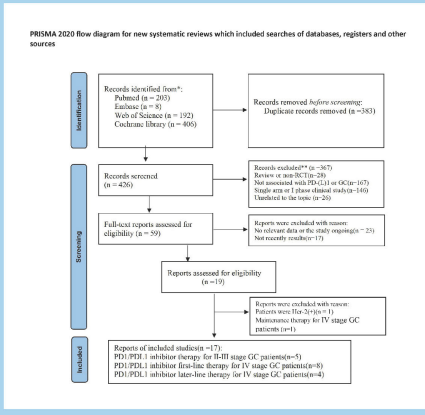
Study population



Methods

Direct meta-analysis
Network meta-analysis

Pathological complete response(pCR);
Objective response rate(ORR) ;
Progression-free survival(PFS);
Overall survival (OS);
≥grade 3 treat-related adverse events(TRAE)

Outcomes

PD-1/PD-L1 inhibitors improved patients' pCR [OR_{PD-1}=5.43(3.25,9.05) and OR_{PD-L1}=2.60(1.86,3.65)] in the locally advanced gastric cancer.

PD-1/PD-L1 inhibitors improved ORR [OR=1.48(1.33, 1.65)] , reduced the OS [HR = 0.79(0.74, 0.83)] and PFS [HR = 0.75(0.70, 0.80)] in first-line therapy for advanced gastric cancer.

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Revista Española de Enfermedades Digestivas (REED)
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Evaluating the efficacy of PD-1 or PD-L1 inhibitors in gastric cancer patients

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Authorship declaration according to CRediT standards

Nan Wang and Zhuo Han were responsible for designing of the manuscript. The data was extracted by Zhuo Han and Haicheng Yang. The analysis of data and draft manuscript were completed by Zhuo Han. Qing Qiao and Tao Wu revised grammar of the manuscript. Nan Wang and Xianli He checked the manuscript.

Conflict of Interest

All authors declare no conflict of interest.

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The Spanish Journal of Gastroenterology

Data availability statement

The data were included in the supplement materials. In addition to, more detailed data
were obtained by contacting corresponding author.

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Keywords: PD-1 inhibitor. PD-L1 inhibitor. Gastric cancer. Efficacy and safety. Network meta analysis.

Abbreviations list

PD-1: programmed death 1

PD-L1: programmed cell death ligand 1

GC : gastric cancer

RCTs : randomized controlled trials

pCR : pathological complete response

ORR : objective response rate

PFS : progression-free survival

OS : overall survival

TRAEs : adverse events

NMA : network meta-analysis

CSCO : Chinese Society of Clinical Oncology

NCCN : National Comprehensive Cancer Network

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HR : hazard ratio

CI : confidence interval

SUCRA : Cumulative Ranking Curve

CPS : combined positive score

EFS : event-free survival

Abstract

Objective: This study aims to assess the therapeutic advantages of PD-1 and PD-L1 inhibitors for gastric cancer (GC) patients and determine which of the two agents confers greater benefits.

Methods: A total of 17 randomized controlled trials (RCTs) were included. The primary outcomes included pathological complete response(pCR), objective response rate (ORR), progression-free survival (PFS), overall survival (OS) and ≥grade 3 treat-related adverse events (TRAEs). Direct meta-analysis and network meta-analysis (NMA) were used to assess the efficacy and safety of PD-1/PD-L1 inhibitors in locally advanced and advanced GC patients.

Results: For locally advanced GC, the direct results indicated that PD-1/PD-L1 inhibitors improved patients' pCR [OR_{PD-1}=5.43 (3.25,9.05) and OR_{PD-L1}=2.60 (1.86,3.65)]. Additionally, the NMA found that PD-1 inhibitors achieved a higher pCR than PD-L1 [OR=2.17 (1.12, 3.93)]. In advanced GC, direct results revealed that PD-1/PD-L1 inhibitors improved ORR [OR=1.48 (1.33, 1.65)] and reduced the risk of death [HR = 0.79 (0.74, 0.83)] and disease recurrence [HR = 0.75 (0.70, 0.80)] in first-line therapy. However, this study not found PD-1/PD-L1 improved the ORR, TRAE, PFS and OS in the later-line therapy. Subsequently, an exploring NMA on specific treatment regimens in first-line therapy for advanced GC was conducted, the results revealed Nivolumab plus chemotherapy enhanced the ORR while having the lowest TRAE, whereas Sintilimab plus chemotherapy provided the greatest benefit in PFS and OS.

Conclusion: The study suggested that PD-1/PD-L1 enhanced anti-tumor efficacy in neoadjuvant therapy and first-line of advanced GC, whereas no benefit was observed in the later-line treatment. And the efficacy of PD-1 was superior to PD-L1 in neoadjuvant treatment.

1.Introduction

Gastric cancer ranks as the fifth most prevalent cancer globally, exhibiting considerable regional disparities in its incidence. In recent decades, there has been a notable decline in the incidence of gastric cancer in Western nations, yet the disease continues to impose a significant burden in East Asia(1). A report from 2018 highlighted that advanced gastric cancer constitutes approximately 30%-40% of all gastric cancer cases in China. Recent research conducted by Hengyi Zhang and colleagues, which involved a 15-year follow-up of a single-center cohort comprising 3,915 gastric cancer patients, revealed that the 5-year overall survival (OS) rate for patients diagnosed with stage I gastric cancer surpassed 90% and remained relatively stable from 2008 to 2022. In contrast, the five-year relative OS rates for patients with Stage II, III and IV gastric cancer improved from 68.2%, 60.3% and 13.8% during the period of 2008-2012 to 85.4%, 70.2% and 29.0% in the subsequent period of 2018-2022(2). These findings suggested that individuals with advanced gastric cancer experience a poorer prognosis compared to those diagnosed with early-stage or locally advanced gastric cancer.

In recent years, the emergence of immune checkpoint inhibitors has provided new treatment options for cancer patients, primarily PD-1(programmed death 1) and PD-L1(programmed cell death ligand 1) drugs(3). The revised 2025 CSCO guidelines advocate for the use of established PD-1 or PD-L1 immune checkpoint inhibitors in the neoadjuvant treatment of locally advanced gastric cancer. In contrast, the therapeutic options for patients with advanced gastric cancer are markedly restricted. Certain researchers contend that the effectiveness of chemotherapy as a standalone treatment for advanced gastric cancer has reached its maximum potential, highlighting an urgent necessity for the identification of novel therapeutic agents to enhance patient survival rates. Consequently, the guidelines advocate for

the implementation of molecular testing for HER2, PD-L1, CLDN18.2 and MSI/MMR in patients who have not yet received treatment, in order to inform and optimize treatment selection(4). The 2025 updated NCCN guidelines recommend different chemotherapy regimens for different subtypes of advanced gastric cancer. For HER2-negative patients with PD-L1 CPS≥1, combination therapy with immune checkpoint inhibitors (pembrolizumab or other FDA-approved generic drugs) is recommended. MSI-H/dMMR patients may also choose to receive treatment with immune checkpoint inhibitors (5).

The Efficacy studies of PD-1 or PD-L1 Inhibitors were conducted in past 10 years. In 2019, Ya-Fang Huang et al. compared the safety of PD-1 and PD-L1 drugs in all malignant tumor patients. The results showed that the incidence of adverse reactions was lowest with anti-PD-L1 monotherapy and highest with anti-PD-1 therapy, but the difference between the two was not statistically significant(6). Andrea Botticelli et al. conducted a study comparing the efficacy of PD-1 and PD-L1 drugs in head and neck cancer patients. The results showed no significant difference in OS between the two groups in the general population. Nevertheless, it is noteworthy that PD-1 exhibited a greater efficacy than PD-L1 in patients with metastatic disease, as evidenced by a hazard ratio (HR) of 0.69 (95% CI:0.53,0.90)(7). In 2024, Liu et al. demonstrated that PD-L1 inhibitors plus chemotherapy and PD-1 inhibitors plus chemotherapy had comparable efficacy and safety in non-small cell lung cancer(8). However, Joe Q Wei and colleagues discovered that patients receiving a combination of anti-PD-1 and chemotherapy exhibited improved median overall survival (mOS), median progression-free survival (mPFS), and ORR in comparison to those treated with anti-PD-L1 and chemotherapy. Notably, the incidence of grade 3 or higher toxicities was comparable between the two treatment groups(9). Thus, the superiority of the two drug classes (irrespective of regimen) remains controversial, and there is a lack of research specifically involving patients with gastric cancer. Therefore, the aim of this study is to compare the efficacy of PD-1 and PD-L1 inhibitors for neoadjuvant therapy in locally advanced gastric cancer and treatment of advanced gastric cancer using a network meta-analysis method.

2. Methods

2.1 Search strategy

This research undertook an extensive and thorough investigation utilizing databases such as PubMed, Web of Science, Embase, and the Cochrane Library, with a specified cutoff date of May 19, 2025. The search terms were set as follows: ① (programmed cell death 1 receptor) OR (PD-1) OR (B7-H1) OR (CD274) OR (PD-L1) OR (programmed cell death ligand 1) OR (immune checkpoint inhibitors); ② (Gastric cancer) OR (Stomach Neoplasm) OR (Gastric Neoplasms) OR (Gastric Neoplasm) OR (Cancer of Stomach) OR (Stomach Cancers) OR (Gastric Cancers) OR (Stomach Cancer). Furthermore, this research exclusively incorporated articles classified as randomized controlled trials (RCTs).

2.2 Inclusion and exclusion criteria

The inclusion criteria for this study are as follows: ① pathologically confirmed gastric adenocarcinoma or esophageal-gastric adenocarcinoma;②RCT study design; ③ Intervention: PD-1 (+Chemo) or PD-L1 (+Chemo); ④Control group: (placebo) + chemo; ⑤Study outcomes reported include ORR, treat-related adverse event (TRAE), PFS, OS.

Exclusion criteria: ①Study type is a review or study protocol; ②Single-arm clinical study; ③Ongoing RCT but no results reported; ④Study subjects are not gastric cancer patients or unrelated to PD-1/PD-L1; ⑤Efficacy comparison of non-immunosuppressive agents in clinical trials; ⑥No available study data; ⑦Same study, only the most recent report results are included.

2.3 Data extraction and quality assessment

To ensure data quality and the reliability of results, this study employed double-blind independent data entry, with any discrepancies in the extracted data discussed and resolved. After carefully reading the full text, the extracted variable names included: ①first author, ②RCT name, ③NCT number, ④study year, ⑤clinical study type, ⑥sample size, ⑦study population, ⑧intervention measures, ⑨control measures, ⑩study results, ⑪age, ⑫tumor location, ⑬region, ⑭microsatellite

instability status, ⑮PD-L1 expression. Outcomes for overall population results and subgroup population results in the research report were extracted separately. For ORR and TRAE, the number of positive events and the total number of participants were extracted. For PFS and OS, the corresponding HR and the associated 95% confidence interval (CI) were extracted for subsequent data analysis.

The Cochrane Risk of Bias Assessment Tool was used to evaluate the quality of clinical studies based on randomization, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias(10). The outcomes of this assessment were classified into three categories: low risk, high risk, and unclear risk.

2.4 Statistical Analysis

Data analysis for this study was conducted utilizing R version 4.3.2. The R packages employed included meta, metafor, netmeta. The findings of the study were delineated for two distinct therapeutic approaches: neoadjuvant therapy and advanced/metastatic therapy. The outcomes evaluated for neoadjuvant therapy encompassed pathological complete response (pCR), whereas the outcomes for advanced/metastatic therapy comprised OS, PFS, ORR and TRAE. OS and PFS were quantified using HR along with 95% CI, while odds ratios (OR) and 95% CI were applied to the pooled metrics of pCR, ORR and TRAE.

First, meta-analysis was used to directly assess the efficacy and safety of PD-1/PD-L1 inhibitors compared with placebo plus chemotherapy in the overall population and in patients with different CPS scores, with results presented using forest plots. Second, a network meta-analysis (frequentist method, netmeta package) was used to compare the effects of PD-1 and PD-L1 inhibitors. The results of pairwise comparisons between interventions were expressed using OR and 95% CI, with league tables created for each efficacy indicator. The Surface Under the Cumulative Ranking Curve (SUCRA) was used to indicate the ranking of efficacy among different interventions, with results presented as bar charts or SUCRA curves. A higher SUCRA value indicates better efficacy. The choice between fixed-effect and random-effects models is based on priori clinical features and methodological

considerations. Generally, heterogeneity primarily stems from patient characteristics, interventions, sample sizes and study designs in clinical trial. However, when clinical characteristics are largely consistent, model selection can be based on the I^2 from the analysis results. Heterogeneity was assessed using statistical values $I^2 \geq 50\%$ and $P<0.05$. If heterogeneity was high, the random-effects model was adopted, otherwise, the fixed-effects model was used. The funnel plot and Egger test was implemented to assess the presence of publication bias.

3. Results

3.1 Screening process and Characteristics included in the study

A thorough investigation yielded a total of 809 pertinent publications, from which 383 duplicate articles were eliminated. Subsequent evaluation of titles and abstracts revealed that 367 articles were deemed ineligible for inclusion in this study. Among these, the treatment regimen for keynote-811 involved induction therapy followed by maintenance therapy. And the JAVELIN Gastric 100 study population was Her-2 positive. Considering the potential for study heterogeneity, these two studies were excluded from subsequent analyses. Ultimately, 17 articles were selected for further analysis(**Figure 1**)(11-27).The **Figure S4c** showed the quality assessment of included studies. The summary graph indicated that the enrolled RCTs all were not high-risk. **Table 1** delineates the fundamental characteristics of the 17 studies included in this review. The sample sizes across the included RCTs varied significantly, ranging from 47 to 1,581 participants. Five studies explored the efficacy of PD-1 or PD-L1 inhibitors as neoadjuvant therapies for patients with resectable locally advanced gastric cancer, while 12 studies focused on the application of these agents in patients with advanced unresectable or metastatic gastric cancer. Table S1 showed the detailed clinical features of included RCTs.

Table 2 presents the main study results of the included studies. In studies using PD-1/PD-L1 inhibitors for neoadjuvant therapy in patients with locally advanced gastric cancer, all 5 studies reported pCR. Subsequently, among the 12 studies treating advanced gastric cancer, 7 studies reported OS, PFS, ORR and TRAE for the entire randomized population.

3.2 Efficacy of PD-1/PDL-1 Inhibitors in Neoadjuvant Therapy

In patients with gastric cancer who received PD-1 or PD-L1 inhibitors as neoadjuvant therapy, this study primarily evaluated postoperative pCR in patients. Direct comparison results (**Figure 2**) showed that compared with (placebo plus) chemotherapy, both PD-1 and PD-L1 inhibitors significantly improved pCR, with corresponding OR and 95% CI values of 5.36 (3.21, 8.96) and 2.47 (1.49, 4.10). The five studies included in the neoadjuvant therapy analysis showed no publication bias (P=0.679, **Figure S4a**).

In the results of the indirect comparison presented in **Figure 2b and 2c**, it was observed that the combination of PD-1/PD-L1 inhibitors with chemotherapy led to a significant enhancement in the pCR rates when compared to chemotherapy alone. The OR and corresponding 95% CI were 4.24 (2.00, 8.15) and 2.00 (1.13, 3.32), respectively. Furthermore, the analysis revealed that the combination of PD-1 inhibitors with chemotherapy resulted in a higher pCR rate (OR=2.17, 95% CI:1.12, 3.93) in comparison to the combination of PD-L1 inhibitors with chemotherapy. The final ranking of the effects on pCR improvement indicated that the combination of PD-1 inhibitors with chemotherapy was superior to that of PD-L1 inhibitors with chemotherapy, followed by chemotherapy alone and the placebo combined with chemotherapy, as illustrated in **Figure 2d**. The results of the network evidence diagram and node inconsistency detection are shown in **Figure S1**.

3.3 Efficacy and Safety of PD-1/PD-L1 Inhibitors in the Treatment of Advanced Gastric Cancer

This study evaluated the efficacy and safety of PD-1 or PD-L1 inhibitors in the treatment of advanced gastric cancer using ORR, TRAE, OS and PFS as key metrics. The studies included in the analysis did not demonstrate any evidence of publication bias (P=0.914,**Figure S4b**) in the first-line therapy. But these was only two studies (overall population) in the later-line therapy, it did not assess the publication bias. In the first-line therapy of advanced GC, direct comparison results (**Figure 3a**) indicated that PD-1/PD-L1 inhibitors significantly improved ORR in advanced gastric cancer

patients compared with (placebo plus) chemotherapy (OR=1.48, 95%CI:1.33, 1.65) in the overall population. Similar results were observed in subgroups with different CPS scores (CPS≥1, CPS≥5, CPS≥10), with more pronounced efficacy in the CPS≥10 subgroup (OR=2.11, 95%CI:1.64, 2.72). Regarding TRAEs (**Figure 3b**), PD-1 /PD-L1 inhibitors significantly increased the risk of adverse reactions compared to (placebo plus) chemotherapy in the overall population, with an OR and 95%CI of 1.45 (1.23, 1.70), while it did not observe the increased risk of treat-related adverse reactions in the CPS≥1 population (OR = 0.75, 95% CI: 0.26, 2.19).

Regarding the survival efficacy of PD-1/PD-L1 inhibitors in patients with advanced gastric cancer, the results of this study confirm that PD-1/PD-L1 inhibitors can reduce the the risk of disease recurrence (HR_{PFS}=0.75, 95% CI: 0.70, 0.80, **Figure 3c**) and risk of mortality (HR_{OS}=0.79, 95% CI:0.74, 0.83, **Figure 3d**) and in the overall population. Different CPS score subgroups showed similar PFS and OS outcomes (**Figure 3c and 3d**). However, this study not found the evidences that PD-1/PD-L1 monotherapy improved the ORR, TRAE, PFS and OS in the overall population in the later-line therapy of advanced GC (**Figure 4**). Similar results also were showed in CPS≥1 population, moreover the PD-1/PD-L1 monotherapy even increased the risk of PFS compare with chemotherapy (HR=1.31, 95% CI:1.09, 1.58, **Figure 4c**).

Due to the limited number of PD-L1 clinical studies, we were unable to evaluate the efficacy and safety of PD-1 vs PD-L1 drugs by network meta analysis in first- and later-line treatments for advanced gastric cancer. However, we conducted an exploring NMA on specific treatment regimens in first-line therapy for advanced gastric cancer. Figure S1a showed the network evidence graph of first-line therapy for advanced GC. The results found the PD-1 plus chemotherapy in first-line therapy could improve the ORR, PFS and OS compared with chemotherapy (plus placebo) (**Figure S2a,c,d,f**). Regarding TRAE, Pembrolizumab or Nivolumab plus chemotherapy maybe increased the risk of treat-related adverse events, corresponding OR and 95%CI were 1.40 (1.04,1.90) and 1.69 (1.33,2.14) respectively. And **Figure S3** revealed that compared with other regimens, Nivolumab plus chemotherapy could enhance the ORR in advanced GC while having the lowest TRAE, whereas Sintilimab plus chemotherapy provided the greatest benefit in PFS and OS.

4. Discussion

This study conducted a comprehensive analysis of the efficacy and safety of PD-1 /PD-L1 inhibitors in gastric cancer patients based on existing RCT results. First, PD-1 or PD-L1 inhibitors demonstrated significantly superior anti-tumor efficacy (pCR) compared to chemotherapy alone in locally advanced gastric cancer. Second, PD-1/PD-L1 inhibitors significantly improved ORR and reduced the the risk of PFS and OS in first-line therapy of different subtypes advanced gastric cancer patients compared with (placebo plus) chemotherapy, but increased the risk of TRAE. However, in the later-line therapy of advanced gastric cancer, this study believed that PD-1/PD-L1 monotherapy not improved the ORR, TRAE, PFS and OS in the overall population. The exploring NMA of first-line therapy for advanced GC indicated that compared with other regimens, Nivolumab plus chemotherapy could enhance the ORR in advanced GC while having the lowest TRAE, whereas Sintilimab plus chemotherapy provided the greatest benefit in PFS and OS.

As multiple drug clinical trials have been conducted, the efficacy and safety of these inhibitors for the treatment of advanced gastric cancer remain to be thoroughly assessed. In 2024, M. S. Beshr et al. assessed the efficacy of PD-1 and PD-L1 inhibitors in combination with chemotherapy or as monotherapy compared to chemotherapy alone in patients with advanced, unresectable HER2-negative gastric cancer or gastroesophageal junction adenocarcinoma. The findings showed that compared with chemotherapy alone, PD-1/PDL-1 inhibitors significantly improved OS (HR=0.86, 95% CI: 0.80, 0.93), while the effect on PFS was not significant (HR=0.97, 95% CI: 0.77, 1.22). Furthermore, subgroup analysis based on CPS revealed that in patients with CPS≥1, CPS≥5, CPS≥10, PD-1/PD-L1 inhibitors combined with chemotherapy also significantly improved OS(28). Wenji Pu et al. reported the latest meta-analysis results in 2025, showing that PD-1 inhibitors combined with chemotherapy significantly improved ORR (RR=1.21, 95% CI: 1.14, 1.29) compared to the control group, and also significantly improved long-term PFS (HR = 0.76, 95% CI: 0.71, 0.81) and OS (HR = 0.81, 95% CI: 0.76, 0.86). Safety analysis revealed a higher incidence of severe treatment-related adverse events (TRAEs) in the immunotherapy

plus chemotherapy group (RR=1.47, 95%CI: 1.24, 1.75), but the efficacy of PD-L1 inhibitors compared to chemotherapy did not demonstrate significant benefits. Subsequent CPS scoring subgroup analysis indicated that the higher the PD-L1 expression level in patients, the more pronounced the reduction in mortality risk(29). The direct comparison results of this study were similar to the conclusions of the aforementioned studies. Compared with chemotherapy alone, PD-1/PD-L1 inhibitors improved ORR (HR=1.48, 95% CI: 1.33, 1.65), OS (HR=0.79, 95% CI: 0.74, 0.83) and PFS (HR=0.75, 95% CI: 0.70, 0.80) in first-line therapy of patients with advanced gastric cancer in the overall population. Additionally, this study conducted subgroup analyses for different PD-L1 expression groups, the results were similar in different CPS groups. However, in the later-line therapy of advanced gastric cancer, PD-1/PD-L1 inhibitors not observed the benefit in ORR, PFS and OS. The study of M. S. Beshr et al not found the improvement of PD-1/PD-L1 inhibitors to PFS, which maybe because the study included some patients with esophageal adenocarcinoma. While the study by Wenji Pu et al. exclusively enrolled patients with advanced GC or GEJ receiving first-line therapy, excluding esophageal adenocarcinoma, other clinical features was not significant differences. Our study also enrolled sinmilar population (GC and GEJ), thus the results were consist with Wenji Pu et al. Furthermore, in our study, the JAVELIN Gastric 100 (PD-L1 drugs) was excluded because the treatment regimen was maintenance therapy following induction, while Wenji Pu et al's study included it and the draw the conclusion that PD-L1 did not demonstrate significant benefits. But we think the effect of PD-L1 drugs still need more studies to verify.

The efficacy of PD-1 and PD-L1 inhibitors in advanced gastric cancer has boosted researchers' confidence in applying them to neoadjuvant therapy for locally advanced gastric cancer. In 2023, Hao Xu et al. evaluated the efficacy of neoadjuvant immunotherapy combined with chemotherapy in Chinese patients with resectable gastric cancer. The results showed that the combined pCR rate was 26.5%, a significant improvement compared to chemotherapy alone, laying the foundation for future phase III clinical trials(30). Keynote-585 was the first global randomized phase III clinical study to evaluate the synergistic effect of PD-1 monoclonal antibodies combined with chemotherapy(31). With the completion of multiple phase III clinical

trials, in 2024, Zhiyuan Yu et al. conducted a meta-analysis on the safety and efficacy of neoadjuvant PD-1 inhibitors combined with chemotherapy in locally advanced gastric cancer. The study included six RCTs and nine retrospective studies, both of which confirmed that the PD-1 inhibitor group demonstrated a higher pCR rate (OR=3.39, 95% CI: 1.92,6.00, OR=3.45, 95% CI: 2.19,5.42), but there was no significant difference in the incidence of adverse reactions compared to the chemotherapy group. Additionally, the study reported that the PD-1 inhibitor group had a lower 2-year recurrence rate post-surgery compared to the chemotherapy group (OR=0.711, 95% CI: 0.583,0.867)(26). A meta-analysis published in 2025, which included seven studies (five retrospective studies and two RCTs), also indicated that the neoadjuvant treatment regimen combining PD-1/PD-L1 inhibitors with chemotherapy was associated with a higher pCR rate (OR=5.94, 95% CI: 13.98,8.87)(32). This study included five RCTs. Unlike the aforementioned studies, the chemotherapy regimens in the five included RCTs did not include targeted drugs, and two studies used PD-L1 drugs. However, the results still showed that compared with chemotherapy alone, PD-1/PD-L1 inhibitors effectively improved pCR rates in neoadjuvant therapy for locally advanced gastric cancer, consistent with previously published findings and confirming that patients with locally advanced gastric cancer can benefit from neoadjuvant immunotherapy combined with chemotherapy.

Compared with chemotherapy alone, this study found PD-1/PD-L1 inhibitors combined with chemotherapy can improve the ORR, PFS and OS in patients with advanced gastric cancer first-line therapy. Unfortunately, due to the heterogeneity between individual studies, we analyzed the first-line and later-line treatments for advanced gastric cancer separately. However, this prevented a network meta-analysis for indirect comparisons between PD-1 and PD-L1 inhibitors and only allowed for a conventional meta-analysis. Nevertheless, we still performed an exploring NMA on specific treatment regimens across the overall population receiving first-line therapy for advanced gastric cancer. The results revealed that Nivolumab plus chemotherapy could enhance the ORR in advanced GC while having the lowest TRAE, whereas Sintilimab plus chemotherapy provided the greatest benefit in PFS and OS. In 2025, Yunnan Zhang et al. conducted a detailed comparison

of the efficacy of PD-1 drugs combined with chemotherapy as first-line treatment for advanced gastric cancer patients. They found that the SUCRA value for OS was highest for sintilimab combined with chemotherapy, while the SUCRA values for PFS and ORR were highest for nivolumab combined with chemotherapy(33). , Yunnan Zhang et al ‘s study included six RCTs, of which five RCTs enrolled the overall population, while one study only included participants with CPS≥1. This study exclusively analyzed studies involving the overall population and extracted the most recent research data, resulting in certain differences in conclusions.

This study had some limitations. First, this study exhibited considerable heterogeneity, primarily stemming from differences in patient characteristics across enrolled studies (regional origin, tumor location, microsatellite status, PD-L1 expression), intervention therapies and chemotherapy regimens in control groups. To mitigate the impact of heterogeneity on the reliability of the findings, this study categorized treatment interventions for advanced gastric cancer into first-line (immunotherapy combined with chemotherapy) and later-line therapies (immunotherapy monotherapy). Subgroup and overall population analyses were conducted based on patients' PD-L1 expression status. Based on the clinical characteristics of the included studies, tumor location and microsatellite status showed relatively consistent distributions across studies. Study region and chemotherapy regimens may exert greater influence on study conclusions. Therefore, sensitivity analyses were conducted to confirm that the original conclusions remained reliable (Figure S5). Second, the existing studies are not enough to conducting a network meta-analysis when analyzing first-line and later-line immunotherapy regimens for advanced gastric cancer separately. Although this study made an exploring NMA on specific treatment regimens across the overall population receiving first-line therapy for advanced gastric cancer, we still hope to carry out a network meta analysis to compare the efficacy and safety of PD-1 vs PD-L1 in first-line therapy of advanced gastric cancer in the future, which need more PD-L1 drugs clinical trials.

In summary, the findings suggested that PD-1/PD-L1 significantly enhances anti-tumor efficacy in first-line therapy and neoadjuvant therapy of patients with GC,

whereas no benefit was observed in the later-line treatment of advanced gastric cancer. And the efficacy of PD-1 drugs was also superior to that of PD-L1 drugs in neoadjuvant treatment for locally advanced gastric cancer.

Ethics approval

Not application.

Acknowledgements

Not application.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Number. 82273375) and Superintendent of Innovation Capability Support Program of Shaanxi(2024RS-CXTD-82).

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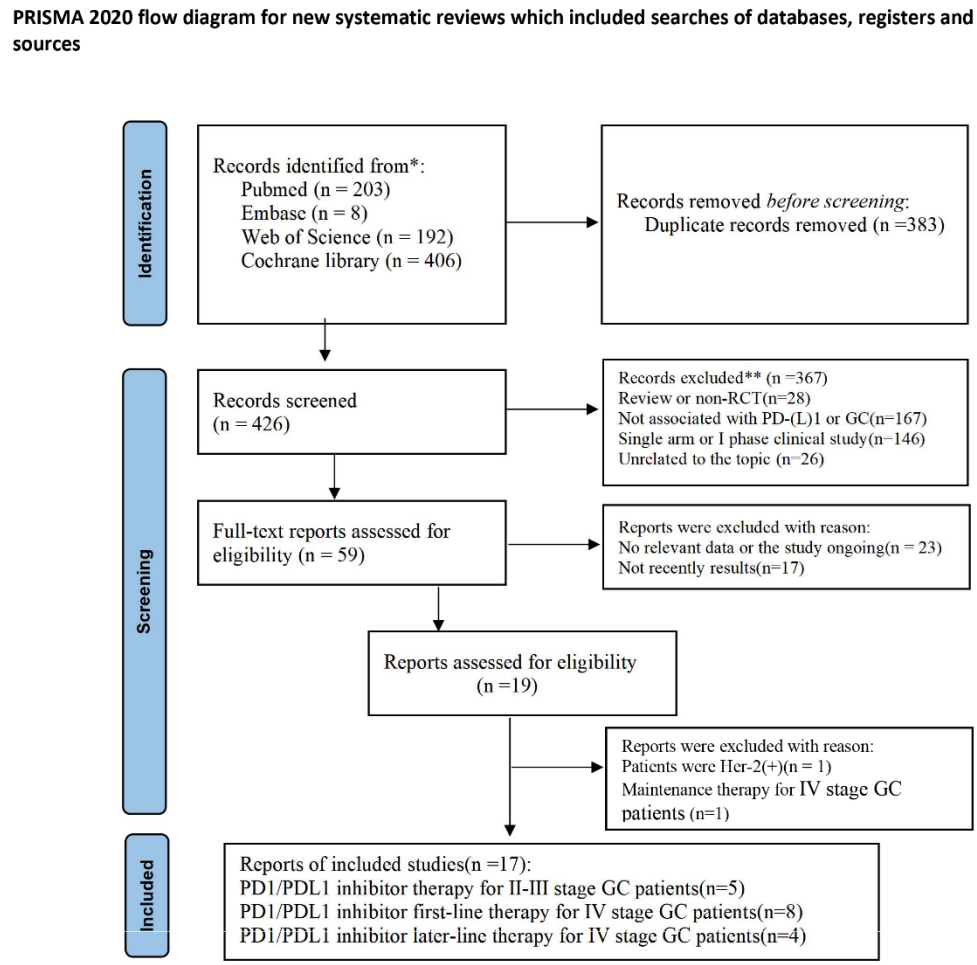

Fig.1: The figure showed the detail screening process of studies.

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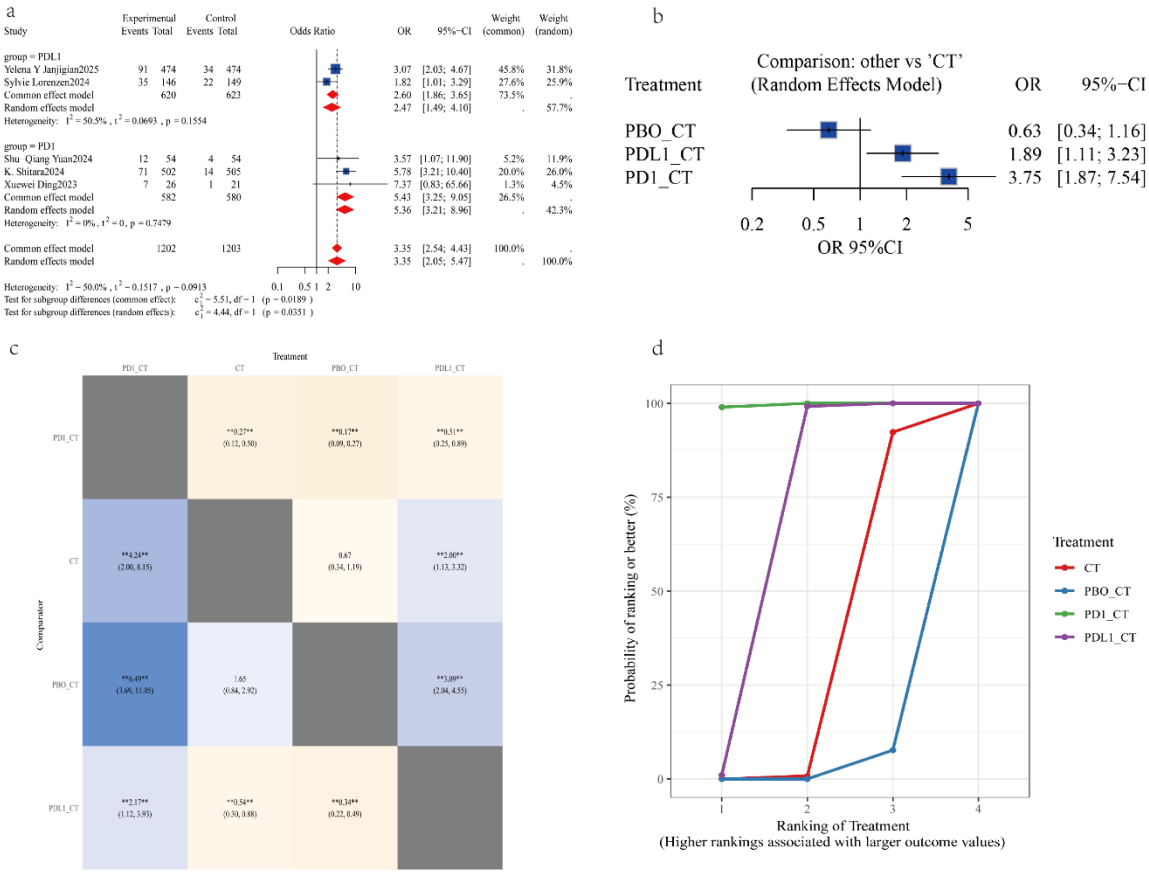

Fig.2: The pCR of PD-1/PD-L1 inhibitors in locally advanced gastric cancer patients. a.direct result; b.indirect result; c. league table of treatment regimens; d. rank of various treatment regimens in patients with locally advanced gastric cancer. pCR:pathological complete response.

e.the neoadjuvant therapy pCR. OS:overall survival; PFS: progression-free survival; ORR:objective response rate; TRAE: adverse evevt; pCR:pathological complete response.

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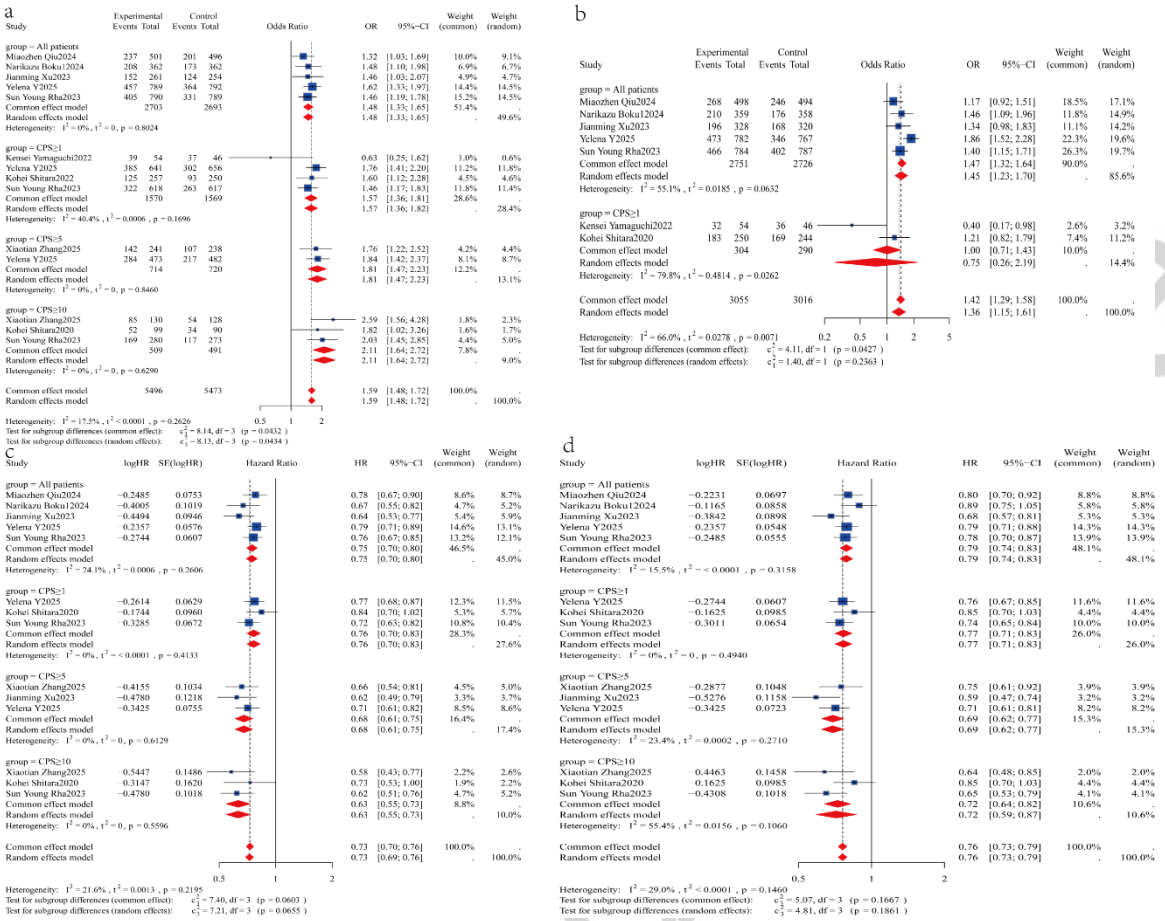

Fig.3: The efficacy and safety of PD-1/PD-L1 in first-line of patients with advanced gastric cancer (overall patients and CPS≥1,5,10 patients). a.ORR; b. grade ≥3 TRAE; c.PFS; d.OS. OS:overall survival; PFS: progression-free survival; ORR:objective response rate; TRAE:treat-related adverse evevt.

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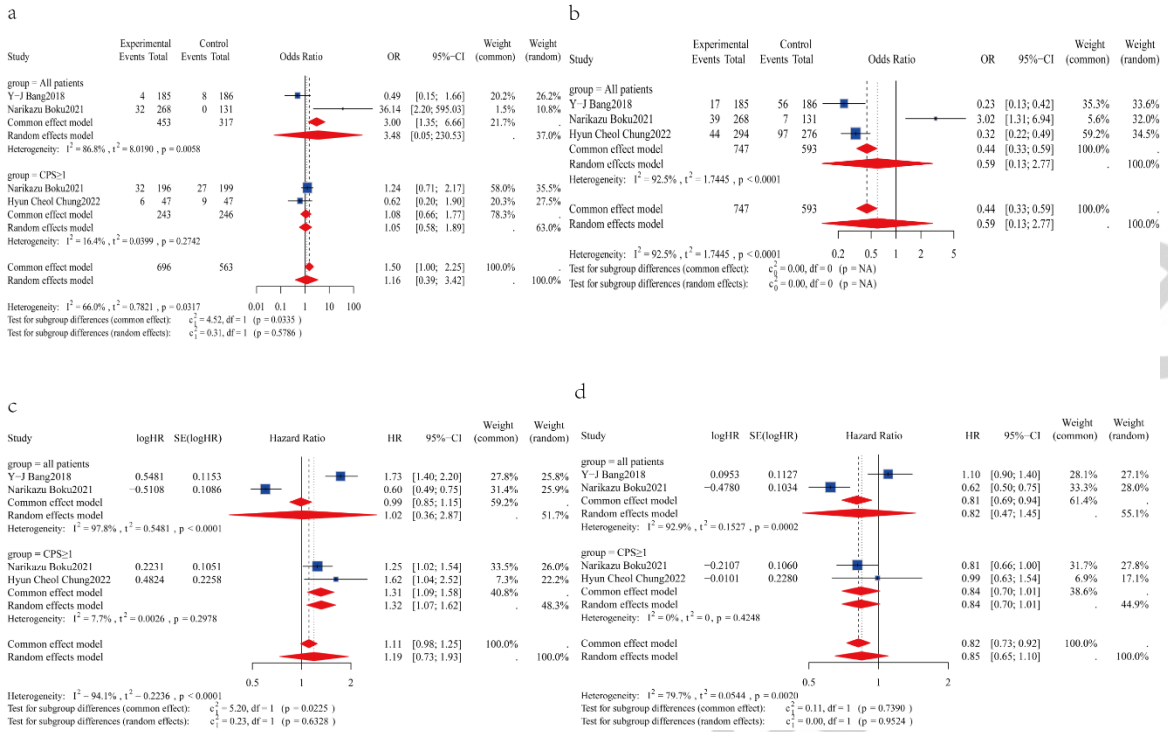

Fig.4: The efficacy and safety of PD-1/PD-L1 in later-line of patients with advanced gastric cancer (overall patients and CPS≥1 patients). a.ORR; b. grade ≥3 TRAE; c.PFS; d.OS. OS:overall survival; PFS: progression-free survival; ORR:objective response rate; TRAE:treat-related adverse evevt.

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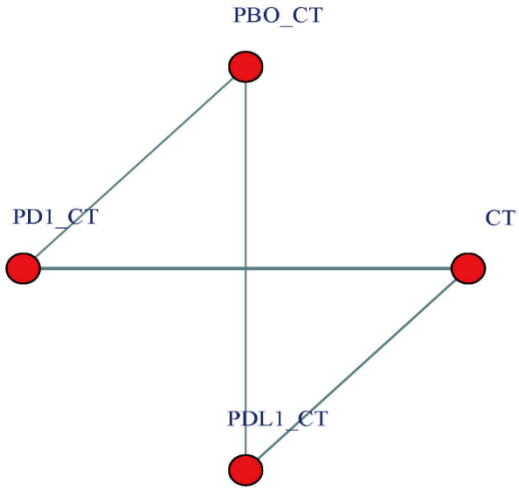

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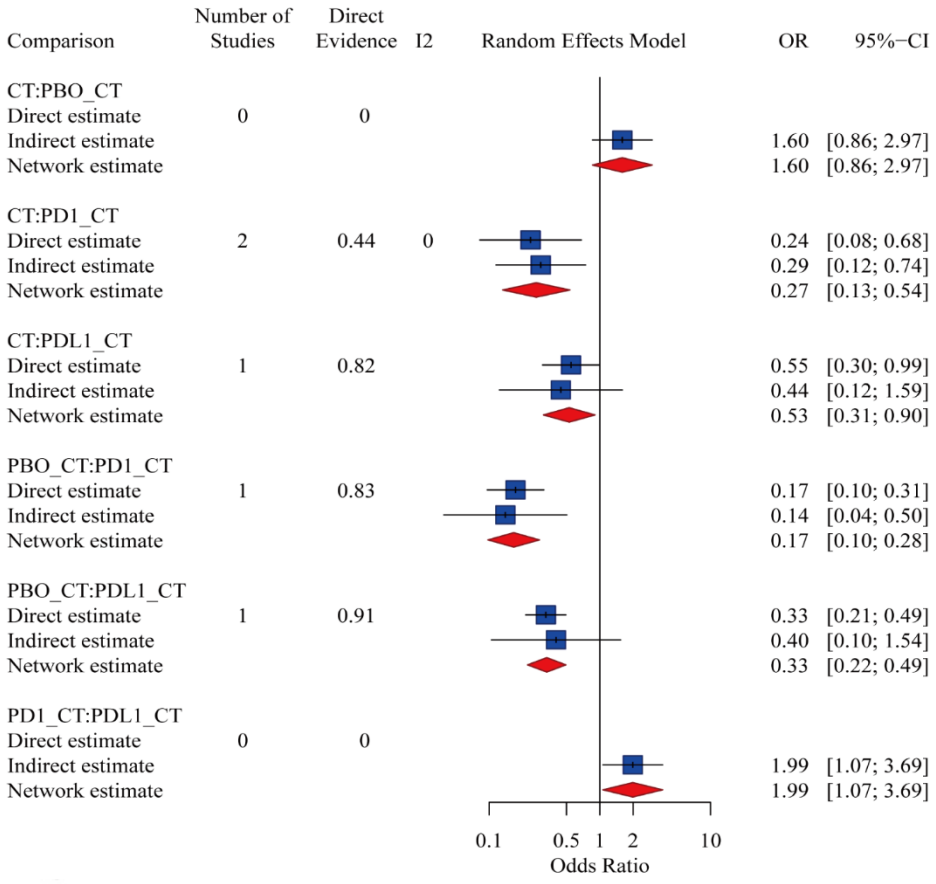

Figure S1: The network evidence graph(a) and node inconsistency detection(b).

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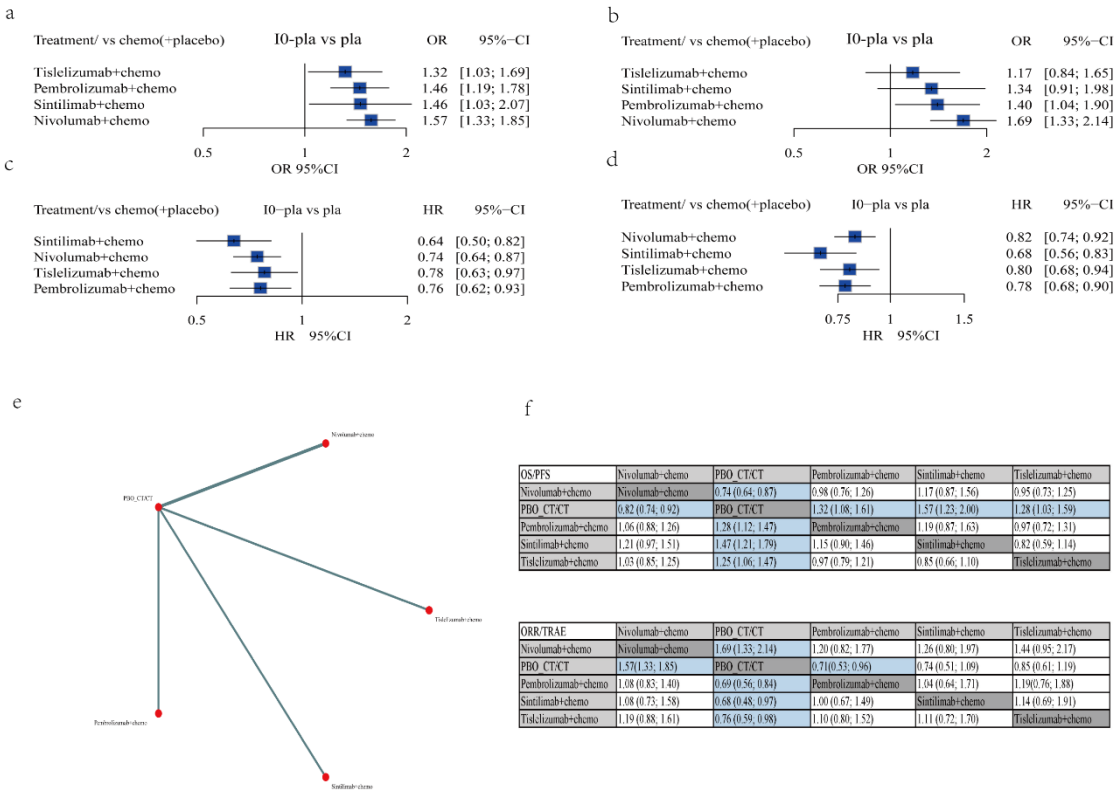

OS/PFS	Nivolumab+chemo	PBO_CT/CT	Pembrolizumab+chemo	Sintilimab+chemo	Tislelizumab+chemo
Nivolumab+chemo	Nivolumab+chemo	0.74 (0.64, 0.87)	0.98 (0.76, 1.26)	1.17 (0.87, 1.56)	0.95 (0.73, 1.25)
PBO_CT/CT	0.82 (0.74, 0.92)	PBO_CT/CT	1.32 (1.08, 1.61)	1.57 (1.23, 2.00)	1.28 (1.03, 1.59)
Pembrolizumab+chemo	1.06 (0.88, 1.26)	1.28 (1.12, 1.47)	Pembrolizumab+chemo	1.19 (0.87, 1.63)	0.97 (0.72, 1.31)
Sintilimab+chemo	1.21 (0.97, 1.51)	1.47 (1.21, 1.79)	1.15 (0.90, 1.46)	Sintilimab+chemo	0.82 (0.59, 1.14)
Tislelizumab+chemo	1.03 (0.85, 1.25)	1.25 (1.06, 1.47)	0.97 (0.79, 1.21)	0.85 (0.66, 1.10)	Tislelizumab+chemo

ORR/TRAE	Nivolumab+chemo	PBO_CT/CT	Pembrolizumab+chemo	Sintilimab+chemo	Tislelizumab+chemo
Nivolumab+chemo	Nivolumab+chemo	1.69 (1.33, 2.14)	1.20 (0.82, 1.77)	1.26 (0.80, 1.97)	1.44 (0.95, 2.17)
PBO_CT/CT	1.57(1.33, 1.85)	PBO_CT/CT	0.71(0.53, 0.96)	0.74 (0.51, 1.09)	0.85 (0.61, 1.19)
Pembrolizumab+chemo	1.08 (0.83, 1.40)	0.69 (0.56, 0.84)	Pembrolizumab+chemo	1.04 (0.64, 1.71)	1.19(0.76, 1.88)
Sintilimab+chemo	1.08 (0.73, 1.58)	0.68 (0.48, 0.97)	1.00 (0.67, 1.49)	Sintilimab+chemo	1.14 (0.69, 1.91)
Tislelizumab+chemo	1.19 (0.88, 1.61)	0.76 (0.59, 0.98)	1.10 (0.80, 1.52)	1.11 (0.72, 1.70)	Tislelizumab+chemo

Figure S2: The results of network meta analysis in specific treatment regimens in first-line therapy overall population with advanced gastric cancer. a:ORR; b: grade ≥3 TRAE; c:PFS; d:OS; e:network evidence graph; f:league of treatment regimens in ORR/TRAE/PFS/OS. OS:overall survival; PFS: progression-free survival; ORR:objective

response rate; TRAE:treat-related adverse event

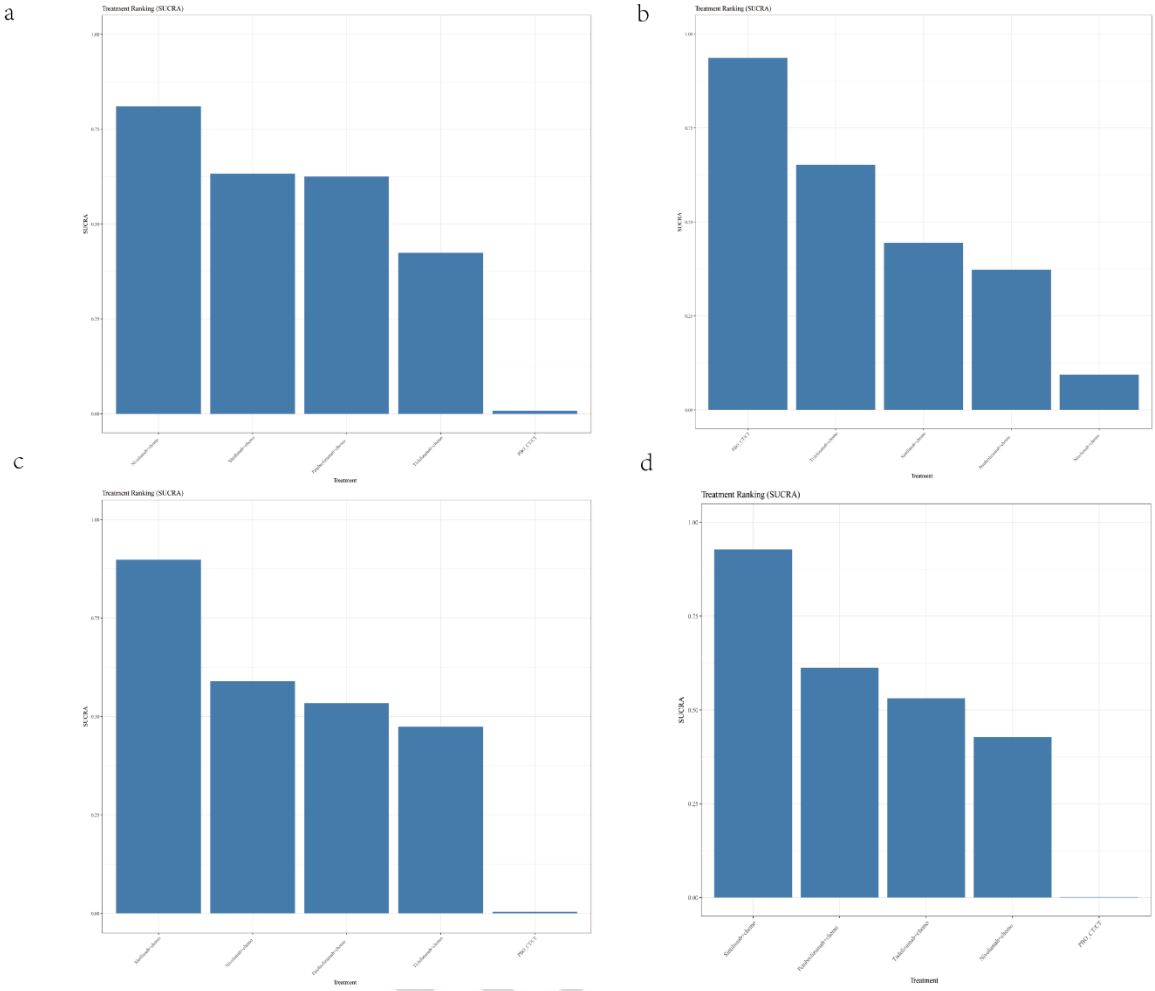

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Figure S3: The rank of various treatment regimens in first-line therapy with advanced gastric cancer patients. a:ORR; b: grade ≥3 TRAE; c:PFS; d:OS. OS:overall survival; PFS: progression-free survival; ORR:objective response rate; TRAE:treat-related adverse evevt.

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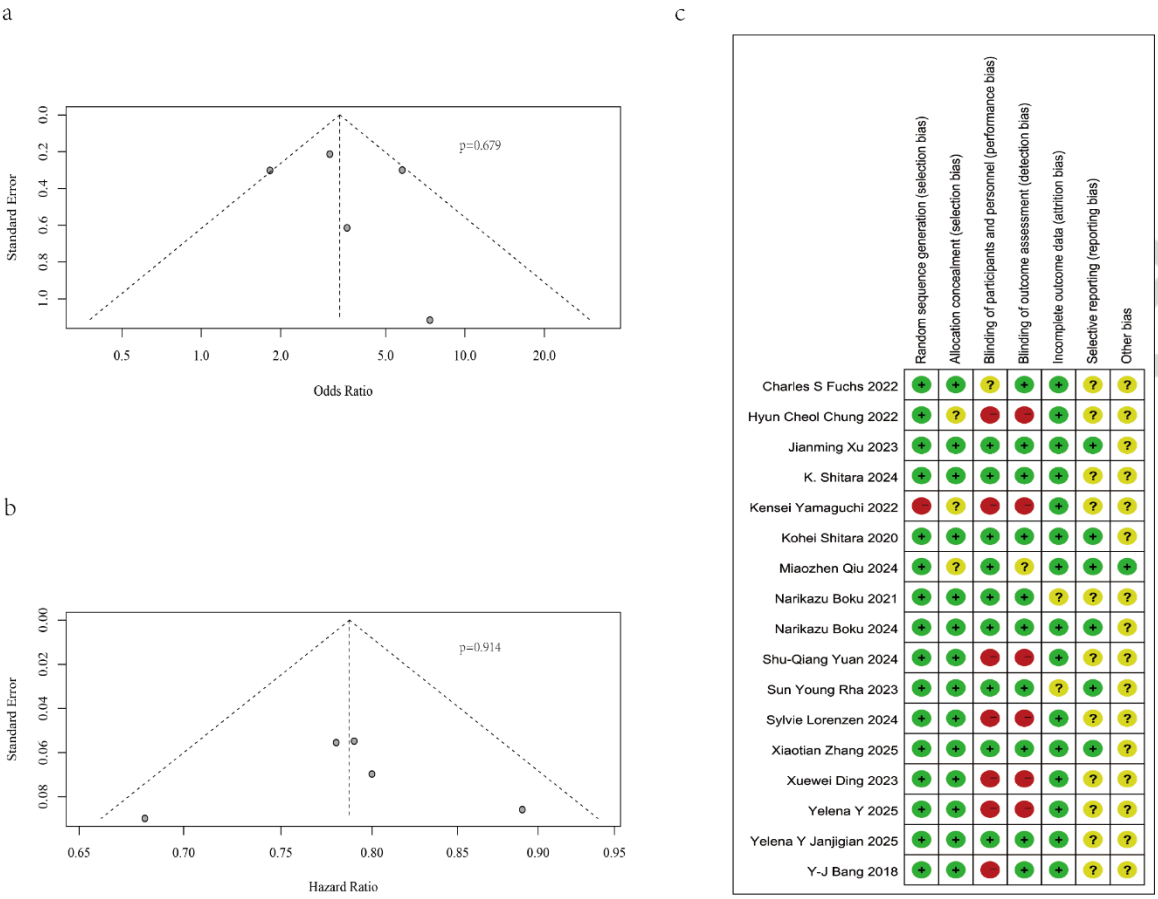

Figure S4: The funnel plot and risk bias of included studies of included studies. a.pCR in the neoadjuvant therapy; b.OS/PFS/ORR/grade≥3 TRAE in first-line therapy of overall population; c. risk bias. pCR: pathological complete response; OS: overall survival; PFS: progression-free survival; ORR: objective response rate; TRAE: adverse evevt.

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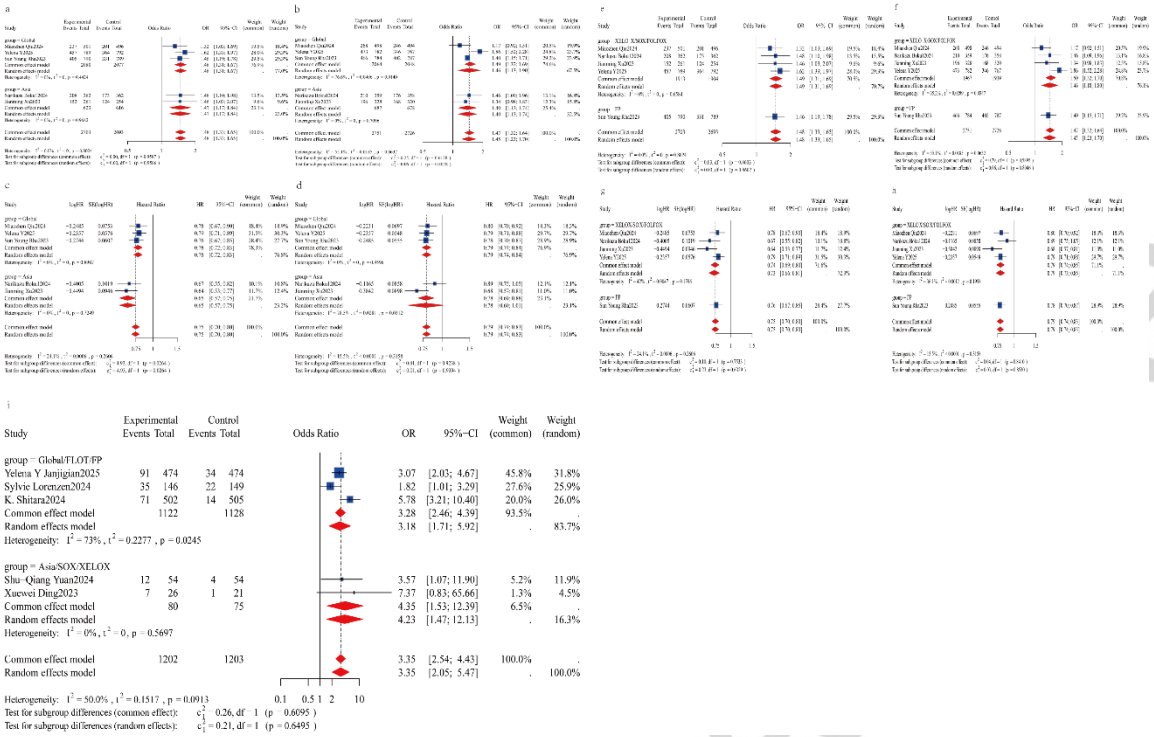

Figure S5: The sensitivity analyses according to study region (a:ORR; b: grade ≥3 TRAE; c:PFS; d:OS) and chemotherapy regimen(e:ORR; f: grade ≥3 TRAE; g:PFS; h:OS) for direct comparisons in first-line treatments for advanced gastric cancer. The sensitivity analyses according to study region and chemotherapy regimen for direct comparisons neoadjuvant therapy for locally advanced gastric cancer(e). OS: overall survival; PFS: progression-free survival; ORR: objective response rate; TRAE: treat-related adverse evevt.

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Table 1 Characteristics of included studies.

First Author	Clinical Trial	NO.RCT	year	Design	Sample size	Subjects	Intervention
Miaozhen Qiu	RATIONALE-305-3 year follow up	NCT03777657	2024	Multi-center,global, Ⅲ phase	997	HER2(-), locally advanced unresectable or metastatic GC/ GEJC	Tislelizumab(PD +Chemo(DF/XE)
Narikazu Boku	ATTRACTION-04-3 year follow up	NCT02746796	2024	Multi-center,Asia,Ⅲ phase	724	HER2(-), untreated, unresectable or recurrent GC/GEJC	Nivolumab (PD- + Chemo (SOX/ XELOX)
Xiaotian Zhang	GEMSTONE-303	NCT03802591	2025	Multi-center,China, Ⅲ phase	479	locally advanced unresectable or metastatic GC/ GEJC	Sugemalimab (I L1) + CapeOX
Kensei Yamaguchi	KEYNOTE-659	NCT03382600	2022	Multi-center,Japan, 2b phase	100	CPS>1、HER2 (-) advanced GC/GEJ	Pembrolizumab (PD-1) +Chemo (SOX)
Jianming Xu	ORIENT-106 Finally	NCT03745170	2023	Multi-center,China, 3 phase	650	untreated, locally advanced unresectable or metastatic GC/ GEJC	Sintilimab（PD ）+Chemo (XEL
Yelena Y	CheckMate 649-5 year follow up	NCT02872116	2025	Multi-center,global, 3 phase	1581	untreated, unresectable, advanced or metastatic, HER2(-) GC/GEJC/EAC	Nivolumab(PD- Chemo(XELOX/ FOX)
Kohei Shitara	KEYNOTE-062	NCT02494583	2020	Multi-center,global, 3 phase	763	CPS≥1, HER2(-), untreated, locally advanced/unresectable or metastatic GC/GEJC	Pembrolizumab (PD-1) + chemo(FP)
Sun Young Rha	KEYNOTE-859-update	NCT03675737	2023	Multi-center,global, 3 phase	1579	HER2(-),untreated, unresectable locally advanced or metastatic GC/GEJC	Pembrolizumab (PD-1) + chemo(FP)
Y-J Bang	JAVELIN Gastric 300	NCT02625623	2018	Multi-center,global, 3 phase	371	Previously treated, unresectable, recurrent, locally advanced, or metastatic GC/GEJC	Avelumab(PD-L
Narikazu	ATTRACTION-02-3	NCT02267343	2021	Multi-	493	Previously treated,	Nivolumab(PD-

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First Author	Clinical Trial	NO.RCT	year	Design	Sample size	Subjects	Intervention
Boku	year follow up			center,Asia,3 phase		unresectable advanced or recurrent GC/GEJC	

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First Author	Clinical Trial	NO.RCT	year	Design	Sample size	Subjects	Intervention

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First Author	Clinical Trial	NO.RCT	year	Design	Sample size	Subjects	Intervention
Narikazu Boku	ATTRACTION-02-3 year follow up						
Charles S Fuchs	KEYNOTE-061-2year follow up	NCT02370498	2022	Multi-center,global, 3 phase	592	advanced GC/GEJC that progressed on first-line chemotherapy	Pembrolizumab -1)
Hyun Cheol Chung	KEYNOTE-063-Asia	NCT03019588	2022	Multi-center,Asia,3 phase	94	CPS≥1 advanced GC/GEJC that received second -line therapy	Pembrolizumab -1)
Yelena Y Janjigian	MATTERHORN	NCT04592913	2025	Multi-center,global, 3 phase	948	resectable GC/GEJC(>$T_2N_{0-3}M_0$ or $T_{0-4}N_{1-3}M_0$)	Durvalumab(PD L1)+FLOT
Sylvie Lorenzen	IKF633/DANTE 2b	NCT03421288	2024	Multi-center,global, 2b phase	295	resectable GC/GEJC(>T2N+M0)	Atezolizumab(P LI)+FLOT
Shu-Qiang Yuan	NEOSUMMIT-01	NCT04250948	2024	Multi-center,China, 2 phase	108	$cT_{3-4a}N+$ M0 GC/GEJC	Toripalimab(PD +SOX/XELOX
K. Shitara	KEYNOTE-585	NCT03221426	2024	Multi-center,global, 3 phase	1007	untreated, locally advanced, resectable GC/GEJC	Pembrolizumab -1)+Chemo(FP/ FLOT)
Xuewei Ding	PERSIST	NCT04982939	2023	Multi-center,China, 2 phase	47	resectable locally advanced GC/GEJC	Sintilimab(PD-1 hemo(SOX)

Note: pCR:pathological complete response;ORR:objective response rate; PFS: progression-free survival; OS:overall survival;TRAE: treat-related adverse evevt. Light yellow represents the studies of first-line therapy for advanced gastric cancer, light blue represents the studies of later-line therapy for advanced gastric cancer, red represents the studies of neoadjuvant therapy for locally advanced gastric cancer.

Table 2 Primary endpoints of included studies.

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First Author	Clinical Trial	Population	Arm a	Arm b	ORR/PCR	Median PFS
Miaozhen Qiu	RATIONALE-305-3 year follow up	ITT	501	496	237(47%) vs 201(41%)	0.78(0.67,0.90)
Narikazu Boku	ATTRACTION-04-3 year follow up	ITT	362	362	208(57.5%) vs 173(47.8%)	0.67(0.55,0.82)
Xiaotian Zhang	GEMSTONE-303	CPS≥5	241	238	142(68.6%) vs 107(52.7%)	0.66(0.54,0.81)
		CPS≥10	130	128	85(71.4%) vs 54(48.6%)	0.58(0.43,0.77)
Kensei Yamaguchi	KEYNOTE-659	CPS≥1	54	46	39(72.2%) vs 37(80.4%)	/
Jianming Xu	ORIENT-106 Finally	ITT	327	323	152(58.2%) vs 124(48.8%)	0.64(0.53,0.77)
		CPS≥5	162	166	/	0.62(0.49,0.79)
Yelena Y	CheckMate 649-5 year follow up	ITT	789	792	457(58.0%) vs 364(46.0%)	0.79(0.71,0.89)
		CPS≥1	641	656	385(60%) vs 302(46%)	0.77(0.68,0.87)
		CPS≥5	473	482	284(60%) vs 217(45%)	0.71(0.61,0.82)
Kohei Shitara	KEYNOTE-062	CPS≥1	257	250	125(48.6%) vs 93(37.0%)	0.84(0.70,1.02)
		CPS≥10	99	90	52(52.5%) vs 34(38%)	0.73(0.53,1.00)
Sun Young Rha	KEYNOTE-859 -update	ITT	790	789	405(51.3%) vs 331(42.0%)	0.76(0.67,0.85)
		CPS≥1	618	617	322 (52%) vs 263(43%)	0.72(0.63,0.82)
		CPS≥10	280	273	169 (61%) vs 117(43%)	0.62(0.51,0.76)
Y-J Bang	JAVELIN Gastric 300	ITT	185	186	4(2.2%) vs 8(4.3%)	1.73(1.40,2.20)
Narikazu Boku	ATTRACTION-02-3 year follow up	ITT	268	131	32(11.9%) vs 0(0%)	0.60(0.49,0.75)
		CPS≥1	196	199	32(16.3%) vs 27(13.6%)	1.25(1.02,1.54)
Charles S Fuchs	KEYNOTE-061-2year follow up	CPS≥5	95	91	19(20.0%) vs 13(14.3%)	0.98(0.71-1.34)
		CPS≥10	53	55	13(24.5%) vs 5(9.1%)	0.79(0.51-1.21)
Hyun Cheol Chung	KEYNOTE-063-Asia	IIT	294	276	/	/

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First Author	Clinical Trial	Population	Arm a	Arm b	ORR/PCR	Median PFS
		CPS≥1	47	47	6(12.8%) vs 9(19.1%)	1.62(1.04-2.52)
Yelena Y Janjigian	MATTERHORN	ITT	474	474	91(19.0%) vs 34(7.0%)	0.71(0.58,0.86)
Sylvie Lorenzen	IKF633/DANTE 2b	ITT	146	149	35(24%) vs 22(15%)	/
Shu-Qiang Yuan	NEOSUMMIT-01	ITT	54	54	12(22.2%) vs 4(7.4%)	/
K. Shitara	KEYNOTE-585	ITT	502	505	71(14.2%) vs 14(2.8%)	0.80(0.67,0.95)
Xuewei Ding	PERSIST	ITT	26	21	7(26.9%) vs 1(4.8%)	/

Note: pCR:pathological complete response;ORR:objective response rate; PFS: progression-free survival; OS:overall survival; TRAE: treat-related adverse evevt. Light yellow represents the studies of first-line therapy for advanced gastric cancer, light blue represents the studies of later-line therapy for advanced gastric cancer, red represents the studies of neoadjuvant therapy for locally advanced gastric cancer.

Table S1 Clinical features of included studies.

First Author	Clinical Trial	Year	Age, M(range)	Region	Tumor location	HER-2	Microsatellite instability statu
Miaozhen Qiu	RATIONALE-305-3 year follow up	2024	I:60(53,66) C:61(54,68) IQR	Asia:376(75%) vs 372(75%) North America/Europe:125 (25%) vs 124(25%)	Gastric:405(81%) vs 395(80%) GEJ:96(19%) vs 100(20%)	HER2(-)	MSI-H: 16(3%) vs 24(5 MSS/L:448(89%) vs 439(89%)
Narikazu Boku	ATTRACTION-04-3 year follow up	2024	I:64(25,86) C:65(27,89)	Japan:198(55%) vs 197(54%) South Korea:148(41%) vs 143(40%) Taiwan:16(4%) vs 22(6%)	Gastric:237(65%) vs 238(66%) GEJ:29(8%) vs 33(9%)	HER2(-)	/
Xiaotian Zhang	GEMSTONE-303	2025	I:63(25,75) C:63(26,75)	China	Gastric:221(91.7%) vs 208(87.4%) GEJ:20(8.3%) vs 30(12.6%)	HER2(-)	/
Kensei Yamaguchi	KEYNOTE-659	2022	I:66(32,75) C:65(30,75)	Japan	Gastric:46(85.2%) vs 40(87%) GEJ:8(14.8%) vs 6(13%)	HER2(-)	/
Jianming Xu	ORIENT-106 Finally	2023	I:62(55,67)	China	Gastric:266(81.3%) vs 263(81.4%)	/	/

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First Author	Clinical Trial	Year	Age, M(range)	Region	Tumor location	HER-2	Microsatellite instability statu
			C:60(52,67) IQR		GEJ:60(18.3%) vs 60(18.6%)		
Yelena Y	CheckMate 649-5 year follow up	2025	I:62(18,88) C:61(21,90)	Asia:178(23%) vs 178(22%) USA/Canada:131(17%) vs 132(17%) Rest of the world:480(61%) vs 482(61%)	Gastric:554(70%) vs 556(70%) GEJ:132(17%) vs 128(16%) EAC:103(13%) vs 108(14%)	HER2(-)	MSI-H: 23(3%) vs 21(3 MSS:696(88%) vs 682(86%)
Kohei Shitara	KEYNOTE-062	2020	I:62(22,83) C:62.5(23,87)	Europe, North America, and Australia:148(57.6%) vs 147(58.8%) Asia:64(24.9%) vs 61(24.4%) Rest of world:45(17.5%)vs 42(16.8%)	Gastric:170(66.1%) vs 181(72.4%) GEJ:85(33.1%) vs 67(26.8%)	HER2(-)	MSI-H: 17(6.6%) vs 19(7.6%) Not MSI-H:240(93.4% 231(92.4%)
Sun Young Rha	KEYNOTE-859-update	2023	I:61(52,67) C:62(52,69) IQR	Europe, Israel, North America, and Australia:201(25%) vs 202(26%) Asia:263(33%) vs 262(33%) Rest of world:326(41%)vs 325(41%)	Gastric:640(81%) vs 603(76%) GEJ:149(19%) vs 185(23%)	HER2(-)	MSI-H: 39(5%) vs 35(4 Not MSI-H:641(81%) 639(81%)
Markus Moehler	JAVELIN Gastric 100	2021	I:62 C:61	Europe:110(44.2%) vs 123(49.2%) Asia:57(22.9%) vs 57(22.8%) North America:34(13.7%) vs 23(9.2%) Rest of the world:48(19.3%) vs 47(18.8%)	Gastric:174(69.9%) vs 181(72.4%) GEJ:75(30.1%) vs 69(27.6%)	HER2(-)	MSI-H: 8(3.2%) vs 5(2 MSS:209(83.9%) vs 210(84%)
Y-J Bang	JAVELIN Gastric 300	2018	I:59(29,86) C:61(18,82)	Europe:111(60%) vs 114(61.3%) Asia:46(24.9%) vs 47(25.3%) North America:14(7.6%) vs 11(5.9%) Rest of the world:14(7.6%) vs 11(5.9%)	Gastric:122(65.9%) vs 138(74.2%) GEJ:63(34.1%) vs 48(25.8%)	/	/
Narikazu Boku	ATTRACTION-02-3 year follow up	2021	I:62(54,69) C:61(53,68) IQR	Japan:152(46%) vs 74(45%) Korea:146(44%) vs 74(45%) Taiwan:32(10%) vs 15(9%)	Gastric:272(82.4%) vs 200(82.8%) GEJ:30(9.1%) vs 12(7.4%)	/	/
Charles S Fuchs	KEYNOTE-061-2ye ar follow up	2022	I:62.5(27,87) C:60(20,86)	Europe, Israel, North America, and Australia:190(64.2%) vs 187(63.2%) Asia:88(29.7%) vs 89(30.1%) Rest of world:18(6.1%)vs 20(6.8%)	Gastric:207(69.9%) vs 200(67.6%) GEJ:89(30.1%) vs 96(32.4%)	Positive: 48(16.2%) vs 62(20.9%)	MSI-H: 15(5%) vs 12(4 Not MSI-H:244(82.4% 243(82.1%)
Hyun Cheol Chung	KEYNOTE-063-Asia	2022	I:61(32,75) C:61(37,91)	China:23(49%) vs 21(45%) Malaysia:2(4%) vs 2(4%)	Gastric:41(87%) vs 44(94%) GEJ:6(13%) vs 3(6%)	/	/

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First Author	Clinical Trial	Year	Age, M(range)	Region	Tumor location	HER-2	Microsatellite instability statu
				South Korea:20(43%) vs 18(38%) Taiwan:2(4%) vs 6(13%)			
Yelena Y Janjigian	MATTERHORN	2025	I:62(26,84) C:63(28,83)	Asia:90(19%) vs 90(19%) Rest of the world:384(81%) vs 384(81%)	Gastric:324(68.4%) vs 316(66.7%) GEJ:150(31.6%) vs 158(33.3%)	/	MSI-H: 25(5.3%) vs24(5.1%) Not MSI-H:301(63.5% 310(65.4%)
Sylvie Lorenzen	IKF633/DANTE 2b	2024	I:61(29,79) C:62(23,80)	German(38) Swiss(11)	Gastric:56(38%) vs 58(39%) GEJ:90(62%)vs 91(61%)	/	MSI:8(6%) vs15(10%) MSS:138(95%) vs 134(90%)
Shu-Qiang Yuan	NEOSUMMIT-01	2024	I:58(48,67) IQR C:62(54,68)	China(2)	Gastric:37(68.5%) vs 34(63.0%) GEJ:17(31.5%)vs 20(37.0%)	/	/
K. Shitara	KEYNOTE-585	2025	I:64(22,90) C:63(25,84)	Asia:193(38%) vs 194(38%) USA/Europe:172(34%) vs 178(36%) Rest of the world:137(27%) vs 133(26%)	Gastric:376(75%) vs 386(76%) GEJ:126(25%)vs 118(23%)	/	MSI-H:43(9%) vs 38(8 Not MSI-H:390(78%) 382(76%)
Xuewei Ding	PERSIST	2023	I:61(31,74) C:61(32,75)	China	Gastric:48(92.3%) vs 44(89.8%) GEJ:4(7.7%)vs 5(10.2%)	/	/

Note: Light yellow represents the studies of first-line therapy for advanced gastric cancer, light blue represents the studies of later-line therapy for advanced gastric cancer, red represents the studies of neoadjuvant therapy for locally advanced gastric cancer.

Table S2. search strategy

Databased	Words
PubMed	(((programmed cell death 1 receptor) OR (PD-1) OR (B7-H1) OR (CD274)OR (PD-L1) OR (programmed cell death ligand 1) OR (immune checkpoint inhibitors)) AND ((Gastric cancer) OR (Stomach Neoplasm) OR (Gastric Neoplasms) OR (Gastric Neoplasm) OR (Cancer of Stomach) OR (Stomach Cancers) OR (Gastric Cancers) OR (Stomach Cancer))) AND ((clinical trial) OR (Randomized Controlled Trial) OR (RCT))
Cochrane	#1 MeSH descriptor: [Programmed Cell Death 1 Receptor] explode all trees #2 MeSH descriptor: [Stomach Neoplasms] explode all trees #3 #1 and #2
Web of Science	#1 (programmed cell death 1 receptor) OR (PD-1) OR (B7-H1) OR （CD274） OR (PD-L1) OR (programmed cell death ligand 1) OR (immune checkpoint inhibitors) (Topic) #2 (Gastric cancer) OR (Stomach Neoplasm) OR (Gastric Neoplasms) OR (Gastric Neoplasm) OR (Cancer of Stomach) OR (Stomach Cancers) OR (Gastric Cancers) OR (Stomach Cancer) (Topic) #3 #1 AND #2 #4 (clinical trial) OR (Randomized Controlled Trial) OR (RCT) (Topic) #5 #3 AND #4
Embase	#1 'stomach cancer'/exp

#2 'programmed death 1 receptor'/exp

#3 #1 AND #2

#4 'rct' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial'

#5 #3 AND #4

Supplement material

Codes:

```
install.packages("netmeta")
library(netmeta)
library(meta)
library(metadat)
getwd()
RCTR$logHR<-log(RCTR$HR)
RCTR$selogHR<-(log(RCTR$upperCI)-log(RCTR$lowerCI))/3.92
m.netmeta_OS<-netmeta(RCTR$logHR,
                      RCTR$selogHR,
                      treat1 = treat1,
                      treat2 = treat2,
                      studlab = studlab,
                      data = RCTR,
                      sm = "HR",
                      random=TRUE,
                      reference.group = "PBO_CT/CT")
summary(m.netmeta_OS)
netgraph(m.netmeta_OS,
     points = T,
     plastic = F,
```

```
        col = "#5C8286",
        col.points = "red",
        bg.points = "black",
        number.of.studies = F,
        cex = 1,
        pos=1,
        lwd = 2,
        start="circle",
        cex.points = 4)
forest(m.netmeta_OS,
      reference.group = "PBO_CT/CT",
      smlab = paste("I0-pla vs pla"),
      drop.reference.group = TRUE,
      label.left="HR",
      col.square="blue",
      drop=TRUE,
      sortvar = -RCTR$logHR,
      label.right="95%CI")
netleague1<-netleague(m.netmeta_OS,
                bracket = "(",
                digits = 2)
write.csv(netleague1$random,"netleague1.csv")

rank<-netrank(m.netmeta_OS)
print(rank)

library(ggplot2)
sucravalue<-rank$Pscore.random
data<-data.frame(Treatment=names(sucravalue),
            SUCRA=as.numeric(sucravalue))
ggplot(data, aes(x = reorder(Treatment, -SUCRA), y = SUCRA)) +
```

```
  geom_col(width = 0.7) +
  geom_col(fill = "steelblue") +
  labs(title = "Treatment Ranking (SUCRA)",
      x = "Treatment",
      y = "SUCRA") +
  theme_bw() +
  theme(axis.text.x = element_text(angle = 45, hjust = 1)) +
  ylim(0, 1)

ns_survival <- netsplit(m.netmeta_OS)
forest(ns_survival,show="direct")

pairwise_data <- pairwise(treat = treatment,
                          event = evevt,
                          n = total,
                          studlab = study,
                          data = RCTR,
                          sm = "OR")
nma_binary <- netmeta(pairwise_data,
                      reference = "CT",
                      random = TRUE)

summary(nma_binary)
netgraph(nma_binary,
         points = T,
         plastic = F,
         col = "#5C8286",
         col.points = "red",
         bg.points = "black",
         number.of.studies = F,
         cex = 1,
```

```
      pos=1,
      lwd = 2,
      start="circle",
      cex.points = 4)
forest(nma_binary,
     reference.group = "CT",
     xlab = "OR 95%CI",
     sortvar = TE,
     col.square = "blue")

league_table <- netleague(nma_binary,
                  bracket = "(",
                  digits = 2)
print(league_table)

ranking <- netrank(nma_binary,small.values = "bad")
print(ranking)
sucravalue<-ranking$Pscore.random
data<-data.frame(Treatment=names(sucravalue),
            SUCRA=as.numeric(sucravalue))
ggplot(data, aes(x = reorder(Treatment, -SUCRA), y = SUCRA)) +
  geom_col(width = 0.7) +
  geom_col(fill = "steelblue") +
  labs(title = "Treatment Ranking (SUCRA)",
     x = "Treatment",
     y = "SUCRA") +
  theme_bw() +
  theme(axis.text.x = element_text(angle = 45, hjust = 1)) +
  ylim(0, 1)

inconsistency_test <- netsplit(nma_binary)
```

```
print(inconsistency_test)


forest(inconsistency_test, show = "all")
forest(inconsistency_test,
     show = "all",
     col.square = "blue",
     col.square.lines = "darkblue",
     col.diamond = "red",
     col.diamond.lines = "darkred",
     col.inside = "black",
     xlab = "Odds Ratio")
```