Efficacy and side effects of pembrolizumab plus chemotherapy vs. chemotherapy alone in patients with advanced gastric or gastroesophageal junction adenocarcinoma: A meta-analysis

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Abstract. Recently, the treatment plan of pembrolizumab plus chemotherapy was regarded as a promising treatment for patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma (GC/GEJC). However, the efficacy and side effects of pembrolizumab plus chemotherapy still lack evidence-based medical evidence to support. Therefore, a meta-analysis was conducted to evaluate the hot issue. By searching PubMed, EMBASE, Cochrane Library, Web of Science, any randomized clinical studies of pembrolizumab plus chemotherapy versus chemotherapy in patients with advanced GC/GEJC met the inclusion criteria were included. The quality of the literature was evaluated and the data was extracted. A correlative software was also used to analyze the data and to draw a conclusion. After screening 14,015 studies, four studies were eligible for the meta-analysis. Compared with chemotherapy alone group, the overall survival (OS) rate was significantly longer. In programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥1 subgroup and PD-L1 CPS ≥10 subgroup analyses, the results showed that the response rate (RR) and complete response rate (CR) were both higher in pembrolizumab plus chemotherapy group compared with chemotherapy alone group. There were not significant differences in the CR, the treatment-related adverse events, succumbed to drug-related events and succumbed to immune-mediated events between the two groups. However, the effect events such as the treatment-related adverse events led to discontinuation, the 3-5 treatment-related adverse events and the immune-mediated adverse events and infusion reactions were more common in pembrolizumab plus chemotherapy group. In conclusion, the current meta-analysis revealed that, in treating advanced GC/GEJC, pembrolizumab plus chemotherapy had improved therapeutic efficacies than chemotherapy alone, as evidenced by the significantly longer OS. Furthermore, the patients in PD-L1 CPS ≥1 subgroup and PD-L1 CPS ≥10 subgroup appeared to benefit from pembrolizumab plus chemotherapy treatment because of higher RR and CR. However, side effects such as the treatment-related adverse events leading to discontinuation, the 3-5 treatment-related adverse events, and immune-mediated adverse events and infusion reactions deserved more attention.

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Introduction

Gastric cancer (GC) and gastroesophageal junction cancer (GEJC) are the fifth most frequently diagnosed cancer and the third leading cause of cancer death globally (1,2). GC and GEJC are frequently asymptomatic in the early stages, and, often diagnosed at advanced disease stages (3,4). At present, a combination of a platinum drug (cisplatin or oxaliplatin) and a fluoropyrimidine (fluorouracil, capecitabine, or S-1) is regarded as the standard first-line palliative chemotherapy regimen (5). In total, ~10% of patients with advanced GC or GEGC will survive for five years, despite advancements in treatment options (3).

The treatment of advanced cancer has been completely transformed in recent years by immunotherapy using immune checkpoint inhibitors. One such checkpoint is the negative costimulatory receptor known as programmed cell death 1 (PD-1), which is mostly expressed on peripheral CD4+ and CD8+ T cells, natural killer T cells, B cells, monocytes and certain dendritic cell subsets upon their activation (6,7). Tumor cells frequently use the PD-1 pathway to evade immune surveillance (6,7). The antitumor immune response is suppressed when PD-1 binds to its ligands, programmed cell death ligand 1 (PD-L1) and PD-L2, inhibiting effector T-cell activity (6,7). PD-L1 is frequently upregulated in GC and correlated with the depth of tumor invasion, lymph node metastasis and American Joint Committee on Cancer (AJCC) stage (8). Pembrolizumab is a humanized, specific monoclonal antibody against immunoglobulin *G4κ* that inhibits the interaction between PD-1 and its ligands, and allows for the reactivation of the immune response against cancer cells (9).

In other malignancies, pembrolizumab plus chemotherapy was shown to be effective and relatively safe (10,11).

Pembrolizumab plus chemotherapy was recently considered a promising treatment for patients with advanced GC/GEJC, with positive reported treatment outcomes in patients with or without surgical treatment (12,13). Fuchs *et al* (14) noted that pembrolizumab monotherapy showed promising activity and a manageable safety profile in patients with advanced GC/GEJC who had previously received at least two lines of therapy, and that a durable response was observed in patients with PD-L1-positive and PD-L1-negative tumors. Shitara *et al* (15) also confirmed that pembrolizumab exhibited a superior safety profile to paclitaxel, despite the fact that it did not significantly increase overall survival when administered as a second-line treatment for advanced gastric or gastroesophageal carcinomas with a PD-L1 combined positive score (CPS) of 1 or higher. Furthermore, chemotherapeutic drugs such as 5-fluorouracil and cisplatin boost the immunogenicity of cancer cells and render them more vulnerable to immune-mediated cytotoxicity (16). However, the efficacy and side effects of pembrolizumab plus chemotherapy still lack evidence-based medical evidence to support. Therefore, a meta-analysis was conducted to evaluate the hot issue.

Materials and methods

Literature search and study selection. PubMed (https://pubmed.ncbi.nlm.nih.gov/), EMBASE (https://www.embase.com), Cochrane Central Register of Controlled Trials (https://www.cochranelibrary.com) and Web of Science (https://clarivate.com) were used for systematic search. The main search strategy was as follows: ('esophagogastric junction carcinoma' OR 'EJC' OR 'esophagogastric cancer' OR 'gastric carcinoma' OR 'gastric cancer' OR 'GC') AND ('immunotherapy' OR 'PD-1' OR 'Pembrolizumab'). The last search was conducted on March 8, 2024. Two authors (JL and XH) independently reviewed the title and abstract of the citation and obtained the full text of potentially eligible studies. Disagreements were resolved by discussion or, if necessary, by a third author (SZ). A reference list review of all retrieved studies was further screened for additional eligible studies.

Inclusion and exclusion criteria. Studies that compared the efficacy and side effects of patients undergoing chemotherapy alone or in combination with pembrolizumab were included. The studies should meet the following criteria: i) Randomized clinical trials; ii) advanced GC or GEJC; and iii) comparable data on overall survival (OS), response rate (RR) or side effects was available. The main exclusion criteria included: i) Reviews, letters, case reports and conference abstracts; ii) animal experiments, *in vitro* studies and ongoing studies; iii) studies a with lack of survival data or adverse effects; and iv) studies were not about advanced GC/GEJC.

Quality assessment. Two authors (JL and XH) conducted independent assessments. Disagreements were resolved by discussion or by a third author (SZ). No studies were excluded on this basis. The risk of bias in the eligible studies was comprehensively assessed according to the Cochrane Collaboration's Risk of Bias tool (17).

Data extraction and synthesis. Two authors (JL and XH) independently extracted the data from the included studies. The information included the following outcomes: Name of the trial, publication time and design of the trial, treatment methods, case characteristics, median follow-up time, therapeutic efficacy and related side effects.

The meta-analysis was conducted according to the Cochrane handbook for systematic reviews of interventions. Every categorical variable in the current investigation was discontinuous. Forest plots were drawn by Review Manager 5.4 software (Cochrane Institute) automatically. Odds ratio (OR), P-value and 95% confidence intervals (CI) were used to assess whether the differences in results were significant. $P>0.05$ was considered to indicate a statistically significant difference. The statistical analysis was deemed to show no substantial heterogeneity if $I^2<50\%$; heterogeneity was deemed to be present if $I^2\geq50\%$. The fixed-effects model (FEM) and random-effects model (REM) were alternated in the calculation mode. FEM was utilized to handle the data if there was no significant heterogeneity; REM was employed in other cases. The publication bias and Egger test were conducted by using STATA 16.0 (Stata Corp LP).

Results

Study selection. Through a systematic literature search, 14,015 studies were retrieved. After removing duplicate studies, irrelevant studies were excluded by checking titles and abstracts one by one. At last, four eligible studies (18-21) were included. The flow chart of selecting literatures according to PRISMA guidelines is shown in Fig. 1.

Methodological quality. All included four studies (n=1,821) were multicenter randomized clinical trials. A total of 3,015 patients were included in the meta-analysis, of which 1,502 patients received chemotherapy alone and 1,513 patients received chemotherapy in addition to pembrolizumab. The baseline characteristics of the included studies are displayed in Table I. Cochrane Collaboration's Risk of Bias tool was used to assess the quality of the included studies. All studies were low risk of bias. The details of the assessment are shown in Fig. 2.

Comparison of OS rate. The meta-analysis of OS following data integration is demonstrated in Fig. 3. Only two studies (20,21) were included. The results demonstrated that, as compared with chemotherapy alone, the OS of the pembrolizumab plus chemotherapy group was statistically significant (OR=1.36; 95% CI: 1.13-1.64; P=0.001). This indicated that OS was higher in the pembrolizumab plus chemotherapy group than in the chemotherapy alone group.

Comparison of response rate (RR). A subgroup analysis was performed in the meta-analysis of RR (Fig. 4). The result identified that the RR both in PD-L1 CPS ≥1 subgroup and PD-L1 CPS ≥10 subgroup was significantly different between the pembrolizumab plus chemotherapy group and chemotherapy alone group (OR=1.59, 95% CI: 1.32-1.91; P<0.00001 and OR=2.12; 95% CI: 1.53-2.93; P<0.00001).

Comparison of complete response (CR) rate. Meta-analysis of CR is revealed in Fig. 5. Because of heterogeneity (P=0.01,

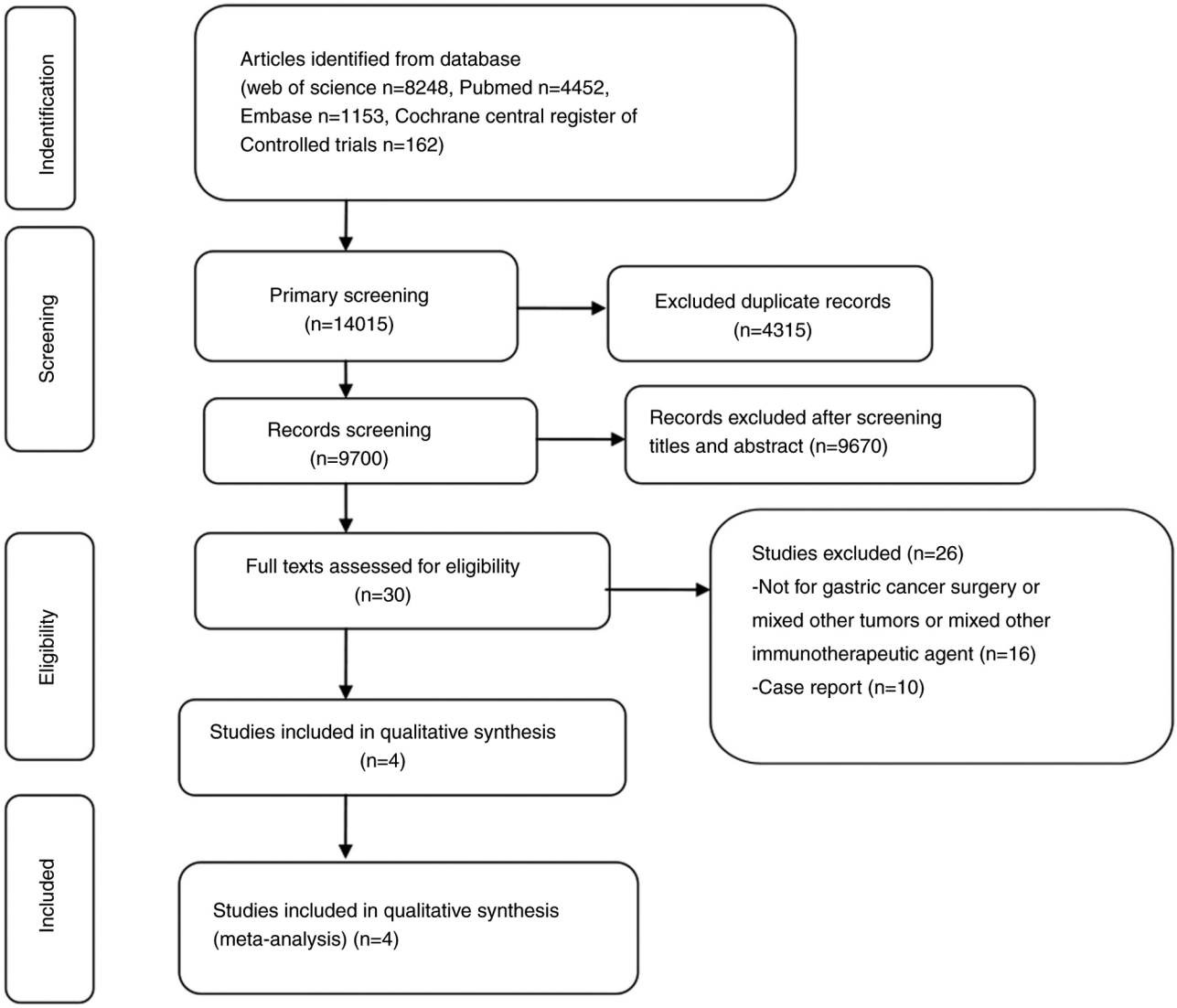

Figure 1. Flow diagram depicting the strategies of meta-analyses.

I^2=63%), a random effects model was used for analysis. The result revealed that the CR rate was not significantly different between the pembrolizumab plus chemotherapy group and chemotherapy alone group (OR=3.36; 95% CI: 0.70-16.04; P=0.13). By contrast, the results showed that the PD-L1 CPS ≥1 subgroup and PD-L1 CPS ≥10 subgroup were significantly different (OR=1.78; 95% CI: 1.29-2.46; P=0.0005 and OR=2.88; 95% CI: 1.54-5.39; P=0.0010).

Comparison of safety. Moreover, an analysis was conducted to explore the side effects of pembrolizumab plus chemotherapy group compared with chemotherapy alone group (Table SI). The data integration demonstrated that the occurrence of treatment-related adverse events leading to discontinuation was more common in pembrolizumab plus chemotherapy group compared with chemotherapy alone group (OR=1.46, 95% CI: 1.23-1.73, P<0.0001) (Fig. 6A), regardless of the 3-5 treatment-related adverse events (OR=1.31; 95% CI: 1.10-1.54; P=0.002) (Fig. 6B) or immune-mediated adverse events and infusion reactions (OR=3.76; 95% CI: 2.28-6.20; P<0.00001) (Fig. 6C). Conversely, compared with chemotherapy alone group, succumbing to drug-related events (OR=0.85; 95% CI: 0.46-1.59; P=0.62) (Fig. 6D) was not statistically significant in pembrolizumab plus chemotherapy group, regardless of succumbing to immune-mediated events (OR=0.99; 95% CI: 0.14-7.04; P=0.99) (Fig. 6E) or the occurrence of treatment-related adverse events (OR=0.93; 95% CI: 0.26-3.39; P=0.92) (Fig. 6F).

Publication bias. Funnel plots (Fig. 7) were chosen to estimate publication bias in the present study, and no obvious bias was observed. No significant publication bias was also identified through the Egger tests (P=0.394).

Discussion

A variety of targeted drugs targeting the programmed cell death protein 1 (PD-1)/PD-L1 pathway have successfully entered clinical trials (22-26). Among them, pembrolizumab, as a representative, has been approved by the FDA for marketing, and has obtained corresponding indications in melanoma and non-small cell lung cancer (27-30). As it has been reported,

Table I. Study characteristics.

Author, year	Country	Study design	Clinical stage	Therapeutic regimen	Age, years [median (range)].	Number of patients	Tumor location G/GEJ	CPS ≥1	CPS ≥10	Median follow-up time, months	Risk of bias	(Refs.)
Shitara *et al*, 2020	Japan	Multicenter	III-IV	i) Pe+C; ii) C	i) 62.0 (22-83); ii) 62.5 (23-87)	i) 257; ii) 250	i) 170/181; ii) 85/67	i) 257; ii) 250	i) 99; ii) 90	29.4 (22.0-41.3)	Low	(18)
Satake *et al*, 2023	Japan	Multicenter	III-IV	i) Pe+C; ii) C	i) 65.0 (34-83); ii) 67.0 (37-85	i) 64; ii) 61	i) 55/9; ii) 57/4	i) 64; ii) 61	i) 26; ii) 22	24 (19-31)	Low	(19)
Shitara *et al*, 2023	Japan	Multicenter	II-IV	i) Pe+C; ii) C	i) 64 (56-70); ii) 63 (55-69)	i) 402; ii) 402	i) 316/86; ii) 322/79	i) 293; ii) 307	i) 104; ii) 116	16.9 (0.2-41.0)	Low	(20)
Rha *et al*, 2023	South Korea	Multicenter	III-IV	i) Pe+C; ii) C	i) 61 (52-67); ii) 62 (52-69)	i) 790; ii) 789	i) 640/149; ii) 603/185	i) 618; ii) 617	i) 279; ii) 272	31.0 (23.0-8.3)	Low	(21)

GEJ, gastroesophageal junction; CPS, combined positive score; Pe, pembrolizumab; C, chemotherapy.

advanced GC/GEJC obtain a poor prognosis, one of the reasons being the poor effect of current drugs (31). The application of pembrolizumab in GC/GEJC opens a new chapter of prognosis. However, there is an urgent need to investigate the side effects and effectiveness of pembrolizumab alongside chemotherapy.

In review of 4 randomized controlled trials (18-21), the result of the present meta-analysis revealed that the pembrolizumab plus chemotherapy group had improved OS than the chemotherapy alone group, but not discovered in RR and CR. According to the trial by Reck *et al* (32), PD-L1 may be a significant biomarker for predicting pembrolizumab response in solid tumors. Thus, it suggests that pembrolizumab may have a more favorable curative outcome for patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10. The meta-analysis verified that the pembrolizumab plus chemotherapy group had superior RR and CR than the chemotherapy alone group in patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10. The difference in OS, RR and CR between PD-L1 positive and negative patients could not be compared. However, the CR was not significantly different between the pembrolizumab plus chemotherapy group and chemotherapy alone group.

The most common treatment-related adverse effects associated with pembrolizumab are fatigue, decreased appetite and nausea; in most cases they are resolved without or with minimal treatment (33,34). The results of the present meta-analysis revealed that compared with chemotherapy alone group, the occurrence of treatment-related adverse events was not statistically significant in pembrolizumab plus chemotherapy group, regardless of succumbing to drug-related events. The most common grade 3-5 treatment-related adverse events occurring are fatigue, diarrhea and anemia, which have great influence on patients. The results of the current meta-analysis revealed that the occurrence of grade 3-5 treatment-related adverse events was higher in pembrolizumab plus chemotherapy group than in chemotherapy alone group; the same result occurred in the occurrence of treatment-related adverse events leading to discontinuation.

Immune checkpoint inhibitors, which enhance the capacity of the immune system to eliminate cancer cells, have revolutionized cancer immunotherapy by focusing on the PD-1 pathway. But because of the way these treatments work, there is a unique set of difficulties associated with this novel strategy. Specifically, immune-related adverse events may result from these therapies. Skin, gastrointestinal tract, liver, endocrine system and lungs are the most frequently affected organ systems by adverse events (35). The efficacy of treatment is influenced by these side effects (36,37). The meta-analysis revealed that the pembrolizumab plus chemotherapy group experienced more immune-mediated adverse events and infusion reactions than the chemotherapy alone group. However, the frequency of drug-related deaths and immune-mediated deaths did not differ statistically significantly between the two groups. New side effects caused by pembrolizumab, such as delayed immune-related hepatitis (35), aplastic anemia (38) and severe mucositis (39), continue to emerge. Therefore, the side effects of pembrolizumab require continuous attention. The development of an aptamer against the target can mitigate these negative effects. Compared with typical antibodies, aptamers have several benefits, including increased

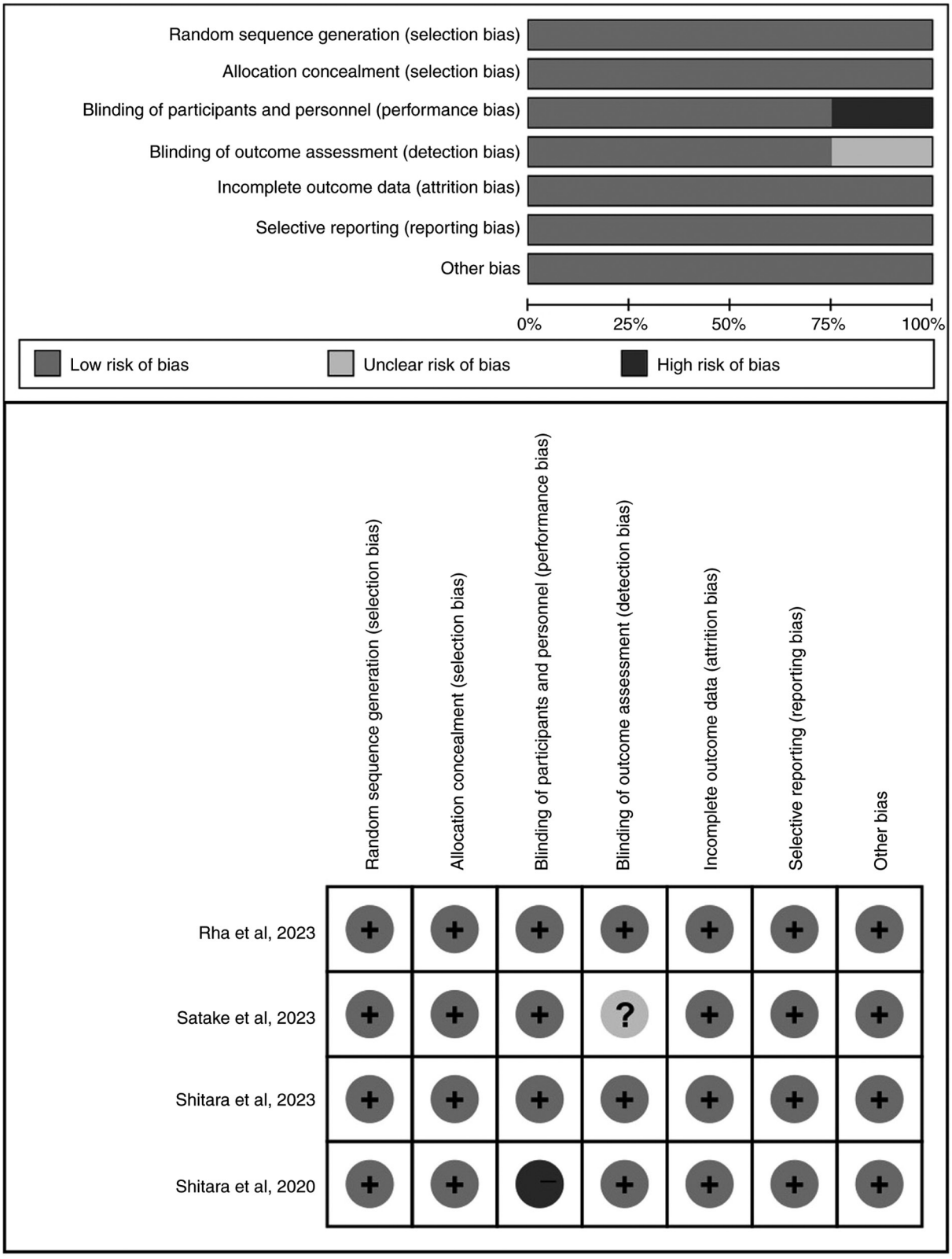

Figure 2. Risk of bias graph and risk of bias summary.

specificity, decreased immunogenicity and flexible design for fewer side effects. Aptamers are particularly designed to target and disrupt receptor-ligand or protein-protein interactions that are involved in immune checkpoint pathways (40).

The present study also has certain limitations. First, it is a meta-analysis based on published literature, which is susceptible to publication bias. Second, the number of included trials in the present meta-analysis was only four; but all are high-quality multicenter randomized trials. Third, there are still insufficient relevant research projects on progression-free survival, alleviating progression symptoms and enhancing quality of life. In the future, it is expected that a more in-depth

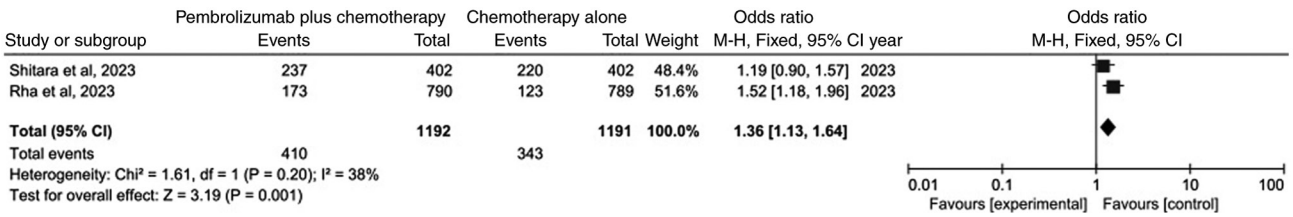

Figure 3. Forest plot of the overall survival rates. CPS, combined positive score; CI, confidence interval.

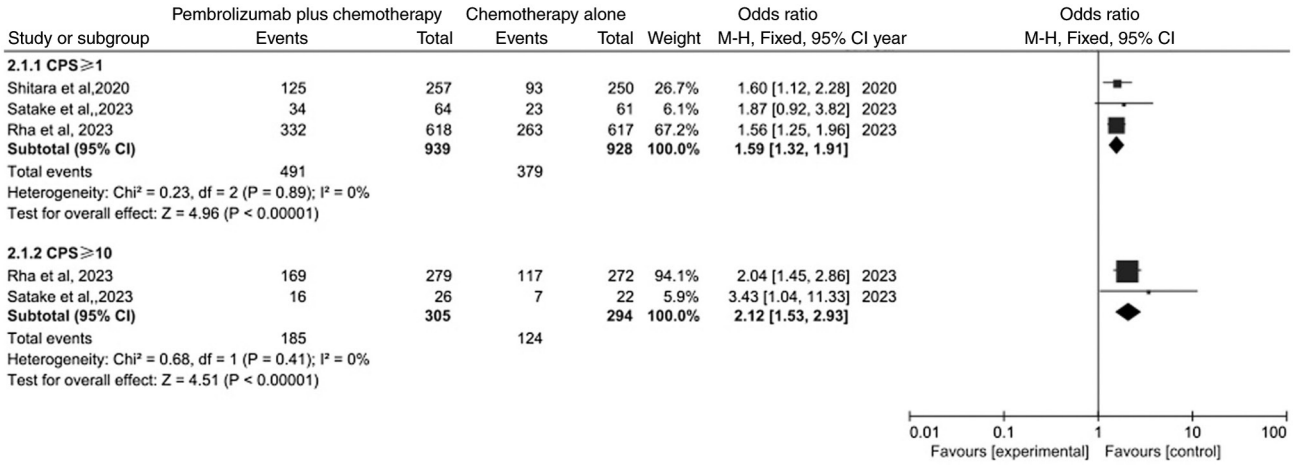

Figure 4. Forest plot of the response rate. CPS, combined positive score; CI, confidence interval.

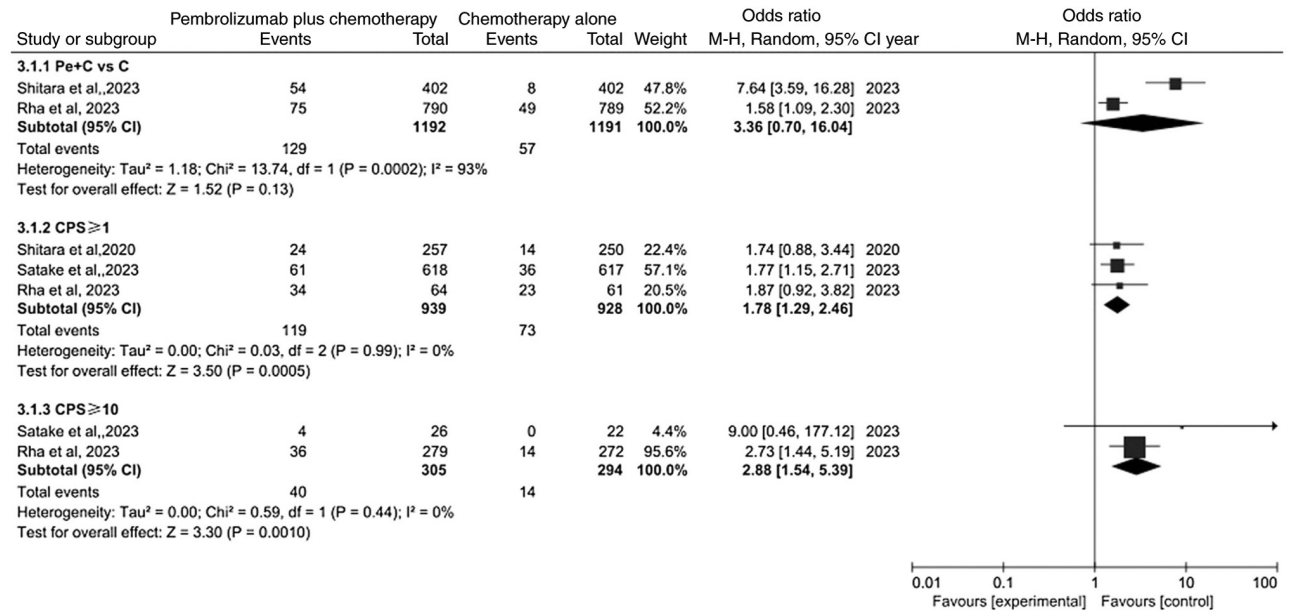

Figure 5. Forest plot of complete responses rate. CPS, combined positive score; CI, confidence interval.

stratified analysis can be conducted to identify the efficacy and safety of pembrolizumab plus chemotherapy versus chemotherapy alone for patients with advanced GC/GEJC. In conclusion, it was revealed that in treating advanced GC/GEJC, pembrolizumab plus chemotherapy had improved therapeutic efficacies than chemotherapy alone, as evidenced by the significantly longer OS. Furthermore, the patients in PD-L1 CPS ≥1 subgroupand PD-L1 CPS ≥10 subgroup appeared to benefit from pembrolizumab plus chemotherapy treatment because of higher RR and CR. However, when compared with the chemotherapy group, the pembrolizumab plus chemotherapy group experienced a higher frequency of immune-mediated adverse events, infusion reactions and treatment-related adverse events that resulted in treatment discontinuation. These side effects should be given more consideration.

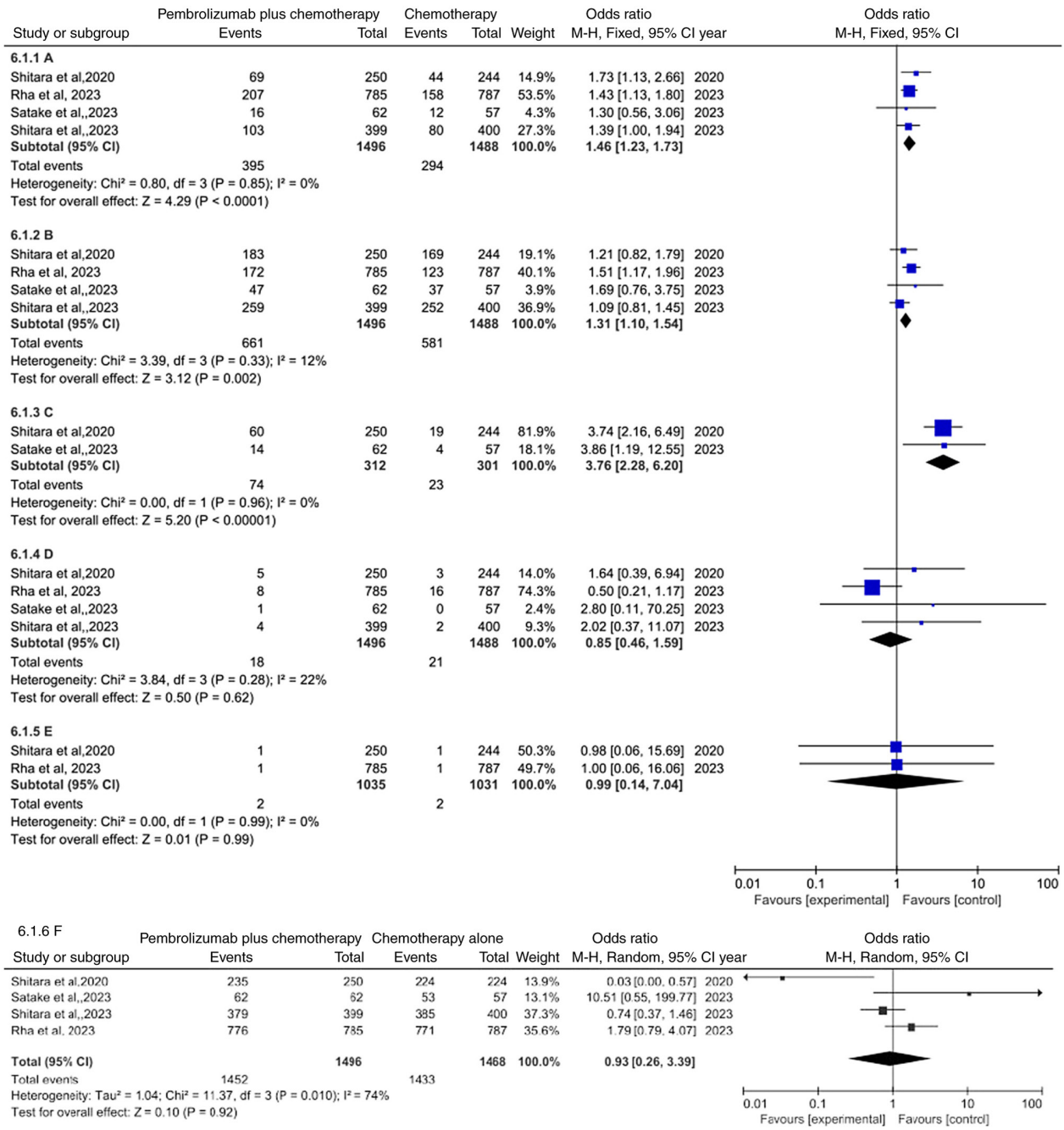

Figure 6. Forest plot of effect events between pembrolizumab plus chemotherapy group and chemotherapy alone group. (A) Treatment-related adverse events leading to discontinuation. (B) Grade 3-5 treatment-related adverse events occurred. (C) Immune-mediated adverse events and infusion reactions. (D) Succumbed to drug-related events. (E) Succumbed to immune-mediated events. (F) Treatment-related adverse events occurred.

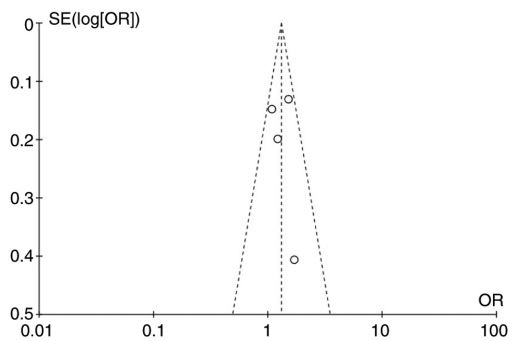

Figure 7. Funnel plot for publication bias.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

JL conceptualized and supervised the present study, and wrote, reviewed and edited the manuscript. JL and XH curated the data. JL and SZ checked and confirmed the authenticity of the raw data. JL, SZ and XH conducted formal analysis, developed methodology, performed software analysis and wrote the original draft. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424, 2018.
3. Li C, Chen D and Yang H: Trends in incidence, survival and mortality of gastric cancer in the United States: A population-based study, 2001-2015. Asian Pac J Cancer Prev 24: 2011-2020, 2023.
4. Li Y, Feng A, Zheng S, Chen C and Lyu J: Recent estimates and predictions of 5-year survival in patients with gastric cancer: A model-based period analysis. Cancer Control 29: 10732748221099227, 2022.
5. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, Vogel A and Smyth EC; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org: Gastric cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 33: 1005-1020, 2022.
6. Francisco LM, Sage PT and Sharpe AH: The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 236: 219-242, 2010.
7. Pardoll DM: Immunology beats cancer: A blueprint for successful translation. Nat Immunol 13: 1129-1132, 2012.
8. Geng Y, Wang H, Lu C, Li Q, Xu B, Jiang J and Wu C: Expression of costimulatory molecules B7-H1, B7-H4 and Foxp3+ Tregs in gastric cancer and its clinical significance. Int J Clin Oncol 20: 273-281, 2015.
9. Russo CD, Gagliardi D, Ramlogan R and Navarra P: Optimizing patient selection to maximize drug efficacy: The expanding role of pharmacogenomics in the clinical development of pembrolizumab for the treatment of non-small cell lung cancer. Clin Ther 41: 982-991, 2019.
10. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Jalal SI, *et al*: Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: A randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 17: 1497-1508, 2016.
11. Cescon DW, Schmid P, Rugo HS, Im SA, Yusof MM, Gallardo C, Lipatov O, Barrios CH, Perez-Garcia J, Iwata H, *et al*: Health-related quality of life with pembrolizumab plus chemotherapy vs placebo plus chemotherapy for advanced triple-negative breast cancer: KEYNOTE-355. J Natl Cancer Inst 116: 717-727, 2024.
12. Wakasugi A, Sasaki A, Okamoto R and Motomura Y: Eldest gastric cancer patient with high microsatellite instability responding to pembrolizumab. Int Cancer Conf J 12: 59-62, 2022.
13. Lin CY, Mehta P, Waters KM, Chang E, Hendifar A, Osipov A, Burch M, Lin DC, Gangi A, Cho M and Gong J: Complete response to neoadjuvant pembrolizumab and capecitabine in microsatellite stable, Epstein-Barr virus-positive, locally advanced gastric adenocarcinoma: Case report. AME Case Rep 5: 30, 2021.
14. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, Sun W, Jalal SI, Shah MA, Metges JP, *et al*: Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: Phase 2 clinical KEYNOTE-059 trial. JAMA Oncol 4: e180013, 2018.
15. Shitara K, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandalà M, Ryu MH, Fornaro L, Olesiński T, Caglevic C, Chung HC, *et al*: Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): A randomised, open-label, controlled, phase 3 trial. Lancet 392: 123-133, 2018.
16. Zitvogel L, Galluzzi L, Smyth MJ and Kroemer G: Mechanism of action of conventional and targeted anticancer therapies: Reinstating immunosurveillance. Immunity 39: 74-88, 2013.
17. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, *et al*: The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 343: d5928, 2011.
18. Shitara K, Van Cutsem E, Bang YJ, Fuchs C, Wyrwicz L, Lee KW, Kudaba I, Garrido M, Chung HC, Lee J, *et al*: Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: The KEYNOTE-062 phase 3 randomized clinical trial. JAMA Oncol 6: 1571-1580, 2020.
19. Satake H, Lee KW, Chung HC, Lee J, Yamaguchi K, Chen JS, Yoshikawa T, Amagai K, Yeh KH, Goto M, *et al*: Pembrolizumab or pembrolizumab plus chemotherapy versus standard of care chemotherapy in patients with advanced gastric or gastroesophageal junction adenocarcinoma: Asian subgroup analysis of KEYNOTE-062. Jpn J Clin Oncol 53: 221-229, 2023.
20. Shitara K, Rha SY, Wyrwicz LS, Oshima T, Karaseva N, Osipov M, Yasui H, Yabusaki H, Afanasyev S, Park YK, *et al*: Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): An interim analysis of the multicentre, double-blind, randomised phase 3 study. Lancet Oncol 25: 212-224, 2024.
21. Rha SY, Oh DY, Yañez P, Bai Y, Ryu MH, Lee J, Rivera F, Alves GV, Garrido M, Shiu KK, *et al*: Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): A multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 24: 1181-1195, 2023.
22. Gong J, Chehrazi-Raffle A, Reddi S and Salgia R: Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: A comprehensive review of registration trials and future considerations. J Immunother Cancer 6: 8, 2018.
23. Lim SH, Lee KW, Kim JJ, Im HS, Kim IH, Han HS, Koo DH, Cho JH, Maeng CH, Lee MY, *et al*: Real-world outcomes of third-line immune checkpoint inhibitors versus irinotecan-based chemotherapy in patients with advanced gastric cancer: A Korean, multicenter study (KCSG ST22-06). BMC Cancer 24: 252, 2024.
24. Lévêque I and Spitzer E: Pembrolizumab with trastuzumab and chemotherapy in advanced or metastatic gastric or gastroesophageal junction adenocarcinomas with surexpression of HER2 and CPS ≥1. Bull Cancer 111: 130-132, 2024 (In French).
25. Li S, Bao J, Li X, Yang Q, Xu J, Chen S, Feng G, Gao C, Feng L, Lu B, *et al*: Multicenter phase I dose escalation and expansion study of pyrotinib in combination with camrelizumab and chemotherapy as first-line treatment forHER2-positive advanced gastric and gastroesophageal junction adenocarcinoma. EClinicalMedicine 66: 102314, 2023.
26. Zhu Y, Liu K, Zhu H and Wu H: Immune checkpoint inhibitors plus chemotherapy for HER2-negative advanced gastric/gastroesophageal junction cancer: A cost-effectiveness analysis. Therap Adv Gastroenterol 16: 17562848231207200, 2023.
27. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, *et al*: Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 372: 320-330, 2015.

28. Hellmann MD, Paz-Ares L, Caro RB, Zurawski B, Kim SW, Costa EC, Park K, Alexandru A, Lupinacci L, de la Mora Jimenez E, *et al*: Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med 381: 2020-2031, 2019.
29. Gong S, Li Q, Yu X and Yang S: Efficacy and safety of different immunotherapies combined with chemotherapy as first-line therapy in patients with small cell lung cancer: A network meta-analysis. Front Immunol 15: 1362537, 2024.
30. Li Y, Liang X, Li H and Chen X: Efficacy and safety of immune checkpoint inhibitors for advanced non-small cell lung cancer with or without PD-L1 selection: A systematic review and network meta-analysis. Chin Med J (Engl) 136: 2156-2165, 2023.
31. Abderhalden LA, Wu P, Amonkar MM, Lang BM, Shah S, Jin F, Frederickson AM and Mojebi A: Clinical outcomes for previously treated patients with advanced gastric or gastroesophageal junction cancer: A systematic literature review and meta-analysis. J Gastrointest Cancer 54: 1031-1045, 2023.
32. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, *et al*: Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375: 1823-1833, 2016.
33. Fuchs CS, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandala M, Ryu MH, Fornaro L, Olesinski T, Caglevic C, Chung HC, *et al*: Pembrolizumab versus paclitaxel for previously treated PD-L1-positive advanced gastric or gastroesophageal junction cancer: 2-year update of the randomized phase 3 KEYNOTE-061 trial. Gastric Cancer 25: 197-206, 2022.
34. Bang YJ, Kang YK, Catenacci DV, Muro K, Fuchs CS, Geva R, Hara H, Golan T, Garrido M, Jalal SI, *et al*: Pembrolizumab alone or in combination with chemotherapy as first-line therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: Results from the phase II nonrandomized KEYNOTE-059 study. Gastric Cancer 22: 828-837, 2019.
35. González FS, Palacios CA, Gordón AM, Gallego JM, Díaz A and Ferrer GM: Delayed immune-related hepatitis after 24 months of pembrolizumab treatment: A case report and literature review. Anticancer Drugs 35: 284-287, 2024.
36. Aggarwal S: Adverse effects of immuno-oncology drugs-Awareness, diagnosis, and management: A literature review of immune-mediated adverse events. Indian J Cancer 56 (Suppl): S10-S22, 2019.
37. Urwyler P, Earnshaw I, Bermudez M, Perucha E, Wu W, Ryan S, Mcdonald L, Karagiannis SN, Taams LS, Powell N, *et al*: Mechanisms of checkpoint inhibition-induced adverse events. Clin Exp Immunol 200: 141-154, 2020.
38. Yeung C, Relke N, Good D, Satkunam N and Mates M: Antithymocyte globulin for aplastic anemia secondary to pembrolizumab: A case report and review of literature. Immunotherapy 15: 323-333, 2023.
39. Huntley RE, DeNiro K, Yousef J, Sheedy M and Dillon JK: Severe mucositis secondary to pembrolizumab: Reports of two cases, review of the literature, and an algorithm for management. J Oral Maxillofac Surg 79: 1262-1269, 2021.
40. Kejamurthy P and Devi KTR: Immune checkpoint inhibitors and cancer immunotherapy by aptamers: An overview. Med Oncol 41: 40, 2023.