

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2024 April 15; 16(4): 1091-1675



EDITORIAL

- 1091** Parallel pathways: A chronicle of evolution in rectal and breast cancer surgery
Pesce A, Fabbri N, Iovino D, Feo CV
- 1097** Hepatitis B virus genotypes in precision medicine of hepatitis B-related hepatocellular carcinoma: Where we are now
Sukowati CHC, Jayanti S, Turyadi T, Muljono DH, Tiribelli C

REVIEW

- 1104** Novel milestones for early esophageal carcinoma: From bench to bed
Qi JH, Huang SL, Jin SZ
- 1119** Colorectal cancer screening: A review of current knowledge and progress in research
Lopes SR, Martins C, Santos IC, Teixeira M, Gamito É, Alves AL
- 1134** New avenues for the treatment of immunotherapy-resistant pancreatic cancer
Silva LGO, Lemos FFB, Luz MS, Rocha Pinheiro SL, Calmon MDS, Correa Santos GL, Rocha GR, de Melo FF

MINIREVIEWS

- 1154** Present situation of minimally invasive surgical treatment for early gastric cancer
Li CY, Wang YF, Luo LK, Yang XJ
- 1166** Mixed neuroendocrine non-neuroendocrine neoplasms in gastroenteropancreatic tract
Díaz-López S, Jiménez-Castro J, Robles-Barraza CE, Ayala-de Miguel C, Chaves-Conde M
- 1180** Esophageal cancer screening, early detection and treatment: Current insights and future directions
Qu HT, Li Q, Hao L, Ni YJ, Luan WY, Yang Z, Chen XD, Zhang TT, Miao YD, Zhang F

ORIGINAL ARTICLE

Retrospective Cohort Study

- 1192** Pre-operative enhanced magnetic resonance imaging combined with clinical features predict early recurrence of hepatocellular carcinoma after radical resection
Chen JP, Yang RH, Zhang TH, Liao LA, Guan YT, Dai HY
- 1204** Clinical analysis of multiple primary gastrointestinal malignant tumors: A 10-year case review of a single-center
Zhu CL, Peng LZ

Retrospective Study

- 1213** Predictive model for non-malignant portal vein thrombosis associated with cirrhosis based on inflammatory biomarkers
Nie GL, Yan J, Li Y, Zhang HL, Xie DN, Zhu XW, Li X
- 1227** Predictive modeling for postoperative delirium in elderly patients with abdominal malignancies using synthetic minority oversampling technique
Hu WJ, Bai G, Wang Y, Hong DM, Jiang JH, Li JX, Hua Y, Wang XY, Chen Y
- 1236** Efficacy and predictive factors of transarterial chemoembolization combined with lenvatinib plus programmed cell death protein-1 inhibition for unresectable hepatocellular carcinoma
Ma KP, Fu JX, Duan F, Wang MQ
- 1248** Should we perform sigmoidoscopy for colorectal cancer screening in people under 45 years?
Leong W, Guo JQ, Ning C, Luo FF, Jiao R, Yang DY
- 1256** Computed tomography-based radiomics diagnostic approach for differential diagnosis between early- and late-stage pancreatic ductal adenocarcinoma
Ren S, Qian LC, Cao YY, Daniels MJ, Song LN, Tian Y, Wang ZQ
- 1268** Prognostic analysis of related factors of adverse reactions to immunotherapy in advanced gastric cancer and establishment of a nomogram model
He XX, Du B, Wu T, Shen H

Clinical Trials Study

- 1281** Safety and efficacy of a programmed cell death 1 inhibitor combined with oxaliplatin plus S-1 in patients with Borrmann large type III and IV gastric cancers
Bao ZH, Hu C, Zhang YQ, Yu PC, Wang Y, Xu ZY, Fu HY, Cheng XD

Observational Study

- 1296** Computed tomography radiogenomics: A potential tool for prediction of molecular subtypes in gastric stromal tumor
Yin XN, Wang ZH, Zou L, Yang CW, Shen CY, Liu BK, Yin Y, Liu XJ, Zhang B
- 1309** Application of texture signatures based on multiparameter-magnetic resonance imaging for predicting microvascular invasion in hepatocellular carcinoma: Retrospective study
Nong HY, Cen YY, Qin M, Qin WQ, Xie YX, Li L, Liu MR, Ding K
- 1319** Causal roles of gut microbiota in cholangiocarcinoma etiology suggested by genetic study
Chen ZT, Ding CC, Chen KL, Gu YJ, Lu CC, Li QY
- 1334** Is recovery enhancement after gastric cancer surgery really a safe approach for elderly patients?
Li ZW, Luo XJ, Liu F, Liu XR, Shu XP, Tong Y, Lv Q, Liu XY, Zhang W, Peng D
- 1344** Establishment of a cholangiocarcinoma risk evaluation model based on mucin expression levels
Yang CY, Guo LM, Li Y, Wang GX, Tang XW, Zhang QL, Zhang LF, Luo JY

- 1361** Effectiveness of fecal DNA syndecan-2 methylation testing for detection of colorectal cancer in a high-risk Chinese population

Luo WF, Jiao YT, Lin XL, Zhao Y, Wang SB, Shen J, Deng J, Ye YF, Han ZP, Xie FM, He JH, Wan Y

Clinical and Translational Research

- 1374** Clinical and socioeconomic determinants of survival in biliary tract adenocarcinomas

Sahyoun L, Chen K, Tsay C, Chen G, Protiva P

- 1384** Risk factors, prognostic factors, and nomograms for distant metastasis in patients with diagnosed duodenal cancer: A population-based study

Shang JR, Xu CY, Zhai XX, Xu Z, Qian J

- 1421** NOX4 promotes tumor progression through the MAPK-MEK1/2-ERK1/2 axis in colorectal cancer

Xu YJ, Huo YC, Zhao QT, Liu JY, Tian YJ, Yang LL, Zhang Y

Basic Study

- 1437** Curcumin inhibits the growth and invasion of gastric cancer by regulating long noncoding RNA AC022424.2

Wang BS, Zhang CL, Cui X, Li Q, Yang L, He ZY, Yang Z, Zeng MM, Cao N

- 1453** MicroRNA-298 determines the radio-resistance of colorectal cancer cells by directly targeting human dual-specificity tyrosine(Y)-regulated kinase 1A

Shen MZ, Zhang Y, Wu F, Shen MZ, Liang JL, Zhang XL, Liu XJ, Li XS, Wang RS

- 1465** Human β -defensin-1 affects the mammalian target of rapamycin pathway and autophagy in colon cancer cells through long non-coding RNA TCONS_00014506

Zhao YX, Cui Y, Li XH, Yang WH, An SX, Cui JX, Zhang MY, Lu JK, Zhang X, Wang XM, Bao LL, Zhao PW

- 1479** FAM53B promotes pancreatic ductal adenocarcinoma metastasis by regulating macrophage M2 polarization

Pei XZ, Cai M, Jiang DW, Chen SH, Wang QQ, Lu HM, Lu YF

- 1500** Transcriptome sequencing reveals novel biomarkers and immune cell infiltration in esophageal tumorigenesis

Sun JR, Chen DM, Huang R, Wang RT, Jia LQ

- 1514** Construction of CDKN2A-related competitive endogenous RNA network and identification of GAS5 as a prognostic indicator for hepatocellular carcinoma

Pan Y, Zhang YR, Wang LY, Wu LN, Ma YQ, Fang Z, Li SB

- 1532** Two missense STK11 gene variations impaired LKB1/adenosine monophosphate-activated protein kinase signaling in Peutz-Jeghers syndrome

Liu J, Zeng SC, Wang A, Cheng HY, Zhang QJ, Lu GX

- 1547** Long noncoding RNAs HAND2-AS1 ultrasound microbubbles suppress hepatocellular carcinoma progression by regulating the miR-873-5p/tissue inhibitor of matrix metalloproteinase-2 axis

Zou Q, Wang HW, Di XL, Li Y, Gao H

- 1564** Upregulated lncRNA PRNT promotes progression and oxaliplatin resistance of colorectal cancer cells by regulating HIPK2 transcription

Li SN, Yang S, Wang HQ, Hui TL, Cheng M, Zhang X, Li BK, Wang GY

SYSTEMATIC REVIEWS

- 1578** Prognosis value of heat-shock proteins in esophageal and esophagogastric cancer: A systematic review and meta-analysis

Nakamura ET, Park A, Pereira MA, Kikawa D, Tustumi F

- 1596** Risk factors for hepatocellular carcinoma associated with hepatitis C genotype 3 infection: A systematic review

Farooq HZ, James M, Abbott J, Oyibo P, Divall P, Choudhry N, Foster GR

META-ANALYSIS

- 1613** Effectiveness and tolerability of programmed cell death protein-1 inhibitor + chemotherapy compared to chemotherapy for upper gastrointestinal tract cancers

Zhang XM, Yang T, Xu YY, Li BZ, Shen W, Hu WQ, Yan CW, Zong L

- 1626** Success rate of current human-derived gastric cancer organoids establishment and influencing factors: A systematic review and meta-analysis

Jiang KL, Wang XX, Liu XJ, Guo LK, Chen YQ, Jia QL, Yang KM, Ling JH

CASE REPORT

- 1647** Pathologically successful conversion hepatectomy for advanced giant hepatocellular carcinoma after multidisciplinary therapy: A case report and review of literature

Chu JH, Huang LY, Wang YR, Li J, Han SL, Xi H, Gao WX, Cui YY, Qian MP

- 1660** Clinical pathological characteristics of "crawling-type" gastric adenocarcinoma cancer: A case report

Xu YW, Song Y, Tian J, Zhang BC, Yang YS, Wang J

- 1668** Primary pancreatic peripheral T-cell lymphoma: A case report

Bai YL, Wang LJ, Luo H, Cui YB, Xu JH, Nan HJ, Yang PY, Niu JW, Shi MY

ABOUT COVER

Peer Reviewer of *World Journal of Gastrointestinal Oncology*, Lie Zheng, Director, Professor, Department of Gastroenterology, Shaanxi Provincial Hospital of Traditional Chinese Medicine, Xi'an 730000, Shaanxi Province, China. xinliwen696@126.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

INDEXING/ABSTRACTING

The WJGO is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJGO as 3.0; IF without journal self cites: 2.9; 5-year IF: 3.0; Journal Citation Indicator: 0.49; Ranking: 157 among 241 journals in oncology; Quartile category: Q3; Ranking: 58 among 93 journals in gastroenterology and hepatology; and Quartile category: Q3. The WJGO's CiteScore for 2022 is 4.1 and Scopus CiteScore rank 2022: Gastroenterology is 71/149; Oncology is 197/366.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xiang-Di Zhang; Production Department Director: Xiang Li; Cover Editor: Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

PUBLICATION DATE

April 15, 2024

COPYRIGHT

© 2024 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Effectiveness and tolerability of programmed cell death protein-1 inhibitor + chemotherapy compared to chemotherapy for upper gastrointestinal tract cancers

Xiao-Min Zhang, Ting Yang, Ying-Ying Xu, Bao-Zhong Li, Wei Shen, Wen-Qing Hu, Cai-Wen Yan, Liang Zong

Specialty type: Oncology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ebrahimifar M, Iran;
Keikha M, Iran

Received: September 21, 2023

Peer-review started: September 21, 2023

First decision: December 19, 2023

Revised: December 27, 2023

Accepted: February 22, 2024

Article in press: February 22, 2024

Published online: April 15, 2024



Xiao-Min Zhang, Ting Yang, Liang Zong, Department of Central Laboratory, Changzhi People's Hospital, The Affiliated Hospital of Changzhi Medical College, Changzhi 046000, Shanxi Province, China

Ying-Ying Xu, Department of Gastrointestinal Surgery, Yizheng People's Hospital, The Affiliated Hospital of Yangzhou University, Yangzhou 225000, Jiangsu Province, China

Bao-Zhong Li, Department of General Surgery, Anyang Tumor Hospital, Anyang 455000, Henan Province, China

Wei Shen, Department of General Surgery, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi 214023, Jiangsu Province, China

Wen-Qing Hu, Liang Zong, Department of Gastrointestinal Surgery, Changzhi People's Hospital, The Affiliated Hospital of Changzhi Medical College, Changzhi 046000, Shanxi Province, China

Cai-Wen Yan, Department of Gastroenterology, Changzhi People's Hospital, The Affiliated Hospital of Changzhi Medical College, Changzhi 046000, Shanxi Province, China

Corresponding author: Liang Zong, PhD, Doctor, Department of Central Laboratory, Changzhi People's Hospital, The Affiliated Hospital of Changzhi Medical College, No. 502 Changxing Middle Road, Luzhou District, Changzhi 046000, Shanxi Province, China.
250537471@qq.com

Abstract

BACKGROUND

The combination of programmed cell death protein-1 (PD-1) inhibitor and chemotherapy is approved as a standard first- or second-line treatment in patients with advanced oesophageal or gastric cancer. However, it is unclear whether this combination is superior to chemotherapy alone.

AIM

To assess the comparative effectiveness and tolerability of combining PD-1 inhibitors with chemotherapy *vs* chemotherapy alone in patients with advanced gastric cancer, gastroesophageal junction (GEJ) cancer, or oesophageal carcinoma.

METHODS

We searched the PubMed and Embase databases for studies that compared the efficacy and tolerance of PD-1 inhibitors in combination with chemotherapy *vs* chemotherapy alone in patients with advanced oesophageal or gastric cancer. We employed either random or fixed models to analyze the outcomes of each clinical trial, encompassing data on overall survival (OS), progression-free survival (PFS), objective response rate, and adverse events (AEs).

RESULTS

Nine phase 3 clinical trials (7016 advanced oesophageal and gastric cancer patients) met the inclusion criteria. Our meta-analysis demonstrated that the pooled PD-1 inhibitor + chemotherapy group had a significantly longer OS than the chemotherapy-alone group [hazard ratio (HR) = 0.76, 95% confidence interval (CI): 0.71-0.81]; the pooled PFS result was consistent with that of OS (HR = 0.67, 95% CI: 0.61-0.74). The count of patients achieving an objective response in the PD-1 inhibitor + chemotherapy group surpassed that of the chemotherapy-alone group [odds ratio (OR) = 1.86, 95% CI: 1.59-2.18]. AE incidence was also higher in the combination-therapy group than in the chemotherapy-alone group, regardless of whether $\geq$ grade 3 only (OR = 1.30, 95% CI: 1.07-1.57) or all AE grades (OR = 1.88, 95% CI: 1.39-2.54) were examined. We performed a subgroup analysis based on the programmed death-ligand 1 (PD-L1) combined positive score (CPS) and noted extended OS and PFS durations within the CPS $\geq$ 1, CPS $\geq$ 5, and CPS $\geq$ 10 subgroups of the PD-1 inhibitor + chemotherapy group.

CONCLUSION

In contrast to chemotherapy alone, the combination of PD-1 inhibitor and chemotherapy appears to present a more favorable option for initial or subsequent treatment in patients with gastric cancer, GEJ tumor, or oesophageal cancer. This holds true particularly for individuals with PD-L1 CPS scores of $\geq$ 5 and $\geq$ 10.

Key Words: Programmed cell death protein-1 inhibitor; Chemotherapy; Oesophageal squamous cell carcinoma; Gastric/gastroesophageal junction adenocarcinoma; Overall survival; Progression-free survival; Objective response rate; Adverse event

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: The combination of programmed cell death protein-1 (PD-1) inhibitor and chemotherapy is approved as a standard first- or second-line treatment in patients with advanced oesophageal or gastric cancer. However, it is unclear whether this combination is superior to chemotherapy alone. We assessed the comparative effectiveness and tolerability of combining PD-1 inhibitors with chemotherapy *vs* chemotherapy alone in patients with advanced gastric cancer, gastroesophageal junction cancer, or oesophageal carcinoma. Our analysis showed that immunotherapy combined with chemotherapy significantly prolonged patients' overall survival and progression-free survival relative to the chemotherapy group, both in the overall population and in the combined positive score (CPS) $\geq$ 1, CPS $\geq$ 5, and CPS $\geq$ 10 subgroup.

Citation: Zhang XM, Yang T, Xu YY, Li BZ, Shen W, Hu WQ, Yan CW, Zong L. Effectiveness and tolerability of programmed cell death protein-1 inhibitor + chemotherapy compared to chemotherapy for upper gastrointestinal tract cancers. *World J Gastrointest Oncol* 2024; 16(4): 1613-1625

URL: <https://www.wjgnet.com/1948-5204/full/v16/i4/1613.htm>

DOI: <https://dx.doi.org/10.4251/wjgo.v16.i4.1613>

INTRODUCTION

Upper gastrointestinal tract (UGT) cancers stand as the prevailing form of malignancy, encompassing oesophageal squamous cell carcinoma (ESCC) and gastric/gastroesophageal junction (G/GEJ) adenocarcinomas[1]. According to Global Cancer Statistics 2020, an estimated 1089103 and 604100 new cases of gastric and oesophageal cancers, respectively, occur each year, and the annual numbers of new deaths are 768793 and 544076[2]. The presently employed methods for treating UGT cancers are surgery, chemotherapy, and radiotherapy. Even with continuous enhancements in chemoradiotherapy, the clinical results for ESCC and G/GEJ adenocarcinoma have not exhibited substantial advancement over time, underscoring the persisting gap in effective treatment[3].

Immunotherapy is an evolving approach to cancer treatment and is designed to destroy cancer cells by strengthening patients' immune capabilities. Various immunotherapies encompass the utilization of immune checkpoint inhibitor (ICIs), chimeric antigen receptor T-cell therapy, cancer vaccines, and adoptive cell therapy[4]. Programmed cell death protein-1 (PD-1) functions as a checkpoint receptor expressed on the surface of diverse immune cells. Blocking the interaction between PD-1 and programmed death-ligand 1 (PD-L1) serves as an effective means to bolster the immune response[5]. Anti-PD-1 antibodies such as nivolumab, pembrolizumab, sintilimab, camrelizumab, and tislelizumab demonstrated improved antitumor activity alongside manageable safety profiles in patients with oesophageal or gastric

cancer[6].

Combinations of a PD-1 inhibitor and chemotherapy have gained approval as standard first or second-line treatment choices for patients with advanced oesophageal and gastric cancer in clinical settings[7]. While various studies have outlined the advantages of pairing PD-1 inhibitor therapy with chemotherapy, it remains undetermined whether the combination of a PD-1 inhibitor + chemotherapy surpasses the efficacy of chemotherapy alone. Tabernero *et al*[8] revealed that the combination of pembrolizumab with chemotherapy did not exhibit superiority over chemotherapy alone in terms of the tested overall survival (OS) and progression-free survival (PFS) endpoints. In a separate study involving patients with gastric or GEJ cancer, the addition of nivolumab to chemotherapy did not lead to a significant improvement in OS compared to the group treated with chemotherapy alone[9]. Therefore, it remains essential to ascertain whether chemotherapy alone or the combination of PD-1 inhibitors with chemotherapy yields a more favorable curative effect. We performed this current meta-analysis to assess the comparative efficacy and tolerability of PD-1 inhibitors combined with standard chemotherapy in contrast to chemotherapy alone, specifically in patients diagnosed with advanced gastric cancer, GEJ cancer, or oesophageal adenocarcinoma. Our aim was to establish a foundation for clinical treatment choices for future patients afflicted with UGT cancer.

MATERIALS AND METHODS

Search strategy

To identify relevant studies, we performed a comprehensive literature search of the electronic databases PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and Embase ([embase.com/](https://www.embase.com/)). Filter articles published before July 2023. We used search terms pertaining to diseases (*e.g.*, GEJ adenocarcinoma, gastric, gastric cancer, gastro-oesophageal junction cancer, oesophageal squamous cell carcinoma, oesophageal cancer, oesophageal adenocarcinoma, oesophageal squamous cell carcinoma) or the therapies established for those diseases (*e.g.*, chemotherapy, nivolumab, pembrolizumab, camrelizumab, sintilimab, tislelizumab). We also set up filters for clinical trials. The search results from each database were combined in Endnote X9, and duplicates were removed. For the rest of the literature, we evaluate whether it is qualified by reading the full text. In addition, we also searched the relevant literature manually to find other potentially relevant articles. The literature selection process was completed independently by two authors (Zhang XM and Yang T).

Meta-analysis inclusion and exclusion criteria

Eligible studies were selected following inclusion and exclusion criteria (Figure 1). A study was considered eligible for inclusion in the present meta-analysis if it met the following inclusion criteria: (1) The study was limited to oesophageal squamous cell carcinoma and/or G/GEJ adenocarcinoma; (2) The study was a phase III clinical trial; (3) The study included a sample of more than 500 patients; (4) The study encompassed at least one group receiving a combination of PD-1 inhibitor and chemotherapy, alongside one group receiving chemotherapy alone; (5) The study's basic data (*e.g.*, trial year, sample size, patient sex distribution, tumor types, trial abbreviation, registry number) were complete. Additionally, it was essential for the study to acquire the hazard ratio (HR) along with its corresponding 95% confidence interval (CI) for OS and PFS, as well as comparable data for objective response rate (ORR) and adverse events (AEs); and (6) The study was reported in English.

The exclusion criteria were as follows: (1) The literature type was meta-analysis, review or letter; (2) Lack of HR values and 95% CIs for OS and PFS comparisons between the two groups, or the number of patients who achieved ORRs and the number of AEs between the two groups were not reported; (3) The study was a non-randomized clinical trial; (4) The study concerned the results of radiotherapy; (5) The study included only results from special patient populations, such as elderly patients; and (6) Research lacking sufficient published data suitable for analysis.

Data extraction

Data were extracted independently by two of the authors (Zhang XM and Yang T). The extraction process encompassed the following items in accordance with the inclusion criteria: (1) General characteristics of the studies: Name of the first author, publication year, trial abbreviation, and registry number; (2) The patients' baseline characteristics: Age, sex, sample size, tumor type, intervention arm, chemotherapy regimens, and PD-L1 combined positive scores (CPSs); and (3) Outcomes: We extracted the HRs and their 95% CIs for each study's OS, PFS, the number of patients who achieved an objective response, all AEs, grade > 3 AEs, and the counts of patients with a PD-L1 CPS of ≥ 5 or ≥ 10 .

Quality assessment of the included studies

We evaluated the potential bias in each study using Cochrane Collaboration's tool (Review Manager 5.3). The primary criteria for this assessment included random sequence generation, allocation concealment, participant blinding, outcome assessment blinding, incomplete outcome data, and selective reporting, as well as other biases. This assessment assigned grades according to levels of risk, *i.e.*, high, low, or unclear risk.

Statistical analyses

Stata ver. 12.0 software was used to perform all statistical tests. For the quantitative aggregation of the survival outcomes, the HRs and their 95% CIs were combined as the effective value. The significance of the pooled OR or HR was assessed using the Z-test, where *P*-values < 0.05 were deemed statistically significant. To evaluate the global heterogeneity between studies, we used the χ^2 -based Q-test (*P* > 0.10 was considered a lack of heterogeneity) and the *I*² test (*I*² ≤ 50%

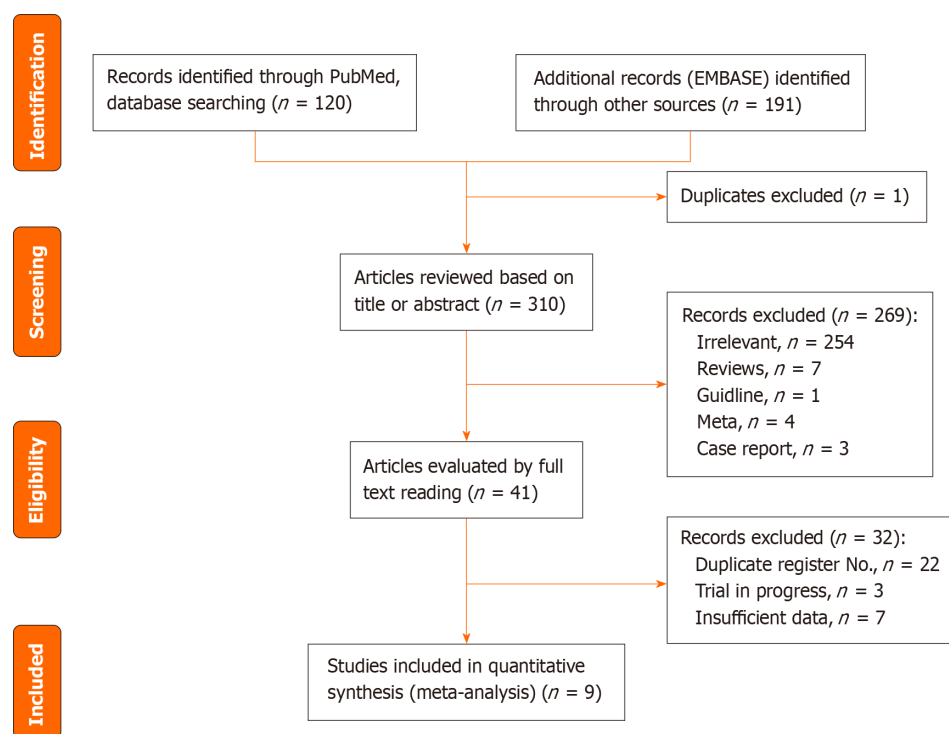


Figure 1 Flow diagram of study inclusions and exclusions for the meta-analysis.

indicated low heterogeneity, while $I^2 > 50\%$ indicated high heterogeneity). We employed the fixed-effects model if the heterogeneity was low; otherwise, we used the random-effects model. Funnel plots were generated to assess the presence of publication bias in the outcomes. An asymmetrical plot indicated possible publication bias. Review of the funnel plots could not rule out the potential for publication bias for the efficacy of PD-1 inhibitors in the treatment of UGT cancers. Further, asymmetry in the funnel plot was evaluated through Egger's test and Begg's test, with P -values < 0.05 indicating significance. If publication bias existed, we assessed the effect of publication bias by using the trim-fill method. Additionally, sensitivity analyses were conducted to assess the stability of the results. The statistical methods of this study were reviewed by Guo-Lin Han from Medical records statistics room of Changzhi People's Hospital.

RESULTS

Search results

A total of 310 articles were retrieved from the PubMed and Embase databases; one duplicate paper was removed, leaving 309 articles remaining. We initially screened the articles according to their titles and abstracts. As a result, we excluded 254 articles as irrelevant and 15 as either meta-analyses, case reports, guidelines, or reviews. We then screened the remaining 41 articles by reading them in full, resulting in the exclusion of 22 articles with the same trial registration number, 3 incomplete clinical trials, and 7 articles lacking the OS, PFS, ORR, and/or AE data required by this study. The final total was 9 articles[10-18]. **Figure 1** is a flow diagram illustrating the inclusion and exclusion of articles.

Study and patient characteristics

All 9 of the articles included in this meta-analysis were reports of phase 3 clinical trials. Among them, 8 were multicenter studies and the remainder was a single-center study. The 9 articles were published between 2020 and 2022 and included a total of 7016 patients, with sample sizes ranging from 596 to 1581. Three articles compared nivolumab in combination with chemotherapy *vs* chemotherapy alone, while two articles compared pembrolizumab + chemotherapy *vs* chemotherapy alone. Two articles examined sintilimab + chemotherapy *vs* chemotherapy alone, and the remaining two articles investigated chemotherapy alone *vs* camrelizumab and tislelizumab, respectively. **Table 1** summarizes the patients' clinical characteristics.

Next, we evaluated the risk of bias for each study, and the outcomes are illustrated in **Figure 2**. One of the sources of bias originated from the absence of blinding, which notably impacted the study quality. The precision of results in another study could have been influenced due to participant withdrawals or losses. Additional biases could have arisen from factors such as an uneven geographic distribution of participants, poor or incomplete patient compliance, or other underlying reasons.

Table 1 Baseline characteristics of clinical trials included in the meta-analysis

Ref.	Treatment stage	Sample size	Male/female	Median age (IQR)	Trial Abbr.	Register No.	Tumor type	Intervention arm	Control arm	CPS subgroup	Reported outcomes
Janjigian <i>et al</i> [12]	Phase 3	1581 (789/792)	1100/481	62 (54-69) vs 61 (53-68)	CheckMate 649	NCT02872116	G/GEJ/oesophageal adenocarcinoma	Nivolumab + XELOX (capecitabine and oxaliplatin) or FOLFOX (leucovorin, fluorouracil, and oxaliplatin)	XELOX (capecitabine and oxaliplatin) or FOLFOX (leucovorin, fluorouracil, and oxaliplatin)	≥ 5, ≥ 1	OS, PFS, ORR
Kang <i>et al</i> [11]	Phase 3	724 (362/362)	523/201	63.5 vs 65	ATTRACTION-4	NCT02746796	G/GEJ	Nivolumab plus oxaliplatin and capecitabine/s-1	Placebo plus oxaliplatin and capecitabine/s-1	NA	OS, PFS
Doki <i>et al</i> [18]	Phase 3	645 (321/324)	528/117	64 (40-90) vs 64 (26-81)	CheckMate 648	NCT03143153	Advanced esophageal squamous-cell carcinoma	Nivolumab + chemotherapy (fluorouracil + cisplatin)	Chemotherapy	NA	OS, PFS, ORR
Shitara <i>et al</i> [10]	Phase 3	763 (257/250)	257/250	62 (22-83) vs 62.5 (23-87)	KEYNOTE-062	NCT02494583	G/GEJ	Pembrolizumab + cisplatin + fluorouracil or capecitabine	Cisplatin + fluorouracil or capecitabine	≥ 1, ≥ 10	OS, PFS, ORR
Sun <i>et al</i> [16]	Phase 3	749 (373/376)	625/124	64 (28-94) vs 62 (27-89)	KEYNOTE-590	NCT03189719	Advanced oesophageal cancer	Pembrolizuma + chemotherapy (5-fluorouracil plus cisplatin)	Placebo + chemotherapy (5-fluorouracil plus cisplatin)	CPS < 10, CPS ≥ 10	OS, PFS, ORR
Xu <i>et al</i> [15]	Phase 3	650 (327/323)	NA	NA	ORIENT-16	NCT03745170	Advanced G/GEJ adenocarcinoma	Sintilimab combined with chemotherapy (CapeOX: oxaliplatin + capecitabine)	Placebo and chemotherapy (CapeOX: oxaliplatin + capecitabine)	CPS ≥ 5	OS, PFS, ORR
Lu <i>et al</i> [14]	Phase 3	659 (327/332)	567/92	63 (57-67) vs 63 (56-67)	ORIENT-15	NCT03748134	Oesophageal squamous cell carcinoma	Sintilimab combined with chemotherapy (cisplatin + paclitaxel or cisplatin + 5-fluorouracil)	Placebo and chemotherapy (cisplatin + paclitaxel or cisplatin + 5-fluorouracil)	CPS < 10, CPS ≥ 10, CPS < 5, CPS ≥ 5, CPS < 1, CPS ≥ 1	OS, PFS, ORR
Luo <i>et al</i> [13]	Phase 3	596 (298/298)	523/73	62 (56-66) vs 62 (56-67)	ESCORT	NCT03691090	Esophageal squamous cell carcinoma	Camrelizumab combined with paclitaxel and cisplatin	Placebo and paclitaxel and cisplatin	TPS	OS, PFS, ORR
Xu <i>et al</i> [17]	Phase 3	649 (326/323)	563/86	64 (59-68) vs 65 (58-70)	RATIONALE-306	NCT03783442	Esophageal squamous-cell carcinoma	Tislelizumab + chemotherapy [a platinum agent (cisplatin or oxaliplatin) + a fluoropyrimidine (fluorouracil or capecitabine) or paclitaxel]	Chemotherapy [a platinum agent (cisplatin or oxaliplatin) + a fluoropyrimidine (fluorouracil or capecitabine) or paclitaxel]	TAP	OS, PFS, ORR

IQR: Interquartile range; G: Gastric; GEJ: Gastroesophageal junction; CPS: Combined positive score; OS: Overall survival; PFS: Progression-free survival; ORR: Objective response rate; NA: Not available; TPS: Tumor proportion score; TAP: Tumour area positivity.

Primary outcomes (OS and PFS)

All 9 of the clinical trials provided HR and 95%CI values for the OS and PFS outcomes of patients treated with a PD-1 inhibitor + chemotherapy compared to chemotherapy alone. We pooled the HR values from the 9 clinical trials using randomized- or fixed-effects models, and the results showed that the pooled PD-1 inhibitor + chemotherapy group had

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
H. Yoon 2022	?	?	+	+	+	+	?
Huiyan Luo 2021	+	?	+	+	-	+	-
J. Xu 2021	?	?	+	+	+	+	?
Jong-Mu Sun 2021	+	?	+	+	+	+	?
Kohei Shitara, MD 2020	+	?	?	?	+	+	-
Y. Doki 2022	?	?	?	+	+	+	+
Yelena Y Janjigian 2021	+	+	-	+	+	+	+
Yoon-Koo Kang 2022	+	+	+	+	+	+	?
Zhihao Lu 2022	+	?	+	+	+	+	-

Figure 2 Risk of bias of each included study. Red circles: Studies with a high risk of bias. Green circles: Studies with a low risk of bias. Yellow circles: Studies with insufficient information for assessing the risk of bias.

longer OS than the pooled chemotherapy-alone group (HR = 0.76, 95%CI: 0.71-0.81). **Figure 3A** shows the combined forest plot of the OS data. The combined outcome for patients' PFS corresponded with that of their OS (HR = 0.67, 95%CI: 0.61-0.74), as depicted in **Figure 3B**.

Secondary outcomes: ORR and AEs

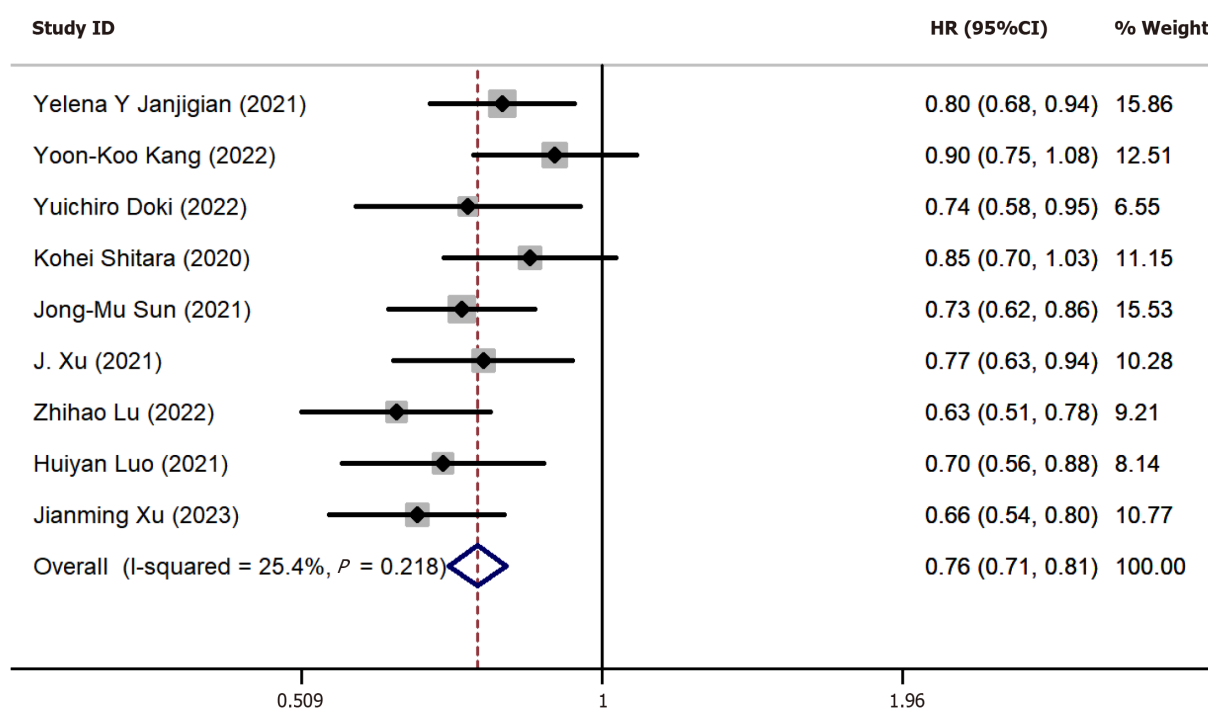
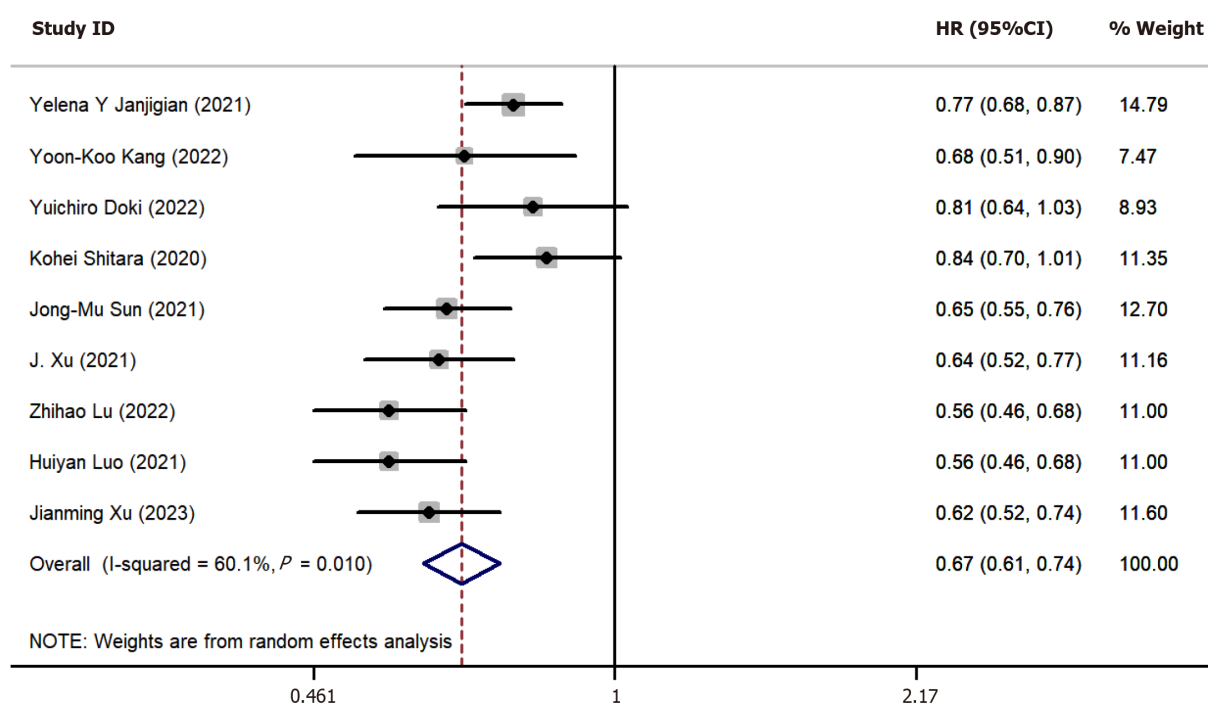
Of the 9 studies, 8 provided ORR data, and we gathered the count of patients who obtained an objective response in each study. The findings suggested that the count of individuals achieving an objective response in the PD-1 inhibitor + chemotherapy group exceeded that in the chemotherapy-alone group (OR = 1.86, 95%CI: 1.59-2.18) (**Figure 3C**). Regarding the AEs observed in the studies, we aggregated both the AEs of all grades and those rated $\geq$ grade 3. As shown in **Figure 3D**, the meta-analysis of AEs indicated that the frequency of AEs in the PD-1 inhibitor + chemotherapy group exceeded that in the chemotherapy-alone group. This held true for AEs of all grades (OR = 1.88, 95%CI: 1.39-2.54) as well as for AEs rated $\geq$ grade 3 (OR = 1.30, 95%CI: 1.07-1.57) in **Figure 4C**.

Subgroup analyses of OS and PFS

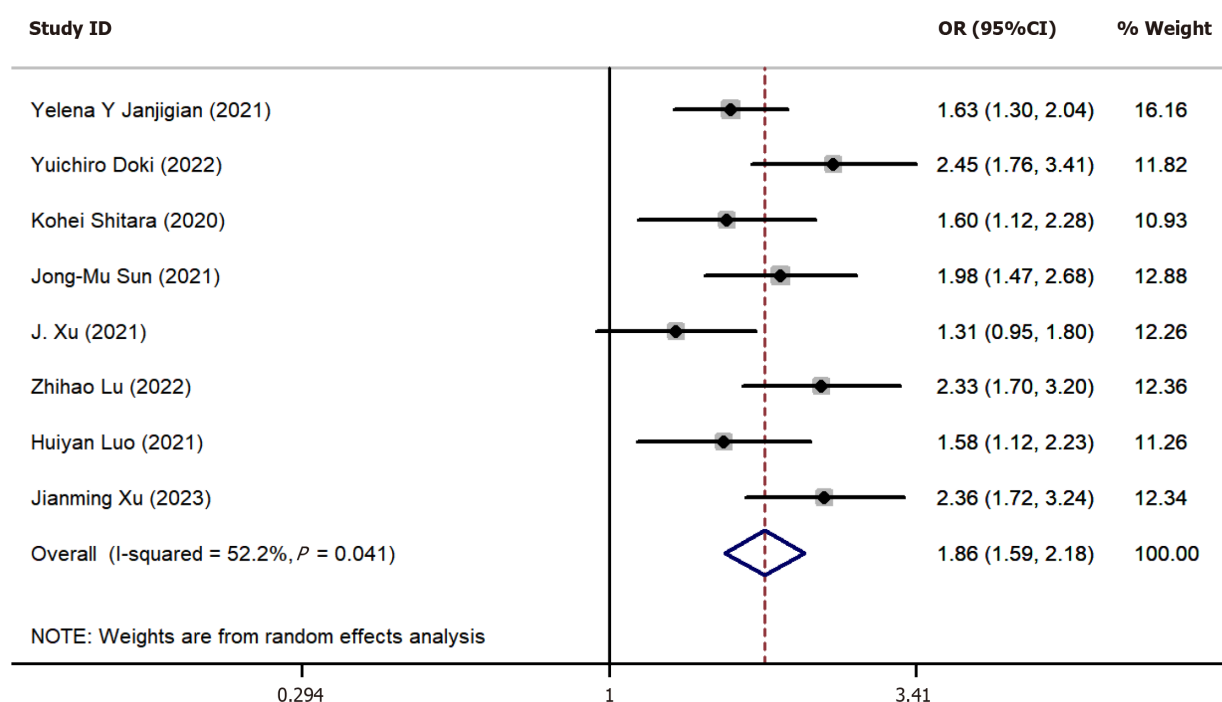
We employed the patients' PD-L1 CPS scores as a measure to assess the efficacy of immunotherapy against tumors. Of the 9 clinical trials, 5 reported treatment outcomes in different PD-L1 CPS subgroups. Consequently, we conducted a subgroup analysis of OS and PFS based on the patients' PD-L1 CPS scores. The subgroup analysis of OS (**Figure 4A**) indicated that patients treated with a PD-1 inhibitor + chemotherapy exhibited prolonged OS compared to those treated with chemotherapy alone, irrespective of the subgroup CPS ≥ 1 (HR = 0.73, 95%CI: 0.60-0.90, $P = 0.002$), CPS ≥ 5 (HR = 0.68, 95%CI: 0.60-0.78, $P < 0.001$), or CPS ≥ 10 (HR = 0.68, 95%CI: 0.57-0.82, $P < 0.001$). The outcomes of our subgroup analysis for PFS (**Figure 4B**) aligned with those for OS across all three groups: CPS ≥ 1 (HR = 0.70, 95%CI: 0.56-0.88, $P = 0.002$), CPS ≥ 5 (HR = 0.63, 95%CI: 0.56-0.72, $P < 0.001$), and CPS ≥ 10 (HR = 0.54, 95%CI: 0.46-0.64, $P < 0.001$).

Publication bias

To minimize the effects of publication bias, we expanded database searches and performed a thorough search for unpublished studies, and used funnel plot to quantify the potential presence of publication bias. We utilized funnel plots of the OS and PFS data to evaluate potential publication bias (**Supplementary Figure 1**). The outcomes of the Begg's test (OS: $P = 0.25$; PFS: $P = 0.532$) and Egger's test (OS: $P = 0.336$; PFS: $P = 0.512$) for both the OS and PFS funnel plots

A**B**

C



D

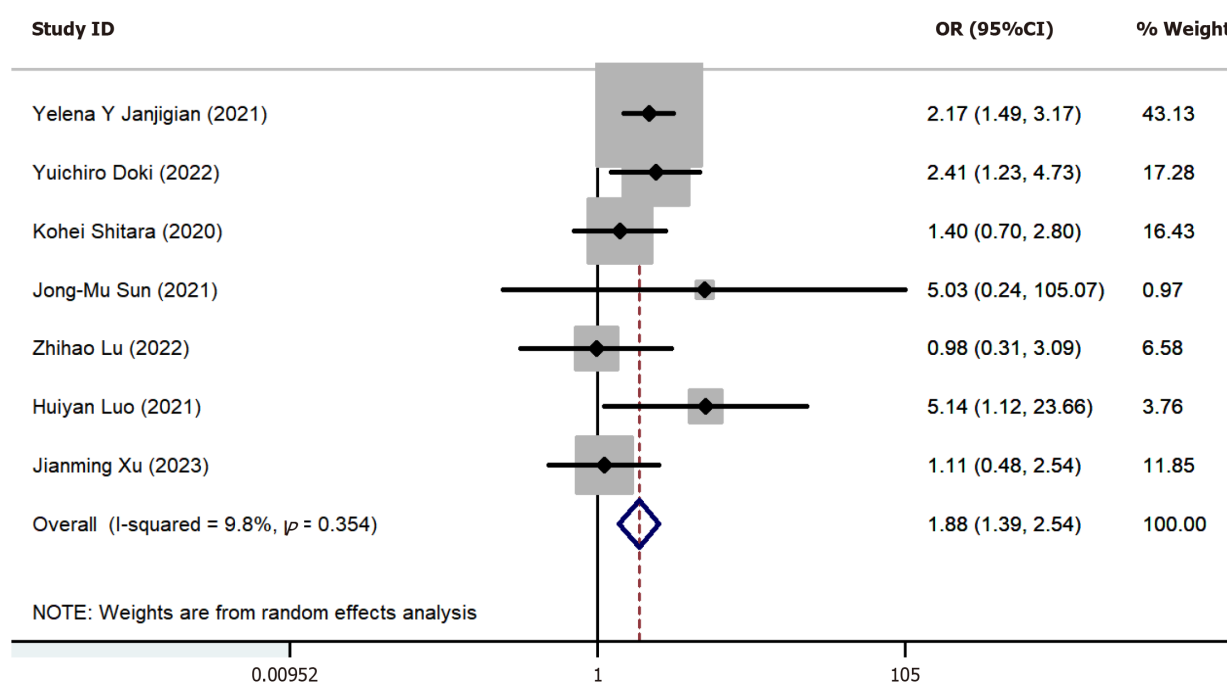
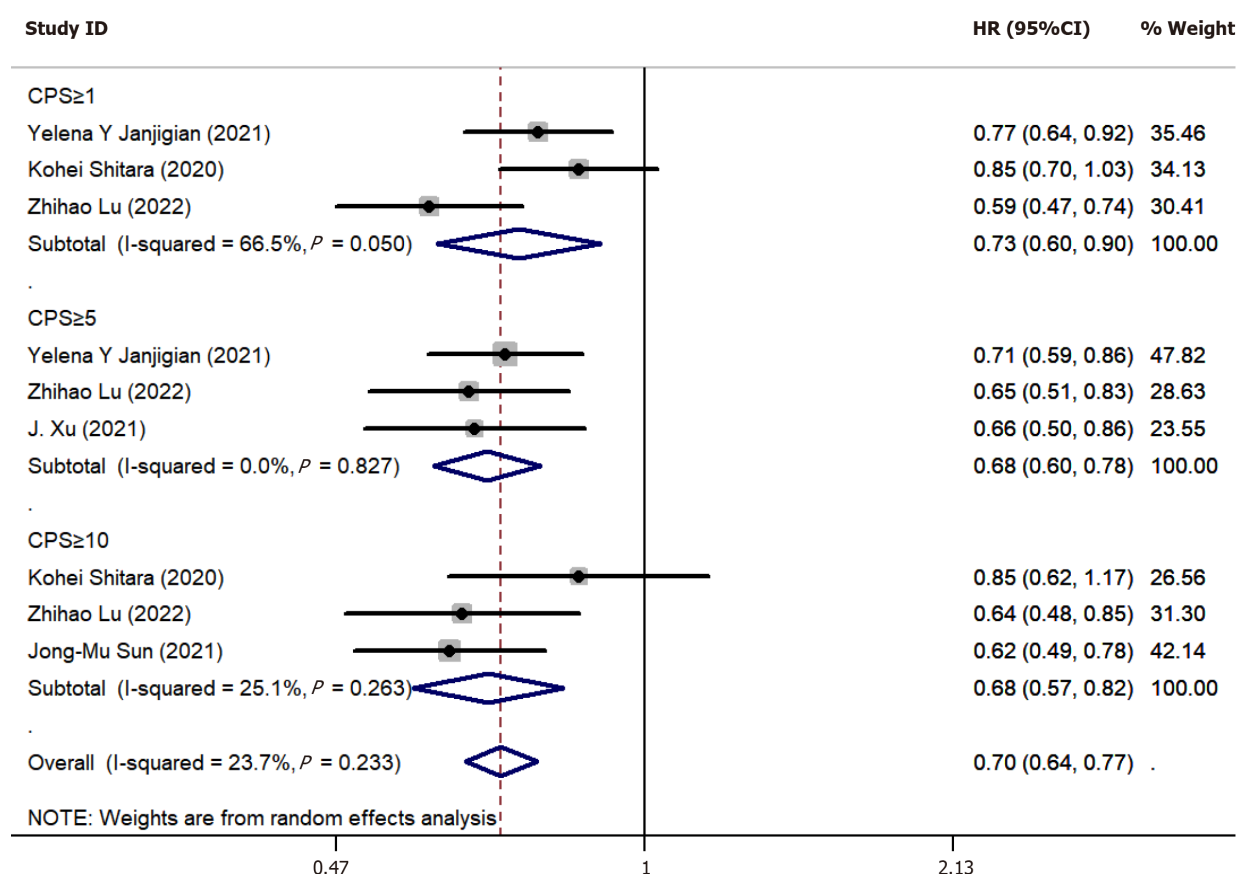
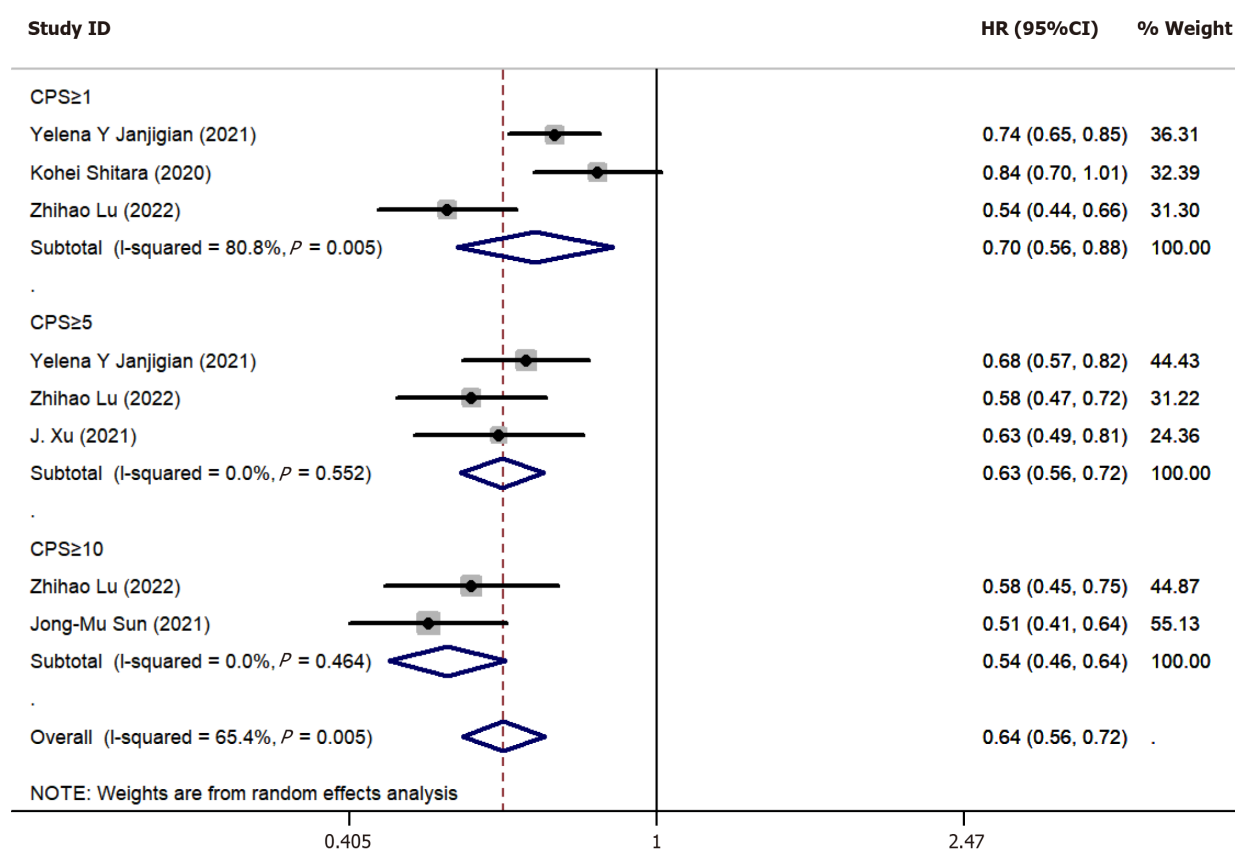


Figure 3 The forest plot of overall survival, progression-free survival, objective response rate and all grades adverse events. A: The forest plot of overall survival; B: The forest plot of progression-free survival; C: The forest plot of objective response rate; D: The forest plot of all grades adverse events. HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval.

indicated the absence of substantial publication bias in this meta-analysis.

Sensitivity analysis

The Stata sensitivity analysis (Supplementary Figure 2) revealed that the exclusion of any of the 9 articles had a minimal impact on the overall effect size. This suggested that the sensitivity of this meta-analysis was low and that the removal of a single article did not significantly alter the results. In order to further explore the source of heterogeneity of OS and PFS, we used meta-regression to analyze whether the year of publication, sample size, and tumor type were the source of heterogeneity of OS and PFS. The results of meta-regression showed that the year of publication, sample size, and tumor type were not sources of heterogeneity in OS (year of publication: $P = 0.167$; sample size: $P = 0.233$; tumor type: $P = 0.247$).

A**B**

C

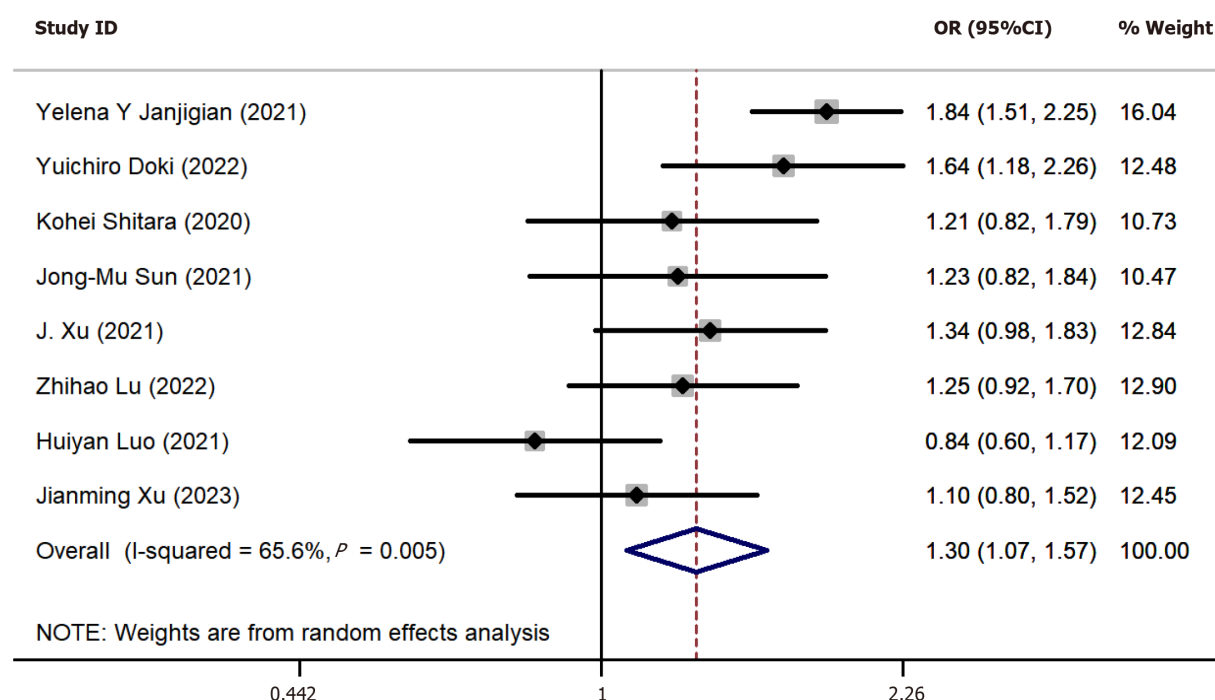


Figure 4 Subgroup analysis of overall survival and progression-free survival based on programmed death-ligand 1 combined positive score and ≥ 3 grades adverse events. A: Subgroup analysis of overall survival based on programmed death-ligand 1 (PD-L1) combined positive score (CPS); B: Subgroup analysis of progression-free survival based on PD-L1 CPS score; C: Subgroup analysis of ≥ 3 grades adverse events. HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval.

and PFS (year of publication: $P = 0.574$; sample size: $P = 0.609$; tumor type: $P = 0.914$).

DISCUSSION

The combination of ICIs with chemotherapy has emerged as a potent targeted therapy for advanced or metastatic gastrointestinal tumors. Across various studies, the utilization of a PD-1 inhibitor + chemotherapy notably enhanced both patients' OS and PFS, including the PD-1 inhibitors nivolumab[12], pembrolizumab[10], camrelizumab[13], and sintilimab[14]. Guo *et al*[19] performed an independent meta-analysis concerning PD-1 inhibitor + oxaliplatin or cisplatin-based chemotherapy. Thus far, however, there hasn't been a meta-analysis comparing the effectiveness of PD-1 inhibitors + chemotherapy and chemotherapy alone. We therefore conducted a meta-analysis to assess and contrast the efficacy and safety of PD-1 inhibitors + chemotherapy *vs* chemotherapy alone.

Several clinical trials of PD-1 inhibitors in combination with chemotherapy *vs* chemotherapy alone have been completed or are under way. In terms of efficacy, however, it remains unknown whether a PD-1 inhibitor + chemotherapy can significantly prolong patients' OS and PFS compared with chemotherapy alone. CheckMate 649[12] is a multicenter, randomized, phase 3 trial that compared nivolumab + chemotherapy *vs* chemotherapy alone as a first-line treatment for advanced gastric cancer, GEJ cancer, and oesophageal adenocarcinoma. The results revealed that nivolumab + chemotherapy substantially extended patients' OS (HR = 0.8, $P < 0.0002$) and PFS (HR = 0.8, $P < 0.0002$) in comparison to chemotherapy alone. Nevertheless, in the KEYNOTE-062 trial[10], which compared pembrolizumab + chemotherapy to chemotherapy alone, the combination of pembrolizumab + chemotherapy did not extend patients OS compared to chemotherapy alone (HR = 0.85, $P = 0.05$). Similar results were obtained in the ATTRACTION-4 trial[11] (nivolumab + chemotherapy *vs* placebo + chemotherapy) (HR = 0.90, $P = 0.26$). Our present meta-analysis of 9 clinical trials revealed that treatment with a PD-1 inhibitor + chemotherapy significantly prolonged both OS (HR = 0.76, 95%CI: 0.71-0.81) and PFS (HR = 0.68, 95%CI: 0.64-0.72) in patients with gastric cancer, GEJ cancer, or oesophageal cancer.

The ORR is the proportion of patients who respond to treatment, which is a key measure of a drug therapy's effectiveness. The results of our meta-analysis demonstrated that the PD-1 inhibitor + chemotherapy group had superior ORR to that of the chemotherapy-alone group. We also conducted an analysis of the incidence of AEs between the two treatment approaches. This revealed a heightened occurrence of AEs in patients receiving immunotherapy combined with chemotherapy compared to those undergoing chemotherapy alone. This trend was consistent whether we examined AEs of all grades (OR = 1.88, 95%CI: 1.39-2.54) or evaluated AEs rated $\geq$ grade 3 (HR = 1.30, 95%CI: 1.07-1.57). The AEs of immunotherapy are referred to as immune-related (ir)AEs. These irAEs have been documented to be generally mild and manageable, often not necessitating specific interventions. More importantly, they are noted to have minimal impact on treatment efficacy[20,21].

PD-L1 expression levels are frequently employed as predictive biomarkers to ascertain whether patients are likely to derive benefits from immunotherapy. The CPS score has been indicated to be a more effective method of assessing PD-L1 expression than the tumor proportion score (TPS)[22]. In the present meta-analysis, we therefore conducted subgroup analyses of OS and PFS based on the CPS scores for PD-L1. The outcomes demonstrated that within the subgroup with a CPS ≥ 5 or CPS ≥ 10 , patients in the immunotherapy + chemotherapy group exhibited longer OS periods. The PFS subgroup analysis revealed that the patients in the subgroup with a CPS ≥ 10 were more likely to benefit from immunotherapy + chemotherapy. Based on the results of our analysis, PD-1 inhibitor + chemotherapy can be recommended as a suitable first-line treatment for patients with PD-L1 CPS scores of ≥ 5 or ≥ 10 . This study has two limitations. First, not all of the included articles provided survival data for CPS subgroups, opening the possibility of bias in our CPS subgroup analysis. Second, the limited number of articles focused on the same tumor type precluded the possibility of conducting a subgroup analysis based on tumor type.

CONCLUSION

The outcomes of this meta-analysis illustrated that patients receiving a PD-1 inhibitor + chemotherapy experienced notably prolonged OS and PFS compared to patients treated with chemotherapy alone. The ORR and the rate of AEs were both higher in the group treated with a PD-1 inhibitor + chemotherapy than in the chemotherapy-alone group. For the subgroups with a CPS ≥ 5 or CPS ≥ 10 , the patients in the immunotherapy + chemotherapy group had longer OS and PFS. Considering both efficacy and safety, PD-1 inhibitor + chemotherapy could potentially emerge as a preferable first-line treatment option for patients diagnosed with gastric cancer, GEJ tumor, or esophageal cancer, particularly for those with a PD-L1 CPS score of ≥ 5 or ≥ 10 .

ARTICLE HIGHLIGHTS

Research background

Programmed cell death protein-1 (PD-1) inhibitor has shown effective anti-tumor immune activity by blocking the interaction of PD-1 with programmed death ligand 1 (PD-L1), and it combined with chemotherapy has been approved as a standard first- or second-line treatment option for patients with gastric cancer, gastroesophageal junction (GEJ) cancer and advanced esophageal cancer.

Research motivation

Several clinical trials of PD-1 inhibitors combined with chemotherapy *vs* chemotherapy alone have been completed or are ongoing. However, in terms of efficacy, it is controversial whether PD-1 inhibitor plus chemotherapy can significantly prolong patients' overall survival (OS) and progression-free survival (PFS) compared to chemotherapy alone.

Research objectives

To compare the efficacy and safety of PD-1 inhibitor combined with chemotherapy and chemotherapy alone, and provide treatment options for patients with advanced gastric cancer, GEJ cancer and advanced esophageal cancer.

Research methods

We searched PubMed and Embase databases for clinical trials comparing the efficacy and safety of PD-1 inhibitors combined with chemotherapy and chemotherapy alone in gastric cancer, GEJ tumors, and esophageal cancer. The effect value of OS, PFS, objective response rate and adverse events were combined using random or fixed effects models. The significance of the pooled odds ratio or hazard ratio was assessed using the Z-test. We used the χ^2 -based Q-test and the I^2 test to evaluate the heterogeneity between studies. Funnel plots were generated to assess the presence of publication bias in the outcomes. Additionally, sensitivity analyses were conducted to assess the stability of the results.

Research results

A total of 9 clinical trials were included in this study. Compared with the chemotherapy group, the PD-1 inhibitor + chemotherapy group had longer OS and PFS, and more patients achieved objective response rates. In addition, the number of adverse reactions in the combined treatment group was higher than that in the chemotherapy group alone. The results of subgroup analysis showed that compared with the subgroup of combined positive score (CPS) ≥ 1 , patients in the CPS ≥ 5 and CPS ≥ 10 subgroups were able to achieve better therapeutic outcomes with PD-1 inhibitor combined with chemotherapy.

Research conclusions

The efficacy of PD-1 inhibitor combined with chemotherapy was superior to the chemotherapy group alone in patients with gastric cancer, GEJ tumors, and esophageal cancer. Subgroups with PD-L1 CPS ≥ 5 and ≥ 10 were more likely to benefit from PD-1 inhibitor combined with chemotherapy.

Research perspectives

Our findings provide reference for the treatment of patients with advanced gastric cancer, GEJ tumors, and advanced esophageal cancer. Therefore, our next step is to conduct a randomized controlled trial of PD-1 inhibitors combined with chemotherapy for gastric cancer and GEJ tumors to further improve the management of these patients.

ACKNOWLEDGEMENTS

We would like to thank Guo-Lin Han for statistical contributions to this article.

FOOTNOTES

Co-first authors: Xiao-Min Zhang and Ting Yang.

Author contributions: Zhang XM and Yang T contributed equally to this work. Zhang XM, Yang T, and Xu YY contributed to the acquisition, analysis and interpretation of data, and manuscript drafting; Zhang XM and Yang T revised the manuscript; Li BZ, Shen W, Hu WQ, and Yan CW were involved in the drafting and critical appraisal of manuscript; Zong L participated in the study design, data interpretation, final approval of the manuscript; and all authors have given final approval to this version of the manuscript to be published.

Supported by the Wu Jieping Medical Foundation, No. 320.6750.2020-11-5; the Health Commission of Shanxi Province, No. 2020130; and the Resource and Social Security of Shanxi Province, No. 20220056.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Xiao-Min Zhang 0000-0002-2500-6471; Ting Yang 0000-0003-4935-4478; Ying-Ying Xu 0000-0002-7575-4419; Bao-Zhong Li 0000-0002-1035-4991; Wei Shen 0000-0002-4069-7397; Wen-Qing Hu 0000-0003-3364-1034; Liang Zong 0000-0003-4139-4571.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Zhao YQ

REFERENCES

- 1 **Qiu HB.** Safety and efficacy of tislelizumab plus chemotherapy for first-line treatment of advanced esophageal squamous cell carcinoma and gastric/gastroesophageal junction adenocarcinoma. *Thorac Cancer* 2020; **11**: 3419-3421 [PMID: 33043992 DOI: 10.1111/1759-7714.13690]
- 2 **Sung H,** Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
- 3 **Chen M,** Li C, Sun M, Li Y, Sun X. Recent developments in PD-1/PD-L1 blockade research for gastroesophageal malignancies. *Front Immunol* 2022; **13**: 1043517 [PMID: 36505480 DOI: 10.3389/fimmu.2022.1043517]
- 4 **Jin X,** Liu Z, Yang D, Yin K, Chang X. Recent Progress and Future Perspectives of Immunotherapy in Advanced Gastric Cancer. *Front Immunol* 2022; **13**: 948647 [PMID: 35844558 DOI: 10.3389/fimmu.2022.948647]
- 5 **Tang Q,** Chen Y, Li X, Long S, Shi Y, Yu Y, Wu W, Han L, Wang S. The role of PD-1/PD-L1 and application of immune-checkpoint inhibitors in human cancers. *Front Immunol* 2022; **13**: 964442 [PMID: 36177034 DOI: 10.3389/fimmu.2022.964442]
- 6 **Kono K,** Nakajima S, Mimura K. Current status of immune checkpoint inhibitors for gastric cancer. *Gastric Cancer* 2020; **23**: 565-578 [PMID: 32468420 DOI: 10.1007/s10120-020-01090-4]
- 7 **Yuan H,** Lu S, Shi M, Yang Z, Liu W, Ni Z, Yao X, Hua Z, Feng R, Zheng Y, Wang Z, Sah BK, Chen M, Zhu Z, He C, Li C, Zhang J, Yan C, Yan M. Sintilimab combined neoadjuvant intraperitoneal and systemic chemotherapy in gastric cancer with peritoneal metastasis. *Future Oncol* 2023; **19**: 2517-2523 [PMID: 37212686 DOI: 10.2217/fon-2022-0738]
- 8 **Tabernero J,** Shen L, Elimova E, Ku G, Liu T, Shitara K, Lin X, Boyken L, Li H, Grim J, Ajani J. HERIZON-GEA-01: Zanidatamab + chemo ± tislelizumab for 1L treatment of HER2-positive gastroesophageal adenocarcinoma. *Future Oncol* 2022; **18**: 3255-3266 [PMID: 36000541 DOI: 10.2217/fon-2022-0595]
- 9 **Shah MA,** Kennedy EB, Alarcon-Rozas AE, Alcindor T, Bartley AN, Malowany AB, Bhadkamkar NA, Deighton DC, Janjigian Y, Karipott

- A, Khan U, King DA, Klute K, Lacy J, Lee JJ, Mehta R, Mukherjee S, Nagarajan A, Park H, Saeed A, Semrad TJ, Shitara K, Smyth E, Uboha NV, Vincelli M, Wainberg Z, Rajdev L. Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline. *J Clin Oncol* 2023; **41**: 1470-1491 [PMID: 36603169 DOI: 10.1200/JCO.22.02331]
- 10 **Shitara K**, Van Cutsem E, Bang YJ, Fuchs C, Wyrwicz L, Lee KW, Kudaba I, Garrido M, Chung HC, Lee J, Castro HR, Mansoor W, Braghiroli MI, Karaseva N, Caglevic C, Villanueva L, Goekkurt E, Satake H, Enzinger P, Alsina M, Benson A, Chao J, Ko AH, Wainberg ZA, Kher U, Shah S, Kang SP, Tabernero J. 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* 2020; **6**: 1571-1580 [PMID: 32880601 DOI: 10.1001/jamaoncol.2020.3370]
- 11 **Kang YK**, Chen LT, Ryu MH, Oh DY, Oh SC, Chung HC, Lee KW, Omori T, Shitara K, Sakuramoto S, Chung IJ, Yamaguchi K, Kato K, Sym SJ, Kadowaki S, Tsuji K, Chen JS, Bai LY, Oh SY, Choda Y, Yasui H, Takeuchi K, Hirashima Y, Hagihara S, Boku N. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2022; **23**: 234-247 [PMID: 35030335 DOI: 10.1016/S1470-2045(21)00692-6]
- 12 **Janjigian YY**, Shitara K, Moehler M, Garrido M, Salman P, Shen L, Wyrwicz L, Yamaguchi K, Skoczylas T, Campos Bragagnoli A, Liu T, Schenker M, Yanez P, Tehfe M, Kowalyszyn R, Karamouzian MV, Bruges R, Zander T, Pazo-Cid R, Hitre E, Feeney K, Cleary JM, Poulart V, Cullen D, Lei M, Xiao H, Kondo K, Li M, Ajani JA. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021; **398**: 27-40 [PMID: 34102137 DOI: 10.1016/S0140-6736(21)00797-2]
- 13 **Luo H**, Lu J, Bai Y, Mao T, Wang J, Fan Q, Zhang Y, Zhao K, Chen Z, Gao S, Li J, Fu Z, Gu K, Liu Z, Wu L, Zhang X, Feng J, Niu Z, Ba Y, Zhang H, Liu Y, Zhang L, Min X, Huang J, Cheng Y, Wang D, Shen Y, Yang Q, Zou J, Xu RH; ESCORT-1st Investigators. Effect of Camrelizumab vs Placebo Added to Chemotherapy on Survival and Progression-Free Survival in Patients With Advanced or Metastatic Esophageal Squamous Cell Carcinoma: The ESCORT-1st Randomized Clinical Trial. *JAMA* 2021; **326**: 916-925 [PMID: 34519801 DOI: 10.1001/jama.2021.12836]
- 14 **Lu Z**, Wang J, Shu Y, Liu L, Kong L, Yang L, Wang B, Sun G, Ji Y, Cao G, Liu H, Cui T, Li N, Qiu W, Li G, Hou X, Luo H, Xue L, Zhang Y, Yue W, Liu Z, Wang X, Gao S, Pan Y, Galais MP, Zaanen A, Ma Z, Li H, Wang Y, Shen L; ORIENT-15 study group. Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15): multicentre, randomised, double blind, phase 3 trial. *BMJ* 2022; **377**: e068714 [PMID: 35440464 DOI: 10.1136/bmj-2021-068714]
- 15 **Xu JM**, Jiang H, Pan Y, Gu K, Cang S, Han L, Shu Y, Li J, Zhao J, Pan H, Luo S, Qin Y, Guo Q, Bai Y, Ling Y, Guo Y, Li Z, Liu Y, Wang Y, Zhou H. LBA53 Sintilimab plus chemotherapy (chemo) vs chemo as first-line treatment for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (ORIENT-16): First results of a randomized, double-blind, phase III study. *Ann Oncol* 2021; **32**: S1331 [DOI: 10.1016/j.annonc.2021.08.2133]
- 16 **Sun JM**, Shen L, Shah MA, Enzinger P, Adenis A, Doi T, Kojima T, Metges JP, Li Z, Kim SB, Cho BC, Mansoor W, Li SH, Sunpawaravong P, Maqueda MA, Goekkurt E, Hara H, Antunes L, Fountzilas C, Tsuji A, Oliden VC, Liu Q, Shah S, Bhagia P, Kato K; KEYNOTE-590 Investigators. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet* 2021; **398**: 759-771 [PMID: 34454674 DOI: 10.1016/S0140-6736(21)01234-4]
- 17 **Xu J**, Kato K, Raymond E, Hubner RA, Shu Y, Pan Y, Park SR, Ping L, Jiang Y, Zhang J, Wu X, Yao Y, Shen L, Kojima T, Gotovkin E, Ishihara R, Wyrwicz L, Van Cutsem E, Jimenez-Fonseca P, Lin CY, Wang L, Shi J, Li L, Yoon HH. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2023; **24**: 483-495 [PMID: 37080222 DOI: 10.1016/S1470-2045(23)00108-0]
- 18 **Doki Y**, Ajani JA, Kato K, Xu J, Wyrwicz L, Motoyama S, Ogata T, Kawakami H, Hsu CH, Adenis A, El Hajbi F, Di Bartolomeo M, Braghiroli MI, Holtved E, Ostioich SA, Kim HR, Ueno M, Mansoor W, Yang WC, Liu T, Bridgewater J, Makino T, Xynos I, Liu X, Lei M, Kondo K, Patel A, Gricar J, Chau I, Kitagawa Y; CheckMate 648 Trial Investigators. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. *N Engl J Med* 2022; **386**: 449-462 [PMID: 35108470 DOI: 10.1056/NEJMoa2111380]
- 19 **Guo X**, Yang B, He L, Sun Y, Song Y, Qu X. PD-1 inhibitors plus oxaliplatin or cisplatin-based chemotherapy in first-line treatments for advanced gastric cancer: A network meta-analysis. *Front Immunol* 2022; **13**: 905651 [PMID: 36003374 DOI: 10.3389/fimmu.2022.905651]
- 20 **Aggarwal S**. Adverse effects of immuno-oncology drugs-Awareness, diagnosis, and management: A literature review of immune-mediated adverse events. *Indian J Cancer* 2019; **56**: S10-S22 [PMID: 31793438 DOI: 10.4103/ijc.IJC_448_19]
- 21 **Urwyler P**, Earnshaw I, Bermudez M, Perucha E, Wu W, Ryan S, McDonald L, Karagiannis SN, Taams LS, Powell N, Cope A, Papa S. Mechanisms of checkpoint inhibition-induced adverse events. *Clin Exp Immunol* 2020; **200**: 141-154 [PMID: 31989585 DOI: 10.1111/cei.13421]
- 22 **Yamashita K**, Iwatsuki M, Harada K, Eto K, Hiyoshi Y, Ishimoto T, Nagai Y, Iwagami S, Miyamoto Y, Yoshida N, Komohara Y, Ajani JA, Baba H. Prognostic impacts of the combined positive score and the tumor proportion score for programmed death ligand-1 expression by double immunohistochemical staining in patients with advanced gastric cancer. *Gastric Cancer* 2020; **23**: 95-104 [PMID: 31451991 DOI: 10.1007/s10120-019-00999-9]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

