Int J Clin Exp Pathol 2025;18(3):96-109
www.ijcep.com /ISSN:1936-2625/IJCEP0160964

Review Article

Evaluation of the efficacy and safety of toripalimab combination therapy for treatment of advanced gastric cancer: a meta-analysis

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Received October 6, 2024; Accepted February 12, 2025; Epub March 15, 2025; Published March 30, 2025

Abstract: Background: To systematically evaluate the efficacy and safety of combination therapy with toripalimab in the treatment of advanced gastric cancer (GC). Methods: We conducted a thorough search for relevant studies in PubMed, Embase, Cochrane Library, and Web of Science. Effect estimates were computed utilizing Stata software (version 14.0) and either random or fixed effects models, as applicable. A subgroup analysis was undertaken to assess the effect of various combination therapies on overall response rate (ORR). Begg and Egger's tests were employed to assess publication bias. Results: The study consisted of 8 trials, which included 277 participants with advanced gastric cancer. The overall ORR was 41.4% (95% CI, 32.4%-50.3%), with a disease control rate (DCR) of 83.6% (95% CI, 74.6%-92.7%), a median overall survival (mOS) of 11.0 months (95% CI, 9.6-12.4), and a median progression-free survival (mPFS) of 4.2 months (95% CI, 2.5-6.0) for the combination therapy with toripalimab. Subgroup analysis revealed that the combination of toripalimab and chemotherapy achieved a greater ORR compared to the non-chemotherapy group, with ORR rates of 49.8% (95% CI, 42.2%-57.4%) and 31.9% (95% CI, 26.7%-37.1%), respectively. The combination therapy with toripalimab led to adverse events (AEs) of any grade at 94.0% of cases (95% CI, 89.5%-98.5%) and grade 3 AEs at 32.4% (95% CI, 17.8%-47.1%). The sensitivity analysis indicated that no single study affected the overall results. Conclusions: Combination therapy of toripalimab can improve clinical efficacy, although with increased but manageable toxicity. Additional clinical trials are required to assess comprehensively the efficacy and safety of alternative toripalimab regimens. The review agreement has been recorded with PROSPERO (CRD42024585696).

Keywords: Immunotherapy, toripalimab, gastric carcinoma

Introduction

Advanced gastric cancer (GC) ranks as the third most frequent cause of cancer-related mortality worldwide and is the second most lethal malignant neoplasm in China. The primary risk factors for mortality in advanced gastric cancer are extensive metastasis, compromised immunity, inadequate nutrient absorption, hemorrhage, organ failure, comorbidities, and therapeutic efficacy. More than 80% of patients are diagnosed at advanced stages, leading to a five-year survival rate of less than 20% [1, 2]. For patients with late-stage, metastatic, unresectable solid tumors of the gastric (GI) system, cytotoxic chemotherapy, with or without immune checkpoint inhibitors (ICIs), is suggested as the first-line treatment [3]. Systemic chemotherapy constitutes the primary treatment for metastatic gastric cancer (mGC), with a median overall survival (mOS) of 12 months for patients undergoing conventional chemotherapy [4]. The severity of cytotoxic chemotherapy may hinder patients from receiving second-line treatments, which are often less effective. Because the patients' health usually gets worse and they become resistant to chemotherapy after multiple treatments, we need to find chemotherapy-free regimens right away to help people with advanced gastric cancer and other gastrointestinal cancers have better outcomes.

Programmed cell death protein 1 (PD-1) antibodies, specifically nivolumab and pembroli-

https://doi.org/10.62347/GZOW5960

zumab, have shown impressive effectiveness in cancer therapy and have received approval from the U.S. Food and Drug Administration for first-line chemotherapy in GC. While patients with high PD-L1 Combined Positive Score (CPS) benefit significantly, the response rate remains low across a broader patient population [5]. Current research aims to determine the most effective combinatorial techniques for PD-1 inhibitors [6]. Tyrosine kinase inhibitors (TKIs) may enhance the efficacy of anti-PD-1 antibodies through modulation of the tumor microenvironment (TME), although the optimal combination for gastric cancer remains uncertain. Fukuoka et al. investigated the combination of regorafenib with nivolumab, revealing promising safety and anti-tumor efficacy [7]. Similarly, Japanese studies on lenvatinib combined with pembrolizumab reported an ORR of 69% and a PFS of 7.1 months, though with a high incidence of treatment-related adverse events (TRAEs) [8]. Additionally, research indicates that the immune microenvironment of HER2-positive GCs is highly inflammatory, supporting the use of HER2-targeted antibody-drug conjugates (ADCs) combined with PD-1 inhibitors, which exhibit synergistic anti-tumor effects and favorable tolerability [9, 10]. Toripalimab, an innovative anti-PD-1 antibody that targets the FG loop, is works differently from nivolumab and pembrolizumab. *In vitro* studies have shown that it promotes T cell proliferation and boosts interferon-γ production more effectively than nivolumab. Clinical studies have demonstrated a favorable safety profile of toripalimab. The objective response rate (ORR) for treating refractory cancers in the Chinese population is equivalent to that of alternative therapies, exhibiting tolerable toxicity.

Nonetheless, the adverse events linked to toripalimab combination therapy are troubling, necessitating a balance between efficacy and safety. The simultaneous administration of toripalimab alongside targeted treatments, antibody-drug conjugates, or chemotherapy may lead to systemic consequences, with an elevated risk of leukopenia being the most severe recorded adverse effect. This meta-analysis seeks to evaluate the efficacy and safety of toripalimab combination therapy for advanced gastric cancer treatment. The findings of this investigation may broaden the spectrum of clinical management alternatives.

Methods

Search strategy

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. Literature searches were done in accordance with established reporting methods, evaluations, and meta-analyses of initiatives. The PubMed, Cochrane Library, Web of Science, and Embase databases were examined from inception until August 9, 2024, to assess the efficacy and safety of treatments for advanced gastric cancer. The search keyword or medical topic keyword (MESH) terms were as follows: "Toripalimab" AND ("gastric cancer" OR "Stomach Neoplasms" OR "Gastric Neoplasms" OR "Cancer of Stomach" OR "Gastric Cancer"). The identification of other the qualified personnel for research, references in research, or related reviews was by manual review. Non-English articles were excluded from searches.

Selection criteria

The criteria for inclusion were as follows: (1) Participants: all patients diagnosed with advanced gastric cancer; (2) Intervention: Patients received toripalimab combination therapy; (3) Result: At least one clinical tumor outcome was recorded in the literature, such as ORR, disease control rate (DCR), complete response (CR), partial response (PR), median progression-free survival (mPFS), and adverse events (AEs); (4) The Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 was used to evaluate the tumor response. According to the RECIST 1.1 standard, the diameter changes of tumor lesions are measured by imaging methods before and after treatment, and the therapeutic effect is evaluated by combining clinical symptoms and laboratory test results. According to the magnitude of diameter changes in tumor lesions, therapeutic efficacy is divided into four levels: complete resolution, partial resolution, disease stability, and progressive disease. The Common Terminology Criteria for Adverse Events (CTCAE) standard was used to evaluate the incidence rate and severity of toxic effects; (5) Research: Prospective interventional research, retrospective analyses, or randomized controlled trials. The exclusion criteria were: (1) pathologic research, animal experiments, case reports, reviews, letters, com-

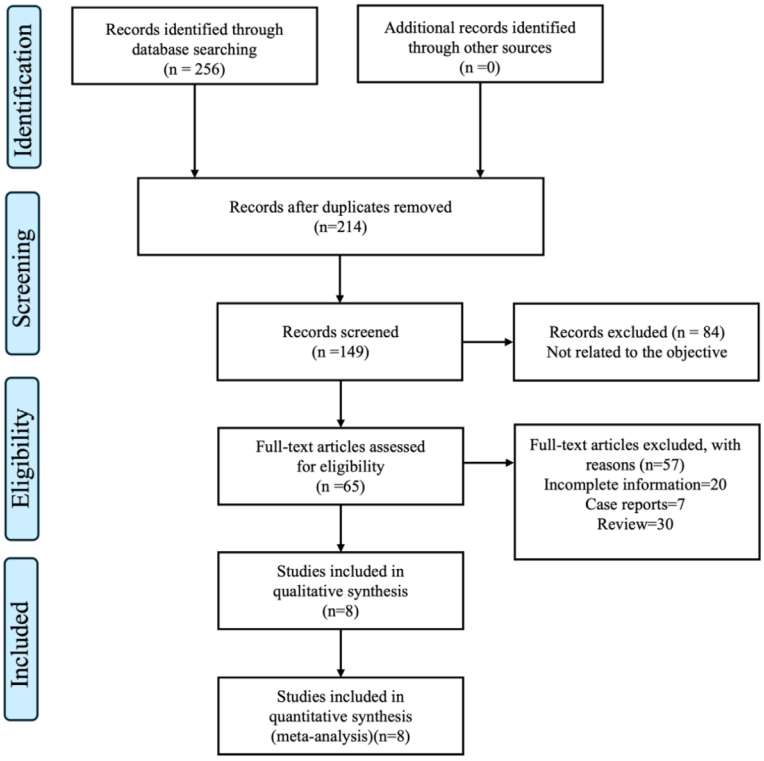

Figure 1. Flow diagram of the meta-analysis for the inclusion/exclusion of studies.

ments, and editorials; (2) literature in languages other than English or with inadequate data; (3) absence of original literature.

Two researchers independently evaluated the eligibility of an article based on inclusion and exclusion criteria. With the support of the third researcher, all inconsistencies were resolved.

Data extraction and quality assessment

Two investigators collected data from all included studies independently and evaluated the research's quality. The extracted data consisted of the author's name, publication year, study type, sample size, intervention, and reported results. Clinical and safety results were evaluated using ORR, DCR, mPFS, mOS, AEs, and the presence of grade 3 or higher AEs.

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included trials.

Statistical analysis

This meta-analysis was conducted using STATA 14 software (StataCorp LP, College Station, TX, United States) to analyze the data. Heterogeneity among studies was assessed with the chi-square test and I^2 statistic, with p values < 0.1 denoting significant differences. In cases where there was significant variability ($P < 0.1$ and $I^2 > 50\%$), the analysis used a random effects approach. On the other hand, for scenarios with lower variability, a fixed-effects approach was chosen. Furthermore, sensitivity analyses were performed to evaluate the robustness and reliability of the findings. The possibility of publication bias was assessed using Begg's and Egger's tests.

Ethics approval and consent to participate

This meta-analysis was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the participants of all included studies, and the study was approved by their respective institutional ethics committees. Since we used previously published data, no additional informed consent was needed.

Results

Study selection

The preliminary search across four databases: PubMed (n = 18), Embase (n = 214), Cochrane Library (n = 7), and Web of Science (n = 17) - yielded 256 pertinent published studies. After removing duplicate papers and reviewing titles and abstracts, 214 research papers were retained. A thorough review of the full-text of papers resulted in the exclusion of 20 studies due to a lack of full text, insufficient sample sizes, or a focus on non-chemotherapeutic drugs. A total of eight studies, encompassing 277 patients, met the inclusion criteria and were included in this meta-analysis [11-18]. **Figure 1** depicts the selection technique, and **Table 1** summarizes the details of each study.

Quality assessment

The quality of eight studies was evaluated using the NOS, which assesses research through three domains with eight specific criteria in-

Table 1. Characteristics of studies included in the meta-analysis

Study, Year	Study type	Sample size	Combination therapy	Intervention	Endpoints
Panpan Zhang 2024	Phase II	20	Targeted drug	Toripalimab plus surufatinib	ORR, DCR, mOS, mPFS, AEs
Yakun Wang 2024	Phase I	30	ADCs	Toripalimab plus RC48 dosages	ORR, DCR, mOS, mPFS, AEs
Man Jiang 2022	Single-armed	62	Targeted drug	Toripalimab plus anlotinib	ORR, DCR, mOS, mPFS, AEs
Qing Wei 2024	Phase II	25	Targeted drug	Toripalimab plus apatinib	ORR, DCR, mOS, mPFS, AEs
Shuqiang Yuan 2024	Phase II	54	Chemotherapy	Toripalimab plus SOX/XELOX	ORR, AEs
Mengrui 2024	Single-armed	17	Targeted drug, Chemotherapy	Toripalimab plus fruquintinib plus SOX	ORR, DCR
F. Wang 2019	Phase II	18	Chemotherapy	Toripalimab plus XELOX	ORR, DCR, AEs
Hongli Li 2024	Phase II	51	Chemotherapy	Toripalimab plus FLOT	ORR

ADCs, antibody-drug conjugates; ORR, objective response rate; DCR, disease control rate; mOS, median overall survival; mPFS, median progression-free survival; AEs, adverse events.

Table 2. Quality assessment of included studies Newcastle-Ottawa Scale (NOS) for non-randomized studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	TOTAL
Panpan Zhang 2024	1	0	1	1	0	1	0	1	5
Yakun Wang 2024	1	0	1	1	0	1	0	1	5
Man Jiang 2022	1	0	1	1	0	1	0	1	5
Qing Wei 2024	1	0	1	1	0	1	0	1	5
Shuqiang Yuan 2024	1	0	1	1	0	1	0	1	5
Mengrui 2024	1	0	1	1	0	1	0	1	5
F. Wang 2019	1	0	1	1	0	1	0	1	5
Hongli Li 2024	1	0	1	1	0	1	0	1	5

cluding: selection of study groups, comparability of groups, and ascertainment of outcomes for cohort studies or exposures for case-control studies. The specifics of these quality assessments are shown in **Table 2**.

NOS for non-randomized studies

The NOS comprises the following eight items (Q1 to Q8): Q1, representative of the exposed cohort; Q2, representative of the nonexposed cohort; Q3, ascertainment of exposure; Q4, representative of the presence of the outcome of interest at the start of the study; Q5, representative of the cohorts based on the design or analysis; Q6, representative of the cohort assessment; Q7, duration for outcomes to occur; Q8, adequacy of follow-up of cohorts.

Tumor response

All trials incorporated in this analysis assessed the efficacy of toripalimab combination therapy for the treatment of GC. The measured ORR in these studies exhibited considerable variability, ranging from 32.4% to 50.3%. Due to considerable heterogeneity among the studies (I^2 = 66.6%, P = 0.00), a random-effects model was employed for the meta-analysis. The analysis demonstrated a combined ORR of 41.4% (95% CI: 32.4%-50.3%) (**Figure 2**).

According to different stratifications of combination therapy, the ORR of patients receiving combined non-chemotherapy therapy was 31.9% (95% CI, 26.7%-37.1%, I^2 = 7.5%, P = 0.36) (**Figure 3A**). The ORR of patients receiving combined chemotherapy was 49.8% (95% CI, 42.2%-57.4%, I^2 = 8.0%, P = 0.36) (**Figure 3B**). The working hypothesis was that the heterogeneity was caused by the inconsistency of different combination therapy methods. Therefore, meta-regression analysis was chosen to determine whether the factors contributing to heterogeneity were different combination therapy methods. The results showed that the p of regression variables for different combination therapy methods was 0.022, indicating that different combination therapy methods were the main source of heterogeneity.

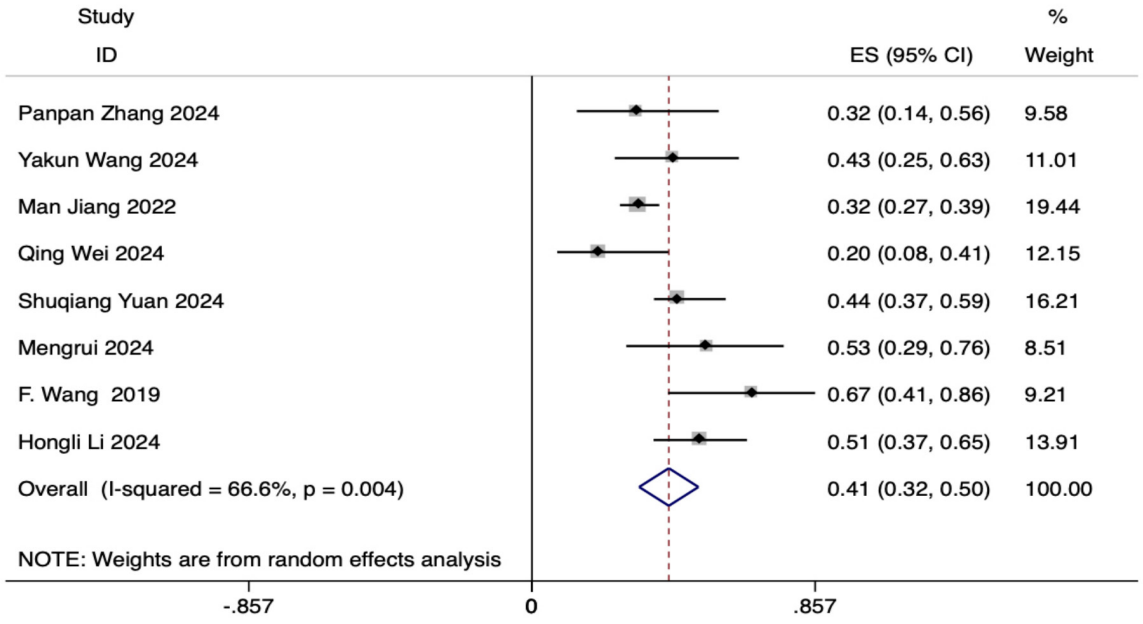

Figure 2. Forest plot of the pooled ORR. ORR, objective response rate.

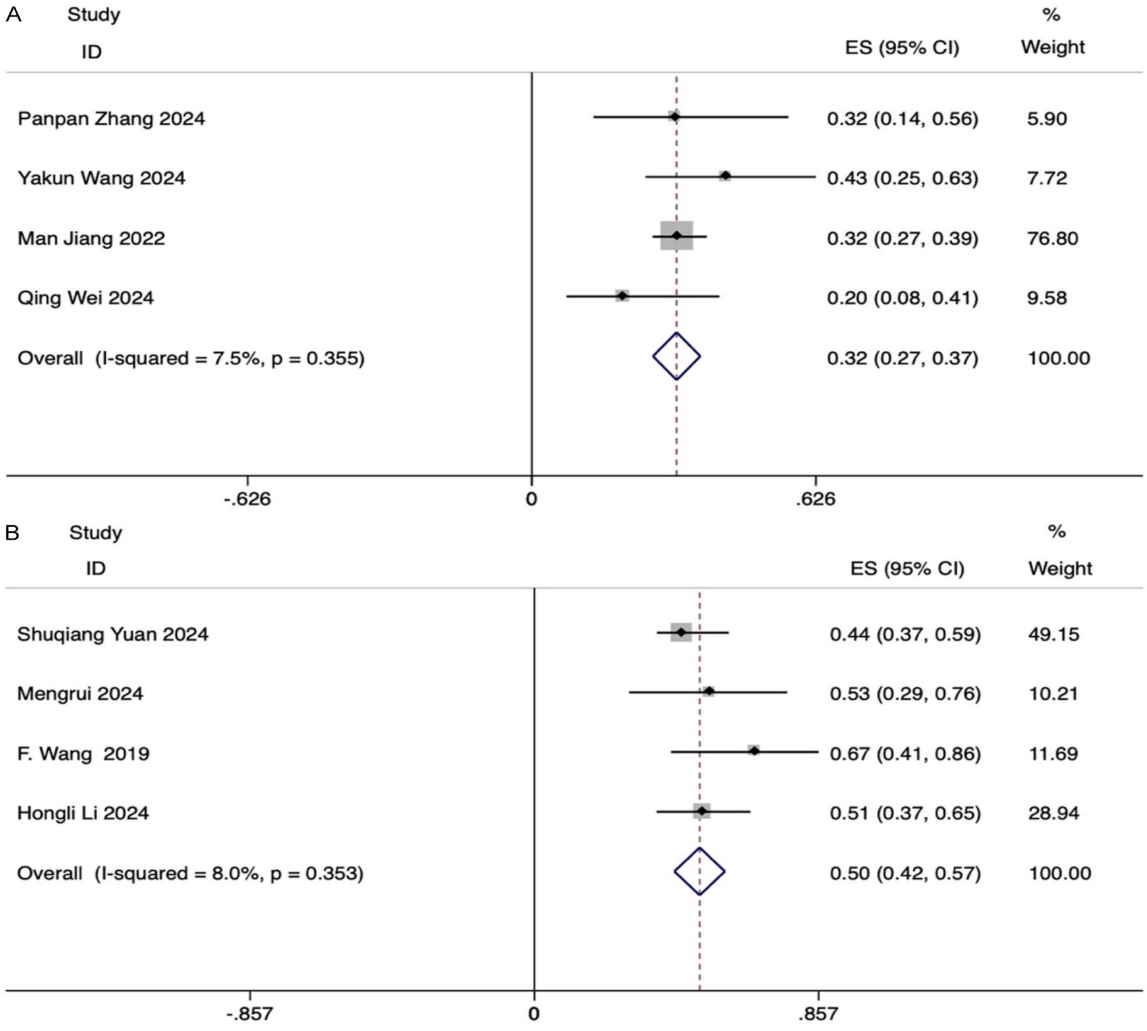

Figure 3. Forest plot of the pooled ORR. A. ORR of non-chemotherapy subgroups; B. ORR of chemotherapy subgroups. ORR, objective response rate.

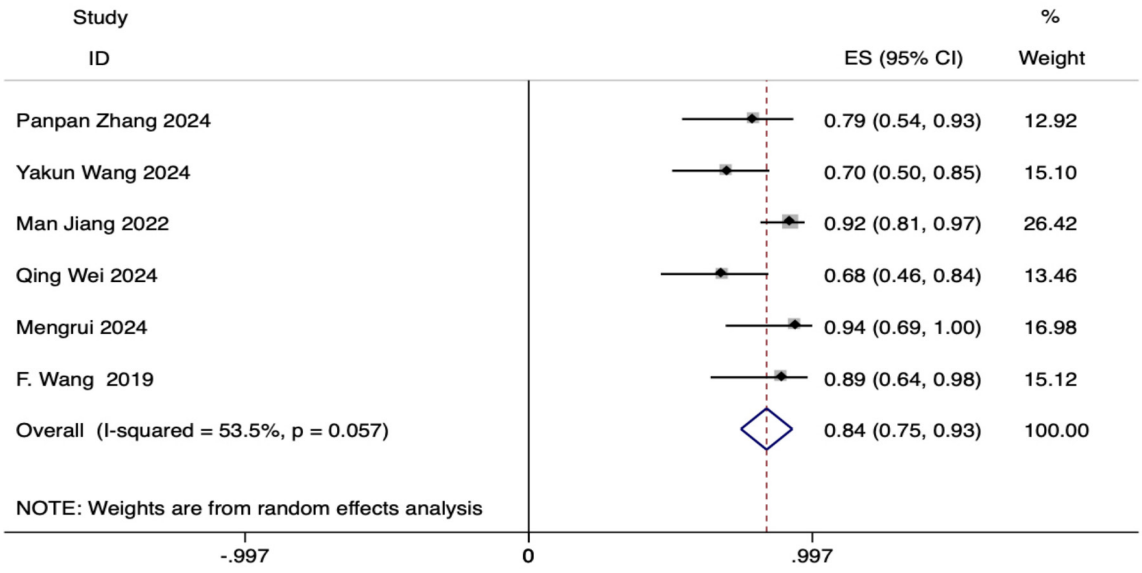

Figure 4. Forest plot of the pooled DCR. DCR, disease control rate.

The analysis revealed a combined DCR 83.6% (95% CI, 74.6%-92.7%, I^2 = 53.5%, *P* = 0.06) (**Figure 4**).

Survival

After comprehensive analysis of 4 studies, mPFS and mOS were evaluated. Heterogeneity testing of mPFS (I^2 = 83.8%, *P* = 0.00) and mOS (I^2 = 12.6%, *P* = 0.33) revealed moderate heterogeneity between studies. Therefore, a random effects model was used for meta-analysis, and the results showed that the mPFS was 4.2 (95% CI, 2.5-6.0, **Figure 5A**), and mOS was 11.0 (95% CI, 9.6-12.4, **Figure 5B**) for toripalimab combination therapy.

Toxicities

The AEs associated with toripalimab combination therapy for advanced GC at all levels are analyzed and summarized in **Table 3**; **Figure 6A**. Most patients reported grade 1-2 AEs, which were generally well tolerated at 94.0% (95% CI, 89.5-98.5%, I^2 = 0.0%, *P* = 0.57). The analysis identified the three most common AEs as Leukopenia, Pruritus, and Hypertension, with incidence rates of 37.3% (95% CI, 20.3-53.4%), 30.3% (95% CI, 22.3-38.3%), and 29.8% (95% CI, 0.0%-71.0%), respectively. Importantly, the incidence of grade III or higher adverse events was significantly lower at 32.4% (95% CI, 17.8%-47.1%, I^2 = 84.1%, *P* = 0.00) (**Figure 6B**). A very small number of cases exceeded 10%. Specifically, the incidence rates of the most common grade III or higher adverse events (i.e. neutropenia, thrombocytopenia, and fatty change) were only 13.7% (95% CI, 1.7%-25.7%), 12.9% (95% CI: 4.0%-25.4%), and 8.9% (95% CI, 3.3%-20.3%), respectively, as shown in **Table 3**. There was no statistical difference between AEs by subgroup analysis (**Table 4**).

Sensitivity analysis

Sensitivity analysis was done by systematically excluding one study at a time to evaluate its effect on the overall results. The analytical results demonstrate that the summary conclusions and their 95% confidence intervals were mostly unaffected, irrespective of the study eliminated. This confirmed the overall credibility of the meta-analysis results presented in **Figure 7**.

Publication bias

Egger and Begg's tests were employed to evaluate potential publication biases, hence ensur-

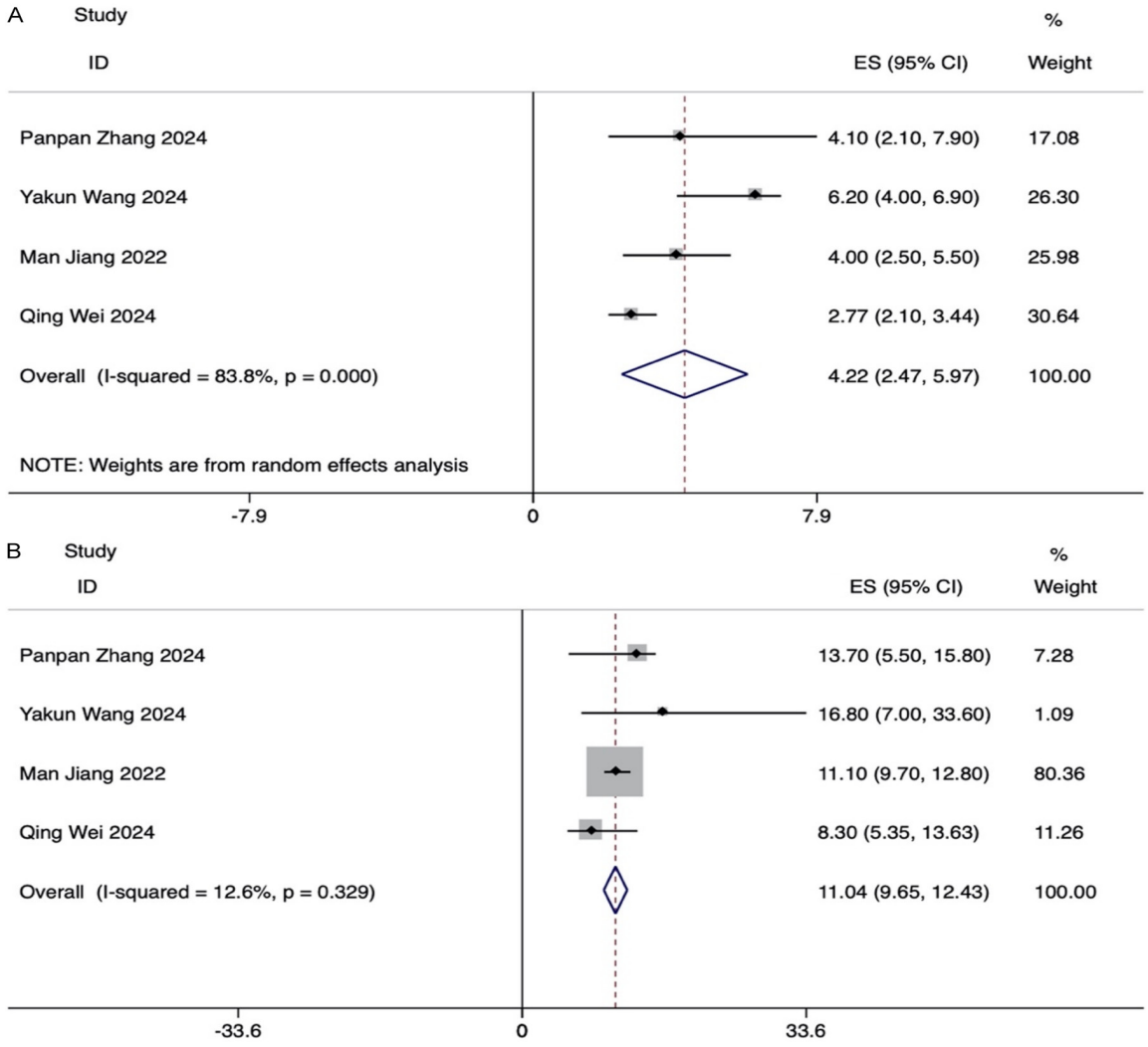

Figure 5. Forest plot of the pooled mPFS and mOS. A. mPFS; B. mOS. mPFS, median progression-free survival; mOS, median overall survival.

Table 3. Adverse events of included studies

Event	All grade		≥ Grade III	
	ES, % (95 CI)	I^2, %	ES, % (95 CI)	I^2, %
Leukopenia	37.3	89.1	6.2	54.3
Pruritus	30.3	3.5	0.0	0.0
Hypertension	29.8	97.6	2.2	0.0
Proteinuria	29.7	83.7	6.2	0.0
Thrombocytopenia	27.2	91.0	12.9	71.6
Nausea	26.1	73.1	0.0	0.0
ALT increased	23.7	92.0	3.6	0.0
Neutropenia	24.4	95.8	13.7	81.1
Thyroid dysfunction	19.4	0.0	0.0	0.0
Fatigue	18.9	90.1	8.9	0.0
Diarrhea	15.9	0.0	3.5	0.0
Decreased appetite	14.9	82.4	0.0	0.0

Vomiting	12.9	50.0	0.0	0.0
Constipation	12.9	84.5	0.0	0.0
Blood bilirubin increased	11.2	64.7	2.2	0.0
Pneumonia	10.2	89.3	0.0	0.0
Pain	8.4	40.7	0.0	0.0
AST increased	6.1	54.6	2.4	0.0
Numbness in the hands and feet	2.9	45.2	0.0	0.0
All	94.0	0.0	32.4	84.1

AEs, adverse events; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

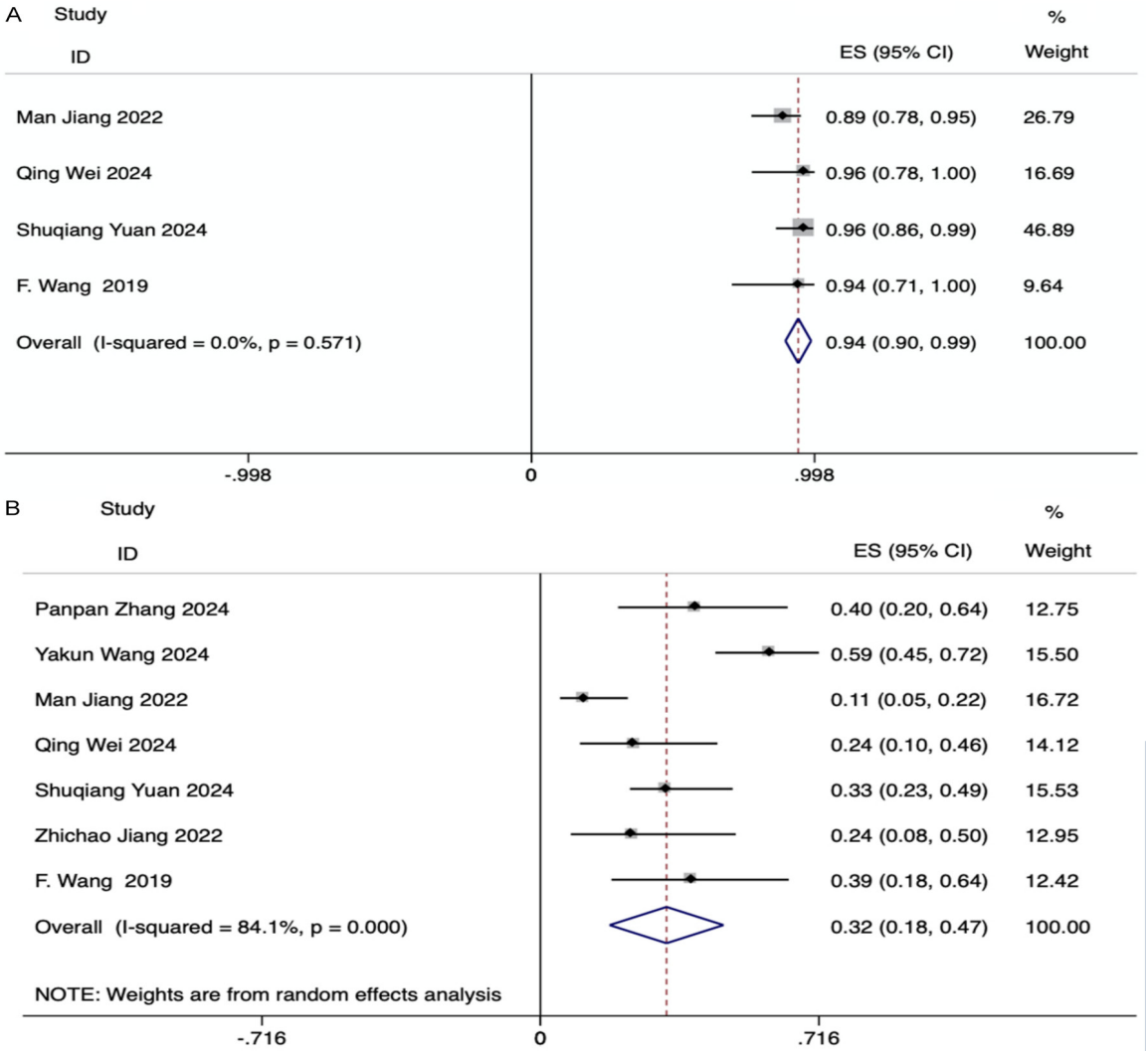

Figure 6. Forest plot for AEs. A. Combined incidence of all-grade AEs. B. Combined incidence of grade 3 and higher AEs. AEs, adverse events.

ing the robustness of the meta-analysis results. The test results are fundamentally aligned with the overall outcomes. However, it is worth noting that there were indications of publication bias in AEs when it comes to safety considerations. The evaluation results showed that for the RECIST 1.1 standard, there were ORR (Egger's test P = 0.54, Begg's test P = 0.36), DCR (Egger's test P = 0.13, Begg's test P = 0.06), mPFS (Egger's test P = 0.22, Begg's test P = 1.0), mOS (Egger's test P = 0.84, Begger's test P = 0.73), AEs (Egger's test P = 0.85,

Table 4. AEs for subgroups and CheckMate 459

AEs	All grade ES, % (95 CI)			*p*
	non-Chemotherapy	Chemotherapy	Neosummit-01	
Fatigue	24.6	1.6	NA	0.87
Numbness in the hands and feet	2.5	12.7	1.9	0.93
Pruritus	31.8	22.2	NA	0.45
Leukopenia	33.8	47.0	50.0	0.45
Neutropenia	24.4	52.5	57.4	0.34
Thrombocytopenia	16.6	40.7	57.4	0.20
Proteinuria	32.2	22.2	NA	0.80
Nausea	20.1	35.5	22.2	0.73
Pain	12.1	7.0	5.6	0.55
Diarrhea	15.0	17.2	14.8	0.76
Vomiting	9.7	26.2	18.5	0.24
Constipation	18.7	6.4	1.8	0.29
ALT increased	25.4	16.7	NA	0.97
Decreased appetite	17.8	13.5	3.7	0.51
All	94.0	94.4	96.2	0.40

AEs, adverse events; ALT, Alanine Aminotransferase.

Begg's test $P = 0.73$), and AEs of grade 3 or above (Egger's test $P = 0.15$, Begg's test $P = 1.0$). The statistical significance of Egger's test ($P > 0.05$) and Begg's test ($P > 0.05$) confirmed this.

Discussion

Recent progress in tumor immunology has enabled the development of immunotherapy as a new treatment approach for gastric cancer. Despite the disappointing outcomes of two pivotal phase III clinical trials - Nivolumab's Attraction-5 and Pembrolizumab's Keynote-585 - in the perioperative setting of gastric cancer, which has raised concerns about the future of immunotherapy, numerous studies have shown that the combination of immunotherapy with chemotherapy and targeted therapy in neoadjuvant treatment can significantly improve response rates and extend patient survival.

The MAGIC and FNCLCC studies have confirmed that perioperative chemotherapy improves the prognosis of gastric cancer, with the neoadjuvant chemotherapy group showing significantly higher R0 resection rates and 5-year survival rates compared to the surgery-only group [19, 20]. Further optimization in the FLOT4 study led to a significant increase in the pCR rate to 16% and improved R0 resection rates compared to the ECF regimen [21]. However, the JCOG0501 study did not demonstrate additional benefits of neoadjuvant therapy on the 3-year survival rate [22]. During the 2019 ESMO meeting, the RESOLVE and PRODIGY studies from South Korea demonstrated the beneficial effects of neoadjuvant chemotherapy on patients with LAGC [10, 23].

For HER2-positive locally advanced GC, trastuzumab combined with chemotherapy has become the standard treatment. However, resistance is a major issue, with about 70% of patients developing resistance or recurrence within one year [24, 25]. To address this challenge, the combination of cetuximab with the XELOX regimen in neoadjuvant therapy has shown promising results. Phase II clinical studies reported a pCR rate of 31.3%, an MPR rate of 56.3%, and good tolerability [26]. The Gastric Cancer Immune Consensus 2024 advises that for resectable stage III-IVa HER2-positive gastric and esophagogastric junction tumors, neoadjuvant immunotherapy in conjunction with chemotherapy and HER2-targeted therapy may be contemplated within a clinical research context [27]. With ongoing studies, this extensive treatment approach is anticipated to yield prolonged survival and enhanced quality of life for a greater number of HER2-positive gastric cancer patients.

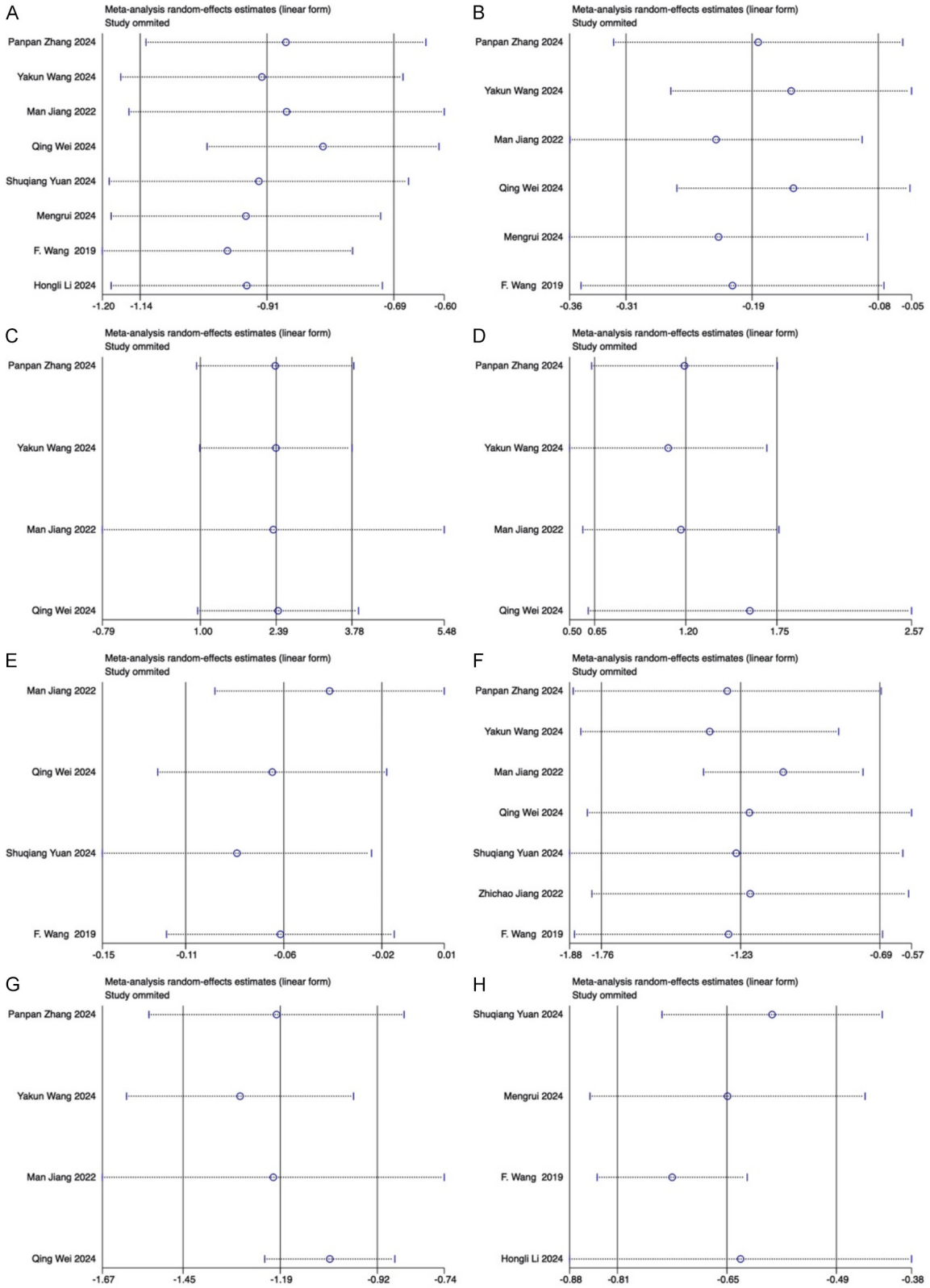

Figure 7. The results of sensitivity analysis. A. ORR; B. DCR; C. mOS; D. mPFS; E. Occurrence of AEs of all grades; F. Prevalence of AEs graded 3 or higher in severity; G. ORR of non-chemotherapy subgroup; H. ORR of chemotherapy subgroup. ORR, objective response rate; DCR, disease control rate; mOS, median overall survival; mPFS, median progression-free survival; AEs, adverse events.

This study conducted a single-arm meta-analysis to evaluate the efficacy and safety of immune checkpoint inhibitors combined with radiotherapy for treating advanced gastric cancer. We focused on assessing the efficacy and safety of toripalimab combination therapy by consolidating data from eight studies, including 277 participants. The findings indicated that the combination therapy exhibited notable efficacy, with an ORR of 41.4% (95% CI, 32.4%-50.3%) and a DCR of 83.6% (95% CI: 74.6%-92.7%). The mPFS of patients was 4.2 months (95% CI: 2.5-6.0), while the mOS was 11.0 months (95% CI: 9.6-12.4). These data further validate the effectiveness of immune checkpoint inhibitors in combination with radiotherapy for the treatment of advanced gastric cancer.

These research results clearly demonstrated the significant efficacy improvement of combination therapy in advanced GC compared to toripalimab monotherapy. Specifically, the CT5 study (NCT02915432) served as a reference for the first-line treatment of toripalimab monotherapy [14], with an ORR of only 12.1%, DCR of 39.7%, mPFS and mOS of 1.9 months and 4.8 months, respectively. In contrast, our data indicate that combination therapy can provide a higher overall response rate (41.4%) and increased longevity, particularly with a median overall survival of 11.0 months. The examination of these results highlights the substantial synergistic effects that may arise when toripalimab is used with targeted, immunological, or antibody-drug conjugate therapy. This combinatorial method improves therapy effectiveness and significantly enhances patients' quality of life.

The improved efficacy of combination therapies can be attributed to chemotherapy drugs, such as allicin and coumarin, which induce immunogenic cell death, increase tumor antigenicity, eliminate immunosuppressive cells, and enhance effector cell function [28]. PD-1/PD-L1 inhibitors combined with chemotherapy have become a preferred treatment for various cancers, and ongoing clinical trials are investigating their efficacy and safety [29]. While this combination has proven effective for some cancers, it is not universally applicable to all solid tumors, and further research is required to determine the optimal combinations and underlying mechanisms.

Anti-angiogenic medicines, such as anlotinib, have shown significant success in modifying the tumor microenvironment (TME) and enhancing the efficiency of immunotherapy. These drugs improve the tumor microenvironment by promoting the infiltration of immune cells, including CD8+ and CD3+ T lymphocytes, and may aid in overcoming resistance to PD-1 therapy [7, 30-32]. Research indicates that anlotinib can increase the phosphorylation of STAT1/STAT3, a vital mechanism in PD-L1 synthesis, hence intensifying the inflammatory response and immune cell infiltration in tumors. This mechanism transforms "cold" tumors into "hot" tumors, hence improving their susceptibility to immunotherapy and broadening the therapeutic scope of anti-PD-L1 antibody.

Our thorough analysis revealed substantial differences in the efficacy of several combination therapy regimens. Relative to the 12.1% ORR documented in the CT5 study (NCT02915432), the non-chemotherapy combination cohort had a 31.9% improvement in ORR, whereas the chemotherapy combination cohort revealed a significant 49.8% increase, exceeding the former group. The strong efficacy of toripalimab alongside chemotherapy for advanced gastric cancer suggests that the combined approach of chemotherapy and immunotherapy exceeds the effectiveness of antibody-drug conjugates or targeted therapies alone. This advantage presumably arises from the synergistic interplay between chemotherapy and immunotherapy, in which chemotherapy not only directly inhibits tumors but also enhances the efficacy of immunotherapy by stimulating systemic immune responses. This comprehensive approach offers an improved treatment option.

Toripalimab has demonstrated an outstanding balance of efficacy and safety in combination therapy for advanced gastric cancer. The comparative analysis in this study revealed that in the Neosummit-01 trial, there was no statistically significant difference in the occurrence of adverse events between the non-chemotherapy and chemotherapy combination regimens relative to the toripalimab combined chemotherapy group ($P > 0.05$). This finding demonstrates that, despite the complex pharmaceutical combinations employed in combination therapy, it does not increase toxicity concerns for patients and maintains a safety profile akin

to monotherapy. Consequently, the combination therapy with toripalimab enhances efficacy while preserving a favorable safety profile.

Despite the strong safety profile of toripalimab combination therapy in advanced gastric cancer, additional optimization of the immunotherapy regimen is essential. The effects of different combination drugs on efficacy and toxicity are not well understood, highlighting the need for standardized and thorough assessment of treatment procedures. Furthermore, more investigation is required to determine the optimal timing, sequencing, and the existence of a therapeutic window for combination therapy. Future research should focus on the design and thorough assessment of various pharmaceutical administration systems to enhance treatment programs, improve efficacy, reduce toxicity, and improve outcomes for advanced gastric cancer.

Some of the findings of our study should be approached with caution. Although there is no substantial difference in adverse events between combination therapy and monotherapy, this precludes making conclusive determinations regarding safety. The study is constrained by factors such as sample size, follow-up duration, and design heterogeneity, which may have compromised the quality and consistency of the evidence and led to biased results. Furthermore, publication bias may have inflated the perceived treatment advantage, underscoring the need for further rigorous research to validate these results.

Conclusions

Combined therapy with toripalimab has shown promising outcomes in advanced gastric cancer, including notable ORR, extended mOS and mPFS, and acceptable safety profiles. Subgroup analysis indicated that toripalimab in conjunction with chemotherapy demonstrated superior efficacy relative to targeted therapies or ADCs. To improve the therapy methodology, additional investigation is necessary through comprehensive, rigorously designed prospective clinical research.

Disclosure of conflict of interest

None.

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