Evaluation of immune checkpoint inhibitors for colorectal cancer: A network meta-analysis

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Abstract. Colorectal cancer (CRC) is challenging to treat due to its high metastatic rate. Recent strategies have focused on combining immune checkpoint inhibitors (ICIs) with other treatments. The aim of the present study was to conduct a network meta-analysis of randomized controlled trials (RCTs) to assess the efficacy and adverse effects of different ICI treatments for CRC. A literature search for RCTs was conducted using PubMed, the Cochrane Library, Embase, ClinicalTrials. gov and Web of Science databases, covering the period from the inception of each database until April 2024. A total of 12 RCTs involving 2,050 participants were selected for inclusion in the analysis. The network meta-analysis employed the MetaInsight tool to assess multiple endpoints. The criteria for study selection were based on the Population, Intervention, Comparison, Outcome and Studies framework as follows: i) Population, patients with CRC; ii) intervention, studies using ICI to treat CRC; iii) comparison, active comparators, including placebo; iv) outcome, overall survival, progression-free survival, objective response rate and adverse events; and v) study design, RCTs. The results of the analysis revealed that programmed cell death-ligand 1 (PD-L1) inhibitors significantly improved

overall survival time [mean difference (MD), 2.28 months; 95% confidence interval (CI), 0.44 to 4.11], while programmed cell death protein 1 (PD-1) inhibitors exhibited a superior progression-free survival time (MD, 4.79 months; 95% CI, 3.18 to 6.40) compared with active comparators. However, none of the ICI treatments had significant differences in odds ratios for the objective response rate and adverse events compared with active comparators. These findings indicate that treatment with PD-L1 and PD-1 inhibitors improved the overall survival time and delayed disease progression in patients with CRC. These findings offer valuable insights for future research aimed at improving CRC patient outcomes.

Introduction

Colorectal cancer (CRC) ranks globally as the third most frequently diagnosed form of cancer and second in terms of mortality (1). Countries with high socioeconomic status report a high incidence of CRC, and the incidence of CRC is expected to double in less-developed countries over the next decade (2). Approximately 20% of patients with CRC already have metastases at the time of diagnosis, and an additional 25% with localized disease subsequently develop metastases, primarily in the liver (3). The selection of first-line treatment is often guided by the molecular profile and specific biomarkers associated with the tumor (4). Local treatments for CRC metastasis include surgery, radiation and trans-arterial chemoembolization. Despite recent advancements in treatment methodologies, the progression-free survival time for most patients with stage IV CRC remains at <1 year (5).

Immune checkpoint inhibitors (ICIs) are a class of drugs used to enhance the immune response against cancer cells. These inhibitors function by blocking proteins such as programmed cell death protein-1 (PD-1), programmed cell death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which would otherwise inhibit the immune system

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from attacking cancer cells. ICI therapy has demonstrated promising outcomes in various types of cancer, including melanoma and lung cancer (6). Studies have shown that patients with metastatic CRC and high microsatellite instability or deficient DNA mismatch repair respond well to PD-1 blockade immunotherapy. Phase II trials have reported clinical benefits in these patients when treated with nivolumab and pembrolizumab, which are both PD-1 ICIs (4). Since 2017, ICIs such as pembrolizumab, nivolumab and ipilimumab have been approved by the U.S. Food and Drug Administration for use in the treatment of CRC (7). However, the overall efficacy of ICIs remains largely unclear, despite the abundance of relevant trials.

To date, only one meta-analysis, involving three randomized controlled trials (RCTs), has revealed the limited efficacy of ICIs in the treatment of advanced or metastatic CRC (5). Additionally, there is a notable absence of RCTs in which various classes of ICIs are directly compared. Therefore, the present study aimed to evaluate the efficacy and treatment-associated adverse effects of ICIs to identify their potential benefits for patients with CRC using a network meta-analysis.

Materials and methods

General guidelines for the study. The present study was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for network meta-analysis (8). The study was registered in the International Platform of Registered Systematic Review and Meta-analysis protocols (INPLASY) database (registration no. INPLASY202440067).

Data extraction. The studies were independently screened by two authors, who also assessed the risk of bias and extracted the necessary data from the articles. Any discrepancies were resolved with the involvement of a third author. If the studies lacked sufficient detail, the authors of the study were contacted to obtain the original data. Data extraction, conversion and the merging of results were carried out following the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions and relevant medical literature (9-12).

Search strategy. A comprehensive search for RCTs on CRC was conducted using several databases, namely PubMed (https://pubmed.ncbi.nlm.nih.gov/), the Cochrane Library (https://www.cochranelibrary.com/), Embase (https://www.embase.com/), ClinicalTrials.gov (https://clinicaltrials.gov/) and Web of Science (https://clarivate.com/zh-hant/solutions/web-of-science/) databases. The search covered the period from the inception of each database to April 2024, with no restrictions on the starting date. Additionally, all available original studies and reviews were manually searched. The search key words comprised 'colorectal tumor', 'colorectal neoplasm', 'colon cancer', 'rectum cancer', 'PD-1', 'PD-L1', 'CTLA-4' and 'immune checkpoint inhibitor' (Table SI). No language restrictions were imposed. The search was conducted independently by the two authors, and any differences were resolved by mutual conversation and consensus.

Selection criteria. The Population, Intervention, Comparison, Outcome and Studies framework was used to define the selection criteria, which comprised the following: i) Human participants diagnosed with CRC; ii) studies using ICIs to treat CRC; iii) active comparator, including placebo; iv) overall survival, progression-free survival, objective response rate and adverse events; and v) RCT, respectively.

The inclusion criteria for the selected studies were: i) RCT, ii) involvement of patients with CRC and iii) at least one treatment group received any ICI. Conference abstracts and data available at clinicaltrials.gov regarding eligible RCTs were also included. The exclusion criteria were as follows: i) Lack of a fully documented cohort consisting exclusively of patients with CRC in the study; ii) not including any efficacy outcomes for overall survival, progression-free survival or objective response rate; and iii) studies were duplicates or involved participant subsets that were in previously included studies. Additionally, treatment arms featuring the same combination of regimens but varying dose intervals were consolidated and analyzed as a single arm before proceeding to subsequent analyses.

Methodological quality appraisal. The revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (13) was used to evaluate the methodological quality of the included studies. This tool was used to evaluate six key elements of study quality: method of randomization, adherence to the intervention, outcome measurement, incomplete outcome data, selective reporting and overall risk of bias.

Outcomes. The primary outcomes were as follows: i) overall survival time, defined as the duration in months from the initial diagnosis of CRC to the latest point at which a patient was still alive; and ii) progression-free survival time, defined as the period in months during medical treatment when a patient showed no signs of CRC progression. Secondary outcomes comprised the following: i) objective response rate, defined as the proportion of patients in the trial experiencing significant tumor shrinkage or disappearance following treatment; and ii) adverse events, specifically grade 3 and 4 events, as defined by the U.S. Food and Drug Administration, where grade 3 comprises events requiring medical intervention and grade 4 comprises events requiring hospitalization (14).

In the network meta-analysis, overall survival and progression-free survival times were treated as continuous variables, and point estimates of the mean difference (MD) and standard error were calculated. The objective response rate and adverse events were treated as binary variables, quantified and synthesized using odds ratios (ORs). For cells with 0 events, 0 was replaced by 0.5 to ensure the model could be applied effectively in the subsequent analysis (10).

Statistical analyses. Due to the diverse types of treatment options included, a random-effects model was adopted for the network meta-analysis (15). This analysis was conducted using MetaInsight (version 4.0.2; National Institute for Health Research Complex Reviews Support Unit) operating within a frequentist framework. MetaInsight is an online platform that facilitates network meta-analysis using the netmeta R software package to perform frequentist statistical analyses (16). Forest and network plots were then generated to illustrate all pairwise comparisons derived from the individual studies. In addition, forest plots were created to depict the MD in overall survival

and progression-free survival times, as well as the OR for the objective response rate and adverse events. Effect sizes are displayed as point estimates with 95% confidence intervals (CIs). The various interventions were ranked according to their effects, and the results of direct and indirect comparisons are presented in tabular form. Consistency tests were conducted to assess the agreement between the indirect and direct data. These tests were conducted using the MetaInsight software. P<0.05 was considered to indicate a potential risk of inconsistency.

Results

Search results. The initial search yielded 10,478 publications. After the identification of duplicates and title/abstract screening, 10,444 articles were deemed irrelevant and excluded from the analysis. Full texts of the remaining 34 studies were then examined. Of these, 22 studies were excluded for various reasons: Specifically, 2 articles were duplicate entries of the included trials, 8 did not provide data exclusively for patients with CRC and 12 lacked outcome data (Table SII). Consequently, a total of 12 RCTs were included in the final quantitative analysis (Fig. S1).

Study characteristics. Table I outlines the principal characteristics of the 12 included RCTs (17-28). The RCTs included 11 two-arm trials and 1 three-arm trial, which collectively included 2,050 participants. There were 10 phase II trials and 2 phase III trials. Reports of these trials were published between 2019 and 2023. The participants in the studies were identified as having metastatic or advanced CRC, or anal carcinoma, all of which were classified under the general CRC category.

Quality assessment. A total of 11 studies (17-27) were classified by the RoB 2 tool as having some risk of bias due to not providing information on allocation concealment. The remaining study (28) was rated as having a low risk of bias for all measures, and none of the studies were classified as having a high risk of bias overall (Fig. S2; Table SIII).

Primary outcomes
Overall survival time. The analysis of overall survival time included 6 RCTs, which involved 887 patients in total. The treatment types in the included studies were categorized as follows: PD-L1, PD-L1 + CTLA-4 and active comparators. The comparators included the following: Regorafenib; best supportive care; avelumab + cetuximab; chemotherapy only; folinic acid/5-fluorouracil (5-FU)/oxaliplatin/irinotecan + bevacizumab; folinic acid/oxaliplatin (FOLFOX); placebo + bevacizumab + capecitabine; oxaliplatin/5-FU/leucovorin + bevacizumab; fluoropyrimidine + bevacizumab; 5-FU/leucovorin or capecitabine + bevacizumab; and FOLFOX or folinic acid/5-FU/irinotecan (FOLFIRI). It is important to note that bevacizumab, a widely accepted standard of care in clinical practice, frequently appears as a comparator in various treatment regimens. The network model for the treatment interventions is shown in Fig. 1A.

Treatment with PD-L1 inhibitors was shown to lead to a significant increase in the point estimate of overall survival time (MD, 2.28 months; 95% CI, 0.44 to 4.11), while PD-L1 + CTLA-4 (MD, 1.28 months; 95% CI, -1.56 to 4.11) did not show a significant difference from the active comparator (Fig. 2A). Detailed pairwise comparisons between the study arms, as reported in the individual studies, are shown in Fig. 3.

The treatment interventions were ranked according to their point estimates of relative treatment effects on overall survival, derived from the network meta-analysis results. PD-L1 exhibited the highest point estimate, followed by PD-L1 + CTLA-4 and then the active comparator (Table SIV).

A network was constructed by establishing a node for each treatment and performing direct and indirect comparisons to determine consistency. The results of the treatment-effect inconsistency tests are presented in Table SV. All available comparisons had P>0.05, indicating no evidence of inconsistency between the direct and indirect comparisons.

Progression-free survival time. Overall, 12 RCTs with a total of 2,050 participants were included in the progression-free survival time analysis. Treatment types were classified as follows: PD-1, PD-L1 + CTLA-4, PD-L1 or active comparators. Fig. 1B shows the network model of the treatment interventions.

Based on the network comparison, PD-1 (MD, 4.79 months; 95% CI, 3.18 to 6.40) had a substantially longer progression-free survival time than the active comparator group (Fig. 2B), whereas PD-L1 (MD, -0.63 months; 95% CI, -1.38 to 0.11) and PD-L1 + CTLA-4 (MD, -0.47 months; 95% CI, -1.98 to 1.05) did not exhibit a significant difference. Fig. 4 shows a full pairwise comparison of the research arms, as reported in each of the studies.

Point estimates of the relative treatment effects on progression-free survival time, derived from the network meta-analysis results, were used to rank the therapeutic interventions. PD-1 had the highest point estimate, followed by the active comparator, PD-L1 + CTLA-4 and PD-L1 in decreasing order (Table SVI). A network was constructed by establishing nodes for each treatment, and performing direct and indirect comparisons to determine consistency. The results of the treatment-effect inconsistency tests are presented in Table SVII. All available comparisons had P>0.05, indicating no evidence of inconsistency between direct and indirect comparisons.

Secondary outcomes
Objective response rate. Objective response rates were determined in 12 RCTs comprising 2,050 participants. The analyzed treatment modalities were classified into four categories: PD-1, PD-L1, PD-L1 + CTLA-4 and active comparators. The network model of these interventions is shown in Fig. 1C. As shown in Fig. 2C, the network comparison revealed that none of the treatment options had a markedly higher objective response rate than the active comparator group. PD-1 (OR, 0.89; 95% CI, 0.43 to 1.85), PD-L1 (OR, 0.95; 95% CI, 0.60 to 1.49) and PD-L1 + CTLA-4 (OR, 0.65; 95% CI, 0.06 to 6.94) did not show a significant difference from the active comparator. Fig. 5 shows pairwise comparisons between the study arms, as reported in the individual studies.

The treatment effects were ranked based on the point estimate of the objective response rate obtained from the network meta-analysis results (Table SVIII). The active comparator

Table I. Summary of the retrieved trials investigating the effects of immune checkpoint inhibitors on patients with CRC.

First author, year	NCT code	Trial name	Phase	Disease setting	Markers used for inclusion criteria	Markers used for stratification	Subjects in each arm	Description of intervention	(Refs.)
Eng et al, 2019	NCT02788279	IMblaze 370	III	Locally advanced or metastatic CRC	None	RAS	273 / 90	PD-L1 inhibitor: Atezolizumab + cobimetinib[a] / Active comparator: Regorafenib	(17)
Chen et al, 2020	NCT02870920	CO.26	II	Advanced CRC	None	None	119 / 61	PD-L1 + CTLA-4 inhibitor: Durvalumab + tremelimumab + best supportive care / Active comparator: Best supportive care	(19)
Lonardi et al, 2021	NCT03944252	CARACAS	II	Advanced or metastatic squamous cell anal carcinoma	None	None	30 / 30	PD-L1 inhibitor: Avelumab / Active comparator: Avelumab + cetuximab	(20)
André et al, 2020	NCT02563002	KEYNOTE-177	III	Advanced CRC	dMMR/MSI-H	None	153 / 154	PD-1 inhibitor: Pembrolizumab / Active comparator: Chemotherapy only	(18)
Antoniotti et al, 2022	NCT03721653	AtezoTRIBE	II	Unresectable metastatic CRC	None	None	142 / 72	PD-L1 inhibitor: FOLFOXIRI + bevacizumab + atezolizumab / Active comparator: FOLFOXIRI + bevacizumab	(21)
Meltzer et al, 2022	NCT03388190	METIMMOX	II	Metastatic CRC	Proficient MMR/MSS	RAS/BRAF	37 / 35	PD-1 inhibitor: FOLFOX + nivolumab / Active comparator: FOLFOX	(22)
Mettu et al, 2022	NCT02873195	BACCI	II	Refractory metastatic CRC	None	RAS	82 / 46	PD-L1 inhibitor: Atezolizumab + bevacizumab + capecitabine / Active comparator: Placebo + bevacizumab + capecitabine	(28)
Redman et al, 2022	NCT03050814	N/A	II	Metastatic CRC	None	None	16 / 10	PD-L1 inhibitor: Bevacizumab + capecitabine + avelumab + Ad-CEA vaccine / Active comparator: mFOLFOX6 + bevacizumab	(23)
Tabernero et al, 2022	NCT02291289	MODUL (cohort 2)	II	Unresectable metastatic CRC	BRAFwt	None	297 / 148	PD-L1 inhibitor: Fluoropyrimidine + bevacizumab + atezolizumab / Active comparator: Fluoropyrimidine + bevacizumab	(24)

Table I. Continued.

First author, year	NCT code	Trial name	Phase	Disease setting	Markers used for inclusion criteria	Markers used for stratification	Subjects in each arm	Description of intervention	(Refs.)
Ducreux et al, 2023	NCT02291289	MODUL (cohort 4)	II	Unresectable metastatic CRC	HER2/MSS/BRAFmut/RASmut	None	65	PD-L1 inhibitor: Atezolizumab + cobimetinib	(25)
							34	Active comparator: 5-FU/LV or capecitabine + bevacizumab	
Monge et al, 2023	NCT03206073	N/A	II	Refractory metastatic CRC	Proficient MMR/MSS	None	16	PD-L1 inhibitor: Pexa-Vec + durvalumab	(26)
							18	PD-L1 + CTLA-4 inhibitor: Pexa-Vec + durvalumab + tremelimumab	
Taïeb et al, 2023	NCT03186326	SAMCO-PRODIGE 54	II	Metastatic CRC	None	BRAF	61	PD-L1 inhibitor: Avelumab	(27)
							61	Active comparator: FOLFOX or FOLFIRI	

[a]With or without cobimetinib; two arms were merged for subsequent analysis. Ad-CEA, adenovirus targeting carcinoembryonic antigen; BRAF, gene encoding B-Raf protein; BRAFmut, mutant MRAF; BRAFwt, wild-type BRAF; CRC, colorectal cancer; CTLA-4, cytotoxic T-lymphocyte associated protein 4; dMMR, deficient MMR; FOLFIRI, folinic acid/5-FU/irinotecan; FOLFOX, folinic acid/oxaliplatin; FOLFOXIRI, folinic acid/5-FU/oxaliplatin/irinotecan; 5-FU, 5-fluorouracil; HER2, human epidermal growth factor receptor 2; LV, leucovorin; MMR, mismatch repair; MSI-H, microsatellite instability-high; MSS, microsatellite stability; mFOLFOX6, oxaliplatin/5-FU/leucovorin; N/A, not applicable; NCT, National Clinical Trial; PD-1, programmed cell death protein 1; Pexa-Vec, pexastimogene devacirepvec; PD-L1, programmed cell death-ligand 1; RAS, gene encoding Ras protein; RASmut, mutant RAS.
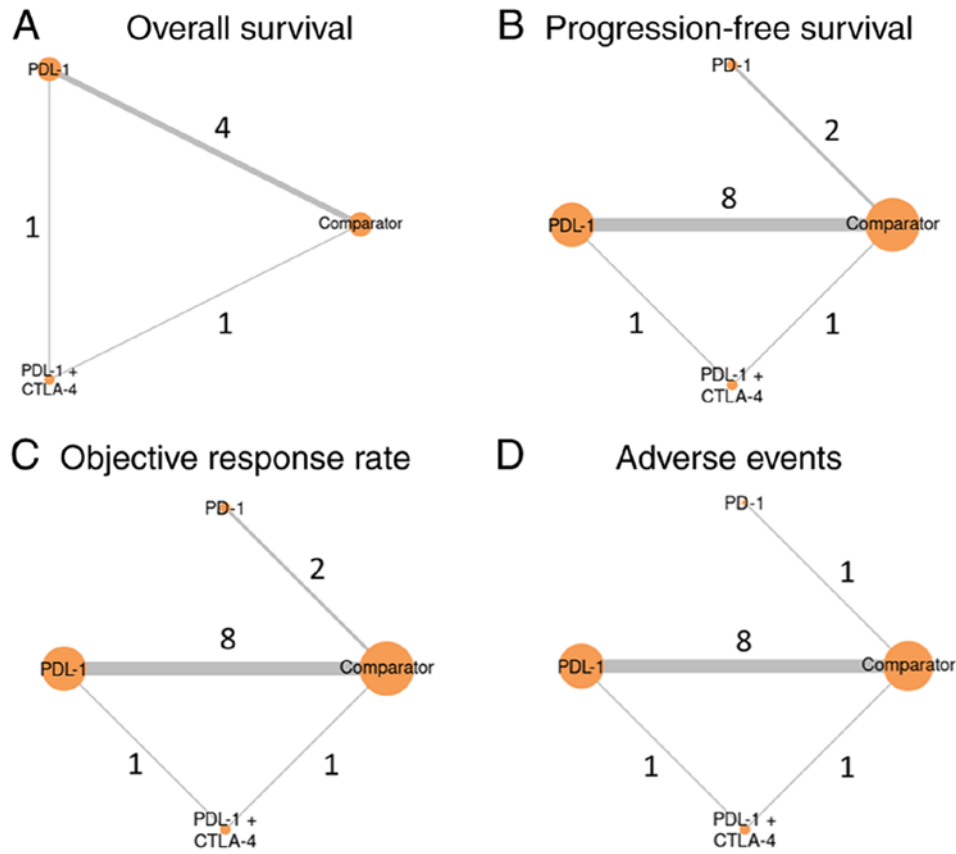
Figure 1. Network plots illustrating the effects of different pharmacological interventions in patients with colorectal cancer. Network plots for (A) overall survival, (B) progression-free survival, (C) objective response rate and (D) adverse events are shown. The size of the nodes and thickness of edges represent the number of studies that compared two given treatments. Numbers on the lines indicate the number of trials conducted for the comparison. CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.
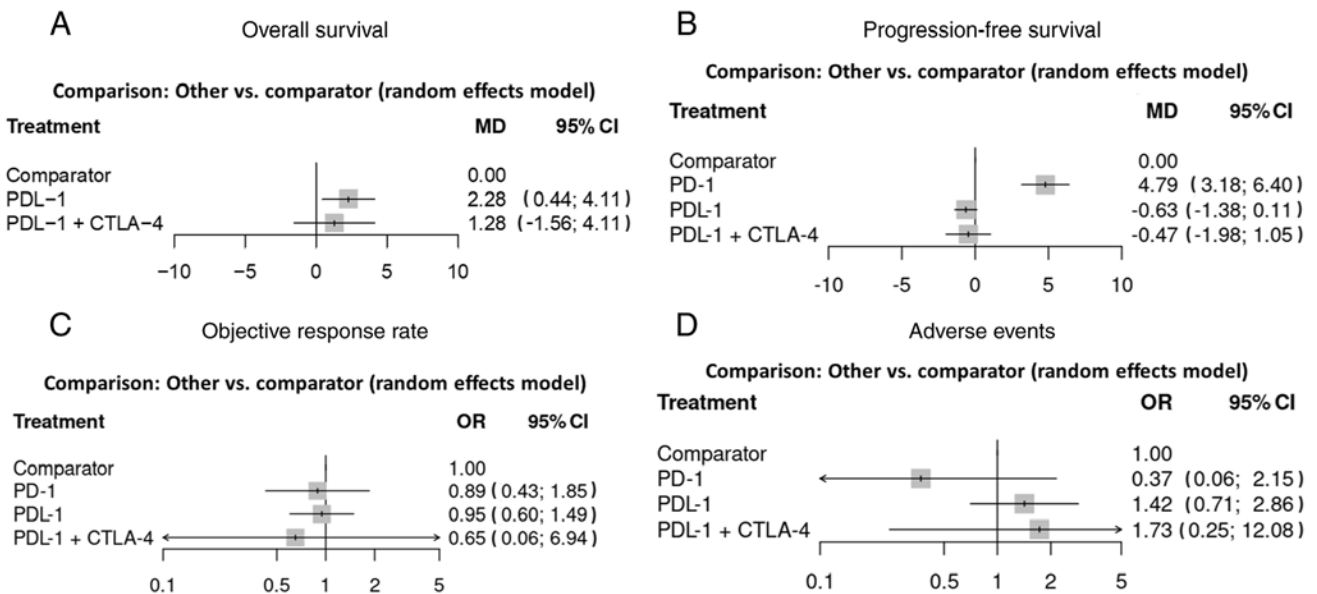

Figure 2. Forest plots illustrating the mean difference in outcomes for different immune checkpoint inhibitor combinations. Forest plots for (A) overall survival, (B) progression-free survival, (C) objective response rate and (D) adverse events are presented. CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte associated protein 4; MD, mean difference; OR, odds ratio; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

achieved the highest point estimate, followed by PD-L1, PD-1 and PD-L1 + CTLA-4, respectively. Table SIX displays the results of the inconsistency tests for treatment effects in terms of the objective response rate. All available comparisons had P>0.05, suggesting that there was no inconsistency between the direct and indirect comparisons.
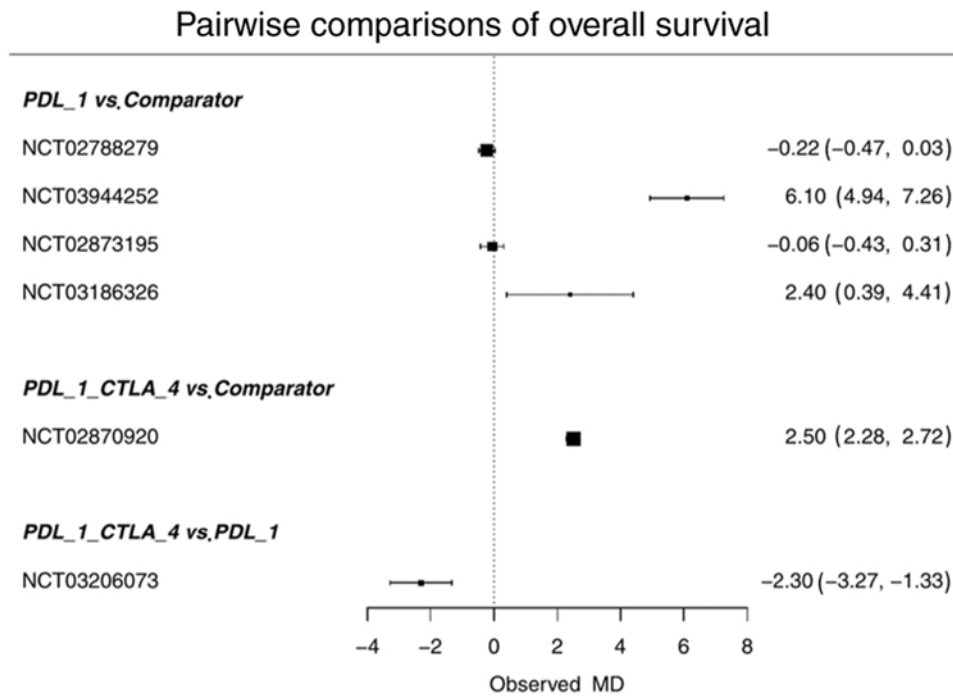
Pairwise comparisons of overall survival

Figure 3. Pairwise comparisons of overall survival between study arms as reported in individual studies. CTLA-4, cytotoxic T-lymphocyte associated protein 4; OR, odds ratio; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; RCT, randomized control trial.

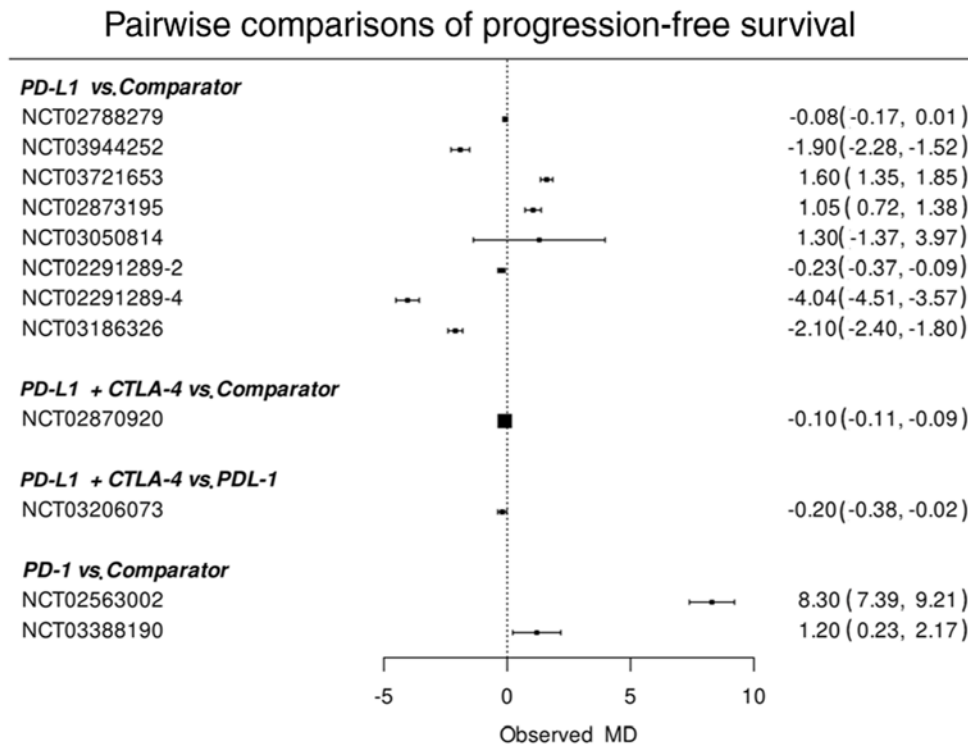## Pairwise comparisons of progression-free survival

Figure 4. Pairwise comparisons of progression-free survival between study arms as reported in individual studies. CTLA-4, cytotoxic T-lymphocyte associated protein 4; MD, mean difference; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; RCT, randomized control trial.

Adverse events. Data on adverse events were available from 11 RCTs involving 1,978 participants. The treatment modalities were classified into four groups: PD-1, PD-L1, PD-L1 + CTLA-4 and active comparators. Fig. 1D shows the network model for these interventions.

Among all the analyzed interventions, PD-1 (OR, 0.37; 95% CI, 0.06 to 2.15), PD-L1 (OR, 1.42; 95% CI, 0.71 to 2.86) and PD-L1 + CTLA-4 (OR, 1.73; 95% CI, 0.25 to 12.08) did not show a significant difference in adverse events compared with the active comparator (Fig. 2D). Fig. 6 shows the pairwise

Pairwise comparisons of objective response rate

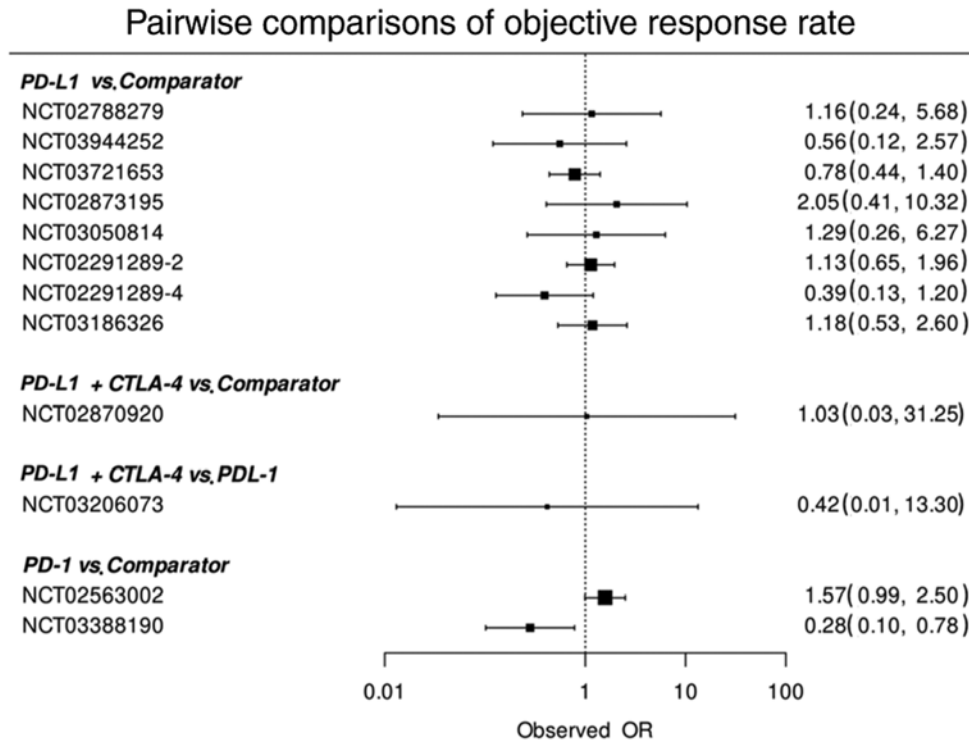| PD-L1 vs. Comparator	
NCT02788279	1.16 (0.24, 5.68)
NCT03944252	0.56 (0.12, 2.57)
NCT03721653	0.78 (0.44, 1.40)
NCT02873195	2.05 (0.41, 10.32)
NCT03050814	1.29 (0.26, 6.27)
NCT02291289-2	1.13 (0.65, 1.96)
NCT02291289-4	0.39 (0.13, 1.20)
NCT03186326	1.18 (0.53, 2.60)
PD-L1 + CTLA-4 vs. Comparator	
NCT02870920	1.03 (0.03, 31.25)
PD-L1 + CTLA-4 vs. PDL-1	
NCT03206073	0.42 (0.01, 13.30)
PD-1 vs. Comparator	
NCT02563002	1.57 (0.99, 2.50)
NCT03388190	0.28 (0.10, 0.78)

Observed OR (0.01, 1, 10, 100)

Figure 5. Pairwise comparisons of objective response rate between study arms as reported in individual studies. CTLA-4, cytotoxic T-lymphocyte associated protein 4; OR, odds ratio; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; RCT, randomized control trial.

Pairwise comparisons of adverse events

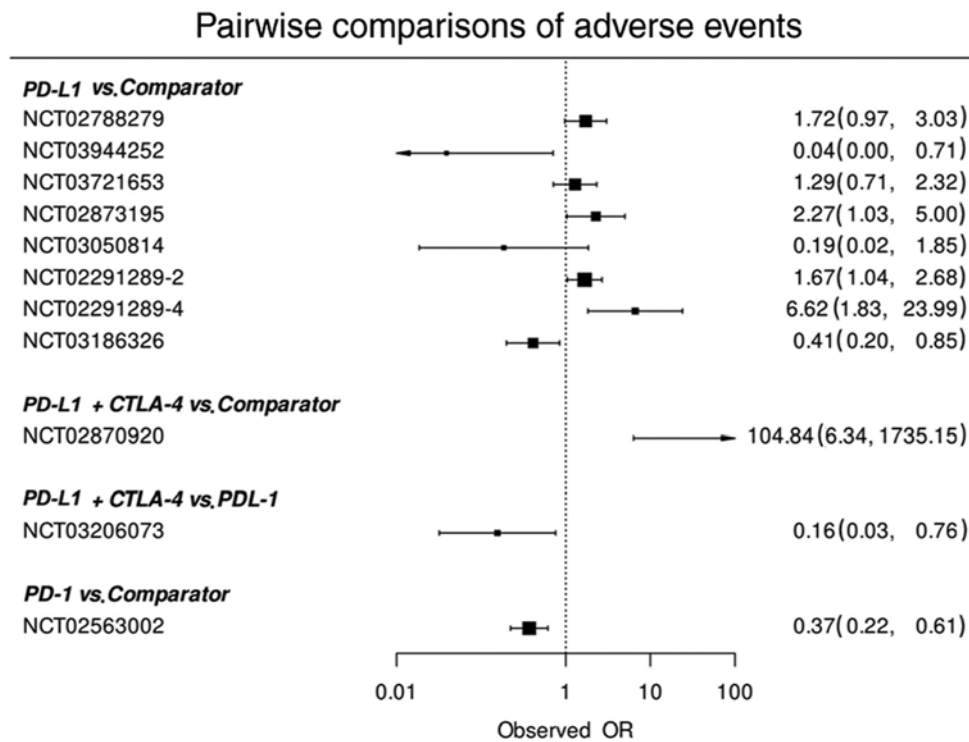| PD-L1 vs. Comparator	
NCT02788279	1.72 (0.97, 3.03)
NCT03944252	0.04 (0.00, 0.71)
NCT03721653	1.29 (0.71, 2.32)
NCT02873195	2.27 (1.03, 5.00)
NCT03050814	0.19 (0.02, 1.85)
NCT02291289-2	1.67 (1.04, 2.68)
NCT02291289-4	6.62 (1.83, 23.99)
NCT03186326	0.41 (0.20, 0.85)
PD-L1 + CTLA-4 vs. Comparator	
NCT02870920	104.84 (6.34, 1735.15)
PD-L1 + CTLA-4 vs. PDL-1	
NCT03206073	0.16 (0.03, 0.76)
PD-1 vs. Comparator	
NCT02563002	0.37 (0.22, 0.61)

Observed OR (0.01, 1, 10, 100)

Figure 6. Pairwise comparisons of adverse events between study arms as reported in individual studies. CTLA-4, cytotoxic T-lymphocyte associated protein 4; OR, odds ratio; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; RCT, randomized control trial.

comparisons between the study arms, as reported in the individual studies.

The point estimates of the relative adverse event rates of various ICI treatment combinations, as determined by the network meta-analysis, were ranked. PD-1 had the lowest point estimate of all interventions, followed by the active comparator, PD-L1 + CTLA-4 and PD-L1 in increasing order (Table SX). Table SXI presents the findings of the

treatment effect inconsistency tests. For all available comparisons, P<0.05 was observed, indicating some inconsistencies.

Discussion

The present network meta-analysis analyzed 12 studies that evaluated the effects of ICIs on patients with CRC. The results revealed that the group of patients treated with PD-L1 inhibitors exhibited the most advantageous outcomes regarding overall survival, whereas the patients in the PD-1 inhibitor group had marginally improved progression-free survival outcomes compared with those of other treatment groups. No group of patients treated with an ICI had a significantly higher objective response rate than that of the active comparator group. In addition, none of the patient groups treated with ICI exhibited a significantly increased rate of adverse events compared with that of the active comparator.

Although surgery and chemotherapy have historically served as the mainstay of CRC treatment, the prognosis of metastatic CRC remains poor. The current first-line treatment strategy for CRC includes chemotherapy combinations, such as FOLFOX, FOLFIRI or capecitabine + oxaliplatin (7). However, targeted therapies incorporating agents such as bevacizumab and cetuximab provide a promising approach to extend the overall survival time of patients with CRC. Despite these advancements, the treatment of metastatic CRC faces challenges, including systemic toxicity, suboptimal response rates, unpredictable resistance mechanisms and low tumor specificity, highlighting that ongoing innovation in CRC therapy is necessary (7).

The present analysis revealed that the overall survival time of patients with CRC was significantly improved by PD-L1 inhibitor treatment compared with that of other treatments. Additionally, treatment with a PD-1 inhibitor resulted in a notable increase in progression-free survival time. However, the lack of overall survival data for PD-1 inhibitors prevents a direct comparison being performed to determine whether PD-1 inhibitors outperform PD-L1 inhibitors in terms of overall survival time, as they do for progression-free survival time. Based on the present study findings, it is advisable for PD-L1 or PD-1 inhibitors rather than CTLA-4 inhibitors to be considered as treatment options for patients with CRC, as they may have the potential to increase patient survival time.

Increased PD-L1 expression in tumor cells has been shown to be associated with more advanced tumor stages and to promote immune evasion via the suppression of T-cell growth and function, leading to T-cell death and inactivity, and the accumulation of regulatory T cells, thus permitting tumor expansion (29). PD-1 inhibitors disrupt the interaction between the PD-1 receptor on T cells and its ligand PD-L1, which is frequently elevated in CRC (30). Although PD-L1 and PD-1 inhibitors target components of the same ligand-protein pair, PD-1 inhibitors have shown greater efficacy for CRC than PD-L1 inhibitors combined with chemotherapy (31). This observation may be attributed to the fact that PD-1 inhibitors block PD-1 from binding to PD-L2 as well as PD-L1, leading to a more effective blockade of immune evasion (31).

Overall survival and progression-free survival data consistently show that PD-L1 and PD-1 inhibitors outperform CTLA-4 inhibitors. A potential explanation for this is the difference in their mechanisms of action. CTLA-4 primarily interacts with the B7 ligand expressed on antigen-presenting cells, which are located in lymph nodes or the spleen (32). This interaction affects the early stages of the immune response, particularly T-cell activation by antigen-presenting cells (33). Although CTLA-4 blockade enhances antigen presentation, it may paradoxically activate regulatory T cells (34). The activation of regulatory T cells is problematic, as these cells suppress the immune response, particularly by inhibiting the action of effector T cells, which are critical for attacking cancer cells. Therefore, cancer cells are more likely to evade immune detection. This phenomenon is particularly pronounced in cancers with a high mutational burden, such as CRC and pancreatic cancer (34).

In the present analysis, the objective response rates of ICIs were not demonstrated to be superior to those of combination therapies across all patient groups. However, the objective response rate may not fully reflect the benefits of treatment in patients with terminal cancer, as it only accounts for tumor regression and does not include cases whose conditions have remained stable. Furthermore, the addition of ICIs to conventional therapeutic agents does not necessarily lead to an increase in side effects compared with those observed with traditional chemotherapy or targeted therapies. Immune-related adverse events for ICIs differ markedly from conventional adverse events in terms of toxicity profiles, affected organs, severity and timing. It is crucial to closely monitor patients and promptly intervene to effectively manage these adverse events (35).

Immunosuppressive drugs such as corticosteroids are used to manage immune-related adverse events during immunotherapy, which may interfere with antitumor efficacy (36). However, while clinical trials have shown inconsistent results (37-39), most evidence suggests any detrimental effect of corticosteroids on ICI efficacy is likely to be minimal (40,41). Therefore, current guidelines recommend the use of steroids as in existing protocols, although further research on optimal dosing and timing is necessary (40). In addition, a meta-analysis of eight retrospective studies found that corticosteroids do not significantly affect the efficacy of immunotherapy regarding progression-free survival [hazard ratio (HR), 0.87; 95% CI, 0.68 to 1.12], overall response rate (OR, 0.92; 95% CI, 0.58 to 1.44) and overall survival (HR, 0.79; 95% CI, 0.59 to 1.05) when used for non-cancer-related indications, after adjusting for the potential confounding effects of corticosteroids administered for palliative purposes (41). It appears that the early and high-dose use of corticosteroids may slightly reduce the benefits of ICIs, but the overall effect is low.

Another noteworthy point is the timing of corticosteroid administration. In mice, the early administration of corticosteroids was indicated to impair the antitumor response to ICIs, leading to the regrowth of tumors that had initially responded to treatment (42). In addition, a retrospective study showed that corticosteroid administration initiated <2 months after the commencement of ICI treatment could impair the overall survival and progression-free survival of patients (43). These findings may be attributed to the immunosuppressive drugs being used before antitumor immunity has fully developed.

Combining hyperthermia with ICI therapies has shown promise in the enhancement of cancer immunotherapy

efficacy (44). Hyperthermia boosts the immune response by increasing the permeability of tumor cells, making them more susceptible to immune attack, and promoting the release of heat shock proteins, which increase the presentation of tumor antigens to the immune system (44,45). Several trials had investigated the efficacy of a combination of hyperthermia and ICI treatments. A trial combining Tremelimumab with hyperthermia in advanced hepatocellular carcinoma have shown promising clinical results, while increased intratumoral CD8+ T-cell accumulation may be observed (46). Furthermore, the addition of hyperthermia has demonstrated improved objective response rates and overall survival in advanced hepatocellular carcinoma patients during anti-PD-1 therapy (47). Further investigations, including meta-analyses, are required (44).

The present study offers novel insights into the efficacy of PD-L1 and PD-1 inhibitors in CRC and emphasizes the superior overall survival benefits of PD-L1 inhibitors. The network meta-analysis provides a comprehensive comparison across multiple ICIs and active comparators, including standard chemotherapies and targeted therapies. This broad perspective underscores the unique contributions of the present research to the advancement of treatment strategies.

Although the present meta-analysis provides valuable insights into the efficacy of the interventions under investigation, it is imperative to acknowledge several inherent limitations. First, the incorporation of studies with varying quality increases the potential for bias. Second, flaws and inconsistencies in reporting outcomes across studies were noted, particularly the absence of overall survival data for PD-1 inhibitors, which hinders the direct comparison of the superiority of PD-1 inhibitors over PD-L1 inhibitors in terms of overall survival time. Third, despite the focus on RCTs, there was an inevitable inherent heterogeneity among the included studies due to differences in baseline patient characteristics and treatment protocols. However, the heterogeneity test results indicated the heterogeneity was insignificant. Furthermore, the MetaInsight platform lacks an algorithm for computing publication bias and presenting a funnel plot. In addition, the Cochrane Handbook notes that evaluating the impact of small study sizes in a network meta-analysis presents significant challenges (9). There are numerous biomarkers, such as tumor mutation burden, that could be critical indicators of whether ICIs are effective for individual patients, and omics-based approaches are currently being used to predict these markers (19,21). Therefore, the absence of relevant bioinformatics data and further comparative analysis in the present study constitutes a significant limitation.

In conclusion, the findings from the present network meta-analysis suggest that patients treated with PD-L1 inhibitors exhibited the most favorable results in terms of overall survival time. In addition, the patients treated with PD-1 inhibitors exhibited slightly improved progression-free survival outcomes. However, the objective response rate to ICIs was not found to be significantly enhanced compared with that of conventional non-ICI treatments. It is suggested that future research should investigate the efficacy of PD-L1- and PD-1-based ICI therapies in patients with CRC with the aim of optimizing treatment outcomes.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CCT, YWL, WTW and KVC contributed to the conception and design of the study. CCT, YWL, WCL and TYL collected the data. CCT, LHL and YFK performed the analysis. WTW and KVC confirm the authenticity of all the raw data. CCT, YWL and TYL drafted the manuscript. All authors revised the manuscript. All authors read and approved the final version of the 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.

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