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Original Research

Comparative efficacy and safety of anti-PD-1 therapies used in metastatic colorectal cancer: a systematic review and network meta-analysis

Qinbo Wang, Qirong Tan, Junrong Chen, Yingjuan Ou, Lihong Huang, Wenfeng Li, Xiaoyan Li, Guozeng Ye

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Abstract

Objective: Systemic studies on anti-PD-1 therapy in patients with metastatic colorectal cancer (mCRC) with microsatellite instability or mismatch repair defects are lacking. We aimed to summarize the evidence regarding the efficacy and safety of pembrolizumab, nivolumab, ipilimumab, and tislelizumab in mCRC. **Methods:** Network meta-analyses (NMAs) can provide comparative efficacy and safety data for clinical decision-making. In this NMA, eligible publications from PubMed, EMBASE, Web of Science, and Cochrane Library from 2016 to April 2023 were identified through a systematic literature review. Literature screening and data extraction were performed according to established criteria. The quality of the literature was evaluated using the Cochrane risk of bias tool, and statistical analysis was performed using Revman5.4 and R language. The main outcome indicators, DCR, ORR, PFS, and OS, were used to evaluate the effectiveness of the drugs, and the main outcome indicators AE and SAE were used to evaluate the safety of each program. **Results:** Fifteen studies with a sample size of 798 patients were included. In terms of effectiveness, the disease control rate DCR of PD-1 inhibitors was 0.727[95% CI:0.654-0.794]; objective response rate ORR was 0.448[95% CI:0.382-0.514]; and the 1-year progression-free survival rate was 0.551[95% CI:0.458-0.642]. The 1-year overall survival rate was 0.790[95% CI:0.705-0.865]. The adverse events associated with anti-PD-1 were 0.567[95% CI:0.344-0.778] in terms of safety. The total incidence of grade 3 or higher adverse events was 0.241[95% CI:0.174-0.313]. In the subgroup analysis results, the incidence of DCR in the nivolumab + ipilimumab group was 0.826[95% CI:0.780-0.869], the ORR was 0.512[95% CI:0.377-0.647], and the PFS was 0.668[95% CI:0.516-0.804]. The incidence of AE was 0.319 [95% CI:0.039-0.700] and SAE was 0.294 [95% CI:0.171-0.433]. **Conclusions:** The efficacy of nivolumab + ipilimumab was superior to that of pembrolizumab and nivolumab, with a low incidence of side effects and controllable safety..

Keywords: metastatic colorectal cancer; microsatellite instability; pembrolizumab; nivolumab

Qinbo WANG. Department of Pharmacy, Department of Graceland Medical Center, Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, 26# Erheng Road, Yuan Village, Tianhe District, Guangzhou 510655, China.
Qirong TAN. Department of Graceland Medical Center, Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, 26# Erheng Road, Yuan Village, Tianhe District, Guangzhou 510655, China.
Junrong CHEN. Department of General Practice, Department of Graceland Medical Center, Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, 26# Erheng Road, Yuan Village, Tianhe District, Guangzhou 510655, China.
Yingjuan OU. Department of Pharmacy, Department of Graceland Medical Center, Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, 26# Erheng Road, Yuan Village, Tianhe District, Guangzhou 510655, China.
Lihong HUANG. Department of Pharmacy, Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, 26# Erheng Road, Yuan Village, Tianhe District, Guangzhou 510655, China.
Wenfeng LIU. Department of Pharmacy, Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, 26# Erheng Road, Yuan Village, Tianhe District, Guangzhou 510655, China.
Xiaoyan LI*. Department of Pharmacy, Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, 26# Erheng Road, Yuan Village, Tianhe District, Guangzhou 510655, China. Email: lixyan5@mail.sysu.edu.cn.
Guozeng YE*. Department of Pharmacy, Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, 26# Erheng Road, Yuan Village, Tianhe District, Guangzhou 510655, China. Email: yegz@mail.sysu.edu.cn

INTRODUCTION

Globally, colorectal cancer (CRC) is one of the major causes of cancer-related death, and its related morbidity is steadily increasing in both developed and developing countries, ranking third in the world.[1] More than 900,000 people die from CRC every year, ranking second in mortality rate and second only to lung cancer.[2] Micro-satellites are short and repetitive DNA sequences found throughout the tumor genome. Compared to normal tissues, the occurrence of new alleles due to the insertion or deletion of repeat units at a microsatellite site in a tumor is called microsatellite instability (MSI). Defects in DNA mismatch repair in tumor cells can lead to microsatellite instability. Clinically, microsatellite instability (MSI) and DNA mismatch repair defects (dMMR) are important tumor markers with far-reaching significance for tumor diagnosis, treatment,

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and prognosis.[3-4]

Nearly 15% of colorectal cancer patients are characterized by this unstable phenotype, known as mismatch repair defect/high microsatellite instability (dMMR/MSI-H), and its percentage is related to tumor stage.[5] Although early screening reduces the risk of onset and death of colorectal cancer, 25%-50% of patients still develop metastasis after early diagnosis, and approximately 25% of patients are already in the advanced stage at the time of diagnosis, which often results in poor treatment.[6-7] At this point, immunotherapy for metastatic colorectal cancer with mismatch repair defects/high microsatellite instability (dMMR/MSI-H) was developed.[8-9] With the development of oncology, immunology, and other related disciplines, previous studies have shown that immunotherapy has effective and lasting antitumor clinical benefits in dMMR/MSI-H metastatic colorectal cancer.[10]

Although immune checkpoint inhibitors have been used in the treatment of colorectal cancer,[11] the efficacy and safety of PD-1 inhibitors in dMMR/MSI-H patients with mCRC remain uncertain. This study aimed to systematically summarize the available evidence and provide an efficient overview of published meta-analyses (MAs) on the efficacy and safety of pembrolizumab, nivolumab, ipilimumab, and tislelizumab monotherapy or combination therapy in patients with metastatic colorectal cancer with microsatellite instability or mismatch repair defects (dMMR/MSI-H), and hopefully support clinical decision-making.

MATERIALS AND METHODS

Literature search

The PubMed, EMBASE, Web of Science, and Cochrane Library databases were searched Jan from 2016 to April 2023, and patients with mCRC and dMMR/MSI-H included identified systemic monotherapy or systemic therapy and reported efficacy or safety, search terms included metastatic colorectal cancer, pembrolizumab, nivolumab, ipilimumab, tislelizumab, microsatellite instability, and DNA mismatch repair. The search was limited to papers published in English or in international scientific journals. Conference abstracts were excluded as they usually present the results of preliminary analyses, which later appear as full-text publications. The references were screened to identify additional eligible publications that might have been missed by the electronic search.

Eligibility criteria

Patients with pathologically confirmed MCRCS, which can also be referred to as “Stage IV CRC”, “Advanced CRC” or “first-line treatment failure CRC”. The MSI/MMR status of the patient was clearly described as MSI-H/dMMR. The intervention methods included anti-PD-1 monotherapy or combination therapy with other drugs. Patients were at least 12 years old and were not restricted by gender, nationality or race. Literatures were excluded from experience summary, case reports and reviews.

Main outcome indicators: (1) objective response rate (ORR), (2) disease control rate (DCR), (3) incidence of adverse events (AE), (4) incidence of serious adverse events (SAE), (5) complete response rate (CR), (6) partial response rate (PR), (7) stable disease (SD), (8) progressive disease (PD), (9) 1-year progression-free survival rate (PFS), (10) 1-year overall survival rate (OS), DCRS and ORRs were evaluated according to RECIST version 1.1. In addition, SAE refers to grade 3 and above adverse events. In this study, ORR, DCR, PFS, and OS indices were used to evaluate the effectiveness of the drug, AE and SAE outcome indices were used to evaluate the safety of the drug, and other indices were used as reference indices when the main outcome indices were not statistically significant.

Literature screening and data extraction

Two researchers independently selected the literature, and the literature retrieved using the search strategy was summarized and imported into Endnote20. Repeated literature was excluded by automatic re-checking, and non-conforming literature was excluded by manual re-checking for a second time. The full text of the remaining literature was obtained and carefully read, and the literature to be studied was included according to the established criteria. Finally, we compare the results of the screening, disagreement through discussion, or by third party participation decision. Data extracted from the literature included author, publication year, intervention regimen, drug dose, sample size, follow-up time and outcome indicators.

Quality evaluation of the literatures

Cochrane bias risk assessment tool was used to evaluate the quality of the included studies from six dimensions, and selection bias was used to evaluate the generation of random sequences and allocation hiding. The bias dimension was used to evaluate whether the subjects and test personnel were blinded. The measurement bias dimension evaluation blinded the outcome evaluator, completeness of the results of the follow-up bias dimension evaluation data, and whether the report bias evaluation selectively reported the study results and evaluated other sources of bias.

Statistical Analysis

R software was used for statistical analysis, and was statistical significance was set at $P < 0.05$. I^2 was used to quantify the heterogeneity among the multiple research results. Heterogeneity was considered when I^2 was less than 50%. A random effects model and double arcsine conversion were used in this study. Subgroup analysis was used to explore the source of heterogeneity, which was divided into monotherapy and combination therapy subgroups, including pembrolizumab, nivolumab and ipilimumab subgroups, and the Egger test was used to evaluate publication bias.

RESULTS

According to the literature search strategy, 442 studies were retrieved, including 96 studies from PubMed database, 299 studies from EMBASE database, and 47 studies from Cochrane database. The literature was sorted, duplicates were removed, titles and abstracts were read, and the full text was reviewed. The literature screening flow chart (Figure 1) showed that 15

studies were qualitatively and comprehensively included in the meta-analysis. The basic information of the included literatures was obtained (Table 1), and 15 studies were selected.

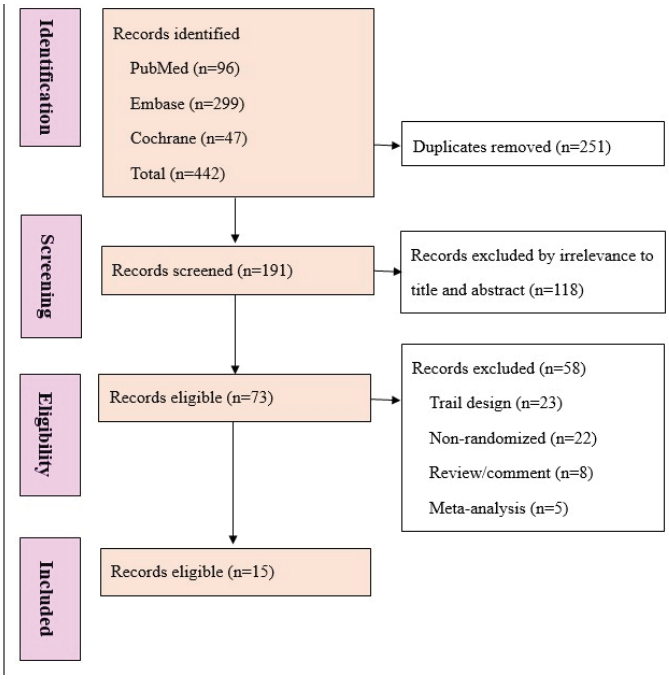

Figure 1. Flow diagram of the study selection process

Results of literature quality evaluation

Owing to the characteristics of single-arm trials, only four studies used randomized controlled trials, seven of which were open trials, three of which had incomplete outcome data. The higher risk of bias was evaluated in three aspects: random sequence generation, assignment hiding, and incomplete outcome data (S).

Validity and Subgroup Analysis

Disease control rate (DCR) and Objective response rate (ORR)

A total of 564 patients included in the study assessed disease control rate (DCR) for immunotherapy for metastatic colorectal cancer (Figure 3A). There was high heterogeneity among the studies (P<0.01, I^2=75.26%), and the overall DCR incidence was 0.727 [95%CI: 0.654-0.794]. The incidence of DCR in the pembrolizumab group was 0.673 [95%CI: 0.5777-0.763]. The incidence of DCR in the nivolumab group was 0.792 [95%CI: 0.710-0.864]. The incidence of DCR in the nivolumab + ipilimumab group was 0.826 [95%CI: 0.780-0.869]. There were 366 patients recorded objective response rate (ORR) of immunotherapy for metastatic colorectal cancer (Figure 3B). There was heterogeneity among the studies (P<0.01, I^2=68.75%), and the overall ORR incidence was 0.448 [95%CI: 0.382-0.514]. In subgroup analysis, the heterogeneity of pembrolizumab group was (P=0.26, I^2=20.22%), and the ORR was 0.415 [95%CI: 0.355-0.476], which was not statistically

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

Author, Year	Intervention	Dosage	Median Survival Time (MST)	Subjects (n)	Male ratio (%)	Median age	Outcomes
Sinicrope FA,2018[12]	Pembrolizumab	200mg q3w	13.5	24	N/A	N/A	①②⑤-⑨
Kawazoe A,2020[13]	Pembrolizumab	200mg q3w	10.4	10	50	53	①-⑧
Shiu KK,2020[14]	Pembrolizumab	200mg iv q3w	32.4	153	46	63	①②④-⑨
Kuang C,2020[15]	Pembrolizumab	200mg iv q3w	24	30	54.8	61	①-⑧
Yoshino T,2021[16]	Pembrolizumab	200mg iv q3w	28.7	22	46.4	61.9	①-⑥⑨⑩
Ghaus A,2022[17]	Pembrolizumab	200mg iv q3w	9	39	N/A	68	①②④-⑧⑩
Leal AD,2017[18]	Pembrolizumab	2mg/kg q3w,200mg q3w	29	19	59	48.6	①②④-⑩
Omar NEH,2019[19]	Pembrolizumab	200mg q3w	41	9	N/A	N/A	①②④-⑧⑩
Le DT,2020[20]	Pembrolizumab	200mg iv q3w	31.3	61	59	53	①-⑩
			24.2	63	52	59	①-⑩
Bergamo F,2018[21]	Nivolumab	3mg/kg q2w	21	74	N/A	N/A	①-⑩
LenZ HJ,2021[22]	Nivolumab + Ipilimumab	N:3mg/kg q2w I:1mg/kg q6w	29	45	N/A	66	①②④-⑩
CohenR,2022[23]	Nivolumab + Ipilimumab	N:3mg/kg q3w/q2w I:1mg/kg q3w	34.5	57	52.6	56.5	①②④-⑩
Andre T,2022[24]	Nivolumab + Ipilimumab	N:3mg/kg q3w/q2w I:1mg/kg q3w	50.9	119	59	58	①-⑩
Lam JJM,2020[25]	Nivolumab + Ipilimumab	N:3mg/kg q3w I:1mg/kg q3w	12	46	44.9	57	①②⑤-⑧
Andre T,2017[26]	Nivolumab + Ipilimumab	N:3mg/kg q3w/q2w I:1mg/kg q3w	≥6	27	N/A	N/A	①-⑧

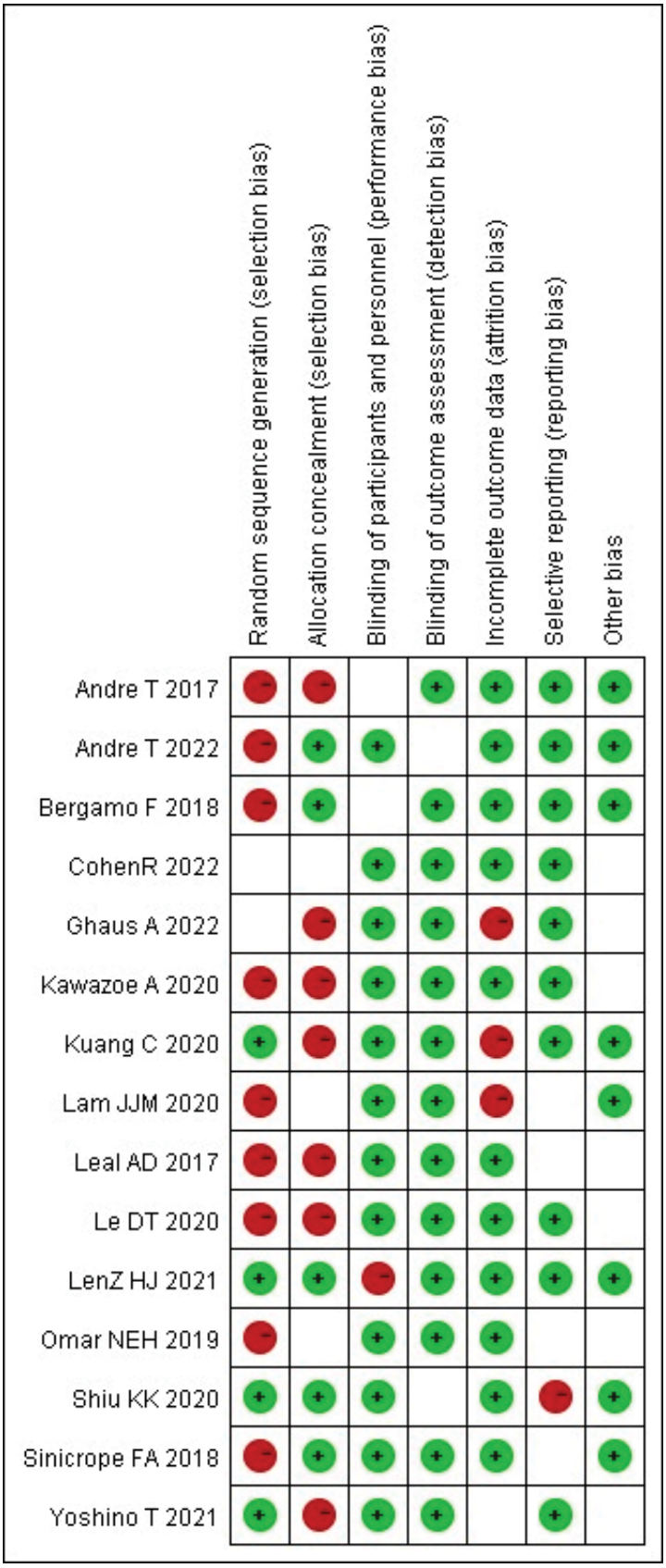

Figure 2. Bias risk bar chart

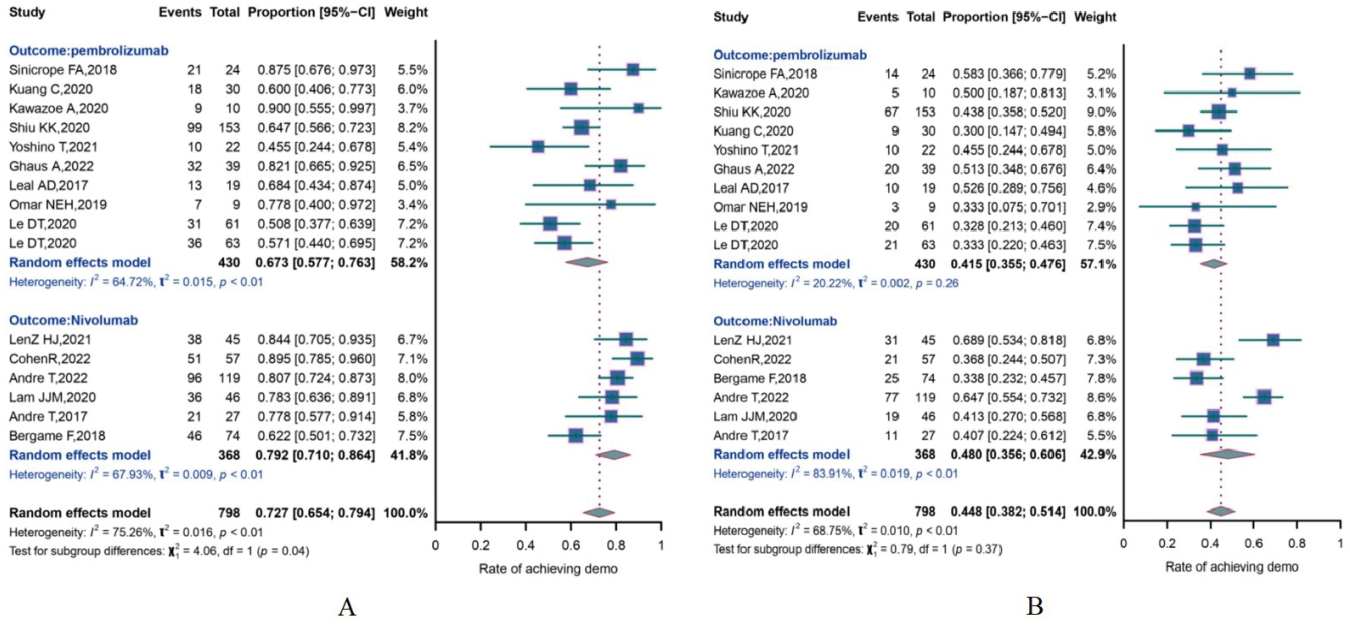

Figure 3. Forest plot (DCR, ORR)

significant due to P>0.05. The incidence of ORR in the and nivolumab group was 0.480 [95%CI: 0.356-0.606]. The ORR in the nivolumab + ipilimumab group was 0.512 [95%CI: 0.377-0.647]. The results suggested that the group of nivolumab + ipilimumab has a better DCR and ORR than pembrolizumab group.

Progression-free survival (PFS) and overall survival rate (OS)

Nine studies evaluated 1-year progression-free survival for immunotherapy of metastatic colorectal cancer, including 334 patients (Figure 4A). Heterogeneity existed among the studies (P<0.01, I^2=77.16%), and the overall 1-year progression-free rate was 0.551 [95%CI: 0.4588-0.642]. The subgroup analysis showed that the incidence of PFS in the pembrolizumab group was 0.497 [95%CI: 0.393-0.601]. In the nivolumab group, the value was 0.614 [95%CI: 0.462 to 0.756]. The incidence rate was 0.668 in the nivolumab + ipilimumab group [95%CI: 0.516-0.804]. In conclusion, the 1-year progression-free survival rate was highest in the nivolumab + ipilimumab group.

Thirteen studies evaluated the 1-year overall survival rate of immunotherapy for metastatic colorectal cancer, including 391 patients (Figure 4B). Heterogeneity existed among studies (P<0.01, I^2=70.96%), and 1-year overall survival was 0.790 [95%CI: 0.75-0.865]. The subgroup analysis showed that the incidence of OS in pembrolizumab group was 0.802 [95%CI: 0.638-0.929]. In the nivolumab group, the value was 0.768 [95%CI: 0.717-0.75617]. The incidence was 0.787 in the nivolumab + ipilimumab group [95%CI: 0.724-0.844]. There was no statistical significance in the nivolumab group (P=0.34, I^2=9.9%) and the nivolumab + ipilimumab group (P=0.37, I^2=0.14%), P > 0.05.

Security Analysis

Adverse event (AE) and Serious adverse events (SAE)

Adverse effects of immunotherapy for metastatic colorectal cancer were reported in 13 studies, involving 431 patients (Figure 5A). There was significant heterogeneity among the studies (P<0.01, I^2=97.24%), and the overall incidence of adverse events was 0.567 [95%CI: 0.344-0.778]. The incidence of AE was 0.723 [95%CI: 0.466-0.924] in the pembrolizumab group, 0.295 [95%CI: 0.067-0.059] in the nivolumab group, and 0.319 [95%CI: 0.039-0.700] in the nivolumab + ipilimumab group. This indicated that the risk of AE was higher in the pembrolizumab group, followed by the nivolumab + ipilimumab and nivolumab monotherapy groups.

Fourteen studies involving 214 patients evaluated the incidence of grade 3 or higher adverse events in immunotherapy for metastatic colorectal cancer (Figure 5B). There was heterogeneity among the studies (P<0.01, I^2=77.58%), and the overall incidence of grade 3 or higher adverse events was 0.241 [95%CI: 0.174-0.313]. The incidence of SAE was 0.213 [95%CI: 0.128-0.311] in the pembrolizumab group, 0.277 [95%CI: 0.174-0.392] in the nivolumab group, and 0.294 [95% CI: 0.171-0.433] in the nivolumab + ipilimumab group. In conclusion, the incidence of serious adverse reactions was higher in the nivolumab + ipilimumab group than in the nivolumab and pembrolizumab groups.

Publication Bias

The Egger test was used to evaluate the publication bias of each outcome indicator, and it is generally believed that a significant publication bias exists when p < 0.05 (Table 2). The Egger test of disease-stable SD showed publication bias, which may have been caused by small sample study effects. The P-values of the

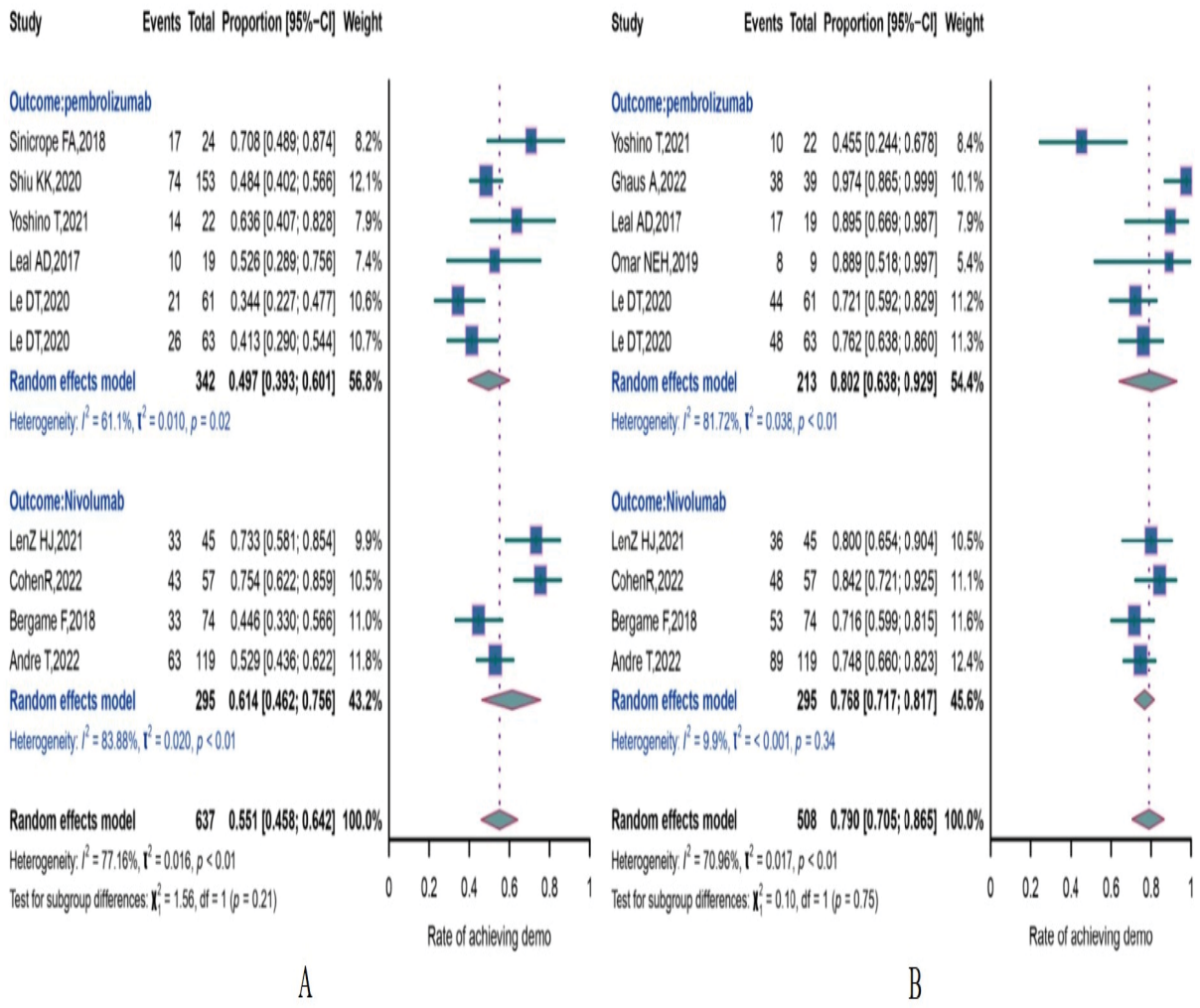

Figure 4. Forest plot (PFS, OS)

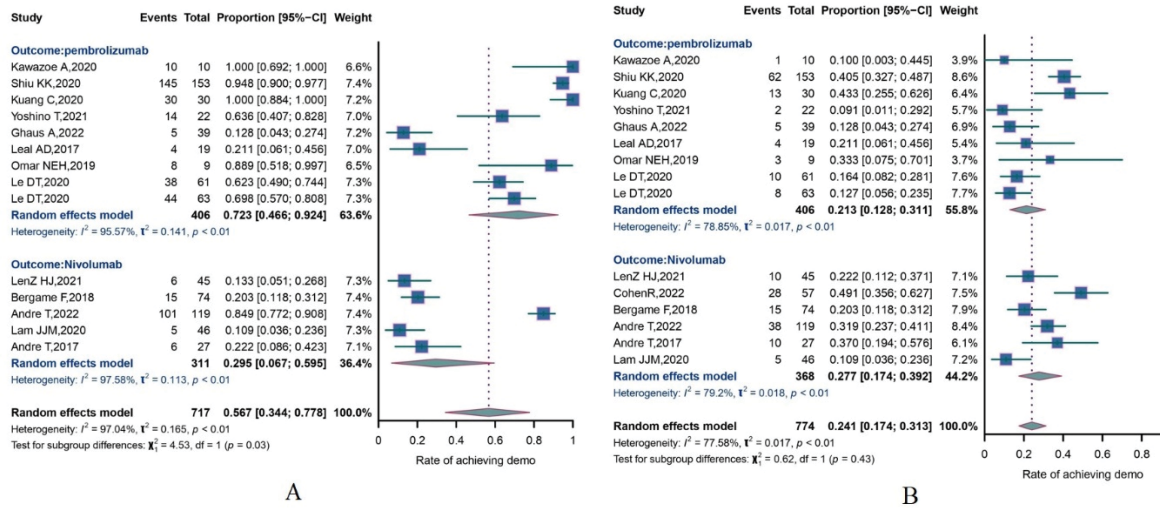

Figure 5. Forest plot (AE, SAE)

Table 2. Egger test publication bias

Parameter	t value	P value
Objective response rate (ORR)	-0.47	0.6456
Disease control rate (DCR)	0.39	0.7024
Incidence of adverse events (AE)	-1.39	0.1906
Incidence of serious adverse events (SAE)	-1.39	0.2182
Complete response rate (CR)	0.68	0.5112
Partial response rate (PR)	-0.74	0.4708
Stable disease (SD)	2.36	0.0377*
Progressive disease (PD)	-0.62	0.7954
Progression-free survival rate (PFS)	1.09	0.3128
Overall survival rate (OS)	0.37	0.7228

other outcome indicators were all greater than 0.05, indicating that there was no significant publication bias in other included studies.

Sensitivity Analysis

Sensitivity analysis was performed on all indicators in this study, the result of the sample DCR indicator showed the heterogeneity did not change significantly after the deletion of references individually, indicating the robustness and reliability of the combined results of the meta-analysis (Figure 6).

DISCUSSION

Colorectal cancer is caused by environmental, genetic, and other factors. Conventional treatments include traditional chemotherapy, radiotherapy and surgery. In recent years, although great progress has been made in the treatment of colorectal cancer, the treatment effect of advanced colorectal cancer is still not ideal, and the prognosis is poor. Immune checkpoint inhibitors have been shown to shine in gastric cancer and non-small cell cancer,[27,28] and immunosuppressive agents have shown good efficacy in the treatment of advanced colorectal cancer patients.[29] The KEYNOTE016 study administered pembrolizumab 10mg/kg every 2 weeks to patients who had failed standard therapy. The primary endpoint was objective response rate (ORR), which was 40%, 71%, and 0%, respectively.[30] It can be seen that patients with advanced dMMR colorectal cancer can benefit from PD-1 inhibitor monotherapy.[31] The 2020 KEYNOTE-177 study showed that pembrolizumab significantly prolonged PFS over standard chemotherapy, with a median PFS16.5 months (5.4 to 32.4 months) vs 8.2 months (6.1 to 10.2 months).[32] The ORR was as high as 67% in the pembrolizumab group, compared with 51% in the chemotherapy group.[33] Immunotherapy is becoming the first-line treatment for MSI-H/dMMR patients with mCRC.

According to the standard strategy developed in this study, there is no relevant literature on the use of tirellizumab in the treatment of advanced metastatic colorectal cancer, and its efficacy, safety, and economy are unknown. Only pembrolizumab, nivolumab and ipilimumab, which are PD-1 inhibitors, were included in study. The Cochrane risk assessment tool was used for quality evaluation of the literature. Nine studies, Andre T,2017 et al, were non-randomized trials assessed as high risk in random sequence generation and LE DT, and seven studies, 2020 et al, were open trials and assessed as high-risk factors in allocation hiding. Therefore, we added the MINOROS quality evaluation to the nine studies of non-randomized trials, and the result was 13-14 points, indicating that the included literature was of high quality. Since all of

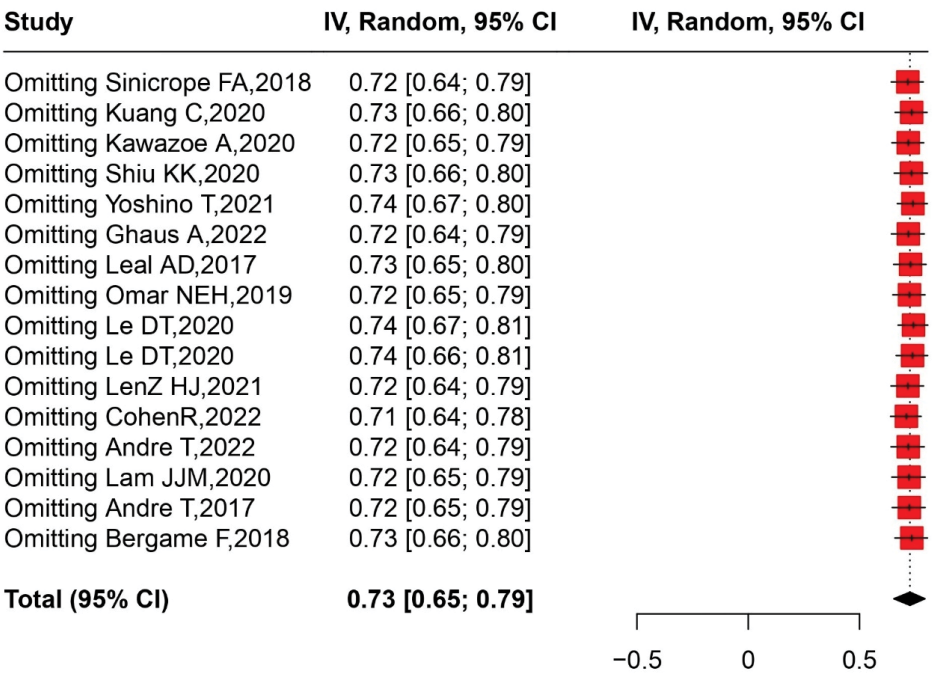

Figure 6. Sensitivity chart (DCR)

these researchers met our requirements, our study included a one-arm trial and a two-arm trial for meta-analysis. Median progression-free survival and median overall survival were not found in individual studies at the end of follow-up; therefore, our outcome measures used 1-year progression-free survival and 1-year overall survival. When data records were missing, we tried to contact the author or publisher for information but received no response.

Based on the results of the meta-analysis, the disease control rate for evaluating the effectiveness of PD-1 inhibitors was 0.727 [95%CI: 0.654 to 0.794]. ORR was 0.448 [95%CI: 0.382-0.514]. The 1-year progression-free survival rate was 0.551 [95%CI: 0.4588-0.642]. The 1-year overall survival rate was 0.790 [95%CI: 0.705-0.865]. Adverse events evaluated for the safety of PD-1 inhibitors was 0.567 [95%CI: 0.344-0.778]. The overall incidence of grade 3 and above adverse events was 0.241 SAE [95%CI: 0.174-0.313], consistent with the results of most studies; immunotherapy resulted in good outcomes for patients with advanced colorectal cancer. Owing to the characteristics of the one-arm trial, there was significant heterogeneity among the results of various studies. We conducted a subgroup analysis to explore the sources of heterogeneity. The subgroups were divided into pembrolizumab group, nivolumab group, and nivolumab + ipilimumab group based on whether the median follow-up time was greater than 25 months. The median follow-up time was correlated only with SD heterogeneity, and the type of PD-1 inhibitor selected: pembrolizumab or nivolumab correlated with AE, DCR, and PD heterogeneity. The type of PD-1 inhibitor selected: pembrolizumab+ ipilimumab or nivolumab + ipilimumab was associated with DCR, PR, and PD.

In the efficacy results of subgroup analysis, the DCR of pembrolizumab group was 0.673 [95% CI: 0.5777-0.763], the PFS was 0.497 [95% CI: 0.393-0.601], and the OS was 0.802 [95% CI: 0.638-0.929]. In the nivolumab group, the DCR was 0.792 [95% CI: 0.710-0.864], the ORR was 0.480 [95% CI: 0.76-0.606], and the PFS was 0.614 [95% CI: 0.462-0.756]. The OS was 0.768 [95% CI: 0.717-0.75617]. The incidence of DCR was 0.826 [95% CI: 0.780-0.869], ORR was 0.512 [95% CI: 0.377-0.647], and PFS was 0.668 [95% CI: 0.516-0.804] in the nivolumab + ipilimumab group. When the result is $P > 0.05$, it is generally considered that the difference is not statistically significant, so we excluded this outcome indicator from the comparison of efficacy or safety. The analysis showed that nivolumab plus ipilimumab achieved good results in the treatment of patients with microsatellite instability or mismatch repair defect (MSI-H/dMMR) metastatic colorectal cancer.

For the safety assessment of PD-1 inhibitors, we selected AE and SAE (grade 3 or above) as indicators. Among the subgroup analysis results, the incidence of AE in the pembrolizumab group was 0.723 [95%CI: 0.466-0.924] and that of SAE was 0.213 [95%CI: 0.128-0.311]. The incidence of AE in the nivolumab group was 0.295 [95% CI: 0.067-0.059] and SAE was 0.277 [95%CI: 0.174-0.392]. The incidence of AE was 0.319 [95%CI: 0.039-0.700] and SAE was 0.294 [95%CI: 0.171-0.433] in the nivolumab + ipilimumab group. The incidence of AE was higher in the pembrolizumab group, while there was no significant difference in the incidence of AE and SAE between the nivolumab and nivolumab + ipilimumab groups, and the safety was higher than that in the pembrolizumab group. We conducted publication bias and sensitivity analysis of the safety and effectiveness results. In view of the large heterogeneity and small sample size of the one-arm test, it is not appropriate to use funnel plot asymmetry to assess publication bias. In this study, the Egger test was used, which can more accurately detect publication bias. The sensitivity analysis showed that the results were robust and reliable. The results of this study indicate that PD-1 inhibitors play an important role in the effectiveness of immunotherapy for advanced colorectal cancer. In subgroup analysis, the efficacy of nivolumab plus ipilimumab was superior to that of pembrolizumab and nivolumab. In terms of safety, the incidence of side effects in the nivolumab and nivolumab + ipilimumab groups were low, and safety was controllable.

This study has some limitations. Most of the projects in this study were single-arm trials with small sample sizes and large differences in treatment cycles and follow-up times, which would affect the statistical results and have certain limitations. Therefore, more reliable and high-quality clinical studies are required to confirm our findings. The results of the meta-analysis depended on all included studies. Some uncontrollable factors, such as lack of standardized and rigorous design, small sample size, and publication bias of experimenters, will affect the statistical results. The results of the meta-analysis are also constantly updated, and more high-quality trials are needed to support the conclusions.

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AVAILABILITY OF DATA AND MATERIALS

All data are available upon request from the authors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

None.

DISCLOSURE STATEMENT

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data and analysis, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

References

1. Baidoun F, Elshiwy K, Elkeraie Y, et al. Colorectal Cancer Epidemiology: Recent Trends and Impact on Outcomes. Curr Drug Targets. 2021; 22(9):998-1009. https://doi.org/10.2174/1389450121999201117115717
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for36 cancers in 185 countries [J]. A Cancer Journal for Clinicians.2021;71(3):209-249. https://doi.org/10.3322/caac.21660
3. Sinicrope FA, Sargent DJ. Molecular Pathways: Microsatellite Instability in Colorectal Cancer: Prognostic, Predictive, and Therapeutic Implications [J]. Clin Cancer Res an Off J Am Assoc Cancer Res. 2012; 18(6):1506–1512. https://doi.org/10.1158/1078-0432.ccr-11-1469
4. Lin A, Zhang J, Luo P. Crosstalk Between the MSI Status and Tumor Microenvironment in Colorectal Cancer. Front Immunol. 2020;11:2039. https://doi.org/10.3389/fimmu.2020.02039
5. Boukouris AE, Theochari M, Stefanou D, et al. Latest evidence on immunecheckpoint inhibitors in metastatic colorectal cancer: A 2022 update[J]. Critical Reviews in Oncology/Hematology. 2022;173(5):103663. https://doi.org/10.1016/j.critrevonc.2022.103663
6. Fan A, Wang B, Wang X, et al. Immunotherapy in colorectal cancer: current achievements and future perspective[J]. Int J Biol Sci. 202;17(14): 3837-3849. https://doi.org/10.7150/ijbs.64077
7. Casak SJ, Marcus L, Fashoyin-Aje L, et al. FDA Approval Summary: Pembrolizumab for the First-line Treatment of Patients with MSI-H/dMMR Advanced Unresectable or Metastatic Colorectal Carcinoma. Clin Cancer Res. 2021; 27(17):4680-4684. https://doi.org/10.1158/1078-0432.CCR-21-0557
8. Kishore C, Bhadra P. Current advancements and future perspectives of immunotherapy in colorectal cancer research. Eur J Pharmacol. 2021;893:173819. https://doi.org/10.1016/j.ejphar.2020.173819
9. Wang C, Fakih M. Targeting MSS colorectal cancer with immunotherapy: are we turning the corner? Expert Opin Biol Ther. 2021;21(10):1347-1357. https://doi.org/10.1080/14712598.2021.1933940
10. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade[J]. Science. 2017;357(6349):409-413. https://doi.org/10.1126/science.aan6733
11. Marcus L, Lemery SJ, Keegan P, et al. FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors[J]. Pazdur Richard Clinical cancer research. 2019;25(13):3753-3758. https://doi.org/10.1158/1078-0432.ccr-18-4070
12. Sinicrope FA, Chakrabarti S, Eiring R, et al. Clinical outcome of patients with microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC) treated with pembrolizumab[J]. Journal of Clinical Oncology. 2018;36(15):24127.
13. Kawazoe A, Kuboki Y, Shinozaki E, et al. Multicenter phase I/II trial of napabucasin and pembrolizumab in patients with metastatic colorectal cancer (EPOC1503/SCOOP Trial)[J]. Clinical Cancer Research. 2020;26(22):5887-5894. https://doi.org/10.1158/1078-0432.ccr-20-1803
14. André T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med. 2020;383(23):2207-2218. https://doi.org/10.1056/nejmoa2017699
15. Kuang C, Park Y, Bahary N, et al. Biomarker analysis for UPCI 14- 118: Phase II study of pembrolizumab in combination with azacitidine in patients with refractory metastatic colorectal cancer[J]. Journal of Clinical Oncology. 2020;38(4):173-173.
16. Yoshino T, Kim TW, Yong WP, et al. PS1-2 Pembrolizumab vs chemotherapy for MSI-high/dMMR metastatic colorectal cancer: Asia subgroup of phase 3 KEYNOTE-177[J]. Annals of Oncology. 2021;32(4):284.
17. Ghaus A, Pheely A, Murdock V, et al. Real-world experience of pembrolizumab in microsatellite instability-high CRC: A Scottish multicenter analysis[J]. Journal of Clinical Oncology. 2022;40(4):54-5
18. Leal AD, Paludo J, Finnes HD, et al. Response to pembrolizumab in patients with mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC)[J]. Journal of Clinical Oncology. 2017;35(4):714-714.
19. Omar NEH, Nasser S, Gasim M, et al. Safety of immune checkpoint inhibitors in cancer patients with microsatellite instability-high (MSI-H) status: An experience from Qatar[J]. JNCCN Journal ofthe National Comprehensive Cancer Network. 2019;17(3-5):45-45.
20. Le DT, Kim TW, Van CE, et al. Phase II Open-Label Studyof Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient MetastaticColorectal Cancer: KEYNOTE-164[J]. Journal of clinical oncology. 2020;38(1):11-19.
21. Bergamo F, Overman MJ, McDermott RS, et al. Nivolumab in patients with DNA mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer (mCRC): Long-term survival according to prior line of treatment from CheckMate-142[J]. Journal of Clinical Oncology. 2018;36(4):554-555.

www.pharmacypractice.org (eISSN: 1886-3655 ISSN: 1885-642X)

22. Lenz HJ, Van Cutsem E, Luisa Limon M, et al. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/ Mismatch Repair-Deficient Metastatic Colorectal Cancer: the Phase II CheckMate 142 Study[J]. Journal of clinical oncology. 2021;40(2):161-170. https://doi.org/10.1200/jco.21.01015
23. Cohen R, Meurisse A, Pudlarz T, et al. One-year duration of nivolumab plus ipilimumab in patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI/dMMR) metastatic colorectal cancer (mCRC): Long-term follow-up of the GERCOR NIPICOL phase II study[J]. Journal of Clinical Oncology. 2022;40(4):13. https://doi.org/10.1136/jitc-2020-001499
24. André T, Lonardi S, Wong KYM, et al. Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142[J]. Annals of Oncology. 2022;33(10):1052-1060. https://doi.org/10.1016/j.annonc.2022.06.008
25. Lam JJM, Bridgewater J, Alani M, et al. Nivolumab, alone or with ipilimumab, for mismatch repair deficient metastatic colorectal cancer: A United Kingdom multicentre analysis of patient outcomes[J]. Annals of Oncology. 2020;40(2):161-170.
26. Andre T, Lonardi S, Wong KYM, et al. Combination of nivolumab (nivo) + ipilimumab (ipi) in the treatment of patients (pts) with deficient DNA mismatch repair (dMMR)/high microsatellite instability (MSI-H) metastatic colorectal cancer (mCRC): CheckMate 142 study[J]. Journal of Clinical Oncology. 2017;35(15):3531-3531.
27. Higgins JP, Altman DG, Gotzsche PC et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. https://doi.org/10.1136/bmj.d5928
28. Wang FH, Zhang XT, Li YF, et al. The Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer, 2021[J].Cancer Commun (Lond). 2021;41(8):747-795. https://doi.org/10.1002/cac2.12193
29. Huynh JC, Schwab E, Kim E, et al. Recent advances in targeted therapies foradvanced gastrointestinal malignancies[J]. Cancers. 2020;12(5):1168. https://doi.org/10.3390/cancers12051168
30. Cho BC, Lee KH, Ahn MJ, et al. 474O - Efficacy and safety of first-line durvalumab (D) ± tremelimumab (T) vs chemotherapy (CT) in Asian patients with metastatic NSCLC: Results from MYSTIC [J].Annals of Oncology. 2019;30(9):157-158.
31. Buchroithner J, Pichler J, Marosi C, et al. Vascular endothelia growth factor targeted therapy may improve the effect of dendritic cell-based cancer immune therapy. Int J Clin Pharmacol Ther. 2014;52(1):76-7. https://doi.org/10.5414/CPXCES13EA02
32. hiu KK, Diaz LA, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label,phase 3 study[J]. Lancet Oncol. 2022;23(5):659-670. https://doi.org/10.1016/s1470-2045(22)00197-8
33. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603). J Clin Oncol. 2020;38(18):2053-2061. https://doi.org/10.1200/JCO.19.03296