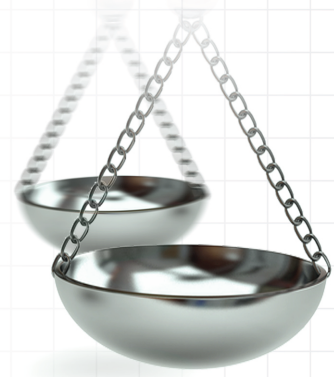
Meta-Analysis



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Efficacy and safety of PD-1/PD-L1 and CTLA-4 immune checkpoint inhibitors in colorectal cancer: a meta-analysis

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Aims: To evaluate the efficacy and safety of PD-1/PD-L1 and/or CTLA-4 inhibitors in the treatment of colorectal cancer (CRC) by meta-analysis. **Methods:** Electronic databases were searched. Eligible studies included investigations of efficacy and safety of anti-PD-1/PD-L1 or anti-CTLA-4 agents in patients with CRC. Corresponding indicators were calculated. **Results:** A total of 15 articles were included. The pooled objective response rate, overall survival rate, progression-free survival rate and adverse event rate were 33, 56, 46 and 59%, respectively. The objective response rates for CRC with deficient mismatch repair and CRC with proficient mismatch repair were 43 and 3%, respectively, in patients treated with PD-1 inhibitors. **Conclusion:** The authors' study indicates that PD-1/PD-L1 inhibitors manifest promising clinical responses in the treatment of CRC with deficient mismatch repair with acceptable treatment-related adverse events.

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Keywords: clinical trials • CTLA-4 colorectal cancer • immune checkpoint blockade • meta-analysis • PD-1/PD-L1

Colorectal cancer (CRC) is one of the most commonly diagnosed malignant tumors worldwide, with an annual incidence of 19.7 in 100,000 and a mortality of 8.9 in 100,000 [1,2]. It accounts for about 10% of global diagnosed cancers and cancer-related deaths every year [3]. The main causes of the high mortality associated with advanced CRC are malignant cancer progression and metastases. Furthermore, despite advances in the standards of treatment, prognosis remains poor for patients with metastatic CRC, with a median 5-year survival rate of 14% [4]. Environmental risk factors, including alcohol and tobacco use, aging, diet and sedentary lifestyle, contribute to the development of CRC [5–7]. Moreover, genetic instability, including chromosome abnormality, microsatellite instability and CpG island methylator phenotype, is an important cause of CRC [8]. Cases of CRC can be divided into those that involve deficient mismatch repair (dMMR) or high levels of microsatellite instability and those that involve proficient mismatch repair (pMMR) or low levels of microsatellite instability, among which dMMR CRC with high levels of microsatellite instability is associated with high tumor mutation load and immune cell infiltration [9]. Thus, patients with CRC are in urgent need of more effective therapies.

Currently, the standard first-line therapy for local metastatic CRC is adjuvant chemotherapy and a biologic agent, including anti-EGFR and anti-VEGF antibodies; however, the specific regimen depends on cancer characteristics. Several factors may affect therapeutic options in patients with metastatic CRC, including patient characteristics, tumor characteristics, molecular characteristics and patient preference [10–12]. However, most patients progress within 1 year [13]. The human immune system plays a major role in the suppression of tumor initiation and progression [14]. $CD8^+$ T cells can seek out and destroy precancerous and cancerous cells in the human body. However, tumors have the potential to evade immune response through different mechanisms, including upregulation of ligands that synergistically inhibit immune checkpoint receptors, which leads to impotent T cells [1,14,15]. Novel methods of immunotherapy have been attracting attention because of their ability to prime the immune system to attack cancer cells [5,16]. Inhibition of the known interaction between PD-1 and PD-L1 can restore the activity of T cells against tumor cells [17–19]. Over the past decade, monoclonal antibodies that target PD-1/PD-L1 (nivolumab,

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pembrolizumab, avelumab, atezolizumab and durvalumab) have demonstrated promising clinical responses in patients with CRC [20–31]. Furthermore, CTLA-4 is another checkpoint that has been found to be a reliable target, and antibodies targeting CTLA-4 (ipilimumab and tremelimumab) have manifested profound outcomes in treatment for advanced cancers [32–35]. However, only a fraction of patients have been found to respond to immune checkpoint inhibitor (ICI) monotherapy [33]. In previous clinical trials, outcomes were improved when patients received a combination of anti-PD-1/PD-L1 and anti-CTLA-4 agents [28,36,37].

To the best of the authors' knowledge, several studies with small sample sizes have investigated the efficacy and safety of PD-1/PD-L1 and/or CTLA-4 inhibitors in patients with CRC. The aim of this study was to conduct a meta-analysis by collating the available evidence to generate an accurate and sound assessment of the efficacy and toxicity of anti-PD-1/PD-L1 and/or CTLA-4 agents and to subsequently provide evidence and insight with regard to clinical implementation, decision-making and future research.

Methods

Statement

This meta-analysis was based entirely on previously published studies with declared ethical approval, and no original raw clinical data were collected or utilized; therefore, ethical approval was not required for this study. This review was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [38].

Search strategy & selection criteria

The authors conducted a computerized search of the electronic databases PubMed, Web of Science and Embase from inception to April 30, 2021, with articles in English considered. The following search strategy was used: (((((((((Nivolumab[Title/Abstract]) OR Pembrolizumab[Title/Abstract]) OR Durvalumab[Title/Abstract]) OR Tremelimumab[Title/Abstract]) OR Avelumab[Title/Abstract]) OR ((((PD1[Title/Abstract]) OR PDL1[Title/Abstract] OR CTLA-4[Title/Abstract]) OR immune check point[Title/Abstract]) OR immune therapy[Title/Abstract])))) AND (((((Colon cancer[Title/Abstract]) OR colorectal adenocarcinoma[Title/Abstract]) OR colorectal cancer[Title/Abstract]) OR colorectal carcinoma[Title/Abstract])))). The references of these articles were also searched to assay any additional studies not previously identified in the initial literature search. The inclusion criterion was clinical trials demonstrating the utility of PD-1/PD-L1 or CTLA-4 inhibitors in patients with CRC. To avoid duplications, if studies recruited participants over the same period of time or in the same study center, only the study with the largest sample size or yielding the most pertinent outcomes was included. Exclusion criteria included case reports, review articles, news and editorials.

Two independent investigators (C Jin and X Zhu) conducted the literature search and process of study inclusion. When disagreement occurred, the investigators discussed their differences, and a third reviewer (X Huang) was involved in cases in which no consensus was achieved. The authors used the Methodological Index for Non-Randomized Studies to evaluate the quality of studies included in this meta-analysis [39].

Data extraction & quality assessments

Two reviewers independently screened the titles and abstracts according to the inclusion criterion. A full-text reading of the literature was performed for the final inclusion. The following information was extracted from each study: name of first author, year of publication, number of patients, name of inhibitors, type of ICI, sex and age of patients, molecular CRC phenotypes and outcome parameters. The primary outcomes were objective response rate (ORR), complete response rate, partial response rate, stable disease rate, disease progression rate, disease control rate, 12-month overall survival (OS) rate, 12-month progression-free survival (PFS) rate and treatment-related adverse event (AE) rate of any grade. Clinical response and disease progression were assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 [40].

Statistical analysis

The authors used R 4.0.2 software for statistical analyses. The efficacy of ICIs in CRC was assessed based on the aforementioned indicators. Cochran's Q test was used to assess heterogeneity between studies, and the I^2 statistic was used to investigate the magnitude of the heterogeneity. Pooled indicators and their respective 95% CIs were calculated with a random effects model or fixed effects model. If the I^2 value was $>50\%$, a random effects model was used; otherwise, a fixed effects model was used. Egger's tests were performed to assess potential publication bias.

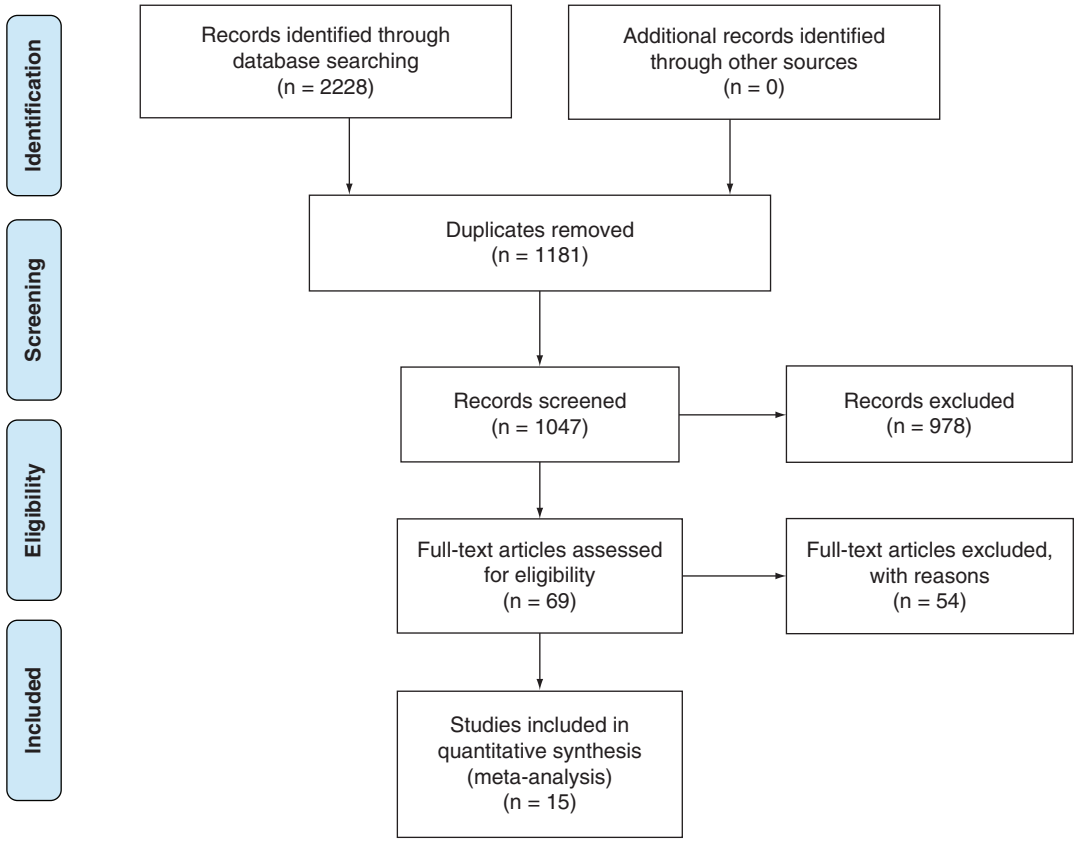

Figure 1. Search results and flow chart of the meta-analysis.

Furthermore, the authors conducted a sensitivity analysis to check the stability of pooled outcomes. A probability of $p < 0.05$ was regarded as statistically significant.

Results

Study selection & characteristics

A total of 2228 articles were identified from the databases searched. Of these, 1181 duplicates were removed and 978 studies were excluded through an initial screening. After a full-text assessment of the remaining 69 articles for eligibility, 15 articles were identified for inclusion in this meta-analysis. No additional studies were found through reference screening of the included articles. Figure 1 shows the flow chart and results of the literature search and study selection process. The selected 15 studies, which contained a total of 924 patients diagnosed with CRC, provided the relevant eligible outcomes required for this study. Of note, results of two studies [26,28] originated from the CheckMate 142 cohort and had different indicators. Table 1 shows the details of the studies included.

Efficacy & safety of ICIs

The numbers of articles included in the analysis of ORR, complete response rate, partial response rate, stable disease rate, disease progression rate, disease control rate, OS rate, PFS rate and AE rate were 10, 8, 10, 11, 10, 6, 8, 7 and 10, respectively. The pooled ORR, complete response rate, partial response rate, stable disease rate, disease progression rate, disease control rate, OS rate, PFS rate and AE rate were 33% (95% CI: 23–45; $I^2 = 86\%$; $p < 0.01$), 11% (95% CI: 8–15; $I^2 = 46\%$; $p = 0.08$), 27% (95% CI: 18–36; $I^2 = 81\%$; $p < 0.01$), 30% (95% CI: 23–38; $I^2 = 74\%$; $p < 0.01$), 35% (95% CI: 19–53; $I^2 = 95\%$; $p < 0.01$), 59% (95% CI: 35–81; $I^2 = 95\%$; $p < 0.01$), 56% (95% CI: 32–79; $I^2 = 97\%$; $p < 0.01$), 46% (95% CI: 32–61; $I^2 = 91\%$; $p < 0.01$) and 59% (95% CI: 55–63; $I^2 = 49\%$; $p = 0.05$), respectively (Table 2). Detailed results of the analyses are shown in Supplementary Figures 1–9.

Table 1. Study characteristics.

Author	Year	Sample size	Sex, M/F	Age, years (range)	Name of ICI	Dose of ICI	Type of ICI	Molecular phenotype	MINORS score	Ref.
Chung	2010	47	29/18	62 (39–79)	Tremelimumab	15 mg/kg	CTLA-4	NR	15	[21]
Lipson	2013	14	NR	NR	BMS-936558	NR	PD-1	dMMR	15	[41]
Le	2015	32	19/13	NR	Pembrolizumab	10 mg/kg	PD-1	dMMR/pMMR	13	[24]
Segal	2016	26	10/16	55 (18–80)	Pembrolizumab	200 mg every 3 weeks for up to 24 months	PD-1	pMMR	14	[30]
Overman	2017	74	44/30	52.5 (44.0–64.0)	Nivolumab	3 mg/kg	PD-1	dMMR	16	[29]
O'Neil	2017	23	13/10	57 (40–78)	Pembrolizumab	10 mg/kg	PD-1	pMMR	14	[27]
Overman	2018	119	70/49	58 (21–88)	Nivolumab + ipilimumab	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	PD-1 + CTLA-4	dMMR	15	[28]
Sinicrope	2018	24	NR	NR	Pembrolizumab	200 mg a day	PD-1	dMMR	14	[31]
Le	2019	61	36/25	53 (21–84)	Pembrolizumab	200 mg every 3 weeks	PD-1	dMMR	15	[23]
Morse	2019	119	70/49	58 (21–88)	Nivolumab + ipilimumab	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	PD-1 + CTLA-4	dMMR	14	[26]
Andre	2020	153	71/82	63 (24–93)	Pembrolizumab	200 mg every 3 weeks	PD-1	dMMR	14	[42]
Chen	2020	119	74/45	65 (39–87)	Tremelimumab + durvalumab	75 mg of tremelimumab every 28 days for the first four cycles plus 1,500 mg durvalumab every 28 days	PD-L1 + CTLA-4	NR	14	[37]
Cohen	2020	57	30/27	57 (46–64)	Nivolumab + ipilimumab	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	PD-1	dMMR	13	[43]
Kim	2020	33	44403	60 (25–88)	Avelumab	10 mg/kg	PD-L1	dMMR	14	[44]
Kanikarla-Marie	2020	23	12/11	56 (28–69)	Tremelimumab + durvalumab	75 mg of tremelimumab every 28 days for the first four cycles plus 1,500 mg durvalumab every 28 days	PD-L1 + CTLA-4	dMMR/pMMR	13	[36]

dMMR: Deficient mismatch repair; F: Female; ICI: Immune checkpoint inhibitor; M: Male; MINORS: Methodological Index for Non-Randomized Studies; NR: Not reported; pMMR: Proficient mismatch repair.

Table 2. Results of pooled analysis of immune checkpoint inhibitors.

ICI indicator	% pooled outcome	% LCI	% HCI	% I^2 value	p-value
ORR	33	23	45	86	< 0.01
Complete response rate	11	8	15	46	0.08
Partial response rate	27	18	36	81	< 0.01
Stable disease rate	30	23	38	74	< 0.01
Disease progression rate	35	19	53	95	< 0.01
Disease control rate	59	35	81	95	< 0.01
OS rate	56	32	79	97	< 0.01
PFS rate	46	32	61	91	< 0.01
AE rate	59	55	63	49	0.05

AE: Adverse event; HCI: Highest CI; ICI: Immune checkpoint inhibitor; LCI: Lowest CI; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

Efficacy & safety of monotherapy

Eleven articles reported the efficacy and safety of PD-1 antibodies. The pooled ORR, OS rate, PFS rate and AE rate for PD-1 inhibitors were 32% (95% CI: 20–45; I^2 = 85%; $p < 0.01$), 67% (95% CI: 49–83; I^2 = 85%; $p < 0.01$), 43% (95% CI: 25–61; I^2 = 68%; $p < 0.01$) and 61% (95% CI: 48–74; I^2 = 84%; $p < 0.01$), respectively (Figure 2). The ORRs for dMMR CRC and pMMR CRC were 43% (95% CI: 34–54; I^2 = 68%; $p < 0.01$) and 3% (95% CI: 0–10; I^2 = 0%; p = 0.42), respectively (Figure 3). The pooled OS and PFS rates for dMMR CRC were 76% (95% CI: 69–82; I^2 = 7%; p = 0.34) and 53% (95% CI: 40–66; I^2 = 83%; $p < 0.01$), respectively (Figures 4 & 5). O'Neil *et al.* reported a 12-month OS rate of 30% and PFS rate of 4% for pMMR CRC [27]. The overall AE rates for dMMR CRC and pMMR CRC were 64% (95% CI: 48–78; I^2 = 88%; $p < 0.01$) and 54% (95% CI: 18–88; I^2 = 86%; $p < 0.01$), respectively (Figure 6).

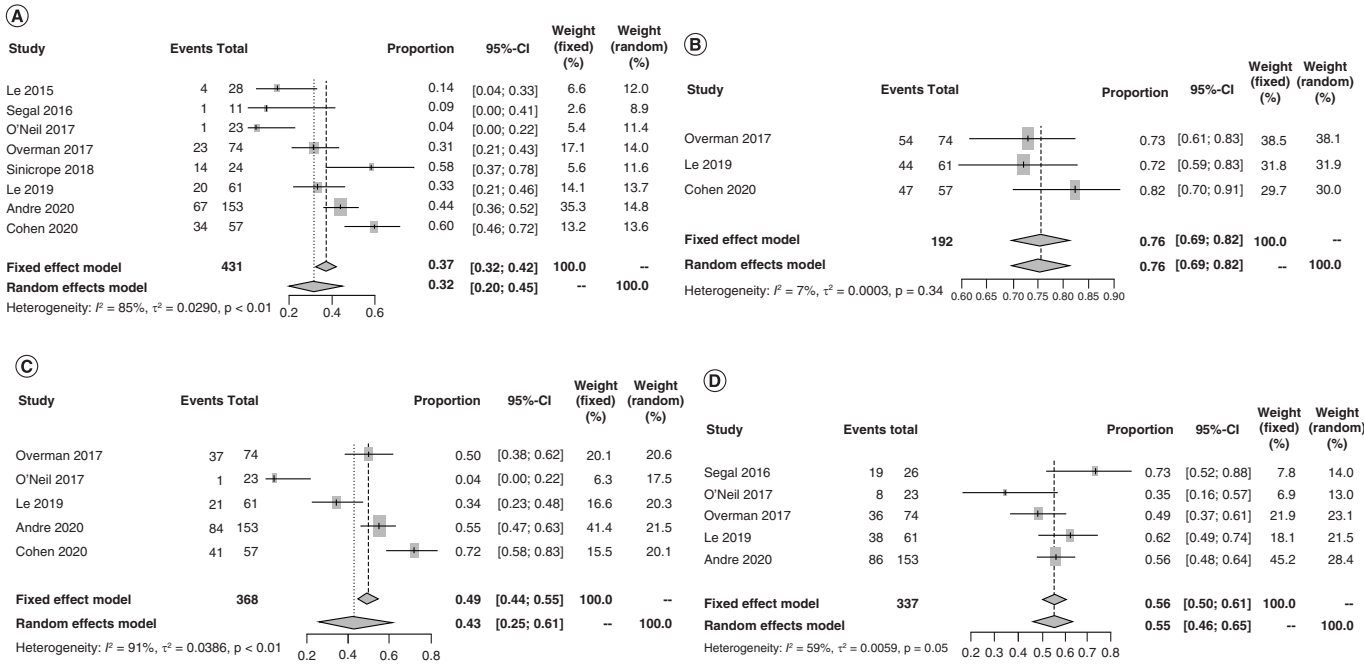

Figure 2. Forest plots of efficacy and adverse event rates in PD-1 subgroup. (A) Forest plot of ORRs in PD-1 subgroup. **(B)** Forest plot of 12-month OS rates in PD-1 subgroup. **(C)** Forest plot of 12-month PFS rates in PD-1 subgroup. **(D)** Forest plot of treatment-related AE rates in PD-1 subgroup.
AE: Adverse event; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

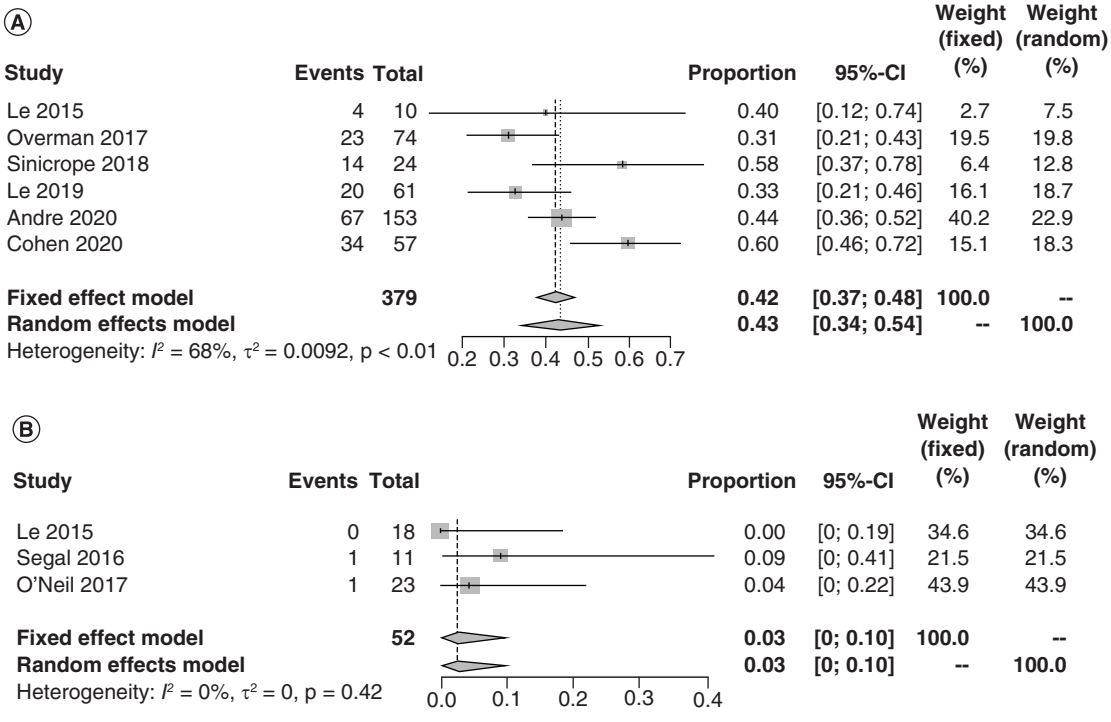

Figure 3. Forest plots of objective response rates in patients with colorectal cancer with deficient and proficient mismatch repair in PD-1 subgroup. (A) Forest plot of ORRs in patients with dMMR CRC in PD-1 subgroup. **(B)** Forest plot of ORRs in patients with pMMR CRC in PD-1 subgroup.
CRC: Colorectal cancer; dMMR: Deficient mismatch repair; ORR: Objective response rate; pMMR: Proficient mismatch repair.

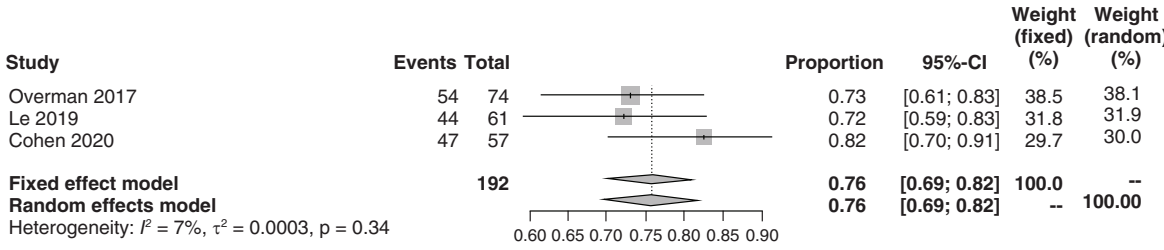

Figure 4. Forest plot of 12-month overall survival rates in patients with colorectal cancer with deficient mismatch repair in PD-1 subgroup.

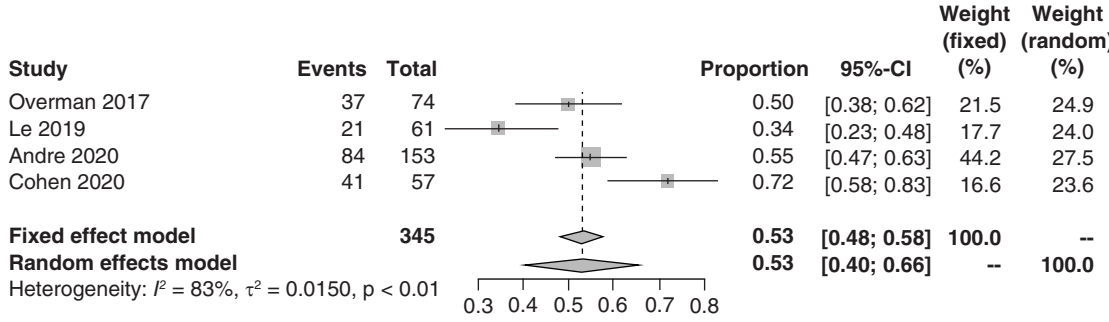

Figure 5. Forest plot of 12-month progression-free survival rates in patients with colorectal cancer with deficient mismatch repair in PD-1 subgroup.

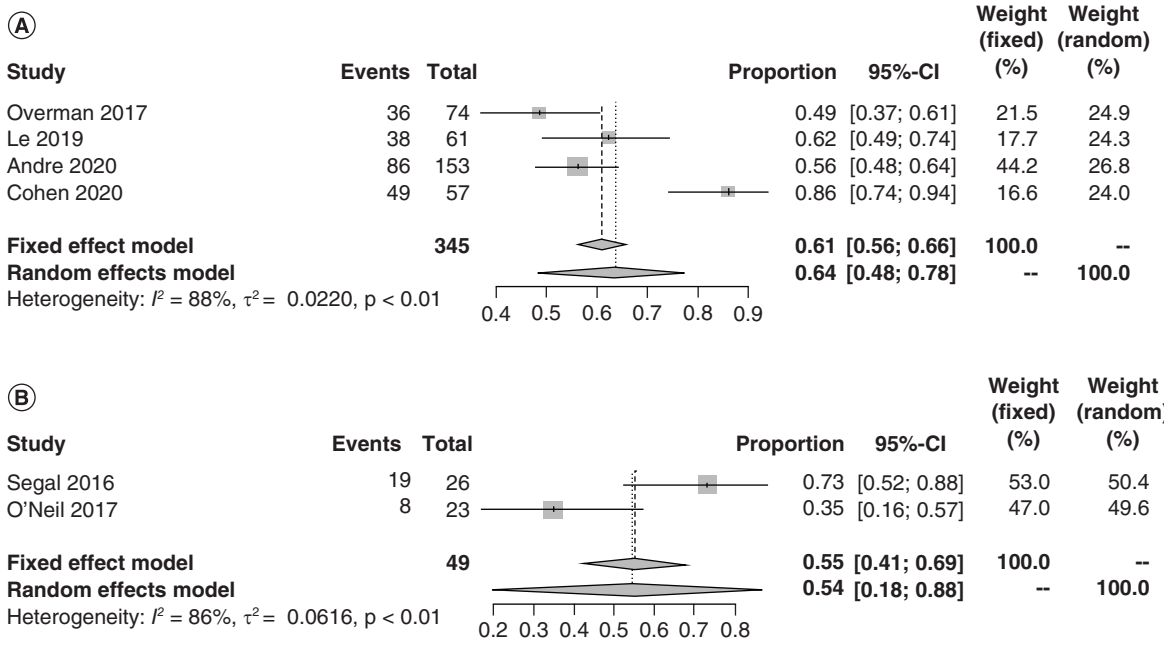

Figure 6. Forest plots of treatment-related adverse event rates in patients with colorectal cancer with deficient and proficient mismatch repair in PD-1 subgroup. (A) Forest plot of treatment-related AE rates in patients with dMMR CRC in PD-1 subgroup. **(B)** Forest plot of treatment-related AE rates in patients with pMMR CRC in PD-1 subgroup. AE: Adverse event; CRC: Colorectal cancer; dMMR: Deficient mismatch repair; pMMR: Proficient mismatch repair.

Results of a study by Kim *et al.* demonstrated that the ORR, OS rate, PFS rate and AE rate of avelumab monotherapy in 33 dMMR CRC patients were 24, 67, 36 and 73%, respectively [44]. Chung *et al.* reported a disease progression rate of 96% and OS rate of 11% in 47 CRC patients treated with tremelimumab [21].

Efficacy & safety of combined immunotherapy

Results of the Checkmate 142 study demonstrated that in dMMR CRC patients treated with nivolumab plus ipilimumab, the ORR, 12-month OS rate, 12-month PFS rate and AE rate were 55, 87, 71 and 56%, respectively. Two studies assessed the efficacy and/or safety of combined therapy with durvalumab and tremelimumab. The complete response rate observed in the study by Kanikarla-Marie *et al.* was 17%, with a stable disease rate of 65% [36]. In the study by Chen *et al.*, the disease control rate was 23%, AE rate was 64% and 12-month OS rate was 20% [37].

Publication bias

Egger's tests for publication bias yielded p-values of 0.0729, 0.2898, 0.0287, 0.1502, 0.3349, 0.3021, 0.7798, 0.0964 and 0.5735 in the pooled analysis of ORR, complete response rate, partial response rate, stable disease rate, disease progression rate, disease control rate, OS rate, PFS rate and AE rate, respectively. The respective p-values for ORR, OS, PFS and AEs in the PD-1 subgroup were 0.2112, 0.1396, 0.2675 and 0.8366.

Sensitivity analysis

The authors performed a sensitivity analysis to assess the impacts of a single study on the overall outcomes. The I^2 value was reduced from 66 to 46% by omitting the study by Overman *et al.* [29] from the meta-analysis of complete response rate, with a pooled rate of 11% (95% CI: 8–15). In the pooled analysis of 12-month OS rate in the PD-1 subgroup, the I^2 value was reduced from 85 to 7% when the study by O'Neil *et al.* was omitted, with a pooled rate of 76% (95% CI: 69–82) [27]. With regard to the analysis of AE rates, results of the sensitivity analysis revealed that the I^2 value decreased from 75 to 49% after omitting the study by Cohen *et al.*, with a pooled rate of 59% (95% CI: 55–63) [43]. Likewise, the I^2 value decreased from 84 to 59% after omitting the study by Cohen *et al.* from the analysis of AE rates in the PD-1 subgroup, with a pooled rate of 56% (95% CI: 50–61). Nevertheless, after excluding one study after another, the other pooled results demonstrated the robustness of the results.

Discussion

CRC is one of the most common tumors, with high rates of incidence and mortality worldwide [3]. Recently, immune checkpoint molecules such as PD-1/PD-L1 and CTLA-4 have been identified as possible targets for immunotherapy in CRC [45]. A number of clinical trials assessing PD-1/PD-L1 and/or CTLA-4 inhibitors in the treatment of dMMR CRC and CRC with high levels of microsatellite instability have demonstrated practice-changing results [21–31,36,37,41–44]. In this meta-analysis, 15 published articles containing 924 CRC patients treated with anti-PD-1/PD-L1 and/or CTLA-4 agents were included. Six articles were published within 2 years. The pooled ORR, complete response rate, partial response rate, stable disease rate, disease progression rate, disease control rate, OS rate, PFS rate and AE rate were 33, 11, 27, 30, 35, 59, 56, 46 and 59%, respectively. With regard to ICI monotherapy, only studies using PD-1 inhibitors were pooled analysis, whereas results of studies estimating CTLA-4 agents were not pooled up due to insufficient numbers of studies. Results revealed significant response and survival outcomes with anti-PD-1 agents in patients with dMMR CRC compared with patients with pMMR CRC. Unfortunately, patients with dMMR CRC account for approximately 15% of all cases of CRC [1]. The lack of recruitment of tumor immune cells appears to be the fundamental obstacle to the curative effect of CRC patients with pMMR subtype [9]. As for the dMMR CRC subset, high neoantigen expression and elevated degree of intraepithelial T-cell infiltration make tumor cells especially susceptible to ICIs, which promotes T-cell-mediated antitumor activities [46]. The results of this meta-analysis demonstrated superior efficacy of anti-PD-1 agents compared with PD-L1 and CTLA-4 inhibitor monotherapy. Furthermore, combined anti-PD-1 and CTLA-4 immunotherapy appeared to be even more effective, with a lower AE rate compared with ICI monotherapy. The US FDA has approved combination immunotherapy (nivolumab and ipilimumab) for use in CRC [28].

In this meta-analysis, the authors did a systematic literature search in the English language to enhance the probability of retrieving as many relevant studies as possible. Data extraction was conducted by two independent investigators using a well-designed form. The authors intended to use individual patient data for this meta-analysis. However, as these data were difficult to acquire, the authors eventually decided to conduct this meta-analysis at the study level. In addition, no randomized controlled trials were included in the authors' study. Nevertheless, the authors assessed the quality of studies included using the Methodological Index for Non-Randomized Studies scale. The heterogeneity among studies was statistically evaluated, and there was significant heterogeneity in most indicators. The heterogeneity may be attributed to differences in baseline characteristics of the study participants,

study design, drug compliance, median lines of prior therapy in each study and other relevant factors. The authors were unable to conduct meta-regression because of the limited information on covariates provided by each included study. Sensitivity analysis revealed that after omitting studies that affected the pooled results, the degree of heterogeneity decreased in the meta-analysis of complete response rate, 12-month OS rate and AE rate in the PD-1 subgroup as well as overall AE rate. Furthermore, with the exception of the partial response rate analysis, Egger's tests indicated that there were no potential publication bias in the studies included. Because of the heterogeneity of information included in each study, the authors did not meta-analyze specific adverse reactions. Despite the existence of heterogeneity and publication bias, the results of this analysis may provide insight into and assistance with the design of clinical trials with larger sample sizes and longer follow-up periods for the evaluation of the efficacy and safety of PD-1/PD-L1 and/or CTLA-4 inhibitors.

Based on the outcomes of this meta-analysis, the authors can conclude that PD-1 inhibitors and combination immunotherapy demonstrate promising and profound clinical response and OS rates with durable treatment-related AEs in the treatment of dMMR CRC. However, the pathogenesis of treatment-related AEs remains poorly understood [47]. Interestingly, the majority of treatment-related AEs were manageable with and resolved using the recommended evidence-based algorithms for early intervention and treatment [26]. Although immunotherapy is the standard of care for dMMR CRC patients, several questions remain to be addressed, including optimal duration of immunotherapy, combination of agents, drug-resistance mechanisms of unresponsive patients, and the development of new agents targeted to enhance treatment effectiveness in the pMMR subtype. Moreover, the assessment of the long-term outcomes of patients with long survival and those are now undergoing adjuvant clinical trials ought to be focused in the future.

Summary points

- Over the past decade, monoclonal antibodies that target PD-1/PD-L1 have demonstrated promising clinical responses in patients with colorectal cancer.
- Antibodies targeting CTLA-4 manifest profound outcomes in the treatment of advanced cancers.
- Several studies with small sample sizes have investigated the efficacy and safety of PD-1/PD-L1 and/or CTLA-4 inhibitors in patients with colorectal cancer.
- The authors conducted a meta-analysis to generate an accurate and sound assessment of the efficacy and toxicity of anti-PD-1/PD-L1 and/or CTLA-4 agents.
- The results of this meta-analysis demonstrated superior efficacy of anti-PD-1 agents compared with PDL-1 and CTLA-4 inhibitor monotherapy.
- Combined anti-PD-1 and CTLA-4 immunotherapy appeared to be even more effective, with a lower adverse event rate compared with immune checkpoint inhibitor monotherapy.
- PD-1 inhibitors and combination immunotherapy demonstrate a promising and profound clinical response and overall survival rate with durable treatment-related adverse events in the treatment of colorectal cancer with deficient mismatch repair.
- Questions remain to be addressed, including optimal duration of immunotherapy and combination of agents and drug resistance mechanisms of unresponsive patients.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2021-0134

Author contributions

C Jin and X Huang conceived and designed the study. C Jin and X Zhu were responsible for the collection, extraction and analysis of the data. C Jin and T Gong were responsible for writing the manuscript. Z Wei and J You performed the quality evaluation and completed data analysis. J You polished the English language usage. All authors reviewed the manuscript and approved the final version.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

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