Combining PD-1/PD-L1 and CTLA-4 inhibitors for the treatment of colorectal cancer: A systematic review and meta-analysis

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Abstract. Objective: The objective of this study is to evaluate the effectiveness of employing both PD-1/PD-L1 and CTLA-4 inhibitors in the treatment of cancer, with a specific emphasis on colorectal cancer (CRC). Approaches: A methodical search of internet databases was performed to discover pertinent studies. The eligible studies included those that examined the management for those had colorectal cancer with the combined medications. Afterwards, the pertinent indicators were computed. Results: Eight publications were included in the study, and they provided data on the objective response rate, disease control rate, progression-free survival rate, and overall survival rate. The reported rates were 64.6%, 82.68%, 64.60%, and 73.11%, respectively. Conclusion: The findings of this investigation suggest that using both PD-1/PD-L1 and CTLA-4 inhibitors together is of great development potential when treating CRC with mismatch repair errors. Additionally, the treatment-related side effects are manageable.

Keywords: Immunotherapy; CTLA-4; PD-1/PD-L1; meta-analysis; colorectal cancer.

1. Introduction

CRC is a significant global public health problem, accounting for almost 10% of all cancer-related deaths globally as recorded in recent epidemiological studies [1, 2]. Despite numerous advances in medical therapies and early screening techniques, the condition—particularly when metastatic-yields a grim prognosis, evidenced by distressingly low median five-year survival rate of approximately 14 % [3]. These statistics reveal a challenging reality for those diagnosed with CRC, emphasizing the urgent requirement for new and more effective therapeutic strategies. CRC tends to take a severe progression route characterized by the spread of cancerous cells to different parts of the body, making therapy more challenging and complicated [4]. The rate at which the disease progresses is closely connected to genetic and epigenetic factors that contribute to the development of tumors. A noteworthy aspect is the classification of CRC according to mismatch repair (MMR) proficiency, which is essential for preserving genomic stability. A noteworthy aspect is the classification of CRC based upon mismatch repair (MMR) proficiency—a system critical for maintaining genetic stability. Tumors that exhibit a deficient Mismatch Repair (dMMR) or high Microsatellite Instability (MSI-H) are distinguished by a higher mutational load, which may result in the new antigen formation and subsequent immune recognition [5]. This distinction is crucial for tailoring more effective therapies, as the current treatment landscape fails to meet the needs of many patients. This discovery has important implications for personalized cancer treatment techniques, emphasizing the importance of customizing treatment based on the molecular characteristics of each individual instance.

The human immune system, particularly through the action of CD8+ T cells, plays a pivotal role in curbing tumor emergence and advancement by targeting precancerous and cancerous cells. However, the cunning nature of cancer allows it to deploy various tactics to evade such surveillance, including the upregulation of proteins (ligands) that bind and deactivate crucial immune checkpoints, leading to T cell inactivation or 'exhaustion' [6]. This allows the tumor to thrive undetected by the alert immune system.

In order to counteract this harmful process, recent advancements in immunotherapy focus on disrupting the PD-1/PD-L1 interaction to reinvigorate T cell activity against tumor cells. The past decade has seen the emergence of novel monoclonal antibodies named ICIs targeting PD-1/PD-L1 demonstrating promising results in increasing the immune system's capacity to fight against colorectal cancer [7]. Likewise, therapies targeting another regulatory protein, CTLA-4, have seen the approval

of agents like ipilimumab and tremelimumab. These treatments have made significant advancements in the field of advanced cancer therapy methods.

However, it is crucial to note that using ICIs alone has resulted in varying and occasionally limited rates of response. The improved advantages are shown in complementary combination therapy, specifically the combination of anti-PD-1/PD-L1 with anti-CTLA-4 treatments. This suggests a multiplicative or even exponential therapeutic effect [8]. This has strengthened the idea that harnessing various aspects of the immune response can produce impressive outcomes in the fight against CRC.

Based on the strong evidence from previous trials, this meta-analysis aims to incorporate these separate study findings into a comprehensive overview that will provide medical professionals with a complete understanding of the effectiveness and tolerability of combined PD-1/PD-L1 and CTLA-4 inhibitors. Moreover, our meta-analysis will intensively investigate the adverse effects associated with the combination therapy. One of the chief concerns surrounding these potent immunotherapies lie in the potential exacerbation of immune-related adverse events (irAEs). The dual blockade of these checkpoints has been observed to augment the immune response, a factor which, while beneficial for tumor clearance, can also result in collateral damage to healthy tissue, manifesting as a wide range of inflammatory side effects. The aim of this analysis is to combine different datasets, analyze statistics obtained over a long period of time, and conduct a thorough analysis of the current status of CRC immunotherapy. This compilation of information is expected to improve the clinical decision-making processes, promote patient-centered treatment, and open up possibilities for further investigation into personalized immunotherapeutic approaches.

2. Experimental Procedure

This review was conducted following a specified process that was based on the PRISMA declaration [9].

2.1. Search strategy and selection criteria

A comprehensive search was conducted in the EMBASE, PubMed, Cochrane Central, and Web of Science databases using a unique search method: (((((((((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] AND 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])))). During the initial stage of the review process, two autonomous reviewers meticulously analyzed the headings and abstracts of the ties that were discovered. Afterwards, a thorough evaluation was conducted on the complete texts of these publications to ensure they met the predetermined criteria for inclusion. In addition to the computerized search, we conducted manual searches to find references to the included studies and associated citations. Any inconsistencies that occurred throughout the screening process were carefully resolved through talks between the reviewers or by seeking guidance from a third senior author.

2.2. Inclusion and exclusion criteria

During the initial screening procedure, two reviewers assessed the titles and abstracts of candidate studies separately, using predetermined inclusion criteria. Afterwards, a comprehensive analysis of the complete body of literature was carried out to decide the final selection. Subsequently, each study was thoroughly examined to extract crucial details such as the identity of the principal investigator, the date of release, and the number of patients, inhibitors utilized, kind of ICI, CRC phenotypes, and the specific outcome factors. Additionally, this meta-analysis will only include research articles that

are original in nature. In contrast, this meta-analysis will exclude studies conducted in languages other than English, articles that are not original, as well as research conducted on animals or cell lines.

2.3. Statistical analysis

STATA 14.2 software was used to analyze all information included in this meta-analysis. Heterogeneity was assessed using the I2 ratio. A statistically significant difference was shown by $p < 0.05$. A random-effects model was utilized when there was substantial variance (p-value <0.05 and I2>30 %) [10]. Also, sensitivity analysis was done to check how stable and reliable the combined results were.

3. Results

3.1. Assortment for research

The initial analysis yielded a cumulative count including 301 relevant studies that were published and retrieved from four different databases. The distribution of these studies throughout the databases is as follows: PubMed (122), Embase (37), Web of Science (62), other resources (48), and Cochrane Library (32). After eliminating duplicate entries and evaluating the titles and abstracts, around 16 studies were included. Subsequently, the remaining full-text publications were thoroughly evaluated, resulting in the exclusion of eight studies. These exclusions were based on the unavailability of full text, incomplete research, and the absence of necessary data in the form of corrigendum. Ultimately, a total of eight trials, comprising 824 patients, were deemed eligible and incorporated into this meta-analysis. Figure 1 displays the flowchart illustrating the selecting procedure. The specifics of each investigation are detailed in Table 1.

Table 1. Study characteristics.

study	No. of patients	Name of ICI	Molecu-lar pheno -type	primary end points	Ref.
Ovweman et al., 2018	109 pts	Nivolumab (NIVO) ± ipilimumab (IPI)	dMMR mCRC	ORR	[11]
Lenz et al., 2020	45 pts	Nivolumab (NIVO) ± ipilimumab (IPI)	dMMR mCRC	ORR by INV	[12]
Lenz et al., 2023	45 pts	Nivolumab (NIVO) ± ipilimumab (IPI)	dMMR mCRC	ORR by INV	[12]
Ovweman et al., 2022	CheckMate 142**;** 1-3 (C1-3); 45p ts	Nivolumab (NIVO) ± ipilimumab (IPI)	dMMR-mCRC	ORR by INV	[13]
Andre et al.,2022	119 pts	Nivolumab (NIVO) ± ipilimumab (IPI)	dMMR-mCRC	ORR by INV	[14]
Andre et al.,2024	171 pts	NIVO+IPI vs. NIVO	dMMR-mCRC	PFS by BICR, PFS by INV, ORR by BICR, OS, safety	[15]
Manca et al., 2023	110 pts with dMMR/MSI-H mCRC**;** 30 were treated with combination therapy	anti-PD1 vs anti-combination	dMMR-mCRC	PFS, OS	[16]
Chen et al., 2020	121 men and 59 women**;** 179 were treated	durvalumab+tremelimumab	MSI-H	ORR, DCR, DOR, PFS, OS	[17]

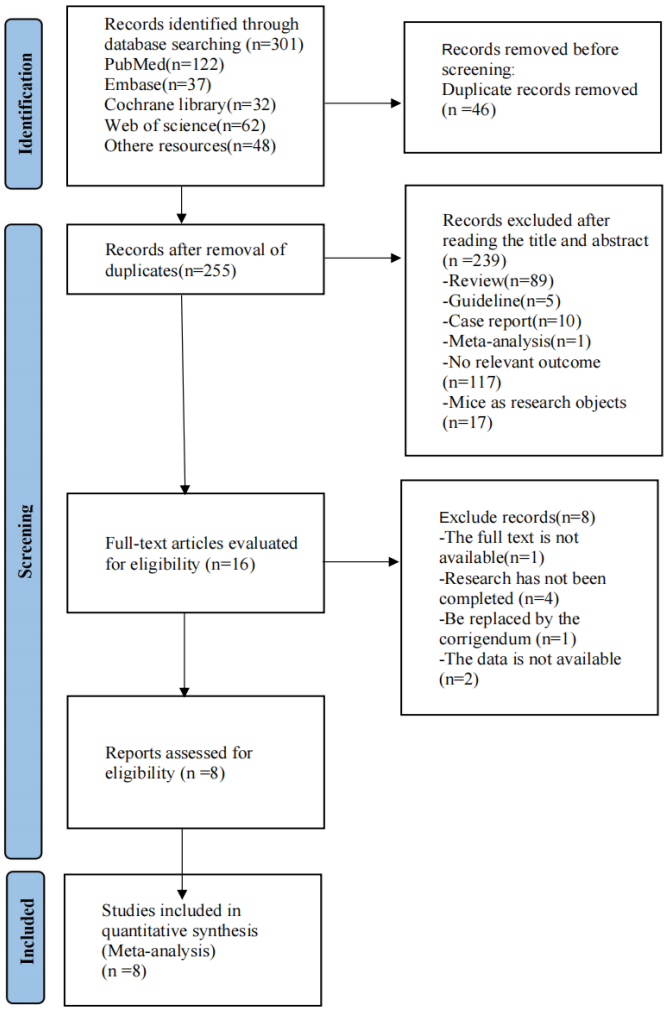


Fig 1. PRISMA flow diagram of the study process. PRISMA, Preferred Reporting Items for Systematic review and Meta- analysis.

3.2. Quality Evaluation

The Newcastle–Ottawa Scale (NOS) for Case Series was used to assess eight retrospective studies. The ten components of this protocol assess the caliber of case reports, encompassing the case selection process, evaluation of the illness or health concern, and exposition of case information. The specifics of the quality evaluation can be found in Table 2.

Table 2. Quality evaluations.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total
Ovweman et al.,2018	1	1	1	0	1	1	0	1	0	1	7
Lenz et al.,2020	1	0	1	0	1	1	0	1	0	1	6
Lenz et al.,2023	1	0	1	0	1	1	0	1	0	1	6
Ovweman et al.,2022	1	0	1	0	1	1	0	1	0	1	6
Andre et al.,2022	1	0	1	0	1	1	0	1	0	1	6
Andre et al.,2024	1	1	1	0	1	1	0	1	0	1	7
Manca et al.,2023	1	1	1	0	1	1	0	1	0	1	7
Chen et al., 2020	1	1	1	0	1	1	0	1	0	1	7

Q1: Were there clear rules about who could be in the succession of cases? Q2: Was the state assessed precisely and uniformly for all the people in the succession of cases? Q3: Were rigorous methods applied to figure out what was wrong with all of the people in the succession of cases? Q4: Were opponents added one after the other in the sequence of cases? Q5. Did all of the people who were supposed to be in the succession of cases actually show up? Q6: Was it clear what kind of people took part in the study and what their numbers were? Q7: Was it clear how the subjects' medical information was reported? Q8: Was there clarity on the circumstances or subsequent outcomes of the cases? Q9: Was it clear what demographic information was given about the presentation site(s) or clinic(s)? Q10: Was statistical research the right thing to do?

3.3. Tumor response

Within this comprehensive study, we have condensed and synthesized information from a total of eight polls. The studies reveal a wide variability range for ORR between 55% and 71%. Given the significant diversity in the research findings, we chose to utilize the random effect model for analysis. This model yielded an I2 value of 38.76% (p = 0.00). Based on a comprehensive analysis, I discovered that the mean ORR of these studies was 64.6% with a 95% CI ranging from 58.01% to 71.18%.

Furthermore, we also assessed the DCR data associated with all the studies. In these studies, the comprehensive DCR calculation results were displayed as 82.68% (95%CI: 77.71%–87.65%), indicating that they have good disease control effects in the patient group. The heterogeneity between the data for illness control rate is quite low (i2 = 0.00%, P = 0.00), which suggests that the disease control rate reported is relatively consistent.

Overall, the findings of this contingency analysis emphasize the positive impact of the combined therapy in the management of colorectal cancer. The patients benefit from its potent OR and high DCR. These findings emphasize the significance of thorough conversations in subsequent research and clinical assessment. (Fig. 2-3).

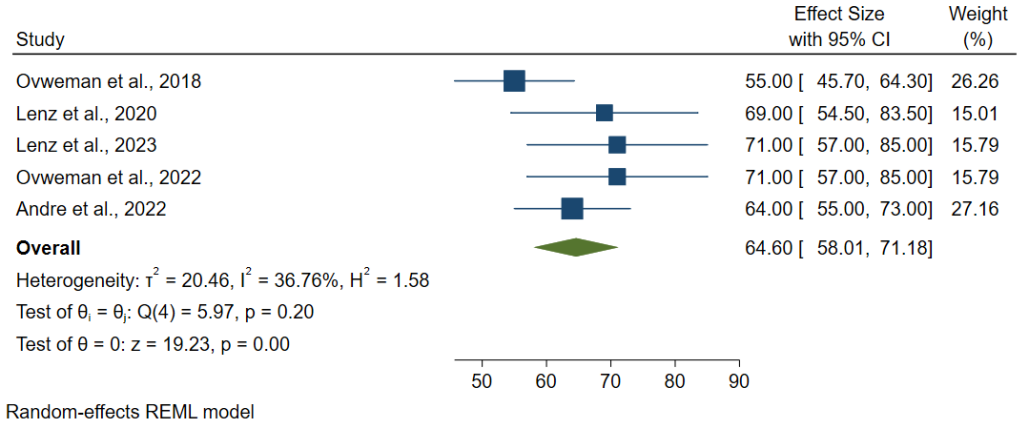


Fig 2. Forest plot of ORR rates.

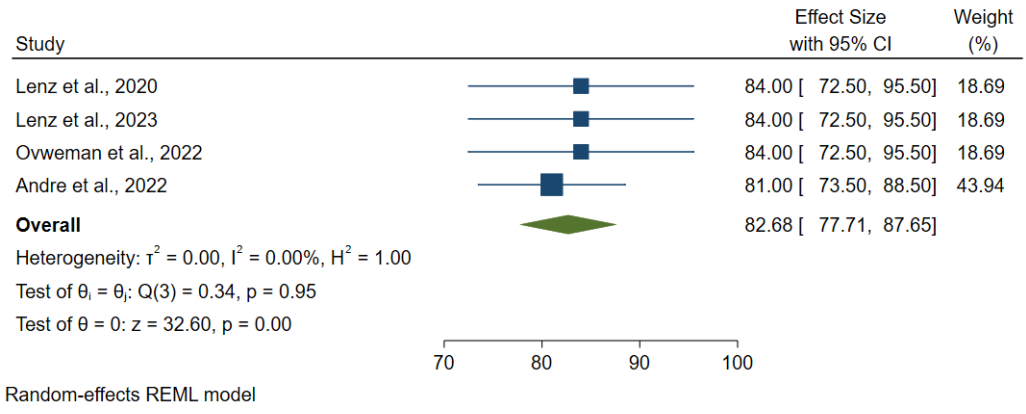


Fig 3. Forest plot of DCR rates.

3.4. Survival

Upon meticulous scrutiny of the compendium of research articles, a consistent trend emerged, indicating that patients exhibited prolonged OS and PFS following administration of PD-1/PD-L1 +CTLA-4 inhibitors. To provide more clarity, Figure 5 displays the combined median OS data obtained using the random-effects model. The data shows a very low I2 value of 0.00%, indicating minimal heterogeneity, and a statistically significant result with a p-value of 0.000. The duration was calculated to be 73.11 months, with a narrow 95% confidence interval ranging from 65.53 to 80.68 months. To analyze the dynamics of PFS, a systematic approach using the random-effects model (I2 = 36.76%, p = 0.00) was employed. The further examination showed that the median PFS duration was determined to be 64.60 months, with a more accurate 95% confidence interval ranging from 58.01 to 71.18 months, as shown in Figure 4. These research results clearly highlight the therapeutic effectiveness of using a combination of PD-1/PD-L1 and CTLA-4 inhibitors, which can potentially lead to long-term survival improvements for patients.

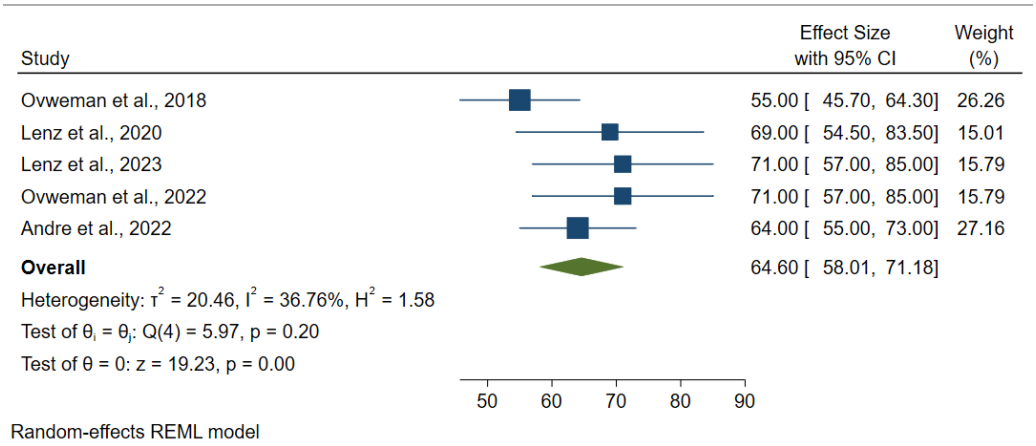


Fig 4. Forest plot of PFS rates.

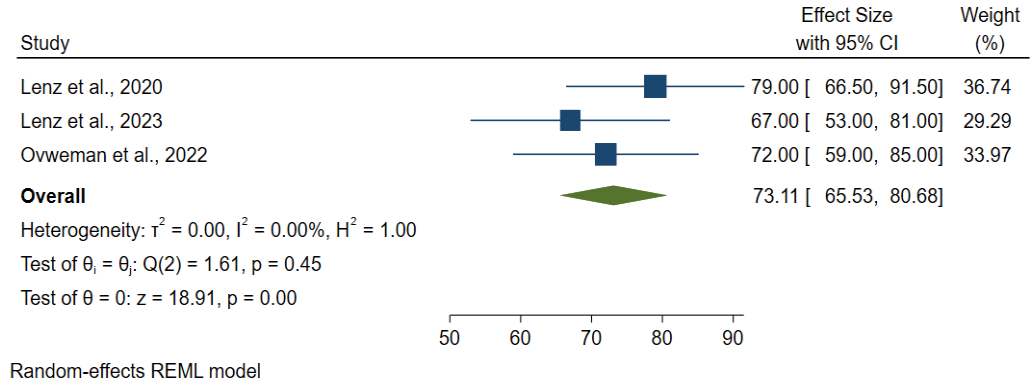


Fig 5. Forest plot of OS rates.

3.5. Adverse Events

Chen et al. conducted a comprehensive investigation into the safety profile of patients undergoing combined immunotherapy with tremelimumab—a CTLA-4 inhibitor—and durvalumab—an anti-PD-L1 agent. Their findings revealed that adverse events (AEs) were universal among the study participants, with a noteworthy 62% experiencing severe AEs (grade 3 or higher). The most frequently encountered severe AEs included an array of symptoms such as fatigue, anorexia, pain of unknown etiology, dyspnea, and peripheral sensory neuropathy[18]. In line with these results, the research conducted by Overman et al. reflected the concerns over treatment-related adverse events (TRAEs) linked to the use of combination immunotherapy in colorectal cancer. In their cohort, 73% of patients experienced TRAEs, a substantial proportion of which were of a more concerning severity, with 32% being categorized as grade 3 or 4 TRAEs. Among the numerous TRAEs observed,

gastrointestinal symptoms such as diarrhea were reported most frequently, followed by generalized symptoms like fatigue and cutaneous reactions manifesting as pruritus.

The studies conducted by Chen and Overman both emphasized the prevalence of irAEs, which involve a range of organ systems. These included dermatologic presentations like rashes and vitiligo; endocrinopathies manifesting as thyroid dysfunctions; gastrointestinal disturbances, such as colitis; hepatotoxicity indicated by elevated liver enzymes; respiratory complications including pneumonitis; and renal impairment, evidenced by changes in creatinine levels. Notably, the incidence of serious irAEs (those exceeding grade 3 severity) was comparatively low, suggesting that while irAEs were relatively common, most of them could be effectively controlled at the first grade 3 severity level.

The presence of irAEs is a result of the increased immune response caused by pharmacological treatments that aim to activate the immune system against cancer cells. The possible immunological processes responsible for the events encompassed the intricate interaction between T cell activation, cytokine release, and subsequent tissue inflammation, offering a detailed comprehension that could assist in improving future treatment regimens and AE control measures.

3.6. Prospective research direction

Manca et al. discovered that a subset of patients with dMMR/MSI-H mCRC have long-lasting control and even remission after receiving ICI therapy. This finding is corroborated by the four-year report provided by the CheckMate 142 clinical study. Their advanced predictive model highlights the kind of ICI therapy as a crucial component that determines the success of treatment. It specifically emphasizes the improved effectiveness of combining CTLA-4+PD-1 inhibitors in patients with unfavorable clinical prognoses. Significantly, they also advocate for the stratification of patients using TMB; suggesting high TMB levels (≥40 Mut/Mb) may warrant an anti-CTLA-4 approach. Conversely, the merits of such combination therapy in those with intermediate TMB levels should be carefully evaluated against the backdrop of potential toxicities. Future research must therefore focus on two important goals: verifying the predictive effectiveness of TMB in randomized controlled trials and investigating its significance in different therapeutic scenarios, such as first-line and second-line treatments. In the ongoing development of personalized medicine, it will be crucial to incorporate a variety of biomarkers, including TMB, together with clinical data. This will be essential for customizing treatment plans to individual patients. Furthermore, it is crucial to standardize the evaluation of TMB across different platforms in order to effectively use it in clinical settings. This requires the development of consistent measurement techniques and criteria, which is a significant obstacle. Tackling these problems will enhance the accuracy of TMB-focused therapeutic approaches, providing patients with more insightful and customized care options[17].

3.7. Sensitivity analysis

One study was deliberately excluded from the sensitivity analysis to assess its impact on the overall findings. The study findings indicated that none of the separate investigations had a substantial impact on the combined data, as evidenced by the 95% CIs. This showed that, on the whole, the results of this meta-analysis could be trusted.

4. Discussion

CRC ranks among the most prevalent malignancies globally, contributing significantly to both its incidence and mortality rates. Notably, there has been a recent surge in the investigation of immunotherapies targeting ICIs, encompassing PD-1/PD-L1 and CTLA-4, for the management of CRC.

The combined ORR, DCR, PFS, OS were reported as 64.6%, 82.68%, 64.60%, and 73.11%, respectively. It is important to emphasize that dMMR CRC represents only approximately 15% of all instances of CRC. In the dMMR-CRC, the increased expression of high-level antigens as well as the

level of T cell infiltration within the epithelium make cancer cells highly responsive to ICIs, which in turn activates T cell-mediated anti-tumor action.

The consequences of this meta-analysis highlight the greater effectiveness of the combined regimen. The FDA has approved the combination immunotherapy, especially nivolumab and ipilimumab, in the therapeutic management of CRC, acknowledging the significant progress made in this field.

The author conducted a comprehensive and methodical literature search in this meta-analysis to guarantee the retrieval of pertinent articles. The process of extracting data was carried out by two independent investigators utilizing meticulously designed tables. Due to practical problems, the original plan to include individual patient data for analysis was changed to conducting a meta-analysis at the study level. The author's complete evaluation of research quality was not hindered by the lack of randomized controlled trials. This evaluation was conducted utilizing the NOS. Statistical analysis of heterogeneity between studies showed only slight differences in most evaluated measures.

Because of the insufficient covariate information available in the studies, we were not capable of performing a meta-regression analysis. Further sensitivity analysis revealed a decrease in variability within the PD-1 subgroup for important factors, including the rate of full remission, the rate of survival at 12 months, and the overall rate of adverse events, when influential studies were excluded. We concluded that the Utilization in conjunction of PD-1 and CTLA-4 inhibitors showed potential and clinically significant responses and survival outcomes in treating dMMR colorectal cancer, despite the presence of long-lasting treatment-related adverse events. Although these observations have been made, the exact cause of treatment-related adverse events is still unclear. Significantly, most of these occurrences have been proven to be solvable by suggested evidence-based early interventions and treatment regimens. While immunotherapy is the suggested method option for individuals with dMMR CRC, there remain some outstanding matters that require attention and resolution. These include determining the best treatment duration, identifying drug combinations that work well together, understanding the resistance mechanisms in individuals who do not respond to treatment, and developing new targeting agents to enhance the effectiveness of treatment in pMMR subtypes. Furthermore, it is crucial to prioritize future research on doing long-term outcome assessments for both enduring survivors and patients now participating in active adjuvant therapeutic studies.

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