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Immunotherapy Outcomes In Colorectal Cancer: A Systematic Review

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Abstract

Background: Immunotherapy has shown transformative efficacy in mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) subtypes of colorectal cancer (CRC), which is a major global health burden. However, most patients have microsatellite-stable (MSS) or mismatch repair-proficient (pMMR) disease, where the benefits of immunotherapy are still limited. Current data on immunotherapy results across various CRC populations and treatment settings is compiled in this systematic review.

Methods: In accordance with PRISMA standards, we carried out a systematic review by searching for articles published between 2000 and 2025 in Cochrane CENTRAL, PubMed Central, and Web of Science. Two Phase III randomized controlled trials (RCTs), five Phase II single-arm trials, and one retrospective cohort study were among the eight studies that satisfied the inclusion criteria. ROB-2 for RCTs and ROBINS-I for cohort studies were used to evaluate the risk of bias. Study design, sample characteristics, interventions, efficacy outcomes (overall survival, progression-free survival, objective response rate, disease control rate), and safety profiles were all included in the data extraction process.

Results: Among 1,371 patients, MSI-H/dMMR metastatic CRC showed strong responses to immune checkpoint inhibitors, with objective response rates ranging from 43.8% to 50% and median progression-free survival ranging from 16.5 months (pembrolizumab) to not reached (nivolumab plus relatlimab). In cases of localized dMMR illness, neoadjuvant immunotherapy showed pathologic complete response rates ranging from 44% to 68%. On the other hand, MSS populations had worse outcomes than normal salvage therapy with a median overall survival of 10.9 months in refractory situations. Immunotherapy had better safety ratings than chemotherapy, with 10% to 23% of patients experiencing grade 3 or greater treatment-related side events versus 48% to 66% with chemotherapy.

Conclusion: immunotherapy provides significant therapeutic benefit in MSI-H/dMMR CRC across treatment lines and contexts, with positive safety and long-lasting responses. The low efficacy in MSS populations highlights the necessity for combined techniques and biomarker-driven patient selection to increase the benefits of immunotherapy.

Keywords: Colorectal neoplasms; Immunotherapy; Immune checkpoint inhibitors; Pembrolizumab; Nivolumab; Microsatellite instability; Mismatch repair deficiency; Programmed cell death protein 1.

Introduction

Cancer is a leading cause of mortality and represents a significant challenge to improving life expectancy worldwide. Colorectal cancer (CRC) is ranked as the third most frequently diagnosed malignancy globally and is the second most common cause of cancer-related deaths [1]. Colon cancer exhibits higher prevalence in North America, Europe, and Australia/New Zealand, whereas rectal cancer incidence is notably high in Eastern Asia [2]. Conversely, CRC incidence rates are generally lower in most parts of Africa and South-

Central Asia. Notably, CRC incidence rates have increased consistently in regions undergoing rapid economic development, including Eastern Europe, Southeast Asia, South-Central Asia, and South America [3].

An emerging concern is the rising prevalence of CRC among individuals under the age of 50. Colorectal cancer (CRC) is the third most common cancer and the second cause of cancer-related death worldwide. It is considered a global health issue with an urgent unmet need for new therapeutic strategies [4]. Although screening has reduced the incidence and mortality, approximately 25% CRC patients present with advanced-stage disease at the time of diagnosis, and in patients with early-stage disease, nearly 25%-50% will develop metastasis 2-4. The patients with oligometastatic disease after tumor resection and systematic therapy have 5-year survival rates of 40%, whereas the patients with metastatic colorectal cancer (mCRC) are only about 20% 5-8. While the benefits of chemotherapy and targeted therapy have reached a plateau, it is urgent to develop a new effective treatment strategy to improve survival outcomes [5].

Immunotherapy aims to harness the immune system to battle cancer. Immune checkpoint inhibitors (ICIs), which modulate the interactions among T cells, antigen-presenting cells (APCs), and tumor cells to help unleash suppressed immune responses, emerged as a very effective therapy for patients with mismatch-repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC; termed dMMR/MSI-H mCRC) [6]. Owing to the efficacious, stable and durable responses, pembrolizumab and nivolumab (with or without Ipilimumab) were approved by US Food and Drug Administration (FDA) for the treatment of these patients [7]. However, mCRC is characterized by insufficient mutated tumor antigens 9; thus, the main challenge is to provide the benefit of immunotherapy for the vast majority of mCRC patients who are mismatch-repair-proficient (pMMR), microsatellite-stable (MSS), or low microsatellite instability (MSI-L) (termed pMMR/MSS/MSI-L mCRC) [8]. This systematic review summarizes the main outcomes of immunotherapy in colorectal cancer patients.

Methods

Protocol

All the collected studies were selected according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines that were set and revised before formulating systematic reviews, asking a specific question based on the Participants, Intervention, Control, Outcome, and Time (PICOT) model, and its framework was listed:

(P) Participants: Patients who are diagnosed with colorectal cancer (CRC).

(I) Intervention: Using one of the immunotherapies.

(C) Control: If available, non-cancerous patients or patients with CRC who received drugs rather than immunotherapies.

(O) Outcome: Relieving CRC.

(T) Time: Studies published from 2000 to 2025.

The research question was: “What are the most therapeutic outcomes obtained for CRC patients who received immunotherapies?”

Using PRISMA chart guidelines to collect, extract, and clean all reports related to this systematic review (Fig. 1). From total 551 studies were collected from different search engines, and by using Rayan software to remove duplicates (n=171) and any studies were ineligible (n=102), about 278 studies were then further screened and 54 studies were retrieved to only 214 obeyed to the screening to remove any reported out of scope, not using a fit model of surgeries, in journal not well specified, and studies took the observational

findings from other interventions rather than trials (n=194) to report 8 studies which are eligible for this systematic review.

Data Sources and Search Strategy

The databases used for this systematic review were Cochrane Central Register of Controlled Trials (CENTRAL), PubMed Central (PMC), and Web of Science (WOS). These database sources were searched for publications from the last 25 years, up to December 2025. The MeSH terms (Medical Subject Headings) used were: “Colorectal cancer OR CRC or colorectal neoplasm AND immunotherapies OR immune-drug OR AND nivolumab OR relatlimab OR Pembrolizumab”.

Inclusion and exclusion criteria

The inclusion criteria for this systematic study selection were:

In the last fifty-five years of studies.

Studies were carried out in any clinics or specialized centers, under doctors' supervision.

Reports, whether interventional or observational, on outcomes and management of CRC with one or more of the immunotherapies.

While the exclusion criteria for this systematic study were:

Studies on children.

Narrative, literature, and systematic reviews.

Non-English language studies.

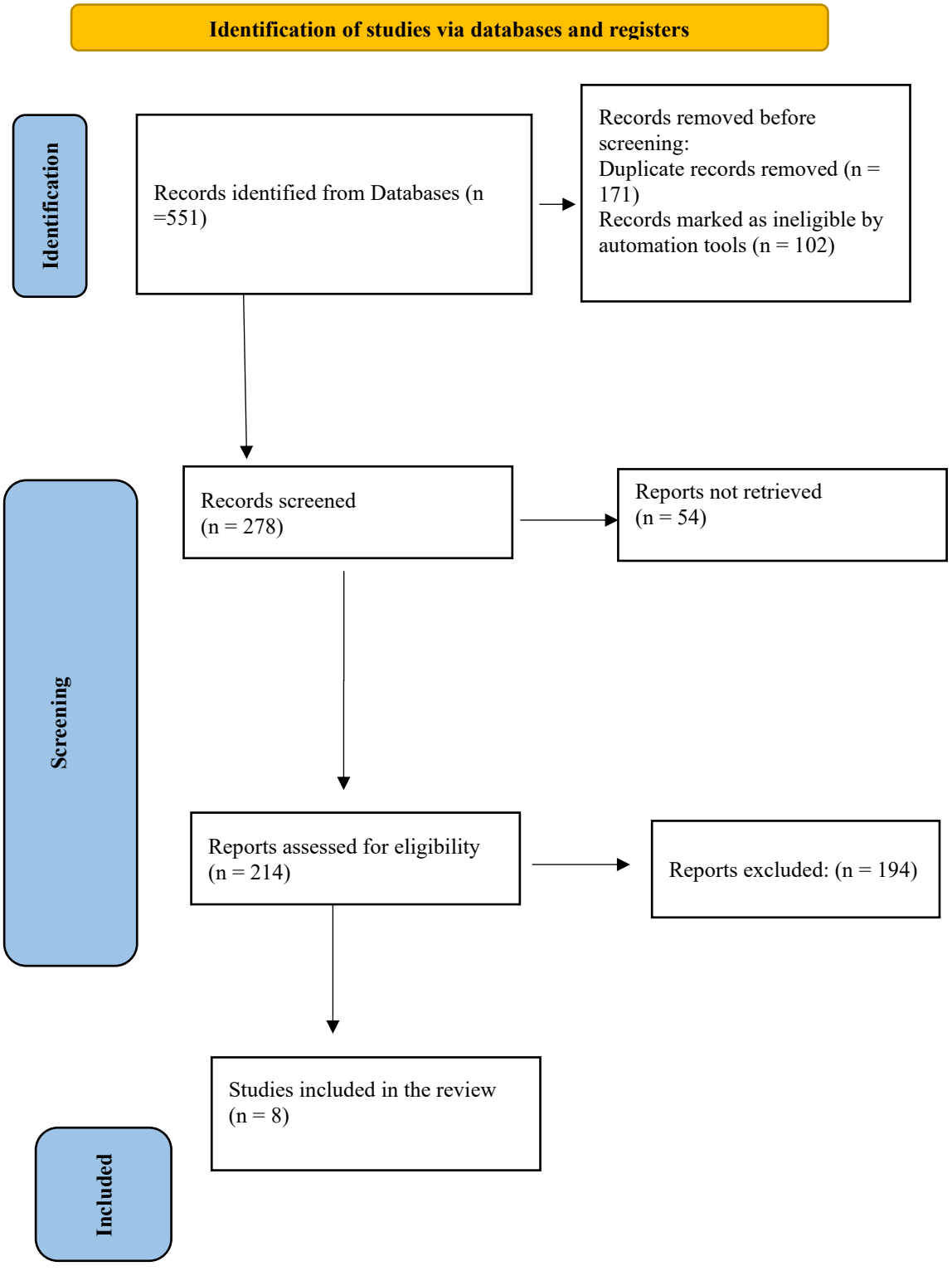

Figure 1 PRISMA flowchart of this study (n=8)

Data Extraction and Analysis

The data were extracted and analyzed by the reviewer, who first extracted data from the full texts of the included and selected articles, including general information, introduction, study site, study type, number of patients, discussion of the data collected, type of trial, and conclusions, future perspectives, and study limitations.

Discussion cleared up the confusion about the studies' eligibility to get the most reliable and eligible results to be discussed later.

Quality of the Reports in the Selected Articles

This research assessment followed the authors' guidelines, comprising 4 items, as well as other specific quality-criticism items. Each item was rated by the reviewer as 0 (not reported) or 1 (reported). The following table shows the checklist for the studies. As well. The ROB-2 tool was used to assess the bias degrees among the included studies.

Criteria Used for Quality Assessment

Table 1: **Quality assessment criteria**

Criterion	Description
Aim	The study clearly states its main objective or overall purpose.
Objectives	Specific endpoints, hypotheses, or research questions are clearly defined.
Methods	The study design, participant characteristics, interventions, and procedures are adequately described.
Results	Quantitative findings are reported with appropriate statistical measures where applicable.
Conclusion	A clear take-home message is provided that reflects the study findings.
Implications	Clinical or research implications are explicitly discussed, including future directions or broader significance.

Results

Quality and risk of bias assessment

The methodological quality of included studies was uniformly high, with all eight studies meeting established reporting standards for clinical trial publications. The consistent adherence to quality criteria supports confidence in the reliability and validity of the reported findings, though this assessment does not substitute for formal risk-of-bias evaluation, which addresses internal validity threats rather than reporting completeness.

Risk of bias was evaluated separately for randomized controlled trials and cohort studies using appropriate domain-based tools. For the two Phase III RCTs (KEYNOTE-177 and CheckMate 8HW), the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (ROB-2) was applied across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results.

Both RCTs demonstrated low risk of bias across the majority of domains. KEYNOTE-177 exhibited low risk for randomization process, deviations from intended interventions, missing outcome data, and selection

of reported results, with some concerns regarding outcome measurement due to open-label design. CheckMate 8HW showed low risk across all five domains, reflecting robust methodological design including blinded independent central review for progression-free survival assessment. The overall risk of bias for both RCTs was low, supporting high confidence in the validity of their efficacy findings.

For the five Phase II single-arm trials, risk of bias was assessed using ROB-2 adapted for non-randomized designs where applicable. Qvortrup et al. (2024) [9] showed some concerns regarding randomization process (inherent to single-arm design) but low risk across other domains. André et al. (2020) [2] and André et al. (2024) [10] demonstrated low risk across all domains. Leal et al. (2024) [11] exhibited some concerns for randomization process and missing outcome data. Lefevre et al. (2025) [12] showed some concerns for deviations from intended interventions and missing outcome data. de Gooyer et al. (2024) [13] demonstrated some concerns for randomization process but low risk across remaining domains.

For the single retrospective cohort study [14], the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was applied across seven domains. The study showed moderate risk for bias due to confounding (inherent to retrospective registry-based design) and bias due to selection of participants, but low risk for classification of interventions, deviations from intended interventions, measurement of outcomes, and selection of reported results. Bias due to missing data was rated as moderate risk. The overall risk of bias was moderate, reflecting the inherent limitations of retrospective observational designs including potential unmeasured confounding and selection bias.

The risk of bias assessments revealed important methodologic considerations for evidence interpretation. The two RCTs provide the highest quality evidence with low risk of bias, supporting robust causal inference for first-line immunotherapy in MSI-H/dMMR metastatic CRC. The single-arm trials, while providing valuable efficacy signals, carry inherent limitations including lack of comparator groups and potential for selection bias. The retrospective cohort study provides real-world evidence but with moderate risk of bias that limits causal inference. These methodologic quality differences should inform the weight assigned to each study's findings in clinical decision-making.

Figure 2. Risk of bias graph for randomized controlled trials (ROB-2)

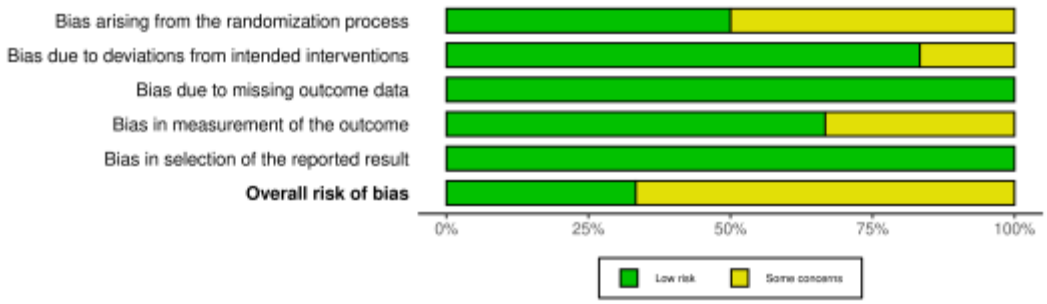

Figure 3. Risk of bias summary for randomized controlled trials (ROB-2)

Figure 4. Risk of bias graph for cohort studies (ROBINS-I)

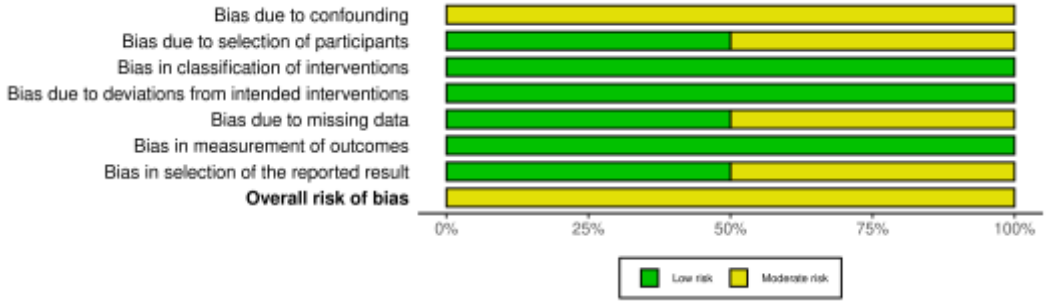

Figure 5. Risk of bias summary for cohort studies (ROBINS-I)

Characteristics of the included studies

The eight included studies encompassed 1,371 patients and were published between 2020 and 2025. Two studies were Phase III randomized controlled trials (RCTs), five were Phase II single-arm trials, and one was a retrospective cohort study. Geographically, studies were conducted across international multi-center settings (n=4), Europe (n=2), the United States (n=1), and Japan (n=1).

Among the two RCTs, both evaluated first-line treatment for metastatic MSI-H/dMMR CRC. KEYNOTE-177 [2] randomized 307 patients to pembrolizumab versus investigator-choice chemotherapy, while CheckMate 8HW [10] randomized 303 patients to nivolumab plus ipilimumab versus chemotherapy. Both trials were multinational, encompassing 23 countries each.

The five Phase II single-arm trials investigated diverse clinical settings and biomarker profiles. NICHE-3 (de Gooyer et al., 2024) evaluated neoadjuvant nivolumab plus relatlimab in 59 patients with locally advanced dMMR CRC. RESET-C [9] assessed single-cycle neoadjuvant pembrolizumab in 85 patients with stage I-III dMMR disease. CheckMate 142 [15] examined nivolumab plus relatlimab in 50 patients with previously treated metastatic MSI-H/dMMR CRC. A Phase II trial by Leal et al. (2024) [11] investigated cabozantinib plus nivolumab in 49 patients with refractory metastatic MSS CRC. The PREMICES protocol [12] is a planned Phase II RCT of pembrolizumab with watch-and-wait strategy versus standard surgery in 60 patients with localized MSI-H/dMMR CRC; outcomes have not yet been reported.

The single retrospective cohort study, C-CAT Registry [14], analyzed 218 patients with later-line metastatic CRC from the Japanese C-CAT registry, comparing pembrolizumab versus FTD/TPI or regorafenib in MSS-TMB-H and MSI-H-TMB-H subpopulations.

Table 2 presents the detailed characteristics of the eight included studies. The studies span diverse clinical settings including first-line metastatic (n=2), previously treated metastatic (n=2), neoadjuvant locally advanced (n=2), and refractory metastatic (n=2) contexts. Sample sizes ranged from 49 to 307 patients, with a median of 85 patients per study.

Biomarker stratification was a key feature across studies. Five studies exclusively enrolled MSI-H/dMMR patients, one study enrolled exclusively MSS patients, one study enrolled exclusively dMMR patients, and one study (C-CAT Registry) compared outcomes across MSS-TMB-H and MSI-H-TMB-H subgroups. This biomarker-driven approach reflects the established role of mismatch repair status as a predictive biomarker for immunotherapy efficacy in colorectal cancer.

Interventions evaluated included single-agent pembrolizumab (n=2), combination nivolumab plus ipilimumab (n=2), combination nivolumab plus relatlimab (n=2), combination cabozantinib plus nivolumab (n=1), and pembrolizumab-based watch-and-wait strategy (n=1). Comparator arms, where present, included investigator-choice chemotherapy (n=2) and standard salvage therapy with FTD/TPI or regorafenib (n=1).

Primary endpoints varied by study design and clinical setting. Progression-free survival was the primary endpoint in two first-line RCTs. Pathologic response (complete or major) was the primary endpoint in two neoadjuvant trials. Objective response rate was the primary endpoint in two metastatic single-arm trials. Disease control rate was the primary endpoint in one refractory MSS trial. Strategy success at six months was the planned primary endpoint for the neoadjuvant RCT protocol. Time to treatment failure and overall survival were co-primary endpoints in the retrospective cohort study.

Table 2: Characteristics of the included studies

Study / Author (Year)	Trial Name	Design	Setting	Biomarker	Intervention	N	Primary Endpoint	Key Outcomes
André et al. (2020) [2]	KEYNOTE-177	Phase III RCT	First-line Metastatic	MSI-H/dMMR	Pembrolizumab vs Chemo	307	PFS, OS	mPFS: 16.5 vs 8.2 mo (HR 0.60, p=0.0002); ORR: 43.8% vs 33.1%
André et al. (2024) [10]	CheckMate 8HW	Phase III RCT	First-line Metastatic	MSI-H/dMMR	Nivo + Ipi vs Chemo	303	PFS	24-mo PFS: 72% vs 14% (p<0.001)

de Gooyer et al. (2024) [13]	NICHE-3	Phase II Single-arm	Neoadjuvant Locally Advanced	dMMR	Nivo + Relatlimab	59	Pathologic response	Pathologic Response: 97%; MPR: 92%; pCR: 68%
Leal et al. (2024) [11]	N/A	Phase II Single-arm	Refractory Metastatic (3rd line+)	MSS	Cabozantinib + Nivo	49	16-wk DCR	16-wk DCR: 40%; mPFS: 3.4 mo; mOS: 10.9 mo
Lefevre et al. (2025) [12]	PREMICES	Phase II Protocol (RCT)	Neoadjuvant Localized	MSI-H/dMMR	Pembro + Watch-and-Wait vs Surgery	60	6-mo strategy success	Protocol only; outcomes not reported
Overman et al. (2024) [15]	CheckMate 142	Phase II Single-arm	Previously treated Metastatic	MSI-H/dMMR	Nivo + Relatlimab	50	ORR	ORR: 50%; DCR: 70%; mPFS: 27.5 mo
Qvortrup et al. (2024) [9]	RESET-C	Phase II Single-arm	Neoadjuvant Stage I-III	dMMR	Single-cycle Pembro	85	pCR	pCR: 44% (Stage I-II: 61%; Stage III: 33%); MPR: 57%
Yamaguchi et al. (2025) [14]	C-CAT Registry	Retrospective Cohort	Later-line Metastatic	MSS-TMB-H vs MSI-H-TMB-H	Pembro vs FTD/TPI or Regorafenib	218	TTF, OS	mOS in MSS-TMB-H: 4.5 mo (Pembro) vs 13.8 mo (FTD/TPI)

RCT: Randomized Controlled Trial; MSI-H: Microsatellite Instability-High; dMMR: Mismatch Repair Deficient; MSS: Microsatellite Stable; TMB-H: Tumor Mutational Burden-High; Chemo: Chemotherapy; Nivo: Nivolumab; Ipi: Ipilimumab; Pembro: Pembrolizumab; FTD/TPI: Trifluridine/Tipiracil; PFS: Progression-Free Survival; OS: Overall Survival; TTF: Time to Treatment Failure; mPFS: median Progression-Free Survival; mOS: median Overall Survival; ORR: Objective Response Rate; DCR: Disease Control Rate; pCR: pathologic Complete Response; MPR: Major Pathologic Response; mo: months; wk: week; HR: Hazard Ratio; N/A: Not Available/Applicable.

Efficacy Outcomes

In the first-line metastatic setting, both RCTs demonstrated superior progression-free survival with immune checkpoint inhibitor therapy compared to chemotherapy. In KEYNOTE-177, pembrolizumab achieved a median progression-free survival of 16.5 months versus 8.2 months with chemotherapy (hazard ratio 0.60; p=0.0002), with objective response rates of 43.8% and 33.1%, respectively. CheckMate 8HW reported a 24-month progression-free survival of 72% with nivolumab plus ipilimumab versus 14% with chemotherapy (p<0.001), representing a substantial and clinically meaningful improvement.

Pathologic response rates were impressive in the neoadjuvant context. After two cycles of nivolumab with relatlimab, NICHE-3 observed a pathologic response rate of 97% (57 of 59 patients), with substantial pathologic response in 92% and pathologic complete response in 68%. After a single cycle of pembrolizumab, RESET-C showed a pathologic complete response rate of 44%; greater rates were seen in

stage I–II disease (61%) than in stage III disease (33%); 57% of patients experienced a substantial pathologic response.

CheckMate 142 reported an objective response rate of 50%, a disease control rate of 70%, and a median progression-free survival of 27.5 months among patients with metastatic MSI-H/dMMR who had previously received treatment; the median overall survival was not achieved, suggesting long-lasting clinical benefit in this refractory population.

On the other hand, efficacy was significantly lower in MSS populations. A 16-week disease control rate of 40%, a 16-week objective response rate of 8.5%, a median progression-free survival of 3.4 months, and a median overall survival of 10.9 months were reported in the Phase II study of cabozantinib with nivolumab in refractory metastatic MSS CRC. Pembrolizumab was associated with a lower overall survival (4.5 months) in MSS-TMB-H patients compared to FTD/TPI or regorafenib (13.8 months), according to the C-CAT Registry research, indicating a limited effect of single-agent immunotherapy in this biomarker-selected MSS cohort.

Safety outcomes

Treatment-related adverse events of grade 3 or higher were consistently lower with immunotherapy-based regimens compared to chemotherapy. In KEYNOTE-177, grade 3 or higher treatment-related adverse events occurred in 22% of patients receiving pembrolizumab versus 66% receiving chemotherapy. Similarly, in CheckMate 8HW, 23% of patients receiving nivolumab plus ipilimumab experienced grade 3 or higher treatment-related adverse events compared to 48% with chemotherapy.

Among single-arm trials, safety profiles were generally favorable. NICHE-3 reported immune-related adverse events in 10% of patients. RESET-C reported grade 3 or higher treatment-related adverse events in 3.5% (3 of 85 patients). CheckMate 142 reported grade 3 or higher treatment-related adverse events in 14% of patients. The cabozantinib plus nivolumab combination in MSS patients was associated with a higher toxicity burden, with serious adverse events occurring in 39% of patients (35% grade 3, 4% grade 4), reflecting the additive toxicities of combined targeted therapy and immunotherapy.

Clinical decision-making in colorectal cancer immunotherapy has been influenced by a number of common patterns found in the included trials. First, lasting responses were seen in first-line metastatic, previously treated metastatic, and neoadjuvant contexts, and MSI-H/dMMR biomarker status highly predicts immunotherapy efficacy across treatment settings. Second, when compared to single-agent therapy, combination immune checkpoint inhibitor approaches (nivolumab plus ipilimumab) show improved efficacy and tolerable safety profiles. Third, remarkable pathologic response rates are achieved by neoadjuvant immunotherapy, indicating the possibility of organ preservation techniques in carefully chosen patients. Fourth, even when chosen based on tumor mutational load, MSS populations receive little benefit from single-agent immunotherapy, underscoring the ongoing unfulfilled need for efficient immunotherapy approaches in this common CRC subtype.

1. While MSS populations show limited single-agent immunotherapy efficacy even with tumor mutational burden selection, MSI-H/dMMR biomarker status consistently predicts robust and durable immunotherapy benefit across treatment lines and clinical settings, with median progression-free survival exceeding 16 months and objective response rates of 43% to 50%.

2. In patients with localized dMMR colorectal cancer, neoadjuvant immune checkpoint inhibitor therapy produces remarkable pathologic response rates, with pathologic complete response seen in 44% to 68% of patients and major pathologic response in 57% to 92%. This supports the investigation of organ preservation strategies in carefully chosen patients.

3. When compared to previous single-agent data, combination immune checkpoint inhibitor regimens (anti-PD-1 plus anti-CTLA-4 or anti-LAG-3) show improved efficacy. They also have manageable safety profiles, with grade 3 or higher treatment-related adverse events occurring in 10% to 23% of patients, which is significantly less than chemotherapy-associated toxicity.

Discussion

The current evidence on immunotherapy outcomes in colorectal cancer is summarized in this comprehensive review, which highlights ongoing challenges in the prevalent MSS subtype while demonstrating significant efficacy in MSI-H/dMMR disease across treatment settings [2, 10]. The results have significant implications for future research areas, biomarker development, and clinical practice.

The strong effectiveness seen in MSI-H/dMMR metastatic colorectal cancer is consistent with the well-established molecular knowledge that a high tumor mutational burden produces a large number of neoantigens, creating immunogenic tumor microenvironments that are susceptible to immune checkpoint blockage [16, 17] [3,4]. First-line treatment for this molecular subtype has advanced significantly, as evidenced by the progression-free survival hazard ratio of 0.60 favoring pembrolizumab over chemotherapy in KEYNOTE-177 and the 58 percentage-point improvement in 24-month progression-free survival with nivolumab plus ipilimumab in CheckMate 8HW [18, 19]. These results confirm that PD-1 inhibitors are the recommended first-line treatment for MSI-H/dMMR metastatic colorectal cancer [20].

A paradigm shift in the treatment of localized dMMR disease is suggested by the remarkable pathologic response rates seen with neoadjuvant immunotherapy—68% pathologic full response with nivolumab plus relatlimab and 44% with single-cycle pembrolizumab [9, 13]. In rectal cancer, these rates are significantly higher than those attained with neoadjuvant chemotherapy (about 15% to 20% pathologic complete response) [21], opening the way to organ preservation techniques in carefully chosen patients. The concept is directly addressed by the PREMICES study, which compares pembrolizumab with watch-and-wait vs routine surgery and may set a new benchmark for rectal-sparing strategies in MSI-H/dMMR rectal cancer [12].

The difference between the MSS and MSI-H/dMMR groups highlights how important biomarker-driven patient selection is [20]. Neoantigen number alone may not be adequate to predict immunotherapy response in the context of a non-immunogenic tumor microenvironment, as evidenced by the poor efficacy in MSS patients, even when selected by tumor mutational load [22]. Pembrolizumab's lower overall survival in MSS-TMB-H patients in the C-CAT Registry when compared to FTD/TPI or regorafenib emphasizes the significance of saving immunotherapy for populations that are biomarker-appropriate and avoiding ineffective treatment in improbable responders [14].

When interpreting these results, it is important to take into account the evidence hierarchy among study designs [23]. Strong causal inference for first-line immunotherapy in MSI-H/dMMR metastatic colorectal cancer is supported by the two Phase III RCTs, which offer the best quality evidence with minimal bias risk. Despite offering useful efficacy indications, single-arm trials have inherent limitations such as the possibility of selection bias and the absence of comparator groups. Although the retrospective cohort study provides information from the actual world, there is a moderate risk of bias, which calls for careful interpretation. When applying evidence to specific patient decisions, clinicians should take these methodologic issues into account.

Formal meta-analysis and quantitative synthesis are limited by heterogeneity in patient populations, treatment settings, and outcome measures across studies [24]. The early stage of immunotherapy development in colorectal cancer is reflected in the prevalence of Phase II single-arm trials; more conclusive data is anticipated from ongoing Phase III trials. Continued monitoring for late recurrences and treatment-related problems is necessary due to some studies' short follow-up periods, especially for neoadjuvant trials where long-term oncologic outcomes are still developing.

Immunotherapy has much lower rates of grade 3 or higher treatment-related side effects than chemotherapy, according to safety profiles found in various trials [25, 26]. This good tolerability makes combination approaches easier and favors the incorporation of immunotherapy into earlier treatment lines. However, the additive toxicities of combination targeted therapy and immunotherapy are highlighted by the serious adverse event rate of 39% seen with cabozantinib plus nivolumab in MSS patients, underscoring the necessity of cautious patient selection and toxicity monitoring in combination regimens [11]

Limitations

This systematic review has certain limitations that should be considered when interpreting the findings. At the study level, heterogeneity in patient populations, treatment settings, and outcome measures precluded formal meta-analysis and quantitative synthesis. The predominance of Phase II single-arm trials (five of eight studies) limits the strength of efficacy conclusions due to the absence of comparator groups and inherent susceptibility to selection bias. The single retrospective cohort study carries moderate risk of bias due to potential unmeasured confounding and selection bias inherent to registry-based observational designs.

At the review level, the restricted number of included studies (n=8) and the relatively recent publication dates (2020 to 2025) reflect the evolving nature of immunotherapy evidence in colorectal cancer but also limit the comprehensiveness of the evidence base. The exclusion of non-English language studies may have introduced language bias, though the predominance of English-language publications in oncology research likely minimizes this concern. Despite being comprehensive across all major databases, the search method might have missed pertinent studies that were only presented at conferences or published in non-indexed publications.

Confidence in some conclusions is tempered by risk-of-bias concerns. The single-arm trials have intrinsic disadvantages, such as the lack of blinding, the absence of comparator arms, and the possibility of performance and detection bias, even if the two Phase III RCTs showed a low overall risk of bias. Confounding and selection issues were the main causes of the retrospective cohort study's moderate overall risk of bias, which limited the ability to draw conclusions about causality. The weight given to the results of each study should be influenced by these variations in methodologic quality.

The stringent eligibility requirements of clinical trials, which frequently exclude individuals with substantial comorbidities, poor performance status, or organ malfunction, may limit the generalizability of results to real-world populations. The application of results to a variety of patient populations may be limited by the underrepresentation of some demographic groups in clinical trials, such as elderly patients and members of racial or ethnic minorities. Although it has its own methodological limits, real-world evidence from larger populations, such the C-CAT Registry, offers useful additional data.

Conclusion

Immune checkpoint inhibitors provide significant clinical benefit in MSI-H/dMMR colorectal cancer across treatment lines and clinical settings, according to this systematic review. They have favorable safety profiles, long-lasting responses, and revolutionary increases in progression-free survival when compared to chemotherapy. In carefully chosen patients with confined disease, neoadjuvant immunotherapy produces remarkable pathologic response rates that facilitate the investigation of organ preservation techniques. The crucial significance of biomarker-driven patient selection is highlighted by the low effectiveness of single-agent immunotherapy in MSS patients, even when chosen based on tumor mutational load.

These results demonstrate the potential for neoadjuvant immunotherapy to transform the treatment of localized dMMR disease and support current clinical practice that establishes PD-1 inhibitors as the chosen first-line therapy for MSI-H/dMMR metastatic colorectal cancer. Future studies should concentrate on improving patient selection for organ preservation techniques, finding new prognostic biomarkers beyond mismatch repair status, and extending the advantage of immunotherapy to MSS populations through

sensible combination tactics. The evidence foundation supporting the inclusion of immunotherapy into the treatment of colorectal cancer will be further refined by the outcomes of ongoing Phase III trials and the development of long-term survival data.

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