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Review Article

Immunotherapy in Colorectal Cancer: A Review

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Abstract

The results of new randomized clinical trials show that immunotherapy is the preferred treatment for a small proportion of metastatic colorectal cancers (mCRCs). For microsatellite instability-high mCRC, pembrolizumab, nivolumab, and ipilimumab are currently authorized as first- and second-line immune checkpoint agents. However, the problem concerns tumors with microsatellite stability where the "cold" microenvironment does not allow immunotherapy to function properly. All efforts are now aimed at ensuring that this microenvironment is inflamed and "hot". In this review, we examine recent studies on immunotherapy for mCRC and assess novel drivers of immunotherapy response.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths and the third leading cause of cancer overall. Treatment strategies for this disease constitute a global health problem.[1] Morbidity and mortality rates are declining due to screening. At diagnosis, 25% of patients with CRC have advanced disease, and 25% to 50% of patients with early-stage disease may have already developed metastases.[2–4] The 5-year survival rate for patients with metastatic disease is 4%, compared to 25% for patients with metastatic colorectal cancer (mCRC) after tumor resection and chemotherapy.[5–8] Even if advantages have been obtained from chemical and targeted therapies, the 5-year prognosis remains poor. Therefore, efforts are being made to develop new drugs. Immunotherapy treats cancer by stimulating the immune system. For patients with deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H), immune checkpoint inhibitors (ICIs) have demonstrated marked effectiveness. By modifying the interaction between T cells, antigen-presenting cells (APCs), and tumor cells, ICIs aim to reinvigorate suppressed immune responses.

Pembrolizumab and nivolumab (with or without ipilimumab) have gained approval from the U.S. Food and Drug Administration as treatments for these patients. However, comprehending the potential benefits of immunotherapy for patients without microsatellite instability (MSS) remains a challenge.[9] This review outlines the present research endorsing the application of ICIs in CRC, emphasizes recent progress in the expanded use of ICIs in MSS/MSI-L CRC patients, and sheds light on emerging biomarkers that could predict the response to immunotherapy.

Methods

We searched PubMed (www.ncbi.nlm.nih.gov/pubmed) for full-text articles published from 2017 to May 31, 2023, using the keywords immunotherapy, cancer, CRC, anti-programmed death ligand 1 (PD-L1), and anti-programmed death-1 (PD-1). The full-text articles found were carefully examined. In addition, all abstracts presented at international conferences between January 2020 and January 2023 were reviewed.

Microsatellites as biomarkers of reactions

DNA integrity relies on the essential function of mismatch repair (MMR).[10] Immunohistochemical staining of MMR proteins—MLH1, MSH2, MSH6, or PMS2—allows the categorization of CRCs into two groups: those with dMMR and those with proficient mismatch repair MMR (pMMR).[11] Microsatellite instability (MSI) can be detected by polymerase chain reaction or next-generation sequencing and may result from insertions or deletions.[11]

MSI refers to changes in microsatellite length resulting from alterations in MMR status. Within the cell surface, major histocompatibility complex class I-peptide complexes contain mutant

Keywords: Colorectal cancer; Immunotherapy; Anti-PD-L1; Anti-PD-1.

Abbreviations: APC, antigen-presenting cell; CR, complete response; clinical CR, cCR; CRC, colorectal cancer; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; DCR, disease control rate; DFS, disease-free survival; dMMR, deficient mismatch repair; FOLFOX, fluorouracil, leucovorin, oxaliplatin; LAG3, lymphocyte-activation gene 3; LARC, locally advanced rectal cancer; ICI, immune checkpoint inhibitor; mCRC, metastatic colorectal cancer; MEK, mitogen-activated extracellular signal-regulated kinase; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, MSI-high; MSS, microsatellite stability; NAR, neoadjuvant rectal cancer; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PFS, progression-free survival; pMMR, proficient mismatch repair; POLD1, DNA polymerase delta 1; POLE, polymerase ε; RT, radiation therapy.

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Table 1. Ongoing trials in patients with dMMR or MSI-H CRC

Treatment	Clinicaltrials.gov Identifier	Phase	Study treatment groups	Primary endpoint	Recruitment status
First-line	NC102563002	III	Pembrolizumab versus standard-of-care chemotherapy	PFS, OS, ORR	Active, not recruiting
	NCT02060188	II	Nivolumab ± ipilimumab or daratumumab or anti-LAG3	ORR	Active, not recruiting
Adjuvant	NC102912559	III	Adjuvant atezolizumab + FOLFOX versus FOLFOX alone	DFS	recruiting
Neoadjuvant	NCT03026140	II	Nivolumab + Ipilimumab ± Celecoxib	safety	recruiting
	NCT02948348	Ib/II	Capecitabine + Radiation + Nivolumab + Surgical therapy	pCR	unknown
	NC102921256	II	Pembrolizumab/veliparib + chemotherapy + radiotherapy	NAR score	Active, not recruiting

CRC, colorectal cancer; DFS, disease-free survival; dMMR, deficient mismatch repair; FOLFOX, fluorouracil, leucovorin, Oxaliplatin; LAG3, lymphocyte-activation gene 3; MSI-H, microsatellite instability-high; NAR, neoadjuvant rectal cancer; ORR, objective response rate; OS, overall survival; pCR, pathological complete response.

peptides recognized as neoantigens that stimulate immune cell priming and infiltration. In the tumor microenvironment, circulating T helper 1 CD4+ T cells, macrophages, and CD8+ tumor-infiltrating lymphocytes release interferons, which exert antitumor effects. However, in dMMR/MSI-H tumor cells, immune evasion is facilitated by continuous upregulation of T-cell inhibitory ligands, such as the B7 family members PD-L1, CD80, and CD86.[12–16] dMMR/MSI-H CRCs account for less than 15% of all CRCs, and their incidence correlates with tumor stage.[17] Only 5% of stage IV patients have dMMR/MSI-H, compared to approximately 20% of patients with stage I or II disease and 12% of patients with stage III disease.[18] As a predictive biomarker for patients at different stages, the dMMR/MSI-H status is important.[18–21] In stages II and III, patients with dMMR/MSI-H tumors exhibit a more favorable prognosis than those with MSI-L tumors. However, intriguingly, even when treated with immune checkpoint inhibitors, stage IV dMMR/MSI-H patients still have a poor prognosis.[22]

Immunotherapy as a second-line treatment for mCRC

Pembrolizumab or nivolumab, with or without ipilimumab, received clinical authorization for use in 2017 as a second-line treatment for mCRC patients with dMMR/MSI-H. Pembrolizumab was administered in the phase II KEYNOTE 016 trial to treat patients with refractory mCRC.[23] Patients with MSI-low achieved an objective response rate (ORR) of 0% and the disease control rate (DCR) was 50%, while patients with dMMR-MSI-H had an ORR of 16% and a DCR of 89%. The CheckMate142 study evaluated nivolumab, with or without ipilimumab, in mCRC and dMMR/MSI-H patients.[24] After 13.4 months, 55% of the patients with MSI-H showed an ORR of 55% and a DCR of 80%, while patients with MSS had an ORR of 0% and a DCR of 16%. The study's 119 participants were assessed for progression-free survival (PFS) and overall survival (OS) at the 12 months, which were 71% and 85%, respectively.[25,26]

Immunotherapy as a first-line treatment in mCRC

Due to the favorable outcomes observed in the second-line treatment of mCRC patients with dMMR/MSI-H tumors, there is growing interest in utilizing immunotherapy as a first-line therapy. Several randomized clinical trials have drawn significant attention (NIH-ClinicalTrials.gov: NCT02563002; NCT02060188).[27]

In a phase III trial called KEYNOTE177, which focused on first-line mCRC patients with MSI-H, pembrolizumab monotherapy was compared to standard therapy (NIH-ClinicalTrials.gov: NCT02563002). A total of 852 screened patients were enrolled, with 307 (36% of those screened) randomized to receive either chemotherapy or pembrolizumab (153 and 154 patients, respectively). Following disease progression, 60% of the patients switched from chemotherapy to anti-PD-1 therapy (56 to pembrolizumab, and 37 discontinued treatment). The median OS with pembrolizumab was not reached at the time of analysis, while it was 36.7 months (with a range of 27.6 to not reached) with chemotherapy. Although pembrolizumab did not demonstrate superiority over chemotherapy in overall survival because the statistical significance threshold was not met (prespecified error of 0.025), the median PFS for pembrolizumab was 16 months (with a range of 5 to 38 months) compared to 8 months (with a range of 6 to 10 months) for chemotherapy. As a result, pembrolizumab as a monotherapy for MSI-H tumors is becoming the standard first-line treatment for mCRC.[28]

In the CheckMate142 trial, the combination of nivolumab and low-dose ipilimumab was evaluated for efficacy and safety as a first-line therapy for patients with MSI-H mCRC.[29] After a median follow-up of 13.8 months, the ORR and DCR were 60% and 84%, respectively, with a complete response (CR) rate of 7%. At 29 months, the ORR increased to 69%, and the CR rate increased to 13%. Notably, the combination of ipilimumab and nivolumab showed superior efficacy and safety compared to pembrolizumab monotherapy.

Additionally, treatment-naive mCRC patients with dMMR/MSI-H were included in the ongoing, randomized phase III COMMIT trial (Table 1), in which 347 patients were enrolled to receive mFOLFOX6/bevacizumab with or without atezolizumab. The primary endpoint of the trial was PFS, and secondary endpoints included OS, ORR, DCR, and frequency of adverse events (NIH-ClinicalTrials.gov: NCT02997228).

Neoadjuvant and adjuvant therapy

Postoperative adjuvant therapy is needed for Stage III CRC patients. The ATOMIC study enrolled 700 stage III dMMR/MSI-H colon cancer patients to evaluate the efficacy of immunotherapy as an adjuvant treatment (NIH-ClinicalTrials.gov: NCT02912559).[30]

The control arm received only FOLFOX for 6 months, while the experimental arm received FOLFOX plus atezolizumab for 6 months, followed by 6 months of atezolizumab alone. The primary endpoint was disease-free survival (DFS), and the secondary endpoints were OS and adverse event frequency. Treatment of early-stage CRC with neoadjuvant immunotherapy has yielded promising results. In the NICHE trial, a phase II study, 40 colon cancer

patients (stage I and III) were included. Among them, 21 had dMMR tumors, and 20 had pMMR tumors (NIH-ClinicalTrials.gov: NCT03026140).[31] All 21 patients with dMMR tumors who underwent ipilimumab and nivolumab treatment after successful surgery achieved a pathological response, indicating the primary endpoint of safety and survival. The efficacy of veliparib or pembrolizumab in combination with chemotherapy and radiation therapy (RT) was evaluated in the NRG-GI002 trial among patients with locally advanced rectal cancer (LARC) (NIH-ClinicalTrials.gov: NCT02921256). The primary endpoint was a reduction in the neoadjuvant rectal cancer score, while the secondary endpoints were sphincter-sparing surgery, pathological CR (pCR), clinical CR (cCR), DFS, toxicity, and OS.[32]

In another study, patients with locally advanced resectable rectal cancer received capecitabine radiation followed by sequential neoadjuvant immunotherapy. Three of the 5 patients with dMMR/MSI-H tumors achieved successful outcomes, specifically, pathologic complete response and major pathologic response (NIH-ClinicalTrials.gov: NCT02948348).[33] These findings suggest that neoadjuvant immunotherapy may replace current CRC treatments for patients with dMMR/MSI-H tumors.

MSS/MSI-L CRC immunotherapy

In contrast to dMMR/MSI-H CRCs, which demonstrate a good response to ICIs, MSS/MSI-L tumors, accounting for approximately 95% of all mCRC, exhibit poor efficacy with ICI treatment due to their low mutational load and limited recruitment of immune cells. To address primary resistance to ICIs, researchers are exploring new approaches and immunomodulatory techniques for MSS/MSI-L CRCs, building on our increasing understanding of the tumor microenvironment in CRCs. Studies have shown that anti-PD-1/PD-L1 and anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibodies have synergistic effects.[34] In the CCTG CO.26 study, the efficacy and safety of combination ICI therapy were evaluated in patients with advanced refractory CRC. This was a phase II trial that compared a combination of PD-L1 and CTLA-4 inhibitors, tremelimumab, and durvalumab, to best supportive care alone in patients with pMMR-MSS/MSI-L CRCs.[35] At a median follow-up of 15 months, the experimental group had a median OS of 6 months, while the best supportive care group had a median OS of 4.1 months. This study was the first to indicate that the combination of anti-CTLA-4 therapy and anti-PD-L1 therapy could improve OS in MSS mCRC patients. Preclinical models have suggested that reducing prostaglandin E2 production could enhance the antitumor efficacy of ICIs.[36,37] In the NICHE phase Ib trial conducted in 2014, patients with pMMR tumors received preoperative treatment with ipilimumab and nivolumab, with or without celecoxib, and a pathologic response was observed in 4 out of 15 patients (27% response rate). In MSI-H tumors, CD8+PD-1+ T-cell infiltration was found to be predictive of response. For KRAS/NRAS/BRAF wild-type mCRC, panitumumab, an epidermal growth factor receptor-targeted monoclonal antibody, was utilized. However, resistance to this treatment has been linked to increased expression of CTLA-4 and PD-L1.[38] In the LCCC1632 single-arm phase II clinical trial, the safety and efficacy of combining nivolumab, ipilimumab, and panitumumab were evaluated in patients with mCRC (NIH-ClinicalTrials.gov: NCT03442569). Among the 49 evaluable subjects, a median PFS of 5.7 months and a 35% response rate at 12 weeks were observed. The trial recruited participants after reaching the primary endpoint due to favorable safety and efficacy outcomes, indicating that the combination of ICI and anti-epidermal growth factor receptor therapy could be used for treating MSS mCRC.

Combination of ICI and radiation therapy

Preclinical investigations have revealed that RT can trigger immunogenic cell death and release damage-associated molecular patterns. Additionally, it can augment antigen presentation by APCs, activate T lymphocytes, and enhance effects through abscopal effects.[39] Damage-associated molecular patterns, characteristic of immunogenic cell death, include immunogenic cell surface markers, inflammatory cytokines, and cancer-related neoantigens that are upregulated on tumor cells. In a single-arm phase II study,[40] the combination of pembrolizumab and external radiation produced a response in only one out of 22 patients with MSI-L CRC. However, more promising outcomes were observed when CTLA-4 and PD-1 were inhibited in combination with RT in a phase II clinical trial (NCT03104439). In this trial, the DCR was 29.2% (7/24), and the ORR was 12.5% (3/24).[41]

Initial findings from the phase I/II VOLTAGE-A trial indicate that a comprehensive approach involving radical surgery, nivolumab, and neoadjuvant chemoradiotherapy could be an effective treatment for MSS patients with LARC.[34] Among the patients in the study, one patient (3%) achieved a cCR but opted out of radical surgery, while 11 out of 37 patients (30%) achieved a pCR. Notably, 38% (14/37) of patients experienced a major pathologic response, illustrating the potential of combining ICIs and RT in the treatment of cancer.

ICI and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor combination

Inhibition of the MEK pathway, a downstream component of the Ras-mitogen-activated protein kinase system, leads to increased expression of MHC-I and PD-L1 within tumors. This enhances the clonal expansion of T lymphocytes surrounding the tumor and improves the effectiveness of ICIs.[42,43] In a phase Ib trial, researchers evaluated a combination approach using the MEK inhibitor cobimetinib and the PD-L1 inhibitor atezolizumab.[44,45] Preliminary results from a 2016 trial indicated that out of 23 patients with CRC, 4 (17%) achieved a partial response. Among them, 3 had MSI-L tumors, and 1 had an unknown status. In the 2018 follow-up data, a total of 7 out of 84 mCRC patients, comprising 6 with MSS/MSI-L and 1 with MSI-H, experienced manageable side effects and partial responses.[46] Despite the potential for synergy that has been established in earlier trials, a subsequent phase III trial, IMblaze 370, which compared atezolizumab versus atezolizumab alone versus regorafenib in refractory CRC patients with MSI-L, did not confirm the anticipated synergistic effects.[47] Nevertheless, several studies have investigated the combination of MEK inhibitors and ICIs (NIH-ClinicalTrials.gov: NCT02060188; NCT03428126; NCT03271047).

ICIs and anti-vascular endothelial growth factor agents

According to preclinical findings, antiangiogenic drugs have the potential to enhance the infiltration of CD8+ T cells into tumors. These drugs can also boost the antitumor activity of CD8+ T cells through various mechanisms, including the upregulation of PD-L1 expression, reduction of immunosuppressive cells such as tumor associated macrophages and Tregs, and improved interaction between APCs and dendritic cells.[48–50]

Additionally, one patient who received ICI therapy combined with an antiangiogenic agent (atezolizumab plus bevacizumab) achieved an objective response.[51,52] Recent studies have also demonstrated remarkable antitumor efficacy with the combination of regorafenib and nivolumab.[53] To investigate the safety and efficacy of the combination of nivolumab and regorafenib, 25 mCRC patients (24 with MSS and 1 with dMMR/MSI-H) were enrolled in the REGONIVO phase Ib/II trial. The results were intriguing, with an ORR of 36% and a median PFS of 7.9 months. The 1-year PFS and OS rates in patients with CRC were 41.8% and 68%, respectively. Given these favorable outcomes, larger cohort studies are warranted.[53] In another study, the combination of pembrolizumab and lenvatinib was assessed in patients with treatment-naive advanced non-MSI-H/pMMR CRC in the LEAP-005 trial, which was an open-label, randomized, phase II trial.[54] At a median follow-up of 10.6 months, the ORR and DCR for the 32 patients were 22% and 47%, respectively. The median PFS and OS were 2 and 3 months, respectively. The duration of the response is still ongoing. Due to the excellent antitumor efficacy and manageable safety profile of these agents, the enrollment in the study was increased to 100 patients.[54]

Biomarkers for immunotherapy

To improve the effectiveness of immunotherapy, it is crucial to investigate biomarkers that contribute to treatment response. The four main categories of biomarkers for CRC immunotherapy include PD-L1 expression, preexisting immune responses, tumor mutations, and the microbiome. Tumor mutation burden (TMB) quantifies the total number of somatic mutations per coding region of the tumor genome and encompasses all nonsynonymous coding mutations in the tumor exome.[55,56] TMB has been shown to be an independent predictor of successful ICI treatment in patients with various malignancies, including CRC.[57–59] Immunotherapy is likely to be more effective for tumors with high TMB due to the correlation between strong immunogenicity and elevated TMB. Notably, both MSI-H and MSS tumors can have increased TMB. Preliminary confirmation of immunotherapy efficacy was obtained in patients with elevated TMB in MSS CRC. In the REGONIVO trial, an exploratory analysis of 23 patients with CRC evaluated the TMB. The group with high TMB had a median PFS of 12.5 months, while the low TMB group had a median PFS of 7.9 months, with ORRs of 50% and 35.3%, respectively. Additionally, the CCTG CO26 trial utilized ctDNA analysis of blood samples to assess plasma TMB. In MSS CRC patients treated with PD-L1 and CTLA-4 inhibitors, improved OS was associated with increased plasma TMB, with a threshold of 28 mutations per megabase. A plasma TMB of 28 was suggested as a potential biomarker for identifying patients who could benefit from receiving durvalumab in combination with tremelimumab.

Role of polymerase ε (POLE)/DNA polymerase delta 1 (POLD1)

Polymerase ε POLE/ DNA polymerase delta 1 (POLD1) play a crucial role in DNA replication.[60,61] In the context of CRC, the development of a hypermutation phenotype in DNA is linked to somatic or germline mutations in POLE and POLD1.[62,63] These mutations are present in approximately 0.1% of tumors classified as MSS or MSI-L, affecting nearly 7.4% of all CRC patients.[64] Notably, POLE-mutant CRCs exhibit distinct characteristics compared to POLE-wild-type CRCs. They are more likely to express effector cytokines, infiltrate CD8+ lymphocytes, express cytotoxic T-cell markers, and have increased levels of PD-L1, PD-1, and CTLA-4.[65] POLE has been found to be more immunogenic than other approved biomarkers, such as MMR and MSI, and it is expected that it could be included as an important biomarker (NIH-ClinicalTrials.gov: NCT03435107; NCT03827044; NCT03150706). The presence of tumor-infiltrating lymphocytes, especially cytotoxic CD8+ T cells, has been associated with improved survival in retrospective studies of CRC.[66] The density and location of T cells within the tumor may have greater predictive value for CRC patients compared to conventional TNM staging approaches.[67] The Immunoscore, a scoring method that assesses the number of CD3+ T cells and CD8+ T cells at the tumor center and infiltrative margins using standardized parameters, was used to evaluate this aspect. Presently, a phase II multicenter trial is underway to evaluate the efficacy of ICIs in combination with chemical and angiogenesis inhibitors as primary therapies for pMMR-MSI-L mCRC patients with high Immunoscores (NIH-ClinicalTrials.gov: NCT04262687). Based on the Immunoscore, tumors are classified as hot, transformed, or cold depending on their immune response. Tumors with T-cell infiltration are referred to as hot tumors, those with inflammation but lacking infiltration are called transformed tumors, and noninflamed tumors are termed cold tumors.[68] This classification considers not only the Immunoscore but also the immune signature and tumor microenvironment. Patients with hot tumors tend to respond better to ICIs, suggesting that they might benefit more from immunotherapy.

PD-L1 levels

The most extensively studied biomarker assessed through immunohistochemistry is the coinhibitory receptor ligand PD-L1. However, it has not been definitively established whether the PD-L1 expression level is linked to the effectiveness of ICIs in treating CRC. In the KEYNOTE016 phase II trial, which evaluated pembrolizumab in patients with refractory mCRC, PFS or OS was observed irrespective of the PD-L1 expression level.[69] Similarly, in the Checkmate142 phase II trial comparing the efficacy of nivolumab monotherapy versus nivolumab in combination with ipilimumab, no significant correlation was found between PD-L1 expression and the ORR.[70]

Role of the microbiota

The gut microbiota plays a significant role in influencing the effectiveness of immunotherapy across various types of cancer. The composition of the gut microbiota might serve as a predictor of the efficacy of ICIs. Certain beneficial bacteria, such as Orcenera, *Lactobacillus johnsonii*, and Muciniphila, have been identified in this context. Moreover, *Inosin-A2A receptor* signaling was found to enhance the antitumor effects of ICI therapy when influenced by *Bifidobacterium pseudolongum* and *A. mucinifera*. A specific mechanism through which the gut microbiota positively interacts with immunotherapy involves T-cell-specific *A2A receptor* signaling. However, further research is needed to fully comprehend how the gut microbiota regulates the host's antitumor immune response in the context of immunotherapy.

Future directions

Given the important results obtained in adjuvant, first-line, and second-line immunotherapy for patients with MSI-H CRC, current research efforts are directed toward achieving similar outcomes in

patients with MSS CRC, where immunotherapy has given disappointing data. Another challenge is to enhance patient profiling and identify new response drivers to optimize immunotherapy response.

Conclusion

In recent years, immunotherapy has led to significant improvements in the survival of a small subset of CRC patients with the MSI-H phenotype. The U.S. Food and Drug Administration has approved pembrolizumab and nivolumab (with or without ipilimumab) as second-line therapies for mCRC patients with dMMR/MSI-H based on strong evidence from two phase II clinical trials. Furthermore, pembrolizumab was approved as a first-line therapy for mCRC with MSI-H status in 2020, following positive results from the KEYNOTE177 trial. Ongoing and upcoming clinical trials suggest that ICIs may also be beneficial as neoadjuvant therapy for early dMMR/MSI-H CRC. However, the majority of mCRC patients with MSI-L tumors face challenges in overcoming primary immunotherapy resistance. To address this subgroup, various ICI-based strategies have been explored to modulate immune cells and enhance therapeutic efficacy. These strategies include RT, combination therapy with antibodies that inhibit PD-1 or CTLA-4, combination therapy with small molecule tyrosine kinase inhibitors such as MEK inhibitors and ICIs, and the use of antiangiogenic agents. Early-phase clinical trials have shown promising results, but further research is necessary to establish the safety and efficacy of these approaches. As immunotherapy progresses, the transition toward biomarker-based therapies is expected. Selection criteria will be crucial in identifying patients who will benefit the most from these therapies. Although some biomarkers have already been identified, ongoing research aims to discover and validate highly sensitive and specific biomarkers.

With expanding knowledge in this field, new combinations of therapies and biomarkers will guide clinicians toward more personalized and targeted treatment strategies for patients with CRC. This personalized approach holds promise for improving outcomes and enhancing the overall effectiveness of immunotherapy in CRC management.

Finally, the limitations of our review are attributed to the small number of studies available for patients with d-MMR and the small number of studies on patients with p-MMR.

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Conflict of interest

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Author contributions

AC and CMP collaborated on the paper's conception and wrote the paper. VG, AC and CMP reviewed the paper and approved the final version of the article to be published

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