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# Advancements and challenges in colorectal cancer immunotherapy: Exploring novel treatment combinations

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## ABSTRACT

Colorectal cancer (CRC) is the most prevalent malignancie worldwide and stands as the 2nd leading cause of cancer-related mortality and the 3rd most frequently diagnosed cancer, showing its substantial impact on global health. While advances in screening and treatment have improved, the clinical management of CRC, mainly in advanced stages pose substantial encounters. Immunotherapy, especially immune checkpoint inhibitors (ICIs) targeting PD-1 and CTLA-4 pathways, has emerged as a promising therapeutic strategy. Agents such as ipilimumab, nivolumab and pembrolizumab have demonstrated clinical benefits in select CRC populations, notably those with mismatch repair deficiency or high microsatellite instability. However, the broader application of ICIs is often constrained by immune-related adverse events (IRAEs), including colitis and severe diarrhea, which compromises treatment adherence and patient quality of life. Increasing attention has turned to natural bioactive compounds (curcumin and resveratrol)-for their immunomodulatory and anti-inflammatory properties. Preclinical and early clinical evidence suggests these compounds may not only enhances the efficacy of ICIs but also reduces the IRAEs. This review explores current

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immunotherapeutic strategies in CRC, evaluates the role of natural immunomodulators as adjuncts to ICIs, and discusses emerging tools such as the immunoscore (IS) for predicting treatment response. By integrating novel combination approaches and predictive biomarkers, future strategies may improve both the effectiveness and safety of immunotherapy in CRC management.

**Keywords:** Colorectal cancer, CRC, Chemotherapy, Combinational therapy, Immunotherapy, Immunoscore, Natural compounds

**Abbreviations:** CTLA-4: Cytotoxic T-lymphocyte-associated antigen 4, CRC : Colorectal cancer, dMMR : Mismatch repair deficiency, DCs : Dendritic cells, ICI : Immune checkpoint inhibitor, IRAEs : Immune-related adverse events, IFN-γ: Interferon-gamma, IS : Immunoscore, mCRC: Metastatic CRC, MSI-H : Microsatellite instability-high, MDSCs : Myeloid-derived suppressor cells, MSS: Microsatellite-stable, MSI-L: Microsatellite instability-low, PD-L1: Programmed death-ligand 1, pMMR: Proficiency mismatch repair, PD-1: Programmed death-1, Tregs: Regulatory T cells, TME: Tumor microenvironment.

## 1. INTRODUCTION

Colorectal cancer (CRC), is the third most frequently diagnosed malignancy and the second leading cause of cancer-related mortality worldwide (69). In United States, survival outcomes vary markedly depending on the stage at diagnosis. The 5-years survival rate for CRC is around 90 % in early stages but decreases to 71 % in stage III and falls sharply to 14 % in stage IV cases (84). A similar trend is observed in China, where 5-years survival rates drop from 85 % at stage I to merely 30 % at stage IV, emphasizing the significance of early diagnosis and revealing regional variations in treatment efficacy (97).

Although treatment advances have significantly improved the prognosis in early-stage CRC, but therapeutic options for advanced disease remain limited. This challenge has spurred growing interest in novel strategies, particularly immunotherapy. A growing body of evidence highlights the prognostic value of cytotoxic $CD8^+$ T cells in CRC, as their infiltration correlates with improved outcomes (11,70,117). Upon activation, these cells secrete interferon-gamma (IFN-γ), which promotes M1 macrophages antitumor activity. However, IFN-γ also induces expression of programmed death-ligand 1 (PD-L1), an immune checkpoint molecule, on tumor and immune cells and programmed death-1 (PD-1) on T cells, facilitating immune escape (33).

Moreover, adenosine released by cancer cells into the tumor microenvironment (TME) promotes the activation of regulatory T cells (Tregs), which suppresses anti-tumor immune responses (33). These Tregs express CTLA-4, a molecule that competes with CD28 for binding to CD80/CD86 on dendritic cells (DCs), ultimately hindering the activation of $CD8^+$ T cells. Immune checkpoint inhibitors (ICIs) targeting PD-1, PD-L1 and CTLA-4 have shown promise in reinvigorating exhausted T cells and restoring antitumor immune responses (78). Thus, immunotherapy has emerged as a pivotal area of research in CRC treatment (Table 1), particularly for patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) tumors, which are more responsive to ICIs (14,40,75).

Table 1. Recent clinical trials in colorectal cancer (CRC) immunotherapy

| Trial | Population | Intervention vs Comparator | Phase / Design | Key Outcome | Ref. |
|---|---|---|---|---|---|
| CheckMate 8HW | MSI-H/dMMR mCRC (n=707) | Nivolumab + ipilimumab (n=354) vs nivolumab (n=353) | Phase 3, randomized, | PFS improved: median PFS not reached vs 39.3 mo (HR 0.62) | 1 |
| KEYNOTE-177 | MSI-H/dMMR mCRC (n=307) | Pembrolizumab (n=153) vs chemo (± bev/cetux) (n=154) | Phase 3, randomized | OS and PFS improved: Median OS 77.5 vs 36.7 mo (HR 0.73); median PFS 16.5 vs 8.2 mo (HR 0.60) | 3 |
| NACRT ± Sintilimab | pMMR CRC locally advance (n=134) | NACRT + sintilimab (n=67) vs NACRT (n=67) | Phase 2, randomized | Pathological complete response 44.8 % vs 26.9 % (p=0.031) | 105 |
| Nivolumab + Relatlimab NICHE-2 | dMMR CRC Non-metastatic (n=115) | Nivolumab + ipilimumab (before surgery) | Phase 2 single-arm | Pathologic response 98 %; pathological complete response 68 % Grade 3-4 in 4 % of patients | 17 |
| Nivolumab + Relatlimab (NICHE-3) | dMMR CRC locally advance (n=59) | Nivolumab + relatlimab (before surgery) | Phase 2, single-arm | Pathologic response 97 %; Pathological complete response 68 % Grade 3 and 4 IRAEs in 80 % and 10 % of patients, respectively. | 27 |
| NEOCAP | dMMR CRC locally advance (n=52) | Camrelizumab + apatinib | Phase 2, single-arm | Pathological complete response 73% Grade 3-5 IRAEs in 38% of patients | 110 |
| LC-CRT + Sintilimab | pMMR/MSS CRC (n=20) | Long-course chemoradiotherapy + sintilimab | Phase 2, single-arm | Pathological complete response 35.0% Grade 4 IRAEs in 60 % of patients | 46 |

This review examines the latest immunotherapeutic strategies for colorectal cancer (CRC) and highlights emerging directions for future research. Key areas of focus include (i). Refining treatment sequences, (ii). Incorporating naturally derived immunomodulators and (iii). Leveraging the immunoscore (IS) as a predictive biomarker. These combined approaches have the potential to enhance the effectiveness of immunotherapy and provide new therapeutic opportunities for patients with advanced CRC.

## 2. ADVANCEMENTS IN IMMUNOTHERAPY FOR CRC

### 2.1. Immunotherapy in the dMMR-MSI-H and MSS CRCs

The conventional hypothesis behind immune checkpoint inhibitors (ICIs) centers on two key regulatory pathways that limit anti-tumor immunity: PD-1/PD-L1 and CTLA-4. The antagonist of CTLA-4 activates T cells by blocking the suppressive CTLA-4 receptor, such as ipilimumab. Similarly, the antagonist of PD-1 inhibitors prevent tumor-induced immune evasion by targeting the PD-1 axis, like nivolumab and pembrolizumab. These ICIs have demonstrated significant clinical benefit in MSI-H CRC patients. In fact, these antagonists are all approved in the MSI-H refractory metastatic CRC (mCRC) treatment, with pembrolizumab currently recommended as a first-line option. Recent evidence from clinical trials also indicates that neoadjuvant immunotherapy may become the standard approach for patients with dMMR-MSI-H mCRC (40). In contrast, MSS CRCs, which represents approximately 85 % of all CRC patients, remains largely unresponsive to immunotherapy. This resistance is primarily attributed to the lower mutational burden and reduced neoantigen presentation in MSS tumors, resulting in a less immunogenic tumor microenvironment.

#### 2.1.1. Benefits of dMMR-MSI-H CRC

Immunotherapy is effective in tumors characterized by dMMR-MSI-H (9,10,24,37,60,94). The primary studies (2010 to 2013) highlighted the limited efficacy of ICIs conducted in unselected CRC populations. However, in a subset of dMMR-MSI-H CRC patients, early trials reported encouraging outcomes: 4 out of 10 patients achieved partial responses, while 5 experienced stable disease at 20 weeks. Subsequent investigations further validated these findings, demonstrating response rates up to 40 % and disease control up to 78 % in dMMR-MSI-H cohorts (54,55). The CheckMate 142 trial provided additional support, evaluating nivolumab monotherapy in 74 dMMR-MSI-H mCRC patients. The study demonstrated an objective response rate of 31 % and a disease control rate of 69 %, both sustained for minimum of 12 weeks (81). Interestingly, the combination nivolumab with ipilimumab increases a response rate of 55 %, with 52 % of patients experiencing stable disease. However, the enhanced efficacy came with an increased incidence of immune-related adverse events (79,80). These cumulative findings led the U.S. FDA to approve both nivolumab and pembrolizumab in 2017 for dMMR-MSI-H mCRC in the second-line treatment. Based on this, a landmark phase III clinical trial published in 2020 compared pembrolizumab with standard chemotherapy in 307 treatment-naïve patients with metastatic dMMR-MSI-H CRC (2). Pembrolizumab significantly improved progression-free survival (16.5 months vs. 8.2 months) and was relate to a substantially lower rate of severe adverse events (22 % vs. 66 %), supporting its use as a safer and more effective therapy in this molecularly defined patients.

However, despite these promising findings, not all dMMR-MSI-H CRC patients respond to immunotherapy (36). In some cases, tumors are intrinsically resistant and fail to respond to treatment from the beginning, while in others, resistance emerges over time despite an initial therapeutic effect. These patterns emphasize the urgent need to identify biomarkers that can predict treatment outcomes and to develop combination strategies to effectively counteract both primary and acquired resistance.

#### 2.1.2. Overcoming resistance in MSS CRC

Enhancing the effectiveness of immunotherapy in MSS CRC represents a critical frontier in research. Multiple factors contribute to the resistance observed, including the complex tumor microenvironment (TME), tumor immunogenicity, dysfunctional major histocompatibility complex molecules, T cell dysfunction and tumor gene mutations. The TME, including tumor cells, non-cellular signals, immune cells and fibroblasts, plays a pivotal role in this resistance (14,25,42).

Although advancements have been made with combination of CTLA-4 inhibitors with PD-1/PD-L1 inhibitors, oncolytic viruses, modulation of the gut microbiota, antiangiogenic agents, chemotherapy, radiotherapy and epigenetic drugs, the treatment of CRC with pMMR and low microsatellite instability (MSI-L)/MSS status remains a significant challenge. Nonetheless, growing evidence suggests that multi-pathway combination strategies involving PD-1/PD-L1 inhibitors may offer therapeutic potential in this context (14,25). Although immune checkpoint inhibitors have shown limited effectiveness in MSS CRC, researchers are actively investigating new strategies to overcome this resistance and improve therapeutic outcomes (36,107). One promising direction is the integration of immunotherapy with targeted therapies, aiming to increase tumor immunogenicity and remodel the tumor microenvironment to enhance responsiveness to checkpoint blockade (86). Additionally, personalized immunotherapeutic strategies are under investigation, utilizing advanced genomic profiling to identify actionable mutations or predictive biomarkers that may inform and optimize individual treatment plans.

### 2.2. Combination treatment

The limited efficacy of ICIs in mCRC is largely attributed to the tumor's innate resistance to immunotherapy. To address this challenge, recent studies have explored strategies to boost treatment responsiveness by combining ICIs with conventional approaches-including targeted therapies, radiotherapy and agents that modify the TME (101).

The TME is a key driver of cancer initiation, progression and metastasis (82). It comprises not only tumor cells but also a dynamic interplay of fibroblasts, endothelial cells, pericytes and both adaptive and innate immune cells. In addition to cellular components, TME includes structural and signaling elements such as the extracellular matrix and various soluble factors (22,77). Its heterogeneous and dynamic nature heavily influences immune cell infiltration and consequently, the effectiveness of PD-1/PD-L1 blockade therapies (77,116). Immunosuppressive elements within the TME, such as cancer-associated fibroblasts, regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages and suppressive cytokines, further contribute to resistance against ICIs by maintaining an immune-evasive environment (82). Thus, therapeutic strategies increasingly aimed at remodeling the TME to overcome these barriers. Effective strategies focus on enhancing cytotoxic $CD8^+$ T cell infiltration into the tumor and counteracting the immunosuppressive environment that hinders antitumor immunity. By targeting these aspects of the TME, researchers aim to restore immune responsiveness and improve the efficacy of immunotherapy in mCRC.

#### 2.2.1. Targeted therapy enhances immunotherapy

Epigenetic modulation and targeted therapies are useful in promoting the effectiveness of ICIs in CRC. Decitabine, a DNA methyltransferase inhibitor, has been reported to activate immune-related genes (109). In murine CT26 CRC models, decitabine increased lymphocyte infiltration at tumor sites. Notably, Combining decitabine with PD-1 blockade resulted in substantially greater tumor growth inhibition and significantly extended survival compared to either treatment alone, suggesting synergistic effects that enhances antitumor immunity.

Similarly, regorafenib, a multikinase inhibitor, has demonstrated synergistic activity in preclinical models of MSS CT26 and hypermutated MC38 colon cancers with anti-PD-1 therapy (29). Regorafenib reduced the existence of tumor-associated macrophages and immunosuppressive regulatory T cells (Tregs) in the TME, while PD-1 blockade elevated IFN-γ levels. The combined treatment promoted sustained M1 macrophage polarization and reduced Treg infiltration, collectively contributing to enhanced tumor suppression.

In addition, hydrogen sulfide, a gasotransmitter implicated in CRC pathogenesis, supports an immunosuppressive tumor milieu by promoting Treg activation and impairing CD8+ T cell trafficking (113). Experimental reduction of hydrogen sulfide levels significantly decreased Treg populations and improved the CD8+/Treg ratio. This immune reprogramming enhanced the responsiveness to anti-PD-L1therapy and anti-CTLA-4 therapy, indicating that modulation of hydrogen sulfide signalling is a viable approach to overcome resistance to immunotherapy in CRC.

### 2.2.2. Radiotherapy enhances immune cell infiltration

Radiotherapy has emerged as a key component in combination cancer therapies due to its multifaceted role in not only directly killing tumor cells but also modulating the TME. It can enhance tumor immunogenicity, trigger local inflammatory responses and facilitate the infiltration of immune cells. A recent preclinical study investigated a triple-combination strategy involving the ATR inhibitor berzosertib, radiotherapy and anti-PD-L1 therapy in CRC mouse models with different microsatellite statuses (64). The dual treatment of berzosertib and radiotherapy activated the innate immune response and upregulated type I interferon-associated genes. This immunomodulation helped convert the immunologically "cold" TME into a "hot" one, significantly increasing $CD8^+$ T cell infiltration and therapeutic efficacy.

### 2.2.3. Photothermal therapy induces immunogenic cell death

Photothermal therapy (PTT) represents an innovative strategy in cancer treatment, when integrated with immunotherapy. In a recent study (98), researchers engineered a multifunctional nanocomposite (GNC-Gal@CMaP) that includes hollow gold nanocages, anti-PD-L1 antibodies and a TGF-β inhibitor. This nanoplatform specifically targets colon cancer cells, enabling low-temperature photothermal ablation. The treatment triggers immunogenic cell death, which in turn activates antibody-responsed cells and promotes the recruitment and activation of the effector T cells. This synergistic effect significantly enhances the PD-L1 immune checkpoint inhibitor anti-tumor activity.

### 2.2.4. Gut microbiota and immunotherapy resistance

Emerging evidence highlights the gut microbiota as a critical determinant of both CRC progression and response to immunotherapy. In patients with mCRC who had not previously received immune checkpoint inhibitors, elevated levels of *Fusobacterium nucleatum* and succinic acid were associated with resistance to immunotherapy (49). This resistance is driven by the inhibition of the cGAS-interferon-β signaling pathway, which impairs $CD8^+$ T cell trafficking to the tumor site. Therapeutic strategies targeting the microbiota have shown promise. The antibiotic metronidazole reduces the *F. nucleatum* abundance and restore responsiveness to immune checkpoint blockade. Furthermore, an advanced nanomedicine combining *F. nucleatum* cytoplasmic membranes with colistin-loaded liposomes selectively eradicated the bacterium, thereby, reinvigorating anti-tumor immune responses.

Additionally, probiotics such as *Lacticaseibacillus rhamnosus* Probio-M9 have demonstrated potential to sensitize tumors to immunotherapy (38). Probio-M9 supplementation reshaped the gut microbial community, increased beneficial metabolites in both the intestine and bloodstream, suppressed regulatory T cell (Treg) activity and enhanced cytotoxic T lymphocyte infiltration in the TME, collectively supporting improved immunotherapy outcomes.

## 3. CHALLENGES IN IMMUNOTHERAPY FOR CRC

### 3.1. Adverse effects of immunotherapy

While immunotherapy has revolutionized cancer treatment, its clinical use in CRC poses significant challenges, particularly regarding immune-related adverse events (IRAEs). These side effects, ranging from mild to life-threatening, can contribute to increased morbidity and even mortality, especially when they delay critical interventions such as surgery in the neoadjuvant setting.

IRAEs may affect multiple organ systems, including the colon, liver, lungs, pituitary gland, thyroid, skin, heart and nervous system. The severity and type of toxicity are influenced by the specific ICIs administered. Agents like ipilimumab, nivolumab and pembrolizumab are associated with distinct profiles and combination regimens present a heightened risk of complications such as colitis and multi-organ involvement (51,68).

The clinical management of IRAEs typically involves immunosuppressive agents, most commonly corticosteroids. However, the impact of these treatments on cancer outcomes remains a topic of debate. Although some meta-analyses have indicated that corticosteroid use does not compromise the efficacy of ICIs, other findings-such as those reported by Burdett *et al.* (12) suggest inconsistent effects on survival outcomes. Moreover, in cases of steroid-refractory IRAEs, the use of anti-tumor necrosis factor (TNF) agents in combination with steroids has poorer survival compared to steroid use alone (4).

Timely recognition and management of IRAEs are critical, yet these side effects often go unrecognized in general clinical settings. With the increasing adoption of immunotherapy, it is essential to improve awareness across the healthcare system. Early diagnosis, prompt discontinuation of the offending agent, initiation of steroid therapy and appropriate supportive care are crucial in managing IRAEs such as colitis and diarrhea, ultimately reducing the risk of adverse outcomes (76). Continued research is essential to deepen the understanding in the complex interactions between the immunosuppression, IRAEs and cancer outcomes.

### 3.2. Role of natural compounds in enhancing immunotherapy

Emerging preclinical evidence suggests that certain natural compounds may improve the immunotherapy effectiveness in CRC by modulating immune responses and mitigating side effects. Among the most studied are resveratrol and curcumin, both of which exhibit immunomodulatory, anti-inflammatory and anti-tumor properties (99).

Resveratrol has protective effects in experimental models of colitis, such as DSS-induced ulcerative colitis, by attenuating inflammation, suppressing autophagy and regulating the SIRT1/mTOR pathway (115). These effects are particularly relevant for CRC patients, where intestinal inflammation contributes to tumor progression (21,67,104). Resveratrol and its derivatives have also been shown to influence tumor immunity by reducing regulatory T cell (Treg) activity and enhancing cytotoxic CD8+ T cell responses (6,20). Notably, resveratrol disrupts PD-L1 membrane localization by interfering with N-glycan branching and promoting PD-L1 dimerization, potentially enhancing tumor sensitivity to ICIs by limiting PD-1/PD-L1 interactions (19,89,96).

Curcumin, the active constituent of turmeric (*Curcuma longa*), has similarly drawn attention for its broad anti-inflammatory and immunoregulatory activities (62,86). It has proven effective in reducing inflammation in both preclinical and clinical models of colitis, including ulcerative colitis (66,95). Curcumin modulates Treg functions by inhibiting immunosuppressive signaling molecules such as CTLA-4 and reducing the secretion of inhibitory cytokines. Additionally, it alters IL-2 availability, a key cytokine in Treg survival and proliferation (90).

In the CT26 murine colon cancer model, combining curcumin with anti-PD-1 therapy amplifies the tumor-suppressive effects of PD-1 blockade and promotes a greater accumulation of immune cells with antitumor activity within the tumor microenvironment (45). In CRC patients, curcumin has been associated with a decrease in Foxp3+ Treg populations and a corresponding increase in Th1 cells, driven by inhibition of Foxp3 expression and conversion of Tregs into Th1 cells (106). Similar immune shifts have been observed in lung cancer patients, where curcumin boosts IFN-γ production by CD4+ T cells, suppresses Tregs and promotes a Th1-dominant response (118). Furthermore, curcumin reduces the appearance of immune checkpoint molecules like PD-L1, PD-L2, Galectin-9 and TIM-3 in cancers like head and neck squamous cell carcinoma, thereby, reactivating exhausted CD8+ T cells and restoring their cytotoxic function (62).

While immune-related toxicities (IRAEs) are often seen as drawbacks, their presence has been associated with improved responses to checkpoint blockade, underscoring the delicate balance between immune activation and tolerance. Natural compounds, including resveratrol, curcumin and shikonin (18,41,47,65,85,111), berberine (35,64,88,92), licochalcone A (58,63,112), naringenin (52,74,114), 6-gingerol (28,34,50), *Ganoderma lucidum* polysaccharides (59) and paclitaxel (13,26,53,103) are being investigated for their potential to both enhance antitumor immunity and mitigate IRAEs.

This growing body of research points toward a promising integrative strategy: Combining natural compounds with existing immunotherapies to enhance efficacy, reduce toxicity and improve patient outcomes (56).

### 3.3. Impact of chemotherapy on immunotherapy

Chemotherapy is a fundamental component in the therapeutic arsenal against CRC, significantly improving survival across age groups and disease stages. For instance, a large-scale study by Chen *et al.* (20) involving 34,857 elderly patients (aged ≥70) in China found that chemotherapy improved to 61.3 % in the 5-years survival rate, related to 50.7 % in patients without chemotherapy. Similarly, an analysis of data from 48,336 U.S. patients aged 18 to 65 demonstrated that chemotherapy was related to a significantly higher 5-years survival rate (76.7 %) compared to those who remained untreated (65.1 %). The 10-years survival rate also favoured chemotherapy (63.8 % vs. 49.3 %) (31). Moreover, in a 31,310 stage IV colon cancer patients study in the USA, Xu *et al.* (108) found that the highest 5-years survival rate (28.3 %) occurred in patients who underwent both chemotherapy and primary tumor resection, emphasizing the chemotherapy in advanced disease.

Beyond its direct cytotoxic effects, chemotherapy also influences antitumor immunity. Certain agents, such as 5-fluorouracil (5-FU), promote immune activation by inducing apoptosis in immunosuppressive myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment, thereby reducing immune evasion (43,83,100). Oxaliplatin, another common chemotherapeutic, enhances antigen presentation through immunogenic cell death, leading to stronger tumor-specific immune responses (5,15,87). Preclinical evidence supports this synergy; for example, mouse models treated with oxaliplatin in combination with immune checkpoint inhibitors (ICIs) exhibited improved survival outcomes (93).

Clinically, combining chemotherapy with immunotherapy is being explored as a strategy to enhance treatment efficacy, while potentially mitigating immune-related adverse effects (43,83). Trials involving combinations such as 5-FU and atezolizumab (anti-PD-L1) have demonstrated improvements in some survival metrics, although progression-free survival has shown limited benefit (102). A critical caveat is the dual nature of chemotherapy: While it may potentiate antitumor immunity, its nonspecific cytotoxicity can also impair immune cell function, limiting its long-term compatibility with immunotherapeutic approaches (16,32).

This dual impact has prompted a shift in treatment paradigms. Rather than reserving immunotherapy for the post-chemotherapy phase, recent studies advocate for administering ICIs prior to surgery. This neoadjuvant approach may prime the immune system, enabling more robust recognition and elimination of tumor cells. For example, combining ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) before surgery in early-stage colon cancer patients with the regardless of mismatch repair (MMR) status has led to notable clinical responses, including pathological complete responses and increased $CD8^{+}PD\text{-}1^{+}$ T cell infiltration (72). These results lend support to the idea that carefully timed sequencing of chemotherapy and immunotherapy could enhance clinical outcomes. However, additional research is necessary to confirm the efficacy of such strategies.

### 3.4. Role of immunoscore (IS) in guiding immunotherapy

The IS has emerged as a valuable prognostic and predictive tool in colorectal cancer by quantifying immune infiltration in both the tumor core (CT) and invasive margin (IM), specifically $CD3^{+}$ and $CD8^{+}$ T cells. These T-cell densities are converted into percentiles and their mean is used to stratify patients into three categories: IS-Low (0-25 %), IS-Intermediate (25-70 %) and IS-High (70-100 %).

Numerous studies have established a strong association between elevated immune scores (IS) and favorable clinical outcomes (7,71). A major international analysis involving cohorts from North America, Europe and Asia showed that in stage I/II colon cancer, patients with high IS had the lowest recurrence rates (76.4 % at 3 years), compared to intermediate (65.9 %) and low IS groups (56.9 %). High IS was also linked to longer recurrence-free, disease-free and overall survival.

Importantly, IS may also guide chemotherapy decisions. In stage III colon cancer, where only ~20 % of patients derive significant benefit from adjuvant chemotherapy (7), IS could serve as a stratification tool to identify those who are likely to respond. Patients with high IS and pMMR status, representing approximately 32 % of the population, have shown superior progression-free survival when treated with immunotherapy compared to standard chemotherapy alone (44).

European studies confirmed that IS-low tumors are associated with poorer disease-free survival across treatment regimens, including CAPOX and FOLFOX, regardless of patient demographics or clinical risk factors (30). Notably, patients $\leq$ 65 years old with IS-high tumors consistently had the best outcomes, particularly with CAPOX. Analysis of 1,762 patients by mismatch repair status revealed that IS is a significant prognostic factor in MSS tumors ($P < .001$), but not in dMMR cases ($P = .57$), highlighting IS's relevance in guiding treatment for the majority of CRC patients who are MSS.

Evidence from Tunisia further supports IS as a predictor of survival, with IS-high patients demonstrating significantly improved outcomes ($P < .001$) (48). Additionally, IS may influence the expected benefit from chemotherapy. Patients with high IS appear to derive greater benefit from adjuvant chemotherapy-even among low-risk groups-while those with low IS show minimal benefit (39). In some instances, patients with high IS have remained relapse-free without any chemotherapy (6,71), suggesting that such individuals might safely avoid the toxicity of cytotoxic treatment altogether.

Overall, IS analysis represents a promising tool for guiding personalized treatment in colorectal cancer. By stratifying patients based on their likelihood of responding to immunotherapy or chemotherapy, it enables more precise treatment selection and helps avoid the risks of overtreatment.

## 4. FUTURE PERSPECTIVES

Resistance to immunotherapy in CRC remains a significant challenge, influenced by the unique immune environment of the gastrointestinal tract and severe adverse reactions, such as colitis associated with CTLA-4 and PD-1 antagonists. While immunotherapy has shown promise in treating CRC, its clinical success is often hindered by these issues (Figure 1). A multifaceted approach may be required to overcome these barriers.

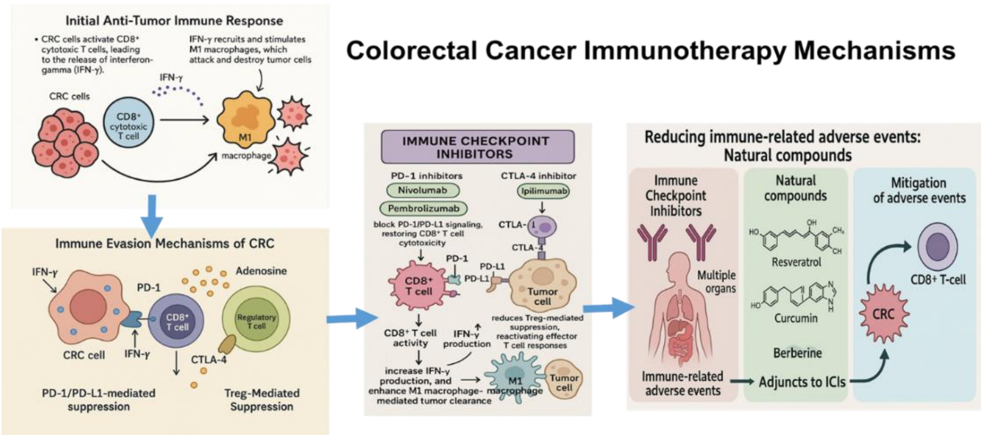


Figure 1. Immune Evasion and Checkpoint Blockade in Colorectal Cancer: Role of $CD8^+$ T Cells, IFN-γ, and Natural Compound Adjuncts. Colorectal cancer (CRC) triggers an initial anti-tumor immune response by activating $CD8^+$ cytotoxic T cells, which release interferon-gamma (IFN-γ). This cytokine enhances the recruitment and activation of M1 macrophages that directly attack and destroy tumor cells. However, CRC develops immune evasion strategies that undermine this defense. IFN-γ upregulates PD-L1 expression on CRC cells and PD-1 on $CD8^+$ T cells, creating an inhibitory PD-1/PD-L1 interaction that suppresses T-cell activity and reduces IFN-γ production. At the same time, CRC-driven adenosine accumulation promotes regulatory T cell (Treg) activation and these Tregs express CTLA-4 to further inhibit $CD8^+$ T cell function. To overcome these suppressive mechanisms, immune checkpoint inhibitors (ICIs) such as PD-1 inhibitors (Nivolumab, Pembrolizumab) and CTLA-4 inhibitor (Ipilimumab) block these inhibitory pathways, restoring effector T cell responses, increasing IFN-γ secretion, and enhancing macrophage-mediated tumor clearance. Despite their efficacy, ICIs are limited by immune-related adverse events (IRAEs), which can affect multiple organs. Natural compounds like resveratrol, curcumin, and berberine, as well as traditional Chinese medicine, show promise as adjunct therapies to improve $CD8^+$ T cell antitumor activity while reducing IRAEs, thereby supporting the safe and effective use of ICIs in CRC treatment.

Natural compounds, such as resveratrol and curcumin have gained considerable attention for their promising immunomodulatory potential that may enhance the effectiveness of immunotherapy, while minimizing off-target side effects (73) (Figure 1). The use of Traditional Chinese medicine, containing natural compounds, could additionally improve immunotherapy by promoting the $CD8^{+}$ T cell proliferation and optimizing the TME, thereby reducing off-target effects (57). Moreover, tumor IS analysis has shown promise as a robust prognostic factor, particularly in MSS CRC cases, supporting precision medicine by pinpointing individuals with a higher probability of immunotherapy responsiveness (39,71).

## 5. CONCLUSIONS

While immunotherapy offers considerable promise in CRC treatment (39,57,71), challenges such as immune resistance and adverse reactions need to be addressed. Further investigations and clinical validations are needed to substantiate these approaches and refine treatment protocols, ultimately improving the therapeutic landscape for CRC patients.

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## FLUNDING

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## AUTHORS CONTRIBUTION

We declare that all authors of this work have made substantial contributions

## CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

## DECLARATION

On behalf of both authors, I confirm that both have made substantial contributions to the conception, design, acquisition, analysis, or interpretation of data for this manuscript. No individual who has made significant contributions has been excluded from authorship. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

## ETHICAL APPROVAL

This is to inform you that in this study, we have not been involved in any animal and human studies.

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