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REVIEW ARTICLE

Emerging evidence of immunotherapy for colorectal cancer

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Abstract

Since the advent of immune checkpoint inhibitors, which modulate the interplay between the tumor cell and immune system, immunotherapy has become widely recognized as a new standard treatment for cancers including microsatellite instability-high (MSI-H) colorectal cancer. Immune checkpoint inhibitors such as pembrolizumab and nivolumab (anti-PD-1 antibodies) that act in the effector phase of T cells and ipilimumab (anti-CTLA-4 antibody) that acts mainly in the priming phase are now in clinical use. These antibodies have shown therapeutic efficacy in MSI colorectal cancer patients who have failed to respond to existing standard therapies. Pembrolizumab is also strongly recommended as first-line therapy for MSI-H metastatic colorectal cancer. Therefore, the MSI status and tumor mutation burden of the tumor should be clarified before starting treatment. Because many patients do not respond to immune checkpoint inhibitors, combination therapies with immune checkpoint inhibitors, including chemotherapy, radiotherapy, or molecularly targeted agents, are being investigated. Furthermore, treatment methods for preoperative adjuvant therapy for rectal cancer are being developed.

KEYWORDS
immune checkpoint inhibitor, locally advanced rectal cancer, metastatic colorectal cancer, microsatellite instability

1 | INTRODUCTION

Immune checkpoint inhibitors (ICIs) have proven to be helpful in treating various cancers.[1–4] ICI monotherapy shows low toxicity and is a promising therapy in terms of balancing efficacy with safety. While ICIs (anti-PD1, anti-PD-L1, and anti-CTLA4) are shown to be effective in some cancer types,[5–7] their efficacy in colorectal cancer (CRC) is still under investigation. However, a long-lasting effect of ICIs has been observed in a subset of patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic CRC (mCRC). Tumors with dMMR/MSI-H harbor hundreds to thousands of somatic mutations in genes encoding potential neoantigens.[8] Therefore, these tumors are likely immunogenic, triggering upregulation of immune checkpoint proteins and are highly responsive to ICIs. In contrast, immune checkpoint inhibitors have little effect on microsatellite stable (MSS) CRC.

This review outlines the latest advances in ICI therapy for dMMR or MSI-H mCRC, preoperative treatment for rectal cancer, and postoperative adjuvant chemotherapy. Furthermore, we discuss the prospects for ICI therapy in colorectal cancer.

2 | IMMUNE CHECKPOINT INHIBITORS

PD-1, a co-inhibitory receptor of PD-L1, inhibits antigen-specific T cell proliferation through ligand binding (PD-L1), which is

indispensable for peripheral immune tolerance.[9–12] PD-1/PD-L1 is a primary immunoregulatory mechanism for cancer cells to escape T-cell immune surveillance.[13] CTLA-4 is expressed on the surface of T cells activated by the presentation of tumor antigens from dendritic cells. CTLA-4 binds to CD80/86 more strongly than CD28, which activates T cells, thereby suppressing T cell activation. Monoclonal antibodies that block these pathways exert antitumor effects by activating tumor-specific cytotoxic T lymphocytes (CTLs) in the tumor microenvironment and reactivating antitumor immunity.[14] These agents, including anti-PD-1 (pembrolizumab, nivolumab), anti-PD-L1 (atezolizumab, avelumab, durvalumab), and anti-CTLA-4 (ipilimumab), have been introduced into clinical practice.

Immune checkpoint inhibitors were initially developed for CRC in several early trials; a phase I study of nivolumab in 20 CRC patients did not demonstrate efficacy, except for one case with complete response (CR).[10] Subsequent analysis showed that this CR case was MSI-H CRC.[15]

3 | MICROSATELLITE INSTABILITY TESTING FOR CRC

Mismatch repair (MMR), which repairs non-complementary base pairings during DNA replication, is essential for genome homeostasis.[16,17] A decrease in MMR function causes a change in the number of microsatellite repeats of one to several bases; a phenomenon termed microsatellite instability (MSI).[18] MSI-H can lead to the accumulation of mutations in genes involved in tumor suppression, cell proliferation, DNA repair, and apoptosis, contributing to tumorigenesis and tumor growth.

Approximately 15% of CRCs are dMMR/MSI-H CRC,[19–21] and a lower percentage (3%-6%) of stage IV CRCs are dMMR/MSI-H CRC.[22–24] dMMR/MSI-H CRC accounts for approximately 20%-30% of Lynch syndrome cases and approximately 70%-80% of sporadic CRCs. Both are more common in the right colon than in the left colon, and a higher percentage of poorly differentiated adenocarcinomas are found.[25] Sporadic MSI-H CRC tumors are associated with specific phenotypes and characteristics, including older age, female, BRAF mutations, and enrichment in CpG island methylation status. Multiple studies have assessed the prognostic value of MSI status in CRC,[26–28] and several retrospective studies and meta-analyses have shown that MSI-H tumors have a better stage-adjusted prognosis than MSS tumors.[29–32] Moreover, MSI or dMMR has been tested as a predictive biomarker of adjuvant therapy in colon cancers at stages II or III. Most studies suggest fluoropyrimidine-based chemotherapy is less beneficial and harmful for patients with MSI-H or dMMR stage II or III colon cancers than pMMR tumors.[27,33,34]

4 | THE EFFICACY OF ICIS IN MCRC

A non-randomized phase II study (KEYNOTE-016) evaluated the efficacy of pembrolizumab in MSI-H solid tumors.[35] The study included 11 patients with dMMR CRC and 21 patients with pMMR CRC. The response rate was 40% (95% CI 12%-74%) in the dMMR group and 0% in the pMMR group. The median PFS was 2.3 (95% CI 1.4%-2.8%) months in the pMMR group. The median PFS in the dMMR group was not reached after a median observation period of 8.4 months, indicating the extremely high efficacy of ICIs in dMMR CRCs. The trial included dMMR solid tumors in cancers other than CRC (biliary tract, endometrial, small bowel, prostate, and gastric cancers) and demonstrated high efficacy of pembrolizumab, as in dMMR CRC. These results indicate that ICIs are effective against dMMR solid tumors regardless of the cancer type.

KEYNOTE-164 was a non-randomized phase II trial of pembrolizumab in previously treated mCRC with MSI-H/ dMMR.[36] Sixty-one patients were enrolled in cohort A (≥2 prior therapies) and 63 in cohort B (≥1 prior therapy). The primary endpoint, the objective response rate, was 33% in both cohorts, with the median duration of response not reached in either cohort. Median OS was 31.4 months in cohort A and not reached in cohort B, which supports the durability of the clinical benefit of pembrolizumab in patients with MSI-H/dMMR CRC. Treatment-related grade 3-4 adverse events occurred in only 18 patients (14.5%). Pembrolizumab monotherapy demonstrated sustained clinical response in previously treated MSI-H/dMMR mCRC.

Based on these favorable results, the therapeutic efficacy of pembrolizumab in chemotherapy-naive patients was evaluated. KEYNOTE-177 was an international phase III trial evaluating the efficacy and safety of pembrolizumab versus standard chemotherapy for the first-line treatment of MSI-H/dMMR mCRC.[37] PFS, the primary endpoint, was 16.5 months in the pembrolizumab group and 8.2 months in the standard chemotherapy group, indicating a significantly longer PFS in the pembrolizumab group (HR = 0.60, 95% CI = 0.45-0.80, $p = 0.0002$). The pembrolizumab group also performed better in subgroup analysis concerning race, BRAF mutation, KRAS or NRAS mutation, and primary tumor location (right/left). In addition, the frequency of grade 3 or higher adverse events was lower in the pembrolizumab group compared to standard chemotherapy (56% vs 78%). The results confirm that pembrolizumab should be the standard of care for first-line treatment of patients with MSI-H/dMMR mCRC.

The KEYNOTE-158 study examined MSI-H solid tumors other than CRC (endometrial, gastric, small intestine, pancreatic, and biliary tract cancers).[38] In this study, patients with MSI-H/dMMR advanced non-colorectal cancer who experienced failure with prior therapy received pembrolizumab monotherapy. The primary endpoint, the objective response rate was 34.3%, and the median PFS and OS were 4.1 and 23.5 months, respectively. Either cancer type suggests a very high efficacy considering the situation in which standard treatment has been completed.

In a prospective exploratory analysis of this study, tumor mutation burden (TMB) was measured by FoundationOne CDx and analyzed separately in TMB-High and non-TMB-High populations.[39] The efficacy evaluation population included 790 patients with evaluable TMB scores (TMB-High: 102 patients, non-TMB-High: 688

patients). Most patients had MSS tumors (MSI: 14% in TMB-High, 0% in non-TMB-High). The primary ORR was 29% in the TMB-High group and 6% in the non-TMB-High group. The results showed that patients with TMB-high were responsive candidates for pembrolizumab therapy. The FDA specified a cut-off point of ≥10 mutations/Mb TMB by the FoundationOne CDx assay. However, TMB is a continuous variable, and whether this is the optimal threshold for all cancers is unclear.

Results of several clinical trials for nivolumab in mCRC were also reported. The CheckMate-142 study was a multicenter phase 2 trial to examine nivolumab as monotherapy in previously treated dMMR/MSI-H mCRC.[40] Seventy-four previously treated patients were enrolled. The primary endpoint, the response rate was 31%, and the disease control rate was 69%; the overall survival (OS) did not reach the median regardless of PD-L1 expression, BRAF/KRAS mutations, or Lynch syndrome. These results suggest that nivolumab could also be a treatment option in previously treated patients with dMMR/MSI-H mCRC.

CheckMate-142 study is a multi-tiered study included two treatment arms: nivolumab monotherapy and nivolumab plus ipilimumab in the MSI-H cohort.[41] The combination therapy group achieved an objective response rate and disease control rate (the primary endpoints) of 69% and 84%, respectively. Complete response (CR) was observed in 13% of patients. The secondary endpoints of progression-free survival (PFS) and median OS were not reached. An indirect comparison of CheckMate-142 cohorts suggested that nivolumab plus low-dose ipilimumab demonstrated improved clinical benefit relative to nivolumab monotherapy, with a favorable benefit-risk profile, in second-line MSI-H/dMMR mCRC. Grade 3 and 4 treatment-related adverse events were more frequent in the combination therapy group (32% of patients), suggesting the need to target patients appropriately. Nivolumab plus ipilimumab therapy is the first combination of immunotherapy drugs approved for mCRC. The combination of ICIs demonstrated extremely high efficacy in this population.

The Checkmate 9x8 study assessed the additional effect of nivolumab combined with mFOLFOX6 plus bevacizumab as a first-line therapy in patients with treatment-naive unresectable CRC.[42] This study included both MSS/MSI-L colorectal cancer cases (93%) and MSI-H cases (7%). There was no difference in PFS, the primary endpoint (11.9 months in both the nivolumab group and standard chemotherapy group). However, PFS rates after 12 months were higher in the nivolumab combination group compared with the standard chemotherapy group. This suggests that there is a subpopulation with prolonged disease control with the addition of nivolumab. The ORR was higher, and responses were more durable with nivolumab + chemotherapy compared with chemotherapy alone. Subgroup analyses showed that long-tale effect was observed with the addition of nivolumab to chemotherapy in CMS1 and CMS3 patients and in patients with high CD8-positive tumor cells (≥2%). The study did not prove that nivolumab + chemotherapy improves outcomes in MSS mCRC, indicating that new combination regimens with clinical activity with immune checkpoint inhibition in mCRC are required.

5 | ICI FOR EARLY-STAGE COLON CANCER

5.1 | Postoperative adjuvant therapy

ACCENT pooled analysis demonstrated that adding oxaliplatin to FP significantly improves disease-free survival and OS of patients with MSI stage III colon cancer (CC).[43] One-third of patients with T4 and/or N2 MSI stage III CC experience disease recurrence or death within 2 years after curative tumor resection, and therefore innovative therapeutic strategies should be sought for this population. However, one-third of patients with high-risk stage III CC experience disease recurrence or die within 2 years of curative resection. Therefore, phase III randomized trials have been conducted to determine the role of ICI as adjuvant therapy for patients with resected dMMR stage III tumors because of the benefit of immunotherapy in the metastatic setting.

The ATOMIC trial[44] is a randomized phase III evaluating adjuvant mFOLFOX6 with or without atezolizumab to determine whether mFOLFOX6 with anti-PD-L1 antibody confers a greater survival benefit than standard chemotherapy alone in dMMR stage III CC(NCT02912559). Some data suggest that FOLFOX may increase intratumoral cytotoxic CD8+ T cells that can act as immune priming cells.[45,46] The primary endpoint is disease-free survival, and 700 patients will be enrolled in this study. POLEM[47] is a phase III study for stage III patients with dMMR or POLE exonuclease domain mutations and has a target accrual of 402 patients. Patients are randomly assigned to receive fluoropyrimidine-based chemotherapy (CAPOX for 12 weeks or capecitabine for 24 weeks) alone or followed by the PD-L1 antibody avelumab. Disease-free survival is the primary endpoint. POLE mutations occur in 1% of patients with CCs, although the incidence ranges between 8% and 10% in patients <50 years.[48] These approaches may help further personalize treatment options in the adjuvant setting of CRC and the results are eagerly anticipated.

5.2 | Neoadjuvant immunotherapy

The use of ICIs in preoperative chemotherapy for stage I-III CRC has also been reported. Recent clinical trials[49–51] have shown that ICIs are more effective against early-stage malignant melanoma, lung cancer, and urothelial carcinoma than against advanced-stage cancers, which may be because of the infiltration of T cells. The NICHE study[52] confirmed the usefulness of nivolumab plus ipilimumab for patients with early-stage CC. In this study, patients with dMMR or pMMR tumors received a single dose of ipilimumab and two doses of nivolumab before surgery. The dMMR arm (n = 20) demonstrated a pathological response rate of 100% with 19 major pathological responses (MPR, defined as ≤10% residual viable tumor) and 12 pathological CRs (pCR). On the other hand, the pMMR arm (n = 15) showed a pathological response rate of 27% of which three patients had an MPR. In addition, CD8 + PD-1+ T cell infiltration was predictive of response in pMMR tumors. The primary endpoint of feasibility was

a 100% resection rate, with all patients undergoing radical resection within 6 weeks of treatment initiation. The incidence of grade 3-4 treatment-related adverse events (TRAEs) was only 13%. This study shows that neoadjuvant treatment of early-stage CCs with PD-1 plus CTLA-4 blockade could be a new standard of care in dMMR and possibly a subgroup of pMMR CCs. Similar to these results, subpopulations of pMMR CCs with elevated IFN-γ and CD8 T effector gene signatures have been reported to benefit from ICIs.[53]

Furthermore, recent exciting data have been reported on neoadjuvant chemotherapy with dorstarlimab, an anti-PD-1 monoclonal antibody, for patients with locally advanced dMMR/MSI-H rectal cancer.[54] Twelve patients have completed the nine planned cycles (6 months) of dostarlimab. The percentage of these patients with a clinical CR was 100%. In addition, all patients could avoid the morbidity associated with radiation and surgery. Although longer-term follow-up is needed, PD-1 blockade alone could be a promising treatment option for patients with dMMR/MSI-H rectal cancer.

5.3 | Total neoadjuvant therapy with ICIs for rectal cancer

Chemoradiotherapy (CRT) followed by radical surgery is one of the standard therapies for patients with locally advanced rectal cancer.[55,56] Recently, total neoadjuvant therapy has become a new treatment for locally advanced rectal cancer.[57–61] The rationale for total neoadjuvant therapy is to intensify the neoadjuvant therapy by adding chemotherapy to CRT, leading to higher rates of resectability and pathological CR.[57,58,62] In addition, one promising approach is the combination of ionizing radiation and ICIs because it enhances both local and distal immunogenic efficacy, as shown in several xenograft models.[63,64] The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site.[65] Current consensus is that combining radiotherapy with immunotherapy provides an opportunity to boost abscopal response rates.[66] Radiation generates neoantigens from tumor cells. Antigens from damaged tumor cells can be taken up by antigen-presenting cells, which travel to the lymph node to prime the T cell-mediated abscopal effect. Clinical trials have shown promising short-term efficacy results of 23%-37.5% of pCR in patients with MSS locally advanced rectal cancer who received the combination of CRT and ICIs (Table 1).[67–71] The Voltage trial examined nivolumab monotherapy and subsequent radical surgery following preoperative chemoradiotherapy in patients with MSS and MSI-H locally advanced rectal cancer.[68] A promising pCR rate of 30%, with mild toxicity, was shown in even MSS locally advanced rectal cancer treated with nivolumab plus radical surgery.

6 | FUTURE PERSPECTIVES

6.1 | Gut microbiota and the efficacy of ICIs

Approximately 1000 species, or 100 trillion bacteria, are present in the human intestine, forming an intestine microflora (also called gut microbiota) that weighs 1.5-2 kg.[72] Recent data have suggested a high correlation of gut microbiota with the therapeutic effects of cancer immunotherapy.[72–75] The intestinal microbiota is altered by various external factors (i.e., childbirth, lactation, aging, diet, exercise, alcohol consumption, antibiotics).[76] The recent progress in the research on gut microbiota is from the advent of next-generation sequencers, which have produced significant advances in gene analysis. Research has shown that intestinal bacteria may be involved in various cancers, including CRC.[77–80] In addition, recent studies have shown that intestinal microbiota significantly impacts the host immune system and is closely related to autoimmune diseases.[81,82]

From these findings, a study examined the relationship between the efficacy/ineffectiveness of ICI therapy and the gut microbiota. The results indicated that certain intestinal bacteria might modulate the clinical efficacy of anti-PD-1 antibodies.[83,84] For example, oral administration of *Bacteroides fragilis* to sterile mice promoted dendritic cell maturation in tumor tissue and enhanced the therapeutic effect of CTLA4 antibodies.[75] Another study showed a robust negative effect of antibiotic administration on the therapeutic effect of ICIs.[85] The OS, PFS, and overall response rates of patients treated with ICIs for renal cell carcinoma and non-small cell lung cancer were examined. The results showed that the non-antibiotic group significantly outperformed the antibiotic group in all outcomes. Similar results were observed in patients with urothelial carcinoma. These data indicate that antibiotics inhibit the efficacy of ICIs across cancer types.

TABLE 1 Clinical trials of total neoadjuvant therapy with immunotherapy for rectal cancer

	MSS/MSI	N	Chemotherapy	Immunotherapy	Chemoradiotherapy	pCR (%)	Reference
NRG-GI002	N.A.	90	mFOLFOX6 (x8) → RT (50.4Gy) with Capecitabine	+Pembrolizumab		31.9	67
		95	mFOLFOX6 (x8) → RT (50.4Gy) with Capecitabine			29.4	
Voltage	MSS/MSI	39 (MSS)	Nivolumab (x5) → RT (50.4Gy) with Capecitabine			30	68
		5 (MSI)	Nivolumab (x5) → RT (50.4Gy) with Capecitabine			60	
AVANA	N.A.	101	RT (50.4Gy) with Capecitabine	+Avelumab		23	69
Averectal	MSS	40	SCRT (25Gy) → mFOLFOX6	+ Avelumab (x6)		37.5	70,71

Abbreviations: MSI, microsatellite instability; MSS, microsatellite stable; N.A., not assessment; pCR, pathological complete response; RT, radiotherapy; SCRT, short-course chemoradiotherapy.

Some studies suggested that gut microbiota transplantation may improve sensitivity or toxicity to ICIs.[74,86] As an example of sensitivity, 10 patients with melanoma resistant to anti-PD-1 ICIs were transplanted with stool samples from two melanoma patients with sustained complete response to ICIs for over 1 year. Of the 10 patients, one had a CR and two had partial responses (PR). Stool samples from patients with CR or PR to anti-PD-1 antibodies were administered to patients with malignant melanoma refractory to anti-PD-1 antibodies by colonoscopy, and five of the six patients showed clinical benefit for 12 months or longer. Therefore, controlling the intestinal microbiota may alter the tumor immune response and improve the efficacy of ICIs. The clinical application of intestinal bacteria in immunotherapy is expected.

6.2 | Combination treatment with VEGF inhibitors

Angiogenesis-promoting factors have been shown to suppress tumor immunity, and preclinical data suggest that angiogenesis inhibitors may activate tumor immunity.[87] Tumor vessels differ from normal vessels both structurally and functionally, regulating immune cell infiltration and suppressing anti-tumor immune activity.[88,89] VEGF regulates the expression of adhesion factors on tumor vascular endothelium and, in concert with various cytokines and chemokines such as CCL2, CCL28, CXCL8, and CXCL12 released by tumor cells, promotes immature dendritic cell (DC), Treg, and MDSC infiltration into tumors.[90,91] In contrast, low-dose anti-VEGFR-2 antibody administration and normalization of vascular architecture increased the number of T cells infiltrating into tumors and induced DC maturation and T cell priming.[92] Dual inhibition of the VEGF and PD-1/PD-L1 axes exerts therapeutic activity in multiple tumor types.[93–95]

A double-blind placebo-controlled multicenter phase 2 randomized clinical trial was conducted to evaluate the combination of capecitabine and bevacizumab with or without atezolizumab in patients with refractory mCRC.[96] Although the primary endpoint of PFS achieved pre-specified statistical significance, the addition of atezolizumab to capecitabine/bevacizumab did not result in a clinically meaningful improvement in PFS (4.4 vs 3.9 months) for chemorefractory mCRC patients. The AtezoTRIBE study was a phase II randomized controlled study that investigated the addition of atezolizumab to initial FOLFOXIRI plus bevacizumab in patients with previously untreated mCRC.[97] There was a statistically significant difference in median PFS (primary endpoint) of 13.1 months versus 11.5 months, favoring the atezolizumab group. This study also provided the first evidence of efficacy of a first-line therapeutic strategy based on immune checkpoint inhibition in patients with unresectable pMMR or MSS mCRC. Other studies are currently ongoing (Table 2).[98–102]

7 | CONCLUSIONS

Immune checkpoint inhibitors have led to significant improvements in the clinical outcomes of MSI-H CRC patients. However, treatment

TABLE 2 Clinical trials for metastatic colorectal cancer with combination immunotherapy and anti-angiogenic therapy

Study	Type	N	MSS/MSI (%)[a]		Treatment regimen	Primary endpoint	PFS (months)	HR (95% CI)	Reference
ACCRU	Phase II RCT	82	MSS/MSI (11%)	Refractory	Capecitabine + Bmab + Atezolizumab	PFS	4.4	0.725	96
		46			Capecitabine + Bmab		3.3	(0.491-1.07)	
AtezoTRIBE	Phase II RCT	134	MSS/MSI (6%)	1st-line	FOLFOXIRI + Bmab + Atezolizumab	PFS	13.1	0.69	97
		67			FOLFOXIRI + Bmab		11.5	(0.56-0.85)	
CheckMate 9x8	Phase II/III RCT	195	MSS/MSI (5%)	1st-line	mFOLFOX6 + Bmab + Nivolumab	PFS	11.9	0.81	42
			MSS/MSI (10%)		mFOLFOX6 + Bmab		11.9	(0.53-1.23)	
COMMIT	Phase III RCT	347	MSI (100%)	1st-line	mFOLFOX6 + Bmab + Atezolizumab	PFS	(-)	(-)	98
					Atezolizumab		(-)	(-)	
NIVACOR	Phase II	70	MSS/MSI (20%)	1st-line	FOLFOXIRI + Bmab + Nivolumab	ORR	(-)		99
NCT03396926	Phase II	44	MSS	Refractory	Capecitabine + Bmab + Pembrolizumab	DLT/ORR	(-)		100
NCT03475004	Phase II	50	MSS	Refractory	Binimetinib + Bmab + Pembrolizumab	PFS	5.8		101
REGONIVO	Phase Ib	25	MSS/MSI (4%)	Refractory	Regorafenib + Nivolumab	DLT	7.9		102

[a]Percentage of MSI tumors in enrolled patients.

Abbreviations: CI, confidence interval; DLT, dose limiting toxicity; HR, hazard ratio; MSI, microsatellite instability; MSS, microsatellite stable; ORR, objective response rate; PFS, progression free survival; RCT, randomized control trial.

efficacy is heterogeneous, even in this selected subset of patients, and acquired resistance has been demonstrated. Therefore, biomarkers and genetic alterations need to be identified to assess the efficacy of ICIs. Furthermore, it is essential to develop effective immunotherapy with appropriate chemotherapies and multikinase inhibitors for patients with MSS CRC.

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