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SYSTEMIC THERAPIES IN COLORECTAL CANCER (SM KAZMI, SECTION EDITOR)

Immune Checkpoint Inhibitors in Metastatic Colorectal Cancer: Current Status, Recent Advances, and Future Directions

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Abstract

Purpose of Review Immune checkpoint inhibitors have shown very promising outcomes in the subset of metastatic colorectal cancers (CRCs) that are mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H). We reviewed the existing literature on immune checkpoint inhibitors in colorectal cancers to highlight the recent advances and future directions.

Recent Findings The significance of immune check point inhibitors in dMMR/MSI-H metastatic CRCs has been validated by several studies employing anti-programmed death cell receptor (anti-PD1) and anti-PDL1 antibodies single agent or in combination with anti-CTLA4 antibodies ("KEYNOTE" and "CHECKMATE" studies). This has led to FDA approval of these drugs. At present, its approval is limited to those who have failed traditional chemotherapy (5-FU, oxaliplatin, and irinotecan). The trials for the dMMR/MSI-H CRCs are now being moved up in terms of first-line, neoadjuvant, and adjuvant settings.

Summary The results of various studies favor the excellent antitumor activity and safety profile of anti PD-1 monoclonal antibodies that include pembrolizumab and nivolumab in MSI-H colorectal cancer. Combination immunotherapy with nivolumab and ipilimumab has also shown significant clinical benefit in dMMR/MSI-H metastatic CRC patients. These have now been FDA-approved. Multiple ongoing studies assessing the safety and efficacy of other anti-PD/PD-L1 agents (e.g., durvalumab, atezolizumab) alone or in combination therapy with classes of drugs are in progress. The goal ideally would be to identify approaches to expand activity of immune checkpoint inhibitors beyond the dMMR/MSI-H subset of CRC, which represent 4–5% of metastatic CRC patients. These are also being moved up in terms of usage in earlier lines of therapy and neoadjuvant/adjuvant approaches.

Keywords Immunotherapy · Immune checkpoint inhibitors · Metastatic colorectal cancer · Microsatellite instability · Mismatch repair deficiency · Keynote studies · Checkmate studies · Pembrolizumab · Nivolumab · Ipilimumab · Durvalumab · Atezolizumab · Tremelimumab · Avelumab · Cancer vaccines

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Introduction

Colorectal cancer (CRC) is the third leading type of cancer in the USA in both males and females [1]. The major treatment modalities for CRC have been surgery, chemotherapy, and radiation therapy. The overall survival (OS) of patients with metastatic CRC has significantly improved over the last few decades. It has not been just one drug or class of drugs. The progress has been due to multiple drugs, chemotherapies, biologics, targeted therapies, and now immunotherapy, alone or in combination that have led to the improvement in OS with metastatic CRCs. This has been paralleled with advancements in surgical, radiation, and interventional oncology disciplines.

Of particular note is the activity and approval of immunotherapy for a subset of colorectal cancers that are mismatch repair deficient (dMMR) or microsatellite

instability high (MSI-H) tumors. The dMMR/MSI-H could be a germline event (Lynch syndrome) or somatic (tumor-Lynch). These are exquisitely responsive to immune checkpoint inhibitors due to the "hyper-mutated" nature of these tumors. The dMMR/MSI-H tumors on average have > 1700 mutations as opposed to approximately 70 in sporadic CRCs.

Overall, depending on the studies/cohorts reported, around 10–20% have DNA mismatch repair deficiency (dMMR/MSI-H tumors) [2, 3]. In the metastatic setting, these represent about 4–5% of cases. What is unique about this subset of tumors is that have a poor response to chemotherapy [4]. However, the same tumor biology makes it inherently resistant to chemotherapy; because of their hypermutated nature, these tumors benefit immensely to immunotherapy with immune checkpoint inhibitors, e.g., pembrolizumab, nivolumab, and ipilimumab [5–8]. In this article, we aim to review the role of immune checkpoint inhibitors in advanced metastatic CRC patients, recent advances, and future directions.

Testing for Mismatch Repair Deficiency/Microsatellite Instability in CRC

The subset of patients with mismatch repair deficiency can be identified through various testing platforms/methodologies. Most of the national and international consensus guidelines and institutions do immunohistochemistry (IHC) for mismatch repair deficiency. Where there is discrepancy or high suspicion, microsatellite instability (MSI) testing can also be done (PCR-based assay) [9]. The hypermutated nature of these tumors can now also be noted on commercially available next generation sequencing (NGS) testing platforms that report the high tumor mutation burden (TMB-High). For stage-II patients, identification of dMMR/MSI-H identifies the cohort that would not benefit from chemotherapy as well as those who may have underlying Lynch syndrome [10]. The immune checkpoint inhibitors at present are approved for the metastatic dMMR/MSI-H subset of CRC patients [6]. Of note, while any of the three commonly used testing strategies, i.e., dMMR through IHC or MSI-H through PCR or now TMB through NGS-based assays identify this subset of CRC patients, it is not a perfect overlap. There are small subsets who are microsatellite stable (MSS) and mismatch repair proficient (pMMR) who may still be hypermutated and be TMB-High (e.g., patients with POLE mutations). This is an area of ongoing research with trials specifically seeking patients who have these tumor characteristics. Theoretically, they should respond similar to dMMR/MSI-H patients.

Role of Immune Checkpoint Inhibitors in MSI-H Metastatic CRC

Immune checkpoint inhibitors target the checkpoint molecules such as PD1, PD-L1, or CTLA-4, thereby leading to the immunotherapy response to the cancer cells [8]. Other targets and combination of these agents with other agents are being explored. Following is an account of the data thus far on the use of anti-PD1 alone or in combination with anti-CTLA-4 agents.

Pembrolizumab Monotherapy

The efficacy of pembrolizumab in patients with metastatic CRC has been well studied by Le et al. A phase 2 multicenter clinical trial was conducted with 41 patients who were divided into three cohorts: (i) patients with dMMR CRC, (ii) patients with pMMR CRC, and (iii) patients with dMMR cancer other than CRC. Ten milligrams per kilogram of pembrolizumab was administered intravenously every 2 weeks. They reported a 40% immune-related objective response rate (ORR) and the 20-week immune-related progression-free survival rate (PFSR) was noted to be 78% for dMMR CRC. In sharp contrast, the ORR and PFSR for pMMR CRC patients was found to be 0 and 11% respectively, thereby emphasizing the clinical activity of pembrolizumab specifically for the dMMR CRC but not the for pMMR CRC. The authors in the same study also reported the somatic mutation load in dMMR versus pMMR CRCs. This was estimated to be a mean of 1782 mutations per tumor in dMMR as opposed to only 73 mutations per tumor in pMMR CRCs. The high mutation load was associated with prolonged PFS [11].

KEYNOTE-028 trial, which is an international, multi cohort, multicenter, non-randomized, open label phase Ib study assessed the anti-tumor activity and safety profile of pembrolizumab in 20 PD-L1 positive metastatic solid tumors. Thirty-three (24%) of the 137 patients with CRC were PDL-1 positive of which only 23 patients were enrolled in the study. After a median follow-up of 5.3 months, the results showed that pembrolizumab had a reasonable safety profile with treatment-related adverse events of fatigue, asthenia, and stomatitis in 35% of the patients with no grade 3 adverse events noted. However, the antitumor activity was seen in only one patient and not surprisingly, the tumor was noted to be dMMR/MSI-H [12].

KEYNOTE-164 study documented reported the antitumor activity of pembrolizumab in 61 patients with dMMR/MSI-H colorectal cancer. Two hundred milligrams of pembrolizumab was administered once every 3 weeks. The results after a median follow-up of 7.4 months demonstrated an impressive objective response rate of 42.9% and a disease control rate of 50.8% [13••]. What is very encouraging and a recurring theme

is not only the initial response but also ongoing response and durability of responses in these studies.

Nivolumab Monotherapy

Similar to studies on pembrolizumab, interim results of the CheckMate-142 (NCT02060188) study also revealed promising results with anti-PD1 therapy with nivolumab monotherapy as well in dMMR/MSI-H metastatic CRCs [14]. In the 33 MSI-H patients who received nivolumab 3 mg/kg every 2 weeks, 82% had ≥ 2 prior regimens and 15% of them were *BRAF-V600E* positive. Investigator reported ORR was of 27% ($n = 9$). None of the patients had complete responses, with 27% ($n = 9$) them having confirmed partial responses. The interim results showed a median progression free survival (PFS) of 5.3 months, 4-month PFS rate of 55%, median overall survival (OS) of 16.3 months, 5-month OS rate of 75%. Seventy-nine percent ($n = 26$) of the patients had treatment-related adverse events (TRAEs) of which diarrhea (27%) and fatigue (27%) were most common. Only 7 patients had grades 3–4 TRAEs, as summarized in Table 1.

Combination Immunotherapy (Nivolumab plus Ipilimumab)

The clinical efficacy of combination immunotherapy with nivolumab plus ipilimumab, which is an anti-CTLA-4 monoclonal antibody, has been presented in the CheckMate-142/NCT02060188—a large, multicenter, open-label phase II trial involving mCRC patients with dMMR/MSI-H patients from eight countries. The patients in the study ($n = 119$) received nivolumab 3 mg/kg IV infusion and ipilimumab 1 mg/kg IV infusion once every 3 weeks for four doses followed by nivolumab 3 mg/kg IV once every 2 weeks unless they had disease progression, severe adverse events, death, or end of study and were followed for median duration of 13.4 months. The outcomes of the study showed an ORR of 54.6% (95% CI, 45.2 to 63.8) according to the investigator, ORR of 49% (95% CI, 39.5 to 58.1) according to blinded independent central review and disease control rate (DCR) of 80% (95% CI, 71.5 to 86.6). In addition, the 9 and 12 month progression-free survival rates (PFS) were 76% and 71% respectively and the 9 and 12 month overall survival rates were 87% and 85% respectively. Thirty-two percent of patients had grades 3–4 manageable adverse events. Combination immunotherapy, thus results in improved efficacy compared with anti-PD-1 monotherapy for dMMR/MSI-H mCRC [15••]. Side effects as noted are higher as opposed to single-agent anti-PD1 therapy. However, these are manageable. Also, it is important to note that there are different dosing regimens employing anti-CTLA4 alongside anti-PD1 therapy. Low-dose ipilimumab ("Ipi-light" or "Ipi-1") employing the 1 mg/kg dosing is lower than the dosing used in the initial studies employing this agent. Learning from clinical trials and our colleagues in melanoma and lung cancer, the lower dosing's adverse events are manageable.

At present, however, with excellent responses to immunotherapy with single-agent anti-PD1, combination immunotherapy even though FDA-approved is not readily used unless dealing with situations where response is the key, e.g., symptomatic/visceral crises cases. Anecdotal cases of patients who have failed single agent anti-PD1 have responded later to combination immunotherapy.

The late-breaking results from the CheckMate-142 study/LBA18_PR were presented at the European Society for Medical Oncology (ESMO) in October 2018. Forty-five patients with no prior therapy for dMMR/MSI-H mCRC were given the combination immunotherapy with nivolumab 3 mg/kg every 2 weeks and a low dose of ipilimumab 1 mg/kg every 6 weeks. After a median follow-up of 13.8 months, the overall response rate (ORR) was 60%, disease control rate (DCR) was 84%, and a complete response rate was 7%. Twelve-month progression-free survival rates (PFS) and overall survival (OS) rates were 77% and 83% respectively. Sixteen percent of the patients had grades 3–4 treatment-related adverse events. The study results established that nivolumab every 2 weeks with a low dose of ipilimumab every 6 weeks demonstrated a strong, durable, and well-tolerated clinical value as a first-line therapy for dMMR/MSI-H mCRC and may epitomize a new first-line treatment choice for this subset of patients [16••].

LBA37_PR study by Chalabi et al. presented at ESMO 2018 is the first study to elaborate the safety and feasibility of neoadjuvant ipilimumab plus nivolumab therapy in early stage dMMR and MMR proficient (pMMR) colon cancers. Fourteen patients of whom 8 had pMMR and 7 had dMMR early stage colon cancer received a low dose of ipilimumab at 1 mg/kg on day 1 and nivolumab at 3 mg/kg on days 1 and 15. One hundred percent of the dMMR patients showed a robust pathologic response with < 5% viable tumor cells. Patients with pMMR tumors did not show a major pathological response, but demonstrated a significant rise in CD8+ T cell infiltration. Therefore, the study recommended that short-term neoadjuvant immunotherapy with ipilimumab plus nivolumab could be a new strategy for patients with dMMR colon cancer [17••].

Immune checkpoint inhibitors are currently approved only for patients with dMMR/MSI-H metastatic colorectal cancer patients, after failure of standard of care chemotherapy with 5-fluorouracil (5-FU), oxaliplatin, and irinotecan. Current NCCN guidelines on their administration and dosage are elaborated in Table 2.

Table 1 Summary of major immune checkpoint inhibitor studies in patient's metastatic colorectal cancer (dMMR/MSI-H CRC versus pMMR/MSS CRC)

Study	Immune check point inhibitor tested	Enrolled patients (*n*)	Complete response *n* (%)	Partial response *n* (%)	Stable disease *n* (%)
Le et al. [11]	Efficacy of pembrolizumab	Total of 41 patients including dMMR CRC, pMMR CRC and dMMR nonCRC	0 for dMMR CRC, 0 for pMMR CRC and 1 (14) for dMMR nonCRC	4 (40) for dMMR CRC, 0 for pMMR CRC and 4 (57) for dMMR nonCRC	At week 12, 5 (50) for dMMR CRC, 2 (11) for pMMR CRC and 2 (29) for dMMR nonCRC
O'Neil et al. KEYNOTE-028 [12]	Safety and antitumor activity of pembrolizumab	Of 137 CRC patients, 23 PD-L1 positive patients enrolled	–	1(4.34)	4 (17.3) at median duration of 5.1 months
Diaz et al. KEYNOTE-164 [13••]	Antitumor activity of pembrolizumab	61 MSI-H CRC patients (90% with ≥ 2 prior therapies)	–	–	–
Overman et al. CheckMate-142 [14]	Efficacy of nivolumab	33 MSI-H mCRC patients	0	9(27)	–
Overman et al. CheckMate-142 [15••]	Clinical benefit of nivolumab plus ipilimumab combination	119 MSI-H mCRC patients	4(3)	61(51)	37(31)
Lenz et al. CheckMate-142/ LBA18_PR [16••]	Clinical benefit of nivolumab plus low dose ipilimumab combination	45 dMMR/MSI-H mCRC patients with no prior therapy	3(7)	24(53)	6(13)
Chalabi et al. LBA13_PR [17••]	Neoadjuvant ipilimumab plus nivolumab in early stage colon cancer	14 patients (7 dMMR and 8 pMMR) colon cancer	4(57) in dMMR colon cancer	–	–
Bendell et al. IMblaze 370 [19•]	Efficacy and safety of atezolizumab+ cobimetinib in MSS CRC	363 patients (1.7% MSI-H, 91.7% MSS, 6.6% missing MSI status)	–	–	–
Chen et al. [20]	Efficacy of durvalumab plus tremelimumab in mCRC patients not selected for dMMR status	180 enrolled and 179 treated as randomized.	–	–	–

Study	Objective response rate (ORR)	Disease control rate (DCR)	Progression free survival rate (PFS)	Treatment-related adverse events (TRAEs) grades 3–4 *n* (%)
Le et al. [11]	40% for dMMR CRC, 0% for pMMR CRC and 71% for dMMR nonCRC	90% for dMMR CRC, 11% for pMMR CRC and 71% for dMMR nonCRC	At 20 weeks, PFS of 78% for dMMR CRC; 11% for pMMR CRC	17 (41)
O'Neil et al. KEYNOTE-028 [12]	4% (95% CI, 0.1%–22%)	–	Median PFS of 1.8 months; 6 month PFS rate of 17.4% and 12-month PFS rate of 4.3%	0 grade 3; 1 (4%) grade 4
Diaz et al. KEYNOTE-164 [13••]	26.2% (95% CI, 15.8–39.1%)	50.8% (*n* = 31; 37.7–63.9%)	–	–
Overman et al. CheckMate-142 [14]	27%	–	4-month PFS rate of 55%	–
Overman et al. CheckMate-142 [15••]	55% (*n* = 65; 95% CI, 45.2–63.8)	DCR for ≥ 12 weeks–80% (*n* = 95)	9 month PFS rate of 76%; 12 month PFS rate of 71%	32(27) grade3 and 6(5) grade 4
Lenz et al. CheckMate-142/ LBA18_PR [16••]	60% (*n* = 27; 95% CI, 44–74)	84% (*n* = 38; 95% CI, 71–94)	12 month PFS rate of 77%	7(16) grade 3–4 adverse events
Chalabi et al. LBA13_PR [17••]	100% pathological response in dMMR patients	–	–	–
Bendell et al. IMblaze 370 [19•]	2.7%	–	–	45%
Chen et al. [20]	–	22.7%	Median PFS of 1.8 months	–

Table 2 Current NCCN guidelines for use of immune check point inhibitors in metastatic CRC. Of note, its use is only approved for patients with dMMR/MSI-H, and at present is after failure of chemotherapy with 5-FU, oxaliplatin, and irinotecan [18]*

Pembrolizumab	Nivolumab	Nivolumab + ipilimumab
• 2 mg/kg every 3 weeks (or) • 200 mg every 3 weeks	• 3 mg/kg every 2 weeks (or) • 240 mg IV every 2 weeks (or) • 480 mg IV every 4 weeks	• Nivolumab 3 mg/kg (30-minute IV infusion) and ipilimumab 1 mg/kg (30-minute IV infusion) once every 3 weeks for four doses; • Followed by nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks
May 23, 2017 First tumor agnostic approval by FDA (for dMMR/MSI-H CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan	July 31, 2017 For CRC dMMR/MSI-H	July 10, 2018 For CRC dMMR/MSI-H

*Of note, it now allows for usage of immunotherapy if someone is not a candidate for chemotherapy

Immune Check Point Inhibitors and MSS Colorectal Cancer

Atezolizumab is an anti PDL1 monoclonal antibody. IMblaze370 study by Bendell et al. compared if atezolizumab in combination with cobimetinib, a MEK1/MEK2 inhibitor may favor better anti-tumor activity than atezolizumab monotherapy or the standard of care regorafenib in patients with MSS/MSI-L metastatic colorectal cancer. Three hundred sixty-three patients were enrolled of which 1.7% were MSI-H mCRC, 91.7% were MSS, and 6.6% had missing MSI status. They were randomized in 2:1:1 ratio to receive atezolizumab+cobimetinib, atezolizumab monotherapy, or regorafenib, respectively. Median overall survival was 8.9 months, 7.1 months, and 8.5 months; overall response rates were 2.7%, 2.2%, and 2.2% for atezolizumab+cobimetinib, atezolizumab, and regorafenib monotherapy respectively. Their results indicated that atezolizumab with cobimetinib did not establish statistically significant improved overall survival, progression-free survival and overall response rate compared with either of the control arms [19•].

A study by Chen et al. presented at ASCO GI symposium 2019 demonstrated the significance of combining durvalumab, a PD-L1 receptor antibody plus tremelimumab, an anti CTLA-4 monoclonal antibody with best supportive care (BSC) versus BSC alone in patients with refractory, metastatic CRC not selected for dMMR status. The study did not include patients with known dMMR status. One hundred seventy-nine patients randomized to the treatment arm were administered durvalumab 1500 mg on day 1 every 28 days and tremelimumab 75 mg on day 1 for the first four cycles. After a median follow-up of 15.2 months, the median overall survival was 6.6 months and 4.1 months for the treatment arm and BSC arm respectively. The disease control rate in the treatment and control arms were 22.7% and 6.6% respectively. Moreover, lower deterioration and well-maintained quality of life were seen in the treatment arm, although grades 3–4 adverse events were higher in the treatment arm as summarized in Table 1 [20].

Radiotherapy With Immunotherapy in Colorectal Cancers

In metastatic cancers, radiotherapy can to be a powerful adjuvant for immunotherapy, amplifying the clinical benefits of immunotherapy to improve survival [21, 22]. Ongoing clinical trials combining immunotherapy with radiation or other locoregional modalities are summarized in Table 3.

Conclusion/Future Directions

At present, immune checkpoint inhibitors have shown promising and durable activity for dMMR/MSI-H CRCs. This has led to FDA approval of anti-PD1 agents alone and now more recently in combination with anti-CTLA4 therapy. However, these as noted earlier, only represent 4–5% of metastatic cancer patients. These agents alone have not shown activity for the pMMR/MSS CRC patients. As noted in some of the studies in Table 3, combination with other classes of immunotherapy, locoregional treatments and/or targeted therapies is being explored. Immunotherapy alongside MEK-inhibition initially was hypothesis generating for pMMR/MSS metastatic CRC

Table 3 Some ongoing clinical trials employing immune checkpoint inhibitors for patients with colorectal cancers

Study/clinical trial number	Intervention	Primary outcomes
Trials employing immune checkpoint inhibitors only		
KEYNOTE-016/NCT01876511 [23]	Efficacy and safety profile of pembrolizumab (MK-3475) in MSI positive colon cancers, MSI negative colon cancers, MSI positive non-colorectal cancers and MSI negative cancers with mutator phenotype.	Immune-related progression-free survival rate and objective response rate
KEYNOTE-164/NCT02460198 [24]	Efficacy of pembrolizumab monotherapy (MK-3475)	Objective response rate
KEYNOTE-177/ NCT02563002 [25•]	Efficiency and safety profile of pembrolizumab (MK-3475) versus standard of care chemotherapy in patients with dMMR or MSI-H Stage IV colorectal cancer	Progression-free survival (PFS) and overall survival (OS)
Trials employing immune checkpoint inhibitors plus chemotherapy		
BACCI study/ NCT02873195 [26•]	Efficacy of atezolizumab plus capecitabine/bevacizumab compared to placebo plus capecitabine/bevacizumab in patients with recurrent, refractory stage IV colorectal cancer.	Progression-free survival
CheckMate 9X8/NCT03414983 [27]	Assess efficacy of nivolumab in combination with standard of care (SOC) chemotherapy with bevacizumab for the treatment of first-line metastatic colorectal cancer	Progression-free survival
NCT02997228 [28••]	Evaluate efficacy of combination of atezolizumab, fluorouracil, oxaliplatin and leucovorin calcium (mFOLFOX6)/bevacizumab as first-line treatment for patients with mismatch repair deficient (dMMR) colorectal cancer	Progression-free survival
Atomic study/NCT02912559 [29••]	Assess efficacy of combination chemotherapy and atezolizumab in patients with stage III dMMR colon cancer	Disease-free survival
Trials employing immune checkpoint inhibitors plus biologic drugs		
MEDIPLEX/NCT02777710 [30]	Evaluating safety and activity of durvalumab (MEDI4736), in combination with, an anti-CSF 1R tyrosine kinase inhibitor-pexidartinib (PLX3397) in metastatic /advanced colorectal or pancreatic cancers	First part of the study (dose escalation part) assesses the dose limiting toxicities. Second part (extension part) assesses the objective response rate.
NCT02484404 [31]	Assess safety and efficacy of durvalumab (MEDI4736) in combination with olaparib and/or cediranib for advanced solid tumors and advanced or recurrent ovarian, triple negative breast, lung, prostate and colorectal cancers	Dose and safety of MEDI4736/olaparib(MEDI-O) and MEDI4736/cediranib(MEDI-C)
AVETUXIRI/NCT03608046 [32•]	Assess tumor response rate in MSI stable metastatic colorectal cancer patients on treatment with avelumab combined with cetuximab and irinotecan	Tumor response rate
Morpheus-CRC/NCT03555149 [33••]	Evaluate efficacy and safety of multiple immunotherapy based treatment combinations including atezolizumab, bevacizumab, isatuximab, selicrelumab, regorafenib in patients with metastatic colorectal cancer	Objective response rate Percentage of adverse events
CheckMate9N9/NCT03377361 [34]	Efficacy of nivolumab in combination with trametinib with or without ipilimumab for metastatic colorectal cancer	Objective response rate Number of adverse events and serious adverse events
NCT03711058 [35]	Evaluate efficacy of nivolumab and copanlisib (PI3Kinase inhibitor) in refractory solid tumors with expansions in microsatellite stable (MSS) colorectal cancer	Maximum tolerated dose 6-month objective response rate
NCT03642067 [36]		Objective response rate

Table 3 (continued)

Study/clinical trial number	Intervention	Primary outcomes
	Assess safety and clinical activity of nivolumab and relatlimab in patients with metastatic or locally advanced MSS colorectal cancer	
Trials employing immune checkpoint inhibitors and radiation therapy		
ILOC/NCT03101475 [37••]	Assess efficacy of immunotherapy (durvalumab, tremelimumab) plus local tumor ablation with radiofrequency ablation (RFA) or stereotactic body radiation therapy (SBRT) in colorectal cancer with liver metastases	Best overall immune response rate
NCT03802747 [38••]	Evaluate efficacy of combination of dual immune checkpoint blockade (durvalumab, Tremelimumab) plus Yttrium-90 (Y-90) radioembolization and stereotactic body radiation therapy (SBRT) in refractory metastatic MSS (microsatellite stable) colorectal cancer with liver metastases	Incidence of treatment related adverse events Dose-limiting toxicity of Y-90+SBRT in combination with dual immune checkpoint blockade
NCT03507699 [39]	Assess safety and tolerability of combination treatment of nivolumab, ipilimumab, CMP-001 and radiosurgery in patients with colorectal cancer with liver metastases	Dose-limiting treatment related adverse events
NCT03104439 [40]	Evaluate safety and efficiency of nivolumab and ipilimumab and radiation therapy in MSS and MSI-H colorectal and pancreatic cancer	Disease control rate
Trials employing immune checkpoint inhibitors plus vaccines		
QUILT-3.050/NCT03169777 [41••]	Assess safety and efficacy of NANT colorectal cancer vaccine: combination immunotherapy in recurrent or metastatic colorectal cancer	Incidence of treatment related adverse events, serious adverse events. Objective response rate
NCT02757391 [42]	Assess safety of personalized adoptive T cell therapy plus pembrolizumab in patients with advanced gastrointestinal malignancies	Incidence of toxicity(grades 3–4 non hematological or grade 4 hematological)
Trials employing immune checkpoint inhibitors and miscellaneous drugs		
NCT03800602 [43•]	Efficacy of nivolumab and metformin in treatment refractory microsatellite stable (MSS) colorectal cancer	Overall response rate

but did not eventually result in a meaningful improvement in OS.

Other novel approaches, e.g., combination with vaccines, are also being explored as summarized in Table 3 [44, 45, 46, 47, 48].

In summary, immune checkpoint inhibitors are one of the most significant advances for colorectal cancers that are dMMR/MSI-H colorectal cancers. Pembrolizumab, nivolumab, and combination therapy with nivolumab and ipilimumab have shown robust antitumor activity in this subset of patients and already are approved after failure of chemotherapy. Further developments and advances in this field will lead to patients benefiting beyond refractory setting and incorporation in earlier stages of disease. Strategies to identify how pMMR/MSS patients can benefit from immunotherapy-based approaches are the most pressing questions being addressed in numerous trials.

Compliance With Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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