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Perspectives on Treatment of Metastatic Colorectal Cancer with Immune Checkpoint Inhibitor Therapy

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Abstract

Despite lengthening survival, death rates from metastatic colorectal cancer (CRC) remain unacceptably high, with a bright spot being the demonstration of durable responses in patients with CRC who have mismatch repair-deficient (dMMR) and/or microsatellite instability-high (MSI-H) tumors and are treated with immune checkpoint inhibitor therapy. Nivolumab and pembrolizumab, as well as nivolumab in combination with low-dose ipilimumab—all checkpoint inhibitors—are currently approved by the U.S. Food and Drug Administration (FDA) for patients with MSI-H/dMMR metastatic CRC that progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Nonetheless, there are a number of questions and considerations in the use of these checkpoint inhibitor therapies. Using a question-and-answer format, this review summarizes the scientific rationale for immune checkpoint inhibitor therapy in CRC, including the effects of tumor factors such as genetic aberrations and mutational load on the immune response, particularly in patients with MSI-H/dMMR disease. We discuss response patterns, response criteria, and immune-related adverse events using findings from published efficacy and safety data of immune checkpoint inhibitor therapy in metastatic CRC. We also discuss issues surrounding treatment sequencing, incorporating approved checkpoint inhibitors into the current treatment paradigm, and the multiple investigational strategies that may optimize immunotherapy for advanced CRC in the future, including novel combination therapies. ***The Oncologist*** 2020;25:33–45

Implications for Practice: Colorectal cancer (CRC) is the third most common cancer in the U.S. Despite advances in chemotherapy, survival remains poor for patients with metastatic CRC. Certain immunotherapy agents have demonstrated long-lasting responses in previously treated patients with immune-responsive microsatellite instability-high/mismatch repair-deficient metastatic CRC, leading to U.S. Food and Drug Administration approval of the immune checkpoint inhibitors nivolumab (with or without low-dose ipilimumab) and pembrolizumab in this population. Combination therapy (e.g., nivolumab with low-dose ipilimumab) has demonstrated numerically higher response rates and improved long-term clinical benefit relative to anti-programmed death-1 monotherapy. Ongoing trials are evaluating immunotherapy in the broader CRC population and novel combinations to optimize immunotherapy for advanced CRC.

Introduction

According to GLOBOCAN estimates, over 1.8 million new cases of colorectal cancer (CRC) were expected to be diagnosed worldwide in 2018, accounting for 10.2% of all cancers [1]. Globally, rates are expected to increase, with more than 2.2 million new CRC cases anticipated by 2030. In the U.S., CRC is the third most common type of cancer [2], although this incidence is decreasing [1]. Despite advances in treatment [3], the 5-year survival rate for patients with metastatic CRC (mCRC) in the U.S. (2007–2013) is only 14% [2].

The U.S. mainstay of first-line therapy for advanced CRC is combination chemotherapy plus an anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR) antibody, depending on tumor characteristics [4, 5]; however, most patients progress within 1 year [6].

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Recently, immune checkpoint inhibitors have demonstrated impressive activity in patients with CRC and other solid tumors that are mismatch repair deficient (dMMR) [7, 8]. An explanation for the sensitivity of dMMR tumors is that the molecular defect results in high levels of frame-shift mutations, detectable as variability in the length of short stretches of DNA (microsatellites) called microsatellite instability. The large number of mutations creates numerous opportunities for new peptide sequences (neoantigens) to be presented by tumor cell human leukocyte antigen (HLA) molecules to cytotoxic T cells with receptors capable of recognizing these unique antigens [9]. In the frequently T-cell-infiltrated microenvironment of microsatellite instability-high (MSI-H)/dMMR tumors, high expression of cell surface inhibitory checkpoint molecules that downregulate the immune reaction (e.g., programmed death-1 [PD-1]/PD-1 ligand 1 [PD-L1], cytotoxic T lymphocyte-associated antigen-4 [CTLA-4]) is the norm [10]. Therefore, blocking PD-1/PD-L1 and CD80/CTLA-4 interactions increases T-cell proliferation and activation [10]. Durable responses of MSI-H/dMMR tumors to checkpoint inhibitors [7, 8] led to accelerated U.S. Food and Drug Administration (FDA) approval of two PD-1 inhibitors—nivolumab (with or without low-dose ipilimumab) and pembrolizumab—for MSI-H/dMMR mCRC after progression on chemotherapy [11, 12]; however, there are many critical questions regarding the use of immune checkpoint inhibitors in mCRC. This article addresses these questions and proposes answers that support clinical decision-making.

What Key Data Are Available on Immune Checkpoint Inhibitors in MSI-H/dMMR mCRC?

Two phase II pembrolizumab trials (KEYNOTE-016 and KEYNOTE-164) and a phase II nivolumab trial (CheckMate 142) were conducted in patients with MSI-H/dMMR mCRC. Of 40 patients with previously treated MSI-H/dMMR mCRC in KEYNOTE-016, the objective response rate (ORR) was 52% (median follow-up, 12.5 months), 2-year progression-free survival (PFS) was 59%, and 2-year overall survival (OS) was 72% [7, 13]. In 61 patients from KEYNOTE-164 cohort A (at least two prior therapies including fluoropyrimidine, oxaliplatin, and irinotecan), ORR was 28% (median follow-up, ≥54 weeks); 12-month PFS was 34%, and 12-month OS was 72% [14]. Of 63 patients from KEYNOTE-164 cohort B (at least one prior therapy including fluoropyrimidine, oxaliplatin, irinotecan, or anti-VEGF/EGFR), ORR was 32% (median follow-up, 12.6 months), 12-month PFS was 41%, and 12-month OS was 76% (Table 1). The smaller study size and use of immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) [26] may account for the higher responses in KEYNOTE-016; the KEYNOTE-164 results likely reflect efficacy in general use. The FDA approved pembrolizumab based on pooled data from 90 patients with MSI-H/dMMR mCRC from KEYNOTE-016 (*n* = 28), -028 (*n* = 1), and -164 trials (*n* = 61), where ORR was 36% [11].

CheckMate 142 evaluated nivolumab with or without low-dose ipilimumab (an anti-CTLA-4 antibody), a combination that previously showed immune activation distinct from each agent alone [27]. In CheckMate 142's cohorts of previously treated MSI-H/dMMR mCRC, ORR was 31% and disease control rate (DCR) for ≥12 weeks was 69% (median follow-up, 12.0 months) in 74 patients receiving nivolumab monotherapy [8]. PD-1/PD-L1 and CTLA-4 checkpoint inhibitors operate at different points of the immune response and act synergistically to promote antitumor responses, providing the rationale for dual checkpoint blockade with nivolumab and ipilimumab [27, 28]. In two melanoma trials, nivolumab plus ipilimumab significantly improved PFS versus ipilimumab alone [29, 30]. In CheckMate 142, nivolumab plus low-dose ipilimumab (1 mg/kg every 3 weeks for four doses) had a favorable benefit-risk profile in previously treated MSI-H/dMMR CRC (*n* = 119; median follow-up, 13.4 months) [31]. This cohort had improved efficacy versus single-agent nivolumab (ORR: 55% vs. 31%, respectively), and DCR (≥12 weeks) was 80% [31]. Twelve-month PFS was 50% and 71%, and 12-month OS was 73% and 85%, respectively. In CheckMate 142's cohort 3, patients with untreated MSI-H/dMMR mCRC received nivolumab plus low-dose ipilimumab (1 mg/kg every 6 weeks until disease progression) and had an ORR of 60%, DCR of 84%, and 12-month PFS of 77% [32].

What Are the Unique Patterns of Efficacy with Immunotherapy?

Across multiple tumor types, checkpoint inhibitors have unique response and survival patterns compared with chemotherapy. Consequently, immune-related response criteria (irRECIST and iRECIST) were developed to assess responses to checkpoint inhibitor therapy [26, 33, 34]. Although one mCRC trial (KEYNOTE-016) used irRECIST to assess the primary endpoint [9], others (CheckMate 142, KEYNOTE-164, COMMIT) continue to use RECIST v.1.1 [8, 13, 35, 36]. This assessment approach might explain the high response rate in KEYNOTE-016, which was not confirmed in KEYNOTE-164.

One striking pattern is pseudoprogression: initial radiographic tumor enlargement (consistent with progression per RECIST) followed by measurable tumor regression, sometimes months to years after therapy initiation [28, 37, 38]. One explanation for this transient increase is immune cell tumor infiltration and proinflammatory cytokine release, which may generate edema; another is possible tumor growth while the immune system mounts a response [39]. Most pseudoprogression has been documented in melanoma [40]. In 327 patients with melanoma from the KEYNOTE-001 trial receiving pembrolizumab who were eligible for atypical response analysis, 7% of tumors exhibited pseudoprogression [41]. Pseudoprogression has also been reported in MSI-H/dMMR CRC, head and neck cancer, non-small cell lung cancer (NSCLC), and other cancers [40].

Complete responses (CRs), uncommon with chemotherapy [13], occur somewhat more frequently with immunotherapy. In CRC, CR rates with combination chemotherapy are 1% to 2% [42]; however, in KEYNOTE-164, the CR rate with pembrolizumab was 3% (median follow-up, 12.6 months) [13]. In CheckMate 142's previously treated cohorts, the CR rate was 3% (median follow-up, 13.4 months) for nivolumab plus low-dose ipilimumab, and 3% (median follow-up, 13 months) for nivolumab monotherapy, increasing to 9% at a median follow-up of 21 months, showing response deepening over time [16, 43]. Response may be correlated with clinical outcome, as CheckMate 142's patients with complete or

Table 1. Efficacy of immune checkpoint inhibitors in advanced CRC trials

Drug; trial name or NCT number	Line of therapy	Trial population	ORR, *n/N* (%)	mDOR	DCR, *n/N* (%)	PFS outcomes	OS outcomes
Pembrolizumab + mFOLFOX6; NCT02375672 [15]	1L	MSI-unselected	12/30 (40)[a]	Not reported	23/30 (77)	PFS rate, not reported mPFS, 16.9 (7.4, 16.9) mo	OS rate, not reported mOS, 18.8 (18.3, NE) mo
Nivolumab; CheckMate 142 [8]	2L+	MSI-H/dMMR	23/74 (31)[b]	NR	51/74 (69)	12-mo PFS, 50% mPFS, 14.3 (4.3, NE) mo	12-mo OS, 73% mOS, NR (18.0, NE) mo
Nivolumab + low-dose ipilimumab; CheckMate 142 [16]	2L+	MSI-H/dMMR	65/119 (55)	NR	95/119 (80)	12-mo PFS, 71% mPFS, NR	12-mo OS, 85% mOS, NR
Pembrolizumab; KEYNOTE-016 [7]	2L+	MSI-H/dMMR	21/40 (52)	Not reported	33/40 (82)	2-year PFS, 59% mPFS, NR	2-year OS, 72% mOS, NR
Pembrolizumab; KEYNOTE-164 [13, 14]	2L+	MSI-H/dMMR	20/63 (32)	NR (2.1+, 13.2+)	36/63 (57)	12-mo PFS, 41% mPFS, 4.1 (2.1, NR) mo	12-mo OS, 76% mOS, NR
	3L+	MSI-H/dMMR	17/61 (28)	NR (2.9+, 12.5+)	31/61 (51)	12-mo PFS, 34% mPFS, 2.3 (2.1, 8.1) mo	12-mo OS, 72% mOS, NR
Pembrolizumab; pooled CRC data from KEYNOTE-016, -028, and -164 [11]	2L+	MSI-H/dMMR	32/90 (36)	NR (1.6+, 22.7+)	Not reported	Not reported	Not reported
Atezolizumab + bevacizumab; NCT01633970 [17]	2L+	MSI-H/dMMR	4/10 (40)	NR	9/10 (90)	mPFS, NR (1.5, 21.9) mo	mOS, NR (2.6, 23.7) mo
Atezolizumab ± bevacizumab and fluoropyrimidine; NCT02291289 [18]	1L (maintenance)	MSI-unselected (cohort 2)	Not reported	Not reported	Not reported	mPFS, 7.2 mo	mOS, 22.1 mo
Pembrolizumab + azacitidine; NCT02260440 [19]	2L+	MSS/pMMR[c]	1/30 (3)	Not reported	4/30 (13)	mPFS, 2.1 (1.8, 2.8) mo	mOS, 6.2 (3.5, 8.7) mo
Atezolizumab + FOLFOX + bevacizumab; NCT01633970 [20]	2L+	Oxaliplatin-naïve mCRC	9/25 (36)	Not reported	Not reported	Not reported	Not reported
Atezolizumab + cobimetinib; NCT01988896 [21]	2L+	MSI-unselected	7/84 (8)	14.3 (6.0, NE) mo	26/84 (31)	6-mo PFS, 18% mPFS, 1.9 (1.8, 2.3) mo	6-mo OS, 65% 12-mo OS, 43% mOS, 9.8 (6.2, 14.1) mo
Pembrolizumab + cetuximab; NCT02713373 [22]	2L+	*RAS*-wt mCRC	0/9 (0)	Not reported	7/9 (78)	mPFS, 4.1 mo	Not reported
Cobimetinib + atezolizumab; COTEZO (IMblaze370); NCT02788279[d] [21]	3L+	Mostly MSS	5/183 (3)	11.4 mo	48/183 (26)	mPFS, 1.9 (1.87, 1.97) mo	12-mo OS, 39% mOS, 8.9 (7.0, 10.6) mo
CEA CD3 TCB ± atezolizumab; NCT02650713 [23]	Majority 3L+	CEA+, MSS[e]	Mono: 2/31 (6) Combo: 2/11 (18)	NR	Mono: 14/31 (45) Combo: 9/11 (82)	mPFS, NR	mOS, NR
Pembrolizumab + RT or ablation; NCT02437071 [24]	3L+	MSS/pMMR	1/22 (4.5)[f]	4.1 mo	Not reported	Not reported	Not reported
Nivolumab + epacadostat; ECHO-204 [25]	Unspecified	Advanced CRC[g]	1/25 (4)	Not reported	6/25 (24)	Not reported	Not reported

[a]Per RECIST.
[b]Locally determined per investigator assessment.
[c]Thirty of 31 enrolled patients had MSS/pMMR CRC.
[d]This study did not meet its primary endpoint of OS versus regorafenib.
[e]Twenty-eight of 31 mono patients had MSS/pMMR CRC, and 11 of 11 combo patients had MSS/pMMR CRC.
[f]Interim ORR in pembrolizumab + RT cohort.
[g]Other solid tumors were included but not presented in this table.
Abbreviations: 1L, first line; 2L+, second line or beyond; 3L+, third line or beyond; CEA, carcinoembryonic antigen; CEA CD3 TCB, CEA CD3 T-cell bispecific antibody; CRC, colorectal cancer; DCR, disease control rate; dMMR, mismatch repair deficient; mCRC, metastatic CRC; mDOR, median duration of response; mFOLFOX6, modified folinic acid (leucovorin)-fluorouracil-oxaliplatin; mo, months; mOS, median overall survival; mPFS, median progression-free survival; MSI, microsatellite instability; MSI-H, MSI-high; MSS, microsatellite stable; NCT, National Clinical Trial; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiation therapy; wt, wild type.

partial responses to nivolumab had a 2-year OS of 100% versus approximately 50% among patients with stable disease (SD) [43]. In cohort 3 of CheckMate 142, patients receiving first-line nivolumab with low-dose ipilimumab achieved a CR rate of 7%; however, this rate may have resulted from the differences in follow-up duration between the cohorts [32].

Also unique to immunotherapy are durable responses; the median duration of response (DOR) was not reached in CheckMate 142 after a median follow-up of 21 months [43]. Given prolonged treatment responses, median efficacy outcomes may also be prolonged in checkpoint inhibitor trials in MSI-H/dMMR mCRC (Table 1) [7, 8, 14, 16, 17, 23]. Thus,

landmark analysis of PFS or OS at specific time points is useful. In previously treated patients in CheckMate 142, median OS with nivolumab or nivolumab plus low-dose ipilimumab was not reached (median follow-up, 13.4 months), and 1-year OS was 73% and 85%, respectively [16, 31]. Median OS was also not reached in untreated patients from cohort 3 (median follow-up, 13.8 months); 1-year OS was 83% [32].

Finally, a significant OS benefit with checkpoint inhibitor therapy versus standard of care, despite a lack of PFS benefit, has been observed in some randomized trials [44]. In a phase III trial of patients with pretreated advanced urothelial carcinoma, pembrolizumab treatment produced a significant 2.9-month improvement in median OS versus chemotherapy ($p = .002$) but no significant benefit in median PFS (hazard ratio [HR], 0.98; $p = .42$) [44]. Similar findings were reported in randomized trials of checkpoint inhibitors in other tumor types [45, 46]. Whether these observations apply to MSI-H/dMMR CRC remains to be determined, which is an objective of the ongoing first-line National Clinical Trials Network (NCTN) COMMIT trial [36].

Do Specific Tumor Subsets Respond Differently to Checkpoint Blockade?

Lynch syndrome (hereditary nonpolyposis CRC) is associated with hereditary receipt of one of four mutated mismatch repair (MMR) genes, resulting in near-universal microsatellite instability (MSI) status [47]. Approximately 3% of all patients with CRC have Lynch syndrome [47]; an additional 12% without Lynch syndrome have sporadic mutations or silencing causing the MSI-H phenotype [48, 49]. In a subset analysis from previously treated MSI-H/dMMR CRC CheckMate 142 cohorts, ORRs with nivolumab alone were numerically higher (but not statistically significant) for patients with Lynch syndrome than for patients with somatic MMR gene defects (33% vs. 29%, respectively) [8]; similarly, higher ORRs with nivolumab plus low-dose ipilimumab were observed in patients with Lynch syndrome versus patients with somatic MMR gene defects (71% vs. 48%, respectively) [16].

In CheckMate 142, patients with *BRAF* mutations, *KRAS* mutations, and wild-type *BRAF* and *KRAS* had similar ORRs with nivolumab monotherapy (25%, 27%, and 41%, respectively) [8] and with nivolumab plus low-dose ipilimumab (55%, 57%, and 55%, respectively) [16]. Similar ORRs with nivolumab monotherapy were observed in patients with tumor cell PD-L1 expression ≥1% or <1% (29% vs. 28%, respectively) [8]. Lynch syndrome, *BRAF* and *KRAS* mutation status, and tumor PD-L1 expression level do not appear clinically important for checkpoint blockade response in MSI-H/dMMR CRC.

What Are the Unique Patterns of Safety with Immunotherapy for CRC?

Checkpoint inhibition safety is distinct from that of chemotherapy, producing skin toxicities such as rash and pruritus, gastrointestinal toxicities including colitis, and endocrinopathies such as thyroiditis, hypophysitis, and adrenal insufficiency [50–52]. Disruption of the checkpoint molecules' role in maintaining immunologic homeostasis likely produces autoimmune-like, T-cell-mediated toxicities affecting numerous organ systems [53, 54], mainly dermatologic, gastrointestinal, pulmonary, and endocrine systems [50]. These immune-related toxicities are largely reversible with proper management, and most are grade 1 or 2 [50, 51]. The most common immune-related toxicities associated with checkpoint inhibitors in key CRC trials are listed in Table 2. Immune-related adverse events occurring in at least 5% of patients receiving immune checkpoint inhibitor monotherapy in key colorectal cancer trials [7, 8, 52] are similar to those reported for checkpoint blockade of other cancers; there do not appear to be any toxicities more common in patients with CRC [53].

Table 2. Immune-related adverse events occurring in at least 5% of patients receiving immune checkpoint inhibitor monotherapy in key colorectal cancer trials [7, 8, 52]

Organ class	Common immune-related adverse events
Dermatologic	Rash
	Pruritus
	Dry skin
Gastrointestinal	Diarrhea
	Colitis
	Nausea/vomiting
	Pancreatitis/hyperamylasemia
	Gastritis/ulcer
Hepatic	Transaminitis
	Increased lipase
	Increased amylase
Endocrine	Thyroid disease (hypothyroidism or hyperthyroidism)
	Hypophysitis
	Adrenal insufficiency
Renal	Acute kidney injury
Pulmonary	Interstitial pneumonitis
Cardiac	Myocarditis

In 119 patients with previously treated MSI-H/dMMR mCRC in CheckMate 142, nivolumab plus low-dose ipilimumab had a manageable safety profile; the most common treatment-related adverse events (TRAEs) with potential immunologic etiology were skin, endocrine, and gastrointestinal toxicities [16]. Grade 3 increases in aspartate aminotransferase (8%) and alanine aminotransferase (7%) occurred at more than 2% incidence. There were no grade 4 events at more than 2% incidence [16]. Patients in the untreated cohort 3 of CheckMate 142 received nivolumab plus low-dose ipilimumab, and the most common TRAEs were pruritus, hypothyroidism, and asthenia; grade 3 or 4 TRAEs occurred at an incidence of 16% [32].

Most immune-related adverse events (AEs) associated with checkpoint inhibitors developed within 12 weeks of treatment initiation and resolved within 12 weeks of onset [55]; some endocrine toxicities were considered unresolved because of the need for continuing hormone replacement therapy [51, 54]. The American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN) together recently developed clinical practice guidelines for the management of immune-related AEs [50].

What Is the Outcome for Patients Who Discontinue Checkpoint Inhibition Because of AEs or Long-Term Responses?

To date, some CRC checkpoint inhibitor trials provided treatment for 2 years (e.g., KEYNOTE-016), whereas others provided treatment indefinitely (e.g., CheckMate 142), discontinuing for treatment progression, intolerable side effects, or other reasons (e.g., inconvenience, cost, long-term CRs).

Memory T cells may be reactivated during checkpoint blockade [56], suggesting that long-term tumor cell surveillance may be possible without continued checkpoint inhibition. Although postdiscontinuation clinical outcomes have not been rigorously tested, 16 patients in CheckMate 142 with previously treated MSI-H/dMMR CRC who discontinued nivolumab plus low-dose ipilimumab because of TRAEs had an ORR of 63%, DCR of 81%, and median DOR that was not reached, demonstrating efficacy consistent with the overall population [16]. Also favorable were data from 18 patients in KEYNOTE-016 with various tumor types who discontinued pembrolizumab after 2 years because of CR (n = 11) or treatment intolerance (n = 7) and showed no evidence of recurrence or progression after median time off therapy of 8.3 and 7.6 months, respectively [7].

Of 105 patients with metastatic melanoma from the phase Ib KEYNOTE-001 trial, 91 with confirmed CR and 6 months of pembrolizumab (87%) discontinued therapy; 67 received no further anticancer therapy [57]. The 24-month disease-free survival (DFS) rate from time of CR was 91% for all 105 patients and 90% for those receiving no further anticancer therapy, showing no decline in DFS with treatment discontinuation [57]. Similar results were observed in a pooled analysis of two melanoma checkpoint inhibitor trials [58].

Although additional long-term follow-up is necessary to determine whether the risk of immune-related AEs associated with prolonged checkpoint inhibitor therapy may exceed the risk of disease progression in patients with sustained responses, the above data suggest that checkpoint inhibitors may produce long-lasting effects with limited treatment duration. Future recommendations may include an optimal treatment duration for checkpoint inhibitors rather than indefinite use.

When Should MSI Testing Be Performed in Patients with CRC?

MSI-H/dMMR status is both a prognostic and predictive biomarker. In stage II disease, MSI-H/dMMR is associated with favorable outcomes compared with microsatellite stable (MSS)/MMR proficient (pMMR) disease [59, 60]. In contrast, in mCRC, MSI-H/dMMR is associated with poor prognosis [61]. Additionally, MSI-H/dMMR mCRC responds more frequently to checkpoint inhibition versus MSI-low/pMMR disease [9, 62]. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer and Rectal Cancer recommend that all patients with CRC, regardless of stage, receive MSI or MMR testing. Without it, clinicians may not detect Lynch syndrome, lose the opportunity to enroll patients with MSI-H/dMMR stage III CRC into clinical trials, fail to identify patients with MSI-H/dMMR mCRC who might benefit from checkpoint inhibition, and potentially overtreat patients with MSI-H/dMMR stage II CRC.

In early unselected CRC trials, nivolumab demonstrated poor clinical activity, with only one CR among 33 patients [63, 64]. However, investigators correctly hypothesized that the single responder had MSI-H disease [65], providing the rationale for a phase II pembrolizumab trial with three cohorts: MSI-H/dMMR CRC, MSS/pMMR CRC, and MSI-H/dMMR non-CRC tumors. MSI-H/dMMR tumors responded to pembrolizumab (objective responses, four of ten CRC tumors and five of seven non-CRC tumors), but MSS/pMMR tumors did not (0 of 18 tumors) [9].

Based on MSI/MMR status predicting response to immunotherapy, two national guidelines recommend MSI/MMR testing for all patients with CRC on initial diagnosis [4, 5, 66]. However, testing is mainly performed during primary tumor resection, possibly years before diagnosis of mCRC. For patients presenting with metachronous mCRC, clinicians should verify that MSI/MMR testing was performed on the primary tumor. MSI/MMR results should be obtained before starting treatment, as they may lead the clinician to initiate immunotherapy directly or through a clinical trial.

In Patients with MSI-H/dMMR CRC, When Should Immune Checkpoint Inhibitors Be Considered?

For most patients, first-line treatment remains intensive combination chemotherapy plus targeted therapy [4, 5]. Nivolumab with or without low-dose ipilimumab and pembrolizumab received accelerated U.S. FDA approval for patients with MSI-H/dMMR CRC upon progression after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [11, 12]. Although no trials have directly determined whether patients should receive nivolumab alone or in combination with ipilimumab, an indirect comparison demonstrated that nivolumab plus low-dose ipilimumab provides improved efficacy versus nivolumab monotherapy, with a favorable benefit-risk profile [31]. Without direct evidence, treatment may be dictated by the patient's overall health status.

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In patients for whom intensive therapy is intensive therapy, NCCN Guidelines for Colon Cancer and Rectal Cancer recommend nivolumab with or without low-dose ipilimumab or pembrolizumab after first-line chemotherapy for patients with MSI-H/dMMR disease (Fig. 1) [4, 5]. In a subanalysis of previously treated patients in CheckMate 142, of 53 patients receiving nivolumab monotherapy, with at least three prior chemotherapies including a fluoropyrimidine, oxaliplatin, and irinotecan, ORR (26%) was comparable to the overall population (34%),

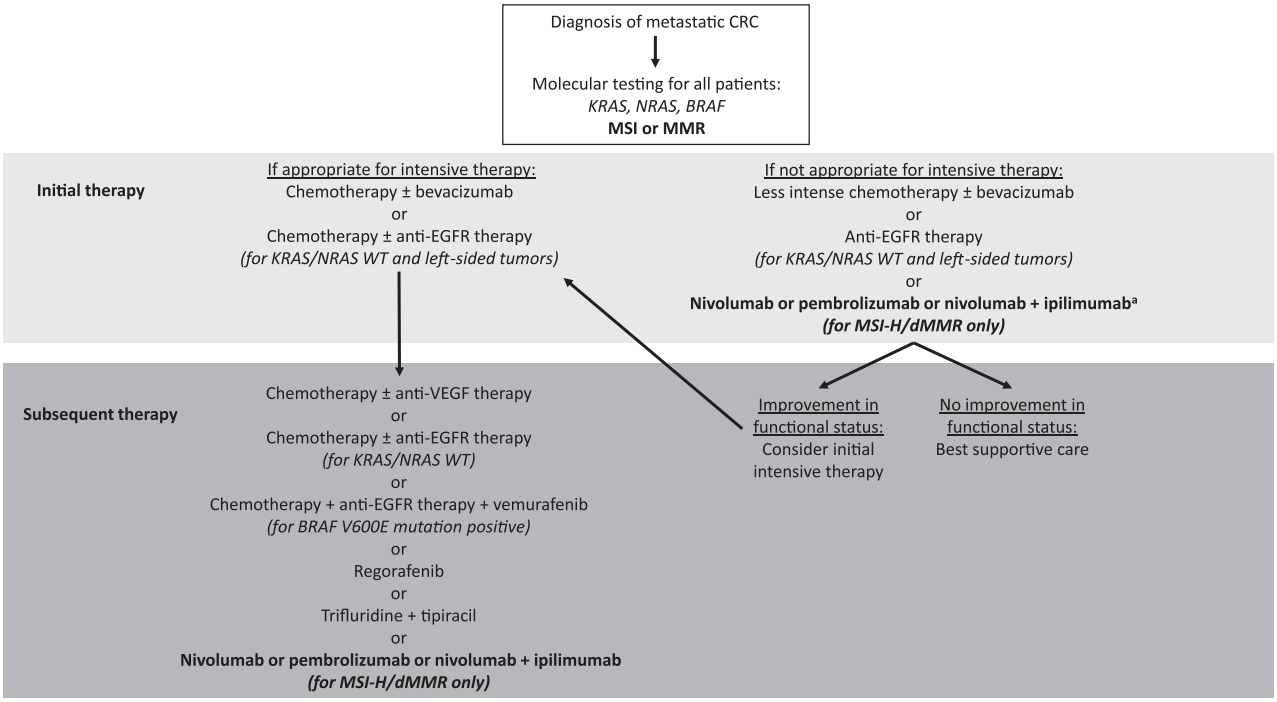

Figure 1. Simplified NCCN Guidelines for Colon Cancer and Rectal Cancer treatment algorithm showing systemic therapy for metastatic colorectal cancer. All recommendations are category 2A (based on lower-level evidence; there is uniform NCCN consensus that the intervention is appropriate) unless otherwise indicated.
[a]Nivolumab plus low-dose ipilimumab is a category 2B recommendation in the first-line setting (based on lower-level evidence, there is NCCN consensus that the intervention is appropriate).
Abbreviations: CRC, colorectal cancer; dMMR, mismatch repair deficient; EGFR, endothelial growth factor receptor; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NCCN, National Comprehensive Cancer Network; VEGF, vascular endothelial growth factor; WT, wild type.
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which included patients receiving fewer lines of prior therapy. Moreover, median DOR was not reached after a 21-month follow-up, demonstrating that previously treated patients can benefit from nivolumab monotherapy. Among 21 patients receiving nivolumab in CheckMate 142 who were not treated with all three prespecified chemotherapy agents and who had a median of one prior line of therapy, ORR was 52% [43].

In the first-line setting, many patients with MSI-H disease responded to chemotherapy and targeted agents [67, 68]; therefore, chemotherapy and checkpoint inhibition sequencing in this population remains unknown. For patients with MSI-H/dMMR tumors, NCCN Guidelines for Colon Cancer and Rectal Cancer recommend nivolumab with or without low-dose ipilimumab or pembrolizumab as one of several first-line regimens, particularly for patients who are not first-line chemotherapy candidates [4, 5]. Given the NCCN recommendation that all patients with CRC have MSI testing at initial diagnosis [4, 5], MSI status should be available before first-line therapy initiation. As mentioned, CheckMate 142's patients with untreated MSI-H/dMMR mCRC showed an ORR of 60%, DCR of 84%, and 12-month PFS of 77% to nivolumab plus low-dose ipilimumab [32]. A phase III trial of pembrolizumab versus chemotherapy (KEYNOTE-177) [69] in the first-line setting for patients with MSI-H/dMMR CRC is in analysis after completing accrual, and the larger NCTN COMMIT trial of atezolizumab alone or chemotherapy plus bevacizumab with or without atezolizumab (GI004/S1610) is actively accruing patients [36] (Table 3).

In contrast to the belief that all chemotherapy is immunosuppressive [82], chemotherapy plus checkpoint inhibition has improved response rates and PFS in patients with NSCLC [83]. In mCRC, trials are examining immunotherapy plus chemotherapy in both first- and second-line settings (Table 3) [36, 70, 74]. Until the possible synergy between chemotherapy and immunotherapy is better understood, clinicians must use other factors to determine how to incorporate checkpoint inhibitors, including expected DOR and anticipated toxicity of regimens.

Regardless of when a checkpoint inhibitor is administered, the NCCN Guidelines for Colon Cancer and Rectal Cancer recommend against treating patients with CRC with a different checkpoint inhibitor if they have progressed on one checkpoint inhibitor [4, 5]. No biologic rationale or clinical evidence for non-cross-resistance exists, so this should be avoided until supportive data are available. Similarly, the

benefit of adding ipilimumab to nivolumab in patients progressing on nivolumab alone is currently unknown.

Despite the well-documented durable responses to checkpoint inhibition experienced by patients with MSI-H/dMMR, some responders progress and other patients are refractory to treatment [8, 13]. This may be due to immune evasion mechanisms that interfere with the immune response. A complex and diverse pattern of immune evasive mutations involving disruption of HLA class I-mediated antigen processing and presentation have been detected in MSI-H/dMMR CRC tumors, including mutations in HLA, β-2 microglobulin, transporter associated with antigen processing proteins, and NOD-like receptor family CARD domain containing 5 [84].

Why Might MSS/pMMR CRC Be Resistant to Checkpoint Blockade, and What Is Being Tested to Enhance Sensitivity?

MSS/pMMR CRC, which makes up the majority (95%) of mCRC [85], has not yet demonstrated responsiveness to immune checkpoint blockade [9]. This can be explained by the lower antigenicity due to the presence of fewer neoantigens [86], regardless of tumor mutation burden [87], resulting in fewer infiltrating CD8+ T cells in general and fewer strongly positive for PD-1 [10]. Recently, several strategies to turn a "cold" CRC tumor into an immunoreactive "hot" tumor were identified [88]. Strategies to improve tumor antigenicity include increasing tumor antigen and major histocompatibility complex class I molecule expression, and strategies to positively alter the tumor microenvironment include vaccination, which increases T-cell infiltration and activation and shifts the cytokine milieu toward interferon-γ production [88]. Clinical trials are now testing some of these strategies. In a phase Ib trial in 84 heavily pretreated patients with mCRC, the mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor cobimetinib was added to atezolizumab (Table 1) [21], based on preclinical data showing increased T-cell tumor infiltration and PD-L1 activity with MEK inhibition [89]. This combination was further assessed versus single agents atezolizumab and regorafenib in a phase III trial in a largely MSS/pMMR population, but the trial did not meet its primary endpoint for the combination versus regorafenib (median OS: 8.9 vs. 8.5 months, respectively; HR, 1.00; Table 1) [21].

Strategies to improve tumor antigenicity include increasing tumor antigen and major histocompatibility complex class I molecule expression, and strategies to positively alter the tumor microenvironment include vaccination, which increases T-cell infiltration and activation and shifts the cytokine milieu toward interferon-γ production.

Atezolizumab was added to first-line maintenance therapy for patients with mCRC—mostly MSS/pMMR—in the phase II MODUL trial. Data from patients with wild-type *BRAF* disease showed no improvement in median PFS (7.2 months) and median OS (22.1 months) compared with controls (7.4 and 21.9 months, respectively; median follow-up, 18.7 months) [18]. Other clinical trials of MEK inhibitors plus immune checkpoint blockade are ongoing.

In an attempt to increase antigen-specific tumor infiltrating lymphocytes, a trial of previously treated patients with mCRC—mostly MSS/pMMR—investigated atezolizumab plus a novel carcinoembryonic antigen CD3 T-cell bispecific antibody (CEA CD3 TCB) designed to bind simultaneously with tumor cells and T cells to promote T-cell activation and infiltration [23]. Enhanced clinical activity was reported with the combination versus CEA CD3 TCB alone (DCR: 82% vs. 45%, respectively; Table 1) [23]. Ongoing trials are evaluating bispecific antibodies of various targets and novel combinations with checkpoint inhibition in MSS/pMMR CRC (Table 3).

How Might Checkpoint Inhibitors Be Used in the Future to Treat Patients With CRC?

Combinations with Chemotherapy or Radiotherapy

Despite the fact that a 2009 meta-analysis demonstrated that MSI-H CRC tends to be more resistant to chemotherapy than MSS CRC [90], clinical data have provided support for combinations of chemotherapy and immune checkpoint inhibitors in both MSS/pMMR and MSI-H/dMMR disease. First-line pembrolizumab plus chemotherapy demonstrated a median PFS of 16.9 months and median OS of 18.8 months (median follow-up, 7.9 months) in patients with primarily pMMR advanced CRC [15]; first-line atezolizumab plus chemotherapy plus bevacizumab produced an unconfirmed ORR of 44% in patients with mCRC [20], and pembrolizumab plus azacitidine in 30 patients with MSS mCRC (ORR, 3%) (Table 1) [19]. Whether PD-1 inhibition plus chemotherapy improves DOR in pMMR tumors requires further investigation. For the MSI-H/dMMR CRC population, the NCTN COMMIT trial will investigate whether atezolizumab plus FOLFOX and bevacizumab is superior to either single-agent anti-PD-1 therapy or chemotherapy alone and is expected to provide a rationale for using immunotherapy in the first-line setting (Table 3) [36]. CheckMate 9X8 is another ongoing first-line checkpoint inhibitor trial, examining the addition of nivolumab to standard-of-care chemotherapy plus bevacizumab in patients with mCRC (Table 3).

In order to examine whether immune checkpoint inhibitors can induce an abscopal effect, some studies are examining checkpoint inhibition in combination with radiation therapy (Table 3). Results thus far have been modest, with pembrolizumab plus radiation therapy producing an ORR of 4.5% in 22 patients with MSS/pMMR mCRC [24]. Nonetheless, multiple studies using this approach are ongoing in the hope of at least one of these regimens demonstrating favorable results in MSI-H/dMMR and/or MSS/pMMR CRC.

Combinations with Targeted Therapies

Checkpoint inhibitors plus approved targeted agents have evidence of activity. Preclinically, cetuximab induces immunogenic cell death, promoting antitumor responses [91]; early clinical data suggest that EGFR-based therapy strongly increases

Table 3. Selected ongoing phase II and III immune checkpoint inhibitor trials in advanced CRC

Trial name; NCT number	Trial sponsor	Regimens tested	Phase	Patient population	Efficacy endpoints	Safety endpoints
First line						
KEYNOTE-177; NCT02563002 [69]	Merck Sharp & Dohme Corp.	Pembrolizumab vs. chemotherapy	III	MSI-H or dMMR stage IV CRC	Primary: PFS, OS Secondary: ORR	Not reported
COMMIT GI004/S1610; NCT02997228 [36]	National Cancer Institute	Chemotherapy + bevacizumab ± atezolizumab	III	dMMR mCRC	Primary: PFS Secondary: ORR, DCR, DOR, OS, surgical conversion rate, PFS (by retrospective central independent scan review)	Secondary: AEs
CheckMate 9X8; NCT03414983 [70]	Bristol-Myers Squibb	Nivolumab + chemotherapy + bevacizumab vs. chemotherapy + bevacizumab	II/III	Previously untreated mCRC	Primary: PFS by IRRC Secondary: ORR, DCR, DOR, and TTR by IRRC, and OS	Secondary: AEs, serious AEs, deaths
CheckMate 142; NCT02060188 [71]	Bristol-Myers Squibb	Nivolumab + low-dose ipilimumab (cohort 3)	II	Previously untreated MSI-H/dMMR mCRC	Primary: ORR by investigators Secondary: ORR by IRRC	Not reported
QUILT-2.004; NCT03050814 [72]	National Cancer Institute	SOC ± Ad-CEA vaccine + avelumab	II	Previously untreated mCRC	Primary: PFS Secondary: immunologic analysis of blood and tumor samples ORR, correlation of immune endpoints with clinical outcomes, OS	Secondary: Safety
NCT02981524 [73]	Sidney Kimmel Comprehensive Cancer Center	Pembrolizumab + GVAX	II	MSS/pMMR advanced CRC	Primary: ORR Secondary: PFS, OS, DOR	Secondary: AEs
Second line and beyond						
CheckMate 142; NCT02060188 [71]	Bristol-Myers Squibb	Nivolumab + low-dose ipilimumab + cobimetinib (cohort 4) Nivolumab + relatlimab (cohort 5) Nivolumab + daratumumab (cohort 6)	II	Recurrent or mCRC (cohorts 4 and 6, non-MSI-H; cohort 5, MSI-H)	Primary: ORR by investigators Secondary: ORR by IRRC	Not reported
NCT02860546 [74]	Taiho Oncology Inc.	Nivolumab + TAS-102	II	MSS-refractory mCRC	Primary: irORR Secondary: ORR, PFS, irPFS, DCR, irDCR, OS	Secondary: RP2D, TEAEs
NCT02873195 [75]	Academic and Community Cancer Research United	Capecitabine + bevacizumab ± atezolizumab	II	Refractory mCRC	Primary: PFS Secondary: ORR, OS	Not reported
NCT03258398 [76]	Effector Therapeutics	eFT508 ± avelumab	II	MSS CRC	Primary (Part 2): ORR	Primary (Part 1): DLT
CheckMate 9N9; NCT03377361 [77]	Bristol-Myers Squibb	Nivolumab + trametinib ± low-dose ipilimumab	I/II	mCRC	Primary: ORR Secondary: DCR, DOR, TTR, PFS, OS	Primary: AEs, SAEs
NCT02713373 [78]	Roswell Park Cancer Institute	Pembrolizumab + cetuximab	I/II	mCRC	Primary: ORR Secondary: PFS, irORR, OS	Primary: AEs
Immune checkpoint inhibitor +/after radiation therapy						
NCT03104439 [79]	Massachusetts General Hospital	Nivolumab + ipilimumab + RT	II	MSS and MSI-H CRC and pancreatic cancer	Primary: DCR Secondary: mPFS, mOS	Not reported
NCT03122509 [80]	Memorial Sloan Kettering Cancer Center	Durvalumab + tremelimumab + RT or ablation	II	mCRC	Primary: ORR	Not reported
NCT03007407 [81]	NSABP Foundation Inc.	Durvalumab + tremelimumab after RT	II	MSS CRC	Primary: ORR Secondary: DCR, DOR	Secondary: AEs

Abbreviations: Ad-CEA, adenovirus serotype 5 carcinoembryonic antigen; AE, adverse event; CRC, colorectal cancer; DCR, disease control rate; DLT, dose-limiting toxicity; dMMR, mismatch repair deficient; DOR, duration of response; irDCR, immune-related disease control rate; irORR, immune-related objective response rate; irPFS, immune-related progression-free survival; IRRC, independent radiology review committee; mCRC, metastatic CRC; mOS, median overall survival; mPFS, median progression-free survival; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NSABP, National Surgical Adjuvant Breast and Bowel Project; NCT, National Clinical Trial; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; RP2D, recommended phase II dose; RT, radiation therapy; SOC, standard of care; TEAE, treatment-emergent adverse event; TTR, time to response.

Table 4. Questions addressed in this article

Question	Summary of discussion
1. What key data are available on immune checkpoint inhibitors in MSI-H/dMMR mCRC?	Two phase II pembrolizumab trials (KEYNOTE-016 and KEYNOTE-164) and one phase II nivolumab trial (CheckMate 142) have been conducted in patients with previously treated MSI-H/dMMR mCRC. Results with pembrolizumab from KEYNOTE-016 (ORR of 52%, 2-year PFS of 59%, and 2-year OS of 72%) combined with mCRC results from KEYNOTE-164 cohort A (ORR of 28% and 6-month OS of 87%) and nivolumab from CheckMate 142 (ORR of 32%, 12-week DCR of 69%, 12-month PFS of 50%, and 12-month OS of 73%) led to approval by the U.S. FDA for their use as monotherapies in patients with MSI-H/dMMR mCRC. The nivolumab plus low-dose ipilimumab cohort from CheckMate 142 has demonstrated improved efficacy (ORR of 55%, 12-week DCR of 80%, 12-month PFS of 71%, and 12-month OS of 85%) relative to nivolumab monotherapy in an indirect comparison and recently received accelerated U.S. FDA approval for previously treated patients with MSI-H/dMMR mCRC. Cohort 3 of CheckMate 142 showed a 60% ORR, 84% DCR, and 77% 12-month PFS rate among patients with untreated MSI-H/dMMR mCRC receiving nivolumab plus low-dose ipilimumab.
2. What are the unique patterns of efficacy with immunotherapy?	Pseudoprogression, complete responses, and durable responses that deepen over time are all patterns of response that are unique to immunotherapy and not generally observed with chemotherapy. Because median values for efficacy outcomes are often not reached in checkpoint inhibitor trials, emphasis is often placed on assessment of OS and PFS rates at landmark time points (e.g., 12 months).
3. Do specific tumor subsets respond differently to checkpoint blockade?	Subgroup analyses from CheckMate 142 suggest that none of the following characteristics are clinically important to tumor response to checkpoint blockade: Lynch syndrome status, *BRAF* mutation status, *KRAS* mutation status, and tumor cell PD-L1 expression level.
4. What are the unique patterns of safety with immunotherapy for CRC?	The safety profile of checkpoint inhibition is distinct from that of chemotherapy. Immune-related toxicities across organ systems are evident with checkpoint inhibitors, but dermatologic, gastrointestinal, endocrine, and pulmonary side effects are the most frequent types of immune-related toxicities in patients with CRC. These include rash, pruritus, dry skin, diarrhea, colitis, nausea/vomiting, pancreatitis, thyroid disease, hypophysitis, and adrenal insufficiency. Onset is generally within 12 weeks of treatment initiation, and most AEs resolve within 12 weeks of onset, except for some endocrine toxicities that require continued hormone replacement therapy. These toxicities are similar to those in other cancers. Dual checkpoint inhibition with nivolumab plus low-dose ipilimumab has a manageable safety profile.
5. What is the outcome for patients who discontinue checkpoint inhibition because of AEs or long-term responses?	Although outcomes associated with discontinuation of checkpoint inhibitors have not been rigorously tested, subgroup analyses have suggested that checkpoint inhibitor therapy may produce long-lasting clinical benefit despite limited treatment duration, owing to potential reactivation of memory T cells that may provide tumor cell surveillance. Sixteen patients from CheckMate 142 with MSI-H/dMMR CRC who discontinued nivolumab plus low-dose ipilimumab because of treatment-related AEs had an ORR of 63%, a DCR of 81%, and a median DOR that was not reached. Eighteen patients from KEYNOTE-016 who discontinued pembrolizumab after 2 years because of CR (n = 11) or intolerance to therapy (n = 7) showed no evidence of recurrence or progression after median times off therapy of 8.3 and 7.6 months, respectively.
6. When should MSI testing be performed in patients with CRC?	MSI-H/dMMR status is a biomarker associated with poor prognosis in metastatic CRC and is predictive for response to immune checkpoint inhibitors. Patients with MSI-H/dMMR mCRC demonstrate improved responses and more favorable survival with checkpoint inhibitor therapy versus those with MSS/pMMR mCRC. The NCCN Guidelines for Colon Cancer and Rectal Cancer recommend that all patients with CRC, regardless of stage, receive MSI or MMR testing at the time of initial diagnosis.
7. In patients with MSI-H/dMMR CRC, when should immune checkpoint inhibitors be considered?	Nivolumab, with or without low-dose ipilimumab, and pembrolizumab are indicated for use in patients with MSI-H/dMMR CRC upon progression after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, typically requiring use in the third-line setting, because oxaliplatin and irinotecan are rarely administered concomitantly. However, the NCCN Guidelines for Colon Cancer and Rectal Cancer list nivolumab, with or without low-dose ipilimumab, or pembrolizumab as a treatment recommendation for patients with MSI-H/dMMR tumors immediately after first-line treatment with a variety of chemotherapy options, and as first-line treatment for patients for whom intensive therapy is not appropriate. The KEYNOTE-177, COMMIT, and CheckMate 142 trials are currently underway to assess immune checkpoint inhibitors in the first-line setting.
8. Why might MSS/pMMR CRC be resistant to checkpoint blockade, and what is being tested to enhance sensitivity?	Microsatellite-stable tumors tend to be resistant to immunotherapy, potentially because of the poor antigenicity of the MSS/pMMR tumor cells, the presence of fewer neoantigens compared with MSI-H/dMMR CRC, and the tumor microenvironment, which is less responsive to checkpoint blockade because of fewer infiltrating $CD8^+$ T cells in general and fewer strongly positive for PD-1. Strategies to improve tumor antigenicity include increasing tumor antigen and major histocompatibility complex class I molecule expression, and strategies to positively alter the tumor microenvironment include increasing T-cell infiltration and activation and shifting the cytokine milieu toward interferon-γ production. Clinical trials are now testing some of these strategies. A phase III trial of atezolizumab plus cobimetinib versus single-agent atezolizumab and single-agent regorafenib in a largely MSS/pMMR population did not meet its primary endpoint of OS versus regorafenib. However, another trial of previously treated patients with mCRC—most with MSS/pMMR tumors—investigated atezolizumab plus CEA CD3 TCB and demonstrated enhanced clinical activity with the combination versus CEA CD3 TCB alone. Atezolizumab has also been added to first-line maintenance therapy for patients with mCRC—most with MSS/pMMR—in the phase II MODUL trial. Data from cohort 2 of patients with wild-type *BRAF* disease showed no improvement in PFS or OS with median follow-up of 18.7 months. Additional studies are underway.

(continued)

Table 4. (continued)

Question	Summary of discussion
9. How might checkpoint inhibitors be used in the future to treat patients with CRC?	Immune checkpoint inhibitors are under investigation in combination with chemotherapy, radiation therapy, and targeted therapy (including other immunotherapies) for the treatment of MSI-H/dMMR mCRC, for expansion to earlier lines of therapy (i.e., first-line setting), and for the treatment of CRC with other characteristics (i.e., MSS/pMMR disease).

Abbreviations: AE, adverse event; CEA CD3 TCB, carcinoembryonic antigen CD3 T-cell bispecific antibody; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; dMMR, mismatch repair deficient; DOR, duration of response; mCRC, metastatic CRC; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, MSI-high; MSS, microsatellite stable; NCCN, National Comprehensive Cancer Network; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, PD-1 ligand 1; PFS, progression-free survival; pMMR, mismatch repair proficient; FDA, Food and Drug Administration.

immune cell infiltration in CRC liver metastases [92]. In a phase Ib/II trial investigating pembrolizumab plus cetuximab in *RAS* wild-type mCRC, seven of nine patients achieved SD, and treatment was well tolerated [22]. This combination is being further investigated in a phase I/II trial [78].

Atezolizumab plus bevacizumab has been studied in an attempt to augment the antitumor immune response in MSI-H/dMMR CRC [17]. VEGF expression negatively correlates with intraepithelial T-cell infiltration, and bevacizumab-based therapy has previously enhanced immune responses in CRC [93, 94]. In a phase Ib trial of ten previously treated patients with MSI-H/dMMR mCRC, atezolizumab plus bevacizumab produced an ORR of 40% and DCR of 90% [17].

Aside from examining nivolumab with or without low-dose ipilimumab in MSI-H/dMMR mCRC (Table 1) [16, 31], CheckMate 142 is also investigating nivolumab plus other immunotherapies, including the anti-lymphocyte-activation gene 3, relatlimab, and daratumumab, an anti-CD38 cytolytic monoclonal antibody that may induce immune-mediated cell death (Table 3) [71]. In a trial of advanced solid tumors (ECHO-204), nivolumab is being evaluated with epacadostat, a selective inhibitor of the immunosuppressive enzyme indoleamine 2,3-dioxygenase 1; preliminary findings showed a 4% ORR and 24% DCR among 25 patients with advanced CRC (Table 1) [25].

Other trials are evaluating the efficacy and safety of checkpoint inhibitor combinations with targeted therapies and immunotherapies (Table 3) [72, 73, 75–77]. For instance, CheckMate 9N9 is testing nivolumab plus the MEK inhibitor trametinib with or without ipilimumab in previously treated mCRC. Checkpoint inhibitors are also being combined with vaccines for untreated CRC [72, 73]; the immune system is anticipated to have the capacity for more robust immune responses.

Conclusion

As immune checkpoint inhibitors are integrated into the mCRC treatment landscape, both as monotherapy and combination therapy, their roles will undoubtedly evolve. Checkpoint inhibitor use has already raised many clinical questions, including the timing of MSI testing; treatment initiation, sequencing, and discontinuation; and management of immune-related AEs (Table 4). The intense interest surrounding checkpoint inhibitors in CRC has launched numerous clinical trials. The greatest remaining challenge is to induce pMMR tumors—the majority of all CRC tumors—to exhibit immunologic properties and/or responsiveness to immunotherapy similar to dMMR tumors. Oncologists should monitor these evolving topics to appropriately incorporate checkpoint inhibitors into their clinical practice.

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References

1. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.

3. Gustavsson B, Carlsson G, Machover D et al. A review of the evolution of systemic chemotherapy in the management of colorectal cancer. Clin Colorectal Cancer 2015;14:1–10.

4. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology (NCCN Guidelines): Colon cancer version 3. 2018. Available at https://www.nccn.org/professionals/physician_gls/recently_updated.aspx. Accessed August 9, 2018.

5. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology

(NCCN Guidelines): Rectal cancer version 3. 2018. Available at https://www.nccn.org/professionals/physician_gls/recently_updated.aspx. Accessed August 9, 2018.

6. Chau I, Cunningham D. Treatment in advanced colorectal cancer: What, when and how? Br J Cancer 2009;100:1704–1719.

7. Le DT, Durham JN, Smith KN et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409–413.

8. Overman MJ, McDermott R, Leach JL et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): An open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182–1191.

9. Le DT, Uram JN, Wang H et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–2520.

10. Zhang Y, Sun Z, Mao X et al. Impact of mismatch-repair deficiency on the colorectal cancer immune microenvironment. Oncotarget 2017; 8:85526–85536.

11. Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co.; 2017.

12. Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2018.

13. Le DT, Kavan P, Kim TW et al. KEYNOTE-164: Pembrolizumab for patients with advanced microsatellite instability high (MSI-H) colorectal cancer. Presented at: American Society of Clinical Oncology; June 1–5, 2018; Chicago, IL. 2018; abstract 3514.

14. Diaz L, Marabelle A, Kim TW et al. Efficacy of pembrolizumab in phase 2 KEYNOTE-164 and KEYNOTE-158 studies of microsatellite instability high cancers. Presented at: European Society for Medical Oncology; September 8–12, 2017; Madrid, Spain. 2017; abstract 386P.

15. Shahda S, Noonan AM, Bekaii-Saab TS et al. A phase II study of pembrolizumab in combination with mFOLFOX6 for patients with advanced colorectal cancer. Presented at: American Society of Clinical Oncology; June 2–6, 2017; Chicago, IL. 2017; abstract 3541.

16. Overman MJ, Lonardi S, Wong KYM et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 2018;36:773–779.

17. Hochster HS, Bendell JC, Cleary JM et al. Efficacy and safety of atezolizumab (atezo) and bevacizumab (bev) in a phase Ib study of microsatellite instability (MSI)-high metastatic colorectal cancer (mCRC). Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 19–21, 2017; San Francisco, CA. 2017; abstract 673.

18. Grothey A, Tabernero J, Arnold D et al. Fluoropyrimidine (FP) and bevacizumab ± atezolizumab as first-line treatment for $BRAF^{wt}$ metastatic colorectal cancer: Findings from the MODUL trial of biomarker-driven maintenance. Presented at: European Society for Medical Oncology; October 19–23, 2018; Munich, Germany. 2018; abstract LBA19.

19. Lee JJ, Sun W, Bahary N et al. Phase 2 study of pembrolizumab in combination with azacitidine in subjects with metastatic colorectal cancer. Presented at: American Society of Clinical Oncology; June 2–6, 2017; Chicago, IL. 2017; abstract 3054.

20. Bendell JC, Powderly JD, Lieu CH et al. Safety and efficacy of MPDL3280A (anti-PDL1) in combination with bevacizumab (bev) and/or FOLFOX in patients (pts) with metastatic colorectal cancer (mCRC). Presented at: American Society of Clinical Oncology; May 29–June 2, 2015; Chicago, IL. 2015; abstract 704.

21. Bendell JC, Ciardiello F, Tabernero J et al. Efficacy and safety results from IMblaze370, a randomised phase III study comparing atezolizumab plus cobimetinib and atezolizumab monotherapy vs. regorafenib in chemotherapy-refractory metastatic colorectal cancer. Presented at: ESMO World Congress on Gastrointestinal Cancer; June 20–23, 2018; Barcelona, Spain. 2018; abstract LBA-004.

22. Boland PM, Hutson A, Maguire O et al. A phase Ib/II study of cetuximab and pembrolizumab in RAS-wt mCRC. Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 18–20, 2018; San Francisco, CA. 2018; abstract 834.

23. Tabernero J, Melero I, Ros W et al. Phase Ia and Ib studies of the novel carcinoembryonic antigen (CEA) T-cell bispecific (CEA CD3 TCB) antibody as a single agent and in combination with atezolizumab: Preliminary efficacy and safety in patients with metastatic colorectal cancer (mCRC). Presented at: American Society of Clinical Oncology; June 2–6, 2017; Chicago, IL. 2017; abstract 3002.

24. Segal NH, Kemeny NE, Cercek A et al. Non-randomized phase II study to assess the efficacy of pembrolizumab (Pem) plus radiotherapy (RT) or ablation in mismatch repair proficient (pMMR) metastatic colorectal cancer (mCRC) patients. Presented at: American Society of Clinical Oncology; June 3–7, 2016; Chicago, IL. 2016; abstract 3539.

25. Perez RP, Riese MJ, Lewis KD et al. Epacadostat plus nivolumab in patients with advanced solid tumors. Preliminary phase I/II results of ECHO-204. Presented at: American Society of Clinical Oncology; June 2–6, 2017; Chicago, IL. 2017; abstract 3003.

26. Wolchok JD, Hoos A, O'Day S et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Cancer Res 2009;15:7412–7420.

27. Das R, Verma R, Sznol M et al. Combination therapy with anti-CTLA-4 and anti-PD-1 leads to distinct immunologic changes in vivo. J Immunol 2015;194:950–959.

28. Luke JJ, Ott PA. PD-1 pathway inhibitors: The next generation of immunotherapy for advanced melanoma. Oncotarget 2015;6: 3479–3492.

29. Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373: 1270–1271.

30. Postow MA, Chesney J, Pavlick AC et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372: 2006–2017.

31. Andre T, Lonardi S, Wong M et al. Nivolumab + ipilimumab combination in patients with DNA mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer (mCRC): First report of the full cohort from CheckMate-142. Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 18–20, 2018; San Francisco, CA. 2018; abstract 553.

32. Lenz HJ, Van Cutsem E, Limon ML et al. Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). Presented at: European Society for Medical Oncology; October 19–23, 2018; Munich, Germany. 2018: abstract LBA18_PR.

33. Seymour L, Bogaerts J, Perrone A et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–e152.

34. Tazdait M, Mezquita L, Lahmar J et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria. Eur J Cancer 2018;88:38–47.

35. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247.

36. U.S. National Institutes of Health. Combination chemotherapy, bevacizumab, and/or atezolizumab in treating patients with deficient DNA mismatch repair metastatic colorectal cancer. Available at https://clinicaltrials.gov/ct2/show/NCT02997228. Accessed April 10, 2018.

37. Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. J Clin Oncol 2015;33:3541–3543.

38. Solinas C, Porcu M, Hlavata Z et al. Critical features and challenges associated with imaging in patients undergoing cancer immunotherapy. Crit Rev Oncol Hematol 2017;120:13–21.

39. Kwak JJ, Tirumani SH, Van den Abbeele AD et al. Cancer immunotherapy: Imaging assessment of novel treatment response patterns and immune-related adverse events. Radiographics 2015;35:424–437.

40. Chae YK, Wang S, Nimeiri H et al. Pseudoprogression in microsatellite instability-high colorectal cancer during treatment with combination T cell mediated immunotherapy: A case report and literature review. Oncotarget 2017;8:57889–57897.

41. Hodi FS, Hwu WJ, Kefford R et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol 2016;34:1510–1517.

42. Ducreux M, Bennouna J, Hebbar M et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. Int J Cancer 2011;128:682–690.

43. Overman MJ, Bergamo F, McDermott R et al. Nivolumab in patients with DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer: Long-term survival according to prior line of treatment from CheckMate-142. Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium; January 18–20, 2018; San Francisco, CA. 2018; abstract 554.

44. Bellmunt J, de Wit R, Vaughn DJ et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017; 376:1015–1026.

45. Motzer RJ, Escudier B, McDermott DF et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–1813.

46. Herbst RS, Baas P, Kim DW et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet 2016;387:1540–1550.

47. Boland PM, Yurgelun MB, Boland CR. Recent progress in Lynch syndrome and other familial colorectal cancer syndromes. CA Cancer J Clin 2018;68:217–231.

48. Copija A, Waniczek D, Witkos A et al. Clinical significance and prognostic relevance of microsatellite instability in sporadic colorectal cancer patients. Int J Mol Sci 2017;18:E107.

49. Sehgal R, Sheahan K, O'Connell PR et al. Lynch syndrome: An updated review. Genes (Basel) 2014; 5:497–507.

50. Brahmer JR, Lacchetti C, Schneider BJ et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2018;36:1714–1768.

51. Wolchok JD, Hodi FS, Weber JS et al. Development of ipilimumab: A novel immunotherapeutic approach for the treatment of advanced melanoma. Ann NY Acad Sci 2013;1291:1–13.

52. Puzanov I, Diab A, Abdallah K et al. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 2017;5:95.

53. Naidoo J, Page DB, Li BT et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 2015;26:2375–2391.

54. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158–168.

55. Weber JS, Dummer R, de Pril V et al. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: Detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer 2013;119:1675–1682.

56. Granier C, De Guillebon E, Blanc C et al. Mechanisms of action and rationale for the use of checkpoint inhibitors in cancer. ESMO Open 2017;2:e000213.

57. Robert C, Ribas A, Hamid O et al. Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. J Clin Oncol 2018;36:1668–1674.

58. Schadendorf D, Wolchok JD, Hodi FS et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: A pooled analysis of randomized phase II and III TRIALS. J Clin Oncol 2017;35:3807–3814.

59. Kawakami H, Zaanan A, Sinicrope FA. Microsatellite instability testing and its role in the management of colorectal cancer. Curr Treat Options Oncol 2015;16:30.

60. Kang S, Na Y, Joung SY et al. The significance of microsatellite instability in colorectal cancer after controlling for clinicopathological factors. Medicine (Baltimore) 2018;97:e0019.

61. Venderbosch S, Nagtegaal ID, Maughan TS et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: A pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res 2014;20:5322–5330.

62. Overman MJ, Kopetz S, Lonardi S et al. Nivolumab alone or in combination with ipilimumab treatment efficacy, safety, and biomarkers in patients with metastatic colorectal cancer with and without high microsatellite instability: Results from the CheckMate 142 study. Presented at: European Society for Medical Oncology; October 7–11, 2016; Copenhagen, Denmark. 2016; abstract 479P.

63. Brahmer JR, Drake CG, Wollner I et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: Safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167–3175.

64. Topalian SL, Hodi FS, Brahmer JR et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366: 2443–2454.

65. Lipson EJ, Sharfman WH, Drake CG et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin Cancer Res 2013;19:462–468.

66. Sepulveda AR, Hamilton SR, Allegra CJ et al. Molecular biomarkers for the evaluation of colorectal cancer: Guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. J Clin Oncol 2017;35:1453–1486.

67. Kim ST, Kim HK, Lee J et al. The impact of microsatellite instability status and sidedness of the primary tumor on the effect of bevacizumab-containing chemotherapy in patients with metastatic colorectal cancer. J Cancer 2018;9:1791–1796.

68. Kim ST, Lee SJ, Lee J et al. The impact of microsatellite instability status and sidedness of the primary tumor on the effect of cetuximab-containing chemotherapy in patients with metastatic colorectal cancer. J Cancer 2017;8:2809–2815.

69. U.S. National Institutes of Health. Study of pembrolizumab (MK-3475) vs standard therapy in participants with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) stage IV colorectal carcinoma (MK-3475-177/KEYNOTE-177). Available at https://clinicaltrials.gov/ct2/show/NCT02563002. Accessed April 10, 2018.

70. U.S. National Institutes of Health. An investigational immunotherapy study of nivolumab with standard of care therapy vs standard of care therapy for first-line treatment of colorectal cancer that has spread (CheckMate 9X8). Available at https://clinicaltrials.gov/ct2/show/NCT03414983. Accessed April 10, 2018.

71. U.S. National Institutes of Health. An investigational immuno-therapy study of nivolumab, and nivolumab in combination with other anticancer drugs, in colon cancer that has come back or has spread (CheckMate142). Available at https://clinicaltrials.gov/ct2/show/NCT02060188. Accessed April 10, 2018.

72. U.S. National Institutes of Health. Standard of care alone or in combination with Ad-CEA vaccine and avelumab in people with previously untreated metastatic colorectal cancer QUILT-2.004. Available at https://clinicaltrials.gov/ct2/show/NCT03050814. Accessed April 10, 2018.

73. U.S. National Institutes of Health. Phase 2 study of GVAX (with CY) and pembrolizumab in MMR-p advanced colorectal cancer. Available at https://clinicaltrials.gov/ct2/show/NCT02981524. Accessed April 10, 2018.

74. U.S. National Institutes of Health. A study evaluating TAS-102 plus nivolumab in patients with MSS CRC. Available at https://clinicaltrials.gov/ct2/show/NCT02860546. Accessed April 10, 2018.

75. U.S. National Institutes of Health. Capecitabine and bevacizumab with or without atezolizumab in treating patients with refractory metastatic colorectal cancer. Available at https://clinicaltrials.gov/ct2/show/NCT02873195. Accessed April 10, 2018.

76. U.S. National Institutes of Health. A study to evaluate eFT508 alone and in combination with avelumab in subjects with MSS colorectal cancer. Available at https://clinicaltrials.gov/ct2/show/NCT03258398. Accessed April 10, 2018.

77. U.S. National Institutes of Health. An investigational immuno-therapy study of nivolumab in combination with trametinib with or without ipilimumab in patients with previously treated cancer of the colon or rectum that has spread (CheckMate 9N9). Available at https://clinicaltrials.gov/ct2/show/NCT03377361. Accessed April 10, 2018.

78. U.S. National Institutes of Health. Cetuximab and pembrolizumab in treating patients with colorectal cancer that is metastatic or cannot be removed by surgery. Available at https://clinicaltrials.gov/ct2/show/NCT02713373. Accessed April 10, 2018.

79. U.S. National Institutes of Health. Nivolumab and ipilimumab and radiation therapy in MSS and MSI high colorectal and pancreatic cancer. Available at https://clinicaltrials.gov/ct2/show/NCT03104439. Accessed April 10, 2018.

80. U.S. National Institutes of Health. A clinical trial of durvalumab and tremelimumab, administered with radiation therapy or ablation in patients with colorectal cancer. Available at https://clinicaltrials.gov/ct2/show/NCT03122509. Accessed April 10, 2018.

81. U.S. National Institutes of Health. Study of durvalumab and tremelimumab after radiation for microsatellite stable metastatic colorectal cancer progressing on chemotherapy. Available at https://clinicaltrials.gov/ct2/show/NCT03007407. Accessed April 10, 2018.

82. Apetoh L, Ladoire S, Coukos G et al. Combining immunotherapy and anticancer agents: The right path to achieve cancer cure? Ann Oncol 2015;26:1813–1823.

83. Langer CJ, Gadgeel SM, Borghaei H et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: A randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497–1508.

84. Ozcan M, Janikovits J, von Knebel Doeberitz M et al. Complex pattern of immune evasion in MSI colorectal cancer. Oncoimmunology 2018;7:e1445453.

85. Ali SM, Gay LM, Elvin JA et al. MSI-stable colorectal carcinomas (CRC): A comprehensive genomic profiling (CGP) study. Presented at: American Society of Clinical Oncology; June 1–5, 2018; Chicago, IL. 2018; abstract 3574.

86. Kather JN, Halama N, Jaeger D. Genomics and emerging biomarkers for immunotherapy of colorectal cancer. Semin Cancer Biol 2018;52(pt 2):189–197.

87. Chalmers ZR, Connelly CF, Fabrizio D et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 2017;9:34.

88. Le DT, Hubbard-Lucey VM, Morse MA et al. A blueprint to advance colorectal cancer immunotherapies. Cancer Immunol Res 2017;5:942–949.

89. Long J, Lin J, Wang A et al. PD-1/PD-L blockade in gastrointestinal cancers: Lessons learned and the road toward precision immunotherapy. J Hematol Oncol 2017;10:146.

90. Des Guetz G, Schischmanoff O, Nicolas P et al. Does microsatellite instability predict the efficacy of adjuvant chemotherapy in colorectal cancer? A systematic review with meta-analysis. Eur J Cancer 2009;45:1890–1896.

91. Pozzi C, Cuomo A, Spadoni I et al. The EGFR-specific antibody cetuximab combined with chemotherapy triggers immunogenic cell death. Nat Med 2016;22:624–631.

92. Inoue Y, Hazama S, Suzuki N et al. Cetuximab strongly enhances immune cell infiltration into liver metastatic sites in colorectal cancer. Cancer Sci 2017;108:455–460.

93. Lanitis E, Irving M, Coukos G. Targeting the tumor vasculature to enhance T cell activity. Curr Opin Immunol 2015;33:55–63.

94. Osada T, Chong G, Tansik R et al. The effect of anti-VEGF therapy on immature myeloid cell and dendritic cells in cancer patients. Cancer Immunol Immunother 2008;57:1115–1124.

For Further Reading:
Michael A. Morse, Michael J. Overman, Leighanne Hartman et al. Safety of Nivolumab plus Low-Dose Ipilimumab in Previously Treated Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer. ***The Oncologist*** 2019;24:1453–1461; first published on May 30, 2019.

Implications for Practice:
Nivolumab (NIVO) plus low-dose (1 mg/kg) ipilimumab (IPI) received U.S. Food and Drug Administration approval for patients with microsatellite instability-high and/or mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) that progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan based on results from CheckMate 142. In this safety analysis, the majority of select treatment-related adverse events (sTRAEs) occurred early, were managed using evidence-based treatment algorithms, and resolved. Efficacy outcomes were comparable between patients with or without sTRAEs regardless of the use of concomitant immune-modulating medications. The benefit-risk profile of NIVO + low-dose IPI provides a promising treatment option for MSI-H/dMMR mCRC.