

Update on the role of pembrolizumab in patients with unresectable or metastatic colorectal cancer

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Abstract: Colorectal cancer (CRC) is the third most common cancer type in both men and women in the USA. Most patients with CRC are diagnosed as local or regional disease. However, the survival rate for those diagnosed with metastatic disease remains disappointing, despite multiple treatment options. Cancer therapies for patients with unresectable or metastatic CRC are increasingly being driven by particular biomarkers. The development of various immune checkpoint inhibitors has revolutionized cancer therapy over the last decade by harnessing the immune system in the treatment of cancer, and the role of immunotherapy continues to expand and evolve. Pembrolizumab is an anti-programmed cell death protein 1 immune checkpoint inhibitor and has become an essential part of the standard of care in the treatment regimens for multiple cancer types. This paper reviews the increasing evidence supporting and defining the role of pembrolizumab in the treatment of patients with unresectable or metastatic CRC.

Keywords: colorectal cancer, mismatch repair deficiency, microsatellite instability, immunotherapy, pembrolizumab

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Introduction

Colorectal cancer (CRC) is the third most common cancer type and the second most common cancer-related cause of death when men and women are combined in the USA.¹ In the last two decades, the incidence and mortality of CRC in patients ages 65 years or older has decreased, primarily due to increased screening; however, the incidence in younger populations has increased. In patients less than 50 years of age, mortality has increased by 1.3% per year since 2004.² Around 22% of newly diagnosed CRC cases have distant metastases at diagnosis and have a 14.3% 5-year survival rate, compared with 90.2% and 71.8% 5-year survival rates for localized and regional disease at diagnosis, respectively.³

About 5% of metastatic CRCs are microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR), including those with hereditary non-polyposis CRC, also known as Lynch

Syndrome (HNPCC).^{4–6} Less than 25% of patients with MSI-H/dMMR CRC are associated with HNPCC.⁷ The majority of MSI-H/dMMR CRCs are sporadic in nature, tend to originate more commonly in the right colon, and are more likely to be associated with a *BRAF V600E* mutation.⁵ A *BRAF V600E* mutation leads to somatic hypermethylation of the *MLH1* promoter and absence of *MLH1* protein expression, one of the DNA MMR proteins.⁸ The presence of a *BRAF V600E* mutation excludes a diagnosis of HNPCC.⁸ MSI-H/dMMR CRCs also tend to be less responsive to traditional cytotoxic chemotherapy.⁹

MSI-H/dMMR tumors have an increased accumulation of somatic mutations due to decreased DNA repair functionality and have a higher mutational burden by 10–100-fold than microsatellite stable (MSS)/mismatch repair proficient (pMMR) CRCs.^{10–12} This decreased DNA repair ability leads to increased immunogenic neoantigen

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expression, lymphocytic infiltration, and immune activation.^{10–12} Thus, the MSI-H/dMMR phenotype is an indicator of genomic instability and is used as a surrogate marker for neoantigen burden.¹³

These neoantigens, presented on the major histocompatibility complex class 1 molecules on the surface of tumor cells, are recognized by T cells as non-self^{11,14} leading to T-cell infiltration.¹⁵ However, T-cell activation, and thus induction of apoptosis, is modulated by a complex interaction between costimulatory and coinhibitory signals.¹⁴ Binding of the cytotoxic T-lymphocyte antigen 4 (CTLA4) or programmed cell death protein 1 (PD-1) on the surface of activated cytotoxic T cells to the B7 ligand or the programmed cell death ligand 1 (PD-L1), respectively, which are expressed on the surface of target cells, inhibits cytotoxic T-cell response.¹⁴ PD-L1 is expressed on the surface of normal human cells as a mechanism to guard against autoimmunity, but can also be expressed on the surface of tumor cells and is a mechanism of immune evasion by cancer cells.¹⁴ Acquisition of various mutations in the *beta2-microglobulin* gene that encodes the light chain required for assembly of the human leukocyte antigen (HLA) class 1 complex or in the antigen-presenting machinery, impair the ability of HLA class I complexes to present antigens to cytotoxic T cells, can occur early in CRC tumorigenesis and are another common mechanism of immune evasion of MSI-H/dMMR CRC due to the high mutational burden.¹⁶

In other tumor types with high mutational burdens, such as non-small cell lung cancer and melanoma, immune checkpoint inhibitors have become the foundation of treatment and have led to improved survival.^{17–19} Immune checkpoint inhibitors are monoclonal antibodies that block the interaction of coinhibitory stimuli, such as PD-L1 with PD-1, or B7 with CTLA-4, thereby preventing suppression of the immune system by cancer cells. Immunotherapy with immune checkpoint inhibition has been a revolutionary discovery changing the standard of care for many tumor types over the past several years.^{14,17–19} Pembrolizumab is an immune checkpoint inhibitor that targets PD-1 on cytotoxic T cells and prevents binding to PD-L1 on tumor cells, which allows T-cell activation and immune-mediated tumor cell apoptosis.²⁰ Pembrolizumab has become part of the standard of care in the

treatment for multiple tumor types. This paper reviews the expanding evidence on the role of pembrolizumab, a PD-1 inhibitor, in the treatment of patients with unresectable or metastatic CRC.

Methods

We performed an electronic search of the Medline (PubMed interface) to find articles relevant to the role of pembrolizumab in unresectable or metastatic CRC available in the English language through 31 October 2020. Search terms included pembrolizumab, immune checkpoint inhibition, immunotherapy, KEYNOTE, microsatellite instability-high [MSI-H], deficient mismatch repair deficiency [dMMR], programmed cell death protein 1 [anti-PD-1], tumor mutational burden [TMB], tumor mutational load, and colorectal cancer [CRC]. Papers were screened by title and abstract. Abstracts and presentations from oncology conferences, including the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology annual conferences, were also explored.

Results and discussion

Current role of pembrolizumab in MSI-H/dMMR

Pembrolizumab received the first tumor-agnostic approval ever by the US Food and Drug Administration (FDA) in 2017, when it was approved for any unresectable or metastatic MSI-H/dMMR solid tumor that had progressed on standard therapy without other available treatment options. The CRC-specific approval listed treatment-refractory MSI-H/dMMR CRC previously treated with a fluoropyrimidine, oxaliplatin, and irinotecan.^{21,22} This approval was based on data from 149 patients with a variety of previously treated advanced solid tumors that were MSI-H/dMMR and were treated with pembrolizumab until progression or intolerance for a maximum of 2 years in a group of single-arm, uncontrolled clinical trials of various tumor types.^{12,22–25} In total, there were 90 patients with MSI-H/dMMR metastatic CRC across these trials and the collective objective response rate (ORR) was 36% [95% confidence interval (CI), 26–46%] in these patients.²¹ Nivolumab, either alone or in combination with ipilimumab, has also been approved by the FDA for MSI-H/dMMR metastatic CRC that has progressed after fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, based on

Table 1. Immunotherapy trials in MSI-H/dMMR metastatic CRC.

| Trial* | Phase | Setting | N patients, biomarker | Primary endpoint |
|------------------------------|----------------------|--|---------------------------------|---|
| KEYNOTE-028 ²³ | Phase 1b | Treatment refractory | 1 MSI-H/dMMR 22 MSS/pMMR | ORR: 4% (<i>only responder was MSI-H/dMMR</i>) |
| KEYNOTE-016 ¹³ | Phase II | Treatment refractory | 10 MSI-H/dMMR 18 MSS/pMMR | irORR: 40% MSI-H; 0% MSS irPFS: [§] 78% MSI-H; 11% MSS |
| KEYNOTE-164 ^{24,30} | Phase II | ≥2 line (cohort A) ≥1 line (cohort B) | 61 (A) and 63 (B) MSI-H/dMMR | ORR: 33% (A) and 33% (B) |
| KEYNOTE-177 ³¹ | Randomized phase III | First-line versus SOC chemotherapy [‡] | 307 MSI-H/dMMR | PFS: median 16.5 months <i>versus</i> 8.2 months; HR 0.60; 95% CI 0.45–0.80; <i>p</i> =0.0002 OS: data not yet available |
| CHECKMATE-142 ²⁶ | Phase II | ≥1 line cohort | 119 MSI-H/dMMR | ORR 55% |
| CHECKMATE-142 ³² | Phase II | First-line single arm cohort | 45 MSI-H/dMMR | ORR 69% PFS: median not reached OS: median not reached |

First-line trials listed in bold.
 *KEYNOTE trials evaluated pembrolizumab-based immunotherapy, CHECKMATE trials evaluated nivolumab-based immunotherapy.
 §irPFS at 20 weeks.
 ‡Chemotherapy doublet ± biologic.
 CRC, colorectal cancer; CI, confidence interval; HR, hazard ratio; irORR, immune-related objective response rate; irPFS, immune-related progression-free survival; MSI-H/dMMR, microsatellite instability-high/mismatch repair deficient; MSS/pMMR, microsatellite stable/mismatch repair proficient; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

the CHECKMATE-142 trial.^{26–29} The relevant immunotherapy trials in MSI-H/dMMR CRC are summarized in Table 1.

In the KEYNOTE-028 study, a phase 1b trial, the activity of pembrolizumab was evaluated in PD-L1-positive advanced solid tumors. In the CRC cohort, 23 patients with PD-L1-positive previously treated metastatic CRC were enrolled regardless of MSI status and treated with pembrolizumab until progression or intolerance for a maximum of 2 years.²³ The sole responder, who also had a *BRAF V600E*-mutated tumor, was the only patient with an MSI-H/dMMR tumor and remained on treatment for nearly 24 months before discontinuing the study.^{23,33} This study could not validate the value of PD-L1 expression as a predictive biomarker for pembrolizumab in CRC, but it provided a signal that MSI-H/dMMR cancers could be responsive to immunotherapy.

KEYNOTE-164 was a phase II non-randomized clinical study that also evaluated pembrolizumab's efficacy in locally advanced, unresectable or metastatic MSI-H/dMMR CRC that had received ≥2

lines of therapy (cohort A) or >1 line of therapy (cohort B).²⁴ The ORR in cohort A was 33% (95% CI, 21–46%) and 33% (95% CI, 22–46%) in cohort B with a DCR of 51% (95% CI, 38–64%) and 57% (95% CI, 44–70%) in cohorts A and B, respectively.²⁴ The duration of response lasted greater than 12 months for both cohorts.²⁴ At a follow-up analysis, 3-year overall survival (OS) was 49% and 52% in cohorts A and B, respectively.³⁰ Those in cohort A had a median progression-free survival (PFS) of 2.3 months (95% CI, 2.1–8.1) and a 3-year PFS of 31%. Cohort B had a median PFS of 4.1 months (95% CI, 2.1–18.9) and a 3-year PFS of 34%.³⁰ Though the median PFS for each cohort was short, the median duration of response was not reached in either cohort, illustrating that those who responded had a durable response.³⁰

The clinically significant duration of response in those with MSI-H/dMMR CRC who responded to pembrolizumab in the above studies led to the clinical utilization of pembrolizumab in later lines of treatment for unresectable and metastatic CRC and formed the foundation for further randomized control trials in the first-line setting.

The KEYNOTE-177 trial was a phase III randomized control trial comparing single agent pembrolizumab to physician-choice of standard cytotoxic chemotherapy-doublet plus biologics as first-line treatment in 307 patients with unresectable or metastatic MSI-H/dMMR CRC. Importantly, the MSI-H/dMMR status ascertainment was based on local assessment with confirmation by central testing. The PFS and ORR analysis of the trial was presented at the 2020 ASCO Annual Meeting and OS data will be reported at a later time point. In the pembrolizumab arm, the ORR was 43.8% compared with 33.1% ($p=0.0275$) in the standard chemotherapy arm.^{31,34} The median PFS for pembrolizumab was 16.5 months *versus* 8.3 months in the standard chemotherapy arm [hazard ratio (HR): 0.60; 95% CI, 0.45–0.80; $p=0.0002$], and the 24-month PFS rates were 48.3% *versus* 18.6%, respectively.³¹ Complete responses were seen in 11.1% of those in the pembrolizumab group compared with 3.9% in the standard chemotherapy group.³¹ Durable responses were also seen; the median duration of response was not reached (2.3+ to 41.4+) in the pembrolizumab arm compared with 10.6 months (2.8–37.5+) in the chemotherapy arm with ongoing responses at 24 months in 82.6% and 35.3% of patients, respectively.³¹ The benefit of pembrolizumab persisted in most of the prespecified subgroups; however, those with a *KRAS* or *NRAS* mutation did not seem to benefit from pembrolizumab compared with standard chemotherapy (HR 1.19; 95% CI 0.68–2.07).³¹ Crossover was allowed and a significant portion did crossover, so it remains to be seen if the OS data will be as impressive as the PFS.

Pembrolizumab was also well tolerated in KEYNOTE-177 with 22% of patients experiencing a grade 3 or greater adverse event based on the National Cancer Institute Common Terminology Criteria for Adverse Events, in relation to 66% of patients in the standard chemotherapy arm who experienced a grade 3 or greater adverse event.^{31,34} In the health-related quality of life analysis, pembrolizumab was also superior to the standard of care chemotherapy.³⁵ The time to deterioration was prolonged for global health status/quality of life (HR 0.61; 95% CI, 0.38–0.98; $p=0.0195$), physical functioning (HR 0.50; 95% CI, 0.32–0.81; $p=0.0016$), social functioning (HR 0.53; 95% CI, 0.32–0.87; $p=0.0050$), and fatigue (HR 0.48; 95% CI, 0.33–0.69; $p<0.0001$)

for those patients receiving pembrolizumab compared with those receiving standard of care chemotherapy.³⁵

Based on the impressive PFS data of KEYNOTE-177, pembrolizumab was approved by the FDA for first-line treatment of patients with unresectable or metastatic MSI-H/dMMR CRC on 29 June 2020 and represents a new standard of care for these patients.³⁶ Data suggest that those patients with MSI-H/dMMR CRC who respond to pembrolizumab have a lengthy duration of response. However, based on the KEYNOTE-177 and prior KEYNOTE trials in metastatic and unresectable CRC, there are a clinically relevant proportion of patients that are refractory to pembrolizumab despite having MSI-H/dMMR CRC. In the KEYNOTE-177 trial, 29.4% of patients were refractory to pembrolizumab whereas only 12.3% of patients were refractory to standard chemotherapy.^{31,34} Consequently, an initial detriment in PFS was seen on the PFS Kaplan–Meier estimate curves in the pembrolizumab group compared with the standard chemotherapy group until about 6 months into treatment when the Kaplan–Meier curves crossed and a striking separation of the curves was seen, demonstrating long-term benefit in those that responded to pembrolizumab.³¹ Thus, further methods to refine patient selection and predict response to immune checkpoint inhibitors are essential.

Nivolumab ± ipilimumab in MSI-H/dMMR CRC

Though the focus of this review is on pembrolizumab, nivolumab, another PD-1 inhibitor, has also been studied in MSI-H/dMMR metastatic CRC, both alone and in combination with ipilimumab, a CTLA-4 inhibitor. In the phase II, non-randomized, multi-cohort CHECKMATE-142 trial, heavily pretreated patients with MSI-H/dMMR CRC treated with nivolumab monotherapy had an ORR of 31% (95% CI, 20.8–42.9%) with a DCR of 69% (95% CI, 57–79%).²⁷ When nivolumab was combined with ipilimumab, the ORR was 54.6% (95% CI, 45.2–63.8%) with a DCR of 80% (95% CI, 71.5 – 86.6%) with 12-month OS of 85% (95% CI, 77.0–90.2%) and was well tolerated.²⁶ Median PFS and median OS were not reached, but 71% of patients were progression free at 12 months (95% CI, 61.4–78.7%), and 12-month OS was 85% (95% CI, 77.0–90.2%).²⁶ The CHECKMATE-142 cohorts

evaluating the combined use of nivolumab and ipilimumab are summarized in Table 1.

In the first-line cohort of the CHECKMATE-142 trial, nivolumab in combination with ipilimumab was also evaluated in the first-line setting with an ORR of 69% (95% CI, 53–82%) and with a DCR of 84% (95% CI, 70.5–93.5%).³² Median DCR was not reached, but 71% of patients had a response lasting ≥ 12 months.³² Median OS was also not reached and 79% were alive at 24 months (95% CI, 64.1–88.7%). In the first-line setting, 13% of patients were refractory to the combination of nivolumab and ipilimumab, while 29.4% of patients in the KEYNOTE-177 trial were refractory to pembrolizumab and 12.3% were refractory to chemotherapy.^{31,32} The KEYNOTE-177 was a randomized phase III trial with 307 patients compared with the CHECKMATE-142 study, a non-randomized phase II trial that included 45 patients and lacked a control group, so comparisons should be made with caution. Nivolumab either alone or in combination with ipilimumab is only FDA approved so far for later line settings in MSI-H/dMMR CRC, and not yet approved as a first-line treatment; however, the relatively low primary resistance rate is encouraging and is similar to the chemotherapy control arm in the KEYNOTE-177 study.

BRAF mutations

The presence of a *BRAF V600E* mutation in metastatic CRC is typically associated with right-sided tumors and portends a poor prognosis.^{37,38} The BEACON trial demonstrated that CRC with *BRAF V600E* mutations can successfully be targeted with encorafenib, a *BRAF* inhibitor, and cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, to improve survival in previously treated patients.³⁸ Patients with MSI-H/dMMR CRC with *BRAF V600E* mutations have also been shown to respond to immunotherapy similarly to *BRAF* wild-type cancers.³¹ In the KEYNOTE-177 trial, 25% of cancers had a *BRAF V600E* mutation, and in the subgroup analysis, patients with *BRAF V600E*-mutated CRC had an HR of 0.48 (95% CI, 0.27–0.86), compared with patients with *BRAF* wild-type CRC, who had an HR of 0.50 (95% CI, 0.31–0.81).³¹ Patients with *BRAF V600E*-mutated CRC had a similar response rate to those that were wild type in the phase II CHECKMATE-142

trial with an ORR rate of 55% in both groups.²⁶ In the first-line cohort of the CHECKMATE-142 trial, 38% of cancers had a *BRAF V600E* mutation with an ORR of 76% (95% CI, 50–93%) compared with an ORR of 62% (95% CI, 32–86%) in those that were *BRAF* wild type.³² Thus, though *BRAF V600E*-mutated CRC tends to have a poor prognosis, they seem to respond to immunotherapy similarly to *BRAF* wild type MSI-H/dMMR CRC.^{26,31,32}

Tumor mutational burden

Tumor mutational burden (TMB), the amount of tumor somatic coding mutations, has been used to approximate neoantigen burden, and as a predictive biomarker of response to immune checkpoint inhibition over multiple tumor types.^{13,39} Whole exome sequencing (WES) is still the gold standard to directly evaluate TMB; however, WES is not realistically available or practical in the clinical setting.¹³ Many current gene panel assays approximate TMB; however, the number of mutations used as a cutoff for defining a high TMB (TMB-H) is not standard, making it difficult to generalize results of clinical trials.¹³

In addition to the approval of pembrolizumab as a first-line treatment for MSI-H/dMMR metastatic or unresectable CRC,³⁶ in 2020, the FDA also granted accelerated approval for pembrolizumab for the treatment of unresectable or metastatic solid tumors in adult and pediatric patients with a TMB-H, defined as ≥ 10 mutations/megabase (mut/Mb), after progression on prior treatment without further acceptable treatment options based on a biomarker analysis of the KEYNOTE-158 trial.⁴⁰

The KEYNOTE-158 was another non-randomized multi-cohort phase II trial of pretreated unresectable or metastatic non-colorectal solid tumors of 10 different origins (anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small cell lung, thyroid, and vulvar) that were treated with pembrolizumab similarly to prior KEYNOTE studies.²⁵ In the biomarker analysis of the KEYNOTE-158 trial, TMB levels for each tumor were determined using the FoundationOne CDx assay (Foundation Medicine, Cambridge, MA, USA) and TMB-H was prespecified and defined as ≥ 10 mut/Mb, in part, because this had been previously validated as predictive of response to immunotherapy with

the FoundationOne CDx assay in non-small cell lung cancer.^{13,41} MSI/MMR status and PD-L1 were also determined.⁴¹ The ORR in all cohorts with TMB-H tumors was 29% compared with 6% in non-TMB-H tumors.⁴¹ This ORR persisted when MSI-H tumors, all of which were in the TMB-H cohort, were excluded from the ORR analysis.⁴¹ Median OS was 11.7 months (95% CI, 9.1–19.1) in the TMB-H group compared with 12.8 months (95% CI, 11.1–14.1) in the non-TMB-H group.⁴¹

It should be noted that CRC and other common malignancies were not included in the TMB biomarker analysis of KEYNOTE-158.⁴¹ Though the cutoff of ≥ 10 mut/Mb as a definition for TMB-H was validated to predict response to immune checkpoint inhibition for non-small cell lung cancer when the FoundationOne CDx assay is used, this definition of ≥ 10 mut/Mb has not been validated in CRC and higher TMB cutoff values have been shown to more accurately predict response to immune checkpoint inhibition.^{13,42} The results of the KEYNOTE-158 trial should not be applied to all tumor types. In fact, recent data suggest against a universal TMB threshold to predict response to immunotherapy in all cancer types.⁴³ Further investigation is needed to determine the most appropriate TMB cutoff and the utility of TMB for prediction of response to pembrolizumab in CRC.

TMB can also vary across tumor types and within specific tumors, and measurement and reporting of TMB can vary across gene panel assays, particularly for CRC.⁴⁴ Consensus between gene panels and across multiple tumor types is necessary. Hence, despite the tumor agnostic approval for pembrolizumab in TMB-H solid malignancies, care should be taken to truly identify those with unresectable or metastatic CRC that are most likely to respond to pembrolizumab.

Other biomarkers

There are other biomarkers and potential biomarkers used to approximate neoantigen burden and, thus, to attempt to predict response to immune checkpoint inhibition. One of the most dramatic predictors of neoantigen burden is a mutation in the *polymerase epsilon (POLE)* gene, though rare in the metastatic setting, that leads to error in DNA proofreading and hypermutated

CRC tumors and immune infiltration.^{4,45} These tumors are almost always MSS/dMMR, but typically have a TMB-H significantly higher than that of MSI-H/dMMR tumors.^{4,46,47} Next generation sequencing was performed retrospectively on tumor samples from randomized patients from the phase III TRIBE2 study cohort that evaluated the clinical utility of upfront FOLFOXIRI plus bevacizumab compared with sequential standard doublets + bevacizumab in treatment-naïve patients with metastatic CRC.⁶ The MI Tumor Seek panel (Caris MI, Irving, TX, USA) was utilized, and TMB-H was defined as >16 mut/Mb, intermediate was 7–16 mut/Mb, and TMB-low was defined as <7 mut/Mb.⁶ Of the three tumors that were TMB-H and MSS, two had a pathogenic *POLE* mutation.⁶ Reports suggest response of *POLE*-mutated CRC to pembrolizumab, and further studies are in progress.^{4,46}

The immunoscore is a scoring system used to represent the densities of CD3+ and CD8+ lymphocytes at the tumor core and invasive margin and is emerging as another predictor for response to immune checkpoint inhibitors and prognosis in the metastatic setting regardless of MSI/MMR status.^{48,49} A higher immunoscore, scaled from 0–4, represents increased density of tumor-infiltrating lymphocytes.⁴⁹ In a cohort of patients with metastatic CRC undergoing complete curative resection of all metastases, a higher immunoscore was associated with an increased response to pre-operative chemotherapy.⁴⁹ Intertumoral heterogeneity of tumor-infiltrating lymphocyte density was also noted, and a higher immunoscore in the least infiltrated metastasis was associated with an increased OS compared with those with a lower immunoscore.⁴⁹ In a small sample of patients with MSI-H/dMMR metastatic CRC treated with pembrolizumab, T-cell density was higher in responders to pembrolizumab than in non-responders.⁴⁸ Intertumoral heterogeneity of immune infiltration in metastatic CRC makes the utilization of the immunoscore in the metastatic setting more complex, especially in those with a high metastatic burden; however, the immunoscore represents another potential emerging biomarker.

Though PD-L1 expression has been shown to be a strong predictor of response to immune checkpoint inhibition in other tumor types, such as non-small cell lung cancer, it does not correlate well with response in CRC.¹² In the hopes of better

selection of patients for treatment with immune checkpoint inhibitors, identification and investigation of other potential biomarkers are emerging.

Future directions

The recent emergence of immunotherapy as an effective tool in the treatment of patients with unresectable and metastatic MSI-H/dMMR CRC continues to fuel further investigations to attempt to expand the role of immunotherapy. In addition to pembrolizumab, there are ongoing trials with other immune checkpoint inhibitors, either alone or in combination with other immune checkpoint inhibitors, in unresectable and metastatic MSI-H/dMMR CRC. Combinations of immune checkpoint inhibitors with traditional cytotoxic chemotherapy, radiation therapy, and targeted therapy with small molecule kinase inhibitors are under examination, as is the role of immunotherapy in the adjuvant setting. Investigations into the identification of additional biomarkers or the improvement of current biomarkers to better predict responses to immune checkpoint inhibition are also ongoing.

Conclusion

The role of immunotherapy in unresectable and metastatic CRC is an exciting and expanding focus, and 2020 has seen the first approval of an immune checkpoint inhibitor in the front-line setting for metastatic or unresectable MSI-H/dMMR CRC with the FDA approval of pembrolizumab and a new standard of care in MSI-H/dMMR CRC in the first-line setting. The role of immune checkpoint inhibitors, in general, in the treatment of CRC is only just beginning to be defined. Further studies evaluating the combination of immune checkpoint inhibitors and the utilization of immune checkpoint inhibition in the non-metastatic setting are ongoing. The next few years of scientific study should lead to further clarity regarding the most effective utilization of pembrolizumab and other immune checkpoint inhibitors in the treatment of CRC and the better delineation of the patients who are likely to receive the greatest benefit, predictors of immune checkpoint response and resistance, and strategies to overcome this resistance, leading to an increasingly individualized approach to therapy in patients with MSI-H/dMMR CRC.

Conflict of interest statement

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