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Advances in immunotherapy for colorectal cancer: a review

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Abstract

Immunotherapy is a new and exciting modality of cancer treatments. Its role in gastrointestinal malignancies has been promising, especially in advanced disease. Although various therapies are available for treatment of advanced colorectal cancer, survival rates for these patients remain very poor. The application of immunotherapy in colorectal cancer has shown remarkable results for a subset of patients with mismatch-repair-deficient mutations or microsatellite instability in their tumors. This literature review evaluates the current role of immunotherapy in advanced colorectal cancer, potential challenges clinicians face with immunotherapy-based regimens, and the possible future approach of combined modality immunotherapy.

Keywords: immunotherapy, advanced colorectal cancer, PDL1, MSIH, dMMR, mCRC, pembrolizumab, nivolumab

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Introduction

Colorectal cancer (CRC) continues to be the second leading cause of cancer death, with an estimated 8.3% of cancer-related deaths annually and about 140,250 new cases of CRC diagnosed in 2018.[1] Although overall mortality from CRC continues to decline, survival remains poor for advanced disease.[2,3] Chemotherapy has been the main modality of treatment for the past two decades, and survival rates have begun to increase even more with the introduction of targeted monoclonal antibodies.[4]

The most exciting paradigm change in cancer treatment in recent years, however, has been immunotherapy.[5,6] Since its initial approval for the treatment of melanoma, it has become the standard of care for numerous other malignancies.[5] Immunotherapy has also demonstrated promising efficacies and good tolerance in gastrointestinal (GI)-related cancers such as a gastroesophageal cancer and hepatocellular carcinoma.[5] Pembrolizumab is a monoclonal antibody to programmed death 1 (PD-1). It showed a median duration of response of 15 months in programmed death ligand 1 (PD L1)-positive gastroesophageal junction tumors, and was approved for use in patients who had previously been treated for advanced esophageal cancer.[7] For patients with hepatocellular carcinoma, Nivolumab, another PD 1 inhibitor, had accelerated approval based on results from the Check-Mate 040 trial. Patients with advanced hepatocellular carcinoma (HCC) who were either sorafenib intolerant or refractory were treated with nivolumab and found to have a median survival of 15 months with a response rate of 15%.[8] Currently, nivolumab is being evaluated as a first-line therapy for advanced HCC in the Checkmate 459 clinical trial in comparison with standard care with sorafenib (ClinicalTrials.gov identifier: NCT02576509). Pembrolizumab has also gained approval for second-line therapy for HCC patients who are refractory or intolerant of sorafenib. This approval was based on a single-arm, open-label KEYNOTE-224 trial. An overall response rate (ORR) of 17% [95% confidence interval (CI) 11–26], including a 1% complete response rate and 16% partial response rate were reported.[9] With multiple clinical trials ongoing across various tumor types, immunotherapy can further improve care for patients with GI-related malignancies. It continues to improve overall survival (OS) with a generally well-tolerated side-effect profile. Therefore, it is important to further investigate the role of immunotherapy in CRC.

Current management of advanced CRC

The last major breakthrough for treatment of advanced CRC was about 20 years ago with the introduction of oxaliplatin and irinotecan in addition to original 5-fluorouracil (5FU) based therapies. Since then, this has been the standard of care, with median survival rates almost doubling.[4] Currently, the average survival for newly diagnosed metastatic CRC is approaching 3 years.[1] The survival improvements seen are likely due to the improvement of a multidisciplinary approach for better management of the disease, better supportive care, and, most importantly, the approval of several new targeted therapies.

In advanced CRC, monoclonal antibodies to specific targets, such as angiogenesis, are widely used and available. Bevacizumab, a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF), has demonstrated efficacy as a first-line therapy for metastatic disease, and was approved as a first-line treatment for metastatic CRC (mCRC) in 2004.[10] Bevacizumab has also shown enhanced efficacy when combined with oxaliplatin-based regimens in the first- and second-line setting as well as in combination with 5FU alone or with irinotecan.[11] Other VEGF inhibitors like ramucirumab and aflibercept have also been approved for second-line therapy for the treatment of metastatic disease.[12] Ramucirumab was studied in a randomized, double-blind phase III study, the RAISE trial. Patients were randomized either to ramucirumab+FOLFIRI (5FU, irinotecan and leucovorin) or placebo + FOLFIRI. Median OS was found to be 13.3 months in the ramucirumab group *versus* 11.7 months in the placebo group [hazard ratio (HR) 0.844, 95% CI, 0.730–0.976; $p = 0.0219$].[13] Based on these results, ramucirumab was approved as a second-line therapy for patients who had failed first-line treatment or progressed. Similarly, the VELOUR trial studied patients with metastatic CRC who had progressed on oxaliplatin-based therapy. Patients were randomly assigned to received afilbercept or placebo followed by FOLFIRI. With medium follow up of approximately 2 years, survival rates were 28% for the aflibercept group *versus* 18.7% in the placebo group, with an overall survival of 13.5 months *versus* 12.1 months $p = 0.0032$.[14] Oral agents also have had some success in treating advanced disease that has progressed through first-line therapy. Regorafenib, a small molecule inhibitor of cell signaling kinases that target angiogenesis has shown success in salvage therapy. Its initial approval was based on the CORRECT trial. The latter was a phase III placebo-controlled trial that randomized patients to either regorafenib after progression or placebo. Median OS was found to be 6.4 months in the regorafenib group *versus* 5 months in the placebo group (HR 0.77, 95% CI, 0.64-0T.94 $p = 0.0052$).[15] Trifluridine/tipiracil, another oral agent, has also been approved as salvage therapy for advanced disease based on a phase III trial showed improvement of overall survival of 7.1 months *versus* 5.3 months with supportive care in the refractory setting ($p < 0.0001$).[16]

Monoclonal antibodies; does tumor location matter?

Monoclonal antibodies against epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, have been used as single agent therapy in advanced disease for patients with wild type KRAS and NRAS tumors. For patients who had progressed on irinotecan-based therapy, a phase III trial compared cetuximab monotherapy with a cetuximab plus irinotecan combination. It was found that, with monotherapy, patients had a response rate of about 11%, but with combination treatment, the rate of response was closer to 17.5–29.1% ($p = 0.007$). This study led to the approval of cetuximab for patients who had been pretreated.[17] Panitumumab showed similar results to cetuximab, with a 10–11% response rate when used as salvage therapy.[18] Activated tumor pathways in cancers arising from right-sided (cecum and ascending colon up to the hepatic flexure) and left-sided colon tumors (splenic flexure, descending colon, including the sigmoid) are known to be different. This is thought to be due to higher concentrations of bile acids in right-sided tumors and differences in the microbiome between the two sides.[19] Changes in practice guidelines resulted from the CALBG/SWOG 80405 study, which looked at OS by tumor location for RAS wildtype and found that left-sided tumors (which are more common than right) had an OS of 39.3 months *versus* 13.6 months for right-sided tumors. Patients with right-sided tumors treated with bevacizumab had longer survival than those treated with cetuximab (24.2 months *versus* 16.7 months). The converse was also seen with left-sided tumors, where cetuximab was associated with increased OS compared with bevacizumab (36 months *versus* 31.4 months).[20] This led to more practitioners prescribing mostly combination therapy with

cetuximab for left-sided tumors, and bevacizumab for right-sided tumors. With such success in the use of targeted monoclonal antibodies, the stage was set for further investigation into harnessing the immune system.

The role of the immune system in CRC

Immunotherapy use in cancer treatment is based on the concept that regulatory T-cell-mediated immunosuppression is one of the main immune evasion techniques used by cancer cells. There are several mechanisms that tumor cells can use to escape immune surveillance. Tumors can manipulate cytokines that promote T regulatory cells and myeloid derived suppressor cells to inhibit cytotoxic T cell function. This can lead to suppression of CD 4 and CD 8+ T lymphocytes that now can no longer be recognized as foreign antigens. There can also be a loss of MHC class expression so that T cells no longer can recognize them. Tumors can upregulate immune checkpoint molecules like PD-L1 that result in peripheral T cell exhaustion, as well as inhibition of apoptosis of malignant cells.[21] It was initially believed that CRC was not immunogenic malignancy and that immunotherapy would not be successful. However, multiple large studies have shown that the lymphocytic reaction is indeed an important prognostic factor for CRC.[22] Mutations in DNA mismatch repair (MMR) genes are generally more often found in Lynch syndrome, which is a hereditary form of nonpolyposis CRC. The role of MMR proteins is to correct single base nucleotide instability such as insertions or deletions that arise during the replication process. MMR-deficient genes have also been associated with about 15% of sporadic colon cancers.[24] Deficient MMR (dMMR) tumors have very high levels of DNA microsatellite instability, which, in turn, overexpress genes specific to cytotoxic lymphocytes.[24] The expectation is that these tumors that lack the MMR mechanism contain a high mutational burden, and the antigens generated from them have the potential to be recognized as foreign bodies, resulting in a profound immunogenic response by the host. This is the rationale behind why microsatellite instability-high (MSI-H) tumors are more often seen in earlier stage cancers and tend to have a better overall prognosis.[25] Only about 3–6% of advanced staged CRC patients have MSI-H or dMMR characterized tumors.[26] Tumors that are MSI-H have upregulation of immune checkpoint proteins (like PD-1 and PD-L1), which, in turn, permit immune evasion not by tumor cells themselves but rather by tumor infiltrating lymphocytes.[27] This concept was further explored by a follow-up, phase II clinical trial exploring MSI status as a predictive marker for response to PD-L1 targeted therapy. Although currently only a small subset of advanced CRC patients who harbor MSI-H or dMMR tumors can benefit from immunotherapy with PD1 inhibitors, studies have shown extremely promising results.

Immunotherapy in MSI-H and dMMR advanced CRC

Currently, there are two immune checkpoint inhibitors that target PD-1 that have been approved by the United States Food and Drug Administration(FDA) for use in MSI-high and dMMR advanced CRC patients who have progressed through first-line chemotherapy (Table 1). KEYNOTE 028 was a phase II study that included metastatic CRC patients with or without MMR deficiency. Patients were given pembrolizumab 10 mg/kg intravenously (IV) every 14 days. A total of 41 patients with 32 CRC were enrolled. Of the 10 patients with dMMR CRC who could be evaluated for RECIST, the objective response rate (ORR) was 40%, compared with 0% for MMR-proficient (MMR-p) CRC. A disease control rate of >12 weeks was achieved in 90% of dMMR CRC and 11% in MMR-p CRC.[24] Based on these results, in May 2017, the FDA granted accelerated approval of pembrolizumab for patients with advanced CRC with MSI-H or dMMR malignancy that had progressed through conventional chemotherapy.

CheckMate 142 was an open-label, multicenter, phase II study initially enrolling patients with dMMR ($n=59$) or MMR-p($n=23$) metastatic CRC to receive nivolumab either with ipilimumab (a monoclonal antibody directed against cytotoxic T lymphocyte antigen 4) or alone as a monotherapy. In a preliminary report presented at the 2016 American Society of Clinical Oncology (ASCO) meeting, immunotherapy was shown to benefit those with dMMR patients with progression-free survival (PFS) of 5.3 months. A later analysis included 74 dMMR and/or MSI-H patients who were treated with only 3 mg/kg nivolumab every 2 weeks until disease progression, death, or unacceptable side effects. At a median follow up of 12 months, 31% of patients

Table 1. Landmark trials leading to FDA approval of immunotherapy in mCRC.

Name of trial	Phase of trial	Drug and dose	Objective response rate in dMMR	Disease control rate >12 weeks in dMMR	FDA approval date
KEYNOTE 028 Le *et al.*[28]	Phase II	Pembrolizumab 10 mg/kg every 14 days	40%	90%	May 2017
CheckMate 142 Overman *et al.*[29]	Phase II	Nivolumab 3 mg/kg every 14 days	31.1%	69%	August 2017
CheckMate 142 (further analysis of subgroup) André *et al.*[30]	Phase II	Nivolumab 3 mg/kg +Ipilumumab 1 mg/kg every 21 days	55%	80%	July 2018

dMMR, DNA mismatch repair deficient; FDA, United States Food and Drug Administration; mCRC, metastatic colorectal cancer; pMMR, proficient mismatch repair proficient.

had achieved objective response (investigator assessed), and 68% had achieved disease control for 12 weeks or longer.[29] Based on these results, in August 2017, the FDA extended approval of nivolumab to MSI-H or dMMR metastatic CRC that had progressed following chemotherapy. Following further analysis of the nivolumab-ipilimumab cohort of the trial, which eventually enrolled 119 patients; at a median follow up of 13.4 months, ORR was 55%, including 51% partial and 3% complete. The disease control rate for 12 weeks was >80%. Responses appeared to be extremely durable given that 71% had remained progression free at 12 months regardless of PD-L1 expression of tumor tissue.[30] These results led to FDA approval, in July 2018, of the combination immunotherapy regimen. It is important to note, however, that compared with Nivolumab monotherapy, combination treatment had increased rates of grade 3 and 4 toxicities, which, in turn, can lead practitioners away from prescribing dual agent therapy.[30] The National Comprehensive Cancer Network (NCCN) clinical practice guidelines in Oncology Version 4.2018 currently recognizes either nivolumab monotherapy, nivolumab+ ipilimumab combination therapy, or pembrolizumab monotherapy as acceptable standard of care treatment options for patients with dMMR/MSI-H mCRC tumors that have progressed after first-line therapy with fluropyrimidine-, oxaliplatin-, and/or irinotecan-containing regimens. Studies assessing the treatment durability for pembrolizumab in MSI-H and dMMR tumors were further evaluated in multiple trials, including KEYNOTE 016, 164, 012, 158 as well as 028 for patients who had progressed through prior treatment or had no further alternative treatment options. Based on accumulated data from five clinical studies, a total of 149 patients were found to have MSI-H/dMMR cancers, with about 60% of patients having mCRC and the other tumor types spanning 14 different types of cancers.[28] Of the originally identified 149 patients, 135 had their tumor types prospectively reviewed for MSI-H or dMMR by PCR and immunohistochemistry. About 40% (59/149) responded to therapy, with an ORR of 39.6% (95% CI 31.7–47.9) and a 7% complete response rate. The response duration lasted anywhere from 1.6 months to 22.7 months, with 78% of responses lasting more than 6 months.[31] Based on the above findings, the FDA approved pembrolizumab for MSI-H/dMMR solid tumor cancers, with the caveat that further exploration of benefit in larger patient populations to verify its efficacy is needed. This landmark approval was the first of its kind to identify a biomarker as an indication for therapy rather than as primary origin of malignancy.

What about immunotherapy in MSS and MMR-p advanced CRC?

With the exciting approval of immunotherapy in MSI-H or dMMR patients, multiple studies are currently evaluating PD-1 inhibitors in combination with other modalities in the setting of microsatellite stable (MSS) or MMR-p disease. MSS or MMR-p metastatic disease encompasses

Table 2. Selective Actively Recruiting Clinical Trials for MSS CRC patients.

Name of study	Clinical phase	Line of therapy	Clinicaltrials.gov Identifier
Nivolumab and Relatlimab in patients with MSS advanced CRC	Phase II	Second Line	NCT03642067
Modulation of the tumor microenvironment using either vascular disruption agents or STAT 3 inhibition in order to synergize with PD1 Inhibition in MSS refractory CRC	Phase II	Second Line	NCT03647839
Nivolumab plus Ipilimumab and Temozolomide in MSS, MGMT silenced CRC	Phase II	Second Line	NCT03832621
Study of Durvalumab and Tremelimumab after radiation for MSS metastatic CRC progressing on chemotherapy	Phase II	Second Line	NCT03007407
Pembrolizumab, Capecitabine and Bevacizumab in treating patients with MSS CRC that is locally advanced, metastatic or cannot be removed by surgery	Phase II	Second Line	NCT03396926
Safety and efficacy of Vicriviroc (MK-7690) in combination with Pembrolizumab (MK-3475) in participants with advanced/metastatic MSS CRC	Phase II	Second Line	NCT03631407
Nivoluman and Ipilimumab and radiation therapy in MSS and MSI-H CRC and pancreatic Ca	Phase II	Second Line	NCT03104439
Avelumab combined with cetuximab and irinotecan for treatment refractory metastatic CRC MSS cancer	Phase II	Third Line	NCT03608046
Nivolumab and metformin in patients with treatment refractory MSS CRC	Phase II	Second Line	NCT03800602

CRC, colorectal cancer; MGMT, O^6-methylguanineDNA methyltransferase; MMR-p, proficient mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; PD1, programmed cell death 1; STAT, signal transducer and activator of transcription.

more than 80% of the pathology seen in advanced disease. The hypothesis is that a combination modality can potentially evoke an immunogenic response that will allow checkpoint inhibitors to be applied successfully to MSS or MMR-p tumors.[32] These multiple ongoing studies include checkpoint inhibitors in combination with traditional 5FU-based regimens, EGFR inhibitors, VEGF inhibitors, radiotherapy, and even vaccines. Although data to support this hypothesis is limited, multiple actively recruiting clinical trials are currently exploring the possibility of evoking immunogenic responses (Table 2). It should be noted, though, that there have been negative trials that were unsuccessful in evoking immunogenic response. For example, the IMblaze370 study failed to improve OS in combination therapy with the PD-L1 inhibitor Atezolizumab and the MEK inhibitor Cobimetinib when compared with Regorafenib in previously treated mCRC patients.[33] The MODUL trial also sought to combine immunotherapy with standard of care regimens. Atezolizumab was added to Fluoropyrimidine (FP) with Bevacizumab to patients with BRAF wild type colon cancer, but, unfortunately, this did not lead to an improvement in outcomes.[34]

It is important to continue to investigate the role of immunotherapy, especially with other potential biomarkers as targets, beyond MSI status and PD-1/PD-L1 expression. This includes encouraging patients to participate in clinical trials and expanding genomic sequencing of tumor tissue to be more readily available in clinical practice. These various combinations and different targeted agents will hopefully lead to more promising results and the use of immunotherapy outside the metastatic setting.

Hurdles of immunotherapy

Common side effects and management

Immune-related adverse events are not uncommon with immune checkpoint inhibitors. Although relatively well tolerated, common side effects include rash, colitis, hepatotoxicity, and pneumonitis, as well as endocrinopathies such as adrenal insufficiency and thyroid dysfunction.[35] The most common side effect experienced is skin rash, which is seen in up to 30% of patients.[36,37] Most skin rashes tend to be grade 1 or grade 2, and can be managed simply with topical corticosteroid creams; however, more severe dermatological manifestations can be seen.[37] High-dose steroids are the modality of choice when it comes to treatment for grade 3 and grade 4 toxicities; however, management of these side effects can be challenging and it is often left up to the provider to determine the course of steroids and taper required based on their clinical judgment. If severe toxicity is experienced, then the offending agent should be discontinued and cancer-directed therapy should be changed from immunotherapy once the patient is stable and off steroids. If symptoms are refractory to first-line management with steroids (such as in severe colitis), tumor necrosis factor alpha (TNFα) binders such as Infliximab can be used to reduce the cytokine release responsible for severe systemic inflammation.[35] In contrast to other side effects, thyroiditis, although common, does not require steroids for treatment unless the patient experiences grade 4 toxicity. Most thyroiditis can be managed with thyroid hormone replacement, and doses are similar to treatment for primary hypothyroidism.[38] Since immune checkpoint inhibitors are relatively new to many general health care practitioners, and the presenting symptoms can be vague and mimic other pathologies, this can cause a delay in diagnosis and treatment, leading to fatal adverse events. As oncologists, it is important to address this delay by providing feedback to physicians in the community, and to encourage earlier intervention and consultation if there is concern regarding an immunotherapy-related adverse event.

Assessing treatment response objectively

Assessing treatment response of immunotherapy can also prove challenging. It has been well documented that, after initial treatment with immunotherapy, radiological assessments can mimic progression of disease, a phenomenon known as "pseudoprogression". Immune-specific related response criteria (irRECIST criteria) were developed to help standardize and guide practitioners in order to differentiate between pseudoprogression and actual disease progression. A recent retrospective study analyzed the radiological patterns associated with 254 patients who received nivolumab. Of the 65% of patients who had experienced clinical benefit from nivolumab, four different types of radiological response were observed.[39] It is important to note that many providers continue with immunotherapy knowing that evidence of tumor regression on imaging studies may lag behind, especially if the patient's clinical status is improving overall. Several other unique radiological patterns of response have been reported with immunotherapy, including rapid progression defined as "hyperprogression," although a standard criteria of definition has not been well established.[40]

Patients with underlying autoimmune disease

Another challenge is to treat patients who have underlying autoimmune disease with immunotherapy. It has been cited many times in the literature that chronic inflammation from autoimmune disease makes patients more susceptible to cancer.[41] In one Swedish study, a cohort of 22,000 patients with Crohn's disease (a type of inflammatory bowel disease) found that there was an increased chance of malignancy translating into an increased standard incidence ratio (SIR) for colon cancer of 2.93, non-Hodgkin's lymphoma of 2.53, and small bowel cancer of 13.82 when compared with the general population.[42] The fear of worsening autoimmune disease with immune check point inhibitors led to exclusion of patients with underline autoimmune disease in the majority of seminal trials. This leaves health care providers without adequate data to make informed decisions regarding therapy options for this specific population. More recently, retrospective studies have begun to address this issue specifically when it comes to checkpoint inhibitors.[43] Menzies *et al*. studied 52 patients with melanoma who had underlying autoimmune disease. Although 38% of patients had flares of their underlying disease, there were no fatal adverse events and most symptoms were easily manageable.[44] Although it has been found that patients with underlying autoimmune disease have a higher probability of experiencing immune-related events, patients who receive checkpoint

inhibitors like anti-PD-1 antibodies do relatively well, and efficacy is usually not compromised. A recent study completed by Danlos *et al.* prospectively analyzed the safety of 45 patients enrolled in the REISAMIC registry (Registry of Severe Adverse Events of Immunomodulating Monoclonal Antibodies in Oncology) and were to receive anti PD-1 antibodies. Outcomes in these patients were compared with those of 352 patients without autoimmune disease included in the registry during the same time period. The majority of patients (80%) had melanoma, and 32% had underlying inflammatory disease such as autoimmune thyroiditis, lupus, type 1 diabetes, and autoimmune psoriasis, amongst others. Pembrolizumab was given to 75% of the patients and other therapies included nivolumab (22.2%) and avelumab (2.2%). Overall, only 24% had a flare of a preexisting autoimmune disease, while 22.2% had an immune-related adverse event not associated with their underlying autoimmune disease. There was no statistical difference between OS in patients who had underlying autoimmune disease *versus* patients who did not ($p = 0.38$).[45] The current consensus in the medical community still remains unclear, and further investigations are warranted in this population. We feel that a trial of immunotherapy in relatively well controlled, uncomplicated autoimmune disease is warranted. The risk *versus* benefit should be clearly discussed between patient and provider and assessed on a case by case basis.

Future of immunotherapy

Immune checkpoint inhibitors have shown excellent tolerability, durable response, and, in some cases, even cure. The field of immunotherapy is growing exponentially and preliminary results have been promising. Immunotherapy has not only been explored as monotherapy or in conjunction with other immune targeted agents, but multiple ongoing studies are assessing the role of immunotherapy in conjunction with radiation and conventional chemotherapy as well as initiating immunotherapy at earlier stages of malignancy. Multiple ongoing clinical trials are assessing the role of immune checkpoint inhibitors in MSS and MMR-p CRC in both the adjuvant and metastatic settings. Vaccine therapy is also currently under study in the treatment of CRC. Chimeric antigenic receptor T cell (CAR-T) is another approach in the early stage (phase I) of evaluation for CRC disease patients.

Introducing immunotherapy upfront and earlier

The COMMIT trial is exploring the role of immunotherapy with atezolizumab (a PD-L1 inhibitor) as front line for metastatic CRC *versus* combination chemotherapy with FOLFOX/bevacizumab in patients with dMMR. Patients are randomized to three arms (1:1:1); FOLFOX with bevacizumab, atezolizumab monotherapy, and atezolizumab in combination with FOLFOX/bevacizumab. The purpose of this trial is to explore preclinical data that showed that oxaliplatin-containing chemotherapy in combination with anti-VEGF enhances anti-tumor activity in the PDL1 pathway (ClinicalTrials.gov identifier: NCT02997228). Initiating immunotherapy at earlier stages of CRC is also being explored. Stage III MSI-H disease is currently under investigation in the A021502 NCTN adjuvant trial with FOLFOX × 12 (standard of care) *versus* FOLFOX with Atezolizumab to determine if FOLFOX could increase intra-tumoral cytotoxic CD8+T cells that may act as "immune primers" (ClinicalTrials.gov identifier: NCT02912559).

CheckMate-142 studied combination immunotherapy with Nivolumab and low dose Ipilimumab in patients with MSI-H metastatic CRC given as first-line therapy and presented as an abstract at the European Society of Medical Oncology (ESMO) conference. With the primary endpoint of the study being ORR, 60% of patients achieved this goal, and 7% of patients were reported to have a complete response ($n = 45$). Duration of response, median PFS, and OS have yet to be reached; however, these preliminary results are promising.[46]

Channeling the gut microbiome

Another exciting field of study involves the interaction of the gut microbiome and the immune system. Recently, there have been studies linking changes in gut microbiome to the propensity of developing CRC, as well as studies suggesting that maladaptation of microbiota can potentially lead to tumorigenesis.[47] Can this relationship also theoretically change the efficacy of immunotherapy? Although well described in mice models,[48] studies are now emerging comparing the gut microbiome of patients receiving immunotherapy who have potentially had disruption to their normal gut flora (for example from antibiotics). Routy *et al.* found that patients receiving anti-PDL1 treatment and antibiotics who had

epithelial tumors had significant improvement in OS as well as PFS if their gut flora was not disrupted by antibiotic use while receiving immunotherapy.[49] How extensively the gut microbiome can influence the response to immune checkpoint inhibitors still remains unknown and must be further explored.

Vaccine use for anti-tumor response

Vaccine therapy is another type of immunotherapy. Vaccines are thought to help facilitate the anti-tumor response by evoking tumor-associated antigens to be targeted by the immune system. Multiple types of vaccines studied in mCRC include autologous, peptide, and dendritic cell vaccines. Overall, cancer vaccines have not resulted in any survival benefit when compared with standard therapy or placebo.[50–53] However, is there a role for vaccines to wake up the immune system and transform the tumor from an immune indolent tumor to a sensitive one? Perhaps studying vaccines in conjunction with checkpoint inhibitors can potentially generate a stronger immunogenic environment to treat metastatic CRC? Data released from the IMPALA phase III clinical trial, which studied the Toll-like receptor 9 (TLR9) agonist Lefitolimod *versus* standard of care as maintenance therapy in patients with mCRC were discouraging. Lefitolimod did not show superiority as a single-agent maintenance therapy.[54] These results, although negative, did not discourage further exploration into combination vaccine therapy. For example, talimogene laherparepvec (T-VEC) is a virally based immunotherapy consisting of herpes simplex-1, which selectively replicates in solid tumors and currently is approved for melanoma. The combination of T-VEC local injection combined with systemic infusion of atezolizumab (PD-L1 blockade) is under evaluation in metastatic MSS CRC patients in clinical trials (ClinicalTrials.gov identifier: NCT03256344).

CAR-T therapy for CRC cancer treatment

CAR-T is a form of adoptive cell transfer immunotherapy. It has been a huge success in treating refractory hematological malignancies, most notably B-cell acute lymphoblastic leukemia.[55] Expanding CAR-T therapy to solid tumors is very attractive but has many challenges. Identifying the precise target antigen and designing CARs that are highly selective are critical for the clinical application of such therapies.[56] T cells expressing human GUCY2C-targeted chimeric antigen receptor have shown potential to eliminate CRC metastases in the mice model.[56] CAR-T immunotherapy is currently being evaluated for CRC in early stage clinical trials (ClinicalTrials.gov identifier: NCT03152435). As more receptors are identified and T cell specific delivery is perfected, this could lead to further breakthroughs in the investigational use of CAR-T immunotherapy. Although there is still a huge gap before clinical use can be initiated, CAR-T provides the possibility of potentially changing the landscape of immunotherapy in CRC disease.

Conclusion

With the generally tolerable side-effect profile of checkpoint inhibitors, and the success in a multitude of different solid tumor malignancies, immunotherapy has become an attractive option compared with conventional chemotherapy for CRC. Currently the role of immunotherapy in metastatic CRC is limited to MSI-H and dMMR-expressing tumors in a chemotherapy refractory setting. Multiple studies are investigating the potential role of immunotherapy at all stages of CRC, and using combination modalities to enhance immune response regardless of microsatellite or MMR gene status.

Author contributions

All authors equally contributed to this paper with literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

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References

1. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; 69: 7–34.

2. Cronin KA, Lake AJ, Scott S, *et al.* Annual report to the nation on the status of cancer, part I: national cancer statistics. *Cancer* 2018; 124: 2785–2800.
3. Goodwin RA and Asmis TR. Overview of systemic therapy for colorectal cancer. *Clin Colon Rectal Surg* 2009; 22: 251–256.
4. Saltz LB, Cox JV, Blanke C, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; 343: 905–914.
5. Stein A, Moehler M, Trojan J, *et al*. Immuno-oncology in GI tumours: clinical evidence and emerging trials of PD-1/PD-L1 antagonists. *Crit Rev Oncol Hematol* 2018; 130: 13–26.
6. Grierson P, Lim KH and Amin M. Immunotherapy in gastrointestinal cancers. *J Gastrointest Oncol* 2017; 8: 474–484.
7. Doi T, Piha-Paul SA, Jalal SI, *et al.* Safety and antitumor activity of the anti-programmed death-1 antibody pembrolizumab in patients with advanced esophageal carcinoma. *J Clin Oncol* 2018; 36: 61–67.
8. El-Khoueiry AB, Sangro B, Yau T, *et al.* Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; 389: 2492–2502.
9. Zhu AX, Finn RS, Edeline J, *et al.* Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018; 19: 940–952.
10. Grothey A and Marshall JL. Optimizing palliative treatment of metastatic colorectal cancer in the era of biologic therapy. *Oncology* 2007; 21: 553–564, 566; discussion 566–568, 577–578.
11. Hurwitz H, Fehrenbacher L, Novotny W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350: 2335–2342.
12. Mody K, Baldeo C and Bekaii-Saab T. Antiangiogenic therapy in colorectal cancer. *Cancer J* 2018; 24: 165–170.
13. Tabernero J, Yoshino T, Cohn AL, *et al.* Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol* 2015; 16: 499–508.
14. Van Cutsem E, Tabernero J, Lakomy R, *et al.* Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012; 30: 3499–3506.
15. Grothey A, Van Cutsem E, Sobrero A, *et al.* Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; 381: 303–312.
16. Mayer RJ, Van Cutsem E, Falcone A, *et al.* Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 2015; 372: 1909–1919.
17. Cunningham D, Humblet Y, Siena S, *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351: 337–345.
18. Van Cutsem E, Peeters M, Siena S, *et al.* Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007; 25: 1658–1664.
19. Bettington M, Walker N, Clouston A, *et al*. The serrated pathway to colorectal carcinoma: current concepts and challenges. *Histopathology* 2013; 62: 367–386.
20. Venook AP, Niedzwiecki D, Innocenti F, *et al.* Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). *J Clin Oncol* 2016; 34(Suppl.): abstract 3504.
21. Tumeh PC, Harview CL, Yearley JH, *et al.* PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* 2014; 515: 568–571.
22. Ogino S, Nosho K, Irahara N, *et al.* Lymphocytic reaction to colorectal cancer is associated with longer survival, independent of lymph node count, microsatellite instability, and CpG island methylator phenotype. *Clin Cancer Res* 2009; 15: 6412–6420.
23. Hampel H, Frankel WL, Martin E, *et al.* Screening for the Lynch syndrome (hereditary

nonpolyposis colorectal cancer). *N Engl J Med* 2005; 352: 1851–1860.

24. 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.

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

26. Nosho K, Baba Y, Tanaka N, *et al.* Tumour-infiltrating T-cell subsets, molecular changes in colorectal cancer, and prognosis: cohort study and literature review. *J Pathol* 2010; 222: 350–366.

27. Llosa NJ, Cruise M, Tam A, *et al.* The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. *Cancer Discov* 2015; 5: 43–51.

28. 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.

29. André T, Lonardi S, Wong M, *et al. Nivolumab + ipilimumab combination in patients with DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer: first report of the full cohort from CheckMate-142*. Paper presented at 2018 Gastrointestinal Cancers Symposium, 20 January 2018. Abstract 553. San Francisco, CA, USA.

30. 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.

31. Marcus L, Lemery SJ, Keegan P, *et al.* FDA approval summary: pembrolizumab for the treatment of microsatellite instability-high solid tumors. *Clin Cancer Res* 2019; 25: 3753–3758.

32. Arora SP and Mahalingam D. Immunotherapy in colorectal cancer: for the select few or all? *J Gastrointest Oncol* 2018; 9: 170–179.

33. Eng C, Kim TW, Bendell J, *et al.* Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol* 2019; 20: 849–861.

34. Grothey A, Tabernero J, Arnold D, *et al.* LBA19Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy. *Ann Oncol* 2018; 29: LBA19.

35. Kroschinsky F, Stolzel F, von Bonin S, *et al.* New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management. *Crit Care* 2017; 21: 89.

36. Della Vittoria Scarpati G, Fusciello C, Perri F, *et al.* Ipilimumab in the treatment of metastatic melanoma: management of adverse events. *Onco Targets Ther* 2014; 7: 203–209.

37. Naidoo J, Schindler K, Querfeld C, *et al.* Autoimmune bullous skin disorders with immune checkpoint inhibitors targeting PD-1 and PD-L1. *Cancer Immunol Res* 2016; 4: 383–389.

38. Weber JS, Postow M, Lao CD, *et al.* Management of adverse events following treatment with anti-programmed death-1 agents. *Oncologist* 2016; 21: 1230–1240.

39. Thomas R, Somarouthu B, Alessandrino F, *et al.* Atypical response patterns in patients treated with nivolumab. *AJR Am J Roentgenol.* Epub ahead of print 27 March 2019. DOI: 10.2214/AJR.18.20938.

40. Borcoman E, Kanjanapan Y, Champiat S, *et al.* Novel patterns of response under immunotherapy. *Ann Oncol* 2019; 30: 385–396.

41. Grivennikov SI, Greten FR and Karin M. Immunity, inflammation, and cancer. *Cell* 2010; 140: 883–899.

42. Hemminki K, Li X, Sundquist J, *et al.* Cancer risks in Crohn disease patients. *Ann Oncol* 2009; 20: 574–580.

43. Johnson DB, Beckermann KE and Wang DY. Immune checkpoint inhibitor therapy in patients with autoimmune disease. *Oncology* 2018; 32: 190–194.

44. Menzies AM, Johnson DB, Ramanujam S, *et al.* Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol* 2016; 28: 368–376.

45. Danlos FX, Voisin AL, Dyevre V, *et al.* Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. *Eur J Cancer* 2018; 91: 21–29.

46. Lenz HJ, van Cutsem E, Limon ML, *et al. Durable clinical benefit with nivolumab plus low-dose ipilimumab as first-line therapy in microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer*. Paper presented at ESMO 2018

Congress, 22 October 2018. Abstract LBA18_PR. Munich, Germany.

47. Hendler R and Zhang Y. Probiotics in the treatment of colorectal cancer. *Medicines* 2018; 5: E101.
48. Li W, Deng Y, Chu Q, *et al.* Gut microbiome and cancer immunotherapy. *Cancer Lett* 2019; 447: 41–47.
49. Routy B, Le Chatelier E, Derosa L, *et al.* Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* 2018; 359: 91–97.
50. Schulze T, Kemmner W, Weitz J, *et al.* Efficiency of adjuvant active specific immunization with Newcastle disease virus modified tumor cells in colorectal cancer patients following resection of liver metastases: results of a prospective randomized trial. *Cancer Immunol Immunother* 2009; 58: 61–69.
51. Hazama S, Nakamura Y, Tanaka H, *et al.* A phase II study of five peptides combination with oxaliplatin-based chemotherapy as a first-line therapy for advanced colorectal cancer (FXV study). *J Transl Med* 2014; 12: 108.
52. Lazoura E and Apostolopoulos V. Rational peptide-based vaccine design for cancer immunotherapeutic applications. *Curr Med Chem* 2005; 12: 629–639.
53. Okuno K, Sugiura F, Inoue K, *et al.* Clinical trial of a 7-peptide cocktail vaccine with oral chemotherapy for patients with metastatic colorectal cancer. *Anticancer Res* 2014; 34: 3045–3052.
54. Schmoll HJ, Wittig B, Arnold D, *et al.* Maintenance treatment with the immunomodulator MGN1703, a Toll-like receptor 9 (TLR9) agonist, in patients with metastatic colorectal carcinoma and disease control after chemotherapy: a randomised, double-blind, placebo-controlled trial. *J Cancer Res Clin Oncol* 2014; 140: 1615–1624.
55. Murad JM, Graber DJ and Sentman CL. Advances in the use of natural receptor- or ligand-based chimeric antigen receptors (CARs) in haematologic malignancies. *Best Pract Res Clin Haematol* 2018; 31: 176–183.
56. Magee MS, Abraham TS, Baybutt TR, *et al.* Human GUCY2C-targeted chimeric antigen receptor (CAR)-expressing T cells eliminate colorectal cancer metastases. *Cancer Immunol Res* 2018; 6: 509–516.