On the Verge: Immunotherapy for Colorectal Carcinoma

David Y. Oh, MD, PhD; Alan P. Venook, MD; and Lawrence Fong, MD

Abstract
Although overall survival from colorectal cancer (CRC) has steadily improved over the past decade, there is still work to be done. The gains associated with improved detection and treatment paradigms with chemotherapy and biologics appear to have reached their ceiling. Immune-based therapies have recently demonstrated clinical benefit in other cancers, including CRC with microsatellite instability (MSI), but patients with CRC without MSI have not yet derived benefit. This article reviews the history of CRC immunotherapy trials, the conceptual basis for why the activity of the immune system may be relevant to survival in CRC, and current efforts in CRC immunotherapy, and speculates about future efforts in this area based on experience with immunotherapy efforts in other classes of solid tumors. (J Natl Compr Canc Netw 2015;13:970–978)

Colorectal cancer (CRC) embodies a paradox encountered by clinicians and researchers. As researchers have dissected its pathophysiology and genetics, and in turn have discovered new chemotherapeutics and biologics and pushed the envelope of technology, clear strides have been made in its prevention or treatment. The incidence of CRC has decreased, more patients—even some with metastases—are being cured than those who are not, and patients with advanced disease will live an average of nearly 30 months. Yet, CRC still remains the fourth most common cause of cancer death.

Although chemoprevention or early detection will continue to improve outcomes of CRC, mutation-targeted therapeutics may not have a major impact any time soon, particularly given the apparent dominant role that RAS mutations play in the disease course. The recent discovery that novel immune-based therapies, such as checkpoint inhibitors, have significant activity in diverse epithelial tumors, such as melanoma and non–small cell lung, renal, bladder, and head and neck cancers, coupled with numerous lines of old and new evidence, collectively raise the possibility that the immune system may represent a promising next avenue for advancing the understanding and management of patients with CRC.

Immune Response to CRC is Prognostic of Overall Survival
The importance of the immune system in the biology of CRC is underscored by retrospective assessments of immune infiltrates in resected CRC specimens, which have been reviewed extensively elsewhere.1 In brief, several analyses have shown that increased infiltration of specific regions of the tumor by CD8+ CD45RO+ T cells (Figure 1) is highly correlated with decreased local and distant tumor spread and improved survival. This T-cell phenotype marks cytotoxic memory T lymphocytes. This observation has led to the development of an “immunoscore,” reflecting the number of tumor regions with these features, that is highly correlated with improved disease-free survival (DFS) and overall survival (OS) at all CRC stages, and actually outperforms the TNM staging system in prognosticating survival.2–5 Although there are caveats to this analysis (retrospective, confined to 1 or 2 centers, uncertain causality), collectively this body of work argues that the presence of memory (rather than naïve) T cells is important in reducing risk of relapse and improving OS.
What Can the Immune System See of CRC?

The prognostic significance of T cells, and not other inflammatory cells, argues that an immune response to specific tumor antigens may drive improved survival. Indeed, some patients have spontaneous measurable immune responses to CRC antigens (Figure 1). These include circulating T cells specific for known tumor-associated antigens (TAAs), such as carcinoembryonic antigen (CEA), epidermal growth factor-receptor (EGFR), MUC-1, and HER2/neu. Humoral responses to cancer-testis antigens, such as NY-ESO-1 (which can be expressed in some CRCs), can also be detected. In addition, local therapies, such as radiofrequency ablation of liver metastases, enhance T-cell responses to autologous CRC cells or TAAs, as measured by interferon (IFN) production, antitumor cytotoxicity, and proliferation. Most TAAs studied thus far are expressed at higher levels in the tumor but are also expressed in other tissues. As a result, the mechanisms of tolerance that suppress immune responses to self-antigens to minimize autoimmune disease may also suppress immune responses to tumor antigens. However, tumors still have the potential to be seen by the immune system; in particular, neoantigens generated from tumor-specific mutations of self-antigens within CRC may be recognized by the immune system as foreign, and could therefore trigger an antitumor immune response. This possibility is supported by a recent analysis of the immunogenicity of mutated antigens in melanoma. In that study, investigators examined what targets can be recognized by expanded tumor-infiltrating lymphocytes infused into patients with melanoma. When melanomas were sequenced from patients who had clinical tumor responses, mutated tumor-specific antigens, rather than nonmutated

![Figure 1](image-url)
melanoma antigens, were the target of the infused T cells. Of note, the neoantigens identified were distinct for each patient, suggesting that patient-specific mutations may determine whether immunogenic responses are produced. Neoantigens also appear to be important for responses to immunotherapy in non-small cell lung cancer, because neoantigen-specific T-cell responses were detected in parallel with tumor regression following treatment with a checkpoint inhibitor blocking programmed death 1 (PD-1), and the degree of nonsynonymous mutational burden appeared to be correlated with clinical responses. A corresponding screening approach may allow identification of immunogenic neoantigens in CRC, using data from large-scale sequencing efforts such as The Cancer Genome Atlas (TCGA) as a catalog of somatic CRC mutations. Patients with CRC with microsatellite instability (MSI) warrant particular scrutiny, because their inactivation of DNA repair pathways has been shown to be associated with large numbers of small 1 base pair insertions or deletions, which may provide a substrate for generation of immunogenic neoantigens. Indeed, patients with CRC with the MSI phenotype appear to be uniquely responsive to immunotherapies, particularly checkpoint inhibition (see later discussion).

**ImmunoModulatory Effects of Conventional Cytotoxic Treatments**

Conventional chemotherapies also may have some effect through the immune system. Oxaliplatin, a stalwart drug in CRC, triggers a form of cell death that is immunogenic, whereas the chemical analogue cisplatin does not trigger the same form of immunogenic cell death and is also a drug with minimal activity against CRC. In preclinical models, injection with oxaliplatin-killed CRC cells enhances the survival of mice that are subsequently challenged with live CRC cells, and this protection requires an intact immune system. Thus, the antitumor activity of oxaliplatin may also be related to its efficacy as an immunomodulatory agent, not solely as a cytotoxic drug.

In addition, a component of the efficacy of some chemotherapeutic agents may be mediated through interactions between the mucosal immune system and resident gut microflora, which would apply particularly to cancers arising in the digestive tract, such as CRC. Treatment with cyclophosphamide in mice results in translocation of gram-positive bacteria from the gut into lymphoid tissues, which can polarize the CD4 helper T cells to produce cytokines, such as IFN and interleukin-17 (IL-17). Remarkably, sterilization with vancomycin not only prevents this immune polarization but also reduces the ability of cyclophosphamide to treat implanted or genetically induced tumors. Giving back specific gram-positive organisms or IL-17–producing cells rescues the chemotherapeutic response. It is tempting to speculate that similar immune-microflora interactions could contribute to chemotherapy-induced responses to CRC.

**Immune-Based Therapies for CRC: What Data Do We Have?**

To date, there is at best mixed evidence for clinical efficacy of immune-based therapies for CRC, with some isolated responses. Some of the earliest efforts attempted to induce antigen-nonspecific immune stimulation with administration of bacillus Calmette-Guérin (BCG) in the adjuvant setting for stage II–III resected CRC. This attenuated mycobacterial product resulted in only a small improvement in OS compared with surgery alone, although this was due to non–cancer-related deaths. Other prior and current strategies for CRC immunotherapy are discussed in more detail in the following sections.

**Whole Cell (Autologous Tumor Cell) Vaccines**

A substantial body of work has used autologous CRC tumor cells in attempts to generate anti-CRC immune responses. Most studies have used BCG in combination with autologous CRC cells. Earlier prospective studies with adjuvant BCG plus neuraminidase-modified autologous CRC cells found a trend towards improved DFS for stage II versus surgery alone that did not reach significance (P=0.35; 129 patients), but no difference was seen in DFS for stage III or OS for either stage. More recent studies have yielded more promising results. When patients with resected stage II–III CRC (41 patients, 17 with colon cancer) were given adjuvant BCG plus autologous tumor cells, compared with surgery alone, significant improvements were seen in DFS (57% vs 33%; P=0.039), DFS for colon cancer specifically (57% vs 25%; P=0.03), and OS (48% vs 17%; P=0.02); however, the subset of patients with rectal cancer did not benefit. More recently, a randomized, multicenter, prospective phase III trial of ad-
Based on these results, the FDA has granted a Special Protocol Assessment for a confirmatory phase IIIb trial of OncoVax in resected stage II CRC which has not yet begun accrual. Autologous CRC vaccination has also been attempted with Newcastle disease virus-infected tumor cells, resulting in some initial signal with OS in resected CRC (2-year survival, 98% vs 67%)\(^\text{20}\); a follow-up prospective randomized phase III trial immunizing patients with CRC with liver metastases after metastasectomy did not demonstrate any difference in OS or metastasis-free survival in the overall cohort, although the colon cancer subgroup demonstrated some improvement in both indices.\(^\text{21}\) There is an ongoing pilot study using GVAX (adenovirus-mediated granulocyte-macrophage colony-stimulating factor [GM-CSF] expression) in irradiated autologous CRC cells in patients with stage IV CRC, examining safety as a primary end point and progression-free survival (PFS) and OS (ClinicalTrials.gov identifier: NCT01952730). In summary, there are some promising data with autologous CRC vaccines, generally favoring colon but not rectal cancer, and stage II but not stage III disease; the reasons for these differences are unclear. Potential barriers to efficacy of these types of vaccines include a potentially low density of relevant antigen, difficulties overcoming self-tolerance because these are host-derived cells, and possible difficulty in terms of standardization of these preparations.

**Dendritic Cell–Based Therapies**

Another strategy for generating immune responses to CRC has involved dendritic cell vaccination. These approaches have used autologous dendritic cells, unmobilized or mobilized with agents such as Flt3 or granulocyte colony-stimulating factor (G-CSF), then loaded with peptides derived from CEA and administered to small cohorts of patients with CRC. Results have been modest, with only a minority of patients with complete or partial responses, and a minority with stable disease, despite demonstration of antigen-specific T-cell responses postvaccination.\(^\text{22–24}\) Ongoing trials include dendritic cells loaded with frameshift-derived neoantigens for MSI-high or Lynch syndrome CRC (ClinicalTrials.gov identifier: NCT01885702), CEA-pulsed dendritic cells administered with tetanus toxoid followed by low dose IL-2 (ClinicalTrials.gov identifier: NCT00154713), and vaccination with dendritic cells primed with putative CRC stem cells isolated based on high aldehyde dehydrogenase expression (ClinicalTrials.gov identifier: NCT02176746). Antigen selection remains a key issue with these dendritic cell–based vaccination approaches. In general, it is unclear whether the specific antigens chosen represent the best targets for immune-directed therapy, and whether any immune response that is stimulated actually contributes to any observed clinical responses. Finally, there is likely to be phenotypic variability in the infused dendritic cell product, making it unclear which particular cell population may be responsible for any clinical activity.

**Viral Vectors**

Several groups have attempted to use immunogenic viral vectors expressing CRC TAAs to stimulate anti-CRC immune responses. In a phase I study, a recombinant fowlpox virus expressing multiple co-stimulatory molecules (B7-1, LFA-3, ICAM-1) and the CEA antigen was administered, alone or in sequence with a recombinant vaccinia virus expressing the same molecules, with or without GM-CSF, to patients with a variety of CEA-expressing tumors, including 35 patients with CRC. This resulted in measurable increases in frequencies of CEA-specific T cells by ELISPOT in most patients tested (serologic responses were more mixed), and prolonged stable disease lasting at least 4 months in 23 of 58 patients.\(^\text{25}\) Similar results were seen with a canarypox vector (ALVAC) expressing CEA and B7.1 costimulation: of 118 patients, 42 (40%) had a complete or partial response, whereas another 42 (40%) had stable disease, with 30% to 50% of patients demonstrating CEA-specific T-cell responses by ELISPOT, but very few experiencing humoral responses.\(^\text{26}\)

**Antibodies as Immunotherapy**

Cetuximab is a chimeric IgG1 monoclonal antibody that competitively binds to the extracellular domain of the EGFR, preventing dimerization, tyrosine kinase phosphorylation, and activation. This antibody
has activity in metastatic CRC as monotherapy in the second- and third-line settings, or in combination with cytotoxic chemotherapy in any line, albeit with limited to no activity in patients with any RAS mutations.\textsuperscript{27} Cetuximab likely acts through multiple mechanisms, including inhibited cell growth and apoptosis following the blockade of receptor activation,\textsuperscript{28} but one additional mechanism is thought to involve antibody-dependent cellular cytotoxicity (ADCC) whereby effector immune cells (natural killer [NK] cells and macrophages) release cytotoxic granules upon binding to the Fc portion of cetuximab bound to a tumor cell. Specific antigen cytotoxicity can be triggered by cetuximab,\textsuperscript{29} suggesting a role for cellular immunity in the protective effects of the antibody; however, the specific mechanisms are unclear, because Fc gamma receptor polymorphisms that affect IgG binding are poorly correlated with clinical outcomes of patients with CRC treated with cetuximab,\textsuperscript{30} and the antibody could mediate tumor killing through noncellular mechanisms, such as complement-mediated lysis. Furthermore, panitumumab, a fully human IgG2 monoclonal antibody directed against EGFR, seems to have similar anti-tumor activity to cetuximab in CRC but does not trigger ADCC, suggesting that ADCC is not absolutely required for clinical activity of EGFR-targeted antibodies. Regarding current antibody-based approaches, an ongoing phase I/II trial is using the chimeric antibody NPC-1C in metastatic CRC; this contains the antigen-binding domains of a murine antibody, which recognize a MUC5AC-related antigen, fused to the constant region of a human IgG1, and is thought to mediate ADCC in preclinical studies (ClinicalTrials.gov identifier: NCT01040000). Another study of interest is investigating Sym004, a novel mixture of anti-EGFR monoclonal antibodies, in patients with KRAS wild-type CRC that has acquired resistance to commercially available anti-EGFR antibodies while also failing to respond to 5-FU, oxaliplatin, and irinotecan (ClinicalTrials.gov identifier: NCT02083653).

**Checkpoint Inhibition**

The development of checkpoint inhibitors is largely responsible for the recent excitement about immunotherapy. These agents are blocking antibodies to inhibitory cell-surface molecules, such as CTLA4 and PD-1/programmed death ligand 1 (PD-L1), which restrain the priming and effector phases of the adaptive T-cell immune response, respectively\textsuperscript{11} (Figure 1). The CTLA4-blocking antibody tremelimumab was assessed in a single-arm, phase II, multicenter trial in 47 patients with heavily pretreated metastatic CRC. With a median duration on study of 2.3 months, 43 of 45 evaluable patients experienced disease progression, although 1 patient had a mixed response with regression of an adrenal metastasis, and OS at 6 months after enrollment was 45%.\textsuperscript{32} In retrospect, several possible explanations exist for the lack of response, which include delayed immune responses in the setting of aggressive metastatic disease in a poor prognosis group, and the possibility that the particular isotype of tremelimumab (IgG2a) is less effective at depleting regulatory T cells (Tregs) via ADCC, which represents a potential mechanism of other anti-CTLA4 antibodies, such as ipilimumab.\textsuperscript{33}

Antibodies blocking the PD-1/PD-L1 axis have also been assessed in CRC. The anti–PD-1 antibody nivolumab did not demonstrate activity in a phase I study of multiple tumor types, which included 17 patients with heavily pretreated, metastatic CRC. However, data from other solid tumors in this study suggest that tumor expression of PD-L1 may predict responses to PD-1 blockade, and it is noteworthy that of 7 patients with CRC in this cohort whose tumors were interrogated for PD-L1 expression, 6 were PD-L1–negative, which may explain some of the observed lack of response.\textsuperscript{34} Nivolumab does show some activity in CRC, with a subsequent case report from the same group describing 1 patient with metastatic CRC (pT3N2, status post right hemicolectomy revealing metastases to 4 of 16 lymph nodes and vascular and perineural invasion), treated with 5 doses of nivolumab, who subsequently demonstrated a complete response after 6 months with no evidence of disease 3 years after his last dose. Notably, the patient’s primary tumor was found to express PD-L1.\textsuperscript{35} PD-L1 blockade has also hinted at clinical activity. The anti–PD-L1 antibody BMS936559 had no activity in a phase I trial that included 18 patients with CRC.\textsuperscript{36} However, preliminary data with another anti–PD-L1 antibody MPDL3280A presented at the ASCO 2013 meeting indicated that 1 of 4 patients with CRC had responses, and that both PD-L1–positive and PD-L1–negative tumors had responses based on in-house immunohistochemistry assays. On the whole, the clinical activity of checkpoint inhibition in CRC needs to be assessed more formally.
in larger numbers of patients, in trials that examine what features can predict response to PD-1 blockade in solid tumors, and whether these biomarkers are relevant in CRC.

One recent intriguing finding with checkpoint inhibitors involves PD-1 blockade in the setting of CRC with MSI. In general, the MSI-high phenotype is associated with more intense immune infiltrates and portends an improved prognosis, in that only 3% to 4% of all patients with metastatic CRC are MSI-high. Recent findings have suggested that the infiltrate in MSI-high CRC is more likely to express PD-L1, which may predict response to PD-1 blockade. A recently published investigator-initiated phase II study with 41 patients presented at the ASCO 2015 meeting demonstrated in dramatic fashion that the MSI phenotype is indeed predictive of responses to PD-1 blockade, because monotherapy administration of the PD-1 blocking antibody pembrolizumab in the setting of progressive metastatic CRC resulted in objective responses in 40% of patients with MSI phenotype and at least stable disease in 78%, compared with 0% and 11% in patients with microsatellite-stable CRC. Median PFS and OS were not reached in the MSI CRC cohort versus 2.2 and 5.0 months in the microsatellite-stable cohort, with a hazard ratio of 0.1 for disease progression or death, and 0.22 for death. Importantly, there were 20-fold more somatic mutations in the MSI cohort, and somatic mutational burden was correlated with PFS, supporting the neoantigen hypothesis. Based on this study, a larger phase II study (KEYNOTE-164) will soon begin enrollment to assess the benefit of pembrolizumab for locally advanced unresectable or metastatic MSI CRC refractory to 2 or more prior lines of therapy (ClinicalTrials.gov identifier: NCT02460198). In general, although the MSI results hold great promise, the complete lack of response in patients with microsatellite-stable CRC, who represent the vast majority of patients with CRC, is sobering. This highlights the ongoing need to understand why patients with conventional CRC lack robust responses to immunotherapy. Can one extrapolate from the MSI responses to understand the lack of response to PD-1 blockade in patients with microsatellite-stable CRC? It will be critical to examine closely the specific somatic mutations seen in responders. Although generation of immunogenic neoantigens may be a critical part of this story, this is only one possibility; it is also possible that the somatic mutations in patients with MSI phenotype amplify specific upstream steps that are required for activation of an immune response, for instance recruitment of immune effector or antigen presenting cells, or antigen processing and presentation.

Adaptive Cell Therapies
Adaptive cell therapies have shown some activity in CRC, using autologous T cells genetically engineered to express high-affinity receptors for CRC TAAs. This approach has been used with dramatic responses in hematologic malignancies and melanoma. Three patients with metastatic CRC who received T cells transduced with high-affinity murine T-cell receptors against CEA demonstrated 74% to 99% reductions in CEA levels, and 2 patients had measurable reduction in their tumor burden, with the adoptively transferred T cells homing to the tumor site and producing IFN within 1 week. However, both biochemical and imaging responses were transient, with eventual progression of disease, which may have been related to lack of persistence of the engineered T cells. In addition, further accrual was halted because all 3 patients developed autoimmune colitis (2 patients with grade 3). Another effort involved autologous T-cell transduction with a chimeric antigen receptor (CAR) whose extracellular domain recognizes HER2/neu in a non–MHC-dependent manner. Unfortunately, within hours of adoptive T-cell transfer, the patient developed respiratory failure associated with release of inflammatory cytokines, hypotension requiring vasopressors, gastrointestinal bleeding, and cardiac arrests followed by death. Postmortem analysis suggested preferential CAR accumulation in the lungs and intra-abdominal lymph nodes, but not in the metastases. These results demonstrate both the potency of adoptive transfer of high-affinity T-cell clones against TAAs and the difficulties with engineering persistent activity and ensuring an adequate therapeutic index of antitumor over autoimmune responses. Numerous trials are ongoing in this space, including a phase I trial of autologous NK cells infused in conjunction with bortezomib in an effort to sensitize tumor to NK cytotoxicity (ClinicalTrials.gov identifier: NCT00720785); a phase I dose escalation of infusion of CTLs specific for TAAs NY-ESO-1, MAGEA4, PRAME, Survivin, and SSX in relapsed or refractory solid tumors (ClinicalTrials.gov identifier:
NCT02239861); a phase I/II study of the safety and efficacy of infusion of peripheral blood lymphocytes transduced with a CAR specific for vascular endothelial growth factor 2 in metastatic CRC following a lymphodepleting conditioning regimen with cyclophosphamide and fludarabine (ClinicalTrials.gov identifier: NCT01218867); a similar phase I/II design of peripheral blood lymphocytes transduced with an EGFR-specific CAR in chemorefractory CRC with liver metastases (ClinicalTrials.gov identifier: NCT01869166); and finally an adjuvant study of cytokine-induced killer cells in combination or in sequence with adjuvant capecitabine plus oxaliplatin for high-risk stage II/III CRC following R0 resection (ClinicalTrials.gov identifier: NCT01929499).

Future Directions for CRC: What Can We Learn From Other Approved Immunotherapies for Solid Malignancies?

Until recently, only a few immune therapies for solid malignancies were FDA-approved: the cytokines IL-2 and IFN-alpha (for renal cell carcinoma and melanoma); the cell-based therapy sipuleucel-T (for prostate cancer); and the CTLA4-blocking antibody ipilimumab (for melanoma). However, the number of approved therapies is rapidly increasing, with the first-in-class approval of the PD-1 blocking antibody pembrolizumab (for refractory metastatic melanoma not responsive to ipilimumab or BRAF inhibitors), and the additional PD-1 blocking antibody nivolumab (for previously treated metastatic melanoma and for metastatic squamous non–small cell lung cancer following platinum-based therapy). Collectively, these approved therapies may provide insights relevant to future investigations of CRC immunotherapy.

Clinical Considerations With Immunotherapies

The kinetics of clinical responses can be very different with immunotherapies. A common feature of several of the approved immune therapies (in particular cytokines and checkpoint inhibitors) is that a fraction of patients objectively respond upfront using standard response criteria. However, in other patients there is often a lag in apparent clinical response, often with growth in some lesions preceding regression, which is not captured by standard RECIST criteria. This has led to the development of response criteria for immune-based therapies that tolerates some interval progression so long as the patient is not significantly deteriorating. These response kinetics also raise the question of the most appropriate clinical setting to study and use immunotherapies. On one hand, the improved survival with approved therapies such as sipuleucel-T and ipilimumab indicates that advanced, pretreated disease does not preclude responses to immunotherapy. However, the latency to response suggests that earlier use of immune therapies in more stable metastatic disease, or possibly as early as the neoadjuvant setting, may be useful in CRC to allow responses to manifest. This would also permit serial biopsies over time to monitor responses.

Immunotherapies are also associated with some unique toxicities, such as colitis, transaminitis, and endocrinopathies for checkpoint inhibitors such as ipilimumab and nivolumab. These toxicities appear to be less pronounced with the PD-1 inhibitors, and are generally manageable with corticosteroids and tumor necrosis factor (TNF)-α inhibitors.

Are We Hitting Our Target?

Both antigen-targeted and antigen-agnostic therapies have shown efficacy in other tumors, and may therefore demonstrate activity in CRC. For antigen-specific therapies, antigen selection and testing will be critical to ensure adequate immunogenicity while also minimizing off-target toxicities. PAP, the antigen in sipuleucel-T, was selected because it is ubiquitous in most prostatic adenocarcinomas, is minimally expressed in nonprostatic tissue, and, based on sequence analysis, is minimally homologous to other host proteins. Extensive preclinical testing of PAP variants was conducted to determine adequate prostatic inflammation and lack of nonprostatic inflammation. For CRC, although many TAAs may demonstrate prohibitive bystander toxicities with other epithelial tissues, patient-specific neoantigens may represent attractive candidates for further investigation. Regarding antigen-nonspecific therapies, such as checkpoint inhibitors, how exactly this shifts the repertoire of the immune response in other tumor types is still unclear, although studies are underway.

Regardless of the type of immune therapy, dissecting the treatment-induced changes in a patient’s immune responses will be critical. One reason is that, despite the clear efficacy of approved immune therapies, a complete understanding of their mechanism is still lacking. One overarching question for all immune-based therapies (antigen-specific, cell-based, or checkpoint inhibition) is how these treatments
Affect the composition and interactions of immune cell populations in the tumor microenvironment to produce durable regression and memory responses. Some understanding exists with ipilimumab, in which analysis of metastatic melanoma biopsies and studies in mice suggest that the ratio of CD8+ cytotoxic T cells to Treg cells is predictive of response, and that ipilimumab could alter this ratio partly through depletion of Treg cells within the tumor. Likewise, following neoadjuvant administration of sipuleucel-T before radical prostatectomy, significant accumulations of CD3+ and CD4+ T cells, and to a lesser extent FoxP3+ Treg cells, are seen at the tumor interface, although the specific nature of the immune response at this site remains unclear. For PD-1 blockade, evidence shows that patients with melanoma who do experience response have preexisting concentrations of CD8+ cells, and increased PD-1 and PD-L1 expression, at the invasive margin of their metastatic tumors, suggesting that responders have a preexisting immune response whose inhibition is relieved by PD-1 blockade. Obtaining serial biopsy samples, although difficult, will be critical in order to perform the detailed functional and immunohistochemical studies needed to monitor immune-based therapies—in CRC or otherwise—because any dynamics in the tissue may not be reflected in changes in the peripheral blood. Beyond a better understanding of mechanism, these studies will also help advance immunotherapy in CRC by allowing clinicians to predict which patients will have durable responses (a key unknown for all approved immune therapies to date), and also to optimize therapies to expand this fraction of responders.

### Combination Therapies

Although how checkpoint inhibitors shape the antigenic repertoire is still unknown, these agents function by releasing inhibition of the immune response, and therefore they likely act in large part by enhancing preexisting antigenic responses; this may provide a rational basis for combinations of antigen-directed therapies (eg, vaccination or cell-based therapies) followed by checkpoint inhibition in CRC (Table 1, Figure 1). Likewise, given the evidence for immunogenic cell death triggered by certain chemotherapeutic agents, such as oxaliplatin, there is similar justification for combinations of first-line chemotherapy and checkpoint inhibition.

### Conclusions

Some ongoing CRC immunotherapy efforts are already suggesting efficacy, and there are also reasons to believe that immunotherapies, such as checkpoint inhibitors, which have demonstrated efficacy in a broad range of solid malignancies, may also have efficacy in carefully selected subsets of patients with CRC. Developing immunotherapies, either approved or under development, hold great promise in this common and often fatal disease.

### Table 1 General Strategies for Immune-Based Therapies in Colorectal Cancer

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checkpoint inhibitors</td>
<td>Multiple antibodies available or in testing</td>
<td>Only fraction of patients respond (unclear predictive markers)</td>
</tr>
<tr>
<td></td>
<td>Potentially stimulates responses to multiple tumor antigens → potentially greater likelihood of clinical response</td>
<td>Latency to response and autoimmune toxicity (CTLA &gt; PD-1)</td>
</tr>
<tr>
<td></td>
<td>Known algorithms for monitoring response and managing toxicities</td>
<td></td>
</tr>
<tr>
<td>Adoptive T-cell therapy</td>
<td>Known specificity of therapy</td>
<td>Unclear persistence of antitumor T-cell activity</td>
</tr>
<tr>
<td></td>
<td>Established methods for ex vivo expansion</td>
<td>Off-target toxicity especially for epithelial antigens</td>
</tr>
<tr>
<td></td>
<td>Autologous therapy</td>
<td>Requires extensive optimization of engineered construct for activity</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Known specificity of therapy</td>
<td>Unclear if immunization to single antigen may result in optimal clinical responses</td>
</tr>
<tr>
<td></td>
<td>Autologous therapy</td>
<td>Off-target toxicity</td>
</tr>
</tbody>
</table>

**Review**

Immunotherapy for Colorectal Carcinoma

**© JNCCN—Journal of the National Comprehensive Cancer Network | Volume 13 Number 8 | August 2015**
References


