An Expanding Role for Immunotherapy in Colorectal Cancer

Katherine M. Bever, MD, and Dung T. Le, MD

Abstract

Colorectal cancer (CRC) is a leading cause of cancer-related mortality in the United States. Response rates to second- and third-line therapy for metastatic CRC (mCRC) remain low, and immunotherapy is an attractive strategy for treatment in these patients given generally better tolerability than conventional chemotherapy and the potential for long-lasting durable responses. In particular, the novel checkpoint inhibitors (CPIs) have demonstrated unprecedented clinical activity in a wide range of cancers. The observation of clinical activity in microsatellite instability–high (MSI-H) mCRC was the first indication of a potential for CRC to respond to these agents, and has led to a breakthrough designation by the FDA for CPI use in this subset. Despite this, a proportion of MSI-H and nearly all microsatellite stable disease will not respond to single-agent checkpoint inhibition, and clinical trials are ongoing to increase responses to immunotherapy in mCRC through both better patient selection and novel combinations of immunotherapeutic agents. This review will provide a focused update on the most compelling clinical results of immunotherapy in CRC to date, as well as a summary of current strategies being tested in clinical trials in increase responses to immunotherapy in CRC.

Colorectal cancer (CRC) is one of the most common cancers in the developed world and is increasing in incidence globally. In the United States, it is the third most common cause of cancer-related mortality in both men and women.1 Survival from CRC in the United States appears to be improving within the past 2 decades,2 but remains low in metastatic CRC (mCRC), with a 5-year survival rate of approximately 13%.3 Recently approved cytotoxic agents in this setting have yielded marginal benefits.4,5 Immunotherapy holds promise as a more targeted, potentially less toxic therapy, and the so-called checkpoint inhibitors (CPIs) have recently received regulatory approval in multiple cancers, including melanoma and lung, kidney, bladder, and head and neck cancers, based on durable clinical responses demonstrated in a subset of patients. However, response rates to these agents were low in unselected patients with CRC.6-8 The more recent demonstration of responses in microsatellite instability–high (MSI-H) CRC to CPIs was a turning point, and has led to several clinical trials and increased efforts to obtain responses in patients with microsatellite stable (MSS) CRC and to identify other predictive biomarkers.

This review provides an update of the activity of immunotherapy in MSI-H CRC and ongoing efforts to increase activity of immunotherapy in MSS CRC through identification of other potentially susceptible subsets of CRC and through novel combination immunotherapies.

MSI is a Biomarker of Response to CPI

MSI-H CRC results from defective mismatch repair proteins (dMMRs), as seen in hereditary Lynch syndrome and in approximately 15% of sporadic cases of CRC, and defines a subset of CRC with unique biology. MSI-H CRC is characterized by exceptionally high mu-
tation burden and an immune-active tumor microenvironment with high levels of tumor-infiltrating lymphocytes (TILs) and high levels of expression of multiple immune checkpoints, including PD-1, PD-L1, CTLA-4, LAG3, and IDO.\textsuperscript{9,11} Given that these features have been observed in other CPI-responsive cancers, a clinical trial of pembrolizumab in dMMR mCRC was conducted and demonstrated response rates of 40% in dMMR tumors versus no response in proficient MMR (pMMR) tumors.\textsuperscript{12} Updated data from this trial were recently presented, and a response rate of 57% and disease-control rate of 89% was seen in dMMR CRC versus 0% and 16%, respectively, in pMMR CRC.\textsuperscript{13} At a median follow-up of 9.3 months, median disease-free survival and overall survival had not yet been reached in the dMMR cohort, suggesting durable responses in this group. As a result of these observations, pembrolizumab has received breakthrough designation by the FDA for use in MSI-H mCRC.

The activity of nivolumab with or without ipilimumab is also being explored in MSI-H mCRC in the Checkmate-142 trial.\textsuperscript{14} At interim analysis, overall response rates of 25% and 33% to monotherapy and the combination, respectively, were reported. Updated results were recently presented of 74 patients treated with nivolumab monotherapy, with an overall response rate of 31% and disease control rate of 69%.\textsuperscript{15}

CPI monotherapy is being further tested in MSI-H/dMMR mCRC in previously treated patients (ClinicalTrials.gov identifier: NCT02460198) and in the first line (NCT02563002). Likely, CPIs will soon enter the standard of care for MSI-H mCRC; however, >95% of mCRC is MSS, and efforts to expand the application of immunotherapy in MSS CRC are ongoing, both through the identification of other potentially susceptible subgroups and through combinatorial approaches.

Other Potential Biomarkers of Response to Immunootherapy in CRC

A unifying feature of many cancers that respond to CPI therapy is high mutational burden, likely because of the production of neoantigens, which can be detected as foreign by the host.\textsuperscript{16-18} MSI-H CRC exemplifies this, with an exceptionally high mutational burden and high predicted neoantigen load associated with these tumors. A recent large-scale study demonstrated that higher neoantigen load was correlated with increased immune infiltration in the tumor and better survival, even in MSS CRC.\textsuperscript{19} In addition to the MMR proteins classically associated with MSI, other mutations may also lead to a hypermutated phenotype in CRC, including mutations in exonuclease domains of the genes encoding DNA polymerase δ (POLD1) and ε (POLE).\textsuperscript{19-24} These data support exploring more broadly the selection of patients with a hypermutated phenotype for treatment with CPI, and, with its increasing availability, next-generation sequencing may have a role.

Extensive efforts to demonstrate the predictive value of PD-L1 expression and response to PD-L1 inhibitors have yielded conflicting results, depending on the tumor type and immunostaining techniques. A meta-analysis of 20 trials involving multiple tumor types demonstrated overall response rates of 34.1% and 19.9% in PD-L1–positive and PD-L1–negative tumors, respectively.\textsuperscript{25} In CRC, few studies have examined the predictive role of PD-L1. In the aforementioned trial of pembrolizumab in mCRC, although the numbers were small, PD-L1 expression was not significantly associated with progression-free or overall survival.\textsuperscript{12} Preliminary results of another trial of pembrolizumab in PD-L1–expressing tumors demonstrated response in only 1 of 23 patients with PD-L1–positive CRC, and this tumor was found to be MSI-H.\textsuperscript{26} In the aforementioned Checkmate-142 trial, responses were observed regardless of PD-L1 status.\textsuperscript{15} These data suggest a limited role for PD-L1 expression as a biomarker of response in CRC.

Immune infiltration is another potential biomarker of response, as a correlation has been observed between pretreatment CD8-positive T-cell infiltration and response to CPI therapy in melanoma.\textsuperscript{27} Immune infiltrates have been extensively studied in CRC for their role in progression of and prognosis from the disease,\textsuperscript{28,29} and it was demonstrated that the densities and distribution of immune cells in the tumor could outperform the UICC TNM staging system in predicting outcome.\textsuperscript{30,31} The Immunoscore emerged from these studies as a simple tool to stratify CRC tumors through the quantification of densities of 2 lymphocyte populations (CD3/CD45RO or CD3/CD8) or CD8/CD45RO in the tumor core and at the invasive margin.\textsuperscript{32,33} Immunoscore correlated with extent of disease and survival in these analyses and, strikingly, Mlecnik et al\textsuperscript{14} demonstrated
that the Immunoscore was more strongly associated with outcome than was MSI-H status. Proponents of the Immunoscore propose to incorporate it into a standardized staging system for routine clinical use.\textsuperscript{32} The role of Immunoscore in predicting response to CPI therapy has not been tested.

Most recently, gene expression analysis has been used to molecularly characterize and risk-stratify CRC, and has provided further evidence of its diverse biology. Four consensus molecular subtypes (CMS) of CRC based on gene expression profiles have been described: CMS1, “MSI-like” or hypermutated tumors; CMS2, canonical tumors associated with high chromosomal instability and activation of WNT and MYC pathways; CMS3, metabolic tumors associated with KRAS mutations and metabolic dysregulation; and CMS4, mesenchymal tumors. This system demonstrated an ability to stratify tumors by prognosis, with CMS1 tumors unsurprisingly associated with the best prognosis and CMS4 tumors with the worst. It also underscored the limitations of using MSI status alone to stratify patients for treatment, because the CMS1/MSI-H–like group included most but not all MSI-H tumors and some MSS tumors.\textsuperscript{35} Becht et al\textsuperscript{10} used transcriptomics to characterize the microenvironment of CRC samples with respect to CMS, and observed high expression of immune signatures not only in CMS1 but also in mesenchymal CMS4 CRCs, in which prominent transforming growth factor β (TGF-β) activation, stromal invasion, and angiogenesis likely have a large role in tumor immune escape. These data suggest a role for such a classification system in personalized immunotherapy.

**Therapeutic Strategies to Enhance Responsiveness to Immunotherapy**

The strategies described may help identify other immunogenic subsets of CRC in which blocking immune checkpoints may be sufficient to yield an effective antitumor immune response. In the remaining poorly immunogenic subsets of CRC, it seems likely that a multipronged approach may be necessary to induce clinically significant responses. To that end, a number of novel immunotherapeutics and combinations are in development to nonspecifically activate the immune system, target the immunosuppressive microenvironment, increase the antigenicity of the tumor, and enhance the antigen-specific immune response (Figure 1).

**Other Immunomodulatory Antibodies**

Immune checkpoints serve to downregulate an overactive cytotoxic T-cell response and are exploited by cancer cells. By blocking these molecules at the tumor–immune cell interface, CPIs can thus activate cytotoxic T cells in a nonspecific manner. The best studied of these are antibodies inhibiting CTLA-4 and the PD-1/PD-L1 interaction. A number of other checkpoints have been identified (eg, LAG3, TIM-3, CEACAM, KIR), and antibodies to these targets are currently in development. In addition, cytotoxic...
T cells can be activated via costimulatory receptors (eg, OX40, CD40, 41BB, ICOS, CD27, GITR), and antibodies targeting these molecules are being tested as monotherapy or in combination with other CPIs in a number of early-phase trials (Table 1).

Dual CPIs have been observed to increase responses over CPI monotherapy in melanoma, and the aforementioned Checkmate-142 trial in CRC also investigated this strategy in MSS CRC. In a preliminary presentation, objective response was reported in only 1 of 20 patients with MSS CRC.14

**Activators of the Innate Immune Response**

Toll-like receptors (TLRs) activate the innate immune system in response to pathogen-associated molecular patterns (PAMPs), “danger signals” associated with microbes. A number of TLR agonists are under development and being tested in clinical trials, including a TLR8 agonist with cyclophosphamide in advanced solid tumors (ClinicalTrials.gov identifier: NCT02650635), a TLR5 agonist being tested in the neoadjuvant setting for CRC (NCT02715882), a TLR3 ligand combined with pembrolizumab in mCRC (NCT02834052), and a TLR9 agonist with ipilimumab in advanced malignancies (NCT02668770) and as maintenance therapy after induction in mCRC (NCT02077868).

Imprime PGG is a fungal PAMP used to activate the innate immune system and enhance cytotoxic killing of opsonized cells (ie, epidermal growth factor receptor [EGFR] antibody–treated). A phase II trial in mCRC in combination with cetuximab showed modest activity, and the combination is being further explored in a phase III trial (ClinicalTrials.gov identifier: NCT01309126).39

**Tumor Microenvironment–Targeted Agents**

Increasingly, it is understood that tumor cells do not exist in a vacuum, and stromal cells and other features in the tumor microenvironment may contribute significantly to the tumor’s ability to escape immune destruction.

Indoleamine 2,3-dioxygenase (IDO) depletes tryptophan in the tumor microenvironment, with a predominant immunosuppressive effect that facilitates tumor immune escape.40 IDO inhibitors have been tested in combination with CPIs and cancer vaccines in preclinical models and have shown synergy.41,42 Clinical trials are ongoing of IDO inhibitor monotherapy (ClinicalTrials.gov identifier: NCT02048709) and combined with CPIs (NCT02327078, NCT02862457). High IDO expression in CRC correlated with a reduction in CD3-positive TILs and was associated with the presence of metastatic disease and outcome, suggesting a role for therapeutic blockade in this disease.

Adenosine is a potent immunosuppressor released in response to cellular stress and has been shown to promote tumor growth and progression through the downregulation of cytotoxic T cells, recruitment of immunosuppressive cells, and enhanced neovascularization. Inhibition of adenosine production with anti-CD73 antibodies and of adenosine signaling through A2A receptor (A2AR) blockade have been shown to enhance the effectiveness of immunotherapies in preclinical models.45 Clinical trials are ongoing to evaluate the use of anti-CD73 antibodies (NCT02754141, NCT02503774) and A2AR blockade (NCT02655822) in combination with the CPIs in advanced cancers, including CRC.

Tumor-associated macrophages of the M2 phenotype are thought to promote tumor growth through the production of proangiogenic and growth factors as well as immunosuppressive cytokines, and M2 macrophages can be depleted with CSF1R inhibitors. A number of clinical trials are investigating the combination of CSF1R inhibitor with PD-L1 blockade (ClinicalTrials.gov identifiers: NCT02777710, NCT02718911, NCT02526017, NCT02829723).

Although not frequently mutated in solid tumors, JAK1 is nonetheless believed to be an important mediator of cell signaling driven by inflammatory cytokines released by tumor cells and the tumor microenvironment, promoting tumorigenesis and metastatic spread and suppression of the antitumor immune response.46 In particular, the JAK/STAT signaling pathway maintains FoxP3 expression on regulatory T cells (Tregs).47 A current trial is investigating the combination of pembrolizumab with a JAK1 inhibitor or with PI3K-delta inhibitor (NCT02646748) and in combination with IDO or PI3K-delta inhibitors (NCT02559492).

CCR4 is expressed at high levels on Tregs, and expression of CCR4 ligand represents another mecha-
Table 1. Select Immunomodulatory Antibodies and Associated Clinical Trials in Solid Tumors Including CRC

<table>
<thead>
<tr>
<th>Target Molecule</th>
<th>Drug (Company)</th>
<th>Select Clinical Trials Including CRC (ClinicalTrials.gov Identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA-4</td>
<td>Ipilimumab (Bristol-Myers Squibb)</td>
<td>NCT02060188 (+ nivolumab) NCT01788922 (+ radiation)</td>
</tr>
<tr>
<td></td>
<td>Tremelimumab (tcilimumab, CP-675,206) (Medimmune/AstraZeneca)</td>
<td>NCT02754586 (+ MED4736 in resectable mets) NCT02888743 (+ MED4736 + XRT) NCT02870920 (+ MED4736) NCT01975831 (+ MED4736)</td>
</tr>
<tr>
<td>PD-1</td>
<td>Nivolumab (Bristol-Myers Squibb)</td>
<td>NCT02860546 (+ TAS-102 in MSS aCRC) NCT02327078 (+ IDO inhibitor) NCT02422395 (+ chemotherapy) NCT02563036 (+ enadenosinerecipe)</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (Merck)</td>
<td>NCT01876511 NCT02460198 (MSI-H/dMMR aCRC) NCT02563002 (MSI-H/dMMR aCRC first-line) NCT02713373 (+ cetuximab) NCT02873263 (+ SBRT in liver mCRC) NCT02437071 (XRT or ablation) NCT02375672 (+ stemness inhibitor) NCT02713529 (+ anti-CSF1R) NCT02298859 (+ VEGF inhibitor) NCT02268825 (+ mFOLFOX6) NCT02231901 (+ cetuximab) NCT02666748 (+ JAK1 or PI3-delta inhibitor in MSI CRC) NCT02178722 (+ IDO inhibitor in MSI CRC) NCT02866425 (+ VEGF inhibitor) NCT02834052 (+ TLR3 agonist)</td>
</tr>
<tr>
<td></td>
<td>PDR001 (Novartis)</td>
<td>NCT02678260 NCT02890069 (+ LCL161, everolimus, or panobinostat) NCT02900664 (+ immunomodulatory agents) NCT02829723 (+ CSF1R inhibitor)</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Durvalumab/MEDI4736 (Medimmune)</td>
<td>NCT02777710 (+ CSF1R inhibitor) NCT02227667 (in MSI-H or H-TIL CRC) NCT02484046 (+ VEGF inhibitor in MSS aCRC) NCT02811497 (+ azacitidine in MSS aCRC) NCT02586987 (+ MEK inhibitor)</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab/MPDL3280A (Genentech/Roche)</td>
<td>NCT02873195 (+ capcetabine/bevacizumab) NCT02788279 (+ MEK inhibitor) NCT02876224 (+ cobimetinib + bevacizumab in MSS aCRC) NCT02655822 (+ AZAR inhibitor) NCT01643970 (+ bevacizumab) NCT01373842 (aCRC) NCT02912359 (+ FOLFOX in adjuvant for stage III MSI/dMMR CRC)</td>
</tr>
<tr>
<td></td>
<td>Avelumab (Pfizer)</td>
<td>NCT01772004 NCT02554812 (+ 4-1BB orOX40 agonist)</td>
</tr>
<tr>
<td>LAG-3</td>
<td>BMS-986016 (Bristol-Myers Squibb)</td>
<td>NCT01968109 (alone or + nivolumab)</td>
</tr>
<tr>
<td></td>
<td>LAG3525 (Novartis)</td>
<td>NCT02460224 (+ PDR001 )</td>
</tr>
<tr>
<td>TIM3</td>
<td>TSR-022 (Tesaro)</td>
<td>NCT02817633 (+ nivolumab)</td>
</tr>
<tr>
<td></td>
<td>MBG453 (Novartis)</td>
<td>NCT02608268 (+ PDR001 )</td>
</tr>
<tr>
<td>CEACAM1</td>
<td>CM-24 (cCAM Biotherapeutics)</td>
<td>NCT02346955 (a pembrolizumab)</td>
</tr>
<tr>
<td>KIR</td>
<td>BMS-986015 (Bristol-Myers Squibb)</td>
<td>NCT02703580 (+ ipilimumab) NCT02174729 (+ nivolumab)</td>
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<tr>
<td>4-1BB</td>
<td>Utomilumab/PF-05082566 (Pfizer)</td>
<td>NCT02554812 (+ avelumab) NCT02444793 (+ mogamulizumab) NCT02179918 (+ pembrolizumab)</td>
</tr>
<tr>
<td></td>
<td>Ureumab/BMS-663513 (BMS)</td>
<td>NCT02253992 (+ nivolumab)</td>
</tr>
<tr>
<td>OX40</td>
<td>MEDI6469 (Medimmune)</td>
<td>NCT02559024 (given before resection of mCRC)</td>
</tr>
<tr>
<td></td>
<td>MEDI0562 (Medimmune)</td>
<td>NCT02705482 (+ tremelimumab or durvalumab) NCT02318394</td>
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<tr>
<td></td>
<td>MOX09016 (Genentech)</td>
<td>NCT02219724 NCT02451052 (+ atezolizumab + bevacizumab)</td>
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<tr>
<td>ICOS</td>
<td>GSK3356909 (GlaxoSmithKline)</td>
<td>NCT02723955</td>
</tr>
<tr>
<td>CD27</td>
<td>Varrilumab/CDX-1127 (Cellidex Therapeutics)</td>
<td>NCT01460134 NCT02331918 (+ nivolumab)</td>
</tr>
<tr>
<td>G/ITR</td>
<td>TRXS18 (Leap Therapeutics)</td>
<td>NCT02628571 NCT01239134</td>
</tr>
<tr>
<td></td>
<td>INCAC01876 (Incyte/Agenus)</td>
<td>NCT02697591</td>
</tr>
<tr>
<td></td>
<td>BMS-986156 (Bristol-Myers Squibb)</td>
<td>NCT02598960 (+ nivolumab)</td>
</tr>
<tr>
<td></td>
<td>AMG 228 (Amgen)</td>
<td>NCT02437916</td>
</tr>
<tr>
<td></td>
<td>MK-1248 (Merck)</td>
<td>NCT02533499 (+ pembrolizumab)</td>
</tr>
<tr>
<td></td>
<td>MK-4166 (Merck)</td>
<td>NCT02133754 (+ pembrolizumab)</td>
</tr>
<tr>
<td></td>
<td>GWN323 (Novartis)</td>
<td>NCT02740270 (+ PDR001 )</td>
</tr>
<tr>
<td></td>
<td>MED1873 (Medimmune)</td>
<td>NCT02583165</td>
</tr>
</tbody>
</table>

Abbreviations: A2AR, A2A receptor; aCRC, advanced CRC; CRC, colorectal cancer; dMMR, defective mismatch repair; H-TIL, high levels of tumor infiltrating lymphocytes; IDO, indoleamine 2,3-dioxygenase; mCRC, metastatic CRC; mets, metastasis; MSI, microsatellite unstable; MSI-H, microsatellite instability–high; MSS, microsatellite stable; SBRT, stereotactic body radiation therapy; VEGF, vascular endothelial growth factor; XRT, radiotherapy.
nism of tumor-mediated immune escape. The CCR4 ligand CCL17 was observed to induce CRC cell migration, suggesting a role specifically in metastatic spread. Clinical trials are currently testing this drug alone (ClinicalTrials.gov identifier: NCT02281409), in combination with CPIs (NCT02301130, NCT02705105), or with anti-4-1BB antibody (NCT02444793) in advanced solid tumors.

Treatment with vascular endothelial growth factor (VEGF) inhibitors appears to enhance lymphocyte endothelial trafficking into the tumor and enhances PD-L1 expression, suggesting a role for combination with CPIs. Several such combinations are currently being tested, including bevacizumab plus atezolizumab (ClinicalTrials.gov identifier: NCT01633970), ziv-aflibercept with pembrolizumab (NCT02298959), and a quadruple combination of bevacizumab, durvalumab, tremelimumab, and FOLFOX chemotherapy (NCT02754856).

Enhancement of Tumor Cell Immunogenicity

Nonspecific activation of the immune system is likely insufficient in poorly immunogenic CRC; however, combination with other therapies that can potentially enhance the immunogenicity of these tumors may be a viable strategy.

A dysfunctional MAPK/ERK pathway is prominent in the pathogenesis of many cancers, including CRC. In preclinical models, treatment with MEK inhibitors increased cytotoxic T-cell infiltration and survival, and increased antigen presentation by tumor cells via class I major histocompatibility complex (MHC) expression, and combination MEK and PD-L1 inhibition appeared to have synergistic effects and induced tumor regression. Based on this rationale, the MEK inhibitor cobimetinib was combined with the PD-L1 inhibitor atezolizumab in a phase Ib clinical trial (ClinicalTrials.gov identifier: NCT01988896). Interim analysis demonstrated partial responses in 4 of 23 patients with advanced CRC; remarkably, 3 of these responders were documented to be pMMR. Enhanced CD8-positive lymphocyte infiltration and MHC class I expression were observed in serial biopsies after cobimetinib alone and appeared to be further enhanced by the combination. This promising data has led to a global phase III study (NCT02788279). Combination co-bimetinib, atezolizumab, and bevacizumab will also be explored in mCRC (NCT02876224).

Epigenetic therapy can induce changes in poorly immunogenic tumors that may sensitize to immunotherapy, likely via effects on tumor cells (ie, increased tumor antigen expression) and host immune cells (enhanced T-cell survival, upregulation of costimulatory receptors, and depletion of myeloid-derived suppressor cells). Preclinical and clinical data suggest a role for combination CPIs with epigenetic therapy, and several clinical trials are evaluating this combination in MSS mCRC (ClinicalTrials.gov identifiers: NCT02811497, NCT02512172), as well as combination epigenetic therapy with a therapeutic cancer vaccine in mCRC (NCT01966289).

Certain chemotherapies, including oxaliplatin, as well as radiation therapy not only work through direct cytotoxic effects but also can generate antitumor immune responses through the induction of a so-called immunogenic cell death and antigenic spread and subsequent activation of antigen-presenting cells. The optimal strategy to capitalize on these effects in combination with immunotherapy is unknown. CPIs are currently being tested in combination with radiation therapy or ablation or chemotherapy in a number of trials in advanced cancer, including CRC (NCT02437071, NCT02843165, NCT02710253, NCT0239900, NCT02423954, NCT02375672, NCT02268825).

Enhancing the Tumor-Specific Immune Response

Antibodies

The anti-EGFR monoclonal antibodies cetuximab and panitumumab have been approved for use in RAS wild-type mCRC. Although their activity as monotherapy is modest, combination with CPIs or other immunomodulatory agents may enhance their efficacy and is being explored (ClinicalTrials.gov identifiers: NCT02318901, NCT02713373). Dual-affinity retargeting (DART) proteins are bispecific antibody constructs that simultaneously target tumor-associated antigens and T-cell surface proteins, thus recruiting and activating T cells at the site of the tumor. This construct has shown efficacy in hematologic malignancies. At least 2 DART proteins are currently under development for use in solid tumors: MGD007 (gpA33 x CD3) is a CRC-
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specific drug (NCT02248805), and MGD009 (B7-H3 x CD3) is in phase I testing in advanced tumors that express B7-H3 (NCT02628535).

Vaccines
Cancer vaccines have shown promise in their ability to induce tumor-specific cytotoxic T cells and humoral responses to tumor antigens; despite this, objective clinical activity has been limited, likely due to the development of T-cell tolerance to self-antigens, which are often the intended targets. Several strategies are currently being explored in CRC, including whole-cell, peptide, dendritic cell, and virus-based vaccines, and several notable CRC vaccines are summarized in Table 2. A meta-analysis of clinical trials of vaccine therapies in CRC published in 2011 demonstrated a benefit in overall survival and dis-

Table 2. Select Vaccine Strategies in CRC

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Phase</th>
<th>Population</th>
<th>Results</th>
<th>Ongoing Clinical Trials (ClinicalTrials.gov Identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendritic cell</td>
<td>MelCancerVac (autologous mononuclear cells pulsed with allogeneic tumor cell lysate)</td>
<td>Phase II</td>
<td>Progressive aCRC</td>
<td>Stable disease achieved in 4 of 17 pts treated (24%), associated with increased Th1 cytokines&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>DC/CIK (dendritic cell/ cytokine-induced killer cell)</td>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole cell</td>
<td>Oncovax (irradiated autologous cells with BCG adjuvant)</td>
<td>Phase III</td>
<td>Resectable stage II and III CRC</td>
<td>Randomized to vaccine vs observation; no significant difference in DFS or OS&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>GVAX (autologous)</td>
<td>Pilot</td>
<td>Resectable stage IV with liver mets</td>
<td>Ongoing</td>
<td>NCT01952730</td>
</tr>
<tr>
<td>GVAX (allogeneic)</td>
<td>Stage IV disease</td>
<td>NCT00019006</td>
<td>9 pts (6 resectable, 3 unresectable) received Cy/GVAX; treatment-enhanced production of MUC-1 antibodies&lt;sup&gt;16&lt;/sup&gt;</td>
<td>NCT01966289</td>
</tr>
<tr>
<td>FANG (autologous cancer cells transfected with GM-CSF and bi-shRNAi targeting furin convertase)</td>
<td>Advanced cancer</td>
<td>NCT02432963</td>
<td>46 pts, 27 receiving ≥1 vaccine, positive ELISPOT correlated with OS&lt;sup&gt;12&lt;/sup&gt;</td>
<td>NCT1505166</td>
</tr>
<tr>
<td>Peptide</td>
<td>Personalized</td>
<td>Previously treated aCRC</td>
<td>60 pts; boosted IgG and CTL responses in 49% and 63%, respectively, CTL response correlated with OS&lt;sup&gt;9&lt;/sup&gt;</td>
<td>NCT0260949</td>
</tr>
<tr>
<td>Mutated RAS peptide + detox-II</td>
<td>Pilot, phase I</td>
<td>Dukes' C CRC after appropriate adjuvant chemotherapy, mutant RAS&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Study completed, no data available</td>
<td>NCT00019006</td>
</tr>
<tr>
<td>EP2101 (10 synthetic peptide epitopes [2 each from CEA, p53, HER2/neu, and MAGE 2/3] plus Montanide ISA 51 adjuvant)</td>
<td>Stage II/III A NSCLC and stage III CRC who completed standard treatment</td>
<td>NCT02432963</td>
<td>13 pts treated, 12 of whom developed vaccine-induced CTL responses&lt;sup&gt;11&lt;/sup&gt;</td>
<td>None</td>
</tr>
<tr>
<td>Viral vector</td>
<td>PANVAC (vaccinia Ankara; NSCLC, non–small cell lung cancer; OS, overall survival; pts, patients; RFS, recurrence-free survival; SD, stable disease; Th1, T helper 1.</td>
<td>NCT01505166</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Pexavec/JX 594 (thymidine kinase-deactivated vaccinia virus + GM-CSF)</td>
<td>Phase II</td>
<td>Resected stage IV CRC</td>
<td>74 pts randomized to DC/PANVAC vs PANVAC/GM-CSF, 2-y RFS 47% and 55%, respectively; superior to historical controls&lt;sup&gt;12&lt;/sup&gt;</td>
<td>NCT00088413</td>
</tr>
<tr>
<td>MAV vaccine expressing p53</td>
<td>Phase I</td>
<td>Treatment refractory, measurable CRC</td>
<td>15 pts treated; 10 (67%) with SD at day 29&lt;sup&gt;16&lt;/sup&gt;</td>
<td>NCT02432963</td>
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<tr>
<td>MAV encoding the tumor antigen ST4 (TroVax)</td>
<td>Phase III</td>
<td>mCRC</td>
<td>Several clinical trials demonstrated vaccine-induced cellular and humoral responses&lt;sup&gt;16&lt;/sup&gt;</td>
<td>None</td>
</tr>
<tr>
<td>Adenoviral Ad-sig-HMUC-1/ ecdCD40L vector</td>
<td>NCT02415609</td>
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<tr>
<td>CEA(6D) VRP vaccine (AVA701)</td>
<td>Phase I</td>
<td>Select advanced cancers including CRC</td>
<td>18 pts treated on 3×3 dose escalation; 2 pts had SD, 1 pt with CR of small liver lesion CD4+, CD8+, CEA-specific T-cell and antibody responses observed&lt;sup&gt;18&lt;/sup&gt;</td>
<td>NCT01890213</td>
</tr>
<tr>
<td>Other</td>
<td>CDX-1307 (mannose receptor-targeted i-hCG vaccine)</td>
<td>Phase I</td>
<td>Select advanced cancers including CRC; administered ID or IV, alone, or with GM-CSF or poly-ICLC or resiquimod or all agents</td>
<td>89 pts enrolled; hCG-b–specific T-cell responses and antibody induced to combination + TLR agonist but not to monotherapy</td>
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Abbreviations: aCRC, advanced colorectal cancer; BCG, Bacillus Calmette–Guerin; CEA, carcinoembryonic antigen; CR, complete response; CRC, colorectal cancer; CTL, cytotoxic T lymphocytes; Cx, cyclophosphamide; DC, dendritic cell; DFS, disease-free survival; GI, gastrointestinal; GM-CSF, granulocyte macrophage colony-stimulating factor; hCG, human chorionic gonadotropin; ID, intradermal; IgG, immunoglobulin G; IV, intravenous; mCRC, metastatic colorectal cancer; mets, metastasis; MVA, modified vaccinia Ankara; NSCLC, non–small cell lung cancer; OS, overall survival; pts, patients; RFS, recurrence-free survival; SD, stable disease; Th1, T helper 1.
ease-free survival when used in the adjuvant setting, but little benefit in advanced disease, and accordingly much of the focus in clinical trials has shifted to the adjuvant setting. However, combinations with CPIs or other immunomodulatory therapy may overcome tolerance mechanisms and yield greater activity. In addition, next-generation sequencing has allowed the prediction of neoantigens and the possibility of manufacturing patient-specific vaccines.

Adaptive T-Cell Transfer

Adaptive T-cell transfer represents another potential strategy to enhance the tumor-specific adaptive immune response. Most promising among the adaptive T-cell transfer strategies is chimeric antigen receptor (CAR) T-cell therapy, in which autologous T cells are engineered to express tumor-specific receptors, allowing for increased specificity and activation on binding. Although CAR T-cell therapy has seen great success in the treatment of lineage restricted hematologic malignancies, its applicability to solid tumors remains to be seen due to a lack of suitable antigen targets.

Summary and Future Directions

Although previously thought to be a poorly immunogenic cancer, CRC is increasingly understood to be multiple, distinct entities with differing biology and different potential to respond to immunotherapy. Currently, MSI is the only biomarker of response to CPIs, and PD-1–directed therapy may soon become an option for patients with MSI-H CRC. However, other classification systems, such as the Immunoscore and molecular profiling, have shed light on the varying biology of CRC and provide clues that can further increase the ability to predict which patients may benefit from certain immunotherapeutic strategies. Additionally, whole-exome sequencing may have a role in identifying which patients are likely to respond to immunotherapy and identifying potential neoantigens that may serve as the basis for individualized therapies. In most patients, it is likely that combination immunotherapy will be necessary to overcome multiple immune tolerance mechanisms active in these cancers.

References

Immunotherapy in Colorectal Cancer


