Editorial Commentary

A new immunotherapy regimen in metastatic colon cancer: implications for palliative practice

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Introduction

Colo-rectal cancer is the fourth most common non-cutaneous malignancy in the US, and the second most common cause of cancer death (1). Early-stage colon and rectal cancer (CRC) can frequently be cured with surgery, chemotherapy, and/or radiation, but the overall 5-year survival for patients with metastatic CRC (mCRC) is poor at 14% (2). The palliative physician may encounter patients at a variety of disease stages, but may most commonly be referred patients at more advanced disease stages who may have the highest disease burden, difficult symptoms, and limited life expectancy. However, recent developments in systemic and locoregional therapies may offer select patients a chance at prolonged disease-free survival or even cure in spite of seemingly advanced disease. The CheckMate 142 study, published in January 2022 in the *Journal of Clinical Oncology*, is a phase II study investigating a combination immunotherapy regimen, nivolumab in combination with low-dose ipilimumab, in the first line setting for select patients with mCRC (3).

Current options for tumor-directed therapies in mCRC

An exhaustive review of the variety of treatment options for mCRC patients is beyond the scope of this commentary, but a discussion of the landscape may be useful to provide context for the addition of CheckMate 142. For the palliative provider, close collaboration with colleagues in medical, surgical, and/or radiation oncology is especially important in this disease, as different patients' treatment courses and expected outcomes may vary significantly in spite of all being classified as Stage IV CRC. The options available for a given patient may depend on a variety of individual and institutional factors.

Surgery, which is the mainstay of treatment for early-stage disease, has a more limited but still relevant role in mCRC. Metastasectomy of limited liver-only or intra-thoracic disease has become the standard of care for selected patients (4). Resection of the primary tumor may be performed with palliative intent for symptomatic lesions, and is of possible benefit (though debated) for patients with asymptomatic tumors (5). Patients with CRC with peritoneal metastases may be treated with cytoreductive surgery and heated intraperitoneal chemotherapy (6). Radiotherapy is a cornerstone of neoadjuvant therapy for rectal cancer, and may be utilized in the setting of metastatic colon or rectal cancer for treatment of oligometastatic sites or for consolidation when some sites have responded while others progress (4,7).

As with most metastatic solid tumors, cytotoxic

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chemotherapy has long been the standard of care for mCRC. Regimens containing 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and/or irinotecan are typically utilized in the first line, with the addition of bevacizumab, cetuximab, or other targeted agents depending on the molecular profile of the tumor (4). These regimens are still the mainstay of tumor-directed therapy for most patients and are the reference against which other treatments must be compared. Nausea, diarrhea, cytopenias, and peripheral neuropathy (from oxaliplatin) are common adverse effects, but the regimens are typically well-tolerated by fit patients (8).

Immunotherapy in mCRC

In 2020, the Keynote-177 study demonstrated impressive results for improved progression-free survival (PFS) for pembrolizumab as compared to standard 5-FU-containing cytotoxic chemotherapy (16.5 *vs.* 8 months), with a significant reduction (66% *vs.* 22%) in Grade 3 or higher treatment-related adverse events, for those mCRC patients with mismatch repair deficient (MMRd) tumors (9). Interestingly, although there was a persistent improvement in PFS in the final survival analysis published in 2022, there was not a statistically significant difference in overall survival (10).

The MMRd subset, also described as microsatellite instability-high (MSI-high), makes up about 15% of all CRC patients, and can be found in either a sporadic or familial context (9). These patients had been previously demonstrated to respond to immunotherapy in later lines of therapy after progression on standard chemotherapy regimens, and Keynote-177 showed that immunotherapy could be moved into the front line. This subset of patients have a hyper-mutated cancer genome that may carry orders of magnitude more mutations than mismatch repair proficient (MMRp) tumors, rendering them both more sensitive to immunotherapy due to the increased number of tumor neo-antigens and less responsive to conventional chemotherapy for reasons that are not yet clear (9,11). Keynote-177, as mentioned above, demonstrated the efficacy of single-agent programmed cell death protein 1 (PD-1) blockade with pembrolizumab; CheckMate 142 as presented in *JCO* January 2022 investigates the utility of adding CTLA-4 inhibition with ipilimumab to PD-1 blockade with nivolumab (3). This combination "ipi-nivo" regimen has previously demonstrated activity in advanced melanoma, among other settings (12).

CheckMate 142

Published in the January 2022 issue of *JCO*, the phase II CheckMate 142 study built upon a prior iteration which had explored the use of nivolumab with or without ipilimumab in the second line setting for MMRd mCRC (3). The *JCO* report demonstrates response rates and toxicities for 45 non-randomized patients receiving the combination therapy in the first line. As with many clinical trials, the patient population was relatively young (median age 66) and healthy with good performance status (ECOG 0 or 1). All had MMRd mCRC without other active malignancies. Patients with brain metastases or autoimmune conditions were excluded, and most were diagnosed with metastatic disease after an initial course of treatment for Stage I–III tumors, with a minority (38%) enrolled with metastatic disease at presentation. Patients were diverse in terms of location of the primary tumor and *BRAF/KRAS* mutational status (3).

The primary outcome of objective response was achieved in 69% of patients, with 13% complete response. In terms of overall survival, a secondary outcome of interest for the investigators for this publication, the median OS was not reached by 3-year follow-up. An impressive 24-month OS rate of 79% was reported. In comparison, the Keynote-177 study reported a median OS for chemotherapy of 37 months, and an OS median that was also not reached by the median follow-up of 44 months for patients treated with first-line pembrolizumab (10). In terms of PFS, the CheckMate 142 investigators report a 24-month PFS of 74%, with median PFS not reached (3). This is sharply contrasted to 16.5-month PFS reported for pembrolizumab monotherapy versus 8.2 months for cytotoxic chemotherapy in Keynote-177 (9). Although the cohorts in Keynote-177 and CheckMate 142 are broadly comparable in terms of demographics and tumor characteristics, caution is still required when making such cross-trial comparisons to historical cohorts. If these results are replicated in future randomized studies, though, it would represent a significant advance for the outcomes of patients with MMRd mCRC.

Although the combination regimen utilized in CheckMate 142 achieved impressive response rates and PFS, this did come at the cost of some treatment-related adverse events. Eighty percent of patients reported any adverse event related to the study drug, most commonly pruritus which was reported in 36% of the patients in the study overall, followed by arthralgias (20%), hypothyroidism (18%),

and asthenia, rash, fatigue, and diarrhea (16% each) (3). Grade 3 or greater events were reported in 20% of patients, including colitis, adrenal insufficiency, congestive cardiomyopathy, hypothyroidism, pneumonitis, and a variety of laboratory abnormalities including transaminitis, hypophosphatemia, and increased creatinine. Overall, 13% of patients discontinued treatment due to drug-related adverse events (3).

We commend the authors of CheckMate 142 for the inclusion of robust patient-reported outcomes (PRO) in the study design (3). Health-related quality of life was assessed using the validated European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (EORTC-QLQ-30) and 5 sub-surveys, and assessed at baseline and throughout treatment (13). Although compliance with patient completion of the survey instruments was high, there were few significant changes in patient-reported outcome measures across the course of the study period. Minor improvements at the borderline for statistical or clinical significance were reported for insomnia and dyspnea, with no changes reported for diarrhea, nausea/vomiting, constipation, or cognitive function (3).

Discussion

The recent publication in the *Journal of Clinical Oncology* of the phase II results of the CheckMate 142 study of combination nivolumab and ipilimumab for MMRd mCRC represents a significant advance in care for these patients (3). While we await the subsequent phase III studies to fully assess the comparative long-term efficacy and safety of this regimen, the publication of these results may permit more MMRd mCRC patients to achieve durable or even permanent responses to systemic therapy. The implications of this finding for the oncologic and palliative care of these patients may be significant.

In general, the addition of immunotherapy to the armamentarium for advanced solid tumors has improved outcomes for these patients, but presents some new challenges for the palliative provider. For one, patients (or indeed oncologists) may be excited by reports of dramatic responses to immunotherapy and even cases of unexpected durable cures, even though these medications are only available for some sub-sets of patients, with extraordinary results achieved only in a minority of those treated (14). This may complicate prognostication and understanding of patients' priorities and goals (14).

Although treatment-related adverse events have often been noted to be less severe for these medications than for cytotoxic chemotherapies, unique toxicities do exist which may present new challenges for palliative and oncology teams (14,15). Fortunately, oncologists and palliative providers have developed more experience in the decade or so since the widespread adoption of checkpoint inhibitor immunotherapy, and comfort with patient selection and management of adverse events for these medications has improved (15). The CheckMate 142 combination regimen may offer greater intensity of checkpoint inhibition than PD-1 inhibitor monotherapy, but with that may come an increase in adverse events and undesired side effects for which palliative teams should be attentive as the protocol makes its way from the trials setting into real-world practice.

In light of these considerations, the addition of a new immunotherapeutic regimen into this setting is a meaningful advance for patients who are candidates for this therapy. Palliative providers are becoming more and more comfortable with seeing patients on these regimens and helping to manage toxicities and associated symptoms, and the addition of this regimen adds incremental complexity in this regard. Navigating the familiar yet challenging discussions around goals of care, prognosis, and quality of life for patients considering initiating or extending immunotherapy is also becoming more routine, informed by continued progress in outcomes for patients using these regimens. In leading these multidisciplinary encounters with patients and families, palliative teams can ensure clear understanding from all parties as to the hopes for best case scenarios and preparations for the alternatives (16).

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