Emerging Treatment Options for the Management of Metastatic Colorectal Cancer

Presented by Dustin A. Deming, MD

ABSTRACT

An improved understanding of the molecular landscape of metastatic colorectal cancer (CRC) has opened the door for new treatment options. Clinicians should test for molecular alterations that predict resistance to epidermal growth factor receptor (EGFR) inhibitors, such as *KRAS* and *NRAS*, and additionally clinically actionable alterations, including *BRAF* V600 mutations, *HER2* amplification, *NTRK* fusions, and mismatch repair deficiency. Improved outcomes can be achieved with precision treatment strategies for the various CRC subtypes, although clinical features, such as tumor bulk and patient performance status, still help to guide treatment choice. Immune therapies have also produced impressive results in patients with mismatch repair–deficient/microsatellite instability–high tumors. These newer approaches were recently incorporated into the NCCN Guidelines for Colon and Rectal Cancers. In the future, these newer approaches may be used in earlier treatment settings.

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The treatment paradigm for metastatic colorectal cancer (CRC) has significantly changed in recent years. “It’s no longer just FOLFOX and FOLFIRI,” said Dustin A. Deming, MD, Associate Professor, Carbone Cancer Center at the University of Wisconsin, during his presentation on emerging treatment options for this malignancy at the NCCN 2020 Virtual Annual Conference.

Historically, for virtually all patients with metastatic CRC, treatment was initiated with cytotoxic chemotherapy independent of any molecular features of the tumor. Across the continuum of treatment, patients usually received FOLFOX (5-FU/leucovorin/oxaliplatin) and/or FOLFIRI (5-FU/leucovorin/irinotecan) ± bevacizumab and an agent targeting the epidermal growth factor receptor (EGFR). Salvage regimens included regorafenib, tipiracil, and trifluridine.

An improved understanding of the molecular profile of CRC made it clear, however, that “this is not one disease, and the molecular subtypes of CRC are important in guiding treatment strategies,” Dr. Deming said. Although many patients still receive conventional treatments in the first line, “for many patients we should think about other regimens, both in the first-line setting and potentially in the treatment-refractory setting,” he said. Examples are FOLFOXIRI (5-FU/leucovorin/oxaliplatin/irinotecan) + bevacizumab in earlier lines and, for patients deemed unsuitable for intensive cytotoxic chemotherapy, more targeted therapies and immunotherapies in some subsets of patients.

New treatment approaches for CRC take into account patient, clinical, and molecular features. “We need to know what mutations are present—which subtype of colon cancer we’re dealing with—because that will help us tailor better treatment strategies.”

It is now standard to test all metastatic tumors for *KRAS*, *NRAS*, and *BRAF* V600 mutations, *HER2* amplification, and microsatellite instability (MSI) or mismatch repair deficiency (dMMR). Many patients are also tested for *NTRK* fusions. Updates to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon and Rectal Cancers reflect the importance of these alterations and their targeted treatment.

dMMR/MSI-High Metastatic CRC

dMMR/MSI-high (MSI-H) cancers are a heterogeneous and rare subgroup, constituting approximately 3% of metastatic CRCs.¹ Testing for dMMR/MSI-H status can be performed easily and reliably by immunohistochemistry, which identifies common alterations and is standard of care in many centers. An alternative, the PCR test, is a stand-alone functional assay that is well-validated.

Increasingly, however, clinicians are opting to utilize next-generation sequencing panels to evaluate MSI status. These tests not only detect microsatellite alterations but can also provide information about the actual mutations occurring in the *MMR* genes. The drawback is that the validation of these tests is less robust than for the PCR microsatellite test.

dMMR/MSI-H tumors can have alterations in different *MMR* genes or proteins, can be germline or somatic, and can harbor “hundreds if not thousands” of mutations and fusions. “We think it’s the number of these alterations that gives rise to increased neoantigen load and potentially increases the benefit from immune-based therapy,” Dr. Deming said.

Several studies have documented encouraging outcomes in patients with treatment-refractory dMMR/MSI-H tumors treated with checkpoint inhibitors, including KEYNOTE-164 (single-agent pembrolizumab)² and CheckMate-142 (single-agent nivolumab and nivolumab + ipilimumab).³ Agents targeting PD-1 have become standard of care for patients with dMMR/MSI-H tumors.

“We may also be able to use these new therapies in the first-line setting,” he predicted. In a cohort of patients from the CheckMate-142 trial, upfront use of nivolumab/ipilimumab led to tumor reductions in 84% of patients and a 15-month progression-free survival (PFS) rate of 75%.⁴ Single-agent pembrolizumab also produced a robust benefit in patients with dMMR/MSI-H tumors in KEYNOTE-177,⁵ with a median PFS of 16.5 months versus 8.2 months with treatment of physician’s choice (hazard ratio, 0.60; $P=.0002$). “These are exciting data that indicate that we should use immunotherapy options for patients in the first-line setting with dMMR cancers,” Dr. Deming commented.

The phase III COMMIT trial is now evaluating modified FOLFOX6 + bevacizumab with or without the anti-PD-L1 agent atezolizumab versus atezolizumab alone in the first-line treatment of patients with dMMR tumors (ClinicalTrials.gov identifier: NCT02997228).

BRAF V600–Mutant CRC

BRAF V600–mutated tumors are right-sided predominant and have larger primaries. They are associated with *MMR* deficiency, high-grade peritoneal disease, and metastatic lymph node involvement. Historically, targeting *BRAF* became an exciting concept based on successes seen in melanoma. Although response rates to single-agent *BRAF* inhibitors in CRC are low, results of *BRAF* in combination with MEK or EGFR inhibitors have been more encouraging.

“Not all *BRAF* mutations are equal,” he said. The V600E mutation, which occurs in 8% to 10% of patients with CRC, accounts for 80% of *BRAF* mutations. Prognosis varies by mutation type: overall survival (OS) is poor for patients with V600E mutations, but for patients with non-V600E mutations, survival is comparable to those with *BRAF* wild-type tumors. The NCCN Guidelines state that chemotherapy should be the first-line choice for *BRAF* V600–mutated microsatellite-stable CRC.⁶ Although FOLFOX and FOLFIRI are standard, there is emerging interest in using FOLFOXIRI + bevacizumab, especially for the more challenging V600E-mutant tumors.

In the TRIBE study, FOLFOXIRI/bevacizumab was associated with a median PFS of 7.5 months compared with 5.5 months for FOLFIRI/bevacizumab, and OS was 19.0 versus 10.7 months, respectively.⁷ Recently, TRIBE-2 found median PFS to be 12.0 versus 9.8 months, respectively.⁸

In the BEACON trial,⁹ approximately 50% of patients responded to the triplet regimen of encorafenib/binimetinib/cetuximab, and median PFS was 8 months. These data led to an update to the NCCN Guidelines for patients with *BRAF* V600–mutated disease, although an update of that study concluded that binimetinib is not a necessary component.¹⁰ The doublet of encorafenib and either cetuximab or panitumumab is the new standard of care in this setting, yielding “dramatic improvements” over historical outcomes with second-line cytotoxic chemotherapy, according to Dr. Deming.

HER2-Amplified RAS/RAF Wild-Type CRC

HER2-amplified CRC, which is seen in approximately 5% of patients with metastatic disease, is a new subtype. Given promising treatment options for this subtype, the standard of care is to test all patients for *HER2* amplification and overexpression. This can be performed with *MMR* immunohistochemistry, *HER2* fluorescent in situ hybridization, and, increasingly, next-generation sequencing. Patients with ≥ 10 *HER2* copy numbers are eligible for anti-*HER2* agents, whereas those with levels < 8 are not likely to benefit.

The NCCN Guidelines for Colon and Rectal Cancers were updated to reflect the recommendation of 2 first-line regimens for patients with *HER2*-amplified, *RAS* wild-type tumors deemed unsuitable for intensive chemotherapy: pertuzumab + trastuzumab and trastuzumab + lapatinib. These recommendations are based on the robust and durable responses seen in the MyPathway study¹¹ and the HERACLES study.¹²

“It’s also reasonable to treat these patients with cytotoxic chemotherapy, and even with anti-EGFR agents, especially those with low-level amplification,” Dr. Deming added. SWOG 1613 will compare trastuzumab/pertuzumab with cetuximab/irinotecan in *HER2*-amplified metastatic CRC in patients with treatment-refractory disease and should help settle the issues of the optimal treatment of this population (ClinicalTrials.gov identifier: NCT03365882).

RAS/RAF/HER2 Wild-Type Microsatellite-Stable CRC

For “pan wild-type,” microsatellite-stable tumors, treatment selection can be informed by the location of the primary tumor, based on data from CALGB 80405¹³ and FIRE-3.¹⁴ Patients with left-sided primary tumors are much more likely to have prolonged survival and are

more likely to benefit from anti-EGFR therapy. Those with right-sided primaries are more likely to derive more benefit from bevacizumab than cetuximab in the first-line setting. “There are now data in the first-line and refractory settings that sidedness matters, and that anti-EGFR therapy should be largely reserved for those patients who have wild-type *KRAS*, *NRAS*, and *BRAF* mutations and left-sided primaries,” he said.

Dr. Deming and colleagues have shown that tumor bulk is important from the results of a study of 62 patients with *KRAS* wild-type tumors treated with anti-EGFR therapy. Patients with left-sided nonbulky tumors (no metastatic lesion >3.5 cm) had a median PFS of 7.2 months versus 3.5 months for the bulkier tumor cohort ($P=.001$) and median OS of 23.4 versus 6.0 months ($P<.001$).¹⁵ This suggests that patients with left-sided nonbulky wild-type disease may be best served with an anti-EGFR agent.

There is still debate regarding the best first-line regimen for *RAS/RAF/HER2* wild-type metastatic CRC, and the NCCN Guidelines list many options, which are stratified by whether the patient is suitable for intensive therapy. “My practice is typically to use FOLFOX + bevacizumab for most patients, and there are some settings where I think about using an anti-EGFR agent in the first-line,” Dr. Deming offered.

An attractive new concept for patients who respond to an anti-EGFR agent is to use anti-EGFR therapy again in the course of treatment. This paradigm would start with typical chemotherapy, moving to anti-EGFR as a single

agent in the next line of therapy, followed by more chemotherapy in the next line, and re-treating with an anti-EGFR drug after that. A number of studies have shown the potential for significant response in such patients.^{16,17}

NTRK Fusions

NTRK fusions occur in <0.5% of patients with metastatic CRC and are predictive of potential benefit to NTRK inhibitors, including larotrectinib and entrectinib. *NTRK* mutations, on the other hand, do not predict sensitivity, and these agents should not be prescribed for these patients.

Studies published in 2020 have confirmed that the “vast majority” of patients with NTRK fusions benefit from NTRK inhibitors.^{18,19} The question has thus become: Should all patients be tested?

“In CRC, given the rarity of this alteration, it doesn’t make sense to test specifically for NTRK fusions, but I do favor testing for them as part of a larger panel. It’s in the setting of testing for *KRAS*, *NRAS*, and *BRAF* that we could obtain this information,” Dr. Deming said.

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