

Expert Answers to Clinician Questions on Caring for Patients With Metastatic Colorectal Cancer

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The text below is adapted from expert answers to healthcare professionals' questions submitted as part of the program, "Opportunities and Challenges in Management of Metastatic Colorectal Cancer." To view downloadable slides associated with this program, please visit [here](#).

Genetic Testing

For a patient with Lynch syndrome, at what age would you counsel this family to do genetic testing on the patient's children?

This is an important question. Lynch syndrome is the most common form of hereditary colorectal cancer (CRC) and accounts for 2% to 4% of all CRC cases.^[Nolano 2022; Bhattacharya 2022] This is an autosomal dominant condition characterized by germline mutations in DNA repair genes, with tumors likely to be mismatch repair deficient (dMMR) and/or with high microsatellite instability (MSI-H). Lynch syndrome is associated with a younger age at cancer development, often younger than 50 years. In my clinic, if a patient with CRC has Lynch syndrome, we recommend that the patient's family members also undergo testing. In young children, this becomes a discussion between the parents, the children, and the genetic counselors; it is particularly important to discuss at what age children should be tested.

Current guidelines from the National Comprehensive Cancer Network (NCCN) recommend germline genetic testing for patients younger than 50 years of age at CRC diagnosis, and for patients with a strong family history.^[NCCN Genetic] The recommended surveillance for CRC and other cancer types depends on the specific hereditary syndrome. Experts recommend that in families known to have Lynch syndrome, family members positive for the mutation and those who have not been tested should begin colonoscopy screening early, either at ages 20-25 years or 2-5 years before the earliest Lynch cancer case in the family, whichever came first, for most Lynch syndrome mutations.^[cancer.org; NCCN Genetic] Additional cancer surveillance may be indicated at other anatomic sites.

How do you approach individuals with Lynch syndrome who are not yet showing disease?

It is very important to identify these patients and their family members who have Lynch syndrome. Lynch syndrome is associated with a high risk for CRC and other tumor types, including endometrial, ovary, stomach, small bowel, pancreas, biliary tract, bladder, prostate, and skin. In my clinic, we recommend periodic cancer screening by the time a patient is in their 20s with upper and lower endoscopy. Female patients should also be referred to a gynecologist to discuss endometrial cancer screening as well as potential risk-reducing hysterectomy and bilateral salpingo-oophorectomy. Screening for cancers of other organs should be discussed with patients on an individual basis.



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Treatment Selection

Would you recommend first-line treatment with bevacizumab or an EGFR inhibitor for a patient with newly diagnosed *HER2*-amplified metastatic CRC?

I typically recommend bevacizumab rather than an EGFR inhibitor in the setting of *HER2* amplification. Tumors with *HER2* amplification do not respond as well to EGFR inhibitors compared to tumors with wild-type *HER2*.^[Djaballah 2022] This is because EGFR inhibitors prevent ligand-induced EGFR tyrosine kinase activation by binding to the EGFR extracellular domain, causing cellular internalization and degradation of the receptor. However, *HER2* amplification and resulting overexpression can persistently activate ERK1/2 and other pathways downstream to EGFR, promoting growth and proliferation of malignant cells even in the presence of EGFR blockade.

What are contraindications to immune checkpoint inhibitor (ICI)-based therapy for patients with metastatic CRC?

ICIs are of great benefit in this setting, but are not for all patients.^[Nasca 2023] When considering a patient with CRC for an ICI, physicians must first determine if they have a history of autoimmune disease, chronic active immunosuppression (eg, chronic prednisone ≥ 10 mg/day or higher, which may reduce immunotherapy efficacy), or a history of prior organ transplant. The concern is that an ICI could markedly worsen baseline autoimmune disease or lead to rejection of the transplanted organ. The type, severity, and level of control of autoimmune disease will also influence the risk/benefit discussion; for example, hypothyroidism that is well controlled with oral medication would not be a contraindication, whereas extreme caution should be used when a potentially life-threatening autoimmune condition is present.

Another consideration regarding immunotherapy includes the risk of initial progression after starting therapy. For example, the phase III KEYNOTE-177 trial, which led to the approval of pembrolizumab in the first-line setting in patients with dMMR/MSI-H metastatic CRC, showed that the median progression-free survival (PFS) was nearly double with pembrolizumab compared to chemotherapy, at 16.5 vs 8.2 months, respectively (HR: 0.59).^[Diaz 2022; Pembrolizumab PI] However, 29.4% of patients treated with pembrolizumab had progressive disease as the best response to therapy, compared with 12.3% with chemotherapy. This is because it takes longer for the immune system to activate against the cancer. So, if a patient is highly symptomatic from cancer or could quickly develop complications, such as near complete bowel obstruction or liver failure secondary to extensive liver metastases, I would consider starting with chemotherapy/biologic therapy for a more rapid response. The patient could then be shifted to immunotherapy after a few months.

If a patient with CRC completes first-line treatment with an ICI more than 6 months before progressing, should they receive an ICI in the second-line setting?

I generally do resume ICI therapy in this situation, either with single or dual checkpoint blockade. Melanoma data indicate that we can obtain good responses when stopping and restarting the ICI, depending on the situation.^[Zaremba 2021] However, the bigger question is how long to continue ICIs in patients with responding disease. The clinical trials in CRC and other tumor types typically stopped ICIs after 2 years of treatment, but the optimal duration is unclear. In patients with a complete response, immunotherapy may be stopped earlier. Other patients with continued clinical benefit at the 2-year mark may choose to continue longer. In any case, after stopping an ICI, I would continue with surveillance.

Adverse Event Management

Would you consider changing the ICI schedule after resolution of low-grade colitis?

Yes. For example, I would consider switching to the more-frequent schedule of pembrolizumab every 3 weeks after a patient's colitis has resolved, in order to monitor more closely for side effects. However, if a patient is reliable and consistent in reporting side effects, I would consider continuing with treatment every 6 weeks to allow them more time between clinic visits.

The pharmacokinetics of immunotherapy are interesting because ICIs generally have very long half-lives of 2-4 weeks.^[Centanni 2019] This means that the drug will persist in the system for months after just 1 dose. In my experience, there is not a big difference in side effects between pembrolizumab dosed every 3 vs every 6 weeks, because ICIs do not cause cytotoxic DNA damage. Instead, they activate the body's immune system, which can produce more prolonged responses and more prolonged side effects.

When would you consider using octreotide to treat immune-related colitis?

Octreotide can be considered for refractory diarrhea related to chemotherapy, but it is not typically used for ICIs.^[Octreotide PI; Bossi 2018] NCCN guidelines focus on using loperamide and diet alteration for management of immune-related colitis across tumor types, reserving prednisone or other immunosuppressive medications for persistent or high-grade cases.^[NCCN IRAE] When faced with the need to augment steroid therapy for managing refractory diarrhea, I would prefer to escalate the immunosuppression with higher doses of steroids or adding a biologic, which is likely more effective, rather than adding octreotide.

When starting a patient on second-line trastuzumab and tucatinib for HER2-amplified metastatic CRC, what would you do to reduce the risk of side effects?

I discuss tucatinib-related side effects with the patient before starting therapy; these commonly include diarrhea, hepatic toxicity, hand-foot syndrome, and fatigue.^[Strickler 2022] It is reasonable to give prophylactic loperamide before starting therapy, because diarrhea is a very common side effect with this regimen.

I also discuss the potential for cardiotoxicity with HER2-targeted therapies. Risk factors for a reduction in ejection fraction with or without clinical symptoms include older age, prior or concurrent anthracycline (rare in CRC), preexisting cardiac dysfunction, and obesity. In my clinic, we recommend that patients have an echocardiogram before starting any HER2-directed treatments, with the echocardiogram potentially repeated during treatment. We do not know the optimal interval for echocardiograms during treatment in patients with metastatic CRC; most physicians follow these patients for clinical heart failure signs or symptoms and get an echocardiogram at that time, rather than periodically as is typically done in the adjuvant setting (eg, with breast cancer). It is reasonable to obtain echocardiograms regularly during HER2-targeted therapy, especially for patients who are at high risk.

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