# CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

Section Editor: Axel Grothey, MD

## Immunotherapy in Colorectal Cancer With Mismatch Repair Deficiency

Michael J. Overman, MD
Professor, Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

**H&O** Which immunotherapy agents have been approved for use in colorectal cancer (CRC) with mismatch repair deficiency (MMR-D)?

**MO** We have a choice of 3 drugs for patients in that category who have received standard chemotherapy and have refractory disease: pembrolizumab (Keytruda, Merck), nivolumab (Opdivo, Bristol-Myers Squibb), and ipilimumab (Yervoy, Bristol-Myers Squibb). Patients can receive monotherapy with pembrolizumab or nivolumab, or they can receive combination therapy with nivolumab and ipilimumab.

**H&O** How common is MMR-D in CRC?

**MO** MMR-D is seen in multiple tumor types and is fairly common in CRC. The rate is approximately 10% to 20% in stage I, II, or III CRC and 4% in stage IV CRC. One possible reason why MMR-D is less common in advanced disease is immune surveillance—the immune system is controlling these cancers, so they are less likely to become metastatic. Given the success of immunotherapy in patients with advanced disease, this hypothesis is probably correct.

**H&O** What makes tumors with MMR-D more likely to respond to immunotherapy?

**MO** Tumors with a deficiency in mismatch repair have a high level of mutations, and mutations can lead to novel changes in the amino acid sequence. If the sequence has never been seen by the person's immune system, it functions as if it's a foreign sequence—a neoantigen. Neoantigens are very well recognized by the immune system and tend to be the key drivers behind robust immune responses, and tumors with MMR-D have a lot of neoantigens because they have a lot of mutations.

**H&O** What is the best way to determine MMR status in clinical practice?

**MO** The classic approach is immunohistochemistry testing, which is a good, straightforward technique because the criterion is complete loss of staining, rather than a gradation. An additional advantage of immunohistochemistry testing is that the sample often contains normal cells, so you have a positive control. Another good approach is based on polymerase chain reaction (PCR), which works well in CRC; however, it is less effective in cancers other than CRC and in those with a low level of tumor cellularity. The newest approach is next-generation sequencing, which is similar to PCR in concept but looks at far more microsatellites—hundreds rather than 5 to 7. All 3 of these techniques are very good approaches in CRC.

**H&O** What are the latest findings from CheckMate 142?

**MO** The CheckMate 142 study (An Investigational Immuno-therapy Study of Nivolumab, and Nivolumab in Combination With Other Anti-cancer Drugs, in Colon Cancer That Has Come Back or Has Spread) contains a

number of different cohorts, including nivolumab monotherapy in patients with refractory disease and nivolumab plus ipilimumab in patients with refractory disease. At the 2018 European Society for Medical Oncology (ESMO) annual meeting, Dr Heinz-Josef Lenz presented a recent cohort of this study, in which 45 patients with metastatic MMR-D CRC received nivolumab plus ipilimumab as frontline therapy. Very good outcomes were achieved with this approach: a response rate of 60% and a 12-month progression-free survival rate of 77%. Although these are single-arm data, the high activity rate does suggest that dual immunotherapy is a frontline option for patients with MMR-D CRC.

**H&O** How about the latest findings from KEYNOTE-016?

**MO** An early report on pembrolizumab, which appeared in the *New England Journal of Medicine* in 2015, included patients with MMR-D CRC and patients with CRC that was microsatellite stable (MSS). The results of this report were dramatic because they showed a tremendous difference in activity between these 2 groups, which clearly indicated that the correct biomarker in CRC was MMR-D. In addition, the findings from a cohort of patients with MMR-D non-CRC within this study demonstrated a benefit of pembrolizumab across any tumor type that with MMR-D.

Enrollment continued after this initial report, and a subsequent report of KEYNOTE-016 (Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable Tumors) that appeared in *Science* in 2017, with Le as the first author, supported the robust outcome in MMR-D cancers, with a response rate of 53% and a complete response rate of 21%. In addition, KEYNOTE-164 (Phase II Study of Pembrolizumab for Patients With Previously Treated, Microsatellite Instability-High Advanced Colorectal Carcinoma) was initiated and verified a high level of clinical activity in the 124 enrolled patients with MMR-D CRC.

**H&O** What additional studies are looking at immunotherapy in CRC?

**MO** A number of ongoing phase 3 studies are looking at the use of immunotherapy earlier in treatment. The NRG-GI004/S1610 study (Combination Chemotherapy, Bevacizumab, and/or Atezolizumab in Treating Patients With Deficient DNA Mismatch Repair Metastatic Colorectal Cancer; NCT02997228), for example, is comparing 3 frontline treatments in patients with MMR-D metastatic CRC: the anti–programmed death ligand 1 (PD-L1) drug atezolizumab (Tecentriq, Genentech) alone, atezolizumab in combination with leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) and bevacizumab, and standard treatment with FOLFOX and bevacizumab. Another recently completed clinical trial is KEYNOTE-177 (Study of Pembrolizumab vs Standard Therapy in Participants With Microsatellite Instability-High or Mismatch Repair Deficient Stage IV Colorectal Carcinoma; NCT02563002), which is comparing pembrolizumab alone with FOLFOX/bevacizumab as frontline therapy in advanced MMR-D CRC. These studies are asking a key question: Do we use immune therapy in the first treatment for these patients?

**H&O** What studies are looking at the adjuvant use of immunotherapy in CRC?

**MO** The phase 3 Alliance A021502, or ATOMIC, trial (Combination Chemotherapy With or Without Atezolizumab in Treating Patients With Stage III Colon Cancer and Deficient DNA Mismatch Repair; NCT02912559) is looking at immunotherapy as adjuvant therapy in patients with MMR-D CRC. In this study, patients with MMR-D CRC receive either standard FOLFOX chemotherapy or FOLFOX plus atezolizumab. Although the study does not include an immunotherapy-only arm, we expect it to provide answers regarding whether this immunotherapy can be added to treatment in the adjuvant setting.

I would like to see us using immunotherapy earlier and in a greater number of patients, who often are able to tolerate single-agent anti–programmed death 1 (PD-1)/PD-L1 treatment better than chemotherapy. But for now, adjuvant immunotherapy should be used only in a clinical trial.

**H&O** How should oncologists go about choosing from among the various treatment options for patients with CRC?

**MO** We have a lot of data regarding pembrolizumab and nivolumab across multiple different tumor types. These agents seem to be very similar to each other in regard to activity, so little basis exists for choosing one over the other in a monotherapy approach. The bigger question is whether we should use single-agent immunotherapy or combination immunotherapy. Nivolumab/ipilimumab seems to achieve higher rates of response and progression-free survival when compared across trials with nivolumab or pembrolizumab, but it also causes more toxicity. Is that increased toxicity worthwhile? That depends on the effectiveness of the additional treatment. If combination treatment has the potential actually to cure people's cancer, considering whether to accept greater toxicity is very reasonable.

One area in which we do not have data is sequential therapy. What is the effect of using ipilimumab after an

initial PD-1 inhibitor? How does a sequential approach compare with a combinatorial approach?

Combination therapy is very reasonable and appropriate, and it may be possible to make it less toxic. For example, the CheckMate 142 clinical trial looked at different dosing schedules in the frontline nivolumab/ipilimumab combination cohorts; in one cohort, patients received ipilimumab every 6 weeks rather than every 3 weeks, which is the standard schedule. With this adjustment, the degree of toxicity appeared to be lower when the 2 nivolumab/ipilimumab cohorts were compared. For example, serious grade 3/4 treatment-related adverse events occurred in 20% of patients treated with ipilimumab every 3 weeks vs 7% of those treated with ipilimumab every 6 weeks.

### **H&O** What toxicities become more common with combination therapy?

**MO** We see increases in all the toxicities associated with immunotherapy—colitis, hepatitis, pituitary or thyroid dysfunction, skin reactions, and many others. The most serious immune toxicities that increase with the addition of ipilimumab are colitis and hepatitis.

### **H&O** Does tumor mutational burden affect the selection of immunotherapy?

**MO** Tumor mutational burden does not play a role in the selection of immunotherapy for patients with CRC because of the high degree of overlap with the existing biomarker of MMR-D. As a result, tumor mutational burden in theory has the potential to come into play for patients who have MSS tumors and normally would not receive immunotherapy. Could tumor mutational burden identify a subset of patients with MSS tumors that might be responsive to immunotherapy? At present, we have no clinical evidence to support this idea. Fundamental issues appear to exist that prevent immunotherapy from working in an MSS population.

The only caveat to this rule is the subset of patients called hypermutators; these patients have a mutation in polymerase epsilon and an exceptionally high mutation rate. Preliminary data suggest that in this subset of patients CRC is responsive to immunotherapy. Such tumors are best identified by testing for mutations in polymerase epsilon that are seen in conjunction with a very high tumor mutational burden.

### **H&O** What should researchers focus on going forward?

**MO** We need to learn more about the subset of patients whose tumors do not respond to immunotherapy despite having MMR-D. What are the mechanisms of resistance in these cases? This is an active area of research. As we get more answers to this question over the next year or two, I think we will be able to begin the next wave of trials testing novel treatment combinations.

***Disclosure***

*Dr Overman has received research funding from Roche, Bristol-Myers Squibb, MedImmune, Celgene, Idera Pharmaceuticals, Nektar Therapeutics, Gritstone Oncology, and Merck, and has done consulting for Roche, Bristol-Myers Squibb, MedImmune, Merck, Amgen, Gritstone, Novartis, and Array BioPharma.*

## Suggested Readings

André T, Londardi S, Wong M, et al. Nivolumab + ipilimumab combination in patients with DNA mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer (mCRC): first report of the full cohort from CheckMate-142 [ASCO abstract 553]. *J Clin Oncol.* 2018;36(4)(suppl).

ClinicalTrials.gov. Combination chemotherapy, bevacizumab, and/or atezolizumab in treating patients with deficient DNA mismatch repair metastatic colorectal cancer. https://clinicaltrials.gov/ct2/show/NCT02997228. Identifier: NCT02997228. Accessed January 18, 2018.

ClinicalTrials.gov. Phase 2 study of MK-3475 in patients with microsatellite unstable (MSI) tumors. https://clinicaltrials.gov/ct2/show/NCT01876511. Identifier: NCT01876511. Accessed February 25, 2019.

ClinicalTrials.gov. Study of pembrolizumab (MK-3475) vs standard therapy in participants with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) stage IV colorectal carcinoma (MK-3475-177/KEYNOTE-177). https://clinicaltrials.gov/ct2/show/NCT02563002. Identifier: NCT02563002. Accessed January 18, 2018.

Diaz LA, Le DT, Yoshino T, et al. KEYNOTE-177: Phase 3, open-label, randomized study of first-line pembrolizumab (Pembro) versus investigator-choice chemotherapy for mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal carcinoma (mCRC) [ASCO GI abstract TPS877]. *J Clin Oncol.* 2018;36(4)(suppl).

Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science.* 2017;357(6349):409-413.

Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med.* 2015;372(26):2509-2520.

Le DT, Yoshino T, Jäger D, et al. KEYNOTE-164: Phase II study of pembrolizumab (MK-3475) for patients with previously treated, microsatellite instability-high advanced colorectal carcinoma [ASCO abstract TPS787]. *J Clin Oncol. 2016;*34(15)(suppl).

Lenz H-J, Van Cutsem E, Limon ML, et al. Durable clinical benefit with nivolumab plus low-dose ipilimumab as first-line therapy in microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer [ESMO abstract LBA18]. *Ann Oncol.* 2018;29(8)(suppl).

Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol.* 2018;36(8):773-779.

Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol.* 2017;18(9):1182-1191.

Sinicrope FA, Ou F-S, Shi Q, et al. Randomized trial of FOLFOX alone or combined with atezolizumab as adjuvant therapy for patients with stage III colon cancer and deficient DNA mismatch repair or microsatellite instability (ATOMIC, Alliance A021502) [ASCO abstract TPS3630]. *J Clin Oncol.* 2017;35(15)(suppl).