Immunotherapy in Colorectal Cancer With Mismatch Repair Deficiency

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**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 mono-
thecy 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 dif-
ference 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 Pre-
viously 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, Beva-
cizumab, 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 Par-
cicipants With Microsatellite Instability-High or Mis-
match 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 treat-
ment 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 Atezoli-
zumab 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 combina-
tion 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 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 and an exceptionally high 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.

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Suggested Readings


Diaz LA, Le DT, Yoshino T, et al. KEYNOTE-177: Phase 3, open-label, randomized trial of first-line pembrolizumab (Pembrolizumab) versus investigator-choice chemotherapy for mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal carcinoma (mCRC) [ASCO CI abstract TPS875]. J Clin Oncol. 2018;36(4)(suppl).


Sicincipe 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).