FDA Approval Likely to Change Initial Treatment for Some People with Advanced Colorectal Cancer

The approval was based on updated findings from a large clinical trial called CheckMate-8HW.

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The Food and Drug Administration (FDA) has approved the combination of two immunotherapy drugs for the initial treatment of some people with advanced colorectal cancer. The approval is for the use of nivolumab (Opdivo) and ipilimumab (Yervoy) for people whose tumors are classified as MSI-H or dMMR.

About 5% of people with advanced colorectal cancer have MSI-H or dMMR tumors, which means the tumors are unable to properly repair certain types of DNA damage that can occur during cell division. Several colorectal cancer experts said the approval should immediately make the combination the preferred initial, or first-line, treatment for people with advanced MSI-H or dMMR colorectal cancer.

The approval was based on updated findings from a large clinical trial, called CheckMate-8HW in which all participants had advanced colorectal cancer with MSI-H or dMMR tumors. Patients in the trial who were treated with the combination of nivolumab and ipilimumab lived substantially longer without their cancer getting worse, a measure known as progression-free survival, than patients treated with nivolumab alone.

At 3 years after starting treatment, approximately 68% of patients in the combination group were still alive without their cancer having gotten worse, compared with 51% of the nivolumab-alone group.

Nivolumab is already approved as a standalone initial treatment for people with MSI-H or dMMR tumors, but “it’s now clear that there’s a benefit” to combining it with ipilimumab, said Carmen Allegra, M.D., special advisor on gastrointestinal therapeutics in NCI’s Division of Cancer Treatment and Diagnosis.

Potential cures, increased side effects

Cancer cells are in a constant state of cell division and growth. The DNA repair–defective cancer

cells in MSI-H or dMMR tumors tend to produce abnormal proteins that make the immune system more likely to recognize and attack them.

But tumors have ways of shielding themselves from this assault. Drugs like nivolumab and ipilimumab, known as immune checkpoint inhibitors, can help immune cells overwhelm this protection.

The immune checkpoint inhibitor pembrolizumab (Keytruda) is also already approved as an initial treatment for people with advanced colorectal cancer that is MSI-H or dMMR. But several studies have shown that less than half of patients have long-lasting tumor responses to nivolumab or pembrolizumab when used alone.

In CheckMate-8HW, which was funded by the drugs' manufacturer, Bristol Myers Squibb, more than 800 participants were randomly assigned to one of three treatment groups: nivolumab plus ipilimumab; nivolumab alone; or chemotherapy, possibly along with a targeted therapy.

The trial's initial results showed that people treated with the immunotherapy combination had better progression-free survival than those treated with chemotherapy, regardless of whether the chemotherapy was given with a targeted therapy.

Oncologists, however, had been waiting to see how the nivolumab–ipilimumab combination fared in comparison with nivolumab alone, including whether there were major differences in serious side effects.

Participants randomly assigned to treatment with the nivolumab–ipilimumab combination received both drugs for 4 months and then nivolumab alone (at a higher dose than the initial dose) until their cancer started to progress. Those assigned to the nivolumab-alone group took the drug at the lower initial dose for 4 months and the higher dose after that.

The improvement in progression-free survival in people treated with both immunotherapy drugs was impressive and clinically important, wrote Scott Kopetz, M.D., Ph.D., and S. Daniel Haldar, M.D., of the University of Texas MD Anderson Cancer Center, in an editorial that accompanied the updated results.

For many patients in the trial, the length of time that their cancer has been kept in check "potentially represents [a] cure."

Not enough time has gone by for the researchers to determine whether there will be a substantial improvement in how long people in the combination treatment group live overall. But, based on the progression-free survival results, that's likely to happen, said Christopher Lieu, M.D., who specializes in treating colorectal cancer at the University of Colorado Cancer Center but was not involved in the trial.

"When more effective [treatment] regimens are used in the first-line setting, we should expect to see an overall survival benefit," Dr. Lieu said.

Patients treated with the combination had more serious side effects than those who took nivolumab alone (22% versus 14%) and stopped treatment altogether more often because of side effects (14% versus 6%). And there were two treatment-related deaths in the combination treatment group and one in the nivolumab-alone group.

“This is why having a good discussion about the risks and benefits [of the combination treatment] with our patients is so critical,” Dr. Lieu said.

The need for proper tumor testing for MSI-H/dMMR

Drs. Kopetz and Haldar also stressed the importance of proper tumor testing for MSI-H/dMMR status.

People were enrolled in the CheckMate-8HW trial based on the results of testing performed at their local hospital at the time of their diagnosis. Those results were then confirmed by experts at a single “central laboratory.”

The results from the tests performed at participants’ local hospitals were often incorrect, so some patients were enrolled in the trial who should not have been. (The trial results on which the approval was based included only those patients whose testing results were confirmed by the central laboratory.)

Drs. Kopetz and Haldar encouraged clinicians to follow recent international guidelines on MSI-H and dMMR testing, which, they wrote, call for using “two testing methodologies and referral to an expert diagnostic center in cases of uncertainty.”

The treatment improvements for patients with MSI-H or dMMR tumors have been exciting to see, Dr. Lieu said. A critical next step is to find ways to make immunotherapy more effective for the many patients whose tumors lack these defects.

On that front, he said, “there’s still a lot of work that needs to be done.”

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