Keytruda May Help Prevent Early-Stage Melanoma from Returning

Patients with high-risk Stage II melanoma received Keytruda (pembrolizumab) after surgery to remove their original tumor.

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Some people with early-stage melanoma who have undergone surgery to remove their tumors may soon have a new treatment option to reduce the risk of their disease coming back.

In a large clinical trial, patients who received the immunotherapy drug pembrolizumab (Keytruda) after surgery were less likely to have the cancer come back over the next 14 months than those who received no treatment after surgery. Post-surgical, or adjuvant, treatment with pembrolizumab also lowered the risk of the melanoma recurring in other parts of the body, a significant concern with this form of skin cancer.

The nearly 1,000 patients in the trial, called KEYNOTE-716, had melanoma that had been classified as either stage IIB or stage IIC. In people with stage IIB or IIC melanoma, also known as high-risk stage II melanoma, the disease has penetrated the skin but has not spread elsewhere in the body. The findings were presented September 18 at the European Society for Medical Oncology (ESMO) Congress 2021.

“These data suggest that adjuvant pembrolizumab is an effective treatment option with a favorable benefit–risk profile for patients with high-risk stage II melanoma,” said lead investigator Jason Luke, M.D., of the University of Pittsburgh Medical Center Hillman Cancer Center, during the presentation.

“The results could potentially represent a new standard of care in this group of patients with stage IIB or IIC melanoma,” said Janice M. Mehnert, M.D., an oncologist at NYU Langone’s Perlmutter Cancer Center, which was one of the sites in the trial. But she cautioned that it’s still too early to tell whether pembrolizumab should be prescribed broadly for people with high-risk stage II melanoma.

“We really need to figure out which of the patients are actually going to benefit from a therapy like this, because the [side effects] are not trivial” she said.

The Case for Pembrolizumab

Pembrolizumab is one of several immunotherapy drugs called immune checkpoint inhibitors. The drug works by preventing a protein on immune cells, called PD-1, from binding to a protein on cancer cells, called PD-L1. In doing so, the treatment restores the immune system's ability to recognize and kill tumor cells.

In a previous trial, researchers showed that people with more advanced stage III melanoma who were treated with pembrolizumab after surgery lived longer without their cancers coming back or metastasizing to other parts of the body than people given a placebo. In 2019, the Food and Drug Administration (FDA) approved pembrolizumab as an adjuvant treatment for people with stage III melanoma.

Dr. Luke noted that the risk of cancer returning after surgery in people with stage IIB or IIC melanoma is the same as that of stage IIIA and IIIB disease. But there have been no proven treatments for preventing recurrences of high-risk stage II disease.

Past studies showed that a drug called interferon-α could modestly reduce the risk of recurrence but, given the limited benefit and interferon-α's substantial side effects, it is no longer recommended by professional medical guidelines. Currently, people with high-risk stage II melanoma are not given any treatment after surgery.

"If these patients had stage III melanoma, you would for sure give them adjuvant treatment," said Dr. Luke.

"We need to rethink what constitutes high risk … and how we stratify patients," Dr. Luke continued. "These patients [with stage IIB and IIC melanoma] are at high risk and their cancers [can] recur rapidly. They deserve to be treated."

Reducing the Risk of Recurrence

The trial enrolled 976 patients aged 12 and older who had undergone surgery for stage IIB or stage IIC melanoma. Participants were randomly assigned to receive either pembrolizumab or placebo for a year, or until their cancer came back or they could no longer tolerate the treatment because of side effects. The trial was funded by Merck, which manufactures pembrolizumab.

After a median of 14.4 months, 11.1% of the patients in the pembrolizumab group had experienced a recurrence of their cancer, compared with 16.8% of those given the placebo. Patients treated with pembrolizumab were also much less likely to have their cancer come back, either on the skin or in the nearby lymph nodes (locoregional) or much further away in the body (distant).

Treatment group	Overall recurrences	Locoregional recurrences	Distant recurrences
Pembrolizumab	11.1%	6.4%	4.7%
Placebo	16.8%	8.4%	7.8%

In melanoma, Dr. Luke said, many recurrences “are actually distant recurrences, in the liver, lungs, etc.” So it was particularly noteworthy that treatment with pembrolizumab led to fewer distant recurrences, he said.

“That’s what we’re trying to do. We’re trying to keep people from [developing] metastatic cancer.”

More than one-third of the patients treated with pembrolizumab experienced mild side effects, including hypothyroidism, hyperthyroidism, diarrhea, nausea, fatigue, and rash. Within the group receiving pembrolizumab, 18.6% had thyroid problems that were severe enough to need hormone supplementation.

Richard W. Joseph, M.D., an oncologist at the Mayo Clinic in Jacksonville, Florida, who was not involved in the trial, said that the results of the KEYNOTE-716 trial are encouraging. But the real test, Dr. Joseph stressed, will be how long patients live overall.

“When we have [data showing] overall survival that’s significantly improved, I think that would certainly make a better case for this and make you want to prescribe it more broadly,” he said.

Which Patients Will Benefit?

The use of pembrolizumab as an adjuvant therapy for people with stage IIB or IIC melanoma is currently under priority review by FDA. Dr. Joseph said that if the drug is approved for this use, doctors will need to talk with their patients with stage II melanoma about the potential risks and benefits of taking pembrolizumab after surgery.

Studies are still needed to identify ways to distinguish which patients with high-risk stage II melanoma will respond to pembrolizumab, Dr. Mehnert said, including blood-based and tumor-based biomarkers.

Further study is also needed, she added, to learn how long patients should take pembrolizumab, which in this study was a year.

“Do we really need to give a year of therapy? We’ve adopted that schedule because [patients in] adjuvant trials historically have gotten a year of therapy, but I’ve seen people [develop serious side effects] at some of the later doses,” she said. “Patients developing type I diabetes is extremely rare, but it happens. And that, to me, is one of the most devastating side effects of immunotherapy.”

That’s why it will be important to see if a shorter period of adjuvant treatment can be given without jeopardizing the benefit of reduced recurrence risk, she said.

Despite the unknowns, Dr. Luke said that just having an additional treatment option will help some patients. “In my conversations with patients, the risk of recurrence and metastasis is a significant psychological morbidity that they carry with them, and so being able to address that has value,” he said.

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