Keytruda Provides First-Ever Overall Survival Improvement in Kidney Cancer

The drug is now part of an important milestone in the treatment of kidney cancer.

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The immunotherapy drug pembrolizumab (Keytruda) has rapidly become one of the most widely used cancer treatments. Based on updated results from a large clinical trial, the drug is now part of an important milestone in the treatment of kidney cancer—specifically, clear-cell renal cell carcinoma, the most common form of the disease.

All participants in the trial had earlier-stage kidney cancer and their tumors could be removed with surgery, but they were also at increased risk of their cancer coming back, or recurring. So after undergoing surgery, they were randomly assigned to get pembrolizumab for up to a year or a placebo and routine monitoring.

At 4 years after starting the post-surgical treatment, about 91% of people given pembrolizumab were still alive, compared with 86% of those who received a placebo, according to results published April 17 in the New England Journal of Medicine. Overall, people who received pembrolizumab had a nearly 40% reduced risk of dying during that period.

The findings mark the first time a post-surgical, or adjuvant, treatment for kidney cancer has been shown to help people live longer.

Based on earlier results from this trial, called KEYNOTE-564, the Food and Drug Administration (FDA) approved pembrolizumab in 2021 as an adjuvant treatment for kidney cancer. At the time of the approval, the trial had only gone on long enough to show an improvement in how long people lived without their cancer returning.

But even with the approval, many oncologists haven't been using pembrolizumab routinely as an adjuvant treatment in their higher-risk patients, explained Martin Voss, M.D., and Robert Motzer, M.D., of Memorial Sloan Kettering Cancer Center, in an editorial that accompanied the updated findings.

Instead, they've been waiting to find out whether the treatment improves how long people live overall, Drs. Voss and Mosser wrote. With that question now answered, they continued, "the anticipated effect" on the everyday care of patients "cannot be overstated."

Some experts, however, anticipate a measured change in treatment. “It’s not going to be a total paradigm shift,” said Mark Ball, M.D., of NCI’s Center for Cancer Research, who specializes in treating kidney cancer.

In part, that’s because the updated findings also show that many patients appear to do very well with surgery alone, Dr. Ball said. Giving all patients who meet the approval criteria an expensive drug that can have serious side effects, he continued, would clearly be “overtreatment.”

So from a research perspective, he said, the next steps are clear: “We have to get smarter about identifying who is at the highest risk of recurrence.”

Looking for answers to the overall survival question

Many people with earlier-stage kidney cancer are cured with surgery. But the cancer will return in up to 50% of people, most often those whose cancer has certain high-risk characteristics. Those characteristics include the presence of cancer in the lymph nodes nearest to the tumor or having tumor cells with what are called sarcomatoid features.

Adjuvant therapy is used in many early-stage cancers that can be treated with surgery. It serves as an insurance policy of sorts, reducing the chances of the cancer coming back by killing any cancer cells missed by surgery or that had already escaped from the tumor before surgery.

Until now, only a single adjuvant therapy for kidney cancer has been available: the targeted therapysunitinib (Sutent), which was approved by FDA for this use in 2017.

That approval was based on one clinical trial in which adjuvant sunitinib improved disease-free survival. But the improvement came with severe side effects, and there’s no evidence that the treatment helps people live longer, Dr. Ball explained.

As a result, Dr. Ball said, “sunitinib is really never prescribed” for this use.

In the absence of an adjuvant therapy that’s proven to help people with earlier-stage kidney cancer live longer, many patients only get routine monitoring, or surveillance, afterward.

So oncologists have been especially eager to see if, with more time having passed, the promising recurrence-free survival with pembrolizumab in the KEYNOTE-564 trial translated into longer overall survival.

Improved survival at 2, 3, and 4 years

Nearly 1,000 people participated in KEYNOTE-564, which was funded by Merck, pembrolizumab’s manufacturer. All were at increased risk of their cancer coming back after surgery. Participants assigned to pembrolizumab took the drug every 3 weeks for up to 1 year.

More people in the pembrolizumab group were alive at every time point measured in the study, not just at the 4-year mark.

People in the pembrolizumab group also continued to live longer without their cancer returning. At 4 years, 65% of people in the pembrolizumab group had not had a recurrence, compared with 57% in the placebo group.

The findings represent “a clinically meaningful survival improvement,” said the trial’s lead investigator, Toni Choueiri, M.D., of Dana-Farber Cancer Institute in Boston, during a presentation of the results at the 2024 ASCO Genitourinary Cancer Symposium in January.

As was expected, Dr. Choueiri noted, more people in the pembrolizumab group had treatment-related side effects, including those like fatigue and rash that are commonly seen in people treated with the drug.

Overall, about 20% of people in the pembrolizumab group had serious side effects, and 21% stopped treatment early because of side effects (as did 2% of those in the placebo group).

A major shift in treating early-stage kidney cancer?

More people with early-stage RCC should now get pembrolizumab after surgery, said Pedro Barata, M.D., of the Seidman Cancer Center in Cleveland, who specializes in treating kidney cancer, at the ASCO Genitourinary Cancer Symposium.

Dr. Barata said he generally recommends adjuvant therapy with pembrolizumab to his patients at a particularly elevated risk of the cancer returning, which he assesses using a recurrence risk model for kidney cancer.

Most patients will only have mild side effects from the treatment, he continued. But “some patients will have significant side effects,” and the treatments used to manage those side effects have their own side effects.

So oncologists need to discuss the potential improvements in survival versus the impact of potential side effects, Dr. Barata continued.

“We [must] take into consideration quality of life, patient preferences, and even availability of the drug in some circumstances,” he said. “However, I would argue that [now] the scales favor adjuvant pembrolizumab.”

Dr. Ball agreed. Unlike with some other cancers for which pembrolizumab is a standard treatment, however, there are no tumor or blood markers (biomarkers) that single out patients whose cancer is most likely to respond to the drug.

So for the time being, he continued, oncologists should rely on well-established risk factors to

guide their decision making and treatment recommendations to their patients.

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