More Immunotherapy Options Approved for Treating Endometrial Cancer

FDA approves Imfinzi, Keytruda and Jemperli for some advanced endometrial cancers. All three drugs are immune checkpoint inhibitors.

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By Sharon Reynolds

The Food and Drug Administration (FDA) has approved three new immunotherapy options for people with advanced endometrial cancer. The approvals are for drugs called immune checkpoint inhibitors.

The first approval, announced on June 14, is for durvalumab (Imfinzi) given in combination with chemotherapy to treat people with advanced endometrial cancer whose tumors have certain genetic changes that cause them to have a characteristic known as mismatch repair deficiency (dMMR). Tumors that are dMMR are particularly susceptible to immunotherapy.

The second approval, announced on June 17, is for pembrolizumab (Keytruda) given along with chemotherapy, regardless of whether tumors are dMMR. And on August 1, FDA approved dostarlimab (Jemperli) plus chemotherapy for people with advanced endometrial cancers regardless of dMMR status. Dostarlimab had previously been approved, in 2023, for advanced endometrial cancers that are dMMR.

Under the approvals, the combinations can be used as an initial therapy or as treatment for cancer that has come back after certain previous treatments.

In large clinical trials, the addition of these immunotherapy drugs to chemotherapy led to improvements in progression-free survival, which is how long people live without their cancer growing.

The most recent data from the clinical trial that led to the dostarlimab approval, called RUBY, showed that it improved overall survival for people with dMMR tumors and suggested it may improve it for people whose tumors are not dMMR.

“The fact that three clinical trials strongly confirmed that adding an immune checkpoint inhibitor

to standard chemotherapy markedly improves outcomes for patients with mismatch repair–deficient endometrial cancer is a huge step forward," said Elise Kohn, MD, of NCI's Division of Cancer Treatment and Diagnosis, who was involved with the trial that led to pembrolizumab's approval for this use.

"For people with mismatch repair–deficient endometrial cancer, the data demonstrate unequivocally that the addition of an immune checkpoint inhibitor to standard chemotherapy is beneficial," regardless of which drug is used, Dr. Kohn said.

Most people with endometrial cancer, however, do not have dMMR tumors, said Shannon Westin, MD, of the University of Texas MD Anderson Cancer Center, who led the durvalumab trial.

And although both pembrolizumab and dostarlimab have been found to improve progression-free survival in people with these so-called proficient MMR (pMMR) tumors, Dr. Westin continued, the improvements are "not as profound" as they are in people with dMMR tumors.

This means that the decision to use either drug in people with advanced pMMR endometrial cancer is less straightforward, Dr. Westin explained, noting that researchers are trying to find ways to identify which people with pMMR tumors might be the best candidates to get one of these drugs.

Long treatment, long tumor responses

When endometrial cancer is found early, it can often be cured with surgery alone or surgery followed by radiation or chemotherapy. However, the prognosis is poor for people with endometrial cancer that has spread (metastasized) or returned after initial treatment.

FDA had already approved pembrolizumab and dostarlimab to be used alone to treat people with advanced dMMR endometrial cancer that worsened after initial chemotherapy. The approvals were based on clinical trials in which both drugs improved progression-free survival.

Those positive results led researchers to test these drugs as part of the initial treatment of people with advanced endometrial cancer.

The durvalumab trial—called DUO-E and funded by AstraZeneca, the drug's manufacturer—enrolled more than 700 people with advanced endometrial cancer. The pembrolizumab trial—called NRG-GY018 and funded by NCI and Merck, which manufactures the drug—enrolled more than 800.

In both of those trials, participants were randomly assigned to receive the immunotherapy drug along with chemotherapy for 6 months or to chemotherapy only. And in all three trials, those assigned to the immunotherapy drug continued to receive it alone as maintenance therapy: for up to 2 years in NRG-GY018, up to 3 years in RUBY, and for as long as the drug kept their cancer in check in DUO-E. All three trials included people with dMMR and pMMR tumors.

In the trials, people with dMMR tumors treated with immunotherapy and chemotherapy had substantially longer progression-free survival than those treated with chemotherapy alone. But, thus far, not enough people in the immunotherapy groups have had their cancer start to get worse for researchers to determine precisely how much better.

More than half of the participants who received immunotherapy in the trials experienced at least one serious side effect. The most common severe side effects were drops in blood cell counts, fatigue, gastrointestinal problems, and neuropathy.

Anywhere from 13% to 20% of participants in the immunotherapy groups in the trials stopped treatment because of side effects.

Making immunotherapy work for more people with endometrial cancer

It's unlikely that the three immunotherapy drugs now approved for advanced dMMR endometrial cancer will ever be compared against each other in clinical trials, Dr. Westin said.

"But for patients with dMMR [tumors], we currently believe the best therapy is standard [chemotherapy] plus one of these three [immunotherapy] drugs," Dr. Kohn noted.

Factors such as differing side effects, insurance coverage, and how often people need to come into the hospital for an infusion will all likely play a role in selecting which of the drugs an individual patient gets, Dr. Westin explained.

Several key questions remain about how best to use immunotherapies in people with endometrial cancer, Dr. Westin said. One is how long maintenance therapy should last.

"It's clear that some maintenance is needed," she said. But side effects can make it hard for people to stay on the drugs for long periods. And getting the treatment requires regular trips to a medical facility every few weeks for infusions, she continued, so "it's a big investment of time."

Currently, it's unclear whether stopping at 2 years (or sooner) is sufficient to permanently keep the cancer at bay, or whether that would increase the risk of a recurrence, she explained.

"Perhaps the other most pressing question facing researchers is whether there are ways to make immunotherapy work better in people with pMMR tumors," said Dr. Kohn.

The underlying biology of pMMR tumors can vary among patients, she explained. It's likely that there are different subgroups of pMMR endometrial cancer and each could be treated in different ways. In an ongoing analysis of participants in NRG-GY018, researchers are looking for molecular clues for which pMMR tumors may be most sensitive to immunotherapy and which patients should probably skip it entirely, she added.

Researchers are also looking at whether combining immune checkpoint inhibitors with other treatments, including targeted therapies, could make pMMR tumors more vulnerable to the immunotherapy, Dr. Westin said.

“There’s a lot going on to help improve [effectiveness] in that pMMR group,” she said.

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