FDA Approves Two First-Line Immunotherapies for Endometrial Cancer

Immune checkpoint inhibitors Keytruda and Imfinzi delayed disease progression in Phase III trials.

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The Food and Drug Administration (FDA) has approved two immune checkpoint inhibitor regimens as initial treatment for people with advanced or recurrent endometrial cancer. Merck's Keytruda (pembrolizumab) and AstraZeneca's Imfinzi (durvalumab) both led to improvement in progression-free survival when added to standard chemotherapy in Phase III trials.

Endometrial cancer, which develops in the lining of the uterus, is among the most common gynecological cancers worldwide, and its incidence is on the rise. About 68,000 new cases of uterine cancer will be diagnosed in the United States this year, according to the American Cancer Society.

Immunotherapy helps the immune system fight cancer. Keytruda is a monoclonal antibody that targets PD-1, a receptor on T cells that suppresses immune function. Imfinzi blocks PD-L1, its binding partner on tumors. Checkpoint inhibitors that interfere with the interaction between PD-1 and PD-L1 can release the brakes and restore T-cell activity against cancer.

Normal cells can detect and repair mistakes that arise when DNA is copied during cell division. But some tumors—known as mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H)—lack this mechanism, meaning mutations can accumulate and allow cells to grow out of control. Tumor genomic testing for these biomarkers can help predict whether checkpoint inhibitors are likely to work.

Keytruda plus chemotherapy is now approved as first-line therapy for advanced or recurrent endometrial carcinoma regardless of MMR or MSI status. It was already approved for previously treated endometrial cancer and for any dMMR or MSI-H solid tumors without satisfactory treatment options, so the FDA has broadened the indication. Imfinzi plus chemotherapy is now approved as an initial treatment for advanced or recurrent dMMR endometrial cancer only. Last year, the FDA approved Jemperli (dostarlimab), another PD-1 checkpoint inhibitor, as the first frontline immunotherapy for dMMR or MSI-H endometrial cancer.

Keytruda

The new Keytruda approval is supported by the Phase III KEYNOTE-868 trial (NCT03914612), which enrolled 810 patients with Stage III or IV or recurrent endometrial cancer, including 222 with dMMR tumors and 588 with mismatch repair proficient (pMMR) cancer. They were randomly assigned to receive Keytruda or a placebo every three weeks plus paclitaxel and carboplatin chemotherapy for six cycles, followed by Keytruda or the placebo alone every six weeks for up to 14 cycles. All study medications were administered by intravenous infusion.

In the dMMR cohort, the median progression-free survival (PFS) time was 6.5 months in the placebo group but not reached in the Keytruda group because a majority of patients were still responding, reflecting a 70% reduction in the risk of disease progression or death. In the pMMR cohort, median PFS times were 8.5 months in the chemotherapy group and 11.1 months in the Keytruda group (a 40% reduction). Overall survival data were immature at the time of the analysis.

Treatment was generally safe, but side effects were common. Adverse events were generally similar to those previously reported for Keytruda and chemotherapy, but skin rash was more common; 14% discontinued Keytruda due to adverse reactions.

“The addition of pembrolizumab to chemotherapy represents a new frontline therapeutic option for patients with primary advanced or recurrent endometrial carcinoma, demonstrating a statistically significant and clinically meaningful progression-free survival benefit compared to chemotherapy alone, regardless of mismatch repair status,” study investigator Ramez Eskander, MD, of University of California San Diego Health, said in a Merck news release.

Click here for full prescribing information for Keytruda, including adverse reactions, warnings and precautions.

Imfinzi

The new Imfinzi approval is supported by the Phase III DUO-E trial (NCT04269200), which enrolled 699 patients with advanced or recurrent endometrial cancer stratified by MMR biomarker status. Some participants were randomized to receive Imfinzi or a placebo every three weeks plus paclitaxel and carboplatin for up to six cycles, followed by Imfinzi or the placebo alone every four weeks until disease progression; other patients were assigned to a different investigational combination regimen.

People who received Imfinzi saw a significant improvement in progression-free survival overall, but this was mainly driven by patients with dMMR cancer. Among the 95 people with dMMR tumors, the median PFS time was 7.0 months in the placebo group but not reached in the Imfinzi group, reflecting a 58% reduction in the risk of disease progression or death. Again, overall survival data were immature.

Here, too, treatment was generally safe, but side effects were common and consistent with those previously reported for Imfinzi and chemotherapy.

“With the incidence and mortality of endometrial cancer expected to continue to increase significantly in the coming decades, it is more important than ever that we bring new treatment options to patients at the earliest possible moment in their care,” study investigator Shannon Westin, MD, of the University of Texas MD Anderson Cancer Center, said in an AstraZeneca news release. “This approval underlines clear evidence that durvalumab plus chemotherapy followed by durvalumab monotherapy delivers important clinical benefits for patients with mismatch repair-deficient endometrial cancer.”

Click here for full prescribing information for Imfinzi, including adverse reactions, warnings and precautions.

Click here for more news about endometrial cancer.
