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Checkpoint Immunotherapy Delays Endometrial Cancer Progression

Both Jemperli and Keytruda improved progression-free survival in late-stage clinical trials.

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Two PD-1 checkpoint inhibitors, Jemperli (dostarlimab) and Keytruda (pembrolizumab), reduced the risk of disease progression or death for patients with advanced endometrial cancer when added to standard chemotherapy, researchers reported this week at the Society of Gynecologic Oncology Annual Meeting on Women's Cancer and in The New England Journal of Medicine.

Endometrial cancer, which develops in the lining of the uterus, is among the most common gynecological cancers, and its incidence is on the rise.

In two separate Phase III trials, GSK's Jemperli improved progression-free survival (PFS) by 72% over two years while Merck's Keytruda led to a 70% improvement over one year for women with endometrial tumors with specific genetic characteristics. Commenting on the studies at the conference, Rebecca Arend, MD, of the University of Alabama at Birmingham, called the results "groundbreaking."

Jemperli and Keytruda are both monoclonal antibodies that target PD-1, a receptor on T cells that regulates immune function. Some tumors can hijack PD-1 to dial down anticancer immune responses; PD-1 inhibitors release the brakes and restore T-cell activity.

Both drugs are approved for the treatment of advanced solid tumors anywhere in the body with mismatch repair deficiency (dMMR); Keytruda is also indicated for microsatellite instability-high (MSI-H) tumors. Normal cells are able to detect and repair mistakes that arise when DNA is copied during cell division. But dMMR and MSI-H cancer lacks this mechanism, which means mutations can accumulate and allow cells to grow out of control. Tumor genomic testing for these biomarkers can help predict whether this type of immunotherapy is likely to work.

Jemperli

The RUBY trial (NCT03981796) enrolled 494 patients with advanced or recurrent endometrial cancer. Nearly one quarter had dMMR or MSI-H tumors. They were randomly assigned to receive Jemperli or a placebo in combination with standard-of-care paclitaxel and carboplatin chemotherapy every three weeks for six cycles, followed by Jemperli or the placebo alone every

six weeks for up to three years.

Progression-free survival rates in the dMMR/MSI-H subgroup were 64% at 12 months and 61% at 24 months in the Jemperli arm versus 24% and 16%, respectively, in the placebo arm, reflecting a 72% reduction in the risk of disease progression or death.

Looking at patients without dMMR/MSI-H tumors (known as mismatch repair proficient, or pMMR), the 24-month PFS rate was 28% in the Jemperli arm versus 19% in the placebo arm, for a 25% reduction in disease progression or death.

Although overall survival data are not yet mature, this interim analysis suggests a trend towards a clinically meaningful improvement. In the dMMR/MSI-H subgroup, 83% were still alive after two years in the Jemperli arm versus 59% in the placebo arm.

Treatment with Jemperli plus chemotherapy was generally safe, but side effects were common. There were no new or unexpected adverse events not seen in previous studies. The most common side effects were nausea, hair loss and fatigue. Severe adverse events occurred in about 70% of Jemperli recipients and about 60% of placebo recipients.

Keytruda

The NRG-GY018 trial (NCT03914612) enrolled 816 patients with advanced or recurrent endometrial cancer. About 28% had dMMR or MSI-H tumors. They were randomly assigned to receive Keytruda or a placebo plus paclitaxel and carboplatin every three weeks for approximately six cycles, followed by Keytruda or the placebo alone every six weeks for up to 14 cycles.

After one year of follow-up, estimated PFS rates in the dMMR/MSI-H subgroup were 74% in the Keytruda plus chemotherapy arm and 38% in the placebo plus chemo arm, meaning Keytruda reduced the risk of disease progression or death by 70%. The median PFS time was 7.6 months in the placebo arm but was not reached in the Keytruda arm because most patients were still alive without disease progression.

While this one-year improvement in progression-free survival matches the two-year improvement in the RUBY trial, Keytruda plus chemo led to greater improvement for patients without dMMR/MSI-H tumors, who saw a 46% risk reduction. Median PFS times in this subgroup were 13.1 months in the Keytruda arm and 8.7 months in the placebo arm.

Here, too, treatment with Keytruda plus chemotherapy was generally safe, but side effects were common and consistent with those seen in previous studies. About 60% of patients in the Keytruda arm and 45% in the placebo arm experienced severe adverse events.

Taken together, these two studies show that checkpoint immunotherapy could be an effective option for people with advanced endometrial cancer, especially those with dMMR/MSI-H tumors. According to Arend, both drugs “hit a home run.” While Keytruda appeared to work better for patients without dMMR/MSI-H tumors, these were not head-to-head trials, so their results cannot

be directly compared.

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