FDA Approves Keytruda Combo for Advanced Cervical Cancer

Immunotherapy plus chemotherapy improved overall survival in people with persistent, recurrent or metastatic cervical cancer.

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The Food and Drug Administration (FDA) has approved the checkpoint inhibitor Keytruda (pembrolizumab) plus chemotherapy, with or without Avastin (bevacizumab), as a first-line treatment option for people with persistent, recurrent or metastatic cervical cancer whose tumors express PD-L1.

The approval comes after data presented last month at the European Society for Medical Oncology (ESMO) Congress and published in The New England Journal of Medicine showed that the combination reduced the risk of death by more than a third in the KEYNOTE-826 trial.

Along with the approval of the combination for first-line treatment, the FDA also granted regular full approval of Keytruda as a stand-alone medication for people with PD-L1-positive recurrent or metastatic cervical cancer that has progressed during or after chemotherapy, upgrading the accelerated approval granted in June 2018. Another checkpoint inhibitor, Libtayo (cemiplimab), was found to extend cervical cancer survival, but this too was in previously treated patients. Last month, the FDA approved the antibody-drug conjugate Tivdak (tisotumab vedotin) for advanced cervical cancer, but that approval was also for people whose cancer has progressed despite chemotherapy.

Cervical cancer, caused by human papillomavirus (HPV), can be prevented with a vaccine, and precancerous cervical cell changes can be detected early with regular Pap smears and HPV tests. But if it goes undetected, advanced cervical cancer is difficult to treat, and it is a leading cause of cancer death for women worldwide.

“Cervical cancer more commonly affects younger women and certain women of color in the United States, and unfortunately, women diagnosed with persistent, recurrent or metastatic cervical cancer often have a low survival rate,” KEYNOTE-826 lead investigator Bradley Monk, MD, of the University of Arizona College of Medicine, said in a Merck press release. “There have been no first-line approvals for women with persistent, recurrent or metastatic cervical cancer in the past seven years.”

The trial (NCT03635567) enrolled 617 women with persistent, recurrent or first-line metastatic cervical cancer who had not been treated with standard systemic chemotherapy. However, 39% had previously received chemoradiation using radiosensitizing agents and 17% had received chemoradiation plus surgery. People with any level of tumor PD-L1 expression were eligible. Most patients (548, or 89%) had PD-L1 expression of at least 1%, and just over half had at least 10% expression.

Study participants were randomly assigned to receive Keytruda or a placebo plus platinum-based chemotherapy (paclitaxel and cisplatin or carboplatin), with or without Avastin (used by 63%). Keytruda was administered by IV infusion every three weeks. (The approved indication also gives the option of a double dose every six weeks.) Treatment continued until patients experienced disease progression or unacceptable side effects or reached 24 months of therapy.

Keytruda is a monoclonal antibody that blocks PD-1, an immune checkpoint protein on T cells that regulates immune function. Some tumors can hijack PD-1 to turn off immune responses against them. Drugs that block the interaction between PD-1 and PD-L1, its binding partner on tumors, can release the brakes and restore T-cell activity. Tumors with higher PD-L1 expression typically respond better to this type of treatment.

At ESMO, Nicoletta Colombo, MD, of the University of Milano-Bicocca in Italy, reported that the Keytruda combination improved overall and progression-free survival compared with the placebo. In the subset of patients with at least 1% PD-L1 expression—the group covered by the FDA approval—the median overall survival time was 16.3 months in the placebo arm but was not reached in the Keytruda arm because a majority were still alive. The median progression-free survival times were 8.2 and 10.4 months, respectively.

Two-year overall survival rates for people with at least 1% PD-L1 expression were 53.0% in the Keytruda arm versus 41.7% in the placebo arm, reflecting a 36% improvement. Among those with at least 10% PD-L1 expression, the corresponding rates were 54.4% and 44.6%—a 39% improvement. For the population as a whole, including those with no detectable PD-L1 expression, overall survival rates were 50.4% versus 40.4%, a 33% improvement.

In addition, patients assigned to the Keytruda combination were more likely to experience tumor shrinkage than those receiving the placebo. Among those with at least 1% PD-L1 expression, the overall response rates were 68% (including 23% complete responses) versus 50% (including 13% complete responses), respectively. The duration of response was also longer, 18.0 versus 10.4 months.

Treatment was generally safe, but side effects were common in both the Keytruda and placebo arms (68% and 64% with Grade 3 or higher treatment-related adverse events); 15% of Keytruda recipients stopped treatment due to adverse events, and 5% had fatal adverse reactions. According to the Keytruda prescribing information, common adverse reactions in patients treated with Keytruda, chemotherapy and Avastin include peripheral neuropathy, hair loss, nausea, vomiting, diarrhea, constipation, loss of appetite, hypertension, joint pain, urinary tract infections, rash and hypothyroidism. The treatment can cause depletion of red blood cells (anemia), white

blood cells (neutropenia and leukopenia) and platelets (thrombocytopenia), leading to fatigue, infections and easy bleeding. Checkpoint inhibitors that unleash T cells against cancer can also lead to excessive inflammation and damage to healthy organs and tissues. But despite the side effects, patients who took the Keytruda combo reported a longer time until deterioration of quality of life.

Keytruda plus chemotherapy “provided statistically significant, clinically meaningful” progression-free survival and overall survival improvements in patients with persistent, recurrent or metastatic cervical cancer, regardless of PD-L1 expression or use of Avastin, and the combination had a “manageable safety profile,” the researchers concluded.

Based on these findings, Colombo suggested that Keytruda plus chemotherapy with or without Avastin “may be a new standard of care” for this population. Mansoor Raza Mirza, MD, of the University of Copenhagen, who commented on the presentation at ESMO, went further, saying it “should be” the standard of care.

Click here to read the ESMO study abstract.

Click here for more news about cervical cancer.

Click here for full prescribing information for Keytruda.
