FDA Approves Keytruda for Pre- and Post-Surgery Treatment of Early Triple-Negative Breast Cancer

This is the first immunotherapy approved for previously untreated triple-negative breast cancer that is likely to relapse.

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The Food and Drug Administration (FDA) this week approved the checkpoint inhibitor Keytruda (pembrolizumab) for people with newly diagnosed early-stage triple-negative breast cancer (TNBC) who are at high risk for disease progression. The approved regimen involves Keytruda plus chemotherapy taken before surgery followed by Keytruda alone thereafter.

Breast cancer is classified according to the types of receptors it expresses. A majority of breast tumors carry estrogen or progesterone receptors and can be treated with hormone therapy. Others express a receptor called HER2 and can be treated with HER2 inhibitors. Triple-negative breast cancer doesn't express any of these receptors and is harder to treat. This aggressive type of breast cancer is more common among young women and Black women.

Treatment for nonmetaststic breast cancer typically involves surgery to remove as much of the cancer as possible followed by various medications after surgery (known as adjuvant therapy) to keep it from coming back. In many cases, drugs are also used in advance (known as neoadjuvant therapy) to shrink tumors prior to surgery. If residual cancer can still be detected after surgery, the risk of recurrence is high.

The FDA approval was based on findings from the Phase III Keynote-522 trial (NCT03036488), which evaluated neoadjuvant Keytruda plus chemotherapy for people with previously untreated nonmetastatic TNBC.

Keytruda is a PD-1 checkpoint inhibitor, a type of treatment that helps the immune system fight cancer. PD-1 is a receptor on T cells that plays a role in regulating immune function. Some tumors can hijack PD-1 to turn off immune responses against them. Drugs that block PD-1 or its binding partner, known as PD-L1, can release the brakes and restore T-cell activity. People with high PD-L1 levels tend to respond better to this type of treatment.

Last November, the FDA granted accelerated approval of Keytruda plus chemotherapy for people

with inoperable locally recurrent or metastatic TNBC with tumor PD-L1 expression of at least 10%. This week, the agency upgraded that to regular full approval. The new approval extends Keytruda's indication to include people with earlier stages of TNBC who can still benefit from surgery.

KEYNOTE-522 included 1,174 participants with previously untreated Stage II or III TNBC that was operable but deemed to be at high risk for recurrence based on tumor size and lymph node involvement. Almost all were women, two thirds were white and the median age was 49. Just over half had cancer in their lymph nodes, and more than 80% tested positive for tumor PD-L1 expression.

Before undergoing surgery, the participants were randomly assigned to receive IV infusions of Keytruda or a placebo every three weeks for six months along with two different chemotherapy regimens (four cycles of carboplatin plus paclitaxel followed by four cycles of doxorubicin or epirubicin plus cyclophosphamide). After surgery, they continued to receive Keytruda or the placebo alone for up to nine more cycles.

As previously reported at the 2019 European Society for Medical Oncology (ESMO) Congress, 65% of those treated with neoadjuvant Keytruda plus chemotherapy had a pathological complete response—meaning no evidence of remaining cancer in their breast tissue or lymph nodes—compared with 51% of those in the placebo group (later updated to 63% and 56%, respectively).

Peter Schmid, MD, PhD, of Barts Cancer Institute at Queen Mary University of London, presented update result from the study earlier this month at this years ESMO meeting. After three years of follow-up, event-free survival rates were 85% in the Keytruda group versus 77% in the placebo group. That is, participants who used Keytruda were 37% less likely to experience disease progression that precludes surgery, local or distant recurrence, a second primary cancer or death from any cause. Overall survival was 28% higher in the Keytruda group; this did not reach statistical significance, but the data are immature and follow-up is ongoing.

Treatment was generally safe, though side effects were common. Adverse events in this study were in line with those previously reported for Keytruda plus chemotherapy, and no new safety concerned were identified. Checkpoint inhibitors like Keytruda can cause the immune system to attack healthy organs and tissues; there were two deaths in the study from immune-mediated reactions. One in five Keytruda recipients stopped the drug due to adverse events. The most common adverse reactions to Keytruda plus chemotherapy include fatigue or weakness, nausea, vomiting, constipation, diarrhea, decreased appetite, weight loss, rash, cough, shortness of breath, fever, hair loss, peripheral neuropathy, mucosal inflammation, mouth sores, headache, muscle or joint pain and insomnia.

"Even when TNBC is diagnosed early, 30% to 40% of patients will suffer cancer recurrence after standard neoadjuvant chemotherapy and surgery. Therefore, there is a high unmet need for new treatment options," Joyce O'Shaughnessy, MD, of Baylor University Medical Center in Dallas, said

in a Merck press release. “Today’s approval is very welcome news and has the potential to change the treatment paradigm by now including an immunotherapy as part of the regimen for patients with high-risk early-stage TNBC.”

Click here for full prescribing information for Keytruda.

Click here to learn more about breast cancer.

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