Keytruda Before Surgery May Ward Off Breast Cancer Recurrence

Adding immunotherapy to preoperative chemotherapy increased the likelihood of complete remission.

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Adding Keytruda (pembrolizumab) to chemotherapy prior to surgery for triple-negative breast cancer (TNBC) may reduce the risk of the cancer coming back, according to a study presented at the European Society for Medical Oncology Congress (ESMO 2019) this week in Barcelona.

Women treated with neoadjuvant, or preoperative, Keytruda plus chemotherapy had a 65% pathological complete response rate, meaning no evidence of remaining cancer after surgery, compared with 51% of those who received chemotherapy alone—a difference deemed "clinically meaningful." Prior research has shown that pathological complete response is associated with longer survival.

"The data suggest that the improved pathological complete response with pembrolizumab translates into fewer recurrences," presenter Peter Schmid, MD, PhD, of Barts Cancer Institute at Queen Mary University of London said in an ESMO press release.

Breast cancer is classified by the type of receptors it expresses. A majority of breast tumors carry estrogen or progesterone receptors, making them susceptible to hormone therapy. Others express HER2 and can be treated with targeted therapies like Herceptin (trastuzumab). Triple-negative breast cancer doesn't carry any of these receptors and is more difficult to treat. Accounting for around 15% of all breast cancers, TNBC is more common among young women, Black women and those with BRCA gene mutations.

The Phase III KEYNOTE-522 study evaluated neoadjuvant Keytruda in people with previously untreated nonmetastatic TNBC, meaning it had not yet spread beyond the breast. The standard approach at this stage involves chemotherapy to shrink tumors followed by surgery.

Up to 50% of women who have detectable residual cancer after surgery will relapse, typically within three years, the researchers noted as background. But those with pathological complete response, or no evidence of remaining cancer in breast tissue or lymph nodes, have around a 90% likelihood of being cured.

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.

Chemotherapy disrupts tumors and makes them more vulnerable to immune attack, so using chemotherapy and immunotherapy together can lead to a synergistic effect. People with higher levels of PD-L1 in their tumors tend to do better on checkpoint blockers, but this is not a reliable predictor of individual response across cancer types. TNBC with a greater number of tumor-infiltrating lymphocytes, or TILs, also responds better to checkpoint immunotherapy.

Before undergoing surgery to remove their tumors—the neoadjuvant phase—the 1,174 participants were randomized 2:1 to receive Keytruda or placebo infusions every three weeks. Both groups also received chemotherapy consisting of four cycles of paclitaxel plus carboplatin followed by four cycles of doxorubicin or epirubicin plus cyclophosphamide. After surgery—the adjuvant phase—they continued to received Keytruda or the placebo for nine more cycles or until they experienced disease recurrence or unacceptable side effects.

After a median follow-up period of 15.5 months, among the 602 evaluable patients, 64.8% of Keytruda recipients and 51.2% of placebo recipients had pathological complete response. This difference was statistically significant, meaning it probably was not driven by chance. Results were consistent when using varying definitions of complete response.

Participants whose tumors tested positive for PD-L1 responded better to both Keytruda and chemotherapy alone. Among PD-L1-positive patients, 68.9% of those treated with Keytruda and 54.9% of those who received the placebo achieved pathological complete response. Among PD-L1-negative participants, the rates were 45.3% and 30.3%, respectively. Thus, the Keytruda advantage was similar in both groups.

The researchers reported a “favorable trend” toward an improvement in event-free survival: 91.3% in the Keytruda group versus 85.3% in the placebo group, or a 37% reduction in the risk of cancer recurrence. The difference did not meet the threshold for statistical significance, but Schmid predicted that it may well clear that bar with longer follow-up.

Treatment was generally safe and well tolerated, though side effects were common; 76.8% in the Keytruda arm and 72.2% in the placebo group experienced severe treatment-related adverse events, most commonly neutropenia and anemia. Immune-mediated side effects were twice as common in the Keytruda group (42.3% versus 21.3%), and Keytruda recipients were more likely to stop treatment because of adverse events (23.3% versus 12.3%). However, in both groups, treatment-related adverse events were much less frequent during the adjuvant, or postoperative, phase, when participants were no longer using chemotherapy (5.7% versus 1.9%, respectively). Most people who stopped treatment did so during the neoadjuvant phase.

“This is a good situation to test whether the [Food and Drug Administration] will approve a drug for triple negative breast cancer based on pathological complete response,“ commented Fabrice

André, MD, PhD, of Institut Gustave Roussy in Villejuif, France. ”The combination of the anti-PD-1 monoclonal antibody pembrolizumab plus chemotherapy could become a standard of care if approved."

Keytruda as neoadjuvant therapy for TNBC was granted an FDA breakthrough therapy designation, which speeds up development of experimental therapies that meet an unmet medical need.

With these findings, Keytruda is the first immunotherapy shown to be effective as neoadjuvant therapy for early-stage triple negative breast cancer. In contrast, another study presented at ESMO (KEYNOTE-119) showed that Keytruda did not perform significantly better than chemotherapy as a treatment for more advanced metastatic TNBC, though it did demonstrate greater activity in people with higher PD-L1 levels.

Currently, the PD-L1 checkpoint inhibitor Tecentriq (atezolizumab) is the only immunotherapy approved for the treatment of late-stage TNBC. Tecentriq plus Abraxane (nab-paclitaxel) chemotherapy led to longer progression-free survival than chemotherapy alone, but it did not significantly improve overall survival in the full study population—though here, too, it did appear to confer an advantage for PD-L1-positive patients.

Click here for full prescribing information for Keytruda.

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