Immunotherapy Improves Triple-Negative Breast Cancer Survival

Keytruda plus chemotherapy reduced the risk of death by 27% in people with locally advanced or metastatic disease.

September 23, 2021 By Liz Highleyman

The checkpoint inhibitor Keytruda (pembrolizumab) in combination with chemotherapy improved overall survival for people with metastatic triple-negative breast cancer (TNBC) whose tumors express a biomarker associated with better response, according to data presented this week at the European Society for Medical Oncology (ESMO) Congress 2021.

In the Phase III KEYNOTE-355 trial, first-line treatment with Keytruda plus chemotherapy reduced the risk of death by 27% in TNBC patients with tumor PD-L1 expression of at least 10%.

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 HER2 receptors and can be treated with HER2 inhibitors such as Herceptin (trastuzumab). Triple-negative breast cancer does not express any of these receptors and is harder to treat. About 15% of breast cancer patients have TNBC, which is more common among young women and Black women as well as those with BRCA mutations.

“Metastatic TNBC has the worst survival prognosis among breast cancer subtypes, and there is an urgent need for treatment options that improve survival,” study investigator Hope Rugo, MD, of the University of California San Francisco Helen Diller Family Comprehensive Cancer Center said in a Merck press release.

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 its binding partner, known as PD-L1, can release the brakes and restore T-cell activity. Tumors with higher PD-L1 expression typically respond better to this type of treatment.

The Food and Drug Administration granted accelerated approval of Keytruda plus chemotherapy for people with locally recurrent or metastatic TNBC in November 2020 and regular full approval for this indication in July 2021. Also in July, the agency approved Keytruda for pre- and post-surgery treatment of people with early-stage TNBC.

KEYNOTE-355 (ClinicalTrials.gov NCT02819518) included 847 women with previously untreated inoperable locally recurrent or metastatic TNBC. Two thirds were white, 21% were Asian, 4% were Black and the median age was 53 years. About 75% had tumors with at least 1% PD-L1 expression and about 38% had at least 10% expression.

The participants were randomly assigned to receive Keytruda or a placebo administered by IV infusion every three weeks plus one of three chemotherapy regimens: paclitaxel, Abraxane (protein-bound paclitaxel) or gemcitabine plus carboplatin.

As reported at last year's American Society of Clinical Oncology Annual Meeting, among participants with at least 10% PD-L1 expression, the median progression-free survival time was 9.7 months in the Keytruda group compared with 5.6 months in the placebo group, reflecting a 35% improvement. Those with at least 1% PD-L1 expression saw a 26% improvement. But at that time, overall survival results were immature.

At ESMO, Rugo reported further follow-up data showing that the median overall survival time for patients with at least 10% PD-L1 expression was 23.0 months in the Keytruda group versus 16.1 months in the placebo group—a 27% improvement. The estimated overall survival rates after a median 44 months of follow-up were 58% and 45%, respectively. A survival benefit was seen across the three chemotherapy options. However, there was no significant difference in overall survival for people with at least 1% PD-L1 expression.

In addition, patients assigned to Keytruda were more likely to experience tumor shrinkage than those receiving the placebo (overall response rates of 53% versus 41%, respectively), and the duration of response was longer.

Treatment was generally safe, but side effects were common. The likelihood of severe treatment-related adverse events was about the same in the Keytruda and placebo groups (68% versus 67%), suggesting side effects were largely attributable to the chemotherapy. However, more people stopped treatment in the Keytruda group (18%) than in the placebo group (11%). There were two treatment-related deaths in the Keytruda arm, due to acute kidney injury and pneumonia.

Checkpoint inhibitors that unleash T cells against cancer can also lead to excessive inflammation and damage to organs and tissues. More than a quarter of Keytruda recipients (27%) experienced immune-mediated adverse reactions—most commonly thyroid problems—compared with 6% of placebo recipients.

"I am very encouraged to see these new overall survival data for the Keytruda combination," Rugo said, adding that the results support pembrolizumab plus chemotherapy as "a new standard of care" for patients with locally advanced or metastatic TNBC with PD-L1 expression of at least 10%.

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