Immunotherapy Improves Outcomes for Women With Advanced Breast Cancer

Keytruda may restore immune function in some women who develop resistance to Herceptin.

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The checkpoint inhibitor Keytruda (pembrolizumab) controlled disease progression when used with Herceptin (trastuzumab) in women with advanced Herceptin-resistant HER2-positive breast cancer, according to results from the PANACEA trial presented this week at the San Antonio Breast Cancer Symposium. Keytruda worked only for women with a specific tumor biomarker, however.

“For responders, this combination offers durable disease control without chemotherapy,” Sherene Loi, MD, PhD, of Peter MacCallum Cancer Centre in Melbourne, Australia, concluded.

Breast cancer is classified according to which receptors tumors express, which indicates which type of treatment is likely to work. A majority of tumors carry estrogen receptors (known as ER-positive) or progesterone receptors, and about 20 percent express HER2 (human epidermal growth factor receptor 2) receptors. Triple-negative breast cancer doesn’t express any of these receptors and is hardest to treat.

HER2-positive breast cancer can be treated with Herceptin, a targeted therapy that blocks HER2 receptors. But the cancer often develops resistance and stops working.

Previous research showed that women who respond well to Herceptin and traditional chemotherapy have a larger number of tumor-infiltrating lymphocytes (TILs), immune cells that get inside tumors and attack cancer cells. This suggests that drugs that boost T-cell activity might be a promising approach to overcome resistance, Loi explained.

The PANACEA study (also known as Keynote 014), sponsored by Merck and coordinated by the International Breast Cancer Study Group, tested Keytruda plus Herceptin in women with HER2-positive breast cancer that could not be cured by surgery or had spread elsewhere in the body, a process known as metastasis.

Keytruda is a monoclonal antibody that blocks the PD-1 receptor (an immune checkpoint) on T cells, the main soldiers of the immune system. PD-1 plays a role in regulating immune function,

and some tumors can hijack PD-1 to turn off immune responses against them. Drugs that block PD-1 can release the brakes and restore T-cell activity. Keytruda is currently approved for the treatment of advanced lung, stomach, bladder and head and neck cancers, Hodgkin lymphoma and melanoma, but not yet for breast cancer.

The study enrolled 58 women with an average age of 50. A third had ER-positive cancer. All participants were previously treated with Herceptin and had developed resistance, and many had tried other prior treatments as well. The women were classified based on whether their tumors expressed PD-L1, the ligand or binding partner of PD-1.

After the Phase Ib portion of the trial determined the best Keytruda dose in an initial group of six participants, a larger group of 40 PD-L1-positive and 12 PD-L1-negative women were enrolled in the Phase II portion. In the second portion, all received IV infusions of 200 milligrams of Keytruda plus Herceptin every three weeks for up to two years or until they experienced disease progression or developed unacceptable side effects.

The overall response rate in the PD-L1-positive group, meaning complete or partial tumor shrinkage, was 15 percent. Including patients who maintained stable cancer without progression, the disease control rate was 24 percent. In contrast, none of the women in the PD-L1-negative group had complete or partial responses.

Looking at just the PD-L1-positive group, the median duration of response was 3.5 months and the median duration of disease control was 11.1 months. Five study participants (11 percent) were still responding with no progression when the data were compiled for the report. This offers a "tantalizing suggestion" that treatment response may be long-term or even permanent, Loi said.

Treatment with Keytruda and Herceptin was generally safe and well tolerated. The most common adverse events were fatigue (21 percent), diarrhea (14 percent), joint pain (14 percent), headache (10 percent) and nausea (10 percent).

The major concern with checkpoint inhibitors is immune-related adverse events. These drugs work by restoring immune responses against cancer cells, but they can also take the brakes off the immune system more broadly, leading to excessive inflammation of healthy tissue. In this study, there were six severe immune-mediated adverse events, four of which resulted in patients dropping out. The most common were thyroid damage and pneumonitis (lung inflammation).

The difference in response between the PD-L1-positive and PD-L1-negative groups is interesting because in prior studies of other types of cancer, PD-L1 levels generally have not been a good predictor of how well someone will respond.

Loi's team also found that the presence of TILs at baseline predicted better response. About one in four women in the PD-L1-positive group had a tumor TIL level of at least 5 percent. Overall response rates reached 39 percent for high-TIL women, compared with only 5 percent for low-TIL women.

Loi said that women with an advanced HER2-positive breast cancer who have used prior treatments usually have tumors with poor immunogenicity, meaning T cells are not drawn to attack them. Although some patients at this stage still have enough immune response left to boost, Loi suggested that starting a checkpoint inhibitor sooner would offer a better chance of a good response.

“This proof-of-principle study suggests that immune evasion is a mechanism of resistance to trastuzumab and contributes to disease progression in advanced HER2-positive breast cancer,” Loi said in a SABCS press release. “Our results suggest that PD-1 inhibition is likely to become part of the treatment armamentarium of HER2-positive disease in the future.”

Click here to read the study abstract.

Click here to read a SABCS press release about the study.
