Immunotherapies Show Mixed Results for Triple-Negative Breast Cancer

Keytruda improves response rates for hard-to-treat breast cancer, but Tecentriq falls short.

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Adding Keytruda (pembrolizumab) to chemotherapy before surgery for triple-negative breast cancer improved the odds of pathological complete response—meaning a lower likelihood of relapse—but Tecentriq (atezolizumab) did not perform as well, researchers reported last week at the San Antonio Breast Cancer Symposium.

In the Keytruda study, people with more advanced cancer, including those with lymph node involvement, appeared to benefit most from adding the checkpoint immunotherapy.

"Our results suggest that adding pembrolizumab to neoadjuvant chemotherapy is beneficial for patients with the most aggressive disease and the highest unmet need," presenter Peter Schmid, MD, PhD, of Barts Cancer Institute at Queen Mary University of London, said in a press release. "I think the results have the potential to be practice-changing." Interestingly, these results in people with earlier breast cancer do not correspond to previously reported data from studies of immunotherapy for more advanced metastatic triple-negative breast cancer (TNBC), which appeared to favor Tecentriq.

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 TNBC, which does not carry any of these receptors, can be more aggressive and is harder to treat.

The standard approach for nonmetastatic TNBC, meaning it has not yet spread beyond the breast, involves chemotherapy to shrink tumors before surgery, known as neoadjuvant therapy. If residual cancer is detected after surgery, the risk of relapse is high. But people with a pathological complete response (pCR)—meaning no evidence of remaining cancer in breast tissue or lymph nodes—have a high likelihood of being cured.

Keytruda

Schmid presented updated results from the Phase III KEYNOTE-522 study (ClinicalTrials.gov number NCT03036488), which evaluated neoadjuvant Keytruda plus chemotherapy for people with

previously untreated nonmetastatic TNBC.

Keytruda is a PD-1 checkpoint inhibitor 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 makes cancer more vulnerable to attack from the immune system, so using chemotherapy and immunotherapy together could be a more potent approach.

KEYNOTE-522 included 1,174 participants with operable Stage II or III TNBC. The median age was 49. Just over half had cancer in their lymph nodes, and over 80% tested positive for PD-L1, meaning it was present on at least 1% of tumor cells. People with higher PD-L1 levels in their tumors tend to do better on checkpoint inhibitors, though it is not a reliable predictor of individual response.

Before undergoing surgery, participants were randomly assigned to receive IV infusions of Keytruda or a placebo every three weeks along with chemotherapy. The chemo regimen consisted of paclitaxel plus carboplatin for four cycles, followed by doxorubicin or epirubicin plus cyclophosphamide for four more cycles. After surgery, they continued to received Keytruda or the placebo for nine more cycles or until they experienced disease recurrence or unacceptable side effects.

As Schmid reported at the recent European Society for Medical Oncology (ESMO) Congress, among the 602 evaluable patients, 65% of those treated with neoadjuvant Keytruda had a pathological complete response, compared with 51% of those who received the placebo—a difference he deemed “clinically meaningful.” What’s more, event-free survival rates were 91% in the Keytruda group versus 85% in the placebo group, indicating a 37% reduction in the risk of cancer recurrence, though the difference did not reach statistical significance.

Last week, he reported further details about pCR in patient subgroups, showing that people with more advanced cancer—those with a higher disease stage or cancer in their lymph nodes—stood to benefit most from adding the checkpoint inhibitor.

Among people with Stage IIIB disease—meaning cancer has spread to the chest wall and up to nine nearby lymph nodes but not elsewhere in the body—pCR rates were 49% with Keytruda versus 23% with the placebo (a difference of 26%). Among those with Stage IIIA cancer, the corresponding rates were 67% versus 42% (a 25% difference). Among those with Stage IIB disease—meaning smaller tumors or fewer affected lymph nodes—pCR rates were 56% versus 48%, respectively (an 8% difference). Finally, among those with Stage IIA, the rates were 73% versus 62% (an 11% difference).

Among patients with cancer-positive lymph nodes, the pCR rate was 65% with Keytruda versus 44% with the placebo (a 21% difference). Among those without lymph node involvement, the corresponding rates were 65% versus 59% (a 6% difference).

Participants with higher PD-L1 levels responded better to Keytruda but also to chemotherapy alone. Among those with PD-L1 negative tumors, pCR were 45% with Keytruda versus 30% with the placebo (an 18% difference). The corresponding rates were 69% and 55% for those with PD-L1 positive tumors using the 1% threshold (a 14% difference). Those with 20% or greater PD-L1 expression saw response rates of 82% versus 63%, but here, too, the difference was similar (19%).

Schmid suggested that consideration of disease stage and biomarkers could help determine which patients were likely to benefit most from adding immunotherapy.

Tecentriq

Luca Gianni, MD, of Fondazione Michelangelo in Milan, presented findings from a the NeoTRIPaPDL1 study (ClinicalTrials.gov number NCT02620280), which evaluated neoadjuvant Tecentriq plus chemotherapy for people with nonmetastatic TNBC.

Tecentriq is also a checkpoint inhibitor, but, unlike Keytruda, it targets PD-L1 rather than PD-1.

This Phase III trial included 280 women, half with early high-risk and half with locally advanced TNBC. The median age was 50. Nearly 60% had N1 status, meaning cancer in one to three nearby lymph nodes; 15% had cancer in 10 or more nodes. More than half (56%) tested PD-L1 positive.

Before surgery, they were randomized to receive IV infusions of Tecentriq plus chemotherapy using carboplatin and Abraxane (protein-bound paclitaxel) every three weeks for eight cycles or else chemo alone. After surgery, they received four cycles of chemotherapy using anthracyclines (drugs like doxorubicin or epiribicin).

While the ultimate aim of the study is to compare event-free survival at five years, Gianni reported interim findings on pathological complete response post-surgery.

In this analysis, the pCR rate was 44% in the Tecentriq group versus 41% in the group that used chemotherapy alone—a nonsignificant difference of 2% that could have been attributable to chance. Again, being PD-L1 positive was associated with better response in both the Tecentriq and solo chemotherapy groups (52% versus 48%, respectively).

The overall response rate was 76% with Tecentriq versus 68% with chemotherapy alone. Complete response rates (29% versus 26%) and partial response rates (47% versus 42%) were similar in the two treatment groups.

Side effects were generally similar in both treatment groups, but those who took Tecentriq had more severe adverse events and were more likely to have elevated liver enzymes.

“Our observations may indicate that there is no therapeutic benefit to adding atezolizumab to neoadjuvant chemotherapy compared to chemotherapy alone, or it may simply mean that any beneficial effects of the combination will be seen in the long term,” Gianni said in a press release. “Pathologic complete response does not provide information about the quality of response, which is why we did not use it as the primary endpoint for this study. Further analyses

may reveal differences in the quality of response between the treatment groups."

Early Versus Metastatic TNBC

These findings are interesting given the results of previous studies of checkpoint immunotherapy for more advanced TNBC that appear to give Tecentriq an edge, but those trials are not directly comparable.

As Schimd reported in 2018, the Phase III IMpassion130 trial showed that Tecentriq plus Abraxane improved progression-free survival for people with locally advanced or metastatic triple-negative breast cancer. The absolute difference was small—7.2 versus 5.5 months—but statistically significant. Most of the benefit appeared to be driven by good results in patients with PD-L1 positive tumors.

Based on these findings, the Food and Drug Administration granted Tecentriq accelerated approval as the first immunotherapy for breast cancer in March 2019. But at this year's American Society of Clinical Oncology annual meeting in June, Schmid reported that longer-term follow-up showed the Tecentriq combo did not significantly improve overall survival.

In the Phase III KEYNOTE-119 trial, Keytruda used alone did not improve overall survival compared with chemotherapy for metastatic TNBC. Outcomes were better in people with higher PD-L1 levels, but even here the difference did not reach statistical significance.

But Keytruda might fare better if used in a combination regimen, as done in the Tecentriq trial. KEYNOTE-355 (ClinicalTrials.gov number NCT02819518) is currently evaluating Keytruda plus chemotherapy for people with inoperable locally advanced or metastatic TNBC; results are expected soon.

Click here to read the Keytruda abstract.

Click here to read the Tecentriq abstract.

Click here to learn more about breast cancer.
