

# Clinical trial shows efficacy for atezolizumab combined with carboplatin

December 14 2023

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Immunotherapy in combination with chemotherapy has become an important therapeutic treatment option in some patients with metastatic breast cancer. Which patients will benefit the most, however, remains

unclear; current biomarkers such as PD-L1 that are used to predict response are mediocre at best.

Vanderbilt researchers led a clinical trial combining atezolizumab, an immunotherapy, in combination with chemotherapy in patients with metastatic [triple-negative breast cancer](#) to both evaluate the efficacy of the treatment combination and to understand biomarkers of response to immunotherapy.

Atezolizumab became the first approved immunotherapy for breast cancer when the Food and Drug Administration granted it accelerated approval in 2019, but two years later, its maker voluntarily withdrew the indication after additional data from a follow-up clinical trial failed to corroborate its efficacy.

Atezolizumab had been approved for metastatic PD-L1-positive triple-negative breast cancer in combination with the chemotherapy nab-paclitaxel. Results from Vanderbilt's clinical trial, published Dec. 14 in *JAMA Oncology*, indicate that this immunotherapy does have a clinically meaningful benefit with a different chemotherapy partner and the correlative analyses provide insight to which patients will respond.

The clinical trial combined atezolizumab with carboplatin—a chemotherapy that works differently than nab-paclitaxel. The new combination significantly improved progression-free and overall survival of patients with metastatic triple-negative breast cancer.

Atezolizumab with carboplatin lengthened [progression-free survival](#)—the time a patient lives without the cancer worsening—from a median of 2.2 months to 4.1 months. Overall survival increased from a median of 8.6 months for the control group, who received carboplatin alone, to 12.6 months for those who received the combination therapy.

The Phase II randomized clinical trial was conducted at six cancer centers through the Translational Breast Cancer Research Consortium and involved 106 patients of diverse ethnicities.

"Triple-negative breast cancer is difficult to treat because we don't have a clear target, and understanding the underlying factors that affect response to a treatment is key. This study is so important because we were able to collect biopsies in all of the participants and really understand factors that affect response," said Vandana Abramson, MD, the Donna S. Hall Professor in Cancer Research and co-leader of the Breast Cancer Research Program at Vanderbilt-Ingram Cancer Center.

The researchers hypothesized that atezolizumab would have better efficacy with carboplatin because the chemotherapy is a platinum agent, which causes structural DNA changes and generates neoantigens that may stimulate an [immune response](#). Nab-paclitaxel chemotherapy works differently. It is a microtubule-stabilizing agent that stops [cancer cells](#) from dividing into new cells.

"The tremendous knowledge gained from our multidisciplinary analyses of the patients and their tumors will continue to be important for clinical decision-making. After our first description of the triple-negative breast cancer subtypes over 10 years ago, more recently, we refined the subtypes further into four, which were analyzed in this study: two basal-like subtypes, a mesenchymal subtype and a lumen androgen receptor-expressing subtype," said Jennifer Pietenpol, Ph.D., Chief Scientific and Strategy Officer and Executive Vice President for Research at Vanderbilt University Medical Center, the study's corresponding author.

"When we refined the triple-negative breast cancer subtypes, we revealed an immune-modulatory descriptor or correlation. This *JAMA Oncology* study and others continue to confirm that lymphocytes, as measured by the immune-modulatory correlation, have predictive value

for better relapse-free survival for triple-negative patients."

"Further, this study provides evidence that the luminal androgen receptor subtype is more like estrogen receptor-positive (or ER+) disease. Prior studies investigating immunotherapy in breast cancers have shown that patients with ER+ disease have less benefit from immunotherapy, and we found that to be the case with patients with luminal androgen-positive tumors in this trial."

Interestingly, patients with higher body mass indexes and uncontrolled blood glucose levels had greater benefit from atezolizumab with carboplatin. The researchers noted that these patients may have more immune cells upon which anti-PD1/PD-L1 therapies can act. A lower risk of disease progression was also associated with high mutation burden and increased tumor-infiltrating lymphocytes.

"In this study, we observed that patients received benefit with atezolizumab even if the tumors were PD-L1 negative. We also show that, like prior clinical trials in melanoma and renal and lung cancers, tumors with high mutation burdens and the presence of immune cells within or around the tumor receive greater benefit from immunotherapy," said Brian Lehmann, Ph.D., Research Associate Professor of Medicine and lead correlative scientist on the study.

"This makes sense because each mutation has the potential to be recognized as non-self by the immune system, increasing the probability of immune cells already positioned around the tumor to recognize and target the cancer. One surprising finding was the trend toward greater benefit for patients with higher body mass indexes and patients with uncontrolled blood glucose at prediabetic and diabetic levels while on the study."

"Both obesity and diabetes are linked to systemic inflammation, and the

increased benefit may be attributed to higher adipose tissue composition in the breast and augmented by metabolic syndrome conditions such as type 2 diabetes. Further studies are necessary to validate these findings and delineate the effects of blood glucose and obesity on immunotherapy."

The combination therapy was generally well-tolerated, and toxic effects were consistent with previous reports for atezolizumab. The most common drug complications on the combination arm of the clinical trial were low blood platelet counts, anemia, lymphocytopenia, nausea, fatigue and increased liver enzymes. The participants identified as 69% white, 19% African American, 10% unknown and 1% Asian.

"It is important to highlight that these discoveries would not have been possible without the contributions of [breast cancer](#) patients and their willingness to contribute their time and numerous biospecimens to this study," said Pietenpol, Ingram Professor of Cancer Research and holder of the Brock Family Directorship in Career Development.

"These patients spanned a network of collaborative cancer centers within the Translational Breast Cancer Research Consortium and partnered with oncologists, pathologists, radiologists, basic and translational scientists and biostatisticians to complete this trial. We are so grateful to the [patients](#) and their families."

**More information:** *JAMA Oncology* (2023).

Provided by Vanderbilt University Medical Center

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