Precision Breast Cancer Trial Shows Improved Treatment by Tumor Subtype

I-SPY 2.2 study finds early breast cancer patients may benefit from pre-surgery combination of antibody drug conjugate Dato-DXd and checkpoint inhibitor durvalumab.

October 9, 2024 By University of California San Francisco

Breast cancer is the second leading cause of cancer deaths in the U.S. and worldwide, pointing to the continuing need to improve treatment strategies and therapies that better patient survival and reduce long-term treatment-related toxicities. This is particularly true for aggressive breast cancer subtypes in which many patients are cured of their disease, but at the expense of long-lasting, serious complications, including peripheral neuropathy, adrenal insufficiency, therapy-related leukemia and long-term heart damage.

For over a decade, the UCSF-led I-SPY trial consortium has worked to accelerate the development of new therapeutics for early-stage breast cancer, focusing on rapid identification of targeted treatment regimens for Phase III trials. The follow-up, I-SPY2, focused on patients with stage II and III molecularly high-risk breast cancer with the early endpoint of pathologic complete response (pCR) – the elimination of all signs of cancer in response to treatment – which correlates strongly with fewer complications and prediction of good long-term outcomes.

Like its predecessor, the I-SPY 2.2 trial evaluates multiple agents in parallel, using an adaptive randomization algorithm that preferentially assigned patients to study arms that exhibited efficacy in the same breast cancer subtype. By using a Sequential Multiple Assignment Randomized Trial (SMART) design, the trial has enabled the testing of drugs in sequence and a personalized approach to therapy to optimize therapies based on individual patient responses.

“I-SPY 2.2 is the latest in the I-SPY family of trials and introduces a very patient friendly and straightforward trial design. Ultimately, the goal is to find and develop biologically targeted treatments that help get each patient to the best possible outcome with the least toxicity. I firmly believe this trial is going to do just that,” said Laura Esserman, MD, MBA, founder and principal investigator of I-SPY 2.2, director of the UCSF Breast Care Center and co-leader of the UCSF Breast Oncology Program.

Recent results from one of the I-SPY 2.2 study arms, published Sept. 14 in Nature Medicine, showed that neoadjuvant treatment with the antibody-drug conjugate datopotamab–deruxtecan (Dato-DXd) in combination with the immune checkpoint inhibitor, durvalumab (Imfinzi), produced

high rates of pCR in patients who have an immune breast cancer subtype as well as a subtype of triple negative cancer that would ordinarily have a high risk of recurrence. Among 106 patients with HER2-negative breast cancer, 50% of the patients overall had a complete response. Importantly, for the patients with the immune positive subtype who achieved a complete response, over 50% achieved this without any standard chemotherapy and over 90% did not need doxorubicin-cytoxin (AC), one of the standard treatments that is particularly toxic.

The SMART trial design included three neoadjuvant treatment blocks (across six prespecified HER2-negative subtypes), with patients initially randomized to different experimental agents (block A), followed by a taxane-based chemotherapy regimen tailored to the patient's specific tumor subtype (block B), followed by combination chemotherapy regimen doxorubicin–cyclophosphamide or AC (block C). The clinical goal is to get each patient to pCR with the minimum required amount of therapy, limiting exposure to potential toxicities. Subtype-specific algorithms based on MRI volume change and core biopsy guided treatment redirection after each block, including the option of early surgery in patients who were predicted to have a high likelihood of pCR.

In the immune-positive subtype, Dato-DXd/Imfinzi combination exceeded the expected threshold for success after block A and had a complete response rate of 79% across all blocks. This pCR rate was equivalent to the rate expected for the standard of care (neoadjuvant treatment with chemotherapy), but 54% achieved that result after Dato-DXd/Imfinzi alone (block A) and 92% without doxorubicin–cyclophosphamide (after blocks A + B). For patients in hormone-negative/immune-negative subtypes, treatment with Dato-DXd and Imfinzi led to a pCR rate of 46% across all three blocks of treatment, exceeding the threshold for success.

"It is pretty exciting to see this pace of release of important results," said senior study author Esserman. "Dato-DXd/durvalumab is a promising therapy combination that can eliminate standard chemotherapy in many patients, particularly the immune-positive subtype."

There were no new toxicities from the treatments observed in the study arm. While common side effects of nausea, fatigue, stomatitis and rash were observed in block A, they were almost entirely low grade and resolved after treatment. No patients receiving block A treatment alone had adrenal insufficiency. Side effects like neuropathy and cytopenia in block B and C were consistent with treatment with taxanes and chemotherapy. The SMART design of the trials showed the benefit of being able to evaluate neoadjuvant therapies like Dato-DXd/Imfinzi alone to minimize side-effects.

"The ability to tailor treatment to biology and the observed response represents an exciting advance in personalized therapy," said Esserman. "We have demonstrated that it is possible to conduct a randomized trial that enables individualization of care within the trial. This is a patient-centric feature that makes patients want to participate in these studies. The lessons from this arm and every arm we evaluate continue to inform us and allow us to learn and improve the design."

The trial is ongoing, and the researchers are making adjustments based on specific patients' experiences and treatment outcomes. They hope to continue investigation of Dato-DXd/Imfinzi

treatment combination in the immune-positive and HR−immune−DRD subtypes, which appear to be the most likely to benefit from this combination.

Another intriguing finding from the trial is that 35% of patients with luminal B breast cancer, a subtype that shows particularly low rates of response to chemotherapy, showed no or minimal residual disease after going through the treatment strategy. This may warrant investigation of a longer course of therapy of Dato-DXd, which is already in a phase 3 trial. However, it does suggest that a subtype like luminal B breast cancer may be able to become responsive to immune targeted therapy.

This story was published by the University of California San Francisco on September 27, 2024. It is republished with permission.
