

BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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The Use of Neoadjuvant Therapy to Further Personalize Breast Cancer Treatment



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H&O What are the goals of neoadjuvant treatment in breast cancer?

LE The most important goal is to find out which medicines are effective at reducing an individual patient's chance of having a recurrence and dying of the disease. Beginning with surgery to remove the tumor does not allow us to learn about a person's risk and personalize treatment to the same degree that neoadjuvant treatment does.

If the tumor goes away completely with neoadjuvant treatment, a patient may require only breast-conserving surgery and radiation rather than a mastectomy and radiation. Another patient may be able to choose a mastectomy without radiation, in which case the results with breast reconstruction are better. Having the ability to know what is going on improves both choices and results.

H&O Which patients are candidates for neoadjuvant treatment?

LE People are candidates for neoadjuvant chemotherapy or combination treatment if they have molecularly high-risk disease according to one of the available molecular assays (MammaPrint, Oncotype DX Breast Recurrence Score, or PAM50 risk by subtype or recurrence score). Almost all triple-negative and human epidermal growth factor receptor 2 (HER2)-positive tumors are molecularly high risk. In the I-SPY2 trial, the criteria we use to determine eligibility for neoadjuvant therapy include being at high risk on the MammaPrint test and having a tumor measuring at least 2.5 cm on examination or 2 cm on

imaging. Patients with tumors that are clinically high risk but molecularly low risk are often offered neoadjuvant endocrine therapy (now formally as part of a sub-study of I-SPY2). In practice, I also use a few weeks of endocrine therapy up front in patients with HR-positive tumors, regardless of size, because we can use a Ki-67 test to determine the rate of cell turnover and get a sense of how effective endocrine therapy will be. Several good studies have established the usefulness of this approach, including the POETIC study, by Dr Ian Smith and colleagues.

H&O Can you describe the design of the I-SPY2 trial?

LE I-SPY2 is a phase 2 platform trial, meaning that multiple treatments can be studied within the same trial. Clinicians can make changes within the platform instead of having to start over with a new trial as they gather more information. The platform allows investigators to try new medications, alter the imaging tools they use, and update the molecular tools they use, for example. The trial becomes an engine for learning, and this is a far more efficient way to design trials than the traditional way. It also helps researchers avoid wasting time. I-SPY2 began with 6 sites, and now we have 25 sites participating. The trial has been very popular among both clinicians and patients.

The first step for new participants with locally advanced breast cancer is to classify their cancer into 1 of 10 molecular subtypes. Then, the adaptive randomization engine assigns each participant to a study arm, giving greater weight to arms that have been successful

in treating that participant's tumor subtype. Patients are evaluated at the time of surgery for the endpoint of pathologic complete response (pCR), which has been key to the success of I-SPY2. By starting with systemic therapy, we learn up front what is going to work rather than waiting 3 to 5 years after surgery to learn what will work. No surrogate endpoint is perfect, but it is amazing how well the response to neoadjuvant therapy predicts outcomes. For example, the risk for recurrence can be as low as 5% to 7% in patients with an excellent response to neoadjuvant therapy, and as high as 50% to 90% in those with a poor response, depending on the subtype and the residual cancer burden.

The trial uses a Bayesian framework so we can learn as we go, rather than follow a standard statistical model. We acquire more and more information until we gain certainty regarding whether a specific approach is working in comparison with standard treatment. As we build up data, the confidence interval narrows, and we become more confident that our result is correct. For example, we decided that we would graduate a drug to a head-to-head phase 3 trial if we determined that it was 85% likely to be successful in comparison with standard treatment. Everything that we have graduated has gone on to be of value.

The success of I-SPY2 has already convinced many researchers that its design is the optimal way to test new agents. If we focus on testing new drugs in the metastatic setting only, it can take 10 to 20 years for those agents to be used in patients with earlier-stage disease. With a platform trial, we hope we can get the learning cycle down to 3 to 5 years.

We have recently made a critically important change to the trial to adapt to the response of each individual. If participants do not have a great response to the first treatment tried, we can move on to rescue treatment with the best available therapy for their subtype. So we have a model that provides both personalized care and new information to help future patients. We do not want just to practice the state of the art; we want to advance it. This is the most important thing we can do in medicine. I have yet to meet someone with breast cancer who says everything about the treatment is great. Until that happens, our work is not done.

H&O Could you review the results from the 2 recent arms of I-SPY2 dealing with pembrolizumab (Keytruda, Merck) and durvalumab (Imfinzi, AstraZeneca)?

LE In results that we published in 2020, with Dr Rita Nanda as the first author, we found great success with pembrolizumab for women with high-risk, HER2-negative stage II or III breast cancer. Neoadjuvant treatment

with standard taxane- and anthracycline-based chemotherapy, followed by doxorubicin and cyclophosphamide, was compared with the same treatment plus 4 cycles of pembrolizumab. The addition of pembrolizumab nearly tripled the chance of pCR in the triple-negative cohort, from 22% to 60%. Pembrolizumab also improved the chance of pCR in the HR-positive, HER2-negative cohort, from 13% to 30%. Our next tasks are to build on that success, and to test “de-escalating” therapy (avoiding additional chemotherapy) once a complete response has been achieved with the first treatment regimen.

In results that we published in 2021, with Dr Lajos Pusztai as the first author, we found that the addition of durvalumab and the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (Lynparza, AstraZeneca) to standard paclitaxel neoadjuvant chemotherapy increased pCR rates in stage II or III HER2-negative breast cancer. Patients with HR-positive, HER2-negative cancers who were classified as ultra-high risk by genomic testing were especially likely to benefit from durvalumab, which increased the pCR rate in this group from 22% to 64%. It was interesting to see that certain patients with HR-positive disease responded to immunotherapy in both the pembrolizumab and durvalumab arms. It is clear that immuno-oncology is here to stay, particularly for the treatment of certain types of tumors.

One of the great accomplishments of I-SPY2 is that we have generated new ways to characterize tumors that go beyond just HR and HER2 status. Now we have the ability to look at the immune signature and the DNA repair deficiency signature, as well as the molecular subtype. These new ways of categorizing tumors are very compelling, and we are going to introduce them into the trial this fall.

H&O Could you describe the results from I-SPY2 dealing with SD-101?

LE Those results, which Dr Jo Chien presented at the virtual 2021 Annual Meeting of the American Society of Clinical Oncology, looked at a combination of pembrolizumab and the intratumoral agent SD-101, which is a form of a cytosine-phosphorothioate-guanine (CpG) nucleotide. The hope was that injecting this agent would improve response by making tumors more immunogenic. Unfortunately, the addition of SD-101 did not improve the overall response.

H&O Have any of the results of I-SPY2 driven the design of phase 3 trials?

LE The value of pCR as an endpoint at the time of definitive surgery was underscored by the results of

KEYNOTE-522, which supported the value of pembrolizumab as neoadjuvant therapy in early triple-negative breast cancer. On the basis of this study, the US Food and Drug Administration in 2020 approved pembrolizumab in combination with chemotherapy as neoadjuvant treatment for patients with high-risk, triple-negative early-stage breast cancer, followed by pembrolizumab alone as adjuvant treatment after surgery. The data from KEYNOTE-522 showed that, just as we reported across many arms in I-SPY2 (including the results published by Dr Yee and colleagues in *JAMA Oncology* in 2020), outcomes are excellent if you achieve pCR after chemotherapy, regardless of the treatment (control or experimental). In addition, when Dr Sibylle Loibl and colleagues, in the BrighTNess trial, tested the veliparib/carboplatin regimen that graduated from I-SPY 2, as well as each agent alone, they found that the addition of carboplatin to paclitaxel followed by doxorubicin and cyclophosphamide was what was driving the improvement in the proportion of patients with triple-negative breast cancer who achieved a pCR. That was the combination we trialed in I-SPY2, and their result was the same as ours—another study showing that early response is important.

H&O What are the next steps for I-SPY2?

LE We are moving to I-SPY2.2, in which we are learning how to individualize treatment further. The plan is to test some exciting new targeted therapies in the neoadjuvant setting, including antibody-drug conjugates, and see if we can avoid standard chemotherapy. We use imaging as a biomarker (functional tumor volume) to determine when to escalate therapy early or else de-escalate therapy. All of the agents we use have significant side effects, so we do not want to administer them if a patient will not benefit from them. Our goal is to achieve pCR in at least 90% of patients through the use of highly tailored treatment. I am fully confident that we will get there with the use of new biomarkers and tools that improve our ability to target the right patients with the right drugs.

H&O Who is an appropriate candidate for neoadjuvant endocrine therapy?

LE Anyone who has a relatively large tumor is a good candidate for neoadjuvant endocrine therapy. I-SPY2 contains an endocrine optimization arm because some people with relatively slowly growing tumors are still at elevated risk if the tumor is large. I do not believe that pCR is the right biomarker in these patients, so we are determining what the equivalent of pCR will be as we test some of the new selective endocrine receptor degraders and combinations of endocrine therapy.

H&O Can pCR be used to evaluate efficacy in all settings?

LE It is an excellent predictor of outcomes in molecularly high-risk tumors, whether the tumor is HR-positive or HR-negative, and HER2-positive or HER2-negative. We know from MINDACT and other trials that chemotherapy rarely helps to improve outcomes in patients with tumors that are molecularly low risk, even if the lymph nodes are positive. We are working to determine the right endpoint in low-risk tumors, including HR-positive low-risk tumors, through the endocrine optimization arm of I-SPY2. Could we use reduction in background enhancement on magnetic resonance imaging, or could we use circulating tumor DNA? We are testing multiple approaches to find the right answer.

An increasing number of neoadjuvant trials are being conducted, including trials for women with residual cancer after neoadjuvant therapy.

H&O What other ongoing phase 3 trials are looking at neoadjuvant therapy in breast cancer?

LE I am looking forward to seeing long-term follow up data from the ALTERNATE trial, by Dr Matthew Ellis and colleagues, which is comparing fulvestrant vs anastrozole in postmenopausal patients with stage II or III breast cancer (NCT01953588). An increasing number of neoadjuvant trials are being conducted, including trials for women with residual cancer after neoadjuvant therapy. All of these trials will help us to move the field forward.

H&O Is there anything you would like to add?

LE It is really important for us to educate people that clinical trials are how we advance the field. If none of these trials were done, we would be doing the same old thing. Our outcomes are so much better now than they used to be because we have been able to test new and tailored approaches.

Disclosure

Dr Esserman is an unpaid member of the board of directors of Quantum Leap Healthcare Collaborative, which is the sponsor of the I-SPY trial. She is also a member of the Blue Cross and Blue Shield Medical Advisory Panel, and has received a grant from Merck for an investigator-initiated trial of ductal carcinoma in situ.

Suggested Readings

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