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From ASCO: The Latest Research on Immunotherapy for Triple-Negative Breast Cancer

Announcer:
You're listening to *Breaking Boundaries in Breast Cancer*, sponsored by Lilly.

Dr. Caudle:
Much research has been focused on the need for improved therapies for triple-negative breast cancer, which accounts for 15–20% of all breast cancers. More recently, immunotherapy has emerged as a frontrunner to help meet that need, but there are still many gaps in understanding to fill and more studies to be done. So, to learn more, we'll be reviewing some of the latest abstracts presented at the American Society of Clinical Oncology's Annual Meeting.

Welcome to *Breaking Boundaries in Breast Cancer*. I'm your host, Dr. Jennifer Caudle, and joining me in this discussion is Dr. David Page, medical oncologist at Providence Cancer Center in Portland, Oregon. Dr. Page is a member of the National Cancer Institute's Breast Cancer Immuno-Oncology Task Force, which serves to advise investigators from around the world on the development of immunotherapy for breast cancer.

Dr. Page, welcome to the program.

Dr. Page:
Thank you for the opportunity.

Dr. Caudle:
Absolutely. We're excited that you're here. So, Dr. Page, before we get into some of the standout studies coming out of ASCO, can you tell us about how, in general, this rise of immunotherapy is changing outlooks on breast cancer?

Dr. Page:
Well, I have to say it's been a long time coming and delayed gratification. There have been a number of investigators across the world who have been pursuing immunotherapy in breast cancer, largely inspired by the success that we've seen in melanoma, and now, over the past couple years, we have our first phase III studies that demonstrate improvements in outcomes for triple-negative breast cancer. In ASCO 2020, we have 1 large phase III study that I'd like to share with you guys, and also, we'll put that in the context of the previous studies.

Dr. Caudle:
Let's dive right into some of the latest research, starting with the KEYNOTE-355 trial. What was being investigated? And what kind of

impact has it made in the therapeutic landscape for metastatic triple-negative breast cancer?

Dr. Page:
Well, I'd have to say that this study was conducted in the context of a more recent study that was already reported, the IMpassion130. In the IMpassion130, we learned that in the first-line setting for metastatic triple-negative breast cancer, we could improve responses of cytotoxic chemotherapy by adding a PD-L1 inhibitor, atezolizumab. Now, those responses appeared to be restricted to those patients with PD-L1 positive tumors. And the Merck 355 KEYNOTE study was designed to kind of broaden our scope to look at other chemotherapy backbones in combination with immunotherapy. This was a first-line study enabling investigators to choose the most appropriate chemo for the patient, and those chemotherapies were either Gemzar with carboplatin or a taxane, and then evaluate the question of whether or not anti-PD-1 would improve responses.

Dr. Caudle:
And what do you see as the next directions in research stemming from this trial to get a better read on the use of checkpoint inhibitors in combination with chemotherapy?

Dr. Page:
What we've learned from the KEYNOTE-355 study is that, in a very selected population of patients with first-line PD-L1-positive tumors, the addition of pembrolizumab improved outcomes as measured by progression-free survival. With that being said, there are additional questions that are raised from this study. There's an additional subset of patients with intermediate PD-L1 scores. Those scores are measured on a scale of 0–100, and patients with a score of 1–10 were evaluated for efficacy as well. Unfortunately, in this study we have uncertain outcomes in that subgroup. We see definitively that responses are improved with immunotherapy for patients with very high PD-L1 expression, so I think a future study would have to really evaluate efficacy in that intermediate subgroup of PD-L1 status 1–10.

Dr. Caudle:
Clearly, KEYNOTE-355 wasn't the only study incorporating this immunotherapy agent, so let's turn to the updated results from the ENHANCE-1 trial, which also got a fair amount of attention. So, can you review this study for us and what the updates were there?

Dr. Page:
Sure. The KEYNOTE-355 study focused on evaluating taxanes and/or gemcitabine with carboplatin plus pembrolizumab, but the question remains: If there are patients that would benefit from other types of chemo—for example, eribulin—could you see similar efficacy with other chemotherapy backbones? So that's what the ENHANCE-1 trial was about. It was a smaller study, but it combined very similarly to the 355 pembrolizumab with chemo, and this time it was with eribulin. Now, there were some mixed results with this study. If you looked at different subsets of patients—for example, patients treated in later lines of disease—the outcomes were a bit more modest relative to patients treated in the first-line setting, and very similarly to other studies, patients that had PD-L1-negative tumors had a more modest response. So I think we have to be holistic in our evaluation of these studies and put all this data together.

My impression of this combined data is that the context of when you treat the patient and which type of patient you treat matters for combining chemo with PD-1. For example, you want to treat patients as early as possible, perhaps in the first line of therapy, and you want to combine chemotherapy with PD-1 or PD-L1 inhibitors in patients that are positive for the PD-L1 biomarker. Now, the question of which chemotherapy is best is still unanswered, but what these trials demonstrate is that there's improvement across the board, perhaps.

Dr. Caudle:
Did these updates fall in line with expectations given what had been reported in previous years, or were there any surprises for you here?

Dr. Page:
I would say that the results of this trial are concordant with a number of other trials. What we see across a multitude of pembrolizumab and atezolizumab studies is that responses are generally less favorable in later lines of disease. That could be due to a multitude of reasons. One of them is the toxic effects of chronic chemotherapy, so we treat patients with chemo in the first line, and they lose a portion of their lymphocyte reserves, and then, perhaps, immune responses are suboptimal in later lines. We've seen that across a number of large studies with pembrolizumab. I would say that the message is clear, that chemo plus immunotherapy is perhaps favorable for patients but best when given in earlier lines of disease.

Dr. Caudle:
Excellent. For those of you who are just tuning in, you're listening to *Breaking Boundaries in Breast Cancer* on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me is Dr. David Page from Providence Cancer Center to talk about the latest research updates coming out of ASCO focusing on immunotherapy for triple-negative breast cancer.

So, Dr. Page, let's move on to another notable abstract presented this year, which was ENCORE 602, and I say notable in the sense that it struck a different, more subdued tone from the others we've talked about so far. What can you tell us about it?

Dr. Page:
Well, this was an admirable study because it evaluated a novel combination which aims to stray away from chemotherapy. It was a combination of an HDAC inhibitor, etinostat, with pembrolizumab. This agent is thought to be potentially immunogenic for a variety of reasons, but probably most important is that in a previous study this agent was shown to deplete suppressive immune cells, perhaps enabling or enhancing an antitumor immune response if given with anti-PD-1. In this study, we combined pembrolizumab with etinostat, and unfortunately, as you alluded to, the results were sobering. There was no improvement in progression-free survival, but perhaps there was even more toxicity as you would expect with a combination. What does this say? Well, I think we need to do a lot more of these studies and really look at our wealth of preclinical knowledge about novel combinations, and we need to keep trying, but it's not going to be easy in triple-negative breast cancer.

Dr. Caudle:
Were you surprised by those results at all, or were there reservations already from a mechanistic or resistance level when considering how aggressive triple-negative breast cancer is?

Dr. Page:
Well, I'd have to say I was disappointed, because the preclinical rationale was strong, and we had some biomarker data to suggest that this was going to be a promising combination. That being said, I'd like to reiterate it's the patient population, and the context of the patient might matter explicitly in triple-negative breast cancer. One of the potential flaws of this study is it focused on later lines of disease, so we combined these agents in the second- and third-line setting. Perhaps if we had intervened earlier when patients' functional status was better and resistance responses were less developed in the tumor, maybe we would have seen a positive result, and all the more reason to evaluate these types of approaches earlier, perhaps in the first-line setting.

Dr. Caudle:
So, Dr. Page, let's consider the state of immunotherapy more broadly again based on these various findings. How do you see immunotherapy's role evolving for patients with difficult-to-treat cancers, such as triple-negative breast tumors?

Dr. Page:
Well, I think now we've established that a multitude of chemotherapies could be combined safely and effectively with anti-PD-1 or anti-PD-L1 in the first-line setting and amongst patients with highly expressing PD-L1 tumors, so I think that's going to be established as a

standard of care. Now we have the ability to select the best chemotherapy for the patient. For example, if there was a patient that would be best served with a platinum in combination with PD-1, we have now the Merck 355 data to support that.

That being said, we have a lot more work, and perhaps the next step forward in terms of research is to evaluate patients with intermediate levels of PD-L1 expression to see if they would also benefit and to really advance these novel combination therapies and not be dismayed by failures. I'm happy that the ENCORE study was conducted. For every 3 or 4 failures of novel combination strategies, we may find a success.

Dr. Caudle:
And before we close, Dr. Page, what do you think are some of the critical areas that need to be addressed next in this triple-negative breast cancer space?

Dr. Page:
Well, I think we have to really understand our biomarker approach a little bit better. The problem is that different studies are using different assays for PD-L1, understandably, because they're different therapeutic agents, but we're going to have to harmonize those now that we have 2 positive studies for first-line triple-negative breast cancer. What I would suggest is that, much like we've already evaluated concordance between the VENTANA PD-L1 assay with other assays, we need to go back to those patients that had intermediate scores in the KEYNOTE-355 study, those patients that had modest PD-L1 expression, and see what their biomarker readout would be with other PD-L1 assays. There's a lot more to discover in that intermediate group, and eventually we're going to have to develop a cohesive paradigm for testing PD-L1 in considering a multitude of different PD-1 and PD-L1 agents.

Dr. Caudle:
Well, on that note I would like to thank my guest, Dr. David Page, for joining me to discuss some of the latest therapeutic advances for triple-negative breast cancer as reported at this year's ASCO meeting.

Dr. Page, it was great having you on the program.

Dr. Page:
Thank you for the opportunity.

Announcer:
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