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Research Highlights from ASCO: Evolving Treatment Options for Breast Cancer

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

Mr. Nacinovich:
Historically, breast cancer has often been portrayed as an immunological cold or silent disease, but the emergence of immunotherapies targeting breast cancers has fundamentally changed the way we think about this disease. And with the ongoing evolution of other systemic treatments such as endocrine therapies, targeted treatments and bone-modifying drugs, the opportunities to further change perceptions toward breast cancer are always nearby. Taking us part of the way are the latest research updates coming out of ASCO's annual meeting, and on today's program we'll dive into some highlighted studies making positive impacts in the field.

This is *Breaking Boundaries in Breast Cancer*, and I'm Mario Nacinovich. Joining me is Dr. Bora Lim, Assistant Professor in the Department of Breast Medical Oncology at the University of Texas MD Anderson Cancer Center. Dr. Lim is a translational investigator who is currently overseeing 5 active breast cancer trials and associated biomarker studies.

Dr. Lim, welcome to the program.

Dr. Lim:
Thank you, Mario. I'm glad that I'm here to discuss some exciting findings from the ASCO with you guys.

Mr. Nacinovich:
Before we dig into some of the highlighted studies coming out of ASCO, Dr. Lim, can you give us some background on the expanding range of therapies that have been developed for breast cancer and the impacts they have made in this field so far?

Dr. Lim:
So, the breast cancer research has been exciting. I would say this is one of the most rapidly changing fields within the solid tumor era. The most exciting changes that have been happening in breast cancer for the last few years I would include, No. 1, the immunotherapy, which is one of the topics that we're going to discuss, and the targeted therapies developed, including such as CDK4/6 inhibitor, which has saved a lot of women's lives, as well as the PI 3-kinase-targeted agents and some of the new therapies or combination strategies of all those agents plus chemotherapy or the others.

Mr. Nacinovich:
Thank you for that, Dr. Lim. Let's turn to some reports that got a fair amount of attention at ASCO this year starting with KEYNOTE-355, which focused on immunotherapy for metastatic triple-negative breast cancer. What can you tell us about this study?

Dr. Lim:

The KEYNOTE-355 has been the most exciting study that a lot of people have been reading who study metastatic breast cancer. As you know, there was a study called IMpassion130, which led to the very first approval of checkpoint inhibitor immunotherapy in breast cancer a few years back studying atezolizumab, which is kind of like the companion immunotherapy in combination with Abraxane, nab-paclitaxel, which is similar to this study. However, this specific study also allowed a different regimen called a carboplatin plus gemcitabine that is commonly used for the first-line metastatic triple-negative breast cancer setting, and in there they allowed the patients to be randomized into 2:1 fashion to 2 out of 3 will receive the immunotherapy, which is the pembrolizumab plus either taxane or carboplatin and gemcitabine, or the remaining 1 of 3 who is going to receive the placebo versus chemotherapy, and then compare who did better, how was the survival in 6 months without the progression and so on and so forth.

Mr. Nacinovich:
Did the results align with what you had expected, or were there any surprises for you here?

Dr. Lim:
I would say the surprising part for me was it was very, very similar to what we have seen in atezolizumab, which is anti-PD-L1, compared to pembrolizumab, which was studied in this specific study, which is anti-PD-1 in combination with chemotherapy. So the major difference of these 2 studies were: 1) we're using the nab-paclitaxel versus this specific study used either taxane or carboplatin and gemcitabine, and yet the hazard ratio was exactly around 0.62, 0.65, which is reduction about 40% risk of patients having progressed at 6 months after initiation of the study, which is very identical, which was a surprise to me. But more importantly, this study went 1 step ahead and even studied the patients expressing PD-L1, and in that specific analysis, the benefit was slightly larger in terms of their survival, which was another big success in the story of the immunotherapy in breast cancer.

Mr. Nacinovich:
Turning to targeted therapies, there were several reports coming out of ASCO that got our attention. One was the BYLieve trial. What do we need to know about this study's pursuits and the findings?

Dr. Lim:
The BYLieve study was very exciting for us who are following the PIK3CA mutation, which is common in ER-positive breast cancer, which could be as high as 40% of all the populations. They already had a SOLAR-1 study that was published which led to the approval of PI 3-kinase alpha inhibitor alpelisib. However, even though that study showed the efficacy of using the PI 3-kinase inhibition in ER-positive breast cancer, what we did not know is whether that efficacy will stay after patient has progressed on CDK4/6 inhibitor. This study was specifically designed to test the patient who has progressed on CDK4/6 inhibitor exposure, and excitingly, that efficacy were still the truth. So, even for this patient who had progressed already on CDK4/6 inhibitor, the progression-free survival at 6 months was greater than 50%, which is a success, with a median progression-free survival of 7.3 months, so that tells you that even after patient has failed some of the best therapy out there, if you can target a specific mutation for that patient, that strategy could still work as a well-impacted targeted therapy.

Mr. Nacinovich:
For those just tuning in, you're listening to *Breaking Boundaries in Breast Cancer* on ReachMD. I'm Mario Nacinovich, and joining me is Dr. Bora Lim to discuss recent advances in the breast cancer field presented at this year's ASCO meeting.

Let's stay with targeted therapies for a moment and cover the PARSIFAL trial since this got on our radar for endocrine-sensitive cancers. Can you walk us through the study?

Dr. Lim:
So the PARSIFAL trial is another study that we have been kind of waiting for. As you know, in the ER-positive breast cancer patients with metastatic disease, these patients have a lot more neuro aging; people live long, but there had been a very long debate for patients who have had very little exposure to endocrine therapy or who had a greater than 12 months after they completed the previous endocrine therapy for their previous breast cancer. Do we need to use the fulvestrant, which is a more aggressive form of shot-based endocrine therapy as a combination partner of the Ibrance, like palbociclib, or can we actually keep the aromatase inhibitor, which is a pill form? And some people may actually think that it is easier. That was a stand because we have had a few studies, such as the

FALCON study, showing fulvestrant being superior compared to the pill-based, which is aromatase inhibitor therapy.

Basically, what we did was we just randomly divided them into 1:1 fashion. One group get the palbociclib plus fulvestrant, the other group the palbociclib plus AI, so this was something that was not blinded. The exciting part of the study was the efficacy was exactly the same. The hazard ratio was 1.1. There was no significant difference. We proved that actually the pill form in combination with Ibrance in the endocrine-naive or endocrine-sensitive patients defined by more than 12 months since the completion of the therapy actually is a good strategy. I think this was good news for the patients. And then I think there are a lot of other biomarkers that are coming out from this study which will be further studied by the group.

Mr. Nacinovich:
I want to shift to the diagnostic side for a moment to focus on risk monitoring for breast cancer recurrence. And I understand there was some long-term follow-up data from the MINDACT study which tracked the performance of genetic testing. What were the takeaways from this report?

Dr. Lim:
So the MINDACT study, when it was first published in the *New England Journal of Medicine*, the follow-up median survival was around 5 years, and there the key point of the MINDACT study is that when we're stratifying the patients' risk based on clinical risk factors; can the 70-gene-based signature add any benefit by kind of separating patients into clinically high risk and yet genomically low risk, clinically high risk and genomically high risk? So, in the patients who had a high clinical risk factor that doctors would engage but genomically low risk, the benefit of the chemotherapy was only 1.5% in the original study. Now we are at the point that the median follow-up is up to close to 9 years, 8.7 years to be exact, and then there that difference of the chemotherapy benefit was even lower, so now it's 0.9%. This kind of adds the benefit of having an additional tool of genomic study to tell you whether my giving chemotherapy today for this patient would maybe add toxicity but not truly the clinical benefit.

Mr. Nacinovich:
Lastly, let's take a step back and consider this year's ASCO meeting as a whole. What else has been particularly exciting for you in terms of making new headway into the breast cancer space?

Dr. Lim:
As a researcher, I think the biggest kind of excitement of ASCO 2020 was really the immunotherapy. We already had an immunotherapy-based study that was approved by the FDA. There was a neoadjuvant study that was presented at ESMO. And now with this KEYNOTE-355, this is very, very exciting. People used to tell us that, "Oh, breast cancer is an immune cold cancer. There's no immunotherapy benefit." But I think now we are really learning that that is not the case. What's really left with us is that every single study are using slightly different biomarkers, how to determine the immune cold and immune hot, so that's homework that's left for us, but at the same time, that is a very exciting challenge. In addition, there have been very small studies that have been published and were presented in the ASCO meeting to say there might be even different strategy that can target therapy and the immunotherapy can be combined and actually have a better synergistic effect overall.

Mr. Nacinovich:
Dr. Lim, as a highly active researcher yourself, what's next on the agenda for you?

Dr. Lim:
Personally, I have been very interested in something called cell death pathway. Cells, when they are old and they are damaged, they have to go through a cell death called apoptosis, and yet the cancer cells have a lot of mechanisms to overcome that by expressing different proteins. And to our excitement there has been an approval of something called B-cell 2 inhibitors, such as venetoclax, that has now been studied in breast cancer, so I would love to hear what's happening there. I'm also actively participating in those studies. And so that might be a new, big therapy for breast cancer. Who knows? But that's what is exciting for me.

Mr. Nacinovich:
Well, it's exciting to see how these various research updates are changing the breast cancer landscape for the better. And I want to thank my guest, Dr. Bora Lim, for joining me to discuss some of latest data presented at ASCO.

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

Dr. Lim:
Thank you very much, Mario.

Mr. Nacinovich:
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