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ASCO 2023 Updates on Targeting HER3 in Breast and Lung Cancers

Announcer:
Welcome to CME on ReachMD. This activity is brought to you by Med-IQ and supported by an educational grant from Daiichi Sankyo. Before starting this activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
HER3 has been implicated as a potential therapeutic target due to its high expression levels in many tumor types and presence of genetic mutations in several tumors. This podcast will explore recent updates presented at ASCO 2023 related to HER3-targeted therapies in the area of breast and lung cancers. I'm your host, Dr. Jennifer Caudle, and I'd like to welcome Dr. Sara Hurvitz and Dr. Narjust Florez to the program, who are joining me to discuss targeting HER3 in breast and lung cancers. Dr. Hurvitz, welcome to the program.

Dr. Hurvitz:
Thank you so much.

Dr. Caudle:
And, Dr. Florez, welcome to the program.

Dr. Florez:
Thank you so much for the invitation. I'm delighted to be here.

Dr. Caudle:
Well, we're happy that you're here.

Dr. Hurvitz, you just attended ASCO. Were there any impactful studies related to HER3 in breast cancer?

Dr. Hurvitz:
Yes, actually, there was an interesting study, a phase 2 clinical trial presented by Erica Hamilton, looking at patritumab deruxtecan in patients with metastatic breast cancer. This was a study that enrolled patients with HER2-negative metastatic breast cancer. Patients were treated with patritumab deruxtecan, every 3 weeks, 5.6 mg/kg, and she presented the results from part A, in which 60 patients were enrolled and treated with single-agent patritumab.

The primary endpoint of the study was to look at the objective response rate and the 6-month progression-free survival rate. Patients were allowed on trial if they had hormone-receptor–positive breast cancer and had exhausted endocrine therapy and a CDK4/6 inhibitor and up to 2 prior lines of chemo; patients with triple-negative disease with up to 3 prior lines of chemo in the metastatic setting were also eligible. There were 60 patients who were treated on this clinical trial, and they were treated for a median of about 5.9 months. The patients were pretty heavily pretreated with a median of 3 prior lines of therapy when they went on study. A little more than one-half of the patients had hormone-receptor–positive breast cancer, and around 40% had triple-negative breast cancer. Interestingly, the majority of patients had strongish HER3 expression—64% of patients had a baseline HER3 expression of at least 75%, and 28% had 25% to

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74% HER3 expression.

It's interesting when you look at the outcomes data, the outcomes or the benefit with this agent seem to be sort of regardless of the level of HER3 expression. The objective response rate across all 60 patients was 35%. And that didn't seem to vary much based on level of HER3 expression, which I found to be quite interesting. The clinical benefit rate was 43%. And the duration of response of at least 6 months was seen in 48% of patients.

I think that the data in terms of the length of time patients were able to be on therapy were actually quite promising. The agents seem to be fairly well tolerated with mostly grade 1 and 2 adverse events, such as nausea and fatigue, as well as diarrhea. So the side-effect profile looked pretty good across the board. And there was only 1 case of interstitial lung disease.

So in my opinion, this is really quite exciting data that are adding to the phase 1 data that we saw relating to the activity of this drug, across all breast cancer subtypes in the past. I'm really looking forward to seeing more data in the near future.

Dr. Caudle:
Were there any ongoing studies related to HER3 in metastatic breast cancer to be on the lookout for?

Dr. Hurvitz:
Yes, there's actually the DecipHER trial. This is a phase 1, dose-escalation, dose-expansion trial of intratumoral, HER2 and HER3 prime dendritic cells, so it's like a vaccination strategy where the dendritic cells are conditioned against HER2 and HER3, and then injected into the tumor. In this study, patients with early stage breast cancer that's HER2 negative were eligible, and patients were receiving alternating ultrasound-guided intratumoral HER2 and HER3 dendritic cell injections twice a week for 8 doses, starting 2 weeks prior to neoadjuvant chemotherapy and immune therapy, a la the KEYNOTE-522 regimen.

So the dose-escalation phase of this study has 3 planned cohorts, following a 3 × 3 design with a maximum of 18 patients, and this study is open at the Moffitt Cancer Center. I think this is kind of interesting, it's a different way to go after HER3 than the use of an ADC. Instead of directly targeting HER3 with an antibody drug conjugate, you're instead targeting cancer cells with HER3 expression with conditioned dendritic cells. So I'm excited to see what the results of that study look like.

Dr. Caudle:
There was some exciting information presented at ASCO 2023 related to non–small cell lung cancer and HER3, as well. Dr. Florez, can you please walk me through some of the exciting highlights?

Dr. Florez:
Thank you so much doctor. Compared to breast cancer, in lung cancer we're a little bit behind when it comes to HER3, but we're right there. They just have more experience. So some data were presented that were about BL-B01D1, that's the name of the compound, BL-B01D1, and this is a new ADC, or antibody drug conjugate, that has 2 binding domains for distinct growth factor receptors, the drive cancer cell proliferation and survival. One of the unique things about this compound is that it blocks EGFR and it blocks HER3 signals to cancer cells. So the cells are now not able to proliferate but also induce apoptosis.

This new antibody drug conjugate has 4 different legs, and that's what makes it very innovative because it will be able to attach to the cell in different ways in different areas. This ADC is attached or linked to a very novel topoisomerase inhibitor via a cleavage linker.

So what we heard at ASCO is the first-in-human study dose escalation for this compound BL-B01D1. The study included patients with advanced or metastatic solid tumors, of which 89 patients had non–small cell lung cancer. These patients were heavily pretreated; 18% of the patients had brain metastasis at the moment of enrollment, and 50% had more than 3 lines of therapy.

As a phase 1 first-in-human study, we're going to talk about the adverse events before we talk about efficacy. Phase 1, main goal is still safety. So we did have good toxicity when it comes with what we see with antibody drug conjugates, which is bone marrow suppression. So we have leukopenia around 60%, grade 3 around 30%, neutropenia similar numbers, anemia 15% grade 3, thrombocytopenia all grades 44%, grade 3 19%; as a topoisomerase inhibitor, alopecia is common. We saw alopecia. Nausea and vomiting were also common, but nausea and vomiting did not reach grade 3. Fatigue, decreased appetite, diarrhea, mouth ulcerations. But what is important about the safety data is no interstitial lung disease was observed, which is very different than other antibody drug conjugates that are targeting HER3 and HER2. And for us, as a lung cancer doctor, no ILD is always good.

So quickly, this is still, you know, early data, phase 1, but the overall response rate for these patients was around 45.3%. Very impressive for patients who are in fourth line or higher therapy, with a median follow-up of 4.1 months. The patients who benefited the most had EGFR mutations, but there also was benefit in EGFR wild-type. Through this trial, we were able to find the dosing for the phase 2, which is going to be 2.5 mg/kg for every 3-week dosing. So the compound is going to move to phase 2.

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So the summary of this study is that BL-B01D1 demonstrated encouraging efficacy in heavily pretreated metastatic solid tumors, particularly in patients who have EGFR-mutated non–small cell lung cancer who have progressed on standard therapy. And this is a very big need because 13% of all lung cancers are EGFR plus the HER3. So there's a lot of future for these compounds.

Dr. Caudle:
That's very exciting. Thank you so much for sharing that. Dr. Florez, staying with you, is there any other novel data related to HER3 therapy that we should be on the lookout for?

Dr. Florez:
To our listeners, we need to be very clear, there is no HER3-directed agent approved by the FDA for the treatment of lung cancer to date. And I hope we come back in a year or 2 and that changes. But right now, there is not FDA-approved therapy, so everything is under development in a clinical trial.

Something that we're waiting for is more mature data for this study and other studies to understand testing and the need for biomarkers. HER3 is evolving in lung cancer, so we need to determine the ideal H-score—when we talk about H-score, it's the IHC, or immunohistochemical. What is the cut-off for these patients? Should we use the same cut-off that breast cancer uses? Or should we have our own cut-off for lung cancer? So that is to be determined.

So the compound that is moving faster in HER3 is patritumab deruxtecan, also known as HER3-DX. We call it HER3-DX because it's easier. This is also being studied in EGFR-resistant non–small cell lung cancer. The overall response rate is around 39% with a median progression-free survival of 8.2 months. But we still need larger studies for HER3-DX, including the upcoming phase 2 HERTHENA-Lung01 trial.

But what brings attention is we need to test our patients for biomarkers so they're allowed or given the opportunity to be part of these clinical trials with novel biomarkers. Biomarkers are essential for lung cancer treatment. And we're going to continue to talk about HER3, from predictive biomarkers to new drugs and toxicities associated with these drugs. So the history is continue to be written as we learn more about HER3 and non–small cell lung cancer.

Dr. Caudle:
That's a great way to round out our discussion on HER3 in breast and lung cancers. I'd like to thank my guests, Dr. Sara Hurvitz and Dr. Narjust Florez, for helping us better understand new HER3-targeted treatments for lung and breast cancers. Dr. Hurvitz and Dr. Florez, it was great speaking with you today.

Dr. Hurvitz:
Thank you so much for having me.

Dr. Florez:
Thank you so much for having this conversation with us. Science is moving forward so fast.

Announcer:
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