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Time needed to complete: 58m

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Questions and Conundrums: What Is the Future of ADCs in HR+/HER2-Low MBC?

Announcer:
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Dr. Sammons:
So hello, everyone. My name is Dr. Sarah Sammons from Dana Farber Cancer Institute. And I am joined by my esteemed colleague, Dr. Erica Mayer, also from Dana Farber Cancer Institute. We're going to talk a little bit today about the future of antibody drug conjugates, which I would think we can both agree is very bright. We've had the approval of 2 ADCs in the hormone receptor-positive space in the last year and a half, trastuzumab deruxtecan in the HER2-low subset, and sacituzumab govitecan for all hormone receptor-positive patients. And, you know, hopefully we'll even be expanding our definitions of HER2-low soon, and that's been an investigation. Erica, can you tell me a little bit about that?

Dr. Mayer:
Yeah, so thanks. And I totally agree the future is very bright here for this whole class of agents. Trastuzumab deruxtecan was studied in DESTINY-Breast04, which limited study to HER2-low patients, defined as HER2 1+ or 2+ ISH negative. There's been great debate in the breast cancer world about what does HER2-low mean? Is that a biological definition? Is that more an artifact of the pathology lab? And I think we questioned it a bit because there are some data, for example, from a study called DAISY, that suggested that in patients who are HER2-0, so you know, traditionally HER2-negative, the drugs still has an effect. And also T-DXd was approved in the pretreated setting in patients who'd had at least 1 prior line of chemotherapy. Could it work even better if we used it even earlier?

And so there are many ongoing efforts to explore this. And one of the most prominent is the ongoing prospective DESTINY-Breast06 study, which is looking at both of these questions, looking at T-DXd in the first-line setting as a chemotherapeutic agent, randomizing patients with HER2-low disease to T-DXd or to a treatment provider choice which could be paclitaxel, nabpaclitaxel, or capecitabine, agents that we would traditionally be using in this setting. But the study also includes eligibility for HER2-ultralow, which can expand into this space where we think we also may have candidates who could benefit from this drug but may not meet the criteria that were initially established in DESTINY-Breast04. So it's a really important study. And, you know, we're hopeful that studies like that, or even moving drugs earlier on in treatment, might expand our ability to use what appears to be a very powerful agent for a larger group of patients.

Dr. Sammons:
I would agree. I think right now about by current HER2-low standards, about 65% of patients are considered HER2-low. But the DAISY clinical trial could expand that to probably being the majority of our patients, should be fantastic.

Dr. Mayer:
So I think that's great to think about the 3 components of the molecule and how these are kind of modules that are interchangeable. And there's some really exciting drugs that are coming down the pipeline that look at switching out different components. Which of these new agents are you most excited about? What are you paying most attention to?

Dr. Sammons:

Yeah, I mean, I think that there are 2 that are showing success in early phase clinical trials that really come to mind in the hormone receptor-positive space that I'm excited to see move forward. There's datopotamab, or Dato-DXd, which is a TROP2 monoclonal antibody with a similar linker and payload to T-DXd, or trastuzumab deruxtecan and Dato-DXd has shown excellent results, promising overall response rates in early phase trials and is moving into a phase 3 trial in the hormone receptor-positive HER2-negative space so very excited to see where that one lands. And then there's also patritumab deruxtecan, which is a HER3-targeting antibody drug conjugate with a HER3 monoclonal antibody and a payload that's similar to T-DXd, and that's in the clinic with looking with very good response rates in the hormone receptor-positive space. So I'm excited about that as well.

Dr. Mayer:
Great, really exciting times, lots of terrific agents.

Thank you very much for listening, and I hope you found this helpful.

Announcer:
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