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How Are We Addressing Unanswered Questions Around ADCs in Metastatic TNBC?

Announcer:
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Dr. Tolaney:
Hi, my name is Sara Tolaney. I'm a Breast Medical Oncologist at Dana Farber Cancer Institute. And I'm joined by my colleague, Dr. Sara Hurwitz from UCLA, who I like to call Sara from the West Coast. And today we're going to be discussing antibody drug conjugates.

And Sara, so we've seen a lot of changes with ADCs over the last couple of years, in particular with development of ADCs really moving forward in metastatic triple-negative breast cancer. And now we actually have two ADCs approved for metastatic triple-negative disease both, sacituzumab, as well as trastuzumab deruxtecan for those patients with HER2-low disease. And so one of the questions that comes up a lot is: how do we think about sequencing these ADCs? So for example, if you had a patient with metastatic triple-negative disease, who is also HER2-low, which agent would you think about giving first and why?

Dr. Hurvitz:
It's a great question. And it's something that's actually come up in clinical practice fairly recently, for me, seeing patients with metastatic triple-negative breast cancer whose disease is ready to go on to chemo or a second line of chemotherapy and has both agents available. And because we don't have any direct head-to-head clinical trials comparing these two agents in this setting, it really comes down to the side effect profile, in my opinion, because both agents did demonstrate benefits in triple-negative breast cancer. Now, some would argue that data supporting sacituzumab govitecan is stronger for triple-negative breast cancer, because the ASCENT study entirely included patients who had triple-negative disease, whereas DESTINY-Breast04, only about 10% of the patients had triple-negative HER2-low disease. And so some are choosing sacituzumab first. But I do think going through the side effect profile with patients, including the amount of hair loss, the different

GI side effects and neutropenic effects, and then of course, considerations about ILD, are important to discuss with patients as we make this decision.

It's kind of interesting, you know, at this point, we have no data regarding whether we can sequence these drugs, whether it's okay to try one and then at the time of progression, go on to the next one. I think we're waiting for data to help us understand that. I think there was some data presented at ASCO this past year, a small case series from Mass General looking at sequencing ADCs. And it's going to be this type of real-world data that I think helps us understand if we can sequence ADCs that have similar payloads, going after different targets effectively.

What do you think about this idea of sequencing agents, Sara from the East? Are you doing this in this situation? And how are you choosing which agents to start with?

Dr. Tolaney:
I mean, just like you, I think, certainly, it's a discussion with the patient. But as you alluded to, because we do have level 1 evidence

from a phase 3 trial with sacituzumab, generally, I do tend to prefer using sacituzumab first, then T-DXd, subsequently. You know, with T-DXd, there are only 58 triple-negative patients in D-B04, and it just makes confidence intervals around these efficacy estimates quite wide. And so I've tended to do that.

But, you know, I think you bring up the excellent point that, you know, we don't really know how these ADCs are working one after another. As you pointed out, we did see some data and it did suggest at ASCO that in that second ADC, the PFS is quite a bit shorter than we would anticipate and when using it subsequently.

And I think it begs the question, what's the mechanism of resistance that's driving that ADC to stop working, at least that first one? And how is that then impacting the subsequent ADC? And I guess, what are your thoughts about that? You know, you pointed out that these payloads of sacituzumab and T-DXd are sort of cousins, right? They're both topo 1 payloads. You know, what do we know about ADC resistance? Is it payload dependent? Is it target dependent? And what do you think we need to learn to better understand how these sequencing will work?

Dr. Hurvitz:
Yeah, I don't think we know enough right now, but my suspicion is that there's a variety of mechanisms of resistance in ADCs, for example, that are going after a similar payload. For example, in the HER2-positive space, one could speculate that downregulation of the target is responsible for the development of resistance, but in the case of sacituzumab, and then trastuzumab deruxtecan, they're going after different targets. So it could be that the tumor just has lower levels of the second target that is being pursued.

My suspicion is though, that there is a mechanism of resistance relating to the payload itself, either efflux pumps or just survival of tumor cells that are able to circumvent that mechanism of apoptosis. So, it's going to be very interesting to see how more biomarker data gives us clarity on this particular point.

Dr. Tolaney:
And as you note, you know, it'll be even more interesting as we start getting ADCs that, in essence, have the same target and the same payload, because then, you know, we really will learn, is it another mechanism of resistance maybe even outside of either of those? So I think a lot more to learn and a lot more data needed to understand sequencing. But thank you so much for joining me today and discussing this.

Dr. Hurvitz:
Thank you so much.

Announcer:
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