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Who Is the Best Candidate for Sequencing Trastuzumab Detruxtecan (T-DXd) First?

Announcer:
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Dr. Mayer:
Hi there. I'm Erica Mayer from Dana Farber Cancer Institute. And I want to talk together about best candidates for sequencing T-DXd first.

So let's jump into a patient case. Our patient is 58 years old. Five years ago, she presented with de novo metastatic breast cancer which was hormone receptor-positive, HER2-negative but nowadays we would call this HER2-low, HER 2+. Her therapy included 3 years first-line ribociclib and letrozole. She then progressed and went on to second-line therapy with fulvestrant and everolimus; this was 9 months. And then progressed again and received first-line chemotherapy or third-line systemic therapy with capecitabine, which she's been on for the past year. Unfortunately, her disease is now progressing in the liver and the lymph nodes. We sent ctDNA, but she does not have any actionable mutations in ESR1, PIK3CA, or HER2. We biopsied her liver, and her disease is still hormone receptor-positive and HER2-low.

So let's think together, what's the best next step in treatment for her? Paclitaxel, tamoxifen, trastuzumab deruxtecan, abemaciclib, or sacituzumab govitecan? I'll give you a moment to think about this.

So in this situation, I would vote for trastuzumab deruxtecan as her second-line chemotherapy-based option. Let's think about why this would be. So first of all, we have this beautiful situation of having these 2 new exciting antibody drug conjugates that are available for us to treat metastatic hormone receptor-positive HER2-negative or low breast cancer. This includes sacituzumab, and also trastuzumab deruxtecan.

Importantly, how we sequence them depends on the line of therapy that they were approved for, and also the patient characteristics. In a patient who has hormone receptor-positive HER2-0 disease who exhausts endocrine therapy, they would go on to first-line chemotherapy, usually with capecitabine, second-line chemotherapy would be a more traditional option, for example, taxane, and third line, they would be eligible for sacituzumab.

But if they have HER2-low disease, then after their first-line chemotherapy, let's say capecitabine, based on the results of the DESTINY-Breast04 study, in the second-line setting, they would be eligible for T-DXd. And we know from DESTINY-Breast04, that use of T-DXd was superior than to treatment of provider choice. This also means that this pushes sacituzumab into the third-line setting. We don't know a lot about sequencing ADCs, about using sacituzumab after T-DXd, although it's something definitely worth thinking about.

There are mechanisms of resistance to antibody drug conjugates based on mechanisms of action as listed on the slide. At this time, it's hard to know in a clinical setting if any of these mechanisms exist, but this could cause issues with sequencing from one ADC to another.

We have limited data in clinical practice about the actual effects of sequencing ADC after ADC. There was data presented at this year's

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ASCO, ASCO 2023, looking at a single institution practice of management of patients with metastatic disease. In this analysis, there were 35 patients who were evaluated who had received sequential ADCs. Outcomes are shown in this figure. I think what's interesting is that if you look at patients who had a more prolonged response to ADC1, which is the purple line, this did not predict a more prolonged response to ADC2, which is the pink line. In fact, some patients who had limited response to ADC1 had a longer response to ADC2. And so it suggests that whatever mechanisms of resistance exist, they are not necessarily overlapping, and that resistance to one ADC does not preclude the ability to exploit - exposed to a second ADC.

Now this will be looked at prospectively in some upcoming studies that will be run through the Translational Breast Cancer Research Consortium. There will be a prospective registry study of ADC sequencing that will look at patients who go from T-DXd to sacituzumab, or vice versa. Additionally, TBCRC 064 is going to look at the sequencing of T-DXd and the novel antibody drug conjugates still in development Dato-DXd. And it's hoped that through these efforts, we will have a much better understanding about the ability to sequence ADC after ADC.

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

Announcer:
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