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Exploring T-DXd in HER2-Positive Breast Cancer Treatment

Announcer:
You're listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. And now, here's your host, Dr. Charles Turck.

Dr. Turck:
This is *On the Frontlines of Metastatic Breast Cancer* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss the DESTINY-Breast05 and DESTINY-Breast09 trials and their findings on trastuzumab deruxtecan, or T-DXd for short, for HER2-positive breast cancer is Dr. Jules Cohen. He's a Clinical Associate Professor of Medicine at Stonybrook Cancer Center in New York. Dr. Cohen, welcome to the program.

Dr. Cohen:
Thank you for having me.

Dr. Turck:
I'd like to start with some background on T-DXd, Dr. Cohen. What makes it distinct compared to other HER2-targeted antibody drug conjugates, like ado-trastuzumab emtansine, or T-DM1?

Dr. Cohen:
T-DXd came after T-DM1. T-DM1 is the trastuzumab monoclonal antibody conjugated to a microtubule inhibitor, whereas trastuzumab deruxtecan, or T-DXd, is conjugated to an irinotecan analog and has demonstrated much more potency originally in the second and third-line metastatic setting in the DESTINY-Breast03 trial.

Dr. Turck:
Now, focusing on the DESTINY-Breast05, which compared T-DXd to T-DM1 in patients with residual disease after neoadjuvant therapy, it found that T-DXd reduced the risk of invasive disease recurrence or death by 53 percent compared to T-DM1. From your perspective, what makes that such a profound result for HER2-positive early breast cancer?

Dr. Cohen:
So the standard for the treatment of early-stage HER2-positive breast cancer is frequently neoadjuvant chemotherapy and HER2-targeted therapy followed by surgery, and then there's a differentiation made between patients who achieve a pathologic complete response and patients who have residual disease after that neoadjuvant treatment. Patients with a complete response to neoadjuvant chemotherapy and HER2-targeted therapy tend to have a very good prognosis overall and a lower risk of metastatic recurrence and a lower risk of death. Patients who have residual disease after neoadjuvant therapy have a worse prognosis, so there's a lot of interest in coming up with so-called salvage therapies for patients with residual disease to reduce the risk of metastatic recurrence and ultimately, dying from the disease.

So the D-B05 trial was designed to establish T-DXd as potentially superior to T-DM1 in the salvage setting—again, patients with residual disease after neoadjuvant therapy—and, of course, the results of the D-B05 trial suggest that T-DXd does outperform T-DM1. And the event-free survival at three years was 92.4 percent for T-DXd versus 83.7 percent for T-DM1, a difference of 8.7 percent and a hazard ratio of 0.47, which, as you said, represents a 53 percent reduction in the rate of disease recurrence at three years.

So this is very important because this suggests that one can prevent metastatic recurrence and likely prevent more deaths by switching to T-DXd instead of using T-DM1 in these high-risk patients who have residual disease after neoadjuvant therapy.

Dr. Turck:

And based on these findings, how do you see treatment sequencing evolving for patients with residual disease after neoadjuvant therapy?

Dr. Cohen:
So I think it'll depend on the amount of disease that you have left after neoadjuvant therapy. Patients with a small amount of residual disease may still be candidates for T-DM1, especially if they're node negative, whereas patients who have a significant amount of residual disease and especially patients who are node-positive will likely benefit from T-DXd. The D-B05 trial specifically enrolled patients with so-called high-risk residual disease, and this generally included patients who were node-positive after neoadjuvant therapy.

Dr. Turck:
For those just tuning in, you're listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Jules Cohen about the efficacy and safety of trastuzumab deruxtecan, or T-DXd, for HER2-positive breast cancer.

So, Dr. Cohen, let's shift gears now and talk about Destiny-Breast09, which found that T-DXd plus pertuzumab demonstrated statistically significant and clinically meaningful improvement in progression-free survival versus taxane, trastuzumab and pertuzumab as first-line therapy for HER2-positive disease. How do you interpret these findings, and what could they mean for redefining the standard of care in the metastatic setting?

Dr. Cohen:
So, of course, the balance is always between efficacy and toxicity, and in the metastatic setting, patients are, by definition, incurable. And essentially, you want to give them the most effective therapy possible without necessarily compromising their quality of life. And the D-B09 trial basically tried to—or is trying to—establish T-DXd as a viable option in the first line in HER2-positive metastatic breast. It was a phase III trial. Patients were not allowed to have had prior systemic therapy in the metastatic context. They were allowed to have prior systemic therapy in the neoadjuvant or adjuvant context, provided their disease-free interval between completing their therapy in the early-stage treatment and their metastatic recurrence was more than six months. Patients were randomized 1:1:1 to one of three arms.

The first arm was T-DXd plus pertuzumab. The second one was the conventional standard of care in first-line metastatic HER2-positive breast cancer, which was paclitaxel, trastuzumab and pertuzumab. And the third arm was T-DXd monotherapy plus a placebo. And that third arm still remains blinded for progression-free survival. 1,157 patients were enrolled in the trial. They were stratified by hormone receptor status, whether or not they were de novo patients or recurrent from early-stage disease, and whether or not they had a *PIK3CA* mutation.

The efficacy demonstrated that the progression-free survival by independent central review was superior with the T-DXd plus pertuzumab arm when compared to the conventional standard of care of paclitaxel, trastuzumab and pertuzumab, and the interim results show that progression-free survival was 40.7 months in the T-DXd-pertuzumab arm versus 26.9 months in the standard-of-care arm. This represented a hazard ratio of 0.56. Of note, the overall response rate was 85 percent in the T-DXd arm versus 78.6 in the standard-of-care arm, and the radiologic complete response rate was superior in the T-DXd arm—58 versus 33 percent. Overall survival is immature at this point, but so far it seems to favor the T-DXd arm. The side effects were relatively comparable in both arms. There were more GI side effects and more cytopenias in the T-DXd arm, and there was, of course, a rate of interstitial lung disease: 12 percent but predominantly low grade.

So this basically represents a study that suggests that you can—and in some cases, should—use T-DXd plus pertuzumab in the first line in metastatic HER2-positive disease. And I think we're going to start to stratify patients by whether or not we think they're so-called HER2-dependent or HER2-independent. Patients who are hormone receptor-negative, HER2-positive patients who are *PIK3CA* wild type, and patients who we think are likely to do very well with the conventional taxane-based chemotherapy might get THP in the first line in the metastatic setting, whereas patients who we think are more HER2-independent, possibly some of the patients who are triple-positive, certainly patients who have other pathways that we think are activated—such as the *PIK3CA* pathway or other oncogenic pathways—who we think may not respond as well to THP will likely benefit from T-DXd plus pertuzumab, again, in the first-line setting in HER2-positive metastatic breast cancer.

Dr. Turck:
Jumping back for a moment and touching on those safety findings again, were those fairly consistent with what we know about T-DXd?

Dr. Cohen:
Yeah, I think so. I mean, basically, the dreaded side effect of T-DXd that makes some people apprehensive about using it is the incidence of interstitial lung disease or pneumonitis. And depending on the study, the percentage ranges from, say, 5 percent to 15

percent, so the 12 percent interstitial lung disease rate in D-B09 is right in the middle of what we would expect. Fortunately, it's generally low grade and treatable with steroids and either interruption of dosing or, in some cases, withdrawal of the offending medication. But yes, this is basically what we've seen across the various T-DXd studies in the metastatic and now the early-stage settings.

Dr. Turck:
And before we wrap up our program, Dr. Cohen, do you have any final insights you'd like to leave with our audience?

Dr. Cohen:
Again, we are always concerned about the balance between efficacy and toxicity. We want to offer our patients the most effective treatment but with the least amount of toxicity, if possible. In the early-stage setting, the issue is trying to prevent patients from converting from early-stage disease to developing metastatic disease, from which they will ultimately die. And the question is, can we head that off by more use of T-DXd either in the neoadjuvant or the adjuvant setting?

The downside, of course, is this risk of interstitial lung disease, and in some cases we've seen even deaths from interstitial lung disease in the context of T-DXd treatment, so we don't certainly want to cause any additional deaths in the early-stage setting where these patients essentially have curable disease. And we want to make things better, obviously, and not worse, so we'll probably reserve T-DXd for our particularly high-risk patients—patients who have a lot of residual disease after neoadjuvant treatment, or in the metastatic setting, patients who we think are less likely to respond to first-line standards of care taxane-based therapy.

That said, there's a lot of talk about induction chemotherapy in the first-line metastatic setting where patients might get either 12 weeks of THP or perhaps 12 weeks of T-DXd and pertuzumab and then switch to a more maintenance strategy. And there are a couple of studies that are of interest. There's the PATINA trial that was presented in San Antonio a year ago, which basically showed that after induction chemotherapy, patients did very, very well and had a very prolonged progression-free survival when they were switched to palbociclib and hormonal therapy if they were triple-positive patients—ER, PR and HER2-positive. And then at the recent San Antonio 2025, we saw the HER2CLIMB-05 trial that switched from induction chemotherapy to adding tucatinib plus trastuzumab as a maintenance strategy. And patients had a prolonged progression-free survival, and this may be a good strategy for the patients who are ER-negative and HER2-positive.

Dr. Turck:
That's some fantastic and wide-ranging analysis for us to consider as we come to the end of today's program. And I want to thank my guest, Dr. Jules Cohen, for joining me to discuss how trastuzumab deruxtecan, or T-DXd, is having an impact on how we care for patients with HER2-positive breast cancer. Dr. Cohen, it was great having you on the program.

Dr. Cohen:
Thanks again for having me.

Announcer:
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