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Progress in Breast Cancer Care: Translating SABCS Data Into Practice

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Dr. Geyer:
At the San Antonio Breast Cancer Symposium this year, exciting new data on antibody-drug conjugates were presented that have the potential to shift the treatment paradigm of breast cancer. Are you ready for the next wave of practice changes?

This is CE on ReachMD, and I'm Dr. Charles Geyer.

Dr. Jhaveri:
And I'm Dr. Komal Jhaveri, and it's a pleasure to be here today.

There were some interesting abstracts on new approaches using trastuzumab deruxtecan, or T-DXd, in HER2-positive early-stage breast cancer. Dr. Geyer, why don't you put these studies into review and context for us?

Dr. Geyer:
Yeah, at ESMO 2025, we saw new results on trials that bring T-DXd into the early breast cancer space. The first was DESTINY-Breast05, which was a follow-up trial to KATHERINE, that basically took the KATHERINE patients who, even though they benefited from T-DM1, still had a degree of risk that defined unmet need. We needed to do better. T-DXd was clearly a drug with that potential. So DB05 randomized the high-risk patients—patients who came in with locally advanced cancer initially, patients who still had positive nodes—randomized them to the standard 14 cycles of T-DM1 or T-DXd. And what we saw was with the T-DXd, we had a reduction in risk for invasive disease-free events of 53%. Across all the stratification variables, very consistent benefit.

So what we saw at the meeting update on that here, specifically what we didn't have is information on subsets by HER2-positive status. We know that T-DM1, it's not inactive, but it's not nearly as active in patients who have IHC 2+. Dr. Loibl showed us in her presentation that T-DXd works very well. The hazard ratio was 0.35 relative to T-DM1. So that's something that we're learning there. If you've got 2+, you need to definitely be thinking about T-DXd.

It also showed subset information. Doesn’t matter if the patient had anthracyclines or not; the benefit was there.

We had seen ILD in 9.6% of patients in the studies. We worked very hard to identify ILD. The new thing about early trials from late trials

was we incorporated regular CT scans to try and catch it early, asymptomatic, so you could intervene.

DB11, which was the other trial that we saw at ESMO, was a pCR study using a standard regimen of AC followed by THP versus T-DXd, putting T-DXd in to see if it can replace the anthracyclines. Very positive results. pCR was a primary endpoint; absolute 11% improvement for all comers when you split it out by ER/PR. It was particularly striking that high-risk patients that were in that study as well—and I think that's the thing to take home in the clinic—all this data right now is on high-risk presentation, so it's important to keep that in mind. pCR rate of 83% in HER2-positive ER-negative patients.

Looking at the adverse events, and we'll hear more about the PROs, it really does appear that 4 cycles of T-DXd overall are easier on patients than AC, and you certainly get rid of the anthracycline. I do think we're seeing T-DXd is becoming part of the standard of care for patients who present with higher-risk HER2-positive breast cancer.

So, Dr. Jhaveri, what are the clinical implications of the data? I guess I just gave my opinion. What are your thoughts about how our listeners should incorporate these into their practice?

Dr. Jhaveri:
I think these are very impactful data. I think that's the very first thing. I think they both have these practice-changing implications, I think, for us and how we treat early-stage HER2-positive breast cancer in clinic today.

And I think I completely agree with your assessment in the DB11 data set that, coming from Memorial Sloan Kettering Cancer Center where we still do anthracyclines, it's not that I have not adapted to the non-anthracycline regimens like docetaxel/carboplatin, but for my highest-risk patients, I still have been using anthracyclines and do believe in them.

And it's nice to see, finally, a comfortable dataset which tells you that you can get away with high-risk breast cancer with better efficacy than anthracycline-based therapy and have a safer profile. Very reassuring to see no deaths on the study. Definitely a good safety profile when comparing to anthracyclines from that perspective, and certainly unprecedented rates of pathological complete response rates, overall 67%. But in the HR-negative group, 83%. And even in the HR-positive group, where we tend to see slightly less, it was 61%, which is higher than other trials. So I'm very impressed with the data. Very happy with the data.

DB05, definitive study, such a great dataset. Very nice to now see that despite what we've been able to show with T-DM1, which is a good drug, and we've seen overall survival data from KATHERINE, but we don't see the CNS recurrences to be lower, which we've been able to see with T-DXd in this study as well, in addition to the invasive disease-free survival and other endpoints as well, and a 0.5 hazard ratio. Not a surprise in many ways, right? We've been able to see that in the metastatic setting, T-DXd beating T-DM1.

I think your point about HER2 IHC 2+ favoring T-DXd makes sense. It's approved in HER2-low breast cancer, approved for HER2-ultralow as well. So I think we are recognizing the benefit of these novel, newer antibody-drug conjugates, where the payloads have these bystander effects and is giving us these data. So very exciting to see both of these datasets change our practice.

Dr. Geyer:
That's good to have the option and—because I do think with the surprisingly clear better tolerability overall.

Dr. Jhaveri:
Exactly. In the early-stage setting, that's a plus.

Dr. Geyer:
Yeah. I mean, you've got—it's the win-win. A lot of times we have to accept incremental toxicity for incremental gain, and now you see improvement with less. So that's a very hard space to ignore.

Dr. Jhaveri:
I completely agree. I mean, I think no deaths, the ILD rates are the best it has been, just because it's only 4 cycles. Risk of radiation pneumonitis might be less as well potentially, right? Because you're doing this up front for surgery, then you have a break, then you get surgery, then you get radiation at the back end. I do think that all of those things hopefully will be taken into consideration when we're thinking about the totality of the data with the molecule.

Dr. Geyer:
There were also some interesting abstracts on TROP2-directed ADCs in metastatic breast cancer. Dr. Jhaveri, what do our listeners need to know about these studies?

Dr. Jhaveri:
Thanks, Dr. Geyer, happy to share my thoughts about all the data that actually came out at San Antonio and at ESMO this year.

So starting off with the ASCENT-07 trial. Now, the ASCENT-07 trial was really evaluating the benefit of sacituzumab govitecan compared to physician-choice chemotherapy for patients who've already had endocrine therapy but were chemotherapy naïve, so no chemotherapy in the metastatic setting.

And the reason we wanted to do that is because sacituzumab is already approved in the metastatic setting post-endocrine therapy following chemotherapy. So we already have progression-free survival and overall survival benefit for a later-line use for sacituzumab. So the idea was can we use it sooner?

Turns out, when we tried to do that, our primary endpoint, which was progression-free survival by blinded independent central review, the study did not meet its primary endpoint for statistical significance in this chemotherapy-naïve setting. The median progression-free survival were identical, 8.3 months in the sacituzumab arm compared to 8.3 months in the physician-choice therapy arm.

This is unlike DESTINY-Breast06, which is already approved also in the later line after one line of chemo, but also approved in the chemo-naïve setting post-endocrine therapy for HER2-low and HER2-ultralow tumors. Again, that's a HER2-directed ADC, trastuzumab deruxtecan. What we were talking about is TROP2 ADC.

We have an ongoing study now with datopotamab deruxtecan, another TROP2-directed ADC. This is TROPION-Breast06, and this is really a single-arm study. It's going to accrue 100 patients, trying to just evaluate the activity of datopotamab. It's not a randomized study. It's not a registrational trial. It's a phase 3b study trying to evaluate the activity of datopotamab deruxtecan in this chemo-naïve setting, specifically for IHC 0 tumors.

Moving on from hormone receptor-positive to triple-negative, we can talk about TROPION-Breast02, again evaluating datopotamab versus physician-choice chemotherapy for patients who are not eligible for getting any checkpoint inhibitor in the first-line metastatic triple-negative breast cancer setting. And there, again, not only did we see a progression-free survival benefit, which was a co-primary endpoint with overall survival, we also saw an overall survival benefit. The delta of improvement compared to physician-choice chemotherapy for both PFS and OS was 5 months. Very impressive data there.

We saw that despite 15% of our patient population progressing from their early-stage treatments within 6 months, so that was 15% of the population, yet we saw this benefit in that difficult-to-treat group. Overall response rates were impressive, over 60%. Good safety data. If you look at the exposure-adjusted rates of treatment-related side effects, they were better with datopotamab compared to physician-choice therapy, and lower discontinuation rates as well. Of course, a friendly administration, q3-week schedule, which is helpful for our patients.

We have data for ASCENT-03 and ASCENT-04 for sacituzumab in the triple-negative first-line setting, both for patients who cannot get a checkpoint inhibitor and for PD-L1–positive tumors with a checkpoint inhibitor. Again, showing us a breadth of dataset saying that in the first-line metastatic setting, we should now be thinking about antibody-drug conjugates as well. We look forward to getting regulatory approvals for all these agents so that we can offer them to our patients in clinic.

So maybe, Dr. Geyer, what does this mean for our patients? How do you envision really incorporating these new data into clinical practice?

Dr. Geyer:
Yeah, I mean, I think the challenge of the ADCs for me has always been they look like they are quite active in refractory patients. I know when T-DXd, it was, oh, it should be parked out there. We can do good things with our standard chemotherapy, save it for the end where things don't work. But then when you see it brought forward, clearly doing better, and there's also been this consistent thing that

is seen in these studies: You need your best therapies up early in these more aggressive, particularly the triple-negative breast cancers because you might not have the opportunity in the second line.

So I think we will be moving them to first line for sure as they become available. The challenge, of course, is going to be which one do you use? At progression, what does one do? Will it just be convenience? Side effects? Right now, that's what I would tend to use. You mentioned every-3-week. This is a challenge, I think, for sacituzumab. It's just a little more in for treatments. I think my sense is a little more toxicity.

Dr. Jhaveri:
Yeah, no, I agree with you. I think antibody-drug conjugates are here to stay. I think they are definitely our present. They're definitely going to be our future, and they might be replacing chemotherapy in as many settings as we can see. So we can continue to offer these therapies.

And I agree with you, I also tend to not wait to offer my good therapies later down the line, given the attrition rates we also see, specifically in triple-negative breast cancer, where the attrition rate is 50%. So I think you want to use up your good therapies up front.

But at the end of the day, having good options, knowing the distinct toxicity profiles, and how to manage those toxicity profiles really well so we can offer these best drugs to our patients for a long period of time is key.

Dr. Geyer:
Patient-reported outcomes are becoming increasingly important in clinical trials. Dr. Jhaveri, what were some of the PRO findings from the ADC trials we heard here at San Antonio?

Dr. Jhaveri:
Yeah, no, I think it's very, very important that certainly we want our patients to live longer, but we also want them to live well. So we want newer drugs that are working really well, we want them to be safe, and we want our patients to feel like that's not impacting their quality of life. So hearing from them about how they feel is very, very important.

And thankfully, all the new datasets that we've heard about, whether it's using trastuzumab deruxtecan in the early-stage neoadjuvant setting from DESTINY-Breast11, or using trastuzumab deruxtecan in the first-line metastatic setting where patients received it for a long period of time in the DESTINY-Breast09 study, or our metastatic triple-negative breast cancer patients with ASCENT-03 also receiving sacituzumab in the first-line setting, we heard the patient-reported outcomes were in line with what physicians think as well. The patients tolerated treatments well. They were better than what they were for the physician-choice chemotherapy arm.

So it's very nice to see that they are doing better on these therapies. The therapies are safer and they're feeling their quality of life is maintained. So very reassuring data.

Dr. Geyer:
Yeah, no, I think it's really been quite interesting. The PRO data is really—I think this is the first wave of trials that have had it as intensely collected. So I think it's a nice addition, or reassuring addition, that the patient's opinion has been checked and there's concordance. Yeah, it's a good thing.

Dr. Jhaveri:
Yeah.

Dr. Geyer:
Well, this was a great conversation. But before we conclude, Dr. Jhaveri, what's your one take-home message for our audience?

Dr. Jhaveri:
Yeah, no, it certainly is a very exciting time in breast medical oncology. We saw some great datasets being reported out at the San Antonio Breast Cancer meeting and earlier at the ESMO Annual Meeting as well. And I think the one take-home message would be let's try and offer our most effective therapies first. Let's not hold on to them for later, just to make sure we can offer it to all our patients.

And then while we're doing that, let's make sure we understand the side effect profile for these drugs and provide optimal supportive measures and support to our patients, just so that we can let them have the expected benefit that we hope them to achieve with these new therapies.

Dr. Geyer:
Yeah, I agree. I think this was a very uplifting, encouraging meeting. You really are feeling progress is being made and we are doing a better job. We're getting closer to the goal of curing all of our early breast cancers and doing a much better job of taking care of our patients with recurrence.

So I think San Antonio 2025 has been another success. That's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Komal Jhaveri, for joining me and for sharing all your valuable insights. Great speaking with you today.

Dr. Jhaveri:
Thank you, Dr. Geyer. It was such a great pleasure to speak to you as well.

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