Clinical Updates from San Antonio: HER2+ and HER2-Low Breast Cancer

Rahul Gosain, MD: Good evening, everyone. My name is Rahul Gosain.

Rohit Gosain, MD: And I'm Rohit Gosain.

Rahul Gosain, MD: And we are Oncology Brothers. Today we have the pleasure of having a renowned educator and a clinician, Dr. Erika Hamilton from the Sarah Cannon Research Institute. Dr. Hamilton, we hope to discuss practice-informing studies in HER+ and low HER2 patient population presented at the SABCS 2022. Dr. Hamilton, thank you so much for joining us today.

Erika Hamilton, MD: Thanks so much for having me. It's been a great meeting, and I'm happy to discuss this.

Rohit Gosain, MD: Welcome Dr. Hamilton. As we continue to see these paradigm-shifting studies, if you don't mind touching base with updates in adjuvant settings with APT and ATEMPT trial and study design and some of the key findings please.

Erika Hamilton, MD: Yeah, absolutely. You know, so neither of these are particularly new studies; but we did see updates from them here at San Antonio this year in 2022. If you recall, the APT trial was an attempt really at de-escalation or giving less to those patients with HER2+ breast cancer that may not need it.

And so to qualify for this trial, you had to have a less than 3-centimeter tumor and be node negative, and patients received just paclitaxel and trastuzumab for 12 weeks. So you can kind of think about it as mini HER2 treatment, you know, if we're going to steal things like babytam from the session.

You know, what we saw is now we have 10 years follow-up, and with 10 years follow-up, for those patients that had kind of good clinical risk features in HER2+ breast cancer, the cure rates are still over 95%.

Now functionally, we do have new agents like TCHP and kind of bigger chemotherapy regimens, and so at least who I'm really using those for in my clinic are traditionally the 2 centimeters or less and node negative. But I think this is really, you know, good data, reassuring now especially with long-year follow-up at ten years.

We also saw some data from ATEMPT and, remember, ATEMPT was the opportunity to look at adjuvant T-DM1 (trastuzumab emtansine) in HER2+ breast cancer. Similarly, now with multiple years of follow-up, we also see greater than 95% cure rate. But also remember that when ATEMPT was reported, we actually were a little bit disappointed in tolerability; and it turns out that one year of T-DM1 and antibody drug conjugate might be a little bit too long. And so there is another trial led by Dr. Tolaney looking at ATEMPT 2.0 of whether six months might be enough. So stay tuned on that.

Rohit Gosain, MD: Well, we continue to see the pattern that more is not always better.

Now, focusing on one particular agent here, trastuzumab-deruxtecan. At this conference, we saw updated data on DESTINY-Breast02, DESTINY-Breast03, and DESTINY-Breast04. Can you please start off with DESTINY-Breast02 and -03 study design and its key findings.

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Erika Hamilton, MD: Yeah, absolutely. So DESTINY-Breast02 was kind of the so-called third line and beyond trial that looked at trastuzumab-deruxtecan (T-DXd); I think everyone's familiar with this HER2 antibody drug conjugate at this point, versus treatment of physician's choice. And so we saw data that

for progression-free survival, as well as overall survival, we had about a year improvement on both. So certainly significant.

I think the only kind of popping of our bubble in terms of that study is actually DESTINY-Breast03. And DESTINY-Breast03 was a second-line study looking at trastuzumab-deruxtecan versus T-DM1. And this has been presented multiple times before.

But what we saw this time was overall survival data. So not only is progression-free survival improved by about 22 months or almost 2 years for patients that received trastuzumab-deruxtecan over T-DM1, although the medians weren't reached, overall survival was actually quite significant as well. And so that's really encouraging. It had a hazard ratio of 0.64. And so functionally, I think most patients in the clinic are probably going to receive trastuzumab-deruxtecan second line. And so that's why I said, "Unfortunately, it makes DESTINY-Breast02 a little bit less clinically significant."

You know, one caveat of some patients that may receive something else might be somebody that has very active brain mets and could receive tucatinib for the indication. But I really think, you know, we're continuing to see trastuzumab-deruxtecan go earlier and earlier. And as we all know, there's trials pending in the first line metastatic setting as well as neoadjuvant and adjuvant for trastuzumab-deruxtecan.

Rahul Gosain, MD: Thank you, Dr. Hamilton. As you've said, this just solidifies our second-line treatment. T-DXd is approved in this setting, and based on this data, we also know that T-DXd works after T-DM1. But given the approval, given the data, we'll be using T-DXd in second line and then T-DM1. But we don't have any data on that. What are your thoughts? How would you sequence that?

Erika Hamilton, MD: Yeah, I think you've identified, you know, a key kind of unknown spot in HER2+ breast cancer. I think most of us, you know, as you say, are using trastuzumab-deruxtecan second line. Certainly, the magnitude of the data is just astounding.

I personally am using capecitabine with trastuzumab and tucatinib third line, and I'm coming back to T-DM1 probably fourth line. And that's for a variety of reasons. One, you know, I think T-DM1 is clearly the inferior antibody-drug conjugate at this point; so to kind of use the inferior ADC right after the better ADC just, you know, doesn't feel incredibly great.

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The other thing is, you know, one proposed mechanism of resistance to trastuzumab-deruxtecan is a downregulation of HER2 expression on the cell surface. So meaning those patients that have been on trastuzumab-deruxtecan may not express a lot of HER2 anymore, at least temporarily. And so you could imagine that, as I like to say, naked chemo with capecitabine in combination with trastuzumab and tucatinib may be a better choice and then coming back to T-DM1, you know, a little bit with spatial separation from our trastuzumab-deruxtecan.

Rohit Gosain, MD: Well I think sequencing is certainly going to be the key here. Dr. Hamilton-

Erika Hamilton, MD: Absolutely.

Rohit Gosain, MD: -well we are seeing some ILD (interstitial lung disease) which has been certainly a concern. When T-DXd is utilized in earlier lines, we see less of those incidents. Do you think that is because we are getting better in identifying and managing ILD, or could there be another explanation to this?

Erika Hamilton, MD: Yeah, I think it's certainly that we're getting better and managing it better. You know, in DESTINY-Breast01, you know, the first trial with trastuzumab-deruxtecan, unfortunately, we saw, you know, quite a few cases of fatal ILD or pneumonitis. Overall, pneumonitis rates were about 15%.

And now, if you look at the DESTINY-Breast03 data, although overall ILD is still kind of in that low teens range, we no longer have any cases of Grade 4 or Grade 5 ILD.

Now in DESTINY-Breast-02, we kind of did see just a tad. So, you know, I think part of it is that it's just those fatal cases are becoming exceedingly rare; and what we've done since DESTINY-Breast01 is a lot of education about how to handle it, about being aware that it can happen. And so unlike immunotherapy or other drugs that can cause ILD, where you may not really do much until you see Grade 3, we know that early recognition of ILD pneumonitis with trastuzumab-deruxtecan is really important.

And so, you know, we're not spacing out our scans too much. I continue to scan my patients on trastuzumab-deruxtecan every nine weeks because we really want to catch these cases of ILD when they're asymptomatic, Grade 1. We can kind of get rid of the ILD, hold drug, and get patients back on the drug. The recommendation for Grade 2 or greater ILD is stopping the drug, and you can't continue.

Now I think a lot of us in clinical practice do have questions about the more mild Grade 2 cases and could we continue, and I think we're going to try to gather that data. But really recognizing and catching ILD when it's mild enables us to go back on therapy and prevent these more, you know, challenging cases of ILD and poor outcomes.

Rahul Gosain, MD: Dr. Hamilton, you've mentioned that you do scans every 9 weeks in your clinical practice, but most of these DESTINY trials had scans every 6 weeks. And in the community, we're often used to doing scans every 12 weeks. So there is some of this paradigm shift that a lot of us are going 9 to

10 weeks, usually after 8 weeks, because that is what insurance will allow. But I really think closer scans in the community is very important.

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Erika Hamilton, MD: That's exactly the issue. Realistically, we can't get scans every 6 weeks. No insurance company is going to pay for that. Typically, you know, we can get scans after that 2-month point, and so 9 weeks works out very well.

But, you know, I agree. It's typically these treatments that patients might remain on for a long time. You know, CDK4/6 inhibitors, trastuzumab-deruxtecan, where there's a desire to space out the scans just because they're burdensome on the patient. And obviously, there's a cost issue there as well. But I think with trastuzumab-deruxtecan, we're really taking a close look at these scans. They're too important to space them out much beyond 9 weeks.

Rohit Gosain, MD: I couldn't agree more.

Dr. Hamilton, T-DXd got approved in low HER2-patient population based on DESTINY-Breast04. We also know that there's significant discordance in patients being labeled as low versus HER2-. What are your thoughts and some takeaway from the updates of DESTINY-Breast04 and HER2 IHC. Is it truly the right test for these patients?

Erika Hamilton, MD: Yeah, absolutely. So, you know, DESTINY-Breast04 was a trial that created a paradigm shift for us. You know, historically, you were either HER2+ or you had cancer that was HER2-. There was no concept of HER2-low, right?

And so, you know, it wasn't that it hadn't been looked at. We looked at trastuzumab in those patients that were HER2-low. It was stone cold negative. But with these new drugs and new mechanisms of actions, bystander effect, it's really kind of changed the game here.

And so DESTINY-Breast04 was a trial that looked at trastuzumab-deruxtecan versus treatment of physician's choice, essentially chemotherapy, for patients that had HER2-low expression, 1+ or 2+ and [ISH]-, and really trast (T-DXd) clearly outperformed chemotherapy. And so this is a new standard now.

I think the question you raise is exactly the right question. Is that HER2-low is pretty imprecise. And in reality, IHC was designed to pick out patients that had high expression. It was never designed to pick out the difference between a 0 and a 1+. And in reality, I don't really even know that you need 1+ to have activity.

For example, in the DAISY trial, we've been seeing about a 30% response rate, even in patients that have IHC 0. Now the question is, does 0 mean 0? And no, it doesn't. You can actually have thousands of copies of HER2 on the cell surface and still be classified as a 0.

And so in the session at San Antonio this week, there was a fantastic analogy that you don't weigh a mouse on a scale built for an elephant. And so we're in the situation now that we're trying to look at mouse-like amounts of HER2. And so is there a more quantifiable way that we can really get at that and figure out what's the most appropriate threshold?

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So how do I handle this in the clinic? Well first, I repeat the HER2 because if you're looking at a pathology report that was read by a pathologist two years ago, they didn't really care between a 0 and a 1+. It wasn't actionable. It was going to be HER2- either way, and so they weren't necessarily spending a

lot of time really trying to figure out whether there was any area in that tumor that had 1+ expression. And if there isn't historical material, very appropriate to rebiopsy.

I've also had a lot of people ask, "Well what about if the last result maybe was negative but they've had HER2 positivity in the past?" And I think this gets into tumor heterogeneity where even within the same lesion, you can look at one spot and maybe there's HER2-low expression. In another spot there's not. And certainly, if you go and look at other metastatic sites, we see this.

So really, you know, I think probably all of us are being a little bit liberal on this, that we're really just trying to find a spot that has some HER2-low and kind of considering that actionable.

Rahul Gosain, MD: I mean HER2 0 was actually defined if you were less than 10%, so there's so much room and subjectivity in this.

Erika Hamilton, MD: Absolutely.

Rahul Gosain, MD: Dr. Hamilton, coming back to DB04 (DESTINY-Breast04), this is the same patient population, triple negative, hormone receptor-positive that will be exposed to immunotherapy and mTOR inhibitors before getting T-DXd. If a patient has had pneumonitis but now has resolved from immunotherapy or mTOR inhibitor, how would you tackle T-DXd in that setting?

Erika Hamilton, MD: Yeah, that's a great question; and it's information we really don't have from the clinical trials because, really, patients on clinical trials had not had pneumonitis ILD.

You know, I think, functionally, they're different classes of molecules. You know, if somebody's completely recovered from the pneumonitis, it's hard to say that you're not going to offer somebody a therapy that so clearly improves outcome when they're living with something like metastatic disease

that is going to shorten their life. And so I probably would offer those patients and just keep really close eye.

You know, I think another big thing that doesn't get talked about enough is patient education. Really, you know, "Hey, if you have that cough, if you're short of breath going up the stairs, don't think that you're out of shape or you've caught a virus. I want to know about it, and I want to look into it." And so I think our patients can really help us kind of, you know, sound the alarm if they're having any pulmonary complaints and help us monitor as well.

Rohit Gosain, MD: Well, I think as a community, as well as patient education and training ourself for these side effects is going to be the key with all this.

Getting comfortable with these antibody-drug conjugates is so much more important now than ever before. So thank you so much for taking the time to review this practice reinforcing studies, and updates from San Antonio Breast Cancer Symposium, Dr. Hamilton. We truly appreciate your time.

Erika Hamilton, MD: Thank you so much for having me.