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Navigating the HER2 Treatment Paradigm for Breast Cancer

Announcer:
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Dr. Modi:
Hello, and thank you for joining us on this webcast titled: Navigating the HER2 Treatment Paradigm for Breast Cancer. I'm Dr. Shanu Modi. I'm a Professor of Medicine at Weill Cornell Medical College in New York City and a medical oncologist at Memorial Sloan Kettering Cancer Center. And I'm joined today by my colleague, Dr. Sara Hurvitz of UCLA. Sara, please introduce yourself.

Dr. Hurvitz:
Hi Shanu. It's so good to be here with you today. I'm Sara Hurvitz, medical oncologists and director of the breast cancer trials program at UCLA.

Dr. Modi:
Wonderful. Thanks for joining us, Sara.

So just to start, but before we get started today, let's review our learning objectives. Upon the conclusion of this webcast participants should be able to distinguish between approved HER2-directed therapies to optimize sequencing throughout the treatment continuum, discuss potential additional indications for recently approved agents used in the treatment of metastatic HER2 positive breast cancer based on the currently available data and ongoing trials, and identify the adverse effects seen with recently approved anti-HER2 therapies, and recommend appropriate monitoring and management strategies to optimize therapy.

So maybe to set the stage, I'll just start things off here with a little bit of background. So HER2 positive breast cancer represents approximately 20% of all breast cancer. And it's defined as breast cancers either with amplification of the HER2 gene and/or overexpression of the HER2 protein receptor. So HER2-positive breast cancers fundamentally have an overabundance of the HER2 receptor on the cell surface. And this is a driver of these breast cancers, and it leads to more aggressive disease that can be resistant to conventional therapies. And so ultimately, having established HER2 as a driver in these breast cancers, we've seen the development of a multitude of HER2-targeted therapies. Today, in fact, we have eight approved HER2-targeted agents. And this has really led to improved clinical outcomes for patients with this subtype of breast cancer. So it's really a great success story of molecularly-targeted therapy.

Shown here are real-world curves taken from the French Metastatic Breast Cancer Registry. And you can see that, as we've introduced new HER2-targeted therapies, we've seen an improvement in overall survival for patients with HER2-positive metastatic breast cancer. And in 2013, with the incorporation of the CLEOPATRA regimen, today, we see a median overall survival for our HER2 positive metastatic patients of approximately 5 years, which is more than double what we were able to achieve in an era before HER2-targeted agents.

So as mentioned, there are approximately eight approved HER2-targeted therapies. And we can group these as either monoclonal antibodies, or tyrosine kinase inhibitors, and antibody drug conjugates. And these all work in different and unique ways and have led to improvements in clinical outcomes for patients with HER2 positive disease.

So here is I think, the most I think, updated treatment algorithm for patients with HER2-positive metastatic breast cancer. And you'll see in the first line setting our preferred regimen is the CLEOPATRA regimen which is dual HER2 blockade with trastuzumab plus pertuzumab and a taxane. In the second line, it - we now prefer to use the new HER2 antibody drug conjugate, trastuzumab, deruxtecan, or T-DXd for short. And in the third line, we have a multitude of options, no one particular sequence. And so the treatment decisions are really individualized for the patient.

So let's look now in a little more detail as to how we came to this algorithm today based on line of therapy and reviews of the clinical trial data that led to this sequence that that we're using.

So to jump right in, in the first line setting, these are of, course, the iconic survival curves from the first randomized trial of HER2-targeted agent and that was trastuzumab. And this was the first time we saw that adding a HER2-targeted agent to chemotherapy, improved survival for patients with HER2-positive metastatic breast cancer. And based on this landmark trial, the combination of taxane plus trastuzumab was really a standard of care for HER2-positive metastatic breast cancer patients for at least a decade.

And today, I think the modern landmark trial in this setting is the CLEOPATRA trial. And this was a study where we now added a second HER2 agent, that being pertuzumab to trastuzumab, and taxane therapy, and showed I think, a remarkable improvement in progression-free and overall survival versus taxane, plus trastuzumab doublet therapy.

And shown here, the long-term follow-up from the CLEOPATRA trial, the long-term follow-up curves now with about 100 months of follow-up. And as you can see here, I think there is now a greater number of patients with long-term remissions and a greater number of patients alive today, based on the addition of the second HER2-targeted agent. And I think it's pretty clear from these results that we have changed the natural history of HER2-positive metastatic breast cancer with this approach. And this is still our current first line, preferred regimen for HER2-positive metastatic breast cancer.

So moving on to the second line setting and maybe, Sara, I'll have you take us through the clinical data that have led to the preferred approach in the post CLEOPATRA setting.

Dr. Hurvitz:
Yeah, sure. Thank you so much. It's great to be talking about this topic, because as you've already highlighted, there have been so many amazing advances in recent years. And now, we have a number of new agents, as you highlighted earlier, that have really hit the scene in the last 3 years or so, for patients who have disease that's already been treated with a line or two of therapy.

And the first of these I'd like to highlight is the data surrounding tucatinib. Tucatinib is a HER2 selective tyrosine kinase inhibitor distinguished from lapatinib in its relative selectivity for HER2; therefore, sparing HER1, which causes a lot of Gi toxicity.

Trastuzumab deruxtecan was another very recent addition to our armamentarium. This similar to T-DM1 is an antibody drug conjugate but it differs from T-DM1 in the fact that there's more of the cytotoxic payload loaded onto each antibody, and the payload differs in its mechanism of action being a topoisomerase-1 inhibitor. And it also differs from T-DM1 in that trastuzumab deruxtecan has a membrane-permeable cytotoxic payload, allowing that chemo to leave the cancer cell that it's been targeted to and kill neighboring cancer cells that may have lower expression of HER2.

The DESTINY-Breast01 clinical trial was a phase 2 single-arm study that showed marked activity of this agent in very heavily pretreated patients. Objective response rate of over 60%, median PFS quite long, around 16 months at the initial presentation. And based on these very promising data, the FDA granted accelerated approval of this agents at the end of 2019. The one notable toxicity we'll talk about a little bit later is lung toxicity. So we'll go into that.

But this drug was more recently evaluated in a randomized clinical trial called DESTINY-Breast03. It went head-to0head against T-DM1. So this is the first randomized trial of two ADCs head to head against one another in breast cancer. In this clinical trial T-DXd was given to patients who had previously received trastuzumab and a taxane, so a very similar design to EMILIA. And again was compared to T-DM1. And the results were really quite breathtaking. Actually presented at ESMO in 2021, showing a significant improvement in the progression-free survival with a hazard ratio of 0.28 and a P value with more negative numbers after that to 10, 10 to the negative 22nd, so more zeros than I've ever seen in a P value in my career. And the progression-free survival appeared to be regardless of different page some subgroups. The response rate was close to 80%.

And if you compare these data to the data, we saw with CLEOPATRA in patients who are very naive to prior treatment, these data compare favorably. So it makes me wonder if soon we'll be seeing T-DXd beat THP in the frontline setting. We'll have to wait for that trial

to mature.

So in summary, we have this following approached as of 2022. For treatment for patients with metastatic HER2-positive breast cancer, as you mentioned, as of now, THP is the frontline therapy gold standard.

But in the second line, we have a new gold standard, T-DXd. For those patients with active CNS disease, tucatinib trastuzumab capecitabine is also available, although we are seeing promising activity of T-DXd in patients with stable brain mets at baseline. So stay tuned for more data there because these ADCs may actually cause activity or cause shrinkage of tumors in the brain.

In the third line setting and beyond, we don't have good data to tell us how to sequence these agents. We have T-DM1 available, trastuzumab, tucatinib, capecitabine available, and a number of other agents including neratinib, a pan-HER inhibitor with some interesting activity in the brain. Margetuximab is available in combination with chemo but really seems to work best in those patients with an FC gamma receptor-3 genotype that predicts for benefit from that. And then other data supporting trastuzumab plus lapatinib.

And so this brings us to our discussion of activity of these agents in disease that may not be HER2 amplified. And Shanu, can you maybe take us through some recent very promising and compelling data relating to ADCs and non-HER2 amplified breast cancer?

Dr. Modi:
Yes, I mean, actually started to build on what you had already started to talk about. I mean, trastuzumab deruxtecan specifically is, you know, it's a next generation HER2 antibody drug conjugate. And it does have some unique mechanisms of action and properties. And most important of these, I think, is the bystander effect, which as you described, allows the payload to pass through the HER2-positive cell into surrounding cells and target cells that may not have high levels of HER2 expression. In fact, it can target cells with variable levels of HER2 expression. And so this particular property lends T-DXd to be, you know, broadly active across a range of tumor types and levels of HER2 expression.

And so in the phase 1 trial shown here, the investigators tested trastuzumab deruxtecan in patients with heavily pretreated HER2 low metastatic breast cancer.

And HER2-low metastatic breast cancer is defined as those tumors with IHC scores of 1+ or 2+ without gene amplification, and we previously would have called these HER2-negative breast cancers. And you can see really nicely how active T-DXd is for these - for this subgroup of patients with HER2-low breast cancer.

And remember are the other HER2 targeted therapies we've talked about really have not shown to be active for patients with this low level of HER2 expression. So these were very exciting data for HER2-targeted agent and a new group of patients.

So building on this trial is the DESTINY-Breast04 trial, which is the first randomized phase 3 study of T-DXd versus chemotherapy, a physician's choice for patients with HER2-low metastatic breast cancer. And this was a multicenter study. It was 4 patients who had HER2-low breast cancer who had previously received at least one but not more than two lines of chemotherapy in the metastatic setting. And additionally, patients who had hormone positive HER2-low breast cancer, had to have endocrine refractory disease. So this was a pretty advanced pretreated population of patients.

As mentioned HER2-low was defined as tumors with IHC scores of 1+ or 2+ without gene amplification. And here patients are randomized 2 to 1 to either T-DXd or chemotherapy, a physician’s choice.

The primary endpoint of this trial was to look at progression-free survival by blinded independent review in patients with hormone-positive HER2-low breast cancer. And this group was chosen particularly because it is the predominant subgroup within the HER2-low population.

But there was there were secondary endpoints that were tested in a hierarchical fashion including then progression-free survival for all patients, overall survival for the hormone-positive patients, and again for all patients on study. And the plan was to enroll 540 patients, approximately the majority with hormone-positive breast cancer and a smaller group with hormone receptor negative breast cancer, again, to reflect the natural prevalence of these groups within the HER2-low population.

And so these are the I think the key efficacy findings and starting with the progression-free survival curves on the left for the hormone receptor positive cohort, you can see very early on there was a separation of the two curves in favor of T-DXd, and this was maintained over the course of the follow-up of this trial. The PFS hazard ratio was 0.51 with a significant P value. And the median PFS improved from 5.4 months with chemotherapy to 10.1 months with T-DXd.

And so given the positive results for this group, we were then able to proceed with PFS analysis for the entire study population and those curves are shown on the right. And you can see, so this is now a group that includes the hormone receptor negative HER2-low patients, which we also call triple-negative breast cancer. And the results were identical, nearly identical. The PFS hazard ratio was 0.5,

and the median PFS improved from 5.1 months to 9.9 months in favor of T-DXd.

Overall survival was a key secondary endpoint in this trial. And on the left for the hormone positive cohort, the OS hazard ratio was 0.64. Again, statistically significant. And the median overall survival improved from 17.5 months with chemo to 23.9 months with T-DXd, which is a gain in survival of over 6 months. And on the right, the results were again similar for the whole study population with a gain and survival of 6.6 months in favor of T-DXd.

And just to put these data in context, I mean, they're very compelling, particularly given how rarely we see survival advantage with new therapies in the late line metastatic setting. So these were pretty, I think, exceptional results.

And then finally, these are the curves from an exploratory analysis looking just at those hormone receptor negative patients, the triple-negative patients on trial. And the results are entirely consistent with the primary study results. And the hazard ratio 0.46 and 0.48 for PFS and OS, respectively. This of course, is a particularly poor prognosis population. So the absolute numbers are lower. The median PFS with chemo was only 2.9 months, and that improved to 8.5 months with T-DXd. And the median overall survival with chemo was 8.3 months and that more than doubled to 18.2 months with T-DXd. So I think these are very, very clinically meaningful results.

And so I think, you know, based on the DESTINY-4 data, we may see the first HER2-targeted therapy approved for patients, a new population of patients with HER2-low breast cancer and with T-DXd as the standard of care in that setting. And these data will apply to a pop - almost 50% of patients with HER2 metastatic breast cancer so very, I think, important and potentially practice-changing data. And we look forward to the availability of this drug for that setting.

You know, so moving on. I mean, look, there are many factors we consider when making treatment decisions for our patients. Efficacy often is foremost. However, the counterpart point to this is safety and toxicity. So let's look at some of the key toxicities that we encounter with the common HER2-targeted therapies today.

And so, starting with diarrhea. And I want to say this is a common toxicity of a number of HER2-targeted therapies, probably most prominently pertuzumab, one of the monoclonal antibodies, and also our tyrosine kinase inhibitors, we see fairly consistent rates and high rates of diarrhea in all of the HER2-targeted TKIs. It's interesting to point out that the diarrhea in our patients does not correlate with preexisting GI conditions. So our patients with underlying Crohn's disease or colitis don't have a higher predilection?

And I guess the key with managing the GI toxicity or the diarrhea toxicity in our patients is really to make sure that patients are aware to be well hydrated, to learn to avoid those things in their diet that could be exacerbating the diarrhea, and of course, to use anti-diarrheal therapies promptly to keep the diarrhea under control and avoid the need of dose reductions or changes in therapy.

In particular, one thing that was interesting with the TKI data and of course, neratinib of the three available TKIs has the highest rates of diarrhea, highest rates of high-grade diarrhea, in fact, and it makes it a very challenging therapy to deliver. And so investigators did conduct a really interesting trial called the control trial where they looked at different strategies to mitigate the diarrhea risk from neratinib. And they looked at various different supportive agents like loperamide, steroids, colestipol. What they found was most effective was using a gradual dose escalation approach. And that brought the high-grade rates of diarrhea down to the levels that we see in other therapies. So again, and now making neratinib a more feasible option to deliver.

With regards to cardiac toxicity, and this is either subclinical declines in EF or clinical heart failure. And this is a potential concern with I think, almost any of the HER2-targeted therapies we deliver. And I think we first recognized this risk with trastuzumab. And thankfully, there didn't appear to be any additional or cumulative risk when we added pertuzumab to trastuzumab.

And I think the current recommendation really is for patients at baseline to have an E F, of at least 55%, or 50%. And to monitor these patients regularly while they're on therapy, and if we see declines in EF below 50%, to hold therapy and to optimize cardiac function. And in most cases, we're able to successfully resume.

Moving on to infusion reactions. These are potential with ADCs and monoclonal antibodies, of course. For the majority of patients, you know, these range from mild acute reactions, but occasionally to anaphylaxis. It’s something to be aware of, especially when you're using a new agent for the first time.

Probably an important toxicity to mention is lung toxicity. And we - this is a particular toxicity of trastuzumab deruxtecan. And we learned this from the early trials of this agent. And the lung toxicity ranges from asymptomatic radiographic findings but can go all the way up to fatal cases of ILD. So a really important thing to be aware of when using this drug. Overall, we see rates of 11 to 15%. This is what we saw in the DESTINY-1 trial, which was a trial have heavily pretreated HER2-positive metastatic breast cancer patients. The onset can be between 4 to 5 months of starting therapy. So it's something you have to be aware of throughout the patient's course on treatment.

There are studies that have now looked at identifying risk factors. So this allows us to maybe consider the risk-benefit for an individual

patient based on these factors. And these include things like having a low baseline oxygen saturation, or the presence of other lung comorbidities, and low baseline oxygen saturations.

There are now - there has been a very extensive effort, I think, to educate physicians and patients about this potential risk. And there are guidelines available, so tools for physicians to be able to identify and manage this particular lung toxicity. And the these are widely available. And I think the key really is awareness to have a high suspicion for, you know, this possible toxicity in patients with respiratory symptoms, or with new sort of inflammatory findings on scans. And the first thing is, is to promptly hold therapy and then launch an investigation into possible etiologies. And if this is lung toxicity, then you want to start steroids early. And I think that's the key to managing this particular lung risk.

One of the I think key things to mention is that for patients who have asymptomatic or grade 1 findings, if those findings do reverse fully after holding therapy and instituting steroids, there is a potential to rechallenge patients with the grade 1 recovered lung toxicity. However, very critical to mention that patients who have any kind of symptomatic or grade 2 or higher lung toxicity, really should be permanently discontinued from T-DXd therapy. And I think we need to strictly adhere to these guidelines, because we've seen that if we do that we are able to minimize the high +-grade events and deliver this important therapy safely to our patients.

So Sara, maybe I'm going to end there and ask you maybe to recap our 2022 approach to the treatment of metastatic HER2-positive breast cancer again.

Dr. Hurvitz:
Absolutely. It certainly is quickly evolving, isn't it? We basically have I think at my last count eight HER2-directed therapies FDA approved for our use in the first line setting. Standard of care is to use THP, and the second line new standard is T-DXd, with a number of other agents available to us, including to tucatinib capecitabine trastuzumab, especially for those with active brain metastases. T-DM1 remains a therapy that we can use, and we have a number of other agents available as well. And all of these therapies are helping patients live longer.

We also have data now supporting one ADC, T-DXd, for HER2-low breast cancer. This is a very novel finding, and almost immediately practice-changing. And there are going to be a number of ongoing studies evaluating this agent in triple-negative breast cancer and in patients with active brain metastases. So stay tuned.

There are a number of adverse events we need to follow and notify patients about and monitor and treat proactively. We have to very carefully monitor patients for interstitial lung disease with T-DXd. Most of the time, these are highly treatable as long as we catch them and treat them early.

So I think if we have a meeting, you and I again in 2023, the landscape may again be quite altered based on the results from new clinical trials. But I do think it's an exciting time for us all.

Dr. Modi:
Thank you, Sara, for that excellent summary and recap. And to all of you, thank you for joining us and I hope you found this review of the approach to HER2-positive metastatic breast cancer helpful and informative for your clinical practice.

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