Targeted Therapy for HER2 and HER3-Positive Breast Cancer: Navigating the Evolving Treatment Landscape

CMEO Podcast Transcript

Sara Hurvitz:

Hello, I am Sara Hurvitz. On behalf of CME Outfitters, I'd like to welcome and thank you for joining us for today's educational activity, titled Targeted Therapy for HER2 and HER3-Positive Breast Cancer: Navigating the Evolving Treatment Landscape. Today's activity is brought to you by CME Outfitters, an award-winning accredited provider of continuing education for clinicians worldwide. Today's CME/CE activity is also eligible for ABIM MOC points, so make sure you engage in today's event, answer polling questions, submit answers, and provide your feedback. Once you complete today's program, be sure to provide your ABIM ID and birthdate in the evaluation. CME Outfitters will submit your MOC points.

As I mentioned, I am Sara Hurvitz, Professor of Medicine at the University of California, Los Angeles, Co-Director of the Santa Monica UCLA Outpatient Oncology Practices, and Medical Director of the Clinical Research Unit at the Johnson Comprehensive Cancer Center. Let me introduce our faculty joining me today. Let me first welcome my colleague Shanu Modi. She is an Associate Professor of Medicine, Department of Medicine, Weill Cornell Medical College. She's Associate Member Section Head, HER2 Positive Breast Cancer, Breast Medicine Service at Memorial Sloan Kettering Cancer Center in New York, New York. Welcome Shanu and thank you for joining us today.

Shanu Modi:

Hi Sara. It's great to be here.

Sara Hurvitz:

I'd also like to introduce my colleague Michael Press. Michael is Professor, Department of Pathology and Harold E. Lee Chair in Cancer Research at the Norris Comprehensive Cancer Center, Keck School of Medicine at the University of Southern California just across the road from me. Thank you for being here today Michael. Welcome.

Michael Press:

Thank you. Thank you for having me.

Sara Hurvitz:

So now, let's turn to our learning objectives. The first learning objective is to apply HER2 testing guidelines for improved treatment selection in breast cancer. Our second objective is to evaluate clinical trial data for novel and emerging therapies for the management of patients with low HER2 expression, resistant to HER2-directed therapies, and HER3+ breast cancer. Our final learning objective is to expand the use of telemedicine in breast cancer care, very relevant today in the COVID era. Let's start by discussing how to determine HER2 status to guide treatment. Michael, this is an area with a lot of changes in the last 10 years. Can you start us off with a case first?

Michael Press:

Yes, I can. The first case for today is the case of a 61-year-old woman with metastatic breast cancer. She was diagnosed on a left breast biopsy as having infiltrating ductal carcinoma in March 2015, which was ER-positive, PR-positive, and it was reported to be HER2-positive, IHC 3+ by immunohistochemistry.

Michael Press:

The HER2 FISH assay was reported to have a ratio of 2.3 with an average HER2 copy number of 3.8 and an average chromosome 17, centromere number of 1.6 per tumor cell. Subsequently, in September 2019 she was diagnosed with metastatic carcinoma in pleural fluid. And although ER and PR were not provided to us, we were told from the outside hospital that the HER2 immunohistochemistry status was now scored as IHC 2+ and the FISH assay, which had previously been considered to be positive, was now considered to be negative with an average HER2 copy number and an average chromosome 17 centromere copy number each of the two, so the ratio was one.

Because of the discrepancy between the original biopsy result and the subsequent metastatic tumor, the patient was referred for consultation and for a second evaluation to our laboratory. We received two samples separately, which we will discuss. In the initial left breast biopsy from March 2015, we were asked to perform both immunohistochemistry and FISH. There shown across the middle of the slide, beginning with the hematoxylin eosin stain sections, is a representative microscopic field followed by two immunohistochemical assays and a FISH assay result that is illustrated.

The FDA-approved DAKO HercepTest was scored as 2+. A laboratory developed assay that we use in our laboratory routinely for each case was scored as 1+. Then the FISH assay was evaluated as having an average HER2 copy number of two and a half per tumor cell, chromosome 17 centromere average was 1.5 per tumor cell for a ratio less than 2. And the FISH ratio is illustrated with HER2 copy shown in red in chromosome 17, centromere signal shown in green. This was assessed as HER2 not amplified with low expression. The second sample that was advanced to us demonstrated metastatic carcinoma in pleural fluid as shown on the H&E tissue section with the tumor cells as illustrated.

We were not requested to do the immunohistochemical assay, so we didn't use an FDA-approved assay, but we did run our laboratory-developed assay for 10H8 monoclonal antibody in the background and we also performed the FISH assay on this tissue sample. The FISH assay had an average HER2 copy number of 2.8 and average HER2 chromosome 17 centromere number per tumor cell of 2, for a ratio less than 2 of 1.43. It was interpreted as HER2 not amplified with low expression of the product.

Sara Hurvitz:

So this is an interesting case but I can say I've actually seen it in my own practice before where we initially think it's positive based on one testing and then upon repeat testing of the new sample and repeat testing of the prior sample, we find out it's negative. Can you give us some clinical pearls from this case that are relevant to clinical practice? What are some take homes?

Michael Press:

One of the take homes is that each one of these FDA-approved assays uses a different antibody to recognize HER2. The antigen retrieval conditions are slightly different. And the interpreter may be different from laboratory to laboratory. So, there's going to be some variability in immunohistochemical assay. I think the other thing to keep in mind is that the initial biopsy, which demonstrated positivity both by immunohistochemistry and FISH, you'll note that the average HER2 copy number was rather low. It was less than 4. I think this is something to keep in mind when you have any questions about either of these assays. Or they don't match your clinical expectation to have a high level of suspicion and seek a second opinion.

Sara Hurvitz:

Thank you. That's very helpful. I think in the last decade or so we've seen the evolution of guidelines for interpreting HER2 test results. I know you've been a part of those guidelines along the way. I myself as a clinician have been confused at times by how to interpret and apply these guidelines. There are now three different subgroups that are considered to be indeterminate or borderline for FISH positivity. So, I'm hoping you can take us through an overview, how the tests were developed, and how to interpret the guidelines that we now have today.

Michael Press:

I'll try to briefly cover some of the points that are related to conceptualizing the HER2 testing. One of them is that HER2 gene amplification is directly correlated with HER2 overexpression, especially if you're looking at frozen tissues. Of course clinical samples are formalin-fixed and paraffin-embedded these days. I'll show you some data that we generated in our laboratory that demonstrate that FISH is significantly more accurate than immunohistochemistry in these fixed paraffin-embedded samples.

I'll briefly summarize the high points of the guidelines for HER2 testing in breast cancer from 2007, 2013, 2014, and 2018. I'll talk about each one of the FISH groups that have been now characterized beginning in 2013 and 2014 and where their evaluation stands in the 2018 guidelines. Then finally I'll just say a little bit about the equivocal probes that were used between 2013, 2014, up until very recently and created I think some confusion within the field.

This is a summary slide to summarize data from a study that we did in collaboration with Dennis Slamon quite a few years ago. It was a study of frozen breast cancer samples that were analyzed at the DNA level for HER2 gene amplification by southern blotting at the RNA level for HER2 expression by northern blotting, and then the protein product was characterized by both western immunoblotting and frozen section immunohistochemistry. This slide demonstrates some of the results of that study. The HER2 amplification was determined when the HER2 signal, compared to another gene on the same chromosome, myeloperoxidase. When the ratio between them was greater than or equal to two, they were considered to be HER2 amplified breast cancers. When it was less than two, it was considered to be not amplified.

You'll note that as your progress from right to left across that series, there's a progressive increase in the amount of messenger RNA that's localized by northern blot and in progressive increase in the amount of protein product that's present in those tumor samples, from right to left with increasing amplification, likewise in the frozen section immunohistochemistry there's also a progressive increase in the amount of immunohistochemical staining.

There are a couple points that are worth noting as we look at these. One of them is that as you look at each one of the samples that's illustrated for the immunohistochemistry, they're remarkably similar to one another throughout the tumor cell population. There isn't a lot of variability in the staining. This is not only true in the field that's illustrated, but across the entire slide of these is very typical. You'll also note that for those cases that are not amplified, the 63% that did not have amplification and had low expression of the products of the HER2 gene, that that product at the messenger RNA and at the protein levels and by frozen sections were detectable throughout. So what we call IFC zero, in formalin-fixed and paraffin-embedded tissue, one needs to remember that this gene is still expressed at low levels.

That really leaves us with one other category that characterizes there are 10% of the samples that did not appear to have gene amplification by southern blotting, but nevertheless had overexpression of the messenger RNA and the protein. And on the following slide, it summarizes that just when we characterized those cases by FISH, we found in the lower right hand corner in red, you'll notice multiple signals in each blue tumor cell nuclei.

Michael Press:

These cases actually had gene amplification with overexpression as illustrated by the immunohistochemistry above, that was not appreciated by southern blotting. These were primarily stromal-rich breast cancers where there was relatively little tumor cell extracted. So this is considered a dilutional artifact of the method that we were using. In summary, this indicates that there's a very close relationship between the gene and its products. When the gene's amplified, it's overexpressed; when it's not amplified it's not overexpressed. The next slide, shows an example of when one has such molecularly characterized samples, one can use it to characterize and collect the formalin-fixed, paraffin-embedded tissue blocks. One can then use those blocks and the blinded knowledge of what the status is to characterize assays that become available and are FDA-approved.

So, this shows one of those studies that we conducted across the top series of panels that are illustrated. There are six panels illustrating the result from one breast cancer that was known to be amplified and overexpressed. The left hand side are FDA-approved assays that characterize gene amplification by FISH. One shows the HER2 signals in red. The other shows the HER2 signals in green. You'll notice all four of the immunohistochemical assay results are positive for membrane staining across that breast cancer.

The lower example shows another amplified overexpressed breast cancer that's amplified in both FISH assays, but only one of the four immunohistochemical assays shows membrane staining. If you look across the top, the concordance with known molecular status, the FISH assays were both correlated with 95% with the known HER2 molecularly characterized status, whereas the two FDA-approved immunohistochemical assays approached 90% but didn't reach it. And this difference between over 95% and approximately 90% was statistically significant. So, we would argue that this demonstrates significant, higher accuracy for FISH compared to immunohistochemistry. This summarizes the approach that has been used in the ASCO/CAP guidelines.

I should also mention that I'm a member of those guidelines' committee since 2006, by way of full disclosure. It shows the algorithm that was developed for scoring immunohistochemistry and testing in 2007 and in 2013/2014. Each one of these guidelines, even up to 2018, accepts that immunohistochemistry could be used as a primary screening technique for HER2 status and indicates as shown in the middle bottom of the slide that when the immunostaining is strongly positive 3+ positive, these patients should be considered candidates for targeted therapy, and when it is weak or negative, 0 or 1+, the patient should not be considered for targeted therapy and should be considered low expressers.

The intermediate group, at IFC 2+ should be reflexed for FISH to characterize their status. One of the important differences between 2007 and 2013/2014 is that one of the requirements in 2007 was that any laboratory using immunohistochemistry as a primary assay must demonstrate a 95% concordance or agreement rate between immunohistochemistry categories that are going to be used(0, 1+, 3+) and the FISH status that is determined by immunohistochemistry. This requirement was dropped in 2013 and 2014 and it was recommended that this would be at the lab's discretion to choose what agreement level was necessary.

The next slide shows the series of studies that were published from 2008 to 2014. They're similar to the studies that came before 2008 where it was well recognized that there was considerable disagreement between immunohistochemical studies in different laboratories. These data demonstrate that that remains true between 2008 and 2014. It shows the HER2 gene amplification rate as a percentage for each immunohistochemistry category among studies that had at least 100 or more breast cancers characterized by both immunohistochemistry and FISH. An ideal result for IHC zero would be an amplification rate of less than five. Likewise for 1+, less than 5%. And in the 3+ positive category, one would expect 95% amplification or greater.

Michael Press:

The red boxes indicate that these studies did not achieve that level of agreement. There are only two of these studies that actually have 95% agreement all the way across 0, 1+, and 3+ and the others do not. Subsequently, the approach to immunohistochemistry testing for HER2 has remained essentially unchanged and this issue of both false negatives and false positives by immunohistochemistry has not been, in my opinion, adequately addressed at this time.

The next slide shows the way in which HER2 testing by FISH has been approached beginning in the guidelines from 2013 and 2014. Initially the ratio between HER2 and a control like chromosome 17 centromere, when that ratio was greater than two, the FDA said we'll call those HER2 amplified like we had in southern blotting and when it's less than two we'll call it negative. Subsequently, this was changed and in 2013/2014. They also considered the average HER2 copy number. I'm going to refer to these as groups. Groups one through group five, shown in red. So when the ratio is greater than two and the average HER2 copy number is greater than four, these were to be considered ISH-positive or group one and remain so in the 2018 guidelines.

Among those that have a ratio of greater than two and an average HER2 copy number per tumor cell less than four, they are originally considered ISH-positive and are now going to be further characterized by immunohistochemistry. I'll refer to these as group two. Those cases that have an average ratio less than two and a copy number greater than six, were originally considered ISH-positive. We're calling these group three. They also need immunohistochemistry at this time. Among those that have a ratio less than two and a copy number greater than four but less than six, were considered ISH equivocal. We'll refer to them as group four. They also require immunohistochemistry at this time for further resolution.

The final group, group five, are those with an average HER2 copy number less than four and a ratio less than two and they are considered negative. One of the issues that came up is that at the time when this was published in 2013 and 2014, there wasn't anything known about the distribution of these different FISH groups across the population of breast cancers. So, we published our data from two different datasets. One had to do with a consultation practice. We used about 7,500 cases from the consultation practice and more than 10,000 cases that were available to us from screening for entry to clinical trials by the Cancer International Research Group.

In the red box are shown the categories two, three, and four. You'll notice that those categories are relatively less frequent, respectively, less than 1% and between 4% and 5% of breast cancers. So group one, the amplified cases that are considered overexpressed, is represented by 18% in our consultation practice and those that are HER2 not amplified, approximately three-quarters of the samples.

We'll briefly now deal with resolution of those less frequent categories of two through four. In group two, it's now recommended that one should also perform immunohistochemistry. When immunohistochemistry is performed as you see it there on the left side, IHC 0 or 1+, and I've introduced in black the percentages that we've seen in some of our studies, about 90% of the breast cancers from group two will fall into 0 or 1+ categories. IHC 2+ are about 9%. For IHC 3+, we haven't observed for this particular group. Those that are 0 or 1+ should be considered HER2 negative. Those that are 2+, a FISH assay can be repeated, and when the assay remains unchanged they can be scored as negative with a comment.

I would recommend that if you see 3+ staining in cases that have this FISH outcome, you should consider that they might be false-positive results and refer them for a second opinion. Group 3, and similarly for this group with a ratio less than two and average HER2 copy number greater than six, the majority of cases are 0 or 1+, about three-fourths of them in our studies. The IHC 2+ and 3+ are about equally divided for the remainder.

Michael Press:

And in our hands, we considered this particular group to be a mixed group of breast cancers containing at least two different groups: one that's amplified and one that's not amplified. Although the ASCO/CAP guidelines recommend that if the immunohistochemistry result is 0 or 1+, these should be evaluated as negative with a comment.

If they are IHC 3+, they should be evaluated as HER2+ with a comment. In between, if the immunohistochemistry in the same lab is 2+, they should be further screened in a blinded fashion by FISH. If their results are positive, the ASCO/CAP guidelines recommend considering them HER2+ In our lab, we actually subject them to additional procedures using alternative probes, which I briefly summarized on the subsequent slides.

When we unblinded our data and looked at cases that were screened for entry to Cancer International Research Group clinical trials, these group 3 cases as I've indicated actually were categorized into those that had been reported as amplified and those that had been previously reported as not amplified. We refer to these as group 3A and group 3N to designate amplified or not amplified. The average HER2 copy number of the amplified cases was much higher. It was about 16 per tumor cell, whereas for those that were not amplified it was only about seven. Likewise, with the immunohistochemistry for the amplified cases, the immunohistochemistry was predominately 2+ or 3+, whereas for those that had been previously characterized as not amplified they had predominately 0 or 1+ immunohistochemistry.

On the next slide is an example of one such case. And you'll notice that the average HER2 copy number is relatively high, 23. The signals or groups together with the green chromosome 17 centromere signals and this high copy number with group signals is for us, and is very characteristic of cases that have HER2 gene amplification that typically have 3+ or 2+ immunohistochemical staining. The next slide shows the way in which cases that are characterized by FISH as being in group four and a ratio less than two, with an average HER2 copy number between four and six. When the immunohistochemical staining that is recommended to be done is performed in our laboratory, the vast majority of these are either 0 or 1+. We report them as negative. A small number of them have immunohistochemistry 2+. We do some additional characterization of them and these cases typically are reported out as negative with a comment. Again for this group, if you find that your laboratory says that they are 3+ positive, I recommend a high level of skepticism and recommending them out for a second opinion. That's possibly false-positive immunohistochemistry when there's this conflict between FISH and immunohistochemistry.

The reason is that alternative probe use can be problematic. This is a study that we published a year ago with Christina Curtis' group at Stanford and it demonstrates simply across the top for nearly 2,000 breast cancers that had either slight levels of HER2 loss, HER2 normal, in other words not amplified, HER2 gain which represents four to six, or HER2 amplified.

If we then look at the alternative probe sites, the genomic site that's used on chromosome 17, you'll notice LIS1. For those that have a loss, if we go over in the red box, HER2 gain, more than half of them have heterozygous deletion of this site. Likewise, for P53, more than half have heterozygous deletion. The D17S122, which is quite popular at some referral labs, you'll notice is also more than 50% heterozygously deleted. Likewise, for RA1. And the probe sites that we've investigated that are on the Q arm of chromosome 17 for some reason are more stable and less frequently heterozygously deleted.

So one needs to know when using these to be able to evaluate whether these sites are heterozygously deleted, that can be done by FISH, and we've described an approach that allows it to be done in that paper. The subsequent slide moves on and summarizes the overall approach that we use with these, showing the groups from one to five on the left, the ratios by FISH, the average HER2 copy number by FISH for each of these five groups.

Michael Press:

The original FDA designation is amplified versus not amplified. The way they're currently viewed either in 2014 or 2018 by the ASCO/CAP guidelines is ISH-positive initially for the top three groups, but now the 2nd and 3rd groups are recommended for additional evaluation by immunohistochemistry.

The 4th group has been considered equivocal and recommended for immunohistochemistry whereas the 5th group by ASCO/CAP guidelines is considered HER2 not amplified, and our evaluation of these is summarized on the right-hand extreme in terms of our collaborative data with the Breast Cancer International Research Group now known as TRIO, Translational Research In Oncology. We consider the 1st one amplified with overexpression, the last one not amplified with low expression. The fourth group, not amplified with low expression. The second group, not amplified with low expression. Group three is a mixed group containing both amplified with overexpression and non-amplified cases that lack overexpression.

Sara Hurvitz:

Thank you so much Mike. That was an amazing amount of densely packed but critically important information to help clinicians sort through HER2 FISH testing. I think my take home is, first of all, this last table you've put together, I'm printing and I'm going to use in the clinic to help me sort through pathology reports. Then I'm just going to say it. Why aren't we all doing FISH? Why aren't we getting rid of IHC and only using IHC if we have to sort out one of these indeterminates? Is there any move in the guidelines to go to an all-FISH assay or is there any downside?

Michael Press:

We've advocated that for a long time. In collaboration with Dennis Slamon's group, when we were screening for entropy to BCRG clinical trials in 2000 we needed to choose an assay, and we chose FISH, not immunohistochemistry. In our laboratory, we routinely do both. When we have a request for FISH only, we run our laboratory-developed assay in the background because I like to know the result of both assays. It also allows me to address immunohistochemistry assays that are performed in outside labs, that may or may not differ from what we're finding in our laboratory. So, we run them both. FISH is by far in our laboratory the preferred assay.

Sara Hurvitz:

Thank you so much. And now in the interest of time, we're going to move on to our next section, which relates to the management of treatment-resistant HER2+ breast cancer. And what we're going to do is get the audience involved here. All right. A very nice smattering. Shanu, you've got a lot of work to do here. I certainly think that at least two, three, and four are certainly available to our patients right now. But I think Shanu's going to take us through some data that will help highlight, maybe give us some direction in what we should be doing in the setting of third-line metastatic HER2+ breast cancer.

In the interest of time, I'm going to go to the next question here. Okay, we're seeing here that the winner is actually tucatinib, capecitabine, trastuzumab. So we have a lot of enthusiasm with the recent data related to tucatinib that Shanu will be going through. Trastuzumab emtansine is actually the data-driven, guideline-backed recommendation in the second-line setting right now. So, we don't have yet a study that shows tucatinib, capecitabine, trastuzumab is better than trastuzumab emtansine. But Shanu will talk to you about the FDA approval of tucatinib and how the FDA is actually allowing us to use it in the second line in spite of not having data.

Sara Hurvitz:

All right. Last question before we get to Shanu's data. The COVID pandemic has certainly impacted us and all of our patients. So I'm going to ask a very clinically relevant question right now. Okay, very good. The audience chose number three, which is to hold it, test for COVID and if negative resume trastuzumab deruxtecan. But actually the answer is to hold treatment, test for COVID-19 and if it's negative we should get pulmonology involved because this would be consistent with interstitial lung disease or pneumonitis. So we wouldn't want to just resume trastuzumab deruxtecan. We would want to refer to pulmonology, possibly bronchoscopy, possibly steroids. We're going to talk about a little bit about this further.

So now, this is just to pique your interest, Shanu is going to go through some very exciting data. This is a picture here of all the therapies we now have available to us, according to NCCN guidelines and approvals. Very exciting. Three new approvals just in the last year. Shanu, help us know how and when to use each of these agents.

Shanu Modi:

Thanks Sara. I think what we see here is really, up until very recently, shown in the green boxes, has been sort of approved guidelines or the standard-of-care treatment for HER2+ advanced-stage breast cancer. We've preferred to start off in the first-line setting with a combination of a taxane plus trastuzumab and pertuzumab. This is really based on the unprecedented survival data from the CLEOPATRA study. Our time-honored second-line option has been TDM1 and that's based on the EMILIA data where we saw, again, a survival advantage for TDM1 compared to other standard-of-care therapy.

In the third line and beyond of course there are a number of available therapies and most of these have not been directly compared to each other. Most have a fairly modest level of activity, so there's really no one preferred treatment in that space and it's really been up to the physicians and their patients to choose in that setting. But as you all know, over basically a 6-month span of time this past year we saw the rapid approval of three new HER2-targeted therapies. If we look, based on their approvals, where we would slot these new agents, in the second-line setting we did see an approval for a favored regimen by our audience, which is tucatinib, trastuzumab, and capecitabine. This is based on the data from the HER2 CLIMB study.

Then, in the third line we've seen two new additions. The first being trastuzumab, deruxtecan, previously called DS8201a, and we abbreviate it as T-DXd. This was based on really compelling data from the DESTINY-Breast01 study. And then finally the doublet combination of neratinib plus capecitabine based on the randomized NALA trial. So there are a number of very exciting recently approved drugs and other drugs in testing, in late stages of testing on the horizon for HER2 targeted therapy. I'm just going to take you through the pivotal studies that have led to these new drug approvals and what's waiting in the wings based on recent data from large studies, starting with the antibody conjugates.

Antibody conjugates are actually really interesting drugs. They combine antigen specificity with potent cytotoxicity in a single molecule. In general, they're comprised of a monoclonal antibody, an antigen-specific monoclonal antibody. Attached to this via special linkers is a cytotoxic payload, often a chemotherapy agent. We're very familiar with ADCs because we've been using TDM1, which is the prototype ADC in breast cancer, for many years now, early on in the metastatic setting and more recently in early-stage patients as well. But ADC technology has really evolved over the last few years and there are new linker technologies and there are novel potent payloads. So today there are over 60 ADCs and clinical testing for various types of illnesses including cancer.

Shanu Modi:

On the right is to remind you of how these drugs work. Once the antibody finds its target antigen, the whole complex is internalized. Then within the cell the linkers are cleaved, releasing the chemo to eradicate the cancer cell. Some payloads are actually cell membrane permeable and they have the ability to pass through and then interact with neighboring cells, kill neighboring cells, some which may not even have the target antigen. And this is what we call the bystander effect.

So trastuzumab deruxtecan is a novel HER2 antibody drug conjugate as we've heard about. If we compare and contrast it briefly to TDM1, both of these drugs essentially have trastuzumab as the monoclonal antibody backbone. But the payload in T-DXDd is a topoisomerase 1 inhibitor. It's a very potent chemo agent and it's very novel. Most breast cancer patients are not exposed to chemo therapy of this class, so it's very new for our breast cancer patients.

There are also twice as many chemo molecules linked to each T-DXd monoclonal antibody compared to TDM1. So we deliver a lot more chemotherapy with each one of these antibody-drug conjugate molecules. In fact, the chemotherapy in T-DXd is membrane-permeable so has its potential to induce a bystander effect.

The pivotal study for trastuzumab deruxtecan is DESTINY-Breast01 trial. This was a phase II study and was conducted in patients who had a centrally confirmed HER2+ metastatic breast cancer and all of these patients had to have had prior TDM1 to be eligible. The study was connected in two parts. The first part was the dose-finding phase. Once they defined 5.4 mg/kg, just given every 3 weeks by intravenous infusion as the best phase II dose, all patients in part two were then treated with that dose of T-DXd. Overall, there were 184 patients eligible for this analysis. The primary endpoint of this study was to look at the overall response rate, and this was confirmed by an independent radiology review.

As you can see here, this study enrolled a pretty heavily pretreated group of patients. The immediate number of lines of cryotherapy for metastatic disease was six. All patients had prior trastuzumab and TDM1. Two-thirds also had prior pertuzumab, so a very heavily previously pretreated cohort of patients. This is the waterfall plot that I'm sure many of you have seen. This is efficacy data and I think it's pretty spectacular. I think it's striking and kind of visually shows you just how active this drug is. The confirmed overall response rate was 61% in these pretreated patients.

Even if patients didn't achieve a confirmed response, you can see here that all patients had at least some benefit from this therapy. The disease control rate is exceptionally high. It's 97%. In fact, 6% of patients achieved a complete remission with this therapy and that's very unheard of in such a late-line setting. Very, very impressive efficacy data with this drug.

I think as important as the response rate is the durability of this benefit. On the left is a progression-free survival curve, and you can see the median PFS for this group of patients was 16 months. To put that in perspective, in a late-line setting with other currently available therapies, the median PFS we're seeing with our best drugs is 6 months. So it is pretty striking to see a PFS like this in a late-line setting.

The overall survival was not achieved at the time of reporting and publication of these data. I think we may be seeing some OS data later this year, perhaps at San Antonio. The main duration of benefit also I think are equally impressive, 15 months. Patients stayed on this therapy for over a year. Again, think of the last time you had a patient on 6th-line therapy who lasted on their next treatment that long or had disease control that long.

Shanu Modi:

There was a small group of patients enrolled on this study that had brain metastases at baseline. These were patients who had treated and stable brain metastases.

This a type of patient that is enrolled I think fairly regularly on our systematic therapy trials. This was a small group of 24 patients in this study, but the median PFS for that group of patients was 18.1 months. So they did as well if not slightly better than the overall patient population in the trial. While this doesn't really tell us that there's activity for T-DXd in the brain, there is a hint there that these patients with brain metastases did as well as patients without brain metastases. I think there is, as I was saying, enough of a hint that there may be some benefit with this drug in the CNS. There are studies ongoing now to actively investigate that, so it's pretty exciting.

Sara Hurvitz:

These data are so compelling, Shanu. I don't ever remember seeing a waterfall plot that looked so dramatic in such heavily pretreated patients.

Shanu Modi:

Right.

Sara Hurvitz:

But now we're in the COVID era like our case highlighted, and we have patients who may develop shortness of breath or cough, and we have this AE that occurs with this drug. Can you tell us a little bit more about the toxicity profile with this drug?

Shanu Modi:

I think that's really important. The most frequent toxicities we saw with or we see with T-DXd are of a GI nature or bone marrow suppression. That's typical for a topoisomerase 1 inhibitor payload. On the left, you can see that in fact the most common toxicity was nausea. But these patients weren't premedicated. I think when you give patients premedication, anti-nausea medication, you do see that there is a very manageable level of nausea that we see with this therapy. Overall, you can see by the orange bars that most of the side effects were grade 1 and grade 2 in nature, so very manageable.

There was, as Sara alluded to, one toxicity that was really important and important to highlight. And that's lung toxicity. It ranges all the way from very asymptomatic findings on CAT scans all the way up to, and we saw a few cases of this, fatal lung toxicity as ILD or interstitial lung disease, in patients in this trial. Overall, about 14% of patients will have some level of lung toxicity from T-DXd. And you'll see here, the median onset of that lung toxicity is 4-5 months, so you need to be vigilant over these patients for their whole duration on this therapy.

What that means is both patients and physicians have to be aware of new or worsening pulmonary symptoms and new findings on imaging. It's really important to act early and by that I mean holding the therapy until you rule out or exclude interstitial lung disease or pneumonitis. In many cases, the recommendation is to start steroids early. I think with awareness and prompt intervention, and in some cases you have to discontinue the therapy, we can prevent some of the more serious potential consequences of this lung toxicity.

Shanu Modi:

Following up on the DESTINY-01 study, these are the two follow-up confirmatory phase III trials and both are well underway now. The first study is DESTINY-Breast02 and it's the follow-up study. It's for post TDM1. Patients again comparing now T-DXd to patients who get investigator's choice of treatments, so it's a randomized study. And DESTINY-Breast03 is a study again for HER2+ metastatic breast cancer patients, this time comparing T-DXd directly to TDM1, so patients are being randomized. Really exciting follow-up phase III trials for DESTINY-Breast01.

One of the other things we know, and it's related to, I think, the really superior pharmaceutical properties of T-DXd, the fact that it has this bystander effect in a very potent payload. We've seen activity in HER2 low breast cancer. By that I mean HER2 1+ and HER2 2+ FISH negative breast cancers, what we traditionally call HER2 negative breast cancer and for which our currently available HER2-targeted therapies are inactive, like trastuzumab. But we did see evidence of activity for this group of patients with T-DXd both pre-clinically and shown here as a waterfall plot from a phase I trial of trastuzumab drug scan in patients whose tumors had low HER2 expression.

Again, this is a group of patients who had six or seven prior lines of treatment and again you see a better than expected response rate in the range of about 37%. Very exciting and these phase I data in fact have led to the ongoing randomized phase III trial, which is called DESTINY-Breast04. Again, this is now a randomized study for patients with HER2 low 1+, 2+ breast cancer and they're being randomized to T-DXd or physician's choice of chemotherapy.

Finally, I want to mention another exciting HER2 ADC that is just on the horizon. This one is called trastuzumab duocarmazine, very much an ADC with trastuzumab backbone, but the payload here is an alkylating agent. Duocarmazine is a DNA-damaging agent. This drug also has the potential for a bystander effect. On the top here is a waterfall plot from the phase I study of this new HER2 ADC. You can see for HER2-positive patients, again in a pretreated group of patients, the response rate of 30%. The bottom two waterfall plots are for patients who have HER2 low breast cancer. Again with this bystander effect, this drug is active even for this group, which we traditionally call HER2 negative.

On the left, is the group of patients who are ER-positive, HER2 low and on the right is the group that is ER-negative HER2 low also called triple negative, and we're seeing, I think, pretty dramatic activity in that setting. These data already led to a phase III trial called the TULIP trial, which is a randomized phase III trial of this ADC versus standard care. It's fully enrolled and we're now awaiting results from that trial.

Sara Hurvitz:

Those data are great regarding the ADC world. I think we're going to hopefully see even more ADCs come to light. I'm really excited about the phase III data associated with DS-8201. But there are also a couple of tyrosine kinase inhibitors that have been recently approved as well. Can you take us through the data of these newer orally bioavailable molecules?

Shanu Modi:

Yes. Tyrosine kinase inhibitors block the intracellular tyrosine kinase domain of these receptor tyrosine kinases. Basically, in this way, they're able to block the downstream signaling cascades. As you mentioned, they are also of importance because they're small molecules. They have the potential to pass through the blood brain barrier and be active against CNS disease. As you can see here, there are a number of already approved and other TKIs in development.

Shanu Modi:

Lapatinib was the first of these and it's a HER1/HER2 reversible tyrosine kinase inhibitor used in combination with capecitabine usually in late-line settings and has overall modest activity. Neratinib by contrast is an irreversible pan-HER family kinase inhibitor, so it has the potential for a much more potent HER2 blockade. It was first actually approved in the early-stage setting for HER2+ breast cancer and only recently has received a label for metastatic. This is based on the results of the NALA trial as shown here.

In the NALA trial, a phase III randomized study for patients with pretreated HER2+ breast cancer, patients had to have at least two lines of therapy and then were randomized to either standard of care, lapatinib plus capecitabine, or neratinib plus capecitabine. There are two co-primary endpoints for this study: PFS and OS. Shown here are those two curves on the left. You can see that in the NALA trial there was a statistically significant improvement in PFS with an absolute gain of 2.2 months in favor of the neratinib arm.

Unfortunately, although there was a numerical improvement in overall survival, this was not a statistically significant improvement. But based on the PFS data, this is a positive study. There were also other secondary endpoints that favored neratinib. The overall response rate and the duration of response also were improved in the neratinib arm. I think one of the really interesting secondary endpoint analyses was the time to intervention for CNS, which favored the neratinib arm.

Overall, there were less patients requiring CNS radiation in the neratinib arm and lower overall cumulative incidents of brain metastases also in neratinib arm compared to lapatinib, which is consistent with what we know about this tyrosine kinase and its effect in the CNS space.

In terms of toxicity, I think it's well known to most of us treating breast cancer patients that the main dose-limiting toxicity is diarrhea. In this trial with very aggressive mandated diarrhea prophylaxis, they still saw a grade 3 rate of 24%, which was double that of the lapatinib group. In spite of that, there were less patients who discontinued treatment of the neratinib arm for toxicities compared to the lapatinib arm. So a lot of work has gone into trying to find ways to mitigate these grade 3 diarrhea rates.

In the control trials, several maneuvers were looked at, including aggressive loperamide use, adding budesonide steroid to loperamide, using a bile salt binder with loperamide. They were all effective. But what I think was most effective, if you look in the first box to your left, was a dose escalation strategy. With that approach, we saw the lowest grade 3 diarrhea at 15%.

In that approach, you start by using the half dose and gradually building up to full dose, allowing patients an opportunity to get used to the new therapy, and it seems to work best in medicating the diarrhea. So a more successful way of delivering this therapy. Tucatinib, to differentiate it, is a selective HER2 kinase inhibitor. By specifically not inhibiting HER1, we see less GI and skin toxicity with tucatinib. In fact, that's what we saw in the very first phase I study shown on the right here. With the combination of tucatinib added to standard capecitabine and trastuzumab, there were no grade 3/4 rates, and no cases of diarrhea, only grade 1 and very promising activity.

This phase I then led to the HER2CLIMB study that we made reference to earlier. This is a randomized phase II trial. Again, this is for patients who had a lot of prior therapy with HER2-targeted agents, some of our best drugs: trastuzumab, pertuzumab, and TDM1. These patients were randomized then to either a standard combination of trastuzumab plus capecitabine or trastuzumab, capecitabine and tucatinib. Tucatinib is given as an oral therapy twice a day. One of the most unique features of this trial is that this study enrolled patients with brain metastases.

Shanu Modi:

Almost 50% of patients on the study had brain metastases and they were balanced equally in both arms of the trial. What's interesting is of this group of patients with brain metastases, 60% had treated stable brain metastases. That's a typical group of patients in most of our systemic study trials. But what was atypical is that 40% of that group had active brain metastases either untreated or treated and progressing brain lesions. So, that's a group that's usually excluded from our systemic therapy studies.

This was a really novel design for the HER2CLIMB study. On the left are the primary endpoint curves of the trial, the PFS curves, and you can see there was a statistically significant, almost a 50%, reduction in the risk of progression of death with the addition of tucatinib triplet therapy here. The absolute gain was 2.2 months. On the right is the overall survival curve. The secondary endpoint was again statistically significant, an impressive improvement in OS, with an absolute survival gain of 4.5 months for the tucatinib patients.

Very compelling efficacy data. These are some other secondary endpoints on the left. You can see that there was a doubling of the response rate, which went from 20% to 40% for patients with tucatinib therapy. On the right, they all, again looking just at the group of patients who had brain metastases, remember this was about half the patients on the trial, these are the median progression-free survival curves for the brain metastases patients. Again, even for this group, there was a significant improvement in PFS for the patients who were randomized to tucatinib. With a 2.2 month improvement in PFS.

I think another striking finding in this graph is looking at the 1-year landmark point. You can see that there are only about 25% of patients in the tucatinib arm that have not had any progression at the 1-year point, but all the patients in the control arm have had progression of their disease, more compelling efficacy data for this tucatinib therapy. Overall, it is a well-tolerated triplet regimen. The most common toxicity was diarrhea even though this is a selective inhibitor. But the rates of that diarrhea are predominately grade 1 and grade 2. So only 13% of patients had grade 3 diarrhea in this trial but that was, again, without aggressive prophylaxis.

There was some grade 3 LFT elevation, which was reversible, and more patients on the tucatinib arm had hand-foot syndrome, but also these patients stayed on trial much longer than the patients on the lapatinib therapy, which may explain that particular finding. Overall, there were few patients who discontinued therapy for toxicities. So, the HER2CLIMB study has now led to a confirmatory phase III trial, the HER2CLIMB-02 trial. In this study, patients who've had prior trastuzumab emtansine therapy in a metastatic setting are randomized to either standard of care TDM1 or TDM1 plus tucatinib, and this study is also well underway.

Sara Hurvitz:

That's really exciting and compelling data. I think when we do our Q&A, we're going to probably have to get into the nuts and bolts of how to choose among all of these therapies we now have at our disposal. But before we complete this section, there is a therapy that maybe FDA-approved shortly. Can you talk to us shortly about margetuximab?

Shanu Modi:

Margetuximab is also in late stages of development, as you said. It's with the FDA currently. This a novel HER2 monoclonal antibody, so it's much like trastuzumab. The FC domain, however, has been modified. Specifically, it's been engineered to have enhanced binding to receptors on immune cells.

Shanu Modi:

So specifically, margetuximab has an increased binding for the activating CD16A receptors on immune cells and less binding for the inhibitory CD32B receptors on immune cells. So it has the potential to induce a much more vigorous immune response against cancers.

We see that approximately 85% of the population actually has the genotype for a low binding CD16A receptor. That's by virtue of having an F allele, either heterozygous or homozygous as shown in the bottom right corner there. So this is a group of patients that would be predicted to have a much more pronounced benefit from margetuximab as opposed to trastuzumab. The SOPHIA trial is the pivotal phase III study for margetuximab. In this study, again patients with prior treatment, at least two lines of treatment for HER2+ metastatic breast cancer, were randomized to standard-of-care chemo plus trastuzumab or chemo plus margetuximab.

There are two co-primary endpoints, sequential endpoints I should say: PFS and OS, a really interesting exploratory endpoint looking at the CD16 receptor genotypes that patients had in relation to the efficacy of margetuximab. These are the primary endpoint curves on the left. You can see that there was a statistically significant improvement in PFS going from 4.9 to 5.8 months in favor of the margetuximab arm, which is about a 25% or 24% reduction in the risk of progression with the margetuximab therapy. The absolute gain is modest, however, at only 0.9 months. On the right is an interim, a second interim OS analysis. Again, we are not seeing a statistically significant improvement at this point, but we do expect more mature data for this OS endpoint later this year.

Finally, I think what was most exciting was the exploratory analysis where they looked at response based on patients who had that F allele of the homozygous or heterozygous F allele carriers. Remember, that's the bulk of patients on the trial. It's 86% of the patients on the trial, and you can see this group in fact does have more robust response to margetuximab compared to trastuzumab where there's almost a 2-month improvement in median PFS and a 4-month improvement in overall survival. These are exploratory findings but they are certainly interesting and suggest that perhaps we need to look at the genotype selection as a way to determine which patient may best benefit from this therapy in the future.

Sara Hurvitz:

Thank you so much for that amazing summary. Again, a very dense amount of information, a ton to go over. We're going to go on to another question. We've got HER3 as 23%, which is actually correct. We're going to go into a little bit of data to highlight this. Now HER2 gets activated by dimerizing with other partners, but the preferred partner and the strongest activator of the PI3 kinase signaling pathway is HER3. We're going to now talk a little bit about HER3 in breast cancer. Before we do that, I worked with CME Outfitters to create what I think is a very useful animation that characterizes the unique biology of HER3 initiated signaling in cancer, including activation of downstream signaling pathways. So let's look at a clip of that animation right now. It's only about a minute or so.

Speaker 4:

Shown here is the cross section of the cell, with HER2 and HER3 tyrosine kinase receptors visualized. HER2 does not have any known ligand. However, HER3 does have a ligand, and when that ligand engages with the extracellular domain of HER3, this induces the conformational change in HER3 that exposes the heterodimerization site. This allows HER3 and HER2 to heterodimerize. The activated HER2 then phosphorylates the intracellular C-terminal tail of HER3. The phosphorylated tyrosine residues on HER3 act as docking sites that interact with and recruit downstream signaling protein PI3 kinase and AKT.

Speaker 4:

HER2 and HER3 are a potent heterodimerization pair due to the multiple PI3 kinase docking sites located on HER3. Clinically, this pairing has relevance because the monoclonal antibody pertuzumab has been designed that blocks HER2 at the HER2/HER3 dimerization site.

Sara Hurvitz:

I think that gives us the highlight of how HER2 and HER3 engage to activate the PI3 kinase pathway. This segment in the full animation will be available on CME Outfitters' website and we that hope you'll use it in teaching your peers or patients. Now let's talk a little bit about HER3 somatic mutations and overexpression. We know that a minority of cancers have HER3 mutations, somatic mutations, which can be activating. You see here that breast cancer is around 1%, but you can go up to about 6% in some other cancers like GI cancers and GU cancers. But it's important to also recognize that overexpression has been reported in a number of cases, with overexpression being estimated to occur in breast cancer on the order of 15% to 40% depending on the antibody used. And patients who have HER3 overexpression tend to have a worse outcome.

There are lot of data that actually support that HER3 may be implicated in the pathogenesis of HER2+breast cancers using transgenic mouse models that develop HER2+ breast cancer. When the HER3 is repressed, it actually leads to diminished tumor cell growth and proliferation. And if you do knock out models using Crispr technology, you see the same thing. You can diminish the growth in HER2+ breast cancer. So this may be a strategy to go for in HER2+ breast cancer. In contrast, EGFR, which is HER1 and HER4, don't seem to supplant the requirement for HER3 as the requisite partner for HER2 in these types of experiments.

We know that co-expression of HER2 and HER3 is linked to tamoxifen resistance. ER-positive breast cancer cells when treated with fulvestrant, can induce protein expression and activity of HER3. And targeted therapy of HER2 has been linked to trastuzumab resistance when there is HER3 expression or upregulation, as well as lapatinib resistance. So a growing understanding of HER3 is the principle partner for HER2 in its oncogenic activities in accumulating evidence implicating HER3 activation as a cause of treatment failure, driving the development of numerous HER3-targeted agents.

On this next slide, you can see a table that is summarizing select HER3-targeted agents in clinical development. The most or the furthest along is the U3-1402 antibody, which I'll talk about in the next slide a little bit further. What you can see is this is an antibody-drug conjugate comprised of pertuzumab, which is a HER3-targeted antibody stably linked to a topoisomerase inhibitor, made by the same as trastuzumab deruxtecan; it's got a similar idea behind it.

This has been evaluated in phase I and II clinical trials in heavily pretreated patients and it's shown promising antitumor activity with a confirmed objective response rate of 43% and a median PFS of 8 months. Interestingly, the efficacy does seem to be seen regardless of the metastatic breast cancer subtype. Half of them were hormone receptor positive, about a quarter were triple negative, and 17% were HER2+. I'm actually excited to see more data relating to this exciting molecule and the treatment for all different types of breast cancer with HER3 overexpression.

Now in the last few minutes I'd like to shift gears and move on to COVID-19 in breast cancer. I'm just going to spend 2 minutes on this because I do want to get to a robust Q&A in our last 10 minutes. I want to just highlight some ways that we might consider to provide high-quality care to our patients during this pandemic.

Sara Hurvitz:

There have been a number of guidelines that are really expert recommendations because we don't have enough evidence with the pandemic to actually support level one evidence guidelines. But a number of recommendations have been published or promoted relating to how we should prioritize patients for treatment of breast cancer or of cancer itself.

The highest priority are certainly in patients who have unstable clinical scenarios, active metastatic breast cancer, or a new diagnosis of invasive breast cancer. Certainly breast cancer during pregnancy is important to prioritize, and patients who are on therapy and having important side effects should be seen. But the lower-priority patients we really try to push toward telemedicine or video visits to minimize the foot traffic through our clinics, protecting our clinicians and protecting other patients who do need to come into the clinical and are immune-suppressed. And my bottom line here is use common sense as much as possible in determining how to prioritize.

The next slide shows the 30-day all-cause mortality in patients with COVID-19 and cancer, indicating that those patients who have cancer are at a higher risk of mortality. And a variety of other factors have been identified as being linked to mortality, including active cancer. Whether it be stable or progressing on treatment, a poorer performance status two or above has been associated with worse outcome as well. Of course, patients who have other comorbidities, two or more comorbidities, have a worse outcome so these all make a lot of sense.

Now, there are some considerations you might make for patients who are older with breast cancer during COVID-19. Certainly for HER2+ breast cancer, maybe don't be as aggressive in the neoadjuvant setting with cytotoxic chemotherapy. Consider using hormonal approaches or hormonal with HER2-targeted therapies. Just be mindful of the immune-suppressive therapy we're using; however, we don't have outcomes data to support a full de-escalation approach. So I think if we're really careful with our patients and we have a high-functioning 75-year-old with an aggressive tumor, we need to treat as standard-of-care aggressively.

In terms of metastatic disease, it's important always to talk to patients about goals of care and palliative therapy and consider postponing things that are going to lead to sufficient immune suppression. I have a lot of patients on CDK 4/6 inhibitors and a lot of patients on HER2-targeted therapies who are, during the COVID era, and I don't feel compelled to stop therapy just because of COVID. But I am educating my patients very closely and watching them closely as well as their scans during this time.

So SMART goals is an acronym to help us remember to incorporate and practice specific, measurable, attainable, relevant, timely goals. Optimize HER2 testing, identify HER2+ breast cancer, and know that we are now in an era where we're testing newer therapies that might target patients who have HER2 low disease or HER3+ disease. This is a very exciting area. Sequencing of patients' treatment after the third line or third line and beyond is something that is evolving because we have a number of drugs available and no trials to tell us how to properly sequence them. And it's important to tailor cancer treatment during the COVID era.

Now let's turn to our Q&A. We just have about 5 minutes here to do some questions as well as discussion. One of our patients asked Shanu, in community oncology, is asking, "How do you manage diarrhea?," and I would add nausea, "with T-DXd?" What are you doing clinically? Because I am seeing this as well in my own practice.

Shanu Modi:

So I rushed through this but I think the most common day-to-day toxicity that we saw for patients on T-DXd was nausea. And early in the trial, we didn't premedicate for this. In the label, in fact now that its approved, again there were no recommendations. But I think given the experience and the rates of even grade 1 and 2 nausea that we saw on the trial, we at our own institution have made a decision to use prophylactic antiemetics. So all patients will get a long-acting 5-HT3 antagonists. Palonosetron is what we use. And we give them a small dose of steroids for the delayed nausea as well. So that's the premedication and its standard. You can always scale back for patients who are doing well and don't need it and there are a number of patients who don't.

For post treatment, we give everyone a prescription for, again, something like Zofran or Ondansetron or Compazine to have in case they need something more. So in many ways it's how we would treat our patients who are on a highly emetogenic chemotherapy regimen, basically. In terms of the diarrhea, it's quite funny because this is Topo I inhibitor payload, and diarrhea is what we would expect, but we actually saw probably a balanced amount of diarrhea and constipation with this therapy. So I think as we manage diarrhea from something like irinotecan, for example, the goal here is to use anti-motility agents. So loperamide is what we would go to first.

Sara Hurvitz:

Excellent. Thank you so much. Very useful and certainly seeing more of that than ILD in practice, so it's important to address.

Shanu Modi:

Right.

Sara Hurvitz:

Mike, we got a question for you. How often does the biology of a tumor change, i.e., truly being HER2 negative at the primary diagnosis and then positive at the time of metastases or vice versa? Do you have any data on that or do you have a sense just from all of the opinions you give for people around the country?

Michael Press:

We haven't formally analyzed that data, but it's pretty unusual. What is pretty common if you look at most of the studies that indicate that it changes relatively frequently, let's say 20% of the time, I think a lot of those in the past, they've been predominately immunohistochemical assay studies that have not used FISH. In our lab we see it relatively infrequent. Although we have seen it, it's not common. I would expect that in the 1%-2% range, we're talking single-digit percentages. It's not frequent. We have seen it where the original sample has what we would call HER2 heterogeneity in the biopsy. That happens about 1% of the time in the breast cancers we see and the metastases wind up being either, I suspect, depending on how they've been treated.

Sara Hurvitz:

Excellent, thank you. I think we just have time for one last question. A couple people asked us to go through the initial questions again and give our answer about how we treat these patients. So, the first one we'll take is a patient's second-line treatment. She's had first-line THP, second-line therapy. What would you recommend Shanu?

Shanu Modi:

So, I tended to disagree with the audience. I mean, I don't think anyone can be dogmatic and I selected TDM1. As I said, up until recently TDM1 really was our preferred second-line therapy based on great data from the EMILIA trial. But based on, again, very compelling results as we reviewed from the HER2CLIMB study, we now have a label for tucatinib in the second-line setting as well. So frankly, both options are reasonable. From my perspective what I think is important to point out is that all the patients in the HER2CLIMB study had previously received TDM1. So in that space, those patients were still able to have a really dramatic survival benefit with subsequent use of tucatinib.

We don't actually know about that reverse scenario. If we used tucatinib first, would we still get that great mileage out of TDM1? So I think being a purist and inferring from the data as best as possible today, I would still lean toward using TDM1 as my preferred second-line option in that setting.

Sara Hurvitz:

Sounds good. So the other two. One was addressing third-line and beyond and we do, as Shanu nicely presented, have three new approvals: tucatinib, trastuzumab, capecitabine – great data. And data supporting trastuzumab deruxtecan, also great data. Single-arm phase II trial, so we don't have randomized data, but both are approved there. And then neratinib capecitabine. So I think any of those three options are fine. Neratinib does have more diarrhea associated with it, so my top two options in the third-line setting are DHS201 or tucatinib-based therapy. And I use the presence or absence of brain metastases in cryotherapy to help me determine which way to go. But I think this is going to evolve as the phase III studies begin to query proper sequencing and combination strategies that haven't yet been reported.

Then the last thing was how to manage a patient who has what looks like ILD developing in the setting of being on trastuzumab deruxtecan? The patient's disease is responding but there are ground-glass opacities and you certainly need to stop trastuzumab deruxtecan, even if the patient's asymptomatic and you see possible pneumonitis based on ground ground-glass opacities. Consult with pulmonology, get a COVID test, consider steroids. This can be a fatal reaction to DSH201, so it's important to be very cognizant of that.

So, in the interest of time I know we can talk for another hour and I would love to do so. You guys are so wonderful and interesting to listen to with such a wealth of data. But we're going to move on and close the program now. Remember to receive CME/CE credit. Thank you again Shanu and Michael. It was such a great discussion. And thank you, our audience, for all the great questions you sent. I'm sorry we couldn't get to them all. We hope you'll be able to use these strategies that we've shared in your respective clinical settings. If any of your colleagues missed today's program, it'll be archived at cmeoutfitters.com along with other resources such as animation that you might find useful. So if you need to go back and look at some of those slides that were so data-dense, you are welcome to do so. Thank you again for participating and thank you for providing the best care to patients.

Shanu Modi:

Take care everyone.

Michael Press:

Thank you.