

Transcript Details

This is a transcript of a continuing medical education (CME) activity accessible on the ReachMD network. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: <https://reachmd.com/programs/cme/perspectives-clinical-practice-latest-advances-her2-positive-metastatic-breast-cancer/11712/>

Released: 07/15/2020

Valid until: 07/15/2021

Time needed to complete: 15 minutes

ReachMD

www.reachmd.com

info@reachmd.com

(866) 423-7849

Perspectives for Clinical Practice: The Latest Advances for HER2-positive Metastatic Breast Cancer

Announcer:

Welcome to CME on ReachMD. This activity, entitled "Perspectives for Clinical Practice: The Latest Advances for HER2-positive Metastatic Breast Cancer" is provided by Prova Education and is supported by an independent educational grant from AstraZeneca and Daiichi Sankyo.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the Learning Objectives.

Dr. Gradishar:

Welcome to Clinical Countdown. I'm Dr. Bill Gradishar, Professor of Medicine at Northwestern University in Chicago.

Dr. Schmid:

I'm Dr. Peter Schmid. I'm a Medical Oncologist. I work at Barts Hospital in London.

Dr. Gradishar:

So, welcome to the new reality, all those who are looking on and listening to this. I think we spend most of our time these days doing virtual everything. That includes even patient interactions, which have accounted for a not insignificant fraction of the patients we see virtually. We're doing ad boards, we're doing AACR, ASCO, and everything else virtual, so this is yet another effort to convey new information and give you our impressions about breast cancer and some of the newest findings.

Dr. Schmid:

It is a challenging new world. I hope you like this format. It obviously doesn't replace the social interaction we have, but at least we try to get some of the content across to you, and if you have any questions, we're always happy for us to be directly contacted after this video.

Dr. Gradishar:

So, today on Clinical Countdown, we're going to be focusing on HER2 disease – the HER2 breast cancer edition. We'll be taking a look at some of the most recent data that's emerged and how that integrates with what we view as standard of care and how we're trying to look at the new information as it's emerging. And we've seen a lot of activity, obviously, over the last couple of years with new drugs, new agents being incorporated, particularly into the metastatic disease setting. So, without further ado, Peter, do you want to get going with this?

So, let's take a look at the current standard of care for antibody-drug conjugates, or ADCs, in patients with HER2-positive metastatic breast cancer. Peter, can you give us a rundown on some of the new agents?

Dr. Schmid:

Yeah, thank you, Bill. HER2-positive metastatic breast cancer, until about a couple of years ago, we thought we had reached a ceiling. And we had substantially improved outcome of patients over the last few years, but we couldn't possibly imagine that we could improve

further on this. The standard in most parts of the world in the first-line setting is chemotherapy – taxane-based chemotherapy – in combination with trastuzumab and pertuzumab. As a second-line standard, again, in most parts of the world, the first antibody-drug conjugate was established with T-DM1. The third-line setting, until recently, we had in some parts of the world chemotherapy plus other HER2-targeted therapies, in particular, more lines of trastuzumab, possibly lapatinib. But in other parts, for example, in the UK, a third-line HER2-targeted therapy is currently not reimbursed.

Now what we've recently seen is the emergence of several new, very promising drugs. Two of them got recently approved in the US. One of them – a new antibody-drug conjugate, trastuzumab deruxtecan – which has shown substantial activity in patients as a third-line and subsequent-line settings. Patients who have pretreatment with T-DM1 – so another antibody-drug conjugate – saw a response rate of around 60 percent with a progression-free survival of around 16 months, which is substantial compared to what we have seen in this setting before. It was almost what we have seen in the first-line setting. Equally, we have another interesting drug here recently approved – tucatinib – another tyrosine kinase inhibitor, which is given in combination with capecitabine and chemotherapy and trastuzumab and has shown a substantial improvement in progression-free survival in patients compared to capecitabine and trastuzumab in the third-line setting with specific high activity in patients with brain metastases.

So our armamentarium is increasing rapidly with new, highly active substances, and we will see, in my opinion, how these are moving through the lines, possibly into earlier lines, as we move forward.

Dr. Gradishar:

Yeah, and I would agree with what Peter said. I don't have anything to really rebut. I would just amplify the notion that, you know, we thought, or we're thinking, that as a community we had eliminated or were coming on the cusp of eliminating HER2-positive breast cancer as a recurrent problem. But we found that even with longer follow-up of the adjuvant trials that, you know, a significant fraction of patients, as you go out farther, are developing metastatic disease, which really speaks to the issue of continuing to identify more effective therapies in the metastatic disease setting. And what Peter just mentioned – the inevitable sequence of drug development would lead one to think about some of these drugs in the adjuvant or post-neoadjuvant setting. So we're going to continue to need new drugs, and I think both tucatinib and trastuzumab deruxtecan are two drugs that have really moved the field forward. And I know we'll talk about it, but these, I think, are very active drugs that are doing good things for patients.

Dr. Schmid:

So, Bill, considering some of the latest data we saw recently at ESMO Breast, we saw in San Antonio, and most recently at the virtual ASCO meeting, those new data on ADCs, but also new data on tucatinib. How do you think we will incorporate these treatments into our everyday practice?

Dr. Gradishar:

Yeah, so I think that certainly in the States, we have these drugs now available. And certainly trastuzumab deruxtecan was the one that appeared first in terms of being available to us and to our patients, so we probably had a little bit of a lead time in using that drug even, you know, for many of us who had tucatinib on clinical trials. So, trastuzumab deruxtecan in the patients we have used, we've tended to use it, you know, beyond the typical trastuzumab-pertuzumab-taxane regimen. Patients go on, and after they've had two or more lines of therapy – and today, again, the – and the number of patients we've treated is still modest. We've seen very good activity.

Tucatinib, as demonstrated in the HER2CLIMB trial, which was a randomized trial, clearly demonstrated improvement in outcome, and what was most striking about that data set was what was seen in patients with brain metastases. And although the data set with trastuzumab deruxtecan included patients with brain mets, they were stable brain mets, whereas the tucatinib trial included patients who had already progressed, or they could've progressed. So it's a somewhat more generous inclusion of patients with brain mets, and what was most striking, again, in the HER2CLIMB trial, is the activity in those patients with brain mets who received tucatinib, showing that there was an improvement in outcome in terms of PFS as well as OS even in those with brain mets. So, in my own mind, we've certainly considered tucatinib a treatment of choice in the HER2CLIMB regimen, particularly for those with brain metastases.

I think that these are two active drugs. Trastuzumab deruxtecan is a little bit more attractive in one sense. It's a single drug as opposed to three drugs in the HER2CLIMB regimen, but then, of course, there are potential side effects, which we'll talk about.

Dr. Schmid:

Now, the development program is ongoing, as we're all aware of, and at the moment, at least in the US, DS-8201 is licensed in a setting after T-DM1 in what I would call a third-line setting. But there are two phase III trials ongoing, DESTINY-02 and DESTINY-Breast 03, which we'll see first of all at a randomized setting whether similar impressive results can be obtained post-T-DM1, but also, then, in the earlier line, a head-to-head comparison with T-DM1, which I think will be very interesting to see.

Dr. Gradishar:

So, let's move on. I know that in my response earlier, I touched a little bit on this, but I'd like to get Peter's idea of how he would use these two drugs and how he would sort of characterize the type of patients where he might use either the regimen from the HER2CLIMB trial – tucatinib – or trastuzumab deruxtecan from the DESTINY trial, if there are certain characteristics that would lead him to use one over the other.

Dr. Schmid:

I would like to go to an interesting area, and that's for me around HER2 expression. And one of the things I'm really intrigued with is the high activity we have seen in the early results with DS-8201 in patients who don't meet the classical criteria of HER2L expression, and they're a group of patients we are classifying as HER2-low, which means they're IHC criteria of 1+ or 2+. And I think this is possibly down to this bystander effect, and I think that has obviously implication in possibly how we define HER2-positive breast cancer, how we define patient groups going forward if those later get confirmed in their ongoing trials. But I think it also has – in clinical practice, has relevance for patients who have HER2-positive disease in our current classification but who may have heterogeneous disease. And we're sometimes anxious about if a patient may have two, three biopsies, and two are HER2-positive; one may be HER2-negative. That is a group of patients we'll now much more confidently use DS-8201, for example, compared to other agencies because we know we're likely to see a good activity in patients who have lower or possible heterogeneous HER2 expression.

Dr. Gradishar:

Yes, and I would again agree with what Peter said, particularly when we think about patients who get neoadjuvant therapy, and I think that was a little bit what he was alluding to, data from Metzger and other people who have looked at this question. Well, we've all seen this in clinical practice, that we treat patients neoadjuvantly, they go to surgery, and suddenly they're HER2-negative. Well, does that mean that we eradicated that clone, or we're just not picking up low expression of HER2? And this may, as he said, afford us an opportunity to use a drug that's going to have an effect in that setting, still using HER2-directed therapy. But I think the other issue is it may more broadly just open up another slice of breast cancer, allow us to categorize patients into another category that are HER2-low, and rather than simply give them chemotherapy, we would have an option that could be more attractive and also be more effective. So I think that's an area that some of the trials that are ongoing now will hopefully address and will determine whether or not this becomes an area that we want to incorporate into our thinking with respect to HER2-positive disease.

Now we're moving on to a section that's meant to be pithy and short – I guess 30 seconds, a lightning rundown where we're going to go from topic to topic and have to say what we think in a very brief period of time. So I'll start with you, Peter. And you alluded to, already, the fact that some of these drugs have adverse events, and you were mentioning the expected, or not expected, but the findings from the DESTINY trial that suggested trastuzumab deruxtecan had a risk of interstitial lung disease. And if you could, in a pithy way, elaborate on that very quickly.

Dr. Schmid:

Yeah, it's a really important point, and it's probably the one point we need clarification on this drug and need a little bit more experience. Interstitial lung disease is a term our lung colleagues use very commonly. For breast cancer doctors, it's a little bit unusual, and we tend to use the simple term pneumonitis very often. And pneumonitis is something we see with many drugs. But what was evident in the early study with DS-8201 is that – the pneumonitis ILD, which seems to be higher compared to what has been reported with other drugs.

Dr. Gradishar:

One of the areas that I was asked to comment on was really the risk of cardiotoxicity with these agents or, more globally, the HER2-directed therapies. And I think since trastuzumab was first introduced, it's sort of been ingrained in all oncologists that we have to be monitoring for cardiac toxicity, recognizing that it's still relatively infrequent. But that also holds true for some of the newer drugs as well, including trastuzumab deruxtecan and even within the context of the HER2CLIMB trial where trastuzumab is still part of the regimen.

So, the next question, which goes to you, Peter, is really just a quick comment without going into the details about the trials. But some of the other drugs that are in development, and we're in a sort of corn of plenty here with drugs that are acted in the HER2 space, and there are several that are still in development – a few of which I'd ask you to comment on if you could.

Dr. Schmid:

Thank you, Bill. There's a number of new treatment options, obviously, that are coming through. We thought we wouldn't have more effective treatments in HER2-positive breast cancer; now we have a whole range of new drugs beyond tucatinib, beyond DS-8201, who would show early promise. If you look at new ADCs – SYD985, ARX788, for example – both of those drugs have shown promising objective response in HER2-positive disease in the phase I studies. Interestingly enough, with SYD985, we've also seen encouraging high response rates in patients with HER2-low disease. There are other ADCs coming through, for example, MEDI4276 or XMT-1522 where it's a little bit too early to see.

Dr. Gradishar:

So, thanks, Peter. I think we're sort of ending the time we had to hold this discussion, and I would just add a couple of comments, sort of my overall impression of the data that's emerging. Obviously, we've had a continued advance in HER2-directed therapy over the last two decades, and we find that with each incremental improvement, we're decreasing the number of patients that recur who have early-stage disease. But of those that do develop metastatic disease, we have an increasing number of options available to patients. And one of the continued unmet needs, even though we've made progress, is the observation that 50 percent of patient who have HER2-positive disease in the metastatic setting are going to have brain mets. So now we have some evidence that some of the therapies that are new are actually affecting the outcome of those patients, which is encouraging. So I think the future is bright with respect to these drugs and some of the other ones that are in development, and we'll look forward to sharing those results in the future. Peter?

Dr. Schmid:

Yes, Bill, I would totally agree. And I think the introduction of two highly effective new drugs in the treatment of metastatic breast cancer clearly have a substantial and meaningful benefit for patients, but will also change completely treatment sequences as the establishment over the last ten years. And that will come with great advantages – opportunities, but also challenges. It also opens up a new area in early breast cancer. If you look at the T-DM1 data, we saw there a couple of years ago where we improved the hazard ratio to an 0.5 even a setting post-neoadjuvant therapy. If you can imagine how DS-8201 may possibly function in such a setting looking at the activity we have seen in the metastatic setting, I think we will hopefully – getting closer to a cure with the introduction of those very effective treatments we have now established in the metastatic setting, possibly over time and earlier disease lines in metastatic disease, but also possibly in early breast cancer.

Dr. Gardishar:

Great. Well, that's it. We're out of time. So on behalf of Peter and myself, I want to thank you for joining us, and we look forward to speaking to you again in the future.

Dr. Schmid:

Thank you very much.

Announcer:

You have been listening to CME on ReachMD. This activity is provided by Prova Education and is supported by an independent educational grant from AstraZeneca and Daiichi Sankyo.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Prova. Thank you for listening.