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Evaluating Landmark Clinical Data for HER2-low Breast Cancer

Dr. Chalasani:
Breast cancer treatment landscape continues to adapt and evolve as we are learning about new targets and develop novel treatments. Sometimes old targets are revisited with new therapies. Today we are going to discuss such a groundbreaking high clinical impact study for patients with tumors which were traditionally classified as HER2-negative but now HER2-low.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani. And joining me today to talk about DESTINY-Breast04 trial is Dr. David Cameron, Professor of Oncology and Deputy Director for Innovative Healthcare Delivery Program at the University of Edinburgh.

Dr. Cameron, thanks for being here today.

Dr. Cameron:
A pleasure. Thank you for inviting me.

Dr. Chalasani:
So, to start off our discussion, Dr. Cameron, can you give us some background on the DESTINY-Breast04 trial? What got you and your team interested in exploring this treatment option?

Dr. Cameron:
So we all know about HER2-positive or HER2-amplified breast cancer, somewhere between 15 percent and 20 percent of cases, which have very high levels of the cell surface protein receptor, usually as a consequence of gene amplification, and we got used to thinking that the vast majority of breast cancers as HER2-negative where the HER2 protein plays no part in its biology and therefore offers no therapeutic opportunities.

There was a little bit of evidence that there might be effects on cells adjacent to those in which the T-DXd drug was taken up, and therefore, this raised the possibility that you could use some HER2 on a cell surface of a breast cancer to allow the trastuzumab antibody to bind to it, the antibody-drug complex to be pulled into the cell, but because a potent payload was attached to that antibody, that antibody releases or is released from the payload within the cell, and suddenly, you've delivered a cytotoxic inside a cancer cell that is not HER2-amplified but has some HER2 protein on the cell surface, and that was really the hypothesis. And there were some early phase data to suggest that this hypothesis could be true, and so DESTINY-Breast04 was designed as a full-blown phase III trial, potentially practice-changing, to test this hypothesis in breast cancer patients who had metastatic disease and whose breast cancers expressed a level of HER2 but below the level of what we call HER2-amplified, a term that we now—for a group of cancers we now call HER2-low.

Dr. Chalasani:
Great. Thank you. So, can you hit the key highlights for the results for us?

Dr. Cameron:
Two key highlights: The first, obviously, is efficacy. This drug was superbly efficacious. In our first analysis, we not only crossed the statistical threshold for significant clinical and statistical difference in progression-free survival with almost a doubling of the median progression-free survival in the primary analysis population, those who had hormone receptor-positive disease, but actually, we also crossed the threshold for calling clinical and statistical significant improvement in overall survival. And I think, if I'm honest, I'm not sure many of us expected to see that. The secondary analysis group, which therefore included the smaller subpopulation of triple-negative, was also positive, so we are seeing effect across all the patients in the trial, not just the hormone receptor-positive ones.

The second path or signal, which was less of a surprise but is really important to see, is that the toxicity of this drug was manageable. The pattern is different. So, for example, partly, perhaps, because many of the patients who were given eribulin we saw less neutropenia; we saw less infections. And that's important in a patient population group primarily managed as outpatients who want to stay away from hospital. We did see more nausea, and that's important to bear in mind. This drug can cause nausea. And then, of course, this raises—there is the question of the interstitial lung disease, or pneumonitis. Yes, it happened. We expect to see it with this drug. But the overall rate was modest.

Dr. Chalasani:
Great. Thank you. So, something that I wanted to touch base with you on, you know, the toxicities that you mentioned. Can you comment on how you look for or manage, in your practice—or would you recommend observing for both the ILD and also managing the nausea for these patients?

Dr. Cameron:
One thing I think we've all learned as oncologists, and I'm sure you'd agree with me, is we need to preempt likely toxicities, wherever possible give prophylactic treatments so the patients don't or much less experience the toxicity. So, for things like nausea, I think it's important to recognize it is a side effect of the drug, very manageable. Look out for it. Preempt it. Give patients access to advice and additional therapeutics. If they do experience it, allow them to maintain a good quality of life.

So, in our own practice at the moment, we are doing high-resolution chest CTs every six weeks, and we are picking up patients who have early pneumonitis, which is completely asymptomatic, grade one. The advantage of that, of course, is not only that you preempt them developing more serious pneumonitis, which may be symptomatic, but actually, you can intubate them with additional steroids, get it under control and then potentially continue with the drug.

Dr. Chalasani:
Absolutely. That is definitely something all of us have to keep in mind. So, just to clarify and just follow up on that question, so, do you do the high-resolution CT every 6 weeks for as long as the patient is on?

Dr. Cameron:
My understanding, and I think we do need to see bigger data sets emerge, but my understanding is that the median time to do this is a few months. Most cases emerge within the first year. I suspect after a year we will wind down the frequency, but we haven't quite worked out what that should be, and I think it's something across the globe that we oncologists need to share with each other: "What, what have you learned?" You know, "Can we reduce the frequency at 12 months?" I suspect we can but I don't yet have data to tell you exactly how we should do it.

Dr. Chalasani:
Now, coming to discuss these findings in the context of clinical practice, how do you think these results impact treating our patients with HER2-low metastatic breast cancer. And the most important thing I did want to get your opinion is, going forward, you know, how do you think the classification of HER2 is going to change?

Dr. Cameron:
In terms of clinical practice, I think you raised two critical things. One is, where should we use this drug once it's within license? And the second is, Is our current approach to HER2 testing fit for purpose for HER2-low?

Let me deal with the first one. I think it's very likely that this drug is going to get approved in the U.S. almost certainly first and then in other parts of the world hopefully fairly soon afterwards. And what it tells us is, is that if you have a patient certainly with ER-positive HER2-low breast cancer, when you need to give them chemotherapy in the metastatic setting, this is the most effective chemotherapy agent that we have got.

In the triple-negative setting, we'll obviously have to see what the regulators say because the whole ER-positive plus triple-negative grouping was a secondary endpoint, not the primary. If it's approved in triple-negative too, then I think we've got a drug that, based on a smaller number of patients admittedly, but there's clear evidence of efficacy. And you can look at the efficacy signal in DESTINY-Breast04 for the triple-negative patients, and it's at least on par with what we've seen with sacituzumab, so I think it's very likely to become a drug for those patients too, probably in the second line, but ultimately, people may feel willing and able to move it to first line if that's within license.

At the same time—And I don't think we should wait for licensing. At the same time, we need to be discussing with our pathology colleagues and our experts to say, "Do we think that the current IHC approach of zero, one, two—because, obviously, three is counted as positive—is the best way to identify HER2-low?" And in that setting, there is a small number of patients I think from a study called

DAISY who were HER2 0, and even they had some responses but fewer. So I suspect we may move into a world where we look for amplification, and that defines HER2-positive cases, and for the non-HER2-amplified at the gene level, we make some kind of measurement of the protein level on the cell. Whether it's through IHC with a different set of thresholds or with the same set of thresholds or some other approach, I think it's for others who are pathologists to, to help us understand.

What we've got is okay. I don't think we need to change it now because we're seeing activity in the HER2 1 and 2+ FISH-negative patients, but going forward I suspect it may change.

Dr. Chalasani:
And I just wanted to get your opinion on some practical things that we see, you know, with the HER2-low or IHC and frequently something all of us probably run in clinic is the testing of which sample. Is it the primary tumor? Because sometimes we get frequently, you know, the bone metastasis, and HER2 IHC is hard to interpret in the setting when we have to do that. So, can you comment in the trial how the HER2-low were classified? Was it based on the primary or metastatic, or what would you recommend?

Dr. Cameron:
It was done on both.

Personally, if I want to treat a patient, I would like to know what the receptor status is of the cancer I'm treating rather than the one with which she was diagnosed maybe 1, 5 or 15 years earlier. So I would always advocate if you can to get tissue from the metastatic disease and to assay that for the HER2, but there are sites when you can't do it. The bone is a challenge. And whilst we know that there is some switching of receptor status, it is still only in a minority.. The only time where we have no large-scale data to show that T-DXd would work would be if that cancer has become completely HER2-negative, and that, I think, is a much less common scenario. Some of them switch to becoming HER2-positive, but we know the drug works in HER2-positive patients. So I'm less worried in a way for this drug about subtype switching in terms of HER2 levels because the proportion who go from some HER2 to absolutely none is, in my understanding, relatively small; and therefore, whilst you should go to the metastatic site if you can, if you can't and you've got some HER2 on the initial disease biopsy, I think it's a reasonable clinical judgment, as we do for everything else, to treat on the basis of that.

Dr. Chalasani:
Very important and very critical because these are all practical things that we encounter in clinic. So, before we close, Dr. Cameron, do you have any final thoughts or takeaways you would like to share with our audience?

Dr. Cameron:
I think the only other thing I would raise is the subgroup analysis, which basically shows that the critical subgroups, including prior CDK4/6 inhibitor or the level of HER2, how many prior lines of chemo the patient may have seen, etc., it didn't make any difference. The efficacy signal was essentially the same across all our subgroups: visceral, nonvisceral, etc., and that's important to know. We don't have tools to tell us who are the very small number of patients who showed no signs of drug efficacy, so we can't easily say the drug won't work for this patient, and that's important in considering it with any patient in your clinic.

Dr. Chalasani:
Absolutely. Well, with those insights in mind, I want to thank my guest, Dr. David Cameron, for sharing his insights on the DESTINY-Breast04 trial and its impact on treatment landscape for HER2-low metastatic breast cancer.

Dr. Cameron, thanks for being here today.

Dr. Cameron:
Thank you for inviting me. And I obviously want to thank all those involved in the trial, including all the patients, for being willing to undertake this important piece of research.

Dr. Chalasani:
I'm Dr. Pavani Chalasani. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology where you can be Part of the Knowledge. Thanks for listening.