Metastatic breast cancer: Understanding HER2-low and HER2-ultralow classification
A novel therapeutic framework

Brought to you by;
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Dr Rohit Gosain
Hello again and welcome back to the Oncology Brothers Podcast. I am Rohit Gosain, joined as always with my brother and co-host Rahul Gosain. Both of us are practising medical community oncologists. Our mission with these discussions is to make sure that you leave with the latest and the most practical updates in the cancer care. Today we will be talking about metastatic hormone receptor-positive breast cancer. There is quite a bit happening in this space, but focus of the discussion today is going to be HER2-, which was how it was defined before but now rather termed as low or ultralow HER2 expression. This does not change our first-line treatment option that is still CDK4/6 inhibitor plus endocrine therapy and importantly the need to check for *PIK3CA* mutation or PTEN loss. But if the disease was to progress, that is where the discussion is going to be on focus today. To sort through this space, we are honoured to have Dr Komal Jhaveri, a breast medical oncologist at Memorial Sloan Kettering join us today.

Dr Komal Jhaveri
Thank you so much for having me again.

Dr Rahul Gosain
To set the stage for this discussion in metastatic hormone receptor-positive breast cancer, HER2 status historically was binary, right? It is either positive or negative. But this all changed in 2022 based off DESTINY-Breast04 study where we saw significant improved PFS and OS in low HER2 with trastuzumab deruxtecan and this presentation by Dr Shanu Modi rightly so got standing ovation at ASCO 2022. But then we all started to question saying how low is low for us to see response from trastuzumab deruxtecan in this setting. And that took us to DESTINY-Breast06 which led to the approval of trastuzumab deruxtecan in low and ultralow HER2 breast cancer. Komal, can we start here? Can you touch on the study design of DESTINY-Breast06 and its findings that led to the approval of T-DXd in this space?

Dr Komal Jhaveri
So I think to your point, when we thought about HER2 as a target, we were only focused on HER2 as an oncogenic driver, which is what we thought was happening, which is why we went after it when we thought about HER2 as a binary expression and HER2 subtype as the way to target. We have approval for say T-DM1 initially and then T-DXd for HER2-positive breast cancer. But beyond that now we have learned that HER2 is still a relevant target, but it does not have to necessarily be an oncogenic driver. We could literally use it as a medium as a way for delivering payloads with our newer current novel ADCs such as trastuzumab deruxtecan. That is why we have this subtle loss of boundary between subtypes. We now have HER2-low and HER2-ultralow, which was not necessarily how we thought about subtypes, where we thought about ER+, HER2+, and triple-negative breast cancer as three important subtypes. DESTINY-Breast06 was a step forward after DESTINY-Breast04.
So, DESTINY-Breast04 led to the approval of trastuzumab deruxtecan for HER2-low cancers regardless of hormone receptor positivity. This was in patients who have had at least one line of of chemotherapy and no more than two lines of chemotherapy and predominantly represented the hormone receptor-positive HER2-low cohort. HER2-low being defined as tumours that are IHC 1+ or 2+ that are FISH negative or ISH, not amplified. We had approval there and then we said what if we were to bring it even upfront in the metastatic setting? Could we use it in the chemo-naive setting specifically for hormone receptor-positive tumours, not HR-/HER2-low, but focus on the HR+ and bring it in the chemo-naive setting. And what if the tumours had just some level of HER2 expression? And this is the HER2-ultralow which is more than 0, less than 1+ or tumours that are ≤10% of incomplete membrane staining. So as long as it is not completely null or completely zero and some expression, those were the two kinds of tumours that were the focus for DESTINY-Breast06 and this was for chemo-naive setting, as we said, patients had to have had endocrine therapy and the majority did have CDK4/6 inhibitor. And here we saw an improvement in the progression-free survival compared to the physician choice chemotherapy arm which could have been taxane, capecitabine. So it improved from ~8 months in that control arm to ~13 months with T-DXd use in the chemo-naive setting, so post endocrine therapy chemo

naive setting and we do not have overall survival data yet, but even for the HER2 ultralow tumours the efficacy signal was similar, the response rates looked great, the PFS was in line, of course the subset was smaller and it is exploratory but I think relevant and that is why we have approval for T-DXd in this setting.

Dr Rohit Gosain
It is amazing to see how low of an expression is needed for this drug to actually work. And since the inception of these ADCs, we have been like seeing a whole slew of come out for approval. That is after T-DXd. What we have seen is sacituzumab recently Dato-DXd, which is just in breast cancer world though T-DXd has a bucket approval for all solid malignancies with IHC HER2 positivity. Coming back to our HER2 story, Komal, can you define who qualifies particularly for this HER2-positive, low HER2 and ultralow as you described? But given how heterogeneous this is, how often are we checking for this expression? Every time on progression or how are we gonna manoeuvre through this?

Dr Komal Jhaveri
Yeah, no, I think such an excellent question. As we said, HER2+ tumours are tumours that were either IHC 3+ or they could have been 2+ as long as they had an amplification by ISH. And that is what we still consider as HER2+. Now for HER2-low, we said the definition could be anything less than that, meaning it could be 1+ IHC or it could be 2+ IHC that is not ISH amplified, and that is for HER2-low. And ultralow is more than zero, less than 1 or 10% or less incomplete membrane staining. So as long as they have some HER2 expression, that is enough for us to think that this antibody-drug conjugate can go target that HER2 protein and deliver the payload and derive the benefit that we have seen so far. And I think when it comes to how often do we test it, I think because we have recognised that HER2-low and ultralow can be more dynamic than say HER2+ tumours could be. And even with HER2+ tumours, we do see this change in expression or change in HER2 levels and HER2 loss as a mechanism of resistance with multiple anti-HER2 therapies. But HER2-low tumours is thought to be more dynamic and it could evolve between the primary tumours or the metastatic setting, between one biopsy in the metastatic setting to the other. The way I think about it is as long as I have some HER2 expression, whether it is in the primary, whether it is in the metastatic setting, I definitely do not miss the opportunity to offer T-DXd to my patient unless there is an obvious contraindication with interstitial lung disease or something else that prevents me from doing that. But if I have a consistent IHC true zero with no HER2 expression at all, I might consider doing a biopsy when appropriate to see if this has changed, given that we know that this could be dynamic and maybe I could find some HER2 expression that would allow a new treatment option for my patient in clinic.

Dr Rahul Gosain
Komal, thanks for touching on that. Can I just pick it up where you left, one, HER2 testing is dynamic, also very subjective. Right? So now, given the data in hand with DESTINY-Breast06, you have touched on this, that the data looks very similar for low HER2 and ultralow HER2. But in our clinical settings, one thing that we are always pondering over is, can I use this for

a true HER2 negative patient as well? How important is this expression? On my end in the community, how far do I push my pathologist to label something as low HER2?

Dr Komal Jhaveri
Yeah, yeah. No, I think it is an excellent question. I think given the totality of data that we have with T-DXd and the robustness of efficacy that we have seen across subtypes and across settings, I think it is very tempting to think about, you know, what could I do to make this work? Right? But the good news here is that if you count your HER2+ tumours, you count your HER2 low, and you count your HER2 ultralow, we are talking about 85 to 90% of breast cancer.

Dr Rohit Gosain
Right.

Dr Komal Jhaveri
So, we are really covering the breadth of breast cancer subtypes and we are talking about a small proportion, 10 to 15%, where we truly think that they might be truly HER2 null or truly IHC 0 with no level of expression. And for that patient, I am not going to offer T-DXd. So, certainly I would if needed, now that CAP reporting template has this HER2 ultralow also included, our pathologists have taken that on, and even pathologists that were not doing that right away, some had converted sooner, some are now homogeneously converting. And now in their reports, based on these CAP guidelines, hopefully we do not have to make those phone calls that we did a few months ago asking them, do you really not see anything? So I have not had to do that. And thankfully, community doctors will also have less of an opportunity to necessarily do that. But certainly if there is something that you were considering in clinic and wanted to clarify and make sure, I think we can certainly think about doing that. But I think it is going to be for a smaller group of patients, which is the good news.

Dr Rohit Gosain
That is a small group of patients but when we are deprived of treatment options, especially out in rural setting, there are no clinical trials available, you want to jump on, especially how promising this drug is. And from what we have seen with DAISY trial as well, though that was true HER2-, there was still responsiveness, which is remarkable. But again, that is not where the approval is.

Dr Komal Jhaveri
DAISY did not break down your IHC 0 from ultralow. So what DAISY said was this is IHC 0, but it did not necessarily clarify that. The true negativity, yep. So yes, DAISY was the reason we thought that yes, there might be more to IHC 0, which is how we stumbled upon HER2-ultralow as well. So, I think DAISY helped us guide there, but did not necessarily clarify that directly.

Dr Rohit Gosain

Thanks for clarifying that. Komal, besides the subjectivity which is tied to the HER2, another question that we ponder upon is the sequencing. After upfront CDK4/6 inhibitor, in the absence of AKT pathway mutation, in what line are you utilising this in your clinic today?

Dr Komal Jhaveri
So, I think our goal in hormone receptor-positive breast cancer, at least today, still remains that we try and maximise endocrine based options before we deem a tumour endocrine refractory and then switch over to sequential single agent chemotherapy or antibody drug conjugates. And so I still continue to do that. There might be a patient when I might be able to do up to three lines, four lines of endocrine therapy based options before I move over to chemotherapy. And there might be patients where I am doing that in the 2nd or 3rd line. Right? So, it totally depends on what prior therapies they have had. Is it a de novo tumour? What is the disease burden? And one important thing that I would highlight from the DESTINY-Breast06 that we have data for now, 9% of the patients in DESTINY-Breast06 that were enrolled had this primary endocrine resistance, in that in the metastatic setting, the duration of their 1st line CDK4/6 inhibitor therapy was less than six months. And that really gives us that confidence that for these primary endocrine resistant tumours, we can certainly jump onto an antibody drug conjugate such as T-DXd as the next line of therapy. So, as a 2nd line treatment regimen for true primary endocrine resistant tumours, which included less than six months duration on CDK and were included in the DESTINY-Breast06 trial. But short of that, I am trying to maximize my endocrine based regimens before I move to chemo.

Dr Rahul Gosain
Can I piggyback on the sequencing question as well? We have to keep the disease burden in mind. We have to keep side effects in mind. But we have few ADCs that are approved here. And in clinical practice for hormone receptor-positive, we are often using T-DXd first and then sacitizumab in most cases, whereas in triple-negative we are often doing the other way around where we lean into sacitizumab first and then T-DXd. Komal, do we have any real world data around sequencing one ADC after another?

Dr Komal Jhaveri
We do. I mean we do have some data from small retrospective studies from single institution, from real world data sets. And I think the big picture learnings from those attempts have been that, certainly ADC1 gave us a better durable PFS benefit and ADC2 gave us a slightly shorter duration of benefit. Regardless of what ADC was used first or second. So, it could have been T-DXd first or sacitizumab first and the other one and next. But there are a group of patients where somehow ADC1 did not necessarily work, but it worked really well with ADC2. And we just do not know what the issue there is or what was the holdup there. Is it related to a target? Is it related to a payload issue? I think. Could it be just differences in the potency of the payloads and the drugs itself? Even though all our approved ADCs currently in the hormone receptor-positive space have similar payloads, if you will, they are all topoisomerase inhibitors. There could be some differences in their linker technologies and also their potency of the payloads itself. And so certainly that is

what we have seen. A most recent real world data set that we also saw that was presented at ESMO Breast as well, where post T-DXd they saw that chemotherapy actually had a longer PFS benefit. Eribulin had a longer PFS benefit compared to other ADCs as well. I think we are still learning a little bit more from that. We need a little bit more information.
We have ongoing efforts such as the TRADE-DXd trial where we are trying to see if, between the two deruxtecan payloads, if we are changing the target, would it matter what we use first? So, in this trial, patients would either get T-DXd first and datopotamab at the back end, or start with datopotamab first and get T-DXd at the back end. So, that is TRADE-DXd and then we have registries, we have the registry within the Translational Breast Cancer Research Consortium and the SERIES study looking at T-DXd and sacituzumab, should we start with one and go to the other and what would that look like? Versus start with sacituzumab and go to T-DXd after and what would that look like? So, we will have more data from those studies. But I think at the end of the day, it would be very attractive for us to also have newer payloads, newer targets as well, because as we have learned in the bladder cancer world, where patients got say, enfortumab or sacituzumab and completely different ADC, so enfortumab is Nectin-4-MMAE ADC, those patients did better than say if they would have had a similar target or a similar payload. And so I think, we are looking forward to those new advances as well.

Dr Rohit Gosain
It is amazing how fast the science is changing. There are so many multiple approvals in the same setting. And sequencing is not just an issue here in breast cancer, but as you stated, bladder cancer, kidney cancer, and all throughout solid tumours and hematology world. Komal, we now know how to test HER2 and now we know when to use T-DXd. But importantly, how to manage the toxicities. Especially this. ILD tends to be a hot topic because again, there is mortality associated with it. But again, this also has other side effects like alopecia, nausea and vomiting like other chemotherapies. Any clinical pearls around the side effect profile here?

Dr Komal Jhaveri
Absolutely. Very, very important to think about the side effects and how to manage them. Because without that, without addressing that, we cannot have patients continue on the intended therapy and derive the intended benefit we hope to achieve for them. Let us talk about common toxicities first and then we will talk about the important ones that can be fatal. The common toxicities that we actually face in clinic when we are treating these patients with T-DXd are actually nausea and fatigue. So nausea, vomiting, fatigue are the most common ones that we need to address first. And the very important piece that sometimes I feel like is still not necessarily homogeneously utilised is the triple antiemetic regimen or the quadruple antiemetic regimen that also includes olanzapine. And I think that has been a game changer for my patients in clinic. I think the grade 2 nausea, the grade 3 nausea rates have definitely come down. The dose reductions have reduced as well, and patients are tolerating treatments much better with triple antiemetic and quadruple antiemetic regimen. So, a must do for our patients in clinic. Fatigue, if there is intolerable fatigue it is very hard, it is subjective sometimes to think about fatigue and how a patient.

But you know your patient, the patient gives you good history about it, you can assess that and if it is intolerable and you want these patients to continue on therapy, dose reductions make it easier. And I have certainly resorted to that and have kept patients on for a longer period of time. So those are the most important ones.
Alopecia is a very good one. I absolutely discuss that with every single patient of mine. Although I have to say, when we first had approval for T-DXd, that was DESTINY-Breast01 in the HER2+ late line metastatic setting, we certainly saw a much higher rate of alopecia. In clinic, I am seeing much lower rates of alopecia than what we had seen and that could be because more prior treatments, more treatments that had already caused alopecia, make it very difficult to attribute that to a given treatment in a clinical trial. So in practice, I have definitely upfront prepared patients for alopecia, but I have seen much less alopecia than it was originally reported. The other thing is that the jury is out still whether scalp cooling would help. There are ongoing trials trying to address that question. Now, these are longer acting half-lives, right? These antibody drug conjugates are over three weeks. We do not necessarily know yet whether this would absolutely help or not. Is it because the patient was not going to lose their hair or is the scalp cooling, you know, helping with that? Some patients want to do it. I have never stopped them. I tell them I do not know if this will help, but I have no problem. I have many patients who stay on scalp cooling and we would never find out if it was the drug that was not doing it or if it was the scalp cooling helping, but I let them do it. And last but not the least, I think it is ILD, as you pointed out, it is important because it can be fatal.

Dr Rohit Gosain
Right.

Dr Komal Jhaveri
Thankfully, it is not as common, but it is still present and we really want to know about them. It is very important for us to keep an eye on the radiological exams that we obtain. Now in trials, CT scans were done every six weeks and they had an adjudication committee to review them. In practice, six weeks could be a little tricky. Although some patients, I have done six weeks where I would do their systemic scans every 12 weeks, that the way we would do every three months. But if I am nervous about if they have had prior history, would say everolimus related pneumonitis or a PI3K related pneumonitis or some lung issues that they have had, then I would do a CAT scan just for their chest, a high resolution CT every six weeks. So, I have played it by ear. I either do it every nine weeks or I have done six and twelve, depending on a patient in front of me. It is very, very important to recognise that grade 1, all you have to do is pick that up on your radiological scan. The patient is not going to be symptomatic. You have to hold the therapy. You can give them a quick dose of steroids. If the radiological findings disappear by less than 28 days, you do not even need to dose reduce. You can rechallenge at the same dose. If it takes a longer time, you have to dose reduce. So, it is very important that we are very vigilant about the CAT scans. Then the second thing is grade 2, which is not just the radiological findings, but also symptomatic ILD. In those cases, we are not only holding, but we are permanently discontinuing. There was data presented about rechallenge, and I think with grade 1, I feel like the rechallenge, I think

is easier. With grade 2, I still get a little more nervous about the rechallenge. It depends on the severity of the ILD. But ideally with grade 2, I would discontinue and give a higher dose of steroids and a longer taper. Certainly involve pulmonology for help in there just so that you can get the guidance. But these are the two minimum things that you need to do.

Dr Rahul Gosain
And that rechallenge study was published by Dr Hope Rugo. Similar findings to what you said. Grade 1 ILD with use of steroids patients actually did okay. But within that study, it is a small subset. Grade 2 ILD was a very, very, very small subset. So, we have to be very cautious in our clinical practice because again, there is mortality associated with this ILD here. Komal, before we close, any final thoughts here? And can this data be extrapolated to triple-negative breast cancer with this ultra low HER2?

Dr Komal Jhaveri
Yeah, no, I think that is a great question. So I think triple-negative, you had brought that up as well, that we do some things differently with hormone receptor-positive and we do some things differently with triple-negative. I think we as physicians and trialists and just caregivers, we go after the totality of the data and we go after the robustness of the data. So, the reason we use sacituzumab in triple-negative breast cancer because there we have a robust Phase 3 trial that led to the approval of that ADC in triple-negative breast cancer and we now have more data for even earlier use as well. We also have earlier use for datopotamab now which hopefully will get approved in triple-negative breast cancer as well. The reason we were prioritising T-DXd after is while we have approval for T-DXd for HER2 low, that was based off on a 58 patient exploratory analysis from the DESTINY-Breast04. And so we want to use that, we want to justify that. But we do not necessarily forget our Phase 3 trial that gave us robust data, PFS and OS improvements with sacituzumab. Now could we apply HER2 ultralow? Again, ultralow itself in DESTINY-Breast06 was a smaller cohort and we did not have any data on HR-/HER2-ultralow. So, unless we have more data I would still be nervous about that and we do have sacituzumab. We now have data with datopotamab for HER2 low tumours. We still have T-DXd. I would still rely on those for now.

Dr Rahul Gosain
You briefly alluded to this. There is more to come in triple-negative breast cancer space. But right this minute, ultralow and low HER2 where T-DXd is approved is for hormone receptor-positive breast cancer in metastatic settings. Komal, thank you so much for this fantastic discussion. Metastatic hormone receptor-positive breast cancer space is rapidly evolving and we hope that these bite sized discussions will continue to keep our community colleagues up to date. For those tuning in, let us go over a quick recap from today's discussion.

Dr Rohit Gosain
In today's discussion with Dr Komal Jhaveri, we touched on the role of T-DXd in hormone receptor-positive breast cancer, from DESTINY-Breast04 initially presented in ASCO 2022 for

low HER2 disease to DESTINY-Breast06 for low and ultralow HER2 disease. In earlier lines of hormone receptor-positive breast cancer, T-DXd is now available for our patients based off of improved PFS. Rahul, your thoughts here from the discussion today.

Dr Rahul Gosain
My two big takeaways here. One, the importance of making sure we are partnering up with our pathology colleagues to appropriate and appreciate ultralow or low HER2 for these patients and not only because T-DXd is approved, but this is indeed an active agent, right? Two, keeping side effects in mind and how to manage these from fatigue to nausea to alopecia and of course ILD. We hope you have enjoyed this discussion with COR2ED. We will soon be back to discuss more in detail HER2 testing to make sure we have a good handle on this. Thanks for joining us. Be sure to check out our other episodes for more insights and practice changing data. We are the Oncology Brothers.

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