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Interpreting Oral SERD Trial Data in Metastatic Breast Cancer

Announcer:
You're listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. Here's your host, Dr. Alexandria May.

Dr. May:
Welcome to ReachMD. I'm Dr. Alexandria May, and joining me to share best practices for interpreting oral SERD trial data in metastatic breast cancer are Drs. Donald McDonnell and Neil Iyengar.

Dr. McDonnell is the Glaxo-Wellcome Professor of Molecular Cancer Biology at Duke University School of Medicine in Durham, North Carolina. Dr. McDonnell, thanks for being here today.

Dr. McDonnell:
Thank you very much.

Dr. May:
And Dr. Iyengar is an Associate Professor of Medicine and the Co-Director of Breast Medical Oncology at the Emory Winship Cancer Institute in Atlanta. Dr. Iyengar, it's great to have you here as well.

Dr. Iyengar:
Thanks for having me, Dr. May.

Dr. May:
Well, let's dive right in, starting with you, Dr. Iyengar. As oral SERD data in metastatic breast cancer continues to emerge, clinicians are comparing results across a variety of studies. When interpreting that data, why is it so important to understand not only the efficacy and safety findings, but also the patient populations and trial designs involved?

Dr. Iyengar:
In the landscape where we have multiple new therapies either approved or coming through the pipeline, we really have to pay attention to the trial design and to the populations that were enrolled in those trials. And that is because we understand that the natural history of hormone receptor-positive breast cancer is really dependent on quite a number of factors, which includes exposure to prior therapies, of course, the tumor biology itself, and several other tumor and host-related factors. So it is critical, I would say, to understand the population that is being treated in a particular clinical trial.

We talk about being cautious about cross-trial comparisons, and I think in this current era, this is even more important. Now, it doesn't mean that we need to evaluate a clinical trial and its outcomes in isolation. I think it means that we now have clinical treatment options where we can look to the eligibility criteria of that trial to help guide patient selection—for example, the number of lines of prior therapies and the types of prior therapies that patients were exposed to, whether that included endocrine therapy, monotherapy, or combinations with molecular therapies. We know that the standard of care right now in the first-line setting is a combination of endocrine therapy plus CDK4/6 inhibitors, but not all trials testing novel therapies included patients who got CDK4/6 inhibition in the first line. The molecular landscape is also important in understanding the proportion of patients who harbor certain mutations like *ESR1* mutations, but also co-mutations like PIK3CA alterations, for example. I think this is very critical because it affects not only the natural history of the disease, but response to the therapy that's being tested.

So ultimately, I would say we need to look at the clinical trials and the eligibility criteria even more closely these days and use those

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criteria to help guide treatment selection.

Dr. May:
Building on that, Dr. McDonnell, let's take a closer look at differences in study populations from a molecular perspective. Across oral SERDs and related degrader technologies, what are the most important mechanistic and biologic distinctions to keep in mind when interpreting efficacy outcomes?

Dr. McDonnell:
When we started seeing the clinical data coming from EMERALD and EMBER, all of us who had been in this field for over 30 years were a little bit surprised that the majority of the impact was seen in patients whose metastatic tumors had activating *ESR1* mutations, and I won't say relatively little, but surprisingly little impact in patients whose tumors expressed wild-type receptor. These activating mutations definitely drive the growth of these tumors, and we now know that the drugs that are approved and coming are very effective inhibitors of these particular mutations. These mutations are incredibly powerful drivers of the disease. And so what that basically says is we now have a biomarker to actually identify those patients who have progressed on standard-of-care endocrine therapy plus or minus a CDK4/6 inhibitor and now can start applying these new next-generation ER modulators or SERDs.

Dr. May:
And clinically speaking, Dr. Iyengar, what differences in baseline patient characteristics stand out to you the most across studies, especially in the context of treatment and sequencing decisions?

Dr. Iyengar:
I think now we're in an era where we need to look at not just the efficacy endpoints, but certainly have a deeper understanding of the types of populations that were treated. So I would say that perhaps the most important factors are how heavily pretreated that patient population are, for example, were they exposed to chemotherapy already? How many lines of prior endocrine therapy? What was the duration of that prior endocrine therapy? This gives us a sense of how endocrine sensitive the cancer may or may not be. And then exposure to prior therapies—so not only what types of endocrine therapies were patients treated with, but what was the molecular therapy partner? Was it CDK4/6 inhibition? Was there PI3 kinase inhibition? Was there a PIK3CA alteration or other molecular therapies that were involved? Because we also know that resistance mechanisms are different based on therapy exposure, and that may also impact at that moment in time, if a patient is enrolled in the clinical trial, how they respond to therapy.

And then finally, I would also add that in addition to prior lines of therapy and the types of molecular therapies, I would also say that it's important when thinking about trials that are being conducted in this space, are they testing endocrine monotherapies? Are they testing novel SERD monotherapies, or are they testing combination therapies with molecular therapeutics, for example?

Because again, the patient populations for a monotherapy approach versus a combination therapy approach is going to be different, and of course, the response to those therapies—monotherapy or combination—is going to be different as well.

And it's really great, I have to say, to be in an era right now where we have this diversity of clinical trial options because we certainly have patients who fit very different scenarios, and to have this data allows us to match the appropriate therapy to the appropriate patient sitting in front of us.

Dr. May:
If we come back to you, Dr. McDonnell, *ESR1* mutations have become central in oral SERD development and clinical decision-making. So how should clinicians think about *ESR1* status as both a marker of endocrine resistance and a potential predictor of treatment outcomes across studies?

Dr. McDonnell:
ESR1 mutations were really only discovered about 10 years ago from the group at Sloan Kettering and Dana-Farber. And prior to that, we never really knew what they meant. Now, we actually know that they are very powerful contributors to the pathobiology of the disease. Preclinical and clinical work supports that position. And so what does it mean to the physician now? I think, a priori, it's telling us that tumor has basically found a way to stay dependent on the estrogen receptor. It wants to use the estrogen receptor as a molecular driver of disease, and it has found a way by selecting for these activating mutations. So, at a minimum, what it tells the physician is that although this patient has failed endocrine therapy, there's a really good chance she's going to respond to another endocrine therapy post-AI.

How does it predict outcomes? I think that still remains to be determined. We really don't have a lot of overall survival data on patients who have *ESR1* mutations, who are being treated with these. They definitely improve PFS better than standard of care. So with respect to how it predicts outcomes, I think it predicts you're going to have a better outcome than on standard of care. How to quantitate that, I

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think, is going to be difficult with the data we have right now.

Dr. May:
For those just joining us, this is ReachMD. I'm Dr. Alexandria May, and I'm speaking with Drs. Donald McDonnell and Neil Iyengar about patient differences across oral SERD trials and their implications for treatment decision-making in metastatic breast cancer.

So Dr. Iyengar, let's continue to explore these key differences. When you're making sequencing decisions for your patients, how do prior treatments like fulvestrant, CDK4/6 inhibitors, PI3K inhibitors, or AKT-directed therapies influence how you interpret trial data and apply oral SERD strategies in practice?

Dr. Iyengar:
I would start with what we're doing in clinic already, and that is the current standard of care in the first line, which, of course, is endocrine therapy plus CDK4/6 inhibition. And we've seen some post-hoc analyses initially from the EMERALD trial, but now being applied across multiple trials, which look at the duration of response to first-line CDK4/6 inhibition plus endocrine therapy. And I really think of this as a surrogate marker of endocrine sensitivity and how this then translates to response in later lines of therapy. It's going to be critical to understand, what were those intervening lines of therapy? Were there other molecular therapeutics that were included? What was the endocrine therapy that was used in those intermediate lines of therapy? Certainly, if fulvestrant is being used before a patient comes on to a novel oral SERD trial, that might impact response to the oral SERD given the prior exposure to estrogen receptor degradation.

We also know that the co-mutational status of the tumor may impact response as well. So I'm really looking at, number one, how long was the duration of therapy or response to endocrine therapy in the first-line setting? And number two, what were those intervening lines of therapy? Specifically, what were the endocrine therapies and what were the molecular therapies? And then number three is, how heavily pretreated are these populations? Did they get chemotherapy? What was the absolute number of lines of therapy that patients were exposed to? And this will certainly help me to contextualize the efficacy data.

I think to Don's important point about overall survival, this is why it's actually so challenging to understand the long-term impact of these treatments—because there is variability in treatments that patients go on to receive after they've completed the study treatment. And so I think if we put together understanding the patient population through the eligibility criteria, PFS, and response rates, that can really give us a good guide at least into what will help the patient right now in this moment in time while we await more biomarker development and perhaps more biologically driven strategies for understanding response and treatment selection.

Dr. May:
Beyond efficacy, there's also been increasing discussion about whether oral SERD should be viewed as a uniform class. So, Dr. McDonnell, how should clinicians think about mechanistic differences across agents when interpreting safety findings like photopsia, gastrointestinal tolerability, cardiac effects, and other emerging toxicity patterns?

Dr. McDonnell:
I do need to step back and just give you a 30-second primer on what these drugs really are. And I'm going to take some credit for this from the fellows and trainees in my lab; we started this whole field many years ago. And we made the observation that the estrogen receptor inside a cell can be twisted and turned into different shapes, and those shapes have different biological consequences. Now, I'm not going to go into why that is, but just take it from me that different SERMs and different SERDs bind to the receptor, twist it into different shapes, and allow different biology. So that's extremely important when you talk about pairing individual SERDs for patients because, for instance, some of the SERMs and SERDs are bone protective. That might be something that's very important in a patient. Another series of drugs, maybe photopsia or bradycardia is a significant issue in a patient population. So what I want to let people know is that most of these side effects, positive or negative if you want, really do relate to mechanism. These are not off targets of the drug. They relate to the fact that the cancer cell and the cells in the body don't recognize the different shaped receptors in the same way. It's called functional allostery. It sounds complicated, but it is that which has enabled us to be able to develop these drugs with different profiles. And so we should not be surprised that drug A will be bone protective, drug B will have activity in the brain, drug C will have a photopsia, and drug D will overlap with respect to its impact in the hematopoietic system. This is just part and parcel of what estrogen receptor modulators are.

I do want to make one very clear distinction, though: it is an artificial class. It is not a true recognized functional class of medicines. It's a basket that just describes drugs that downregulate or degrade the receptor. And then there's a distinction between what we call SERDs in that basket and then PROTACs, of which there is one: vepdegestrant. And they are functionally different but ultimately work through similar type of mechanism.

Dr. May:
Let's turn to you, Dr. Iyengar, for the final word. For community providers applying these findings in practice, what practical

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considerations regarding baseline patient characteristics, molecular profiling, and cross-trial interpretation do you believe are the most important for optimizing patient care?

Dr. Iyengar:
This is really where the rubber hits the road, right—in those busy community clinics and patient treatment centers where we're really trying to identify which of these options are best for our patients. It's really critical to understand those populations. Were they upfront? Were they more heavily pretreated? And when you're interpreting the efficacy data, this can be important as well because certainly, we know that response or durability of response is impacted by prior treatment exposure, and also how advanced the disease is as well.

We really need to keep those eligibility criteria front and center. And that includes not just patient factors that we've been discussing, but also how we are using diagnostics like next-generation sequencing, for example. And we really are now in an era where we need to be doing sequencing upfront, and really at the time of progression at least, maybe even more frequently now. But this will help us to understand how the tumor is evolving and how resistance mechanisms are developing, and ultimately, that will also impact our treatment selection.

Dr. May:
With those considerations in mind, I want to thank my guests, Drs. Donald McDonnell and Neil Iyengar, for joining me to share their perspectives on evaluating oral SERD trial outcomes in metastatic breast cancer. Dr. McDonnell, Dr. Iyengar, it was great having you both on the program.

Dr. McDonnell:
Thank you very much.

Dr. Iyengar:
Thank you.

Announcer:
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