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Redefining Endocrine Therapy: The Evidence Behind Oral SERDs and PROTAC ER Degraders

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Dr. Jhaveri:
Hello, everyone, and thank you so much for joining for this activity that is focused on oral SERDs in the metastatic ER-positive breast cancer setting.

I'm Dr. Komal Jhaveri, and in this episode, I will review evolving evidence on oral SERDs and PROTAC degraders for the treatment of ER positive HER2 negative metastatic breast cancer.

And so without further ado, why don't I talk about we currently have aromatase inhibitors. We have fulvestrant as our SERD that is available in clinic. But we know that these have their own limitations.

For instance, under the acquired pressure and selective pressure of aromatase inhibitors, there is emergence of *ESR1* mutations, which leads to ligand-independent yet ER-dependent growth of the pathway and tumor growth. Similarly, with fulvestrant, while it's an estrogen receptor degrader, it has its own limitations, not limited to just its pharmacokinetic abilities – there is lack of oral bioavailability given it's an intramuscular injection – but we've also seen that its activity is rather modest upon progression on a CDK4/6 inhibitor in the metastatic setting. Certainly a burden for the patients to come in to the infusion center to get their injections. And the activity is certainly limited for certain *ESR1* mutations, namely the Y537S.

Hence, these newer novel endocrine agents such as oral SERDs, PROTACs, CDERs, novel SERMs are very, very attractive because they are able to overcome these pharmacologic liabilities, these resistance mechanisms and more. These are oral drugs. They work very effectively, not just for *ESR1* wild type, but also for *ESR1* mutant tumors.

And we now have had approval for two oral SERDs, elacestrant and imlunestrant, based on the phase 3 EMERALD and EMBER-3 trials respectively. We had elacestrant approved back in January of 2023 and imlunestrant that got approved actually in September 2025. And then earlier this year, we also had approval for our PROTAC, a proteolysis targeting chimera, vepdegestrant, based on the phase 3 VERITAC-2 study.

So really, we have three drugs, all three approved in the metastatic setting for *ESR1* mutant tumors. Now, one would expect that these drugs should work in wild type as well, but I think it becomes very complex in the metastatic setting, especially due to the heterogeneity and due to the differences that we see post-progression on a CDK4/6 inhibitor, where we've not been able to demonstrate the statistical

significance for all comers or wild type tumors.

In the EMERALD trial, we did see statistical significant improvement for elacestrant in all patients in *ESR1* mutant tumors. However, the approval is limited to *ESR1* mutations. Similarly, we've seen benefit and statistical significance in EMBER-3 for imlunestrant monotherapy and vepdegestrant monotherapy VERITAC-2, but we did not seem to be able to prove statistical significance in the *ESR1* wild type tumors. We also have combination data that has become available, and we have these combination trial data coming from EMBER-3, for instance, with imlunestrant plus abemaciclib. And more recently, we also saw data from the phase 3 EVERA trial, and we'll talk, more about giredestrant and everolimus and imlunestrant and abemaciclib as well.

And then we're also trying to move these combinations or utilizing these oral SERDs beyond post-CDK4/6 progression, perhaps in the first-line setting, and we'll talk about trials that try it. You know, use the strategy of delaying *ESR1* emergence and where we've landed with that and what more we need to see.

And certainly, we're also trying to see can we intercept right at the time of emergence, even before radiological progression, and what have we learned from such approaches. We'll talk about the safety also in another episode, but I think needless to say, oral SERDs have been effective. Monotherapy certainly approved for *ESR1* mutant tumors.

Combination data is very attractive and very soon will have FDA approval. We already have NCCN endorsement and really very efficacious but also safe class of drugs with only low-grade toxicities. Well, I hope you found this overview helpful. My time is up. Thank you so much for listening.

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