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The Sequencing Puzzle: Integrating Oral SERDs and PROTACs into the mBC Treatment Landscape

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Dr. Kaklamani:
Hello and welcome to CE with GLC. I'm Dr. Virginia Kaklamani, and here with me today, I'm honored to have Dr. Komal Jhaveri. So let's examine evidence-based treatment sequencing with oral SERDs and PROTACs in metastatic breast cancer.

And, Dr. Jhaveri, walk us through the trials that we have, both single agent and combination, when we talk about oral SERDs and PROTACs in metastatic breast cancer

Dr. Jhaveri:
Yeah, absolutely. I think we have appreciated for a number of years that a one-size-fits-all approach does not apply necessarily to breast cancer. And so we're very grateful that we have multiple options. May it be three aromatase inhibitors, may it be three CDK4/6 inhibitors, and now three novel endocrine agents already, and maybe a fourth one on the way.

We'll see. So we have two oral SERDs, elacestrant and imlunestrant. We have vepdegestrant, our PROTAC. And these are all approved as monotherapy for *ESR1* mutant tumors, and we use them upon progression of a CDK4/6 inhibitor. So you have an *ESR1* mutation, we have an effective drug that targets this resistance mechanism.

What we've also seen from EMBER-3, for instance, is that when you have two drugs and you continue a CDK4/6 beyond progression, in this case abemaciclib with imlunestrant, we saw an even better efficacy. So we saw a median progression-free survival of up to 11 months. Similarly, in the phase 3 Evera study, we saw giredestrant plus everolimus, an HR targeting the PI3K/AKT/mTOR pathway.

Together, in a *ESR1* mutant tumor gave us a 10-month median progression-free survival. So obviously, the greedy oncologist in us wants better for our patients. We want our patients to have a longer median progression-free survival, and we can achieve that. That does come in with additional toxicity. But those matter when we make these treatment choices. When would we choose doublet versus single agent? I think we, you know, when we have a disease burden that is bothersome, when we have just bone disease or somebody who's had a long, disease control on a first-line therapy, we could resort to single-agent therapies.

But otherwise, we have these doublet choices. We have these combination choices. And then between the combinations, I think patient comorbidities, patient preferences, you know, their underlying issues that we see, what prior therapy and response they had with the CDK4/6 inhibitor could help guide that, judgment.

Similarly, RB1 mutation, which is an acquired mechanism of resistance to CDK, would make us probably want to choose everolimus over continuing abemaciclib, for instance.

Dr. Kaklamani:
So what I've seen, and, this is going to be a big struggle for us, who are we going give single agent and combination to? And when you look at the progression-free survival curves, right, there's a, a number of patients, around 20 to 30%, that there's a rapid progression in that single agent.

And you don't tend to see that with the combination. With the combination, you're seeing that we're salvaging those early, resistance, patients where we can actually get a nice response. So when you have a patient in clinic, how do you think you would be identifying who the patient is that would be a candidate for that combination versus a single agent?

Dr. Jhaveri:
Yeah. I think, you know, this is more of a complex and not that straightforward a scenario, which is why we see that so much in many of these ER positive trials where the Kaplan-Meier curves initially kind of do this rapid drop off before they start separating. And I think we've appreciated more of that with single agent endocrine therapy post CDK4/6.

I think that was not as apparent when we did not have the CDK4/6 inhibitors approved. And so we're very grateful because that obviously changed the treatment landscape. But that also introduced more change in tumor biology, more aggressiveness potentially, or more heterogeneity in certain tumors. So if you have some co-occurring mutations, perhaps that could be driving the tumor growth in addition to this and maybe a comprehensive blockade with dual agents make more sense there.

If you just have a very sensitive tumor, very prolonged benefit on first line with just *ESR1* mutation, that tells you that that's the driving resistance mechanism, then maybe single agent might be enough. So I think those are the kind of things we take into consideration. And of course, disease burden definitely makes us biased for choosing combinations because we want to try and do more when we see a lot of disease burden or a lot of involvement beyond bone and visceral organs as well.

Not to say that these monotherapies don't work in such scenarios, but I think the combinations work better, and that's what we would reach out for.

Dr. Kaklamani:
We're going to have even more agents potentially, with good phase 3 clinical trial data, such as lasofoxifene and we also have to think about the SERENA-6 approach, right? Where we don't wait for disease progression, we wait for molecular progression, at that point potentially changing or, giving that oral SERD, which may improve outcomes.

We know that on the trial, there's a definite improvement in progression-free survival, and so I think this is going to be really, an approach that a lot of our patients will embrace

Dr. Jhaveri:
Absolutely agree. I think, you remind us of the 3 strategies that are currently being evaluated, right? One that's approved, which is the monotherapy data.

The second strategy is, can we use them in the first line and replace our AI CDK as the standard of care and delay emergence of *ESR1*? Now, unfortunately, the PERSEVERA trial that looked at giredestrant palbo versus letrozole palbo was a negative readout and a negative signal.

It did not achieve statistical significance, but the delta of benefit was five months. So we know that there was some benefit. We were just not able to confirm statistical significance there. And the curve started separating around month thirteen and fourteen, kind of reminding us that maybe this is where the *ESR1* mutations are accumulating, and that's when it starts separating at that time.

So we'll wait for SERENA-4, which is a larger study, to see if maybe a larger sample size could potentially achieve statistical significance. We also have the ongoing OPERA-02 trial that is looking at a CERAN, a complete estrogen receptor antagonist,

palazestrant with ribociclib, compared to letrozole ribociclib in the first-line setting.

And then, as you pointed out, SERENA-6, which is the third strategy, where even before you have radiological progression on first-line therapy, when you capture an *ESR1*, can you intervene and be able to confirm PFS? Certainly, we won't be able to confirm OS. It's complicated there.

On July 20th, the EMA did provide approval for the SERENA-6 approach. So we'll see what the FDA does with that and with that strategy. But I think needless to say, ctDNA is here to stay. Any *ESR1* mutant tumor should see a novel endocrine therapy, either monotherapy or a combination in one strategy.

Dr. Kaklamani:
Well, this was a great discussion on an extremely complex topic that is becoming even more complex as we speak. So thanks everybody for listening.

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