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Navigating Treatment Selection After First-line CDK4/6 Inhibitor Progression

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Dr. Jhaveri:
Hello, and welcome to CE with GLC. I'm Dr. Komal Jhaveri, and here with me today is a dear friend and colleague, Dr. Virginia Kaklamani. In this episode, we're going to review a patient case example that highlights treatment selection for hormone receptor-positive, HER2-negative metastatic breast cancer. So talking about a case example, why don't I tell you about this patient? So this is a 58-year-old woman with ER positive HER2 negative metastatic breast cancer who was treated in the first line metastatic setting with an aromatase inhibitor and a CDK4/6 inhibitor. And now about progression, we've detected an *ESR1* mutation from a plasma sample.

So Dr. Kaklamani, can you take us through your treatment selection decision-making process for a patient such as this woman that we talked about?

Dr. Kaklamani:
Yeah. Thank you so much. So, this is a pretty typical case, and there's a lot of parameters in there that may make us change our decision post-progression on the aromatase inhibitor and CDK4/6 inhibitor. For example, is this de novo disease, or is this metastatic disease after treatment in the adjuvant setting, and what treatment did the patient receive in the adjuvant setting?

But I think even more importantly, how long has the duration on that first-line therapy been? Because this is important for us to understand how endocrine sensitive or endocrine resistant that tumor really is. We know that post-CDK progression, there's a lot of mechanisms that cause this tumor to be endocrine resistant or CDK resistant.

We know there's RB loss, cyclin E amplification, FAT1 loss, and so forth. But we also know that there's other pathways that are related, such as *ESR1*, that do cause that, that resistance to, to endocrine therapy, and this helps us select the endocrine therapy to, to pick. So my question to you, Dr. Jhaveri, is also, let's say that this is a patient that had an aromatase inhibitor and CDK for two and a half years and now has progression in her bones, otherwise doing well, good performance status.

How are you thinking of treating this patient in that second line?

Dr. Jhaveri:
Yeah. No, I think those are important factors that we have to take into consideration. I think patient-related factors, you know, comorbidities, their, treatment factors, meaning how long they stay on their first-line therapy, what do we know about their disease

burden, what are the sites of disease burden, symptoms that the patient is experiencing.

All of those are very, very important factors that we take into consideration, not just for making our own medical recommendation, but then ultimately also discussing with our patient and coming up with a patient-physician decision-making process. And so I say for this patient who was on it for two and a half years, has bone progression, I'd be very comfortable even with monotherapy oral SERD.

We've actually seen data that you presented, a couple of years ago at our San Antonio annual conference, where we showed the subgroup analyses from the EMERALD trial showing that patients who were treated on their prior CDK4/6 inhibitor for twelve or eighteen months or longer, so anything more than twelve months, those patients with single-agent elacestrant had a eight point six-month median progression-free survival compared to two months seen with, say, fulvestrant.

And so I think this would be very, very appropriate scenario to apply for this patient here, who could get away with just single-agent monotherapy, which is very well-tolerated, as we know, and will have a very good quality of life and good disease control.

Dr. Kaklamani:
And I think you're right. We're going to be struggling soon, as, as you mentioned in episode one, with whether to give combination or whether to give agent. And, and obviously the combination is going to add more as far as adverse events. The single agent has a more favorable, AE profile. And this to me would be the perfect patient to look at single agent, activity of either the oral SERDs or our PROTAC.

We have now three options for our patients, which is wonderful to see. And that's what I would be thinking about as well. Now, we don't know whether the tumor has other mutations. potentially the tumor may have a PIK3CA mutation that we need to be thinking about. But, in this case, with a, you know, mild progression, in, in bone-only disease and a patient having a pretty long duration of a prior CDK, I agree as well that SERD or PROTAC monotherapy would be indicated for the patient in this setting.

Dr. Jhaveri:
And I think, you know, for anything more than that, if we did not think that they probably stayed on their first-line therapy for a long period of time, or if they had slightly more disease burden or maybe slightly more symptomatic disease, or a younger patient where we think that maybe, you know, having a additional drug, a second drug, a combination is not necessarily going to pose a whole lot of side effects.

I mean, for instance, the imlunestrant of abemaciclib combination from EMBER-3 turned out to be very well-tolerated. We are very well aware how to manage the diarrhea for abemaciclib given our experience with the drug. Imlunestrant did not add to it beyond. It's now NCC, you know, endorsed and hopefully we'll hear from the FDA about that combination, and soon we'll have combinations like everolimus and goserelin as well.

So certainly we can do more than monotherapy as well. But I agree, I think this would be a good patient, in addition to patients who might not be appropriate for, you know, combinations or are reluctant for combinations and older patients, some frail patient or somebody with really minimal disease, progression.

So I think we can choose those scenarios and make our decisions in clinic.

Well, I think we've nailed this. Thank you so much, Dr. Kaklamani. We'll see you next time.

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