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Expert Perspectives on ER+/HER2- Advanced Breast Cancer Care

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Stemline, a Menarini Group Company. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is *Project Oncology* on ReachMD. I'm your host Dr. Jennifer Caudle, and joining me to share their perspectives on the management of ER+/HER2- advanced breast cancer are Dr. Stephanie Graff and Dr. Pavani Chalasani. Dr. Graff is the Director of the Breast Oncology Program at Lifespan Cancer Institute and Co-Leader of the Breast Cancer Translational Research Disease Group at Brown University in Providence, Rhode Island. Dr. Graff, welcome to the program.

Dr. Graff:
Thanks. It's great to be here.

Dr. Caudle:
We're happy that you're here. And Dr. Chalasani is an Associate Professor of Medicine and Co-Leader of the Clinical and Translational Oncology Program at the University of Arizona Cancer Center. Dr. Chalasani, it's great to have you with us.

Dr. Chalasani:
Thank you for inviting me.

Dr. Caudle:
Dr. Chalasani, can you give us an overview of the current treatment landscape for ER positive HER2 negative advanced breast cancer?

Dr. Chalasani:
Yes. So currently, when a patient is diagnosed with metastatic ER positive HER2 negative breast cancer, the first-line treatment is with endocrine therapy in combination with CDK4/6 inhibitors. We have three CDK4/6 inhibitors which are currently approved in clinic: palbociclib, ribociclib, and abemaciclib. Most recent data has shown overall survival benefit of ribociclib and abemaciclib, but all three CDK4/6 inhibitors have different side effect profiles.

So in general, when a patient comes in, the combination for the frontline treatment recommendation is with an endocrine therapy and a CDK4/6 inhibitor. The choice of endocrine therapy—typically it is with an aromatase inhibitor. However, if a patient has been on aromatase inhibitor when they develop metastatic disease or it is a de novo presentation or they have finished their endocrine therapy and now have a recurrence of disease, what was the window between when they stopped the prior treatment to when the recurrence happened? Those factors are considered and have to be taken into account before making the decision on what is the best endocrine therapy backbone.

Dr. Caudle:
Turning to you now, Dr. Graff, what are some common challenges and limitations associated with the treatment options that Dr. Chalasani just mentioned?

Dr. Graff:
I think one of the common challenges that we have is really understanding and selecting patients for therapy in the hormone receptor positive space. It starts with just testing tissue in the HER2 low space. There's all sorts of controversy about how to define HER2 low. I think that testing somebody early for PIK3CA mutations is important. I think including things like next generation sequencing needs to be

done. And I suspect, especially in the hormone receptor positive space, that we're likely under-utilizing germline testing to identify patients that may be candidates for PARP inhibitors.

And so for me, I think that one of our biggest challenges is analyzing a patient for all of the potential targeted therapies early and incorporating that into our treatment plan in the way that's most successful for that patient.

Dr. Caudle:
And as a quick follow-up to that, Dr. Graff, what are the resulting unmet needs stemming from those challenges?

Dr. Graff:
I think that the biggest sort of unmet need is that if you are going to do early testing, early next generation sequencing for our patients with hormone receptor positive breast cancer, hopefully we're going to start finding those unicorns, right? Those RET fusions, those NTRK, those high tumor mutation burden that happen in 1 percent or less of breast cancers.

And in those tissue agnostic approval indications that we have across oncology as a whole, many of those trials, those basket trials that have been done, did not include breast cancer patients or very many breast cancer patients. And so understanding the efficacy of those tissue agnostic approvals in a breast cancer patient population, understanding how to sequence those medications against the backdrop of all the other approvals we have in breast cancer because, you know, it's weird to consider ourselves lucky in breast oncology, but we have many drugs approved, where other tumor types may not. And so trying to fit those pieces of the puzzle together will be important. I hope that as we identify those patients that we work together to report those outcomes.

Dr. Caudle:
Thank you for that. For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host Dr. Jennifer Caudle, and I'm speaking with Dr. Stephanie Graff and Dr. Pavani Chalasani about managing ER+/HER2- advanced breast cancer.

So Dr. Chalasani, given the challenges that Dr. Graff discussed earlier, how can we use the latest clinical strategies and technological advances to address our patients' unmet needs?

Dr. Chalasani:
While our goal is to improve survival, we also want to make sure our patients also have a good quality of life, and both of them are equally important. So that is how we need to think about strategies.

One of a very clinically meaningful and important endpoint here for a lot of times for patients and for the physicians is time to delay in chemotherapy because chemotherapy does come with additional toxicity. The majority of them are intravenous, so there is a lot of time and commitment from the patient and the toxicity burden is severe too. So delaying chemotherapy is also important.

As we are understanding more about this hormone receptor or endocrine therapy responsive tumors, we are trying to figure out what are the resistance mechanisms. Is it by mutations? Is it some pathway alterations? What exactly is happening, and why these tumors are becoming resistant to these treatments?

So to overcome that, there has been a huge interest to develop oral SERDs. So these will be drugs where we'll be able to overcome that dose limiting and potentially overcome these ESR1 mutations. And that is a mechanism of resistance. So now that we figured out okay, we can overcome the ESR1 mutations, then now the question is: can we prevent or delay the resistance mechanisms? So there's a lot of interesting new hypotheses and ideas that are being tested and investigated right now in clinical trials. And I think they will make impacts potentially in the future as we understand it.

Dr. Caudle:
And now unfortunately, we're almost out of time for today. So before we close, I'd like to hear some final key takeaways from each of you on how we can optimize our approach to ER+/HER2- advanced breast cancer. Dr. Graff, let's hear from you first.

Dr. Graff:
I think it's important that we lay out a thoughtful long-term plan for our patients with hormone receptor positive metastatic breast cancer that starts with early germline and next-generation sequencing so that we know if there are actionable mutations and how we're going to incorporate those into the treatment plan for our patient, and that we talk about what order we're considering so that both us, the treating physician, and the patient can plan for the most successful strategy through their treatment plan.

Dr. Caudle:
Thank you, Dr. Graff. And now Dr. Chalasani, I'll give you the final word.

Dr. Chalasani:
Yeah, so I think it is important for us as physicians that when our patients come in at diagnosis to be cognizant of the fact on what the

presentation is. So is it a de novo presentation? Or is it someone who is on endocrine therapy and developed metastatic disease, or they had a history of breast cancer and now developed recurrent disease? So like I said, that window is important.

And the main reason is the biology of the tumor is different in all these three settings. You know, is it endocrine sensitive versus endocrine resistant? And that is critical for us to figure out which tool we use to kind of get to the patients; which drugs do we reach out to first to ensure we are giving them the longevity and the quality of life. We're not trying to compromise one or the other, but we're trying to do the best for them and having the goals of care discussion too.

So I think initially when we are trying to figure out what is the optimal treatment that is important for us to be aware of and to talk to the patient so that we can pick the right regimen, the right endocrine backbone with the combination targeted treatments.

Dr. Caudle:
Well with those key takeaways in mind, I'd like to thank my guests, Dr. Stephanie Graff and Dr. Pavani Chalasani, for joining me to discuss how we can achieve better outcomes among patients with ER+/HER2- advanced breast cancer. Dr. Graff and Dr. Chalasani, it was great having you both on the program.

Dr. Graff:
Thanks.

Dr. Chalasani:
Thank you for inviting me.

Announcer:
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