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Overcoming Challenges in 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:
Welcome to *Project Oncology* on ReachMD. I'm your host Dr. Jennifer Caudle, and joining me to discuss common challenges in ER+/HER2- advanced breast cancer care is Dr. Stephanie Graff. Dr. Graff is a 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, thanks so much for being here today.

Dr. Graff:
Thanks for having me.

Dr. Caudle:
Well, we're excited that you're here. So let's start off by doing some level setting. How prevalent is ER+/HER2- advanced breast cancer?

Dr. Graff:
So hormone receptor positive breast cancer accounts for about 60 to 80 percent of advanced breast cancer. And when I use the phrase "advanced breast cancer," I mean metastatic breast cancer or breast cancer that has spread. And so it's certainly the most prevalent subtype that we see in the metastatic setting.

Dr. Caudle:
Thank you for that. And with that background in mind, let's turn our attention to some common challenges clinicians face when caring for patients. First, what can you tell us about sequencing treatment?

Dr. Graff:
I think right now it's clear that the first-line standard of care for somebody with a diagnosis of metastatic hormone receptor positive breast cancer is a CDK4/6 inhibitor in combination with endocrine therapy. There are three CDK4/6 inhibitors approved on the market: palbociclib, ribociclib, and abemaciclib. And then it can be combined with any of the available endocrine agents including tamoxifen, which is approved with abemaciclib, or the aromatase inhibitors or fulvestrant. I tend to favor treatment with the aromatase inhibitors. Although if you have a patient whose metastatic disease happened while they were on adjuvant aromatase inhibitors, it would be reasonable to use CDK4/6 inhibitors in combination with fulvestrant in the first-line metastatic setting. We have evidence for all of those different combinations. And it's really a little bit of the physician's preference and patient preference about how these different agents are used in combination.

Dr. Caudle:
And what about endocrine resistance? What challenges can this present? And how can we pivot our approach?

Dr. Graff:
Yeah, I think endocrine resistance is something that we're still struggling to understand at this time, both in terms of how best to treat it and even at the most fundamental way, how to define it. And across a variety of different trials, we've seen endocrine resistance defined molecularly with the presence of ESR1 mutations. We've seen endocrine resistance defined by time; did a patient stay on first-line CDK4/6 inhibitors for 12 months or 18 months, or longer or shorter? And we've seen endocrine resistance defined as disease that progressed in the adjuvant setting on an aromatase inhibitor. And we've seen endocrine resistance defined as metastatic breast cancer

that has already progressed on first-line endocrine therapy and now is in the second-line endocrine therapy settings.

So we've got all of these different definitions of endocrine resistance. And so I think that as we're analyzing that data, just understanding that often we're using this phrase in a very wastebasket kind of way, that it doesn't even always mean the same thing, which is probably our number one problem. So I think that the first challenge is just basic definition.

But in terms of overcoming that problem, I think that as we start to figure out how to pivot the approach, it's really going to depend on figuring out what the driver of resistance is. And we've seen various different drivers in different treatment settings. So for example, for patients that have been on aromatase inhibitors, we often see that they develop ESR1 mutations. And with these emerging classes of selective estrogen receptor modulators and selective estrogen receptor decorators, SERMs and SERDs, there's a lot of evidence that they may be more effective against ESR1 mutations than the historical control of fulvestrant. There was a great poster presentation at San Antonio Breast Cancer Symposium, actually two poster presentations, looking at lasofoxifene against the Y537 mutation, which is maybe the worst of the ESR1 mutations that showed a lot of activity, but in many of the emerging SERDs, things like imlunestrant and elacestrant, we've seen good activity against ESR1 mutations, which is promising.

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 about how we can address some common challenges and ER+/HER2- advanced breast cancer care.

So Dr. Graff, if we focus on one more clinical challenge, what toxicities are associated with treatments for ER+/HER2- advanced breast cancer?

Dr. Graff:
So I think it depends on what type of therapy you're thinking about. So if we kind of break that down, when we look at the CDK4/6 inhibitors, most of the CDK4/6 inhibitors cause myelosuppression to varying different degrees, in particular, low neutrophil counts, maybe most of all with palbociclib and a little less so with ribociclib and abemaciclib. With ribociclib, we also see QT prolongation. With abemaciclib, we see quite a bit of diarrhea, although all of the CDK4/6 inhibitors can cause some GI toxicity.

As we move in to the AKT inhibitors and the PI3 kinase inhibitors, we see side effects like diarrhea, skin rashes, and hyperglycemia, and those can often be difficult to manage.

And so those are sort of the things that we're grappling with and managing commonly in breast oncology right now.

Dr. Caudle:
And as a quick follow-up to that, are there any better tolerated therapies available that can help improve overall survival?

Dr. Graff:
Well, I sure hope that's the direction that we're moving. Right now, I think that our best tolerated therapies are still probably that first-line CDK4/6 inhibitor in combination with endocrine therapy, although I don't want to pretend that those are innocent medicines or that they come without toxicities. Again, you just heard me say that many of those come with myelosuppression and other toxicities.

But we saw some great analysis at ASCO in 2022 that even at the reduced dose of those medicines, efficacy remains intact. So I would encourage oncologists to monitor their patients closely and lower the dose based on the side effects that their patients are experiencing to provide that patient with both tolerability and efficacy.

Dr. Caudle:
And before we close, Dr. Graff, let's look ahead for just a moment. Given everything we've discussed today, is there anything on the horizon that may help us address these unmet needs and challenges?

Dr. Graff:
I'm really excited about the landscape of SERDs that's coming out. I mean, there are many, many SERDs in development. I think the farthest along drugs that we've heard a lot about already include camizestrant, lasofoxifene, and elacestrant. There are many others emerging on the market, like imlunestrant and giredestrant. And as those drugs start to come out, I'm hopeful that both will see more activity against the classically endocrine resistant or ESR1 mutation population. And I'm also hopeful that when those drugs start to be used in combination with CDK4/6 inhibitors that we will get a little bit more bang than we're seeing when we look at the data from those drugs as single agents.

Dr. Caudle:
Excellent. And considering the prevalence of this type of breast cancer, it's great to know that we may soon have options available to us

so that we can better meet our patient's unmet needs. With those final thoughts in mind, I'd like to thank my guest, Dr. Stephanie Graff, for joining me to discuss ER+/HER2- advanced breast cancer. Dr. Graff, it was great having you on the program.

Dr. Graff:
Thanks for having me.

Announcer:
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