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The Next Chapter: SABCS 2025 and the Future of HR+ HER2− Breast Cancer Care

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is brought to you in partnership with AstraZeneca and First Ascent Biomedical. Here's your host, Dr. Pavani Chalasani.

Dr. Chalasani:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and joining me to discuss the future of hormone receptor-positive, HER2-negative advanced breast cancer following the 2025 San Antonio Breast Cancer Symposium is Dr. Alison Stopeck. She is a Professor of Medicine at the Renaissance School of Medicine at Stony Brook University in New York, as well as the Chief of the Division of Hematology Oncology and the Associate Director for Clinical and Translational Research at the Stony Brook Cancer Center. Dr. Stopeck, thanks for being here today.

Dr. Stopeck:
My pleasure.

Dr. Chalasani:
So let's start with the big picture, Dr. Stopeck. Can you give us an overview of what you thought were the most promising presentations at this year's symposium?

Dr. Stopeck:
Yes, I think there are a lot of very important abstracts presented of clinical trials. And, in particular, I was very impressed by how oral SERDs—whether it's giredestrant, elacestrant, or imlunestrant—are really becoming on the forefront of therapy for estrogen receptor-positive disease. And, in particular, for the first time, we saw giredestrant improve disease-free survival in the adjuvant setting. To this date, all the data we've seen on oral SERDs, of course, has been in the metastatic setting, where it's really been most effective in patients who have *ESR1*-mutated tumors. Now we're seeing for the first time that maybe oral SERDs may be more effective than our standard-of-care therapy in the adjuvant setting, and in particular, in this setting, we don't anticipate the tumors to have these *ESR1*-mutations.

Dr. Chalasani:
Yeah, just focusing on that and following up on that, overcoming resistance was something they always focus on, and in the metastatic setting, it was generally with the *ESR1* mutations. As you mentioned, with the adjuvant setting, did the symposium, any presentations, or any other posters reveal potential new directions or hypotheses on why or what other mechanisms they could work on which are helping overcome this barrier?

Dr. Stopeck:
Well, first off, this was the first presentation of this data, so we do have to see longer follow-up of the data to ensure that giredestrant was, in fact, better than standard of care going forward, not just at the first look at the data.

Two, I want more data on the adherence. It could be that these oral SERDs are better tolerated than aromatase inhibitors, for example, so the patient adherence to these drugs may be improved, and that might be one of the reasons why we're seeing better progression-free survival results or disease-free survival results.

In addition, it's possible that these drugs are, in fact, more effective. They have a better suppression of the estrogen receptor, and we have hints of that occasionally in other studies, where, for example, fulvestrant, did better than standard-of-care therapies in the

metastatic and/or adjuvant settings.

Dr. Chalasani:
And in terms of patient experience, were there any discussions around needs that aren't being addressed enough, like quality of life, treatment fatigue, or access to novel agents?

Dr. Stopeck:
I think those are all very important for not just the physician, but the patient. Obviously, the patient—in whatever stage they are, adjuvant or metastatic—they want to have the best quality of life, and then are most likely to adhere to the therapy when they are having a good quality of life.

One of the issues I see with patient-reported outcome data is that I don't think it's sensitive enough to individual patient needs and side effects. And we've seen that over and over again when you look at, for example, patient-reported outcomes when you're given LH/RH agonists versus not, so ovarian function suppression or not. And the patients seem to have the same side effect profile and quality-of-life, when we know that patients who get ovarian function suppression have more symptoms than patients who don't.

With regard to oral SERDs, they seem to be extremely well tolerated, but they do have musculoskeletal symptoms very similar to what you see with aromatase inhibitors, but probably not as extreme or severe. It seems that patients on aromatase inhibitors do stop their drugs or discontinue their drugs more frequently than patients on oral SERDs, though you do have to deal with musculoskeletal symptoms in both disease categories.

In addition, the oral SERDs have some novel therapies that the physician needs to be aware of. One of the class effects might be bradycardia, but again, generally doesn't require therapy. But in somebody who was already on a beta blocker, it's something to think about, as well as some unusual toxicities such as photopsia or flashing lights—sort of similar to when you leave a theater—in the case of camizestrant.

Dr. Chalasani:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking with Dr. Alison Stopeck about next steps for hormone receptor-positive, HER2-negative advanced breast cancer care after the 2025 San Antonio Breast Cancer Symposium.

So there's a lot of new data coming out, so that's exciting, but let's shift gears and look to the future. How do you think the clinical trial designs are evolving to address newer gaps and better reflect patient diversity, tumor biology, or real-world treatment patterns?

Dr. Stopeck:
I think this is a huge issue on clinical trials. I think for the first time ever that there aren't enough estrogen receptor-positive patients to go on all the clinical trials we need to do.

Obviously, one of the issues with all of these new agents is not just toxicity, but also financial toxicity and time toxicity. Some of the new agents coming out, particularly inhibitors against the so-called, quote unquote, PAM inhibitors that inhibit all three mechanisms of resistance—the *PIK3CA*, AKT, and mTOR—some of them are IV. Intravenous administration always takes a lot more time toxicity. There's also the financial toxicity of these new drugs, particularly the oral SERDs. They can be extremely expensive, at least from what we've seen from elacestrant and imlunestrant.

A better strategy may be switching strategies, where you start on standard-of-care aromatase inhibitor or tamoxifen drugs that are extremely inexpensive, and then switch to these drugs later on in high-risk patients. We still have to do studies looking at this and those trials are ongoing, but we haven't seen the results. And how do we combine these agents in the metastatic setting?

I particularly like the new drugs that are coming out that have selective mutations that they're targeting. So they have less toxicity, in particular, when you are targeting a specific mutation and then don't hit the wild-type of either the mTOR, the AKT, or the *PIK3CA*.

Dr. Chalasani:
So, as a follow-up on that, did you come across any investigational agents or trial concepts which were mentioned at the meeting that you're particularly excited about?

Dr. Stopeck:
At this point, for example, I think that patients who have estrogen receptor-positive metastatic disease second-line should all be going on probably an oral SERD or fulvestrant if an oral SERD is not available, and a targeted therapy against a resistant pathway.

And what's nice about, for example, the evERA trial, which was presented at ESMO and then we presented some data at San Antonio, was that mTOR inhibition can be used in everyone. We saw that again at San Antonio, where, whether you had a *PIK3* mutation or not,

you could still get benefit from an mTOR inhibitor. And now that we know how to use everolimus, the toxicity is really very, very limited, and it's a very well-tolerated drug. So, it really can be a go-to for everybody who has estrogen receptor-positive metastatic breast cancer when you A, either don't have availability of the other agents, or B, don't have a way for testing for specific mutations or can't do next-generation sequencing.

Dr. Chalasani:
Yeah, lots of exciting and new promising data and options for our patients.

Before we wrap up our program today, Dr. Stopeck, based on everything you saw and heard at the symposium, what do you think is your go-to or recommendation for practicing oncologists and for treatment decision-making in 2026 and beyond?

Dr. Stopeck:
Well, I think, as always, the first thing you should look at is a clinical trial for your patients, because we're seeing that most of these clinical trials are actually showing more efficacy in the novel agents. So, I really strongly recommend everybody who has access to a clinical trial put their patients on it. And there are so many of these new agents, so we really need to finish up these clinical trials to know the best avenue is in the future.

Two, I think the role of circulating tumor DNA was all over the conference. We're looking at it everywhere, and that's really going to help us do better prediction and prognosis, and also know when to de-escalate and escalate therapy. And that's a very important tool that we're going to be using in the future.

Three, I think another big take-home message that we're going to be seeing in the future is that we're going to be using AI and doing better model predictions and better prediction of what therapy we should be giving.

And the take home notes that I would say that you can take and do tomorrow in clinic is that everybody who progresses on a CDK AI first-line metastatic breast cancer line of treatment should then go on, probably, an oral SERD with another resistant inhibitor. So you have to combine that—it has to be a doublet with either an mTOR inhibitor, an AKT inhibitor, a *PIK3CA* inhibitor, or all three, because just doing one alone is insufficient once a patient has progressed through CDK4/6 inhibition.

Dr. Chalasani:
With those important takeaways in mind, I want to thank my guest, Dr. Alison Stopeck, for joining me today to discuss how hormone receptor-positive, HER2-negative advanced breast cancer care is evolving in the wake of new data from the 2025 San Antonio Breast Cancer Symposium. Dr. Stopeck, it was great having you on the program.

Dr. Stopeck:
Thank you very much for inviting me.

Announcer:
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