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Targeting PI3Kα-Mutated HR+/HER2- Breast Cancer in the Second-Line Setting

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Relay Therapeutics. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to share strategies for personalizing second-line treatment in PIK3CA-mutated HR+/HER2- advanced breast cancer are Drs. Komal Jhaveri and Neil Iyengar. Not only is Dr. Jhaveri an associate attending physician and the section head for the Endocrine Therapy Research Program in the Breast Medicine Service at Memorial Sloan Kettering Cancer Center in New York, but she's also the Clinical Director for the Early Drug Development Service and the Patricia and James Cayne Chair for Junior Faculty. Dr. Jhaveri, welcome to the program.

Dr. Jhaveri:
Thank you so much for having me, looking forward to having our discussion today.

Dr. Turck:
Looking forward to it as well. And Dr. Iyengar is the Co-Director of the Breast Oncology Program and Director of Cancer Survivorship Services at the Winship Cancer Institute at Emory University. Dr. Iyengar, it's great to have you with us as well.

Dr. Iyengar:
My pleasure. Thank you for having me.

Dr. Turck:
So let's start with some background, Dr. Jhaveri. How has the second-line treatment of HR+/HER2-advanced breast cancer evolved in recent years, particularly with the rise of biomarker-driven strategies?

Dr. Jhaveri:
Yeah, I think we've really come a very long way. I think what we had realized and continue to realize is that while endocrine therapies serve as the backbone for ER-positive breast cancer and work effectively, they do stop working after a certain point, and this is what we call as endocrine resistance. We have also seen other mechanisms of resistance, such as activation of growth factor pathways like the PI3K/AKT/mTOR pathway. And then certainly there are tumors that are driven by germline mutations in BRCA1 or 2 or some other rare alterations that we have identified, such as NTRK fusions or RET fusions. And certainly, high-tumor mutational burden seems to be one other biomarker.

And so our strategy beyond the first-line, where we utilize CDK4/6 inhibitors now more unanimously for almost all our patients, has been biomarker driven. For the PI3K/AKT/mTOR pathway, proof of concept was provided by the BOLERO-2 trial with the mTOR inhibitor everolimus. Initially with exemestane in the BOLERO-2 study, but that has been shown to work regardless of any mutation as well. And we've been able to show activity with other endocrine backbones, such as tamoxifen and fulvestrant, as well for that drug.

Similarly, we also have approval for alpelisib, an alpha-specific PI3K inhibitor for tumors that harbor PIK3CA mutations, based on the phase 3 SOLAR-1 trial. More recently, in November of '23, we had approval for an AKT inhibitor, capivasertib, in combination with fulvestrant. And again, those are for patients whose tumors harbor PIK3CA, AKT, or PTEN alterations.

And the last kid on the block targeting this pathway has been another PI3K inhibitor, an alpha-specific inhibitor: inavolisib; however, the

approval here is for a triplet therapy of inavolisib with fulvestrant and palbociclib for first-line therapy in PIK3-mutant tumors, especially for patients who had recurrence on or within 12 months of their adjuvant endocrine therapy.

Dr. Turck:
And if we zero in on how we can target PIK3CA mutations, Dr. Iyengar, what are the key differences between selective and non-selective inhibitors that we should consider when choosing therapy?

Dr. Iyengar:
Well, the evolution of PI3-kinase inhibition has been really important for breast cancer treatment because we've moved from agents that are rather toxic to now newer agents that are really promising in terms of their adverse effects profile being quite limited. So to be very clear, I want to specify that when we talk about PI3-kinase inhibition selectivity, originally, this was in reference to how we are actually inhibiting the enzyme. And we know that PI3-kinase enzyme has multiple subunits and the very original PI3-kinase inhibitors were Pan PI3-kinase enzyme inhibitors—so essentially, they were inhibiting all subunits. This caused quite a bit of toxicity and was essentially not a viable clinical strategy.

Then, we saw the development of PI3-kinase alpha-subunit inhibitors with more specificity to the alpha subunit. But it's also important to note that these agents that were alpha-specific were not mutation-specific. And so non-selective PI3-kinase alpha inhibition also inhibits wild-type PI3-kinase alpha as well as mutated PI3-kinase alpha. This is the reason why we still see fairly significant toxicity with nonselective PI3-kinase alpha inhibition—that is, the inhibition of the wild-type PI3-kinase alpha, which can lead to disruption of normal processes in our body, and that leads to adverse effects that are commonly seen with the currently available nonselective PI3-kinase alpha inhibitors, including hyperglycemia, rash, diarrhea, stomatitis, and other adverse effects.

The newer mutant-selective PI3-kinase alpha inhibitors spare wild-type targeting, and in doing so, this allows for a reduction in adverse effects by not disrupting those normal processes, like glucose transport and so forth. And so the hypothesis, and what we're now seeing in ongoing clinical trials, is that the strategy of targeting allele-specific or mutant-specific PI3-kinase alpha is not only expected to be efficacious—and perhaps even more efficacious—but perhaps more importantly for our patients, it also helps to preserve quality of life by limiting those off-tumor, but on-target adverse effects when you use a nonselective inhibitor.

Dr. Turck:
Now, there has also been some interest in targeting downstream effectors like AKT. So, Dr. Jhaveri, how do these approaches compare to agents directly targeting PIK3CA in terms of precision and adverse effects?

Dr. Jhaveri:
When we're dealing with PI3K inhibitors such as alpelisib, which was the first PI3K that was approved for treatment with endocrine therapy for PIK3-mutant tumors and we utilize that in the second-line setting, the most common side effects we see with that drug are hyperglycemia, diarrhea, and rash. And really, hyperglycemia and rash have been predominantly driving the discontinuation rates with this drug as well. So that has certainly been something that we have to deal with in terms of management strategies when we're using that drug.

In contrast, capivasertib is an AKT inhibitor; it's the central node of the pathway, so certainly it has upstream and downstream effects. So based on the phase 1 trial data where safety, PK, and efficacy was optimized for this AKT inhibitor, the dosing schedule that we've come to utilize in clinic has been an intermittent dosing schedule, wherein patients receive this drug 4 days on, 3 days off, of a 28-day cycle. So for every week, it's 4 days on, 3 days off. And certainly, that has potentially translated into a toxicity profile that might be slightly different, in that we noticed that while there is some hyperglycemia reported, the grade 3 or high-grade hyperglycemia rates are much lower. Specifically in the CAPItello study, which led to the approval of capivasertib, the grade 3 hyperglycemia rates were 2 percent; all-grade hyperglycemia was approximately 16 percent.

But the two most common side effects that I really see with this drug in clinic are diarrhea and rash, and these are things that we really have to keep an eye on when it comes to maximizing or optimizing supportive management for our patients. Not necessarily with primary prophylaxis for diarrhea, but certainly secondary prophylaxis and dietary modifications so we can manage that better for diarrhea.

With respect to rash, we've seen alpelisib give a lot of rash issues, including high-grade rash; we've seen the same thing with capivasertib as well—up to 12 percent of the patients had grade 3 or higher rash. And so certainly, what we have now started doing for both of these drugs in clinic is primary prophylaxis with antihistamines when we're initiating therapy with both of these drugs. And that has been really helpful in lowering both grade and the number of patients who develop these high-grade toxicities.

Dr. Turck:

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Komal Jhaveri and Neil Iyengar about second-line treatment approaches for patients with PIK3CA-mutated HR+/HER2- advanced breast cancer.

So, Dr. Iyengar, if we take a closer look at emerging mutation-specific PIK3CA inhibitors, I'd like to get your take on what we're seeing in terms of their efficacy, safety, and dosing.

Dr. Iyengar:
So in terms of efficacy, the newer mutant-specific PI3-kinase inhibitors also have differences in terms of the way that they bind mutant PI3-kinase alpha. And we believe that this might contribute to better efficacy and better pharmacokinetics, and this is very promising for the newest generation of selective PI3-kinase inhibitors coming through the pipeline. This has perhaps an even greater impact on toxicity. So the improved adverse effect profile of the selective PI3-kinase inhibitors is a major advancement in this field, and particularly, by sparing the metabolic adverse effects, this can dramatically improve patient quality of life because now we're not dealing with all of the other metabolic medications that may need to be used.

Dr. Turck:
Well, we've certainly covered a lot today, but before we close, I'd like to ask each of you one final question regarding shared decision-making. Starting with you, Dr. Jhaveri, how do you balance efficacy considerations with a patient's preferences when selecting a second-line therapy?

Dr. Jhaveri:
Yeah, I think it's very, very important. And that has particularly become important, especially when we're dealing with scenarios with dual mutations that we find on these next-generation sequencing results. For instance, there might be a scenario where a patient's tumor harbors both an ESR1 mutation and a mutation in the PI3K pathway. And that's when we are trying to think about how we can have a shared decision-making process because we don't necessarily have robust data to optimally sequence these drugs. We now have, as I said, elacestrant approved for ESR1-mutant tumors, we have alpelisib and capivasertib for PI3K-mutant tumors, and capivasertib even for AKT and PTEN-altered tumors. But if you have both of these, should you use elacestrant first? Should you use capivasertib first? And we really don't know that. The CAPItello-291 study, for instance, excluded prior fulvestrant, excluded prior PI3K/AKT/mTOR agents, and excluded prior oral SERDs. And the elacestrant study did do a subgroup analyses in tumors that were ESR1-mutant and PIK3CA-mutant, and also these patients stayed on their CDK4/6 inhibitor for over 12 months. There, the PFS when you had both of these mutations was about 5.45 months. In the CAPItello-291 study, the PFS in post-CDK treated patients—so that was 69 percent of the patient population—was also 5.5 months. So one could say you can use this drug or that drug.

That's where the patient decision-making process becomes even more important because that's when we're talking about elacestrant as an oral drug, it's given by itself, and these are the side effect profiles for this drug. We have capivasertib and fulvestrant; these are the way these two drugs are given, and this is the side effect profile for this drug. And we really don't know if one strategy is going to be better than the other in terms of sequencing.

Dr. Turck:
And Dr. Iyengar, I'll turn to you for the final word. What advice would you offer your colleagues who are looking to individualize second-line treatment of PIK3CA-mutated disease?

Dr. Iyengar:
Well, we're in an era of just mushrooming and expanding treatment options, fortunately, for our patients with metastatic breast cancer. And so I would advise early sequencing and understanding of the genomic landscape of a patient who's been diagnosed with metastatic breast cancer. Now that we have and will have, hopefully, successful strategies for targeting PI3-kinase that limit toxicity, we stand to improve or change the course of disease in a disease that typically is associated with poor prognosis.

Dr. Turck:
Well, as those final tips bring us to the end of today's program, I want to thank my guests, Drs. Komal Jhaveri and Neil Iyengar, for joining me to discuss how we can deliver personalized care for patients with PIK3CA-mutated HR+/HER2- advanced breast cancer. Dr. Iyengar, Dr. Jhaveri, it was great having you both on the program.

Dr. Iyengar:
My pleasure. Thank you for having me.

Dr. Jhaveri:
Thank you, Dr. Turck, great discussion.

Announcer:
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