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Optimizing PI3Kα Testing and Therapy in HR+/HER2- Advanced Breast Cancer Care

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:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me today to explore how we can optimize PIK3CA mutation testing and targeted therapies for HR+/HER2- advanced breast cancer is Dr. Hope Rugo. She's the Director of the Women's Cancers Program, Division Chief of Breast Medical Oncology, and Professor of the Department of Medical Oncology and Therapeutics Research at City of Hope Comprehensive Cancer Center. She's also a Professor Emeritus at the University of California San Francisco. Dr. Rugo, thanks for being here today.

Dr. Rugo:
Thank you for having me.

Dr. Turck:
Well, to set the stage for us, Dr. Rugo, would you walk us through the prevalence and clinical importance of PIK3CA mutations in HR+/HER2- advanced breast cancer?

Dr. Rugo:
Yes. I mean, it's really an interesting story. Historically, mutations in PI3 kinase—and really, I think, by extension, the pathway—have been known to be very important in driving resistance to endocrine therapy. And by extension, there is data suggesting that patients with even HER2+ disease who have PI3 kinase mutations and triple-negative disease have a disease that appears to be less responsive, shorter progression-free survival, and shorter overall survival. But where PI3 kinase mutations have really, I think, been explored to the greatest extent—although there are ongoing trials in HER2+ disease now—hormone receptor-positive disease is where we've really seen the most frequent mutations and the best ability to try and target these to alter outcome.

And I think we've actually learned even more information recently. So it was the most commonly mutated pathway that was seen in breast cancer, the most common mutation seen, and the most common clonal mutation that's seen. We do see the acquisition of ESR1 or estrogen receptor mutations that alter the structure of ER that occur under the pressure of treatment. And interestingly, we can potentially see that in up to 40 percent. But ESR1 mutations come and go, whereas mutations in PIK3CA occur very early in the development of cancer and are maintained over time. But we estimate that somewhere in 5 to up to 10 percent or a little less, mutations are acquired under the pressure of treatment.

And then in terms of what amplifications or activating mutations in PI3 kinase do to the cancer itself, it does appear to again correlate with this resistance to endocrine therapy and be associated with more aggressive cancer growth. So in that pathway that promotes the hallmarks of cancer where these mutations in the pathway help cancer cells be resistant to therapy.

We also looked at CDK4/6 inhibitors and how they work in patients who have mutations in PIK3CA. And it's interesting because you see that the hazard ratios are similar to people who didn't have mutations, but the curves are shifted down so you have a shorter PFS with the CDK4/6 inhibitor compared to those who have wild-type with the CDK4/6 inhibitor.

So clearly this is an area that needs better targeting and management, and of course, has been a major focus of study with many

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agents.

Dr. Turck:
So given their impact on patient outcomes, how and when should we test for PIK3CA mutations?

Dr. Rugo:
Well, this is also changing, both with technology and with new clinical trial data, so it's kind of an interesting area of rapid change. These mutations are clonal, as I mentioned, so you can test archival tumor tissue, or you could test blood; ctDNA is also very good at picking up mutations in PIK3CA. You could miss some large deletions, but that really occurs in PTEN primarily, and that's such a minor factor, relatively only 5 percent or less.

So if you had a patient who develops metastatic disease, the question is when do you test? So if a patient develops metastatic disease either de novo or after a long time after finishing their adjuvant endocrine therapy, a year or more—I would say more than a year, I guess, is the best way to put that—then you do the biopsy, evaluate the patient's receptors, decide on the appropriate treatment, make sure that ER hasn't been lost. As I'm sort of evaluating the patient's response, when I start to feel like the patient's cancer is going to progress relatively soon, I'm going to recheck the blood for ctDNA. And in the future, if we're looking for ESR1 mutations, we will get everything together.

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 Dr. Hope Rugo about the importance of testing for PIK3CA mutations in HR+/HER2- breast cancer.

Now, when it comes to integrating PIK3CA mutation testing into clinical workflows, Dr. Rugo, what other challenges might we face? And how can we overcome them?

Dr. Rugo:
I think there are concerns about insurance coverage and reimbursement and whether you need prior auth. Most of these testing strategies do not need prior auth. And authorization is obtained from the testing center itself, and they generally will cover the cost of the test or have patients agree to cover the cost of the test if it's not covered. And I think where we're seeing some challenges are when patients are doing repeated testing.

I think that that's not really an issue for testing for PIK3CA because you test once, you know they have a mutation, and that mutation is not generally going away, in terms of what we understand to date. So you can test it, for example, in archival tumor tissue when you're trying to make decisions about treatment or fresh tumor or ctDNA, and you're going to get good results that are helpful for you for treating, for example, in a next-line treatment—not even now. So you have time to do it, and I think it's important to think about it ahead of time.

There needs to be a pathway within each clinic for obtaining these tests, making sure that they get done, collecting the results when they come back in, and posting them on the electronic health record so that they're there in perpetuity. And I think that that makes a really big difference. It's working together as a team with multidisciplinary collaboration.

Dr. Turck:
Now, circling back to the topic of treatment, we know that current PI3K inhibitors are effective but not uncommonly poorly tolerated. So how might newer therapies address those toxicity concerns?

Dr. Rugo:
In the population that we see overall, in patients who develop this hyperglycemia, one of the difficulties with medical oncologists is just managing this on their own because we have a whole host of new drugs that can be used. We start out using metformin, which is easy, but when you start going up on the dose of metformin, you get nauseated, and then that's a big problem for our patients who might already have nausea for other reasons, and you may not be controlling the glucose well enough.

I've found for patients who have normal glucose and hemoglobin A1c, metformin may be sufficient. But you're really challenged because then with the next set of drugs, you run into issues with insurance authorization, which drugs to give, and what combinations. Because most oncologists are not as familiar with all the variants that are available and how to use them most efficiently. So that means you need to work with your friendly colleague—the endocrinologist—who does diabetes medicine and emphasize that not only are you asking for help earlier than 3 months from now when the next appointment is, but you also want to have a tighter control of glucose than most endocrinologists are used to doing in situations like this because of the risk of DKA, really severe hyperglycemia, and other issues.

So I think that ends up being a major issue in terms of the side effects of the currently approved PIK3CA alpha-specific PI3 kinase inhibitors: alpelisib and inavolisib. Inavolisib, we believe will be easier to manage than alpelisib, but I think it also has more to do with

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differential side effects that are also pathway specific. So those include rash, which can be difficult to manage, and we often use non-sedating antihistamines as a preventive-type approach. And we also see rash with the AKT inhibitor capivasertib. And that can be dose-limiting for some patients. Hyperglycemia is a little less common with the AKT inhibitors; you see mild stomatitis as well—and that's easy to manage, a little steroid mouthwash—but the other major symptom we see is diarrhea, and that varies a lot. Diarrhea can be easily managed or not so much. We do see it a little bit more potentially with the AKT inhibitor capivasertib; it's hard to know.

So now you have this whole host of side effects that you're managing. You're not seeing the neutropenia, for example, that we see with the CDK4/6 inhibitors, but we do see these sort of three hallmark toxicities: hyperglycemia, rash, and diarrhea. So managing them upfront, education, etc., has become a major issue, and some patients just can't tolerate the drugs.

So looking at newer agents that target the PIK3CA pathway and are alpha-specific that don't have these toxicities has been a major goal in drug development and targeting this pathway. And it would really change our thinking about how to give these drugs now that we're exploring CDK4/6 inhibitors after CDK4/6 inhibitors and oral SERDs. I think there's been a question about where we should place these target-specific agents in patients with a known mutation. Should we give the drugs in the second or third line? And some of it has to do with really tolerance of the agents and how we manage toxicity.

So looking at agents that now are able to cause less hyperglycemia, are more sparing of other isoforms outside of alpha, and have less rash, diarrhea, and hyperglycemia is going to be critical. Because if we have drugs like that, it's going to be enormous. I mean, inavolisib doesn't cause as much rash, so that's already a big improvement. But we are needing to manage the hyperglycemia and diarrhea weight loss over time.

So I'm excited about some of the new agents that are coming down the pike that target PIK3CA alpha because the data so far suggests that they may have a better toxicity profile, and this will make targeting this particular mutation that's known to drive cancer growth and occurs in at least 40 percent of the patients we see with metastatic disease more feasible and more tolerable.

Dr. Turck:
And looking ahead before we close, Dr. Rugo, is there anywhere else you see the field going in terms of personalized care for patients with HR+/HER2- advanced breast cancer who have PIK3CA mutations? And what else are you looking forward to?

Dr. Rugo:
Yeah, I think that this is also really a very interesting area. For example, if we go from early to late stage, should we target PIK3CA in the late adjuvant setting? Patients who have mutations, would it benefit those patients to add an agent? There was an adjuvant study with everolimus that showed a benefit in a subgroup—of course, this not their primary outcome, so the trial was negative—but it does bring up the question: if you had more tolerable agents without the toxicities we've discussed, could you look at patients in the early-stage setting who have potentially combined mutations and are at higher risk for recurrence and potentially target this pathway? I think that's still a long way off, but I think it's of great interest.

The metastatic setting—and I think much closer in—is looking at new triplet combinations and different CDK inhibitors. There's a lot of interest in CDK4 and next I think CDK2 as ways to overcome resistance to CDK4/6 inhibitors. Could we use a triplet with an alpha-specific PI3 kinase inhibitor that would even be better than what we've already seen with inavolisib and a triplet?

So it brings up the question about combining an alpha-specific PIK3 kinase targeted agent with an oral SERD, where you could actually overcome doublet mutations as well as mutations in PIK3CA. And I think that as we have more tolerable agents that target PI3 kinase, this could be a really fascinating approach, particularly as we're going to see patients who've been exposed to adjuvant CDK4/6 inhibitors.

So a lot going on in this area of alpha-specific inhibitors that have maintained or improved efficacy and reduced toxicity is an important next step.

Dr. Turck:
Well, with those forward-looking thoughts in mind, I want to thank my guest, Dr. Hope Rugo, for joining me to discuss how we can close the PIK3CA gap in advanced breast cancer care. Dr. Rugo, it's great speaking with you today.

Dr. Rugo:
Thank you so much for talking with me.

Announcer:
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