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Enhancing Efficacy and Safety in HR+/HER2- Breast Cancer with Novel PI3Kα Inhibitors

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. Here with me today to discuss current and emerging PIK3CA-targeted therapies for HR+/HER2- advanced breast cancer is Dr. Neil Iyengar. He's the Co-Director of the Breast Oncology Program and Director of Cancer Survivorship Service at Winship Cancer Institute at Emory University. Dr. Iyengar, welcome to the program.

Dr. Iyengar:

Thank you, Dr. Turck. A pleasure to be here.

Dr. Turck:
Well, to start us off, would you tell us about the toxicity concerns associated with first-generation inhibitors of PI3K, AKT, and MTOR?

Dr. Iyengar:
Absolutely. So I think our introduction to this class of pharmacologics was, to be fair, a little rough because as you alluded to, this class is associated with fairly significant toxicities that are actually on-target effects—what we refer to "as off-tumor, on-target effects" that can cause AEs, including hyperglycemia, rash, and diarrhea. MTOR inhibition can lead to mouth sores. Now, we've gotten better at managing some of these adverse effects, but certainly, these are common and can really impact the quality of life of our patients.

Dr. Turck:
Now, to what you were saying about adverse effects, intermittent dosing has been used to manage some of them associated with AKT inhibitors, but what limitations do we see with that approach?

Dr. Iyengar:
Yes, so we've seen several strategies to manage these adverse effects: other medications, dose modifications, and, as you mentioned, intermittent dosing. Now, as we have gotten newer agents like AKT inhibitors, as you mentioned, we do see some reduction in the frequency of these adverse effects, but they're still quite prevalent. And so for AKT inhibitors, as an example, intermittent dosing has been one strategy to try to limit some of these adverse effects. In this type of strategy, typically we prescribe the drug for several days on and several days off. For example, four days on; three days off. And this can be helpful. However, there are some concerns with this approach in terms of efficacy and what might be happening during those off days.

Dr. Turck:
And how does the inhibition of wild-type PIK3CA contribute to the toxicity profiles we've seen with earlier agents?

Dr. Iyengar:
So I alluded to this a little earlier, but when we target wild-type PIK3CA, we're also targeting normal, functional cellular pathways. And this is why we see those off-tumor but on-target effects. And we know that PI3-kinase is an enzyme that is involved in many normal processes in our body, and that is why we see disruption, for example, of glucose and, subsequently, insulin signaling. PI3-kinase is involved in glucose transportation, and this can lead to extracellular dumping, if you will, of glucose. And that triggers an insulin response, which further perpetuates the hyperglycemia issue. We also see through similar pathways disruption in the GI tract, which

can lead to diarrhea and other GI toxicities, including mucositis. And we see hematologic toxicities given the role of this pathway in cellular proliferation in the bone marrow. And so these are anticipated adverse effects with the first-generation PI3-kinase inhibitors due to the ubiquitous nature of the PI3-kinase enzyme in multiple different pathways.

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. Neil Iyengar about how we can optimize the efficacy and safety of PIK3CA-targeted therapies for HR+/HER2- advanced breast cancer.

So, Dr. Iyengar, now that we have a better understanding of the currently approved PI3-kinase inhibitors and their limitations, let's focus on the emerging approaches that are aiming to fill this gap. Would you tell us about the new generation of PIK3CA-targeted therapies and how they're designed to improve cell activity and, by extension, tolerability?

Dr. Iyengar:
Absolutely. So we are now seeing the development of mutation-specific or allele-specific PI3-kinase inhibitors. And just to be clear, the developmental pathway of PI3-kinase inhibition has been quite a storied pathway. We started with broad PI3-kinase inhibitors that essentially inhibited wild-type but also all of the subunits of the PI3-kinase enzyme. And this led to quite a bit of toxicity. This is why we do not have approval of some of the originally tested PI3-kinase inhibitors.

Then, we saw more specificity in terms of enzyme subunit inhibition, specifically PI3-kinase alpha inhibition; we do have approved agents that specifically target the alpha subunit of the enzyme. But this, to be clear, is enzyme-specific-targeting and not necessarily targeting the mutation. And so what we see with the currently approved PI3-kinase inhibitors are the side effects or the toxicities that we mentioned primarily because of the wild-type inhibition.

Now, with the novel inhibitors coming through the pipeline, we're seeing allele-specific or mutant-specific PI3-kinase inhibition, such that only those cells that contain the mutated pathway are being inhibited. And this is what we see typically in tumors that contain specific PI3-kinase mutations. This allows for selective and specific inhibition of those cancer cells while attempting to spare the wild-type cells or the normal cells in normal processes in our bodies. In order to do that, the newer agents have become very specific, both for the mutation targeting, but also in the way that they bind with PI3-kinase. And this has led to a number of clinical effects, which are favorable. One might be potential improved efficacy—we'll see from ongoing clinical trials. Secondarily, and perhaps even more impactful for the lives of our patients, is less adverse effects. And this is where we see less of those off-tumor effects because of that wild-type sparing, such that normal processes related to glucose transport and the mechanisms we discussed related to diarrhea and rash are spared in those wild-type cells, allowing for lowering or decreased incidence of those adverse effects while maintaining the anti-tumor efficacy.

Dr. Turck:
And how might these newer agents help address the need for simpler and continuous dosing strategies?

Dr. Iyengar:
So with that reduction in adverse effects, we are not needing that off-period. In other words, patients are able to stay on the mutant-specific PI3-kinase alpha inhibitors without needing to go onto an off-period to manage those or lessen those toxicities. And we think this might have positive effects, both in terms of quality of life, but also perhaps in terms of efficacy by maintaining that continuous inhibition of the mutated PI3-kinase.

Dr. Turck:
Lastly, Dr. Iyengar, as these emerging therapies with improved tolerability moved forward, what kind of appreciable impact might they have on the lives of patients with HR+/HER2- advanced breast cancer?

Dr. Iyengar:
Well, I think there are several potential positive impacts for these new mutant-specific PI3-kinase inhibitors, and we've been talking about the reduction in adverse effects, which I really think is a major advance. I can't stress this enough. The use of our current agents that target PI3-kinase, as we've been discussing, has been really limited by the toxicities and makes it really challenging for patients to adhere to the current generation of PI3-kinase inhibitors. So I'm very excited about the new mutant-specific inhibitors because of that one reason: the reduction in adverse effects. But really, that has multiple downstream effects.

Another positive effect of reducing those adverse effects, of course, is better adherence and better dose intensity. We can keep patients, as we discussed, on these drugs for longer and without that off-period. And this might help to improve the efficacy of PI3-kinase inhibition. So with this combination of reduced toxicity and potentially better efficacy, I think we are likely to see really impactful and clinically meaningful advances with the mutant-specific PI3-kinase inhibitors. And ultimately, this will be important not only for the quality

of life and efficacy issues we've been discussing, but also for treatment sequencing because this is a major question and issue in the treatment of metastatic breast cancer. Now that we're fortunate to have several agents coming down the pipeline or already approved that use a molecular approach for targeting breast cancer, the big open-ended question is, what is the optimal sequencing of these agents? And I think a lot of ongoing clinical trials will help us address that question. But if we have PI3-kinase inhibitors that are better tolerated, we can now reintroduce that strategy into our treatment armamentarium and think about inserting yet another line of therapy to help extend the lives of our patients in a way that also preserves quality of life.

Dr. Turck:
Well, with those forward-looking thoughts in mind, I want to thank my guest, Dr. Neil Iyengar, for joining me to discuss the latest efforts to enhance the safety and efficacy of PIK3CA-targeted therapies for HR+/HER2- advanced breast cancer. Dr. Iyengar, it was great having you on the program.

Dr. Iyengar:
Thank you. My pleasure.

Announcer:
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