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Targeting *PIK3CA* Mutations in HR+/HER2- Breast Cancer: New Insights from ReDiscover

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You're listening to *Project Oncology* on ReachMD. This medical industry feature, titled "Targeting *PIK3CA* Mutations in HR+/HER2– Breast Cancer: New Insights from ReDiscover," 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. Today, we'll be reviewing updated safety and efficacy data from the doublet cohort of the ReDiscover study, which investigated combining the mutant-selective PI3Kα inhibitor RLY-2608 with fulvestrant in patients with *PIK3CA*-mutated, hormone receptor–positive, HER2-negative advanced breast cancer.[1] And joining me in this discussion is Dr. Sarah Sammons.

She's a Senior Physician at the Dana-Farber Cancer Institute and an Assistant Professor of Medicine at Harvard Medical School in Boston. Dr. Sammons, welcome to the program.

Dr. Sammons:
Thank you for having me.

Dr. Turck:
To help set the stage for us, Dr. Sammons, would you talk about the current treatment landscape for patients who have HR-positive, HER2-negative breast cancer that harbors PIK3CA mutations with advanced or metastatic disease?

Dr. Sammons:
Of course. So just to give a little background, about 40 percent of patients with metastatic HR–positive, HER2-negative breast cancer have an activating mutation in the PIK3CA gene,[2,3] which plays a key role not only in tumor growth, but also in driving resistance to endocrine therapy.[4-6]

There are several PI3K pathway-targeted agents that are currently FDA-approved for patients with *PIK3CA* tumor mutations, such as alpelisib, inavolisib, and capivasertib.[7-9] These drugs have shown modest efficacy in the post-CDK4/6 inhibitor setting. For instance, the median progression-free survival for those agents—which are often used in combination with endocrine therapy—typically falls around five to eight months, regardless of mutation status.[10-13]

Another major challenge with the current PI3K pathway inhibitors is that they're not mutant-selective, so they inhibit both the mutant and wild-type forms of PI3Kα.[1] This broad inhibition of the PI3K pathway often causes on-pathway effects like hyperglycemia, rash, diarrhea, and stomatitis—all of which can lead to dose modifications or treatment discontinuation.[10,11]

So there's definitely room—and need—for therapies in this setting that are both more effective and better tolerated.

Dr. Turck:
So given that unmet need, let's zero in on the investigational agent, RLY-2608. How is it different from currently approved PI3Kα inhibitors, and how might that translate clinically?

Dr. Sammons:
RLY-2608 is a first-in-class PI3Kα inhibitor that is designed to selectively target mutant forms of the PI3Kα enzyme. And what distinguishes it from earlier PI3K inhibitors is that it doesn't rely on ATP-competitive binding in the active site, like alpelisib or inavolisib.

Instead, it binds at a different site on the enzyme to preferentially inhibit mutant forms of PI3Kα.[14,15]

By sparing the wild-type isoform, RLY-2608 aims to reduce toxicity seen in earlier agents while preserving antitumor activity.[14] So the hope is that this selectivity could allow patients to stay on treatment longer and maintain dose intensity, which is what the ReDiscover study was designed to explore.[1]

Dr. Turck:
Well, with that being said, let's take a closer look at the ReDiscover trial itself.

For some background, this multi-arm, open-label, first-in-human study evaluated RLY-2608 across different advanced solid tumors with *PIK3CA* mutations.[1]

And as I understand it, Dr. Sammons, you actually presented data from the breast cancer cohort at the 2025 ASCO Annual Meeting.

So can you tell us about the study details?

Dr. Sammons:
I'd be happy to. A total of 118 patients with *PIK3CA*-mutant, HR–positive, HER2-negative disease were enrolled in the breast cancer cohort and received RLY-2608 in combination with fulvestrant in 28-day cycles. 64 of these patients were treated with the recommended phase two dose—which was 600 milligrams twice daily, while fasting—across both dose escalation and expansion phases.[16]

We evaluated efficacy in 52 patients who had isolated *PIK3CA* mutations—that is, without concurrent *PTEN* or *AKT1* alterations because downstream alterations may confer resistance to PI3Kα-selective inhibition.[1]

The study's primary endpoints were safety, tolerability, and preliminary efficacy. We also assessed circulating tumor DNA and saw early declines in *PIK3CA* and *ESR1* ctDNA, which supports that RLY-2608's mutant-selective PI3Kα inhibition engaged the tumor target.[1]

Dr. Turck:
Now, before we dive into outcomes, I think it's worth reviewing the patient population, as the cohort reflected some of the complexity seen in real-world practice. From your vantage point, Dr. Sammons, why was this aspect of the trial design so important?

Dr. Sammons:
I'm really glad you brought that up because the ReDiscover trial population was constructed to hopefully give the data broader clinical relevance.

First off, most *PIK3CA* mutations in breast cancer occur at specific hotspot regions within the gene, including both kinase and non-kinase domains. For example, H1047R and H1047L are mutations in the kinase domain exon 20, and they make up between 35 to 41 percent of *PIK3CA* mutations in hormone receptor-positive/HER2-negative advanced breast cancer.

This trial enrolled patients with an even distribution of both mutation types—approximately 50 percent in each group, which is similar to the natural distribution of these mutations.[1,17-19]

Next, patients with a higher metabolic risk have often been excluded from trials of other PI3K inhibitors due to hyperglycemia concerns. But about a third of patients in this ReDiscover cohort had a body mass index over 30 or an HbA1c at or above 5.7, which gives us a more practical look at tolerability in the real world.[1]

And finally, patients in the study were heavily pre-treated in the advanced setting, as about 60 percent had one prior line of therapy and around 40 percent had received two or more. All patients received CDK4/6 inhibitors, and 51 percent also had prior fulvestrant or novel oral SERDs.[1]

At the same time, the study excluded prior exposure to PI3K, AKT, or mTOR inhibitors to help maintain a clear mechanistic signal.[1]

So this was a clinically relevant, molecularly diverse population to observe the safety and efficacy of RLY-2608.

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. Sarah Sammons about updated safety and efficacy results in patients with breast cancer from the ReDiscover study.

So, Dr. Sammons, if we turn now to the radiographic outcomes, what did we see in terms of tumor response for RLY-2608?

Dr. Sammons:

In 31 patients with measurable disease, we saw an overall response rate of about 39 percent. And nearly 81 percent of patients showed some degree of tumor reduction, which is a strong early signal in this heavily pre-treated population.[1]

When we looked more closely at mutation subtypes, the response rate among patients with kinase domain mutations was even higher at about 67 percent.[1]

We also saw responses in patients who had previously received fulvestrant with an overall response rate around 40 percent, suggesting RLY-2608 activity even in endocrine-resistant settings.[1]

The last thing I'll note is that we saw activity across other subgroups regardless of prior lines of therapy, *PIK3CA* mutation domain, or *ESR1* co-mutations, which supports broad applicability.[1]

Dr. Turck:
And how about the durability of that response? What are we seeing there?

Dr. Sammons:
Well, the data we presented at ASCO this year reflect more than 12 months of follow-up, and what's encouraging is that as the data mature, we're not only seeing the signal drop off. If anything, it's reinforcing durability.[1]

In the overall population of patients with isolated *PIK3CA* tumor mutations, the median progression-free survival, or PFS for short, was 10.3 months, with a six-month PFS rate of over 69 percent. The clinical benefit rate, which includes patients with responses and with stable disease lasting six months or more, was about 67 percent.[1]

Another subgroup we specifically looked at was the 30 patients who were in the second-line of treatment, meaning that they only had received one prior line post-CDK4/6 inhibitor. These patients represent the intended population for the upcoming Phase 3 study.[1]

Overall, this subgroup reached a median PFS of 11 months. And when we took a closer look at patients with only kinase domain mutations, the median PFS was 18.4 months.[1] While this data will continue to mature, it's very encouraging.

Dr. Turck:
Now, what did we see in terms of safety, and how does RLY-2608 compare to other agents in this space?

Dr. Sammons:
Right, so what stands out to me with the data here is that even without prophylactic strategies, overall adverse events were low grade. We saw a discontinuation rate of about two percent and no treatment-related grade four or five adverse events, which is lower than what's been seen with other pathway inhibitors.[1]

And the relative dose intensity of 92 percent suggests that most patients were able to stay on the full recommended phase two dose of 600 milligrams twice daily without significant interruptions or dose reductions—which is, again, something that's been a challenge with other PI3K inhibitors.[1]

In terms of class-related toxicities, hyperglycemia is often the one we worry about most because it's a direct result of wild-type PI3Kα inhibition disrupting glucose metabolism. But here, the results were encouraging: about half of patients didn't experience any hyperglycemia, and among those who did, the majority had only grade one events that did not require medical intervention.[1]

Rash and stomatitis—which are also typical of this drug class—were similarly mild. Rash occurred in about 12.5 percent of patients and was mostly grade one or two. Stomatitis was reported in under five percent of patients, with no grade three or higher events. I'd also like to point out that standard prophylactic interventions for stomatitis, such as prescribed mouthwash or steroid rinses, were *not* used in the trial.[1]

We did see some nausea and diarrhea at 50 percent and 39 percent, respectively, but almost all were low grade, and neither required prophylactic measures.[1]

So what we're seeing is a tolerable safety profile, even in a metabolically diverse patient population without pre-emptive interventions. Given this, I think it has potential implications for broader clinical use, especially in patients who may not tolerate high-toxicity regimens.

Dr. Turck:
Well, we've certainly covered a lot of ground today, but before we close, Dr. Sammons, let's look ahead for a moment. What can we expect from the phase three trial that you mentioned earlier?

Dr. Sammons:
So the next step is ReDiscover-2—the phase three trial that will evaluate RLY-2608 in combination with fulvestrant in a randomized setting.

One important update as we move into phase three trial, is the change in dosing from a fasted to fed dose. Based on the pharmacokinetics, 600 milligrams twice daily in the fasted state delivers similar drug exposure as 400 milligrams twice daily with food.[16]

And so, with agreement from global health authorities, we'll be using the 400 milligrams twice daily with food regimen in ReDiscover-2. It's more patient-friendly since there's no fasting required, and the pill burden is lower. This change also reflects feedback from patient advocacy groups, which I think really highlights how trial design can and should consider patients' day-to-day lives.

And speaking of design, the trial will include patients with *PIK3CA*-mutant, hormone receptor–positive, HER2-negative advanced breast cancer who have progressed on both CDK4/6 inhibitors and endocrine therapy. The comparator arm will be capivasertib plus fulvestrant.[20]

ReDiscover-2 will use a hierarchical design, starting with analysis in the kinase-mutant subgroup—where we've seen the strongest early data—before expanding to the full intent-to-treat population. Stratification will include mutation type, visceral disease, and geography.[20]

One additional design feature I think is worth calling out is the inclusion of patients with bone-only disease, as long as they have evaluable lesions.[20] That's relatively uncommon in solid tumor trials but helps ensure the study reflects the broader real-world population.

U.S. enrollment has started as of June 2025, with international sites coming online by the end of the year.[20]

But for now, the key takeaway from the ReDiscover phase one study is that RLY-2608 plus fulvestrant shows encouraging signs of efficacy and tolerability in *PIK3CA*-mutant HR-positive/HER2-negative breast cancer, especially in patients with kinase domain mutations.[1] That being said, it's still early-phase data. We're optimistic, but we'll need more evidence in the post-CDK4/6 inhibitor setting and long-term follow-up, which is why I'm eager for the ReDiscover-2 trial to begin.

Dr. Turck:
As those forward-looking thoughts bring us to the end of today's discussion, I want to thank my guest, Dr. SarahSammons, for helping us better understand how the updated results from the ReDiscover study may inform the future treatment of *PIK3CA*-mutant, HR-positive, HER2-negative advanced breast cancer. Dr. Sammons, it was great speaking with you today.

Dr. Sammons:
Likewise, it's been a pleasure.

ReachMD Announcer:
This medical industry feature was sponsored by Relay Therapeutics. If you missed any part of this discussion or to find others in this series, visit *Project Oncology* on ReachMD dot com, where you can Be Part of the Knowledge.

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