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ReDiscover-2: Currently Enrolling Patients With *PIK3CA*-Mutated Advanced Breast Cancer

Announcer:
You're listening to *Project Oncology* on ReachMD. This medical industry feature, titled "ReDiscover-2: Currently Enrolling Patients With *PIK3CA*-Mutated Advanced Breast Cancer," 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 today to discuss eligibility and screening considerations for the Phase Three ReDiscover-2 trial in *PIK3CA*-mutated HR-positive/HER2-negative advanced breast cancer is Dr. Sarah Sammons. She's the Associate Director of the Metastatic Breast Cancer Program at the Dana-Farber Cancer Institute in Boston, Massachusetts. Dr. Sammons, welcome to the program.

Dr. Sammons:
Happy to be here.

Dr. Turck:
Well, to start us off, Dr. Sammons, we've certainly made a lot of progress in hormone receptor-positive metastatic breast cancer care. But where do you still see unmet needs when patients with a *PIK3CA* mutation progress after a CDK4/6 inhibitor?

Dr. Sammons:
For me, I think the main gap is durability and tolerability. Although we have FDA-approved therapies that target the PI3K pathway in HR-positive/HER2-negative breast cancer with *PIK3CA* mutations, the benefit is often modest. Median progression-free survival with these agents, which are typically given with endocrine therapy, is in the range of about five to seven and a half months after progression on a CDK4/6 inhibitor regimen and we'd like to do better than that.[1]

What's more, is these treatments broadly inhibit the PI3K pathway, so adverse events like hyperglycemia, rash, diarrhea, and stomatitis are common. And those toxicities can lead to dose interruptions or discontinuations, which makes it harder for some patients to stay on therapy long enough to achieve a sustained benefit.[1]

And these challenges have really sparked excitement around next-generation PI3K inhibitors like RLY-2608, now known as zovegalisib, or zovega for short. Zovega is the first pan-mutant-selective PI3Kα inhibitor, designed to selectively target mutant forms of PI3Kα, while sparing wildtype protein. The goal is to preserve antitumor activity while reducing the class-related toxicities that come with inhibiting wildtype PI3Kα.[2] And that brings us to ReDiscover-2, the Phase Three study designed to test this hypothesis.[3]

Dr. Turck:
Well, before we move on to our main focus today, which is ReDiscover-2, let's take a moment to revisit why zovega moved forward into a Phase Three trial. Would you summarize the findings from the ReDiscover first-in-human trial for us?

Dr. Sammons:
Of course. So one cohort of the first-in-human ReDiscover study evaluated zovega with fulvestrant in patients with *PIK3CA* mutated HR+/HER2- advanced breast cancer without concurrent *PTEN* or *AKT1* alterations.[4]

Now, I do want to note one thing on the dosing. Prior data with zovega 600 milligrams twice daily plus fulvestrant in fasted patients demonstrated clinical activity and tolerability, establishing the value of mutant-selective PI3Kα inhibition in this population. And now, data from the patient cohort treated at 400 milligrams twice daily given with food—which is the Phase Three dose—has been presented for

the first time at the ESMO Targeted Anticancer Therapies Congress in Paris. The 400 milligrams BID fed dose of zovega achieves comparable exposures to the 600 milligrams BID fasted dose, enabling a more convenient and patient-friendly dosing option moving into the Phase Three trial.[5]

Now, getting back to ReDiscover findings of zovega recommended Phase Three dose: at a median follow-up of 12 months, the overall median progression-free survival in this population was 11.1 months. And this activity with zovega plus fulvestrant was consistent across all *PIK3CA* mutation subtypes, including both kinase and non-kinase mutations.[5]

So these results are very encouraging for further exploration of zovega's role in selectively targeting the oncogenic *PIK3CA* driver mutation in these tumors.

Dr. Turck:
And what stood out to you from a safety standpoint?

Dr. Sammons:
Consistent with its mutant-selective mechanism of action, the 400 milligrams BID fed dose of zovega plus fulvestrant continues to demonstrate favorable and differentiated safety profile. The treatment-related adverse events were largely low-grade and reversible without needing any prophylactic measures.[5]

The most frequently reported adverse event was diarrhea, but these were sporadic, low grade events, and easily managed with over-the-counter oral medication like loperamide.[5]

From a class perspective, the toxicity we often worry about most with broad PI3Kα inhibition is hyperglycemia but fewer than half of patients experienced hyperglycemia, and most cases were Grade 1, meaning they did not require medical intervention. Other adverse events associated with PI3K pathway inhibitors—like rash and stomatitis—were uncommon and mostly low grade.[5]

So overall, the efficacy and safety data observed with the 400 milligrams twice daily dose of zovega in this first-in-human study were promising for the Phase Three ReDiscover-2 trial.[5]

Dr. Turck:
Thanks for recapping that for us, Dr. Sammons. And with all of that in mind, would you now take us through the design of ReDiscover-2?

Dr. Sammons:
Absolutely. ReDiscover-2 is a global, randomized, open-label Phase Three study enrolling approximately 540 patients with *PIK3CA*-mutated, HR-positive/HER2-negative locally advanced or metastatic breast cancer whose disease has progressed after a CDK4/6 inhibitor and endocrine therapy.[3,6]

Patients are randomized one-to-one to either receive zovega plus fulvestrant or capivasertib plus fulvestrant. And this randomization is stratified by *PIK3CA* mutation type, the presence or absence of visceral disease, and geographic region.[3,6]

Per the FDA label, capivasertib is given at 400 milligrams BID on an intermittent schedule of four days on and three days off, with or without food, while zovega, as we discussed, is administered at 400 milligrams BID with food. Both drugs are combined with standard dose fulvestrant.[3,6]

Dr. Turck:
And as a follow-up to that, what are the primary endpoints of ReDiscover-2?

Dr. Sammons:
The primary endpoint is progression-free survival assessed by blinded independent central review, in patients with *PIK3CA* kinase-domain mutations and in the overall study population.[3,6]

A key secondary endpoint is overall survival, with additional secondary endpoints including objective response rate, duration of response, clinical benefit rate, and quality of life.[3,6]

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Sarah Sammons about the Phase Three ReDiscover-2 trial and practical eligibility considerations.

So, Dr. Sammons, since ReDiscover-2 is actively enrolling, which patients should be screened for this trial, and what are the core

eligibility requirements?

Dr. Sammons:
Yes, the trial is now recruiting patients globally. Similar to ReDiscover, patients must have HR-positive/HER2-negative locally advanced or metastatic breast cancer with a confirmed *PIK3CA* mutation, without concurrent *PTEN* or *AKT* alterations. They must have received only one prior line of CDK4/6 inhibitor therapy and one or two lines of endocrine therapy in the advanced setting. Patients who have recurrence on or within 12 months of (neo)adjuvant completion may count that as their therapy. And it's important to note that prior therapy with a SERD, including fulvestrant, is allowed.[3,6]

Patients will also need to have either measurable disease per RECIST 1.1 or an evaluable bone-only disease. Bone-only disease is not often included in clinical trials, but its inclusion here better reflects the real-world population and provides an important opportunity for patients seeking to enroll.[3,6]

Dr. Turck:
And just to follow up on something you noted earlier, the patients in ReDiscover had tumors with *PIK3CA* mutations. So what mutational testing is required for ReDiscover-2 screening?

Dr. Sammons:
I'm so glad you followed up about that because this is an important clarification. To enter the study, patients need a known *PIK3CA* mutation, but *PTEN* or *AKT* status isn't required upfront because those alterations will be assessed during screening.[3,6]

Now, a patient who's already known to have a *PTEN* or *AKT* alteration wouldn't be eligible, but lack of that information shouldn't prevent screening.[3,6]

Dr. Turck:
And on the flip side, which patients should *not* be considered for ReDiscover-2 based on the exclusion criteria?

Dr. Sammons:
Well, one area to examine closely is prior therapy. Patients are excluded if they've previously received any investigational CDK-targeting agent, immunotherapy, antibody drug conjugates, or an agent that inhibits the PI3K/AKT/mTOR pathway. Disease progression within the first six months of an endocrine therapy regimen in the advanced setting is also exclusionary.[3,6]

Another area that generates a lot of questions is the metabolic criteria. Patients with type one diabetes, or those with type two diabetes who require antihyperglycemic medications, are excluded. Otherwise, patients are eligible as long as their hemoglobin A1c is below seven percent and their fasting plasma glucose is below 140 milligrams per deciliter.[3,6]

In practical terms, patients with prediabetes who are taking antihyperglycemic medication may be eligible. And patients who are taking glucose-lowering medications for reasons other than formal diabetes diagnosis may also be eligible, as long as they meet the laboratory criteria.[3,6]

So it's worth looking closely at both the diagnosis and the labs to avoid excluding patients too early.

Dr. Turck:
Now, if we look at this from a practical standpoint, when should clinicians start thinking about testing for *PIK3CA* mutations?

Dr. Sammons:
I'm glad you asked because this is really about planning ahead rather than reacting at progression. In routine practice, most patients with HR-positive/HER2-negative advanced breast cancer fall into one of two broad categories.

The first, and the most common is patients receiving first-line endocrine therapy plus a CDK4/6 inhibitor for advanced disease. And as it relates to testing, I recommend next generation sequencing on the tumor at metastatic diagnosis. If a *PIK3CA* mutation status hadn't already been assessed at progression, I recommend sending circulating tumor DNA at that time. Discussion of a clinical trial and next line of therapy options could occur before the actual progression, to allow more time for the patient to consider their options.[3,6]

The second situation involves patients on endocrine therapy plus a CDK4/6 inhibitor in the adjuvant setting. In that scenario, patients who recur during treatment or within 12 months of stopping the adjuvant CDK4/6 inhibitor may still be appropriate to test. And this is deemed as one line of prior CDK4/6 inhibitor per the study protocol.[3,6]

And so ultimately, this comes down to confirming *PIK3CA* mutation status and setting expectations early, so that when patients progress on endocrine therapy plus a CDK4/6 inhibitor, you're ready to move forward thoughtfully.

Dr. Turck:
Now with all that in mind, let's walk through some hypothetical case scenarios that highlight how these eligibility decisions play out in practice.

We'll start with a 45-year-old woman with HR-positive/HER2-negative advanced breast cancer. She has metastatic lytic bone lesions, representing evaluable bone-only disease—which you've already highlighted as a feature of the trial—that has progressed after 13 months on a single line of CDK4/6 inhibitor–based therapy in the advanced setting. A *PIK3CA* mutation was identified on local testing. Given that background, Dr. Sammons, let's look at how different details affect eligibility.

Suppose this patient has prediabetes and is taking metformin. Is that an issue?

Dr. Sammons:
This is a great example of where patients can be excluded unnecessarily. As long as the patient doesn't have a formal diagnosis of type two diabetes and their hemoglobin A1c is below seven percent with fasting plasma glucose below 140 milligrams per deciliter, the metformin alone would not exclude them. So in this case, the patient would still be eligible from a metabolic standpoint.[3,6]

Dr. Turck:
Now, Dr. Sammons, what if this patient has received everolimus plus exemestane for her second-line therapy and now has disease progression?

Dr. Sammons:
So in that case, she wouldn't be eligible for ReDiscover-2 because prior treatment with an mTOR inhibitor is exclusionary, unfortunately.[3,6]

Dr. Turck:
I see. And how about if she had received abemaciclib plus fulvestrant in second-line instead?

Dr. Sammons:
In that case, the fulvestrant wouldn't be an issue—prior fulvestrant is allowed and the patient has received no more than two lines of endocrine therapy in the advanced setting. But having more than a single line of CDK4/6 inhibitor treatment in the advanced setting would exclude the patient.[3,6]

Dr. Turck:
OK. Now, what if she developed an *ESR1* mutation and was treated with elacestrant monotherapy?

Dr. Sammons:
In this scenario, the patient could still be eligible, since the protocol allows one to two lines of endocrine therapy in the advanced setting. And importantly, the presence of an *ESR1* mutation does not exclude patients from the study.[3,6]

Dr. Turck:
Interesting. I appreciate you breaking all of that down for us, Dr. Sammons. And before we close, are there any key points you'd like our audience to take away from this discussion?

Dr. Sammons:
Yes, I think there are a few key points.

First, in patients with HR-positive/HER2-negative advanced breast cancer and a *PIK3CA* tumor mutation who progress after endocrine therapy and a CDK4/6 inhibitor, there remains an unmet need driven by challenges with durability of benefit and tolerability of existing PI3K pathway–targeted therapies that are out there.[2]

But the good news is that we have data from the first-in-human ReDiscover study suggesting encouraging clinical activity with zovega plus fulvestrant in patients with PIK3CA-mutant breast cancer.[5,7-9] In CDK4/6 inhibitor–pretreated population, the combination demonstrated a median progression-free survival of 11.1 months and a well-tolerated safety profile consistent with mutant selectivity.[5]

Which brings us to the Phase Three ReDiscover-2 trial that's currently enrolling. This study is designed to build on the ReDiscover findings and aims to clarify the impact of mutant-selective PI3K inhibition in a larger, randomized trial of patients.[3,6]

Zovega plus fulvestrant recently received FDA Breakthrough Therapy Designation for this specific ReDiscover-2 patient population. And this recognition by the FDA, I think, underscores both the promise of the approach and the ongoing unmet need for these patients. And so, I'm really looking forward to seeing what this trial uncovers.[10]

Dr. Turck:
That's a helpful way to frame this as clinicians think about next steps. And I want to thank my guest, Dr. Sarah Sammons, for sharing her insights on eligibility and screening for the ReDiscover-2 trial. Dr. Sammons, it was great speaking with you today.

Dr. Sammons:
Thanks for having me.

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.com, where you can Be Part of the Knowledge.

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