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The Future of PI3K Inhibition in HR+/HER2- Breast Cancer

Announcer:
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Dr. Jhaveri:
Hello, everyone. This is CE on ReachMD, and I'm Dr. Komal Jhaveri, a breast medical oncologist from Memorial Sloan Kettering Cancer Center in New York.

We have PI3K pathway inhibitors that are already approved for ER-positive breast cancer, but there are several other drugs that are also being investigated, and drugs that are approved are also being investigated in other settings. So let's review the most current data from ongoing clinical trials.

Let's start with inavolisib, the most recent PI3K inhibitor that was approved based on the phase 3 INAVO120 trial, which is a first-line study for endocrine-resistant tumors that were PIK3CA-mutant, where we had approval for inavolisib plus fulvestrant and palbociclib. Now, beyond the first line, where we saw PFS and OS benefit with this triplet regimen, inavolisib is also undergoing investigation as a head-to-head comparison in the INAVO121 study in the second-line metastatic setting. So this head-to-head comparison of inavolisib is against alpelisib plus fulvestrant, our very first PI3K inhibitor that was approved in 2019 based on the phase 3 SOLAR-1 trial.

Beyond the second-line metastatic setting, inavolisib is also being evaluated for HER2-positive metastatic breast cancer in the first-line setting. So traditionally, we think about HER2-positive patients, we treat them with the CLEOPATRA regimen, which is a taxane and dual HER2 blockade with trastuzumab and pertuzumab. And after induction-based chemotherapy or maximal response, patients continue maintenance HP or trastuzumab and pertuzumab.

INAVO122 is evaluating the addition of inavolisib for PIK3CA-mutant HER2-positive breast cancer who've completed this induction, and during maintenance we have the regimen of inavolisib/HP versus HP alone. So we'll see what INAVO122 shows us about this role in HER2-positive tumors.

INAVO123 is trying to focus on the triplet regimen with letrozole as a backbone in endocrine-sensitive patients in the first line as well.

So beyond endocrine-resistant where we have approval, we're also trying to get endocrine-sensitive approval with inavolisib.

The MORPHEUS-pan Breast Cancer trial is also evaluating multiple arms, including an arm that is also evaluating the combination of inavolisib with other CDK4/6 inhibitors such as abemaciclib or ribociclib with fulvestrant-based therapy. It's also evaluating a novel oral

SERD, giredestrant, in combination with inavolisib. So more investigation happening in the MORPHEUS-pan Breast Cancer trial to see how we can further expand the role of inavolisib for breast cancer.

Beyond this, when we think about agents targeting this pathway, we have mutant-selective PI3K inhibitors that are currently undergoing investigation. So you might recall from our prior discussions in other episodes that the toxicity profile for PI3K inhibitors could be explained by the wild-type inhibition. And this wild-type PI3K inhibition can explain the hyperglycemia, diarrhea, rash, and stomatitis.

So this is why we've now been focusing on developing mutant-selective PI3K inhibitors that could potentially spare the wild-type inhibition and therefore have a better toxicity profile, and hopefully that could lead to even better efficacy.

At early signals in phase 1 trials, we've seen drugs such as RLY-2608 or STX-478 to be promising. In fact, RLY-2608 plus fulvestrant, when we looked at a cohort of patients in the phase 1 trial that were in the second-line setting, we saw that the median progression-free survival of PIK3-mutant tumors was in the order of nearly 10 months. This is again a phase 1 study, small cohort of patients. But what was really encouraging to see was that the grade 3 rates of hyperglycemia, rash, or diarrhea were really, really low with these newer mutant-selective drugs.

Similarly, STX-478, the overall response rate for monotherapy was 23%, which is very appealing. And currently the phase 1 trial is evaluating STX-478 with fulvestrant and also with CDK4/6 inhibitors including palbociclib and ribociclib. So we will see how this drug will also add to this space. Again, with STX-478 as well, we've seen very low rates of hyperglycemia, diarrhea, or rash. So at least in phase 1 trial, these look very promising.

The RLY-2608 has now begun its journey in phase 3 in the REDISCOVER-2 trial, where RLY-2608 plus fulvestrant will be compared to capivasertib plus fulvestrant. Capivasertib being our AKT inhibitor that is approved in the second-line setting for PI3K/AKT/PTEN-altered tumors. The REDISCOVER-2 trial will focus only on PIK3CA mutations and do this head-to-head comparison. So really exciting times.

So to summarize, I think we have approval for many, many agents, the most recent one being inavolisib as a triplet. We're evaluating it in the second-line setting; we're evaluating it for HER2-positive setting.

And then we also have mutant-selective drugs such as RLY-2608 and STX-478 that look promising from a safety profile, which is why they were being studied. And we also are now going to look at phase 3 trials from RLY-2608 that is already ongoing, and hopefully with STX-478 in the future after the ongoing phase 1 trial shows some good data.

So thank you so much for joining me today, and see you next time.

Announcer:
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