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PI3K Pathway Inhibition in HR+/HER2- mBC: Mechanistic Insights

Announcer:
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Dr. Jhaveri:
Hello, everyone. This is CE on ReachMD, and I'm Dr. Komal Jhaveri, breast medical oncologist at Memorial Sloan Kettering Cancer Center in New York. Our topic today is PI3K pathway inhibition in hormone receptor-positive, HER2-negative metastatic breast cancer.

So let's kick off by talking about the role of PI3K/AKT/mTOR pathway in breast cancer. Now, this pathway is frequently dysregulated in many cancers, including in breast cancer, and really drives cell survival, proliferation, and growth.

Now, how did this pathway get activated? There are a few different ways this pathway can get activated, including and not limited to mutations in genes such as the PIK3CA or loss of tumor suppressor gene such as PTEN. It also involves other nodes in the pathway, including AKT and mTOR. And this activation occurs through growth factor receptor tyrosine kinase activation or genetic mutations and loss of negative regulators.

Now certainly, because it's implicated in cancer and because this pathway is activated in nearly 40% of hormone receptor-positive breast cancers, it has been an important pathway to target to further improve outcomes and to overcome the resistance issues that we face in tumor growth and in clinic.

Now the first lesson that we learned about targeting this pathway is that there is a crosstalk between the estrogen receptor and the PI3K pathway such that if you target just the estrogen receptor, you can have upregulation of the PI3K pathway, and if you go only after the PI3K pathway, you can have upregulation of the estrogen pathway, which is why current approvals that we had in clinic originally, especially in the second-line and beyond setting, have been in combination with endocrine therapy. We're talking about alpelisib, capivasertib; we're talking about everolimus. All of these drugs targeting the PI3K/AKT/mTOR pathway have been in combination with endocrine therapy.

However, more recently, we also learned that there is synergy when you try and do a comprehensive blockade not just of 2 nodes or 2 pathways, such as the estrogen and the PI3K pathway, but also the CDK4/6 pathway. So dual vertical blockade of this pathway would be more synergistic and have better activity. This is what led to trying triplet regimens in phase 1 clinical trials and now in phase 3, which have led to approval.

So when we talk about phase 1s, we initially did this experiment, or this trial, with alpelisib, which was already approved in 2019 with

fulvestrant, to see if you combine a CDK4/6 inhibitor with endocrine therapy and alpelisib, can you improve further outcomes? Unfortunately, that led to additional toxicity.

However, with inavolisib, another PI3K inhibitor, which has a unique mechanism of action that not only inhibits the PI3K alpha isoform, which is what alpelisib does as well, but it also facilitates the degradation of the mutant PI3K alpha protein. And certainly, preclinically, it has shown more in vitro and in vivo potency. It's thought to therefore lead to specific and also potent reduction of the target, which is the PI3K alpha.

And surely that translated in phase 1 clinical trials with triplet strategies to be safe, tolerable, and efficacious enough to justify a phase 3 registrational trial, the INAVO120 study, which then led to the approval of this triplet regimen of inavolisib, fulvestrant, and palbociclib in the first-line endocrine-resistant setting in tumors that harbor a PIK3CA mutation.

So to summarize this episode, I think we have to agree that the PI3K pathway is an important pathway that is implicated in endocrine resistance, an important pathway to target, with agents that are specifically causing activation of this pathway. So we're using agents that are targeting the mutations that are causing activations of this pathway, which could be a PI3K mutation or an AKT alteration, or even loss of PTEN alterations.

We certainly have doublet strategies with endocrine therapy and agents targeting the PI3K/AKT/PTEN pathway and more recently also have approval for triplet regimens such as inavolisib, fulvestrant, and palbociclib in the first-line endocrine-resistant settings with tumors harboring PI3K.

Thanks so much for joining me today and see you next time for another episode of ReachMD.

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