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Triple Threat: Key Data on Simultaneous Estrogen, CDK4/6, and PI3K Inhibition in mBC

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Dr. Jhaveri:
Hello, everyone. This is CE on ReachMD, and I'm Dr. Komal Jhaveri, a breast medical oncologist at Memorial Sloan Kettering Cancer Center in New York. And today I'll be discussing key data on simultaneous estrogen, CDK4/6, and PI3K inhibition in metastatic breast cancer and its role in PIK3-mutant tumors.

So when we think about targeting this pathway, we always thought about combining an agent targeting the PI3K pathway with an anti-estrogen agent. However, we learned that, preclinically, when we combine an agent targeting the PI3K pathway, the estrogen receptor, and a CDK4/6 inhibitor all together in a triplet strategy, there was more comprehensive blockade that translated into synergistic activity. And in fact, this was translated in clinic in phase 1 trials to be efficacious, safe, and tolerable, at least with one of these agents—namely inavolisib, a PI3K alpha isoform inhibitor that also degrades the mutant PI3K alpha.

This phase 1 triplet strategy therefore led to the development of the registrational phase 3 trial called INAVO120. Now, the INAVO120 trial focused on patients who had recurrence on or within 12 months of their adjuvant endocrine therapy, had measurable disease, had no other therapy for metastatic disease, and for whom the PIK3CA mutation was detected predominantly in cell-free DNA. So this detection in the circulating tumor DNA kind of highlights that this is a poor-prognostic group of patients where you see enough tumor burden that is spilling in the plasma and was detected in a ctDNA assay.

325 patients were then randomized to inavolisib/fulvestrant/palbociclib—inavolisib being administered at 9 mg orally daily, and fulvestrant and palbo at standard of care dosing—versus fulvestrant and palbociclib at standard of care dosing. The primary endpoint was investigator-assessed PFS, and key endpoints which are secondary included overall survival.

And at a median follow-up of 34 months, which is the most updated data that has been now published as well, we saw that there was a statistically significant improvement from 7 months in the control arm to 17 months with the addition of inavolisib, which was highly statistically significant.

Moreover, this was the very first time that an agent targeting this pathway has also shown an overall survival benefit. In fact, in the INAVO120 study, overall survival in this first-line metastatic patient population was 27 months in the control arm; that improved to 34 months in the arm with inavolisib—again, unprecedented and really a humbling realization that this was a very poor-prognostic group of patients that did derive benefit with adding a PI3K inhibitor in this setting.

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So needless to say, this has now changed our treatment paradigm. It is now approved and available to us, highlighting the importance of identifying PIK3 mutations as early as first-line metastatic setting.

So we used to think about finding these biomarkers in the second-line metastatic setting given our approvals for biomarker-based treatment selections, but now with the INAVO120 regimen approved in the first-line setting, it really, really is a reminder for all of us to think about this endocrine-resistant group and do this testing—maybe from tissue, maybe from plasma; the tissue could be primary or metastatic—and then offer this regimen to these patients.

So to summarize, I think this is really an important transition in the way we are targeting this pathway—the PI3K pathway—including with triplet strategies in the first-line metastatic setting, where for endocrine-resistant patients, we've seen the prognosis is poor and the outcomes are not that optimal, and we've been able to improve both progression-free survival and overall survival in the first-line PIK3-mutant endocrine-resistant setting.

It has been a great mini lecture. Thank you for joining today, and thanks for listening in.

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