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Case in Point: Applying PI3K Combinations in Early Recurrent HR+/HER2- mBC

Announcer:
Welcome to CE on ReachMD. This activity is provided by Prova Education and is part of our MinuteCE curriculum.

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Dr. Kalinsky:
Hi, this is CE from ReachMD. I'm Kevin Kalinsky, and we're going to be talking about a patient who had developed recurrence despite being on their adjuvant endocrine therapy for 8 months.

So this is a circumstance where it is important to check for next-generation sequencing and identify whether a patient has a PI3K mutation, because this is the sort of patient which fits exactly into the INAVO120 study.

So let's talk about the INAVO120. So this was a randomized phase 3 trial, which randomized patients to either receive the triplet of inavolisib, which is an oral pill that patients take daily, plus palbociclib plus fulvestrant, versus fulvestrant plus palbociclib. So essentially asking the question of doublet versus triplet therapy, and the third drug being the PI3K selective inhibitor inavolisib.

In the study, patients needed to have a hemoglobin A1c of less than 6%. I think I mentioned already that patients needed to have measurable disease. But the data that we saw from this is just a few things. One, the progression-free survival. When you look at the doublet compared to the triplet, it was a difference of about 10 months, with the control arm being about a median progression-free survival of 7 months and in the experimental, or the triplet arm, being 10 months long, of about 17 months. And that's very clinically meaningful, in my opinion.

Also, at ASCO 2025 we saw data with overall survival benefit, with the difference of around 6 months or so in terms of overall survival. About 27 months compared to around 34 months in the control arm compared to the experimental arm.

So ultimately, this has been established as standard of care. Some information that's worth really highlighting in terms of INAVO120. And of course, you would only know if you have a patient with a PI3K mutation if you're actually checking for alterations. We talked about, in other episodes, that I would start with checking in ctDNA. If that's coming up short, it is okay to then look in the primary tumor because PI3K mutations happen early. Different than capivasertib, this is only approved for patients with PI3K mutations, compared to those with capivasertib, with the approval, which is fulvestrant plus capivasertib, it includes those with AKT alterations and P10 alterations.

So back to INAVO120. We do see side effects from inavolisib that can include hyperglycemia, gastrointestinal issues, so it's important to monitor. Though we talked about other studies like the SOLAR-1, which led to the approval of alpelisib, it looks like significant grade 3

or higher events are lower. Though it's also worth noting, across the various studies that led to approval with these agents, that the cutoff for hemoglobin A1c is a little bit different across these trials.

But I do want to reiterate a few things. One, this is an approval with this particular triplet. It commonly comes up, well, what about ribociclib? What about abemaciclib? I wouldn't do that. It is inavolisib plus palbociclib plus fulvestrant right now. There are other studies that are looking at the combination of a PI3K inhibitor with ribociclib, but right now I would not extend this to that. So it is really with this particular triplet.

Also, the other question that I commonly field from the community is, what about patients who may not have endocrine-resistant disease? And I would say this is really meant for a very specific patient population. There is those patients whose tumors recurred within 12 months of their adjuvant endocrine therapy. So I would not apply this to a patient who completed their adjuvant endocrine therapy and then had a tumor that progressed 2 years after completion of their endocrine therapy. This is for a very specific population.

So to summarize, ultimately INAVO120 was a practice-informing study. There were some controversies that came up when this was discussed at ASCO 2025, including the fact that there was not a crossover arm. And also, in the control arm, I mentioned the patients did so poorly that very few of them went on to get a PI3K-targeted drug because they needed to get other treatments like chemotherapy or an ADC pretty quickly thereafter because their tumors were rapidly progressing.

But to me, that also just highlights the unmet need of having good agents for this endocrine-resistant population, and this is a step forward for our patients who have PI3K mutations.

Thank you for your attention and we'll be discussing other topics in other episodes.

Announcer:
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