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Comprehensive Biomarker Testing in mBC Informs Clinical Decision Making

Announcer:

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Dr. Kalinsky:

Hi, this is CE on ReachMD. I'm Kevin Kalinsky from Winship Cancer Institute, and we're going to spend some time focusing on biomarker testing in patients with metastatic hormone receptor-positive, HER2-negative breast cancer.

This is a critically important topic because we have drugs that we can target specific alterations. That includes patients who have alterations in the PI3K/AKT pathway, as well as those with ESR1 mutations. So let's spend a little bit of time talking about alterations in the PI3K/AKT pathway.

Mutations can be frequent in hormone receptor-positive, HER2-negative disease. For instance, PIK3CA mutations, about 40% of patients have an identified PIK3CA mutation. 85% of those happen in hotspot domains. So either the helical domain or the kinase domain. So exon 9 or exon 20. So there are 3 mutations in particular which have a high prevalence of the PI3K mutations; they make up the majority of those PI3K mutations that we can see.

We also see AKT mutations, which is less frequent. We see that at a rate of about somewhere between 3% to 5% in hormone receptor-positive disease. This has significant implications because we have drugs that target this pathway, so we have the approval of capivasertib in patients with alterations of PI3K or AKT, as well as P10. We have PI3K inhibitors like inavolisib, like alpelisib that also are approved in metastatic disease.

It's one thing that's important to know about PI3K and AKT mutations, that those can happen early. Meaning if you have a patient who has metastatic disease and you try to do tumor testing, we can sometimes see if that's coming up short and we can identify mutations. These can happen early, meaning you then can look in the primary tumor and those happen early on in clonal development.

That's a bit different than ESR1 mutations. ESR1 mutations, which are also hotspot mutations, are adaptive resistance mechanisms, meaning that they happen, for instance, after patients take their adjuvant aromatase inhibitor or received an aromatase inhibitor in the metastatic setting. So when you are testing for ESR1 mutations, it's a little bit different. You want to make sure that you're testing after progression on a specific regimen, like in the metastatic setting. Because if you're going to be testing for ESR1 mutations and you're testing the primary tumor, you're not going to find them because the patient hasn't developed resistance to, for instance, aromatase inhibitors.

So when do you do testing? So you do testing in patients who have metastatic disease. If you have a patient who has a tumor that has recurred within 12 months of their adjuvant endocrine therapy, I would do it at the time of metastatic diagnosis because there may be a patient who would be one that we would think about giving inavolisib based upon the INAVO120 regimen.

Oftentimes, you're also checking for, as I mentioned, ESR1 mutations as well, so there are circumstances where one might check it at the time of diagnosis, like for those early relapsers. But for sure, one should be checking for ESR1 and PI3K mutations at the time of progression on an endocrine therapy and a CDK4/6 inhibitor. Oftentimes, we're utilizing CDK4/6 inhibitors frontline given that we can see in, the majority of our studies, overall survival advantages. But for sure you should be testing in that metastatic setting.

Oftentimes, I'm testing by circulating tumor DNA first, but if you find that no alterations are detected or that the sample that you have is just not confirmatory, then at that point I may pivot and try to do tumor testing, based upon a patient tumor sample.

The other thing, just to mention, is that there are broad evaluations for next-generation sequencing that look at multiple alterations. There are ways to do more specific testing, like if one was doing Sanger sequencing and looking for specific alterations. I will say, in the US, we are commonly doing comprehensive testing because we're looking for these different mutations. And also, there are other mutations that I didn't mention that may be actionable like, for instance, ERBB2 mutations, where you may think about giving a HER2-directed therapy if patients have that mutation in the absence of having a HER2 amplification or protein expression.

So in summary, we talked about the different mutations, the importance of checking for PI3K and ESR1 because that has clinical implications. Thank you for your attention and we'll be talking other topics as well.

Announcer:

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