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Biomarker Testing After Progression in HR+/HER2- mBC

Announcer:
You're listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. Here's your host, Dr. Alexandria May.

Dr. May:
This is *On the Frontlines of Metastatic Breast Cancer* on ReachMD, and I'm Dr. Alexandria May. Joining me to discuss how biomarker testing guides treatment after progression in HR-positive, HER2-negative metastatic breast cancer is Dr. Adam Brufsky. He's the co-director of the Cancer Therapeutics Program, UPMC Hillman Cancer Center at the University of Pittsburgh School of Medicine. Dr. Brufsky, welcome to the program.

Dr. Brufsky:
Thank you very much, Dr. May. Thanks a lot for having me.

Dr. May:
So to start us off, Dr. Brufsky, let's say a patient of yours shows progression on a first-line CDK4/6 inhibitor plus endocrine therapy. Could you walk us through what your initial steps would be?

Dr. Brufsky:
Sure. Obviously, the first thing is that we're still going to image them, so they'll get whatever imaging is allowed by their organization or more likely the payer. Some people can get a PET-CT, and some people get a regular CT scan of the chest, abdomen, and pelvis—occasionally a bone scan. It depends where the symptoms are.

I think that after that, one thing that we all have started doing, and it's in NCCN, but we've been doing it even before it was in NCCN guidelines, is next-gen sequencing. Generally, the two major mutations we're looking for are ESR1, the mutation in the estrogen receptor, and PI3 kinase mutations. Occasionally, we'll find AKT mutations. hey're rare, probably about four or five percent. And then, unfortunately, we can't pick up PTEN deletions, which are not common, probably a couple percent. It's really hard to detect them in circulating tumor DNA. And occasionally, we'll go back to the original metastatic biopsy and try to do a next-gen sequencing on that too.

In certain cases, we can have one area that becomes a metastasis. For example, someone who, say, has de novo metastatic disease, and they still have a breast tumor intact. The breast tumor can grow, and the rest of the disease can remain stable. In some cases like that, we'll maybe even do a new biopsy of that lesion to see if it still retains estrogen sensitivity. And at that point, we'll also do next-gen sequencing on that particular tumor. So it's a little bit complicated, but the bottom line, what we're trying to figure out by doing all of this is, as the tumor progresses, is it resistant to the CDK4/6? Is it resistant to the endocrine therapy because it has an ESR1 mutation? Or does it have a bypass pathway like PI3 kinase/AKT/mTOR driving the progression? And that's kind of the idea here, that we're trying to get a sense of what someone progresses on in aromatase inhibitor endocrine therapy.

Dr. May:
Knowing that, how do you decide between ctDNA and tissue testing? What are the strengths and limitations of each, and when do you use both or rebiopsy?

Dr. Brufsky:
I tend to use, personally, liquid. It's much more convenient. I have the kits literally in my office. I can have a medical assistant draw it and send it off to the company, right on the spot. It's very easy to do. There's no real issues with the patient. The advantages of that are that the ctDNA really summarizes all of the DNA shedding of all of the tumors, in theory. So, in other words, if you have bone mets, if

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you have liver mets, or if you have lung mets, all together, the ctDNA can kind of summarize all of that into one kind of test.

The disadvantage is that tumors shed at different rates and different metastases shed at different rates. And breast cancer, it turns out, is one of the tumors that doesn't shed as much as, say, melanoma or bladder cancer or something like that. And so, as a result, we may miss shedding DNA by doing this. The technology is getting better, but the application of deletions is a little bit harder to do off of liquid ctDNA.

So in those cases, especially if we're interested in PI3 kinase mutation, I will go back and either rebiopsy a lesion somewhere, or I will, go back to, say, the first metastatic biopsy, occasionally even go back to the primary, particularly for PI3 kinase mutations. PI3 kinase mutations tend to be better picked up on the solid tissue, as opposed to the liquid biopsy. So the one clinical pearl I'd like to emphasize is that if you get a negative PI3 kinase mutation on circulating tumor DNA, I wouldn't necessarily consider that negative, and I would really seriously consider going back and doing a solid tumor biopsy that may have already been done.

The disadvantage of solid tumor biopsy is there's only one biopsy, and breast cancer is a heterogeneous disease. And so you have to assume that, say, if I biopsy one liver metastasis, all of the liver metastases would be the same way, and that's not necessarily true. That's the first thing. The second thing is that people don't like having needles stuck in them all the time. I mean, obviously, they have metastatic disease, and they want to do everything they can so their disease doesn't come back or get worse. But, on the other hand, it just can be tough. And the biopsy itself needs scheduling, and it has complications depending on where it is. So again, this is why I prefer liquid, unless I really have reasons for the solid tumor to do it.

Dr. May:
For those just tuning in, you're listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Adam Brufsky about sequencing therapy for HR-positive, HER2-negative metastatic breast cancer.

So, Dr. Brufsky, let's say testing shows an ESR1 mutation or a PI3K/AKT pathway alteration. How does that result shape your choice of next therapy?

Dr. Brufsky:
So an ESR1 mutation generally means that the receptor itself has mutations, usually in the hormone receptor binding domain of the estrogen receptor that makes the receptor insensitive to estrogen suppression. So in very limiting amounts of intracellular estrogen or even in the absence of estrogen, the receptor autoactivates.

And so we're looking then, in that case, for interventions that degrade the receptor, and we have a lot of them actually. We have at least four. We have two that are on the market now, but another two are likely to get to market pretty soon. They're oral SERDs. So these are drugs that actually work a little bit better than fulvestrant, which is the oral SERD we've had for 20 or maybe 25 years that went generic a couple years ago in the United States. And the oral SERDs like camizestrant just got approved. But the big ones that are approved are imlunestrant and elacestrant. They are approved either as single agents, or, in the case of imlunestrant, it just got approval with abemaciclib together as a therapy. So those would be very reasonable uses for oral SERDs.

And I think that, clearly, these drugs have, like most oral SERDs, few side effects. There's a few things that we do keep in mind. There's bradycardia with giredestrant. There's a little bit of ocular abnormalities that are very grade one, grade two at the worst, with camizestrant. There's a little bit of occasional nausea with the other ones. So these are very, very safe and well-tolerated drugs, and they can be combined with just about anything that we have. There's a trial called ELEGANT where we combined elacestrant with a whole bunch of different things, and it was pretty safe to use. So that's the intervention if you have an ESR mutation. It used to be single agent, and I think, again, what we'd look at for somebody who we still would give single agent to is someone who's been, say, under CDK4/6 endocrine therapy for years.

And then, as you know, the median progression-free survival of these agents is probably two to three years. And so that means half of the people are going to do better than two to three years. And of those people, if they only have a few bone metastases that have progressed, I think at that point, maybe we just give them single agent elacestrant or imlunestrant. I think that most of us, though, will likely use it in combination.

So giredestrant and everolimus is likely to be approved as therapy. There's a trial called AVERA that was just published in The New England Journal of Medicine. The FDA, I think, has a PDUFA for it the end of November, so it's likely to be approved at that point for this. We can use imlunestrant and abemaciclib. There's a trial called EMBER-3. Again, in CDK4/6 progression, it also gives a lot of benefit. So that's for the ESR-mutant patients.

So then we go to the PI3 kinase-mutant patients. That's a whole other story. And so we have a lot of PI3 kinase inhibitors. The first one that was actually approved was alpelisib, probably before the pandemic, so 2019, something like that. And alpelisib, in my hands, has

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been fairly well tolerated. I think the big problem is hyperglycemia. When it was first developed, it was probably 30 or 40 percent grade three hyperglycemia. I think a lot of physicians don't like using it because of that. But I think if you check someone's fasting glucose weekly while they're on it, and if it's under 150, leave them alone. If it's over 150, keep just boosting up metformin. That takes care of a lot of the hyperglycemia, believe it or not. If you get above 250 despite the metformin, what I tend to do is then reduce the alpelisib, and if that doesn't work, then I stop. I don't use insulin for this. The reason is that by inhibiting PI3-kinase, you're inhibiting the insulin signaling, so you're making someone insulin resistant by giving them the drug.

So there have been a number of other drugs that have been available. Inavolisib also has a little bit less hyperglycemia and more rash. There's capivasertib, which is an AKT inhibitor that is used in the same setting, with fulvestrant, for PI3-kinase mutant patients. Capivasertib is interesting. It's given four days out of seven to try to reduce the toxicity of the drug. But again, you still get the hyperglycemia, a rash, and diarrhea, with these drugs. So they're sometimes not easy to give. They do require a little bit of finesse in treating people.

So for all those reasons, we have yet another drug that's brand new that got approved by the FDA in July called gedatolisib. It's a combined mTOR/PI3 kinase inhibitor. It's given intravenously. That's the problem with this drug. It's given intravenously day one, day eight, and day fifteen of a twenty-eight-day cycle. But because of the pharmacokinetics of the drug, most of the toxicity is really in the first 24 to 48 hours. It's usually stomatitis/mucositis, because that's when you get the peak effect. And then, because it's intravenous, the pharmacokinetics of the drug are such that it rapidly is cleared, but you still have a good steady state. That actually has a lot of efficacy. It's not been approved for PI3 kinase-mutant patients yet. It likely will be. There was a trial at ASCO that showed a PFS of about 11 months in this setting. And I think it'll likely be approved by the FDA. It is approved for PI3 kinase wild-type patients.

So again, you have probably about 40 percent of patients that don't have an ESR mutation and do not have a PI3 kinase mutation. Now, what are you going to do with those patients? Well, it turns out that the gedatolisib, if given with fulvestrant and palbociclib, actually has a PFS of about a little over 9.5, 9.3 months in this setting. So if someone is okay with an intravenous drug, which is the big problem with this—and again, the big side effect of this drug is stomatitis/mucositis. If we can control that… which most of us can, we're medical oncologists. We're used to dealing with this side effect.

So as you can tell, it's complicated, because the next question I'm assuming you're going to ask is, what happens when you have a mutation in both ESR1 and PI3 kinase? And I think, in that case, we make a decision based on clinical judgment. Which pathway do we really think is more at play here? And I think if someone progresses relatively rapidly within a year or something or 18 months, I'd probably be more PI3 kinase. If it's more like toward the outer edge of it, maybe two or three years, I think about the,ESR1 and going for oral SERDs. We have trials now where we're combining the oral SERD with the PI3 kinase to try to do both. And it'll be really interesting to see where this goes.

Dr. May:
If testing comes back without a clear target, how do you choose what comes next?

Dr. Brufsky:
Yeah, it's a really good question. I think the standard of care for a while had been fulvestrant alone or fulvestrant with everolimus or exemestane and everolimus. Everolimus was used a lot. Everolimus is generic now. It's been around for almost 15 or 20 years. A lot of us have gotten really used to it. The major side effect of that is stomatitis/mucositis, and so we give an oral mouthwash three to four times a day for the first month or two that someone's on everolimus. That was a standard of care.

But now, we have what I believe is going to become a new standard of care, which is getadolisib, which is this intravenous drug that's given day one, day eight, and day fifteen intravenously in combination with fulvestrant, with or without palbociclib. And again, the PFS here in these wild-type patients is about nine months or so, nine and a half, 10 months. And I think that, again, the biggest issue with this particular agent is, A, it has to be given weekly IV, and some people won't come in. It's a really easy infusion. There are no pre-meds. It's not like getting chemo. It's basically suspending the drug in D5 and infusing it over half an hour, just like getting an IV infusion of saline or something. There are really very few side effects to it. But on the other hand, the cumulative side effect tends to be stomatitis, and I think that people take steroid mouthwash four times a day for the first two months with this drug.

This is an area of active research. I think a lot of us are trying to figure out what to do with these patients who really don't have a directed therapy like an oral SERD or a PI3 kinase inhibitor. What can we really do for them, and what pathways are the ones that are the most concerning, in this particular tumor? That's really what it's about, I think. I've kind of come to the conclusion that what we're really trying to do when someone progresses on a CDK4/6 inhibitor in the first line is identify, what really is the mechanism of resistance? And the problem is that it's probably heterogeneous. The, the issue is that, sure, maybe it'll help it, but their cancer cells are pretty smart, and we'll figure out other ways around it. There'll be clones that have other mutations in them. So that's what we're trying to

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do with this, and especially in the patients that are clearly wild type for both. Some of us feel it's PI3 kinase/AKT/mTOR pathway overexpression. There's not a mutation driving it. And so that's why I think some of these combo therapies may work. But again, there's a lot of other therapies being tried like this.

Dr. May:
Before we wrap up, Dr. Brufsky, what's one key takeaway from our conversation that you hope our audience brings back to their practice?

Dr. Brufsky:
Clearly, just about everybody who progresses in the setting should have at least a liquid next-gen, if it's available. I think that's the most important thing here. Because again, 60 percent of the patients can have either ESR1 or PFIC mutation that you can direct therapy to. And I think the other major thing is that we now have this intravenous therapy with gedatolisib, and it's available now for the patients that are wild type for both of them.

Dr. May:
With those final thoughts in mind, I want to thank my guest, Dr. Adam Brufsky, for sharing his insights on next-line treatment choices after progression on a CDK4/6 inhibitor plus endocrine therapy. Dr. Brufsky, it was great having you on the program.

Dr. Brufsky:
Thanks a lot for having me, Dr. May.

Announcer:
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