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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

ESR1 Mutations in Metastatic Breast Cancer: A Predictor of Poor Prognosis

Announcer Introduction

You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Stemline, a Menarini Group company. Here's your host, Dr. Pavani Chalasani.

Dr. Chalasani:

Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and joining me to review key takeaways from a recent study focusing on ESR1 mutations in endocrine-treated breast cancer is Dr. Marcela Mazo Canola. She's an Assistant Professor in Breast Medical Oncology at UT Health San Antonio Mays Cancer Center. Dr. Mazo Canola, it's great to have you with us today.

Dr. Mazo Canola:

Thank you so much for the invitation. Happy to be here today.

Dr. Chalasani:

Now before we dive into the research, can you give us some background on ESR1 mutations in metastatic breast cancer?

Dr. Mazo Canola:

Yes, so we know breast cancer is a heterogeneous disease that has different clinical, histopathological, and molecular subtypes. However, we also know that about 70 percent of our patients have expression to estrogen receptor. So multiple studies in the clinical and experimental settings have established the role of the estrogen receptor pathway in tumor growth and creation of metastatic disease in patients with breast cancer. And we know that this estrogen receptor is encoded by the ESR1 gene. So this gene functions as a nuclear protein that is ligand dependent, meaning that when that estrogen comes in and stimulates the estrogen receptor, it down-streams a cascade of cell growth and cell division.

So ESR1 mutations were first described around 1996; in different cell models, they were able to identify some changes in the gene that caused that estrogen receptor to be activated by the presence or absence of the estrogen that stimulated that particular receptor. So we have learned with time that these mutations are extremely rare when patients are treatment naïve, and they tend to appear as we continue to suppress that estrogen pathway through the use of aromatase inhibitors or medications such as tamoxifen.

So now we have learned, thanks to different studies, that the ESR1 mutations can be present in about 40 percent of our patients that have progression after first-line endocrine therapy with CDK4/6 inhibitors in the metastatic setting. And we have also learned that those patients, unfortunately, when they develop these ESR1 mutations, tend to do worst, and they have a more aggressive disease.

Dr. Chalasani:

With that background in mind, let's turn our attention to the study. Can you kind of explain what were the methods used for examining or detecting ESR1 mutations?

Dr. Mazo Canola:

So we resource to the use of next-generation sequencing. So now we have basically two methodologies to do it; we have the option of doing next-generation sequencing on tissue biopsies, and we also now have the option of doing next-generation sequencing once we

gather circulating DNA from tumor cells. I will comment and say that the preferred method nowadays is to resource to the liquid biopsy; basically, it's just an IV poke that the patient goes through, we get those circulating tumor cells, and we're able to sequence them. It's faster, less invasive for our patients, reliable, and it gives us the answer that we're looking for.

I will also comment and say that I frequently get the question: is doing next-generation sequencing on archival tissue appropriate to look for this mutation? So as I mentioned before, these mutations tend to appear as we treat patients with aromatase inhibitor or anti-estrogen therapies more and more, so really doing the testing in archival tissue or in the first biopsy that the patient had when they were first diagnosed wouldn't be ideal as you lose the chance of finding the mutation because it just has not developed yet.

Dr. Chalasani:

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking with Dr. Marcela Mazo Canola about a recent study that examined the implications of ESR1 mutations in endocrine-treated breast cancer.

So, Dr. Mazo Canola, can you tell us what was found regarding the link between ESR1 mutations, endocrine resistance, and prognosis in published studies so far?

Dr. Mazo Canola:

Thank you for that question. So we have learned the clinical implications of these mutations thanks to the SoFEA trial and the EFECT trial. So there was a compound analysis of these two that was published in 2020. And basically, in these two trials, they compared patients with metastatic HR-positive HER2-negative breast cancer treated with either single-agent aromatase inhibitor, in this case it was exemestane, versus treatment with an injectable SERD, in this case fulvestrant. So they compared these groups of patients and looked actively for the development of ESR1 mutations. So in patients that had metastatic disease, they did ctDNA circulating tumor cells and in the ones that they identified the presence of ESR1 mutations. When they compared the progression-free survival and the overall survival, we learned that patients with tumors that have developed ESR1 mutations did much worse when they were treated with aromatase inhibitors when compared to fulvestrant.

These two trials paved the way to show us that when tumors develop ESR1 mutations, those patients are going to have a much inferior response to therapy with an aromatase inhibitor and an anti-estrogen therapy such as SERMs as well, such as tamoxifen.

Dr. Chalasani:

Now with that being said, how do these findings impact the way we approach taking care of patients with metastatic breast cancer?

Dr. Mazo Canola:

I will reference the PADA trial as a proof of concept to show us how these patients behave clinically differently. So the PADA-1 trial was a big phase 3 trial that enrolled more than 1,000 patients. And these patients were treated for a metastatic hormone receptor-positive HER2-negative breast cancer with standard-of-care therapy with CDK4/6 inhibitor, in this case it was palbociclib, with backbone endocrine therapy with an aromatase inhibitor. Patients enrolled in this trial basically were treated with this therapy, and they were checking proactively every 2 months for the development of the ESR1 mutations in their tumors.

So once they identified the presence of the ESR1 mutation in the tumor, they either stayed in the same arm of therapy with palbociclib plus an aromatase inhibitor or crossed in to continuing in the same CDK4/6 inhibitor and switching their backbone endocrine therapy to an injectable SERD, which in this case it was fulvestrant. And the conclusion of the trial was that patients that crossed over the treatment arm to have the fulvestrant when they had the presence of the ESR1 mutation in their tumor responded better to therapy.

So this basically shows that despite the success that we all know with the therapy with CDK4/6 inhibitor, that endocrine pathway still matters. And we have learned that patients whose tumors harbor that ESR1 mutation are going to do worse unless we kind of manipulate that endocrine pathway in a smarter way.

Dr. Chalasani:

Have there been any other recent updates looking at ESR1 mutations? Any newer therapies?

Dr. Mazo Canola:

Yes. So in San Antonio Breast in 2022, we were very excited to see the results of the EMERALD trial. So EMERALD was a phase 3 study that compared patients with a history of stage IV hormone receptor-positive HER2-negative metastatic breast cancer in patients that were treated with CDK4/6 inhibitor and a backbone endocrine therapy or the physician's choice after they progressed. They were randomized into a 1:1 basis to either receive elacestrant, which is an oral SERD, versus the physician's choice of backbone endocrine

therapy.

And in this trial, what they did is patients whose tumor harbored the ESR1 mutations, they did like a subgroup analysis for this specific population. And they were able to identify an improvement in progression-free survival for this patient population. I will also highlight that in EMERALD, we were able to see patients that before they were started on therapy with this oral SERD, if patients stayed on their prior CDK4/6 inhibitor with backbone endocrine therapy for the longest time, and the biggest benefit was seen at 12 months, those patients actually did better when they were started on therapy with an oral SERD.

So elacestrant was FDA approved in January of 2023, and we're very excited to see that we have this new therapy that we can use in patients whose tumors express ESR1 mutation because it gives us another option to attack this specific endocrine pathway and increase the life of our patients with a good quality of life.

I will also highlight that during EMERALD, the rate of adverse side effects to the therapy was actually pretty good, with patients having some nausea as the main side effect that was easily managed with taking the medication with food. They also reported some joint pain, but the rate of grade 3 and grade 4 toxicities was low. So we're happy to see that these therapies are very well tolerated by our patients.

Dr. Chalasani:

So given everything we discussed today, Dr. Mazo Canola, can you provide some final key points our audience can take with them?

Dr. Mazo Canola:

Yes, thank you so much for that question. So it's important to remember that we need to look for this specific mutation. ESR1 mutations are common, and they will happen as our patients have disease progression through their initial endocrine therapy. Remember that at the beginning, when patients are treatment-naïve, you're likely not going to find this mutation, but as patients have evidence of disease progression, about 40 percent of them might develop ESR1 mutations in their tumors, and you need to look for it.

Now we have the option of using a medication, an oral SERD called elacestrant, that was FDA approved for the treatment of patients whose tumors harbor this specific mutation.

And lastly, we're excited because we know that there might be some more oral SERDs coming our way in different settings. We're exploring analysis with combination therapy, such as CDK4/6 inhibitor, mTOR inhibitors, and PIK3CA inhibitors, and these agents may also come earlier in the disease process. And they're being explored in their use in patients after they have early-stage disease.

Dr. Chalasani:

Well, with those key takeaways in mind, I want to thank my guest, Dr. Marcela Mazo Canola, for joining me to talk about the recent findings and the clinical impacts of ESR1 mutations in patients with endocrine-resistant breast cancer. Dr. Mazo Canola, it was great having you on the program.

Dr. Mazo Canola:

Thank you so much for the invitation.

Announcer Close

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