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Treating Metastatic Breast Cancer After the First-Line Setting: What to Do Next?

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. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss how we can treat metastatic breast cancer after first-line therapy is Dr. Hope Rugo, who's a Professor of Medicine in the Division of Hematology and Oncology at the University of California San Francisco Hellen Diller Family Comprehensive Cancer Center.

So let's just dive right in, Dr. Rugo. What are the current second and third-line options for patients with metastatic breast cancer who progress after treatment with a CDK4/6 inhibitor?

Dr. Rugo:
In the second-line setting, we have a host of different options. First and most importantly, we need to evaluate any potential mutations that we can target. So next generation sequencing, usually in the form of a so-called liquid biopsy or circulating tumor DNA, is performed. So we're analyzing for specific mutations that we can target. In this situation, I think we're learning a lot more as we go forward, and there is a whole host of options, which we'll expand on even further. But in patients who have PIK3CA mutations in their tumors, there is the alpha-specific PI3 kinase inhibitor, alpelisib, that can be given with fulvestrant.

For patients who don't have a mutation, there are a number of options, including fulvestrant alone and fulvestrant or even exemestane with everolimus, the mTOR inhibitor.

Recently, we've understood that mutations in the estrogen receptor called ESR1 reduced the responsiveness rather remarkably to aromatase inhibitors so that we wouldn't use exemestane after a nonsteroidal aromatase inhibitor in a patient whose tumor had an ESR1 mutation.

Then there's been a lot of interest because we knew that fulvestrant was better than the nonsteroidal AI exemestane based on the combined data from two trials. But then the next question was whether or not we could find something superior to that. And there's a lot of work going on now looking at oral selective estrogen receptor down-regulators or agents that work on changing the estrogen receptor in some way. There are a number of different agents out there that work and with different mechanisms.

And data from a phase 3 trial, the EMERALD trial, has shown that the oral SERD, elacestrant, was superior to fulvestrant for progression-free survival, and even more so in patients who had endocrine-sensitive disease measured by the duration of time that they'd been on a CDK4/6 inhibitor compared to fulvestrant. So elacestrant was recently approved by the U.S. FDA in patients whose tumors do harbor these ESR1 mutations. And one thing I think that's very helpful here is that we already thought that doing next generation sequencing after progression on first-line endocrine therapy in a CDK4/6 inhibitor was important to identify the PIK3CA mutations. And now we're also going to be using this routinely to identify ESR1 mutations that will help us choose specific therapies.

Dr. Turck:
With that in mind, would you tell us what guidelines are available to help direct therapeutic selection in the second and third-line settings?

Dr. Rugo:

So currently, the guidelines have been updated to include elacestrant, the most recently approved agent to treat patients in the second- and third-line setting. And this includes patients who have ESR1 mutations really mimicking the FDA approval. And so that's one alternative for patients whose tumors have the ESR1 mutations. And the guidelines otherwise follow the discussion I had about different options for treatments in this setting.

One thing I will say about the guidelines is that the guidelines in general recommend that we use sequential endocrine therapy with or without a targeted agent for as long as it's reasonable to expect that therapy to work. So we don't want to jump to chemotherapy in the second-line setting or first-line setting in patients who can potentially use endocrine therapy for their treatment.

Dr. Turck:
And how about clinical data? What are some of the key trials that can help inform our treatment selection?

Dr. Rugo:
All of the randomized phase 3 trials are helpful, but we don't really have sequencing trials to tell us that one sequence is better than another. For example, we do have of course trials like the EMERALD trial that showed the benefit of elacestrant in a subpopulation of patients in particular who've had some response to CDK4/6 inhibitors with endocrine therapy and whose tumors have an ESR1 mutation. We know that alpelisib is effective in patients whose tumors have PIK3CA mutations. Capivasertib is active in patients who have alterations of the AKT pathway, but also seems to be active in patients whose tumors are wild-type for AKT, mTOR, and PIK3CA. So that's really interesting and requires a little bit more analysis, but fascinating data.

And then we, of course, are looking at other agents. Everolimus, based on the BOLERO-2 trial, we didn't find any difference in efficacy based on mutations, but these were older data, so we don't really know it present. But the guidelines do incorporate the understanding of these mutations in terms of recommending particular treatment paths.

Dr. Turck:
So based on your experience, Dr. Rugo, what factors do you consider when selecting an approach after treatment with a CDK4/6 inhibitor has failed?

Dr. Rugo:
The next part of the decision making has to do with the overall functional status of the patient, how easy it is for them to take medication, and the cost of the medication in terms of share of costs, particularly for Medicare patients. And then of course, if they have diabetes that's poorly controlled, alpelisib is not going to be a good option for them. If they've had prior pneumonitis, drugs like alpelisib and everolimus won't be good options. So you really have to individualize the treatment choices based on the patient in front of you.

Dr. Turck:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Hope Rugo about the second and third-line treatment of metastatic breast cancer.

Dr. Turck:
So Dr. Rugo, earlier we discussed some key considerations around current second and third-line treatment options, but now let's look ahead for a moment. What are some emerging therapeutic options we should keep an eye on?

Dr. Rugo:
This whole host of different oral SERDs are really important, and PROTACs, CIRCAs, etcetera. There's like a bunch of different agents and the way they work on the estrogen receptor. And this is a really exciting pathway, I think, to try and create change and have better tolerability for patients and better responses. And so far, it does seem like it is more effective to use these agents in patients who have ESR1 mutations, but we'll see with the larger datasets. I think that I'm excited about combining the oral SERDs with our known targeted agents. So that's a really important area of investigation. We have new agents that block PIK3CA, so the patients whose tumors have PIK3CA mutations, and these drugs block PI3 kinase, so the pathway, and there are some that cross the blood-brain barrier, some that may have less toxicity. And then I think the emerging data on capivasertib from which we expect approval later in 2023 is also really exciting because we'll have yet another targeted agent there.

Dr. Turck:
Now we've certainly covered a lot of ground today, Dr. Rugo, but before we close, do you have any key takeaways you'd like to share with our audience?

Dr. Rugo:
I think the key takeaways are really important. One is that we have an emerging sequence of very active endocrine therapies that can be combined in some settings with targeted agents. We can use next generation sequencing to determine the most appropriate therapies

for patients, looking for the presence of ESR1 mutations PIK3CA mutations, and others that may help us determine what the best treatment strategy is for an individual patient, getting us closer to personalized therapy. The international guidelines, and in the U.S., the NCCN guidelines in particular, are updated every time a new dataset comes out, and every time the FDA approves a new agent or changes, for example, the recommendations for approval, which has happened recently as well. So those guidelines can really help direct you in terms of sequencing and understanding the benefit of different options for your patients. But most excitingly, having more options makes a really big difference to our patients.

Dr. Turck:
Well with those final takeaways in mind, I want to thank my guest, Dr. Hope Rugo, for joining me to discuss treatment strategies for metastatic breast cancer after first-line therapy. Dr. Rugo, it was great having you on the program.

Dr. Rugo:
It was great to talk with you, and I really appreciate our audience as well for listening in.

Announcer Close:
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