Podcast series Title: BREAST CANCER CONNECT PODCAST 2

TITLE: Oral SERDs in ER+ Breast Cancer

Podcast Episode Title: Treatment Selection & Beyond

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Tonke de Jong
Welcome and thank you for listening to this podcast from COR2ED Independent Medical Education. In this episode, the second of a three podcast series, you will hear from internationally renowned experts Dr. Shaheenah Dawood and Dr. Rena Callahan as they discuss oral SERDs, a novel therapy for ER+/HER2- advanced or metastatic breast cancer. The experts take a close look at two patient case studies and discuss strategies to optimise treatment selection and sequencing decisions.

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represent the views of the experts' organisations or the rest of the BREAST CANCER CONNECT Group. For expert disclosures on any conflict of interest, please visit the COR2ED website. Now, with that being said, let's get started.

Dr. Shaheenah Dawood Hello, all. I am Dr. Shaheenah Dawood, a consultant medical oncologist and professor of oncology at Mediclinic City Hospital in the United Arab Emirates in Dubai. I am delighted to be joined again today for our second podcast of the series by Dr. Rena Callahan, an associate clinical professor of haematology oncology at the University of California, Los Angeles. David Geffen School of Medicine.

Dr. Rena Callahan Thank you, Dr. Dawood. It's a pleasure to join you today for the next episode of our series ocusing on new oral endocrine therapy options for patients with estrogen receptor positive HER2 negative, advanced or metastatic breast cancer. In this podcast, we will explore two patient case studies delving into the intricacies of treatment selection and sequencing to maximise outcomes.

Dr. Shaheenah Dawood
I'm thrilled to begin this podcast. Today we will examine real life cases to address the challenges faced by health care professionals and patients. Through these discussions, we aim to enhance our understanding and ultimately improve patient outcomes. So without further ado, let's dive straight into it. Our first patient is a 63 year old postmenopausal woman diagnosed with stage four de novo ER+/HER2- metastatic breast cancer. Two years ago, at the age of 61, she presented with a three centimetre invasive ductal carcinoma in her left breast, characterised by 90% ER positivity staining and zero staining for HER2. Upon further evaluation, a CT scan confirmed the presence of lung metastases, highlighting the extent of disease dissemination beyond the primary site. The patient's treatment journey began with first line therapy consisting of letrozole, an aromatase inhibitor, in combination with ribociclib, a CDK4/6 inhibitor. This regimen was selected based on its proven efficacy in ER+/HER2- metastatic breast cancer. After 24 months during routine follow up, a CT scan revealed enlargement of existing lung lesions and the appearance of the new 1.5 centimetre liver lesion. Now, based on this case study, my first question to you, Dr. Callahan, is what factors should be considered when deciding between continuing the current treatment regimen with modification versus switching to a different treatment approach altogether?

Dr. Rena Callahan Thank you for that question, Dr. Dawood. This is certainly a very interesting case. As you said in the first episode, there is an art to the individualisation of therapy. So there are several factors we need to take into consideration and the approach is very case and patient specific. Generally, assessing the response to the current treatment is crucial. We need to determine if there has been any improvement or disease stabilisation. Additionally, evaluating disease progression and tumour burden is essential in guiding treatment decisions. Another crucial aspect is assessing treatment related toxicities and determining if dose modifications can effectively address them. Patients have preferences and they need to be taken into consideration. Their quality of life should not be overlooked.

This is where shared decision making plays a significant role. Different patients have different preferences, values and treatment goals, and we need to discuss these and assess the impact of the current treatment on their quality of life to determine if modifying the regimen or switching to a different approach would better suit their overall well-being. In the case of this specific patient, I would take several things into consideration. She is postmenopausal. She had done quite well on her therapy with letrozole and ribociclib. She had been on this first line therapy for two years, so duration of therapy with progression free survival on CDK4/6 inhibitor can be useful in determining what our next line of therapy is. And then, you know, we have to look at how this disease progression was discovered. She's essentially asymptomatic. This was found on routine imaging, and we found this 1.5 centimetre liver lesion. So it is definitely disease progression. It's definitive disease progression. And I absolutely think that a switch in therapy is needed. But she is asymptomatic. She's certainly not in visceral crisis. So we have a lot of options. And in this case, I would want to maximise her time with a good quality of life on endocrine based treatment prior to switching to chemotherapy.

Dr. Shaheenah Dawood Thank you for your answer, Dr. Callahan. Now, beyond the identified disease progression, how can the use of liquid biopsy and ctDNA testing contribute to treatment decisions and personalise the approach for this particular patient?

Dr. Rena Callahan Liquid biopsy and ctDNA testing offer valuable insights into potential resistance mechanisms. She had been on an aromatase inhibitor for a while so what happened when she developed disease progression? One thing that could have happened is the development of an ESR1 mutation. As per the recent 2023 ASCO guidelines, testing should be conducted upon progression on or after aromatase inhibitor therapy, irrespective of CDK4/6 inhibitor treatment. Therefore, I would definitely recommend a liquid biopsy for this patient. A question to you then, Dr.Dawood, considering the presence of an ESR1 mutation in this patient and based on her prior treatment lines, what are your treatment recommendations?

Dr. Shaheenah Dawood Thank you. I think that's an excellent question because as you know, in the presence of an ESR1 mutation, we do have the opportunity to give oral SERDs. Now, what's really interesting about this particular case, like you've highlighted before, number one, she's been on combination endocrine therapy with a CDK4/6 inhibitor and aromatase inhibitor for two years. Now when you go back to the subgroup analysis of the EMERALD trial those patients with an ESR1 mutation and who had been on a prior CDK4/6 inhibitor for more months, benefit more from the use of oral SERDs in the form of elacestrant. Now, I echo your thoughts here. If the patient is not in visceral crisis, we need to maximise our endocrine therapy options. So in the presence of an ESR1 mutation and the fact that she had such a good run with the CDK4/6 inhibitor, she would probably benefit now from the use of an oral SERD.

Dr. Rena Callahan Yeah, I absolutely agree. And thank you for your insights, Dr. Dawood. Now let's, let's change the case a little bit. What about if she didn't have an ESR1 mutation, How would you approach this treatment change in this setting?

Dr. Shaheenah Dawood So that's what makes treating patients with ER positive disease so exciting in 2023, because we have other targets to test. Well, I would test certainly for the presence of a PIK3CA mutation. We know that data from the SOLAR-1 trial did show us that patients, when given a combination of alpelisib plus fulvestrant, there's an improvement in progression free survival and a clinically significant, maybe not statistically significant, but a clinically significant improvement in overall survival. Even in the presence of visceral crisis. We need to be looking at other targets, such as the presence of a BRCA mutation or a PALB2 mutation, where a PARP inhibitor has been shown to be efficacious. We need to look at those other agnostic markers, such as an acquired pathogenic HER2 mutation or an NTRK fusion or an MSI-high status in these patients because we know that they are therapeutic agents, they can actually benefit these patients in the presence of those targets. Now you do have a subgroup of patients that will not have any targets. And I think the question as a community oncologist that we ask ourselves is, number one, are we going to use a CDK4/6 inhibitor beyond progression of disease? Well we have three clinical trials that have been presented, all phase two that have actually looked at this question of CDK4/6 inhibitor, beyond CDK4/6 inhibitor, we have the MAINTAIN trial, the PACE trial and the recently presented PALMIRA study that was presented ASCO 2023. I'm not going to go into the details of these three studies, but suffice to say I think it's still a matter of debate as to whether you can give a CDK4/6 inhibitor beyond progression of disease. The second option or the second route that you could potentially take is to give a combination of fulvestrant and everolimus as per the PrECOG data that we have, or perhaps just giving an endocrine therapeutic agent like fulvestrant alone. So I think there are a lot of options and of course we need to have those discussions with our patients highlighting the pros and cons of each option and have a shared decision making process with our patients.

Dr. Rena Callahan Thank you. Dr. Dawood. So, you know, this has been a fascinating discussion of this first case, but let's now shift our focus to a new case that presents a different set of challenges. Our next patient is a 40 year old premenopausal woman diagnosed with de novo metastatic ER+/HER2- breast cancer at the age of 34. She has undergone three lines of endocrine therapy with varying treatment durations and disease progression observation. Her first line therapy was with ribociclib, letrozole and goserelin. She was on this for 18 months prior to disease progression. At that time, she had liquid biopsy, ctDNA testing and there were no detectable mutations found. So she was placed on second line therapy with fulvestrant and goserelin. So fulvestrant single agent. She was actually on this for three years prior to disease progression, so she did great. At that time had liquid biopsy, ctDNA testing, again, no detectable mutations. Her third line therapy was exemestane, everolimus and continued the ovarian suppression with goserelin because she was so young. She was on this for 24 months, then developed disease progression, this time with a few liver mets, though not in visceral crisis. She had liquid biopsy, ctDNA testing done

again. And then at this time, you know third try, she was found to have an ESR1 mutation. So what do you think?

Dr. Shaheenah Dawood Well, the first thing that I think is this is why it's exciting to treat patients with ER+/HER2- metastatic breast cancer, because this case simply highlights how well patients are doing. When you're sequencing endocrine therapy and trying to maximise their options, but indeed, compared to the first patient case, this second case study is obviously more complex due to the extensive treatment history and progression through multiple lines of therapy resulting in a heavily pre-treated status. Now you did mention that she had a few liver mets, but my first question to you, Dr. Callahan, is does this site of disease matter in terms of determining the next steps in therapy? And how does the disease burden actually influence your choice? You mentioned visceral crisis. If you could just elaborate on that a little bit more.

Dr. Rena Callahan Absolutely. An excellent question, Dr. Dawood. So I think it's important to differentiate between visceral metastases and visceral crisis. So this patient has a few liver metastases, asymptomatic. She does not have significant abnormalities in her liver function tests. So it is not essential at this point to have a response. You know, a response would be great, but sometimes stable disease is good enough. And there have been a variety of studies that have demonstrated patients with stable disease who have achieved the same survival as patients who had a response. So disease burden absolutely matters. She's not in visceral crisis. I think, I think for her, we have the opportunity to use, you know, yet another line of endocrine based treatment. Now that we have elacestrant, which is approved for patients with ESR1 mutations, I think she'd be a great candidate for this. In the EMERALD trial, over 70% of patients did have liver metastases. So I think she does fall into this group of patients and it is an appropriate treatment option for her. You know, she'd been on endocrine based therapy for a very long period of time. Probably had a good quality of life during that period of time. And I'm not excited to put her on chemotherapy and especially IV chemotherapy, which is a real game changer in terms of her day to day life.

Dr. Shaheenah Dawood Absolutely. And I love your insights. I echo your thoughts on the fact that when a patient is not in visceral crisis, maximise endocrine therapeutic options for your patient. I think there's also the other angle when your patient has stable disease or even oligoprogression, there is the opportunity to offer some local therapy while continuing the same endocrine therapy option that your patient is on. Now, I would like to pose a question to you, Dr. Callahan, regarding the use of liquid biopsy in this case. As you can see, at each step in her treatment and whenever she progressed in her disease, there was a liquid biopsy that was done. The patient underwent liquid biopsy at each progression. Would you have done the same? And what factors influences your choice between a liquid biopsy and a tissue biopsy?

Dr. Rena Callahan I definitely would have done the same thing. You increase your yield. So, first of all, you know, one of the things that we're looking for in the liquid biopsy is the presence of an ESR1 resistance mutation to aromatase inhibitor. So patients need to have

been on an aromatase inhibitor to pick up these mutations. When you look at first line, even if someone had been on an aromatase inhibitor in the adjuvant setting, you're really, you know, only getting under 5% of patients who are going to have these ESR1 mutations. So this patient did not have it at that time. You know, interestingly, even though she was on aromatase inhibitor for 18 months prior to disease progression, when second line therapy was being considered, she appropriately had a liquid biopsy and again did not have an ESR1 mutation. But finally, third line, when it was time to move on to third line, that's when she had an ESR1 mutation. So you increase your yield, you're going to pick up additional patients with these mutations if you test more. So then we come to the question of liquid versus tissue biopsy. You know, tissue biopsy is very specific to the tissue involved. Many of our patients have bone only disease progression. We know that those biopsies are often not reflective of the true biology of a patient's cancer. And so you may miss mutations if you try to do a tissue biopsy with the bone biopsy. And there is also disease heterogeneity. So you may miss additional patients who have ESR1 mutations that may help them. And so I think this is why the guidelines are, as they are, that recommend a liquid biopsy. It's quick, it's easy. You get your answer very, very quickly. So now, considering this patient's ESR1 mutation status in previous lines of therapy, would you consider oral SERDs as the next line of therapy? And does your approach to treatment differ between premenopausal and postmenopausal patients?

Dr. Shaheenah Dawood Thank you for an excellent question. Let me answer the second part of that question first. For me, when a patient has metastatic breast cancer, I honestly do not differentiate between a pre and postmenopausal woman because a premenopausal woman has to be rendered post-menopausal in the treatment of their metastatic breast cancer, as has been done for this particular patient with ovarian function suppression. So I think whatever treatment options you consider for your postmenopausal patient, you can very reasonably consider it for your premenopausal patient who has been rendered postmenopausal. Now, how would I use other therapy options irrespective of pre or postmenopausal? Well, when I'm considering the use of an oral SERD in a heavily pre-treated patient such as this, such as this particular patient, I will obviously have to look at various variables. Is the patient in visceral crisis or not? If the patient's in visceral crisis, that patient would get chemotherapy. Is the patient in good performance status or not? And the disease burden in general, when patients are such as this patient not in visceral crisis and even in the presence of visceral metastases, but the tumour burden is not that heavy. So they're not going to tip over into visceral crisis very soon. I would very reasonably consider using an oral SERD, such as elacestrant, in the presence of an ESR1 mutation, despite the fact that this patient is heavily pre-treated. We need to maximise our options with the use of endocrine therapy in these sorts of patients.

Dr. Rena Callahan Thank you for your input, Dr. Dawood. Finally, assuming oral SERDs are not immediately available and the patient does receive first line chemotherapy, would you consider oral SERDs as a maintenance therapy or therapy after chemotherapy?

Dr. Shaheenah Dawood Thank you for that question. This is a very practical question that we are going to face in the clinic on a daily basis. So let me tell you that pre oral SERDs era when we had patients who were in visceral crises at the time of presentation with endocrine sensitive disease, we gave them chemotherapy and then we maintained them on endocrine therapy and a CDK4/6 inhibitor. This is what we do for patients. So if this particular patient had for some reason or the other received chemotherapy, either because oral SERD was not available immediately or was in visceral crisis and needed chemotherapy to get over that episode. I would certainly consider using an oral SERD as maintenance therapy so long as that patient has an ESR1 mutation.

Dr. Rena Callahan Yes, Dr. Dawood, I completely agree. And just, you know, note that in the EMERALD trial, there were patients that had prior chemotherapy. So it's certainly supported by data. So this has been a great discussion. You know, thanks for sharing your insights and thoughtful responses to these really challenging questions. And here we are now at the end of our podcast. For today's clinical takeaways we suggest the following for patients with ER+/HER2- advanced or metastatic breast cancer. When deciding whether to adjust the current treatment dosage or switch therapies, it is essential to consider various factors including disease progression, tumour burden, treatment-related toxicities, patient preferences, and quality of life. Additionally, it is recommended to maximise endocrine therapy options for patients without visceral crisis. It should also be noted that current phase III data do not confirm the benefits of CDK4/6i beyond disease progression after prior CDK treatment and that further investigation is necessary to determine the optimal approach. Finally, duration of progression free survival on CDK4/6i therapy can help guide sequencing decisions. For oral SERDs, specifically elacestrant, patients who received prior CDK4/6i treatment for longer duration derived the greatest benefit. We hope our audience finds this information helpful in their clinical practice.

Dr. Shaheenah Dawood Dr. Callahan, It has been a great pleasure to discuss with you today and participate in this podcast. I look forward to our next podcast together where we will have an exciting opportunity to discuss the next two patient case studies and explore further treatment options and considerations according to each case. I'm confident our audience will find it valuable. Thank you all for listening.

Dr. Rena Callahan Absolutely. Thank you to everyone who joined us today. It has been a pleasure discussing these important topics with you, Dr. Dawood. I look forward to our next podcast and continuing the exploration of these very challenging cases. Until then, take care and see you next time.

Tonke de Jong
We hope you found this podcast informative and enjoyable. If you like this episode, you should look on the COR2ED medical education channel for more. In particular, you can find the first podcast of the series where Dr. Callahan and Dr. Dawood discuss oral SERDs, efficacy, safety and place in the treatment landscape. Also keep an eye out for our last podcast of the series where the experts will present the next two patient case studies with

ER+/HER2- advanced or metastatic breast cancer, and once again delve into the intricacies of treatment selection and sequencing to maximise outcome. Don't forget to rate this episode on the COR2ED website and share our podcast on social media or maybe with your colleagues. Thanks for listening and see you next time.

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