De-escalating Breast Cancer Surgery
With Neoadjuvant Endocrine Therapy
Dr. Susan K. Boolbol and Dr. Christy Russell
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Transcript:

Dr. Russell**:** Greetings everybody, and welcome to our presentation today, titled De-escalating Breast Cancer Surgery with Neoadjuvant Endocrine Therapy. I'm going to be doing this symposium today with Dr. Susan Boolbol, who's at the Dyson Breast Center at Nuvance Health. And, I'm Christy Russell, I'm the Senior Director of Oncology Medical Affairs at Exact Sciences. So, just so you can see our titles here, and Susan's lovely picture, but Susan's title is System Chief at the Breast Surgical Oncology and the Breast Program at Nuvance Health.

So, just some disclosures, this presentation is sponsored by Exact Sciences and Dr. Boolbol is a paid speaker on behalf of Exact Sciences for this symposium. And of course, I am an employee of Exact Sciences, so I clearly have a conflict of interest or a bias in some of these conversations. The educational content being presented today focuses on the use of the Oncotype DX Breast Recurrence Score test from Exact Sciences, formerly Genomic Health, in accordance with the legitimate use of the product as defined by the company. So, these are disclosures that we're being asked, I think routinely now, to talk about as part of any product theater. The information that we're providing, however, is not treatment advice for any individual patient. We're not going to address any questions of how should I treat my patient. And, as always, physicians and healthcare practitioners should use their clinical judgement and experience when deciding how to diagnose or treat patients. If you have any questions about the Oncotype Breast Score, you can visit the OncotypeIQ.com website and again, we are not going to be making any particular recommendations for course of therapy. However, Susan, I will be asking you some questions about how you would think about patients and how you would treat them and if you would speak to that.

Dr. Boolbol: Yeah, first, I think I may ask you more questions than you ask me, which is my norm. But, my views that I'm expressing are really my own and not that of the company, especially when we're talking about patient care.

Dr. Russell: Thank you, Susan. All right, so let me start to talk about what we're going to do. Susan and I are going to be presenting some didactics, but we're going to talk conversationally a lot through this presentation. Susan's warned me she may interrupt anything I'm saying to make a certain point. But, in addition, we have some polling questions that you'll be instructed through your Zoom on how to answer them, and we're just going to try to make this very interactive. And, the reason why we're doing this presentation specifically is the issue of neoadjuvant therapy. And, in hormone receptor-positive, HER2/neu-negative breast cancer, I think the question still is what endpoints are we looking at? And, when we're going to offer someone neoadjuvant therapy, what are you expecting to find at the end of that therapy, especially for that group of patients which are the majority of breast cancer hormone receptor-positive and HER2/neu-negative.

So, we'll start with just overall objectives for neoadjuvant therapy for breast cancer, and we're going to talk about neoadjuvant chemo, and then we're going to talk about neoadjuvant endocrine therapy. But, overall, when we think about the trials that have been conducted that have looked at giving a patient neoadjuvant chemotherapy or using that same chemotherapy in the adjuvant setting, there is no survival advantage that's been seen for any of those trials. However, we know that especially for triple-negative breast cancer and for HER2-positive subtypes, pathologic complete response, or PCR, to neoadjuvant chemotherapy is a significant prognostic signal.

So, I think there are two big benefits, or groups of benefits that we can think about if you're going to use neoadjuvant chemotherapy for a patient. One is a surgical benefit, and we'll be talking about this, about surgical endpoints, and especially with Susan, as such an accomplished breast surgeon, how she views these outcomes that we're reaching for patients. But, we do know that in many of the trials, when they look at patients who do not seem to be eligible for breast conserving surgery, that neoadjuvant chemotherapy, and we'll talk about the trials for neoadjuvant endocrine therapy, can increase the opportunity to perform breast conserving surgery, and in some cases reduce the need for full axillary lymph node dissection in patients who initially were clinically lymph node-negative, or clinically lymph node-positive.

We also know now that there are data for patients who have triple negative breast cancer, or who are HER2-positive breast cancer, for whom they get their appropriate neoadjuvant

chemotherapy, in the case of the HER2-positive with trastuzumab and perhaps pertuzumab, but that if they do not achieve a pathologic complete response rate, we know that they have a worse prognosis, and if you offer them subsequent therapy based on trials, you can improve their prognosis again, specifically the CREATE-X trial for the triple negative patients and the KATHERINE trial for the HER2-positive patients, following through with T-DM1. What we don't know, however, for hormone receptor-positive, HER2/neu-negative breast cancers, is if you don't achieve a PCR, and it's overwhelmingly likely that you won't, what is the next thing you're going to do after you take that patient to surgery? And, we would just like to discuss these data as we go along.

So, when we look at a couple of endpoints, and these are specifically data around giving neoadjuvant chemotherapy, if you look on the data on the left, in the ACOSOG Z1071 trial, by the tumor types, for patients who are hormone receptor-positive and HER2/neu-negative, that's the lighter orange, if you're looking for pathologic complete response in the breast, you can see that the chance of that happening with neoadjuvant chemotherapy in an unselected population is very low compared to either the HER2-positive patients getting appropriate therapy or the triple negative patients. So, if you're looking for pCR as your endpoint, that's unlikely to happen, even with optimal therapy. To the right here, in the middle, are the ability to achieve breast-conserving surgery based on the biomarker type. And again, those patients who are hormone receptor-positive, HER2-negative are the least likely with neoadjuvant chemotherapy, again unselected population, to be able to achieve that, and clearly a much better response in the breast to the appropriate therapy for triple negative or HER2-positive. On the right-hand… yes, Susan?

Dr. Boolbol: Just going back to that for breast-conserving surgery, the reality is that is a subjective finding.

Dr. Russell: Yes.

Dr. Boolbol: It really is not an objective finding, and what one surgeon thinks that a patient can have breast-conserving surgery, another surgeon may say no, I really don't think that the tumor:breast ratio is favorable. So, that really is subjective. And really, the esthetic outcome is a subjective thing, also. What I may say to a patient that I don't think that she can have breast-conserving surgery because of the esthetic outcome, another surgeon may think of that quite differently. And, in the era of oncoplastic surgery, I really think it changes it. So, these studies,

we do have to realize it's great data, it's great that we have it, but it's subjective information.

Dr. Russell: I agree with that, and I think that it's not only the perception of the surgeon, as you know, and what they view as an optimal outcome, but of course the patient has influence here as well. They want to avoid full mastectomy for whatever reason, maybe be willing to have an esthetic outcome that we would not find to be optimal, but is certainly satisfactory to them.

Dr. Boolbol: And, the interesting question on that is, is it satisfactory in the short-term?

Dr. Russell: Yeah.

Dr. Boolbol: But, is that still satisfactory in the long-term, where ten years later, they are doing great, but every day that they look at their breast, they're reminded of the fact that they have breast cancer because it's such a poor esthetic outcome?

Dr. Russell: I agree.

Dr. Boolbol: So, are they still satisfied in the long-term? Because, short-term, all they do is want this cancer out.

Dr. Russell: Yeah.

Dr. Boolbol: And they say and how, you know, for the surgeons, we've all heard it over and over again, I don't care what my breast looks like and I'm happy to say I completely understand that today that's your feeling, but in three years, five years, ten years -

Dr. Russell: Right.

Dr. Boolbol: - is that still your feeling?

Dr. Russell: Especially with the long-term effect of radiation, as well, in a contracted breast, right. I agree. I think on the right-hand side is another somewhat subjective question, or I think a little bit of a data-free zone, is you have a patient who is clinically node-negative, or even clinically node-positive. Do you have the opportunity to avoid an axillary lymph node dissection? This is from a Memorial Sloan Kettering cohort, looking at different biomarker subtypes. I think the major point of this grouping over here to the right is that the hormone receptor-positive, HER2/neu-negative patients are the least likely to have an adequate outcome in the axilla, where you would be comfortable in just doing a sentinel lymph node biopsy, for example, or going after a clipped node and anticipating the node to be negative, much more likely to be able to clear the axilla in a triple negative or a HER2-positive patient.

Dr. Boolbol: And again, I think that – just going back to that slide -

Dr. Russell: Yeah.

Dr. Boolbol: - what avoiding an ax node dissection really means. And, in this study, they did an ax node dissection for macromets, micromets, but also ITCs if the patient had neoadjuvant chemo. I'm not sure that today, in 2021, that everyone would agree with that criteria and follow along in that same path. So, we know that many, many surgeons for even after neoadjuvant chemo, doing a central node, if there's still a central node that's positive, many will radiate even though that's extrapolating the data, but that is the real world, what goes on.

Dr. Russell: Right. I think that's a real moving target as we're waiting for some of the large phase III trials to be more definitive at this point.

So, I just… we're going to go through a couple of endpoints that we're seeing in the neoadjuvant trials, and have in mind not so much the triple negative or the HER2-positives, but really the hormone receptor-positive, HER2-negative patients, and we'll talk about unselected patients, but then we can talk about genomic assays and try to hone down and be more selective. So, one is pathologic complete response rate, which we are so used to when we're describing triple negative or HER2-positive, and the question is, is this really an optimal endpoint when you're looking at the hormone receptor-positive? These are data from a meta-analysis, but large… several groups of trials where they looked at patients who had neoadjuvant chemotherapy and their event-free survival. And, if you look at the first five years or so, on the left are patients, they're all hormone receptor-positive, HER2/neu-negative. And the red are those who achieved a pathologic complete response rate; blue is something less than pCR. And, you can see if a patient is grade 1 or 2, you don't get separation of these curves. There's no difference in event-free survival.

On the right-hand side are those patients who are grade 3, and you do see pretty early separation in terms of long-term outcomes. So, much less of an issue of pCR helping you think about less breast surgery. This is pCR looking at long-term outcomes, or long-term prognosis. So, for these data at least, for patients who are hormone receptor-positive, HER2/neu-negative, there's a signal that grade may be influencing the long-term prognosis if you get a pCR. But, in the huge majority of cases, we don't get grade 3 hormone receptor-positive, HER2/neu-negative breast cancers. And, in the huge number of cases, whether you get a pCR or not, it's not a signal for that patient that she's going to have a worse outcome, and I think we need to remember that if

you, you know, that you don't just keep giving that patient chemotherapy because you didn't achieve a pCR. And so, when we look at -

Dr. Boolbol: Also, in that -

Dr. Russell: Yeah.

Dr. Boolbol: - just going back, with that slide, it's… in the grade 3, not only do we see that response, that difference early, but it really carries through late, which really is what we're going for. We don't want to see the improvement early; we want to see the long-term improvement here.

Dr. Russell: Agreed. So, if we look at the pCR and the chances of developing a pCR to neoadjuvant chemotherapy, you can see in red the group we were just talking about, hormone receptor-positive, HER2/neu-negative, pCR rate, at least in this larger trial, so almost 2,000 patients, all new is at 7.5 percent. But, that 7.5 percent, those patients did as well whether they achieved pCR or not, at least up to five years. And, for those who were grade three, you can see the higher chance of developing a pCR, but still both of those are quite low compared to hormone receptor-positive, whether HER2-positive or HER2-positive, hormone receptor-negative or triple negative. And, I think we really recognize the group who is overwhelmingly more likely to achieve a pCR are those who are HER2-positive and hormone receptor-negative.

So, that's pCR, right? So, maybe not the best outcome for patients who are hormone receptor-positive, HER2-neu-negative, and if that's what you're looking for, in an overwhelmingly large amount of time, you're going to be quite disappointed. And so, the question is how do we guide physicians? How do we guide ourselves and patients in terms of what to anticipate as we're using these neoadjuvant therapies?

So, let's talk about a couple more endpoints. There are some trials that have looked at… so, clinical response, right? There are some trials that have tried to look at randomizing the patients to neoadjuvant chemotherapy versus neoadjuvant endocrine therapy. This is an older trial, you can see, published in 2007, but it was a small, you know, randomized trial for postmenopausal women who were fairly higher clinical stage, hormone receptor-positive, no commentary about HER2 because we weren't routinely testing it in the early breast cancer setting in the mid-2000s, and they were randomly assigned to neoadjuvant chemotherapy versus neoadjuvant endocrine therapy.

Now, on the right-hand side, you can see what the clinical responses were, and although I think our knee-jerk, especially in the US, is to use neoadjuvant chemotherapy if we're going to. In this case, the clinical response wasn't different between the two. There's a little bit difference perhaps in the breast-conserving surgery, a little less than the neoadjuvant chemotherapy, but again, as Susan said, this is quite subjective as to when you're offering that to patients. And, very, very little disease progression, whether you use neoadjuvant chemo or neoadjuvant endocrine therapy. And, unfortunately -

Dr. Boolbol: And 9 percent… 9 percent of disease progression is real. I mean, in my practice, we do a lot of neoadjuvant and thankfully, we do not see 9 percent disease progression, whether we're doing neoadjuvant chemo or neoadjuvant endocrine. Maybe it's we're figuring out the correct treatment because of genomic assays, but 9 percent I think is a high disease progression rate. Is that what you are used to seeing in practice?

Dr. Russell: No, I would say it feels like… that also feels high to me, but Susan, I think, you know, this is probably a more unselected population.

Dr. Boolbol: Right.

Dr. Russell: And, as you say, whether you're using a genomic assay or not, you're probably using other biomarkers as well to try to guide you as to, you know, where you think that patient might benefit, whether you're using chemotherapy or endocrine therapy. But, we will talk about the TansNEOS trial, which is neoadjuvant endocrine therapy, where with the oncotype score, there was a larger disease progression for certain groups. So, I think we're all getting smarter in how to think about these patients, but we'll talk about that in a short period of time.

So, the Semiglazov trial is not the only trial that tried to do this kind of randomization. That's the largest of them, with three hundred-some patients, and there are two other smaller trials, but if you look at… if you're going to just truly randomize them between these two arms, without any other selection factor for using chemotherapy versus endocrine therapy, there's no striking finding here that says for patients who are hormone receptor-positive, that you need to give them chemotherapy. Despite that, there are very recent publications, especially around the behavior in the United States of using neoadjuvant endocrine therapy for this group of patients, and less than 3 percent of patients who are hormone receptor-positive who are getting

neoadjuvant therapy, it's neoadjuvant endocrine therapy. I think the pandemic altered that some, and I'll have you speak to that, Susan, in terms of the group from ASBrS and how their consortium approached that issue.

There are also, from the National Cancer database, studies that have looked at axillary downstaging. Now, these patients are not randomized, right? So, there's a huge bias here within these datasets of patients who are offered neoadjuvant endocrine therapy versus neoadjuvant chemotherapy. But, if you're looking specifically for patients who are clinically node-positive and using one or the other for axillary downstaging, I kind of find these data a little bit surprising. I'd like for you to think about them or talk to them, Susan, because an axillary pCR rate for neoadjuvant endocrine therapy, 14 percent seems pretty good to me. You know, so actually with the overall pCR rates -

Dr. Boolbol: (22:57).

Dr. Russell: Yeah. And, I think the story is, you know, there aren't huge differences here between the two, understanding their selection criteria for the smaller percentage of women who are offered the neoadjuvant endocrine therapy.

So, just overall with that kind of grouping, if you're going to give neoadjuvant chemo or neoadjuvant endocrine therapy, there are no data that suggest that one is better than another in an unselected hormone receptor-positive population. And, the National Cancer Database suggests that there are clinically node-positive patients who can get an axillary pCR, whether they're receiving neoadjuvant endocrine therapy or neoadjuvant chemotherapy.

Dr. Boolbol: But Christy, I think that last bullet point is incredibly important, because I do believe that there's a bias. Take genomic assays out of the picture. I think that there's a bias for node-positive patients getting chemotherapy.

Dr. Russell: Um-hmm.

Dr. Boolbol: And, if we're talking about neoadjuvant, I think the bias is even higher to giving them neoadjuvant chemo rather than neoadjuvant endocrine. So, when we see studies like this, even though it's not randomized, if it's retrospective data, it's really important data for us to be aware of, and to really start thinking about and saying let's use the appropriate treatment for the appropriate patient, and it does all come down to patient selection because when you look at the masses, one's not better than the other.

Dr. Russell: Right, right. Thank you. All right, so we're going to talk about a couple of concepts, and I think many of you might be very familiar with these, but they are, in the current clinical trials, asking questions about are there better endpoints. Since pCR in and of itself is so low in these patients who are hormone receptor-positive, HER2-neu-negative, and the breast conserving surgery is somewhat subjective, are there other endpoints that can help us assess whether the patient will have a better long-term outcome that are more reliable than pCR may be for these patients? So, there are two things we're going to talk about. We'll talk about Ki-67, and we'll talk about dynamic Ki-67, and then we're going to talk about the PEPI score, and how people are thinking about using these, especially in the era of using neoadjuvant endocrine therapy or endocrine therapy at all.

Dr. Boolbol: And, you'll define those for the audience?

Dr. Russell: I am going to. Yes, I will.

Dr. Boolbol: All right.

Dr. Russell: So, we, you know, we will ask you a question about who even gets Ki-67 as a baseline, but this concept is using a baseline Ki-67, giving a very short course of neoadjuvant endocrine therapy or endocrine therapy, preoperative endocrine therapy. Most of these trials have used an aromatase inhibitor, most are on post-menopausal women, and then somewhere between two to four weeks after you start that, you either take the patient to surgery and you look at the Ki-67 again then, or you do another core biopsy and decide where to go from that point. But, this is what's called a dynamic Ki-67, or a Ki-67 post, meaning that the breast cancer has been exposed to a couple of weeks of endocrine therapy prior to definitive surgery. So, there is a large -

Dr. Boolbol: Christy, in the ALTERNATE trial, the Ki-67 post, you could do it at 12 weeks also, couldn't you?

Dr. Russell: Right, we'll talk about that, yeah.

Dr. Boolbol: Okay, okay. It wasn't just four weeks.

Dr. Russell: Correct. So, the POETIC trial was two weeks, so you have a core biopsy, you've diagnosed breast cancer, you've diagnosed that she's hormone receptor-positive, HER2-neu-negative, you have your baseline Ki-67, whatever it is. These women got two weeks of endocrine therapy with an aromatase inhibitor, then they went to their definitive surgery. And,

it's the outcome of the patients by what the Ki-67 did in reaction to those two weeks of therapy. The ALTERNATE trial – I'll describe both of these trials, and I'll show them to you – looked at the Ki-67 at the four-week period of time, not at the two-week period of time. But, we're thinking about dynamic Ki-67.

All right, so let me start here. This is the POETIC trial, and this was a pretty large trial, right? There's 2,000-some women who were in this trial, but specifically if you look on the right-hand side, we're looking time to recurrence. And, you can see that the blue line are the patients who started with a Ki-67 under 10 percent, and at the two-week period of time, after getting an aromatase inhibitor, they stayed at under 10 percent. The red line are those women who started over 10 percent and dropped to under 10 percent. And, the green line is the outcome of the women who stayed over 10 percent Ki-67. The point here is not what the local reaction was to your neoadjuvant, or your therapy. This is a really short course of endocrine therapy, and then Ki-67, so you're just looking at the dynamic Ki-67, and you can see that it is prognostic, that it is having an influence on the long-term outcome for these patients, and that's called the POETIC trial.

This is another definition of another way of thinking about what happens, what kind of other outcome can we think about that will give long-term prognostic information. And, this is PEPI. So, PEPI stands for preoperative endocrine prognostic index. So, PEPI is, you have a patient with a hormone receptor-positive, HER2-neu-negative breast cancer, and she is given neoadjuvant aromatase inhibitor, so they are all, you know, post-menopausal, obviously. This was about four months of neoadjuvant aromatase inhibitor. The trial randomized the women to each of the three. This is the Z1031 trial. And then, they went to surgery. And, you're looking on the right-hand side, these curves are for those women who had a PEPI 0 if the line is yellow, or the dotted blue line are those women who did not achieve PEPI 0. So, what is PEPI 0? You can see in the box on the left-hand side, it means after your four months of neoadjuvant endocrine therapy, you can still have up to a 5-cm cancer, but she had to be node-negative, whether she started positive or not, but Ki-67 at the time of the definitive surgery after four months, the Ki-67 had to be less than or equal to 2.7 percent, and the Allred score had to essentially be positive; she still had to be hormone receptor-positive with whatever residual cancer. So, this isn't pCR; you could still have a fair amount of cancer left in the breast, but if

you achieved a significant drop in Ki-67, ER still positive, and she's pathologically node-negative, as long as the cancer's not over 5 cm, you can see this is clearly prognostic. And, on the left are those patients who, all the patients from the 1031 trial, the right-hand side are those patients who they went on to get adjuvant chemotherapy. But, the PEPI 0 was quite prognostic. And so, you have pCR not so prognostic if you're grade one or two in this population. The dynamic Ki-67 appears to be prognostic, and PEPI score seems to be prognostic for long-term outcomes, not the short-term effect on the breast.

All right, so the third trial here is the ALTERNATE trial, and this has now been presented twice, two different components of it. I'm sure many of you had patients that maybe you put into the ALTERNATE trial. This is neoadjuvant endocrine therapy in post-menopausal women who had clinically T2 through T4c cancer, so fairly large cancers, any nodal status, any nodal status. They had to be M0, hormone receptor-positive with the Allred score six to eight, so pretty high ER expression, and HER2-neu-negative. These women received six months of neoadjuvant endocrine therapy. They were randomized to one of three arms – anastrozole alone, fulvestrant, which is the estrogen receptor down regulator, fulvestrant or Faslodex is the trade name, or the combination of the two. So, they get 24 weeks of their neoadjuvant endocrine therapy. But, in this case, at week four, they have to be biopsied again. They can also be biopsied again at week 12, half-way through the neoadjuvant endocrine therapy – most are biopsied at week four – and, if the Ki-67 is not dropping, so that dynamic Ki-67 is not dropping, the presumption is, based on the PEOTIC trial that these patients are not going to do well. And so, in this case, you can either take the patient to surgery at this point, or you could pull her off of your neoadjuvant endocrine therapy and give her neoadjuvant chemotherapy.

So, some of the endpoints of the neoadjuvant endocrine therapy base trial are how many patients get to PEPI 0? How many of the patients are getting to pathologic complete response rate? And, if the patient goes through all six months of her neoadjuvant endocrine therapy and she doesn't get to PEPI 0, it's recommended she get adjuvant chemotherapy. However, if she gets to PEPI 0, it's recommended that she just follow through with further endocrine therapy in the adjuvant setting.

So, there are two groupings of data that have been presented to this point. The first is the patients in general, so you have about 13,000 patients who were in this trial. You have about

430 that are evaluable in those three neoadjuvant endocrine therapy arms. And, here are the outcomes that were reported about a year ago at ASCO 2020. In the three arms, there was no advantage of one endocrine therapy over the other. If you look at pathologic complete response rates in these patients who are strongly ER-positive, post-menopausal, getting standard of care, on neoadjuvant endocrine therapy, pCR rates were less than 1 percent, or about 1 percent in those three groups. That is really disappointing, right? And, you're like oh my God, she didn't get a pCR; you know, what should we do now? The other endpoint -

Dr. Boolbol: That's even lower than… that's lower than any other study, and much lower than we expected.

Dr. Russell: Right?

Dr. Boolbol: But, if we go back to the original trial design, not all patients went through that six months of endocrine treatment.

Dr. Russell: Correct.

Dr. Boolbol: And, we'll see that in a minute -

Dr. Russell: Right.

Dr. Boolbol: Because, if their Ki-67 did not decrease, they were -

Dr. Russell: They pulled out.

Dr. Boolbol: Exactly.

Dr. Russell: Right, so -

Dr. Boolbol: Or, they were supposed to pull out according to the trial design, and we'll see that in a minute.

Dr. Russell: Yes, right, right. So, if we look at the PEPI 0, so we're thinking those patients are going to do well, and these patients then go on to just receive adjuvant endocrine therapy, no chemotherapy, it's, you know, in the range of 18 to 20 percent. So, they created this category, which is called ESDR – endocrine sensitive disease rate – which, you know, just added these two together, pCR and PEPI 0. But, you're really, again, right at that 20 percent range. And so okay, that's lovely; you've got this population, ER-positive, HER2-neu-negative, you gave her six months of neoadjuvant endocrine therapy, and the best we're doing is 20 percent of patients are achieving some endpoint where we think they're going to really have a good outcome. And so, they asked a couple of questions, and I think I saw a question come up on

chat, which very interesting in this trial is that the Ki-67 started under 10 percent, as your baseline Ki-67 – this is in the three arms, those who went over 10 percent at week four – is very rare. And, one of the recommendations after this presentation was that if you're starting under 10 percent, you're going to have to presume that dynamic Ki-67 is not going to rise over 10 percent. It would be very unusual. So, there's probably no benefit of repeating a Ki-67 in the middle of your neoadjuvant endocrine therapy to prove anything. If it started over 10 percent at baseline, about a quarter of the women remained over 10 percent. And, those are the women who are supposed to come off and either go right to surgery or go to neoadjuvant chemotherapy.

So, we're going to ask a polling question. So, I want you all to read with your Zoom question, do you use a baseline Ki-67 to decide between neoadjuvant chemotherapy and neoadjuvant endocrine therapy, or upfront surgery? So, do you use a baseline Ki-67 to think about meh, it's really low; I'll give neoadjuvant endocrine therapy, or chemotherapy if it's high? So, do you use a baseline Ki-67 if you're going to use neoadjuvant therapy to make a decision as to which, frequently, in some patients but it depends upon other clinical pathologic features, rarely, or my pathologist does not routinely perform Ki-67? Susan, how are you approaching this?

Dr. Boolbol: No, it's interesting. So, at my hospital system, our pathologists perform Ki-67 on all invasive breast specimens. If they're done at an outside lab initially and then come to us for treatment, we will perform it on the surgical specimen as opposed to doing a core. If we have to redo a biopsy for some reason, then we'll get it on that. I honestly, I use it to frame my discussion with the patient about their options, and I think it's very useful for that. What I think is interesting is that it's not even routinely used across the country. Many, many centers, and I don't know the percentages of how many breast cancer patients get Ki-67 and how many do not, but I think it's interesting that we have studies designed around it, and yet it's not routinely even used or obtained.

Dr. Russell: Right, I believe it's based on the dynamic Ki-67 data from POETIC, and the fact that you have to have a Ki-67 to get your PEPI score 0, so it's, you know, incorporated into all those, too. If I look at the polling results, you can see that about a third of the patients… a third of the centers don't even do a baseline Ki-67. And, only about 7 percent are using it frequently to decide on their neoadjuvant therapy.

Dr. Boolbol: And, is it something that you think we should be using, that, in and of itself alone, just to be deciding obviously in hormone receptor-positive, HER2-negative patients, should that be what we use to decide on what treatment the patients get? Or, should we be using other factors?

Dr. Russell: I think it's… well, my personal belief with the literature is that Ki-67 is giving some signaling if you're going to use neoadjuvant endocrine therapy. I don't believe it's been a very good signal for neoadjuvant chemotherapy, as a standalone marker at this point. All right, I'll keep going -

Dr. Boolbol: People say that they don't, you know, pathologists will say that they don't get it and people don't use it as it's not that reproducible. But yet, we're using it in major trials, so -

Dr. Russell: Right.

Dr. Boolbol: There's definitely a disconnect with this marker.

Dr. Russell: But, like the ALTERNATE trial, these are all central Ki-67s.

Dr. Boolbol: Right.

Dr. Russell: These are not the community Ki-67, and they needed to wait for the central testing result to make a decision as part of this trial. So, one of the interesting things about ALTERNATE, and this was presented at the San Antonio meeting just this past year, is you would think that those patients who were getting neoadjuvant endocrine therapy, and at week four or at week 12 – again, it was mostly week four – are not dropping their Ki-67. But, there's a signal that somehow they're resistant to endocrine therapy, and that there must be something better that we can do for them. And, what was presented were the data on the patients who received neoadjuvant chemotherapy if they weren't dropping their Ki-67. And so, when we look at this cohort of patients who start at either week four, which is the huge percentage of patients where they checked the Ki-67 over ten percent, so just 286 of that entire trial of about 1,300 patients, and you can see those… of the 286, 168 were switched to neoadjuvant chemotherapy. Others got some other kind of treatment – we're not sure what – and then about 32 of the patients went to immediate surgery. And -

Dr. Boolbol: But, if you look at that -

Dr. Russell: Yeah.

Dr. Boolbol: If you look at that number, I mean 86 out of… so, about 30 percent, almost a third of patients pursued other treatments. I suspect many of them continued on endocrine treatment. We don't know that.

Dr. Russell: Right.

Dr. Boolbol: We haven't been given that information. But, that's a large number of patients.

Dr. Russell: I agree. And so, this has not been published yet, so we're waiting for the details around these patients. So, of the patients who received the neoadjuvant chemotherapy, this is a group of patients you think are going to be primed to be responsive to that neoadjuvant chemotherapy. You can just see the numbers are trickling down here; it's still not an overwhelming number of patients, but if you're using RCB, or if you're looking at pathologic complete response rate for this group of patients who you think would be signaling… they're resistant to endocrine therapy, they're not dropping their Ki-67, only 5 percent of patients achieved a pCR. Susan, do you want to… what do you think about these data?

Dr. Boolbol: You know, again, I think that we look at something like RCB, residual cancer burden, and I'm not sure that the majority of institutions use, or even obtain, RCB after… as a part of the pathology report after neoadjuvant treatment of any sort. So again, I think it's interesting that we're using these factors in clinical trials that are not used every day in the real-world setting. So, when we look at this, again, this is endocrine treatment, but we're looking at this and seeing under 5 percent pCR for -

Dr. Russell: With chemotherapy after failing -

Dr. Boolbol: - with chemotherapy -

Dr. Russell: Right.

Dr. Boolbol: - after the endocrine treatment.

Dr. Russell: Right.

Dr. Boolbol: A very, very low number.

Dr. Russell: Right, and it should -

Dr. Boolbol: You can look at it in two ways. Is pCR the correct endpoint? Is that the end all and be all and the only thing we should be looking at? And, if it is, then why are we doing this at all? Less than 5 percent obtaining that gold, you know, the gold store endpoint.

And really, is that what we should be doing? And, is that what people are looking at in the real world?

Dr. Russell: Right. Okay, so this is just the conclusion of the slides that I just showed to you, but I think that the question is the value of this strategy, the value of this strategy by POETIC of doing the two-week Ki-67 to assess a long-term outcome, the value of the way it was done in the ALTERNATE trial, where they don't seem to be dropping their Ki-67, how much chemo benefit really is being signaled from that group of patients? So, the question is whether any of these modalities are giving us enough information to either achieve pCR or to give us evidence of long-term outcomes. And, there are no long-term outcomes that have been presented from the ALTERNATE trial to this point, and that will be important information as well.

So, another polling question – outside of a clinical trial, do you assess tumors for dynamic Ki-67, or do you do a PEPI score to decide between pulling them off their, you know, giving them neoadjuvant chemotherapy or endocrine therapy? Do you use either one of these modalities? So, frequently, in some patients depending upon other clinical or pathological features, or rarely? Susan?

Dr. Boolbol: You know, I think these are fascinating issues, and I think that these are being discussed at tumor boards across the country every single day, is you treat someone with neoadjuvant, either… and this is for ER-positive, HER2-negative, you treat them, whether it's neoadjuvant chemo or neoadjuvant endocrine, and they have residual disease. Well, how much residual disease? How are we classifying it? And now, what do we do? And that's the question at tumor boards every day. It is what do we do? I don't know that many places are really getting dynamic Ki-67s on their patients. In my institution, I know that all markers, if someone typed neoadjuvant, all markers are repeated at the time of surgery. So, whether they intend to get a dynamic Ki-67 or not, we're getting it because we know what's going on, where we started and where we end. Are they using that? Are the medical oncologists using that for determination of further treatment? I don't know that people really are. I think, again, people look at the PEPI score, but what are they doing with it?

Dr. Russell: Right.

Dr. Boolbol: It's nice information to have, but is that influencing treatment at all? And, I'm not convinced that it is.

Dr. Russell: So, you can see from the polling answer, 92 percent of our patients -

Dr. Boolbol: (47:13) adults.

Dr. Russell: Yes. 92 percent of the… not patients but responders are not using either one of these measures to make a decision of neoadjuvant/adjuvant chemo or endocrine therapy.

Dr. Boolbol: And, I do think that that's the real-world answer.

Dr. Russell: Yeah.

Dr. Boolbol: You know, sometimes we're even surprised at the polling results. This one, I'm not surprised at all.

Dr. Russell: All right, second polling question – what is the optimal endpoint for assessing the efficacy of neoadjuvant endocrine therapy, right? Unlikely that you're going to get a pCR. So, clinical response, the patient had to have a mastectomy and you're trying to get her to breast-conserving surgery conversion, that's your endpoint, the most important one. Complete axillary response and avoidance of an axillary lymph node dissection, your optimal endpoint is distant recurrence over a long period of time, or your optimal endpoint is a dynamic Ki-67.

Dr. Boolbol: So Christy, when you were practicing, what was your endpoint here, and what did you do with it?

Dr. Russell: Right, so I think, you know, I was probably typical that I would really sub-select the patients getting neoadjuvant endocrine therapy. For the most part, for the patients who were hormone receptor-positive, HER2/neu-negative, I'd say for the most part, I would recommend that I was either going to give neoadjuvant endocrine therapy, or I was recommending that the patient go to immediate surgery because the data around chemotherapy have been so poor. And, you know, I began to use a genomic marker to help me think about that at some point but, at the University of Southern California where I practiced for thirty years, we never used Ki-67, so it just wasn't part -

Dr. Boolbol: You don't look old enough to have been practicing for thirty years.

Dr. Russell: (Laughing) Thank you. Right. So, you can see that people just have differing thoughts about, you know, what they think is the optimal endpoint.

Dr. Boolbol: Do we have the polling results?

Dr. Russell: Excuse me?

Dr. Boolbol: Were the polling results up?

Dr. Russell: They are, and I'm seeing them. It suggests that the optimal endpoints… so, clinical response is 40 percent, mastectomy converting to BCS 27, axillary response 17 percent, distant recurrence 12, and dynamic Ki-67 4 percent.

Dr. Boolbol: So, the interesting thing here is if you look at the top two choices, so the majority… 67 percent of people say clinical response and mastectomy to BCS conversion. Those are both subjective responses.

Dr. Russell: Right, right.

Dr. Boolbol: So, it's interesting that that's what the majority of surgeons use. It's not right or wrong, it's just an interesting thing that we're using more subjective responses to make these determinations.

Dr. Russell: Right.

Dr. Boolbol: And that's the optimal endpoint.

Dr. Russell: So Susan, I'm reminded that we have about ten minutes, so I'm going to fly a little bit here.

Dr. Boolbol: Yep, I'll stop asking questions.

Dr. Russell: We'll be less chatty. Okay, so… because I'd like to get to some of the questions. So, does neoadjuvant endocrine therapy have a role in the management of hormone receptor-positive, HER2-negative? You've seen the ALTERNATE date; we just haven't seen long-term outcomes from the ALTERNATE trial. There are a couple of case studies here. I think I'm going to perhaps go past those and let's now talk about genomic assay in this particular case because of my massive bias that you've already heard about.

We're going to talk about the oncotype breast recurrence score test, and what data exists for this specific genomic assay for patients for neoadjuvant endocrine therapy. There are a couple of trials that are really small. This is from Harry Bear in Richmond, and he tried to do sort of a neoadjuvant tailor-X, right? So, they took patients, they did a core biopsy to get the recurrent score. If it was under 11, they got neoadjuvant endocrine therapy. If it was over 25, they got neoadjuvant chemotherapy. And, if it was 11 to 25, they randomized the patients to neoadjuvant endocrine versus neoadjuvant chemotherapy, but if you look at the N, it is really, you know, a small number of patients here. But, if you look at the group that is recurrence score under 11, you can see that with neoadjuvant endocrine therapy, pCR in breast is about 8 percent

of patients. Clinical complete remission is about 8 percent of patients, right? But, clinical cPR was about 75 percent. On the far right are those with recurrence scores of 26 and above. You're getting much higher pathologic complete response rates, 21 percent in the breast, 14 percent in breast and axilla. And, in the randomized patients, you know, one patient getting neoadjuvant endocrine therapy essentially had a pCR. But, in that 11 to 25, just like in tailor-X, there's just not a whole lot of chemo-sensitivity here, and you wouldn't expect big numbers of pCR.

And then finally, as a validation trial based on NEOS, this is a Japanese trial which had 900 post-menopausal women, but relatively low clinical risk or clinical disease. So, T1c to T2 cancers, clinically node-negative, and they received six months of neoadjuvant endocrine therapy, and we did a trial called TransNEOS, which is the translational part of NEOS where we did oncotype breast scores on 295 of the 900-some patients, for whom there were blocks available. And, the objective of this translational program was to look at the clinical response to six months of neoadjuvant endocrine therapy. If the recurrence score was under 18 or 31 and greater, the original oncotype cut points, again, six months neoadjuvant, aromatase inhibitor, all in post-menopausal women. And, what it showed was here on the left, for women with a recurrence score under 18, if you're looking at clinical complete and partial remissions with neoadjuvant endocrine therapy, 55 percent had complete or partial remission together, so a response, 45 percent stable disease, and one patient, or less than 1 percent of this group of women had progression. As the recurrence scores increased, they're still doing fairly well with a recurrence score of 18 to 30. But, for those patients with a recurrence score of 31 or greater, this is where we speak about progression – that 9 percent that we saw previously – 17 percent of the patients have progression through their neoadjuvant endocrine therapy, and this is a group of patients, personally, I think if you're going to do this genomic assay, you should not be thinking about neoadjuvant endocrine therapy. If you saw that recurrence score in a patient who had had a surgery, you are probably going to give her adjuvant chemotherapy, and so I think this is not an appropriate, personally, is not an appropriate group for neoadjuvant endocrine therapy. I think the risk is progression during the therapy.

Dr. Boolbol: And, I think it goes to show the importance of obtaining genomic assays for patients – and this is my personal belief – for patients undergoing neoadjuvant treatment. If we're going to do it for them adjuvantly, we wouldn't think of not getting a genomic assay

adjuvantly. Why not do it neoadjuvantly, and treat the appropriate patient with the appropriate treatment?

Dr. Russell: So, just what's of interest is the breast-conserving surgery outcomes. And so, they we look at this, and we talked about how subjective that is. But, if you started with a low recurrence score, under 18, and you were not originally eligible up here for breast-conserving surgery, if you got six months of neoadjuvant endocrine therapy, you dropped from 31 percent unable to have breast-conserving surgery to 21 percent. However, for those who start with a recurrence score over 31, 37 percent of them were not eligible for breast-conserving surgery, and after six months of neoadjuvant endocrine therapy, it didn't budge. And so, you just… if that is one of your endpoints, the recurrence score could probably guide you so that you would understand, if that is your endpoint, then giving neoadjuvant endocrine therapy to that group with a high recurrence score is probably not optimal. And, they had put a poster together a few years ago; they are writing this publication at this point, but for patients in the overall NEOS trial, if you look at their response, whether it was a complete remission, partial remission or stable disease clinically, they actually all do pretty well. It is these patients who have progression during their neoadjuvant endocrine therapy who are doing particularly poorly.

So, just to save time, I have case studies, but I think what I'd like to do, Susan, is maybe just go to questions. We are about four minutes before the end of our grouping, so just -

Dr. Boolbol: You want to just do the summary slide, and then -

Dr. Russell: Yeah.

Dr. Boolbol: - and then we'll do the questions?

Dr. Russell: Perfect. So, the summary is that endocrine therapy can be used in the neoadjuvant setting to deescalate surgery for the patients who are hormone receptor-positive, HER2-neu-negative. There are many studies that I hope that you saw that would suggest that you can use that safely, even though it is very uncommonly used in the United States. Post-neoadjuvant endocrine therapy assessments have been studied to select patients for systemic therapy. you can think about PEPI 0 for long-term outcomes, or a dynamic Ki-67, but I think we've learned from ALTERNATE that dynamic Ki-67 are not dropping under 10 percent, is not enriching in ER-positive population to go on to chemotherapy and benefit from that chemotherapy. And, in this case, the oncotype breast recurrence score on core biopsy samples is

validated as a predictor of clinical response to neoadjuvant endocrine therapy in post-menopausal women with hormone receptor-positive, HER2-neu-negative, clinically node-negative breast cancer patients from the TransNEOS trial.

All right, so, let's do question and answer.

Dr. Boolbol: So, there's several questions in the chat that have come in, and I think that this is a big thing in the United States, is how long do we treat women with neoadjuvant endocrine? How do we assess it, and is there a standard? Can we just keep them going on it?

Dr. Russell: Do you want to answer that?

Dr. Boolbol: Well, I can tell you from a surgical viewpoint, but let's hear it from a medical oncology viewpoint.

Dr. Russell: Yeah, I mean I think my standard was six months. I also think at some point, the patient gets a little itchy, you know, watch… knowing that she has a palpable cancer that we're, you know, we're doing ultrasounds, we're kind of following it clinically by physical exam, but also, some other type of radiographic procedure. And, you know, from my point of view, you can always attain a pathologic complete response if you remove the cancer, right? So, at some point there's a surgical pCR that we need to put into the mix. However, data looking at small trials, looking at six versus twelve months of neoadjuvant endocrine therapy, your chance of pCR grows the longer you have her on that neoadjuvant endocrine therapy. But, it's the same therapy you were going to use anyway in the adjuvant setting, so I think, to me, it's a relationship between the patient, the surgeon and the medical oncologist. If we're getting to the point where her goal is breast-conserving surgery, where the axilla now is feeling clinically negative, have we achieved a local endpoint where everybody is satisfied, let's go to surgery and follow through with our adjuvant endocrine therapy?

Dr. Boolbol: And, this is where I think expectations come into play in a very large way. It all depends on those initial conversations that the surgeon has with the patient, that the medical oncologist has with the patient as to what are we expecting? What are we looking for? So, I say to my patients, as long as we're seeing progress here, meaning that it continues to decrease in size, what's the rush? We can go to surgery at any time. I can operate at any time. But, if this continues to get smaller, that's great; I can do better surgery… we can have a better esthetic outcome with oncoplastic surgery, with breast-conserving surgery. So, I think it depends on how

we lay out these expectations from the initial discussion of this. My question back to you is, is there a difference if we see a real response in the first few months, let's say we get an ultrasound at three months and we see a 50 percent decrease in size, which I'm shocked that that happens, but it definitely happens. Is that a good prognostic indicator? Do we have any information on that?

Dr. Russell: We only have the information, really, about around the dynamic Ki-67 and the PEPI scores. We do have, as I showed, the validation of using the oncotype for using neoadjuvant endocrine therapy, but that does not talk about the speed of shrinkage, and that was not assessed as any of these endpoints. So, I think the endpoint that you're looking at, the rapidity of clinical response, has not been a component of any of these trials that I've seen.

There's just one or two questions, and we're now a minute over time, Susan. But, it's around reimbursement for oncotype in the neoadjuvant setting. There are some insurers who still feel that that's an exclusion for any genomic assay unless they know the axillary status. I would say that since the RxPONDER trial has reported, and we know how to think about node positivity and the oncotype score, that that has been loosened a lot, and it is much easier now to get coverage if you're going to do an oncotype on the core biopsy for neoadjuvant decision making.

Dr. Boolbol: Yeah, in the peer review, it's interesting, when you do a peer review with that, and as we all know with peer review, we are rarely speaking to someone in our specialty. One of my first questions always is oh, what is your specialty, just so we can even the playing ground here, and that always changes the dynamic of the conversation when I am speaking to a podiatrist about how to treat breast cancer here.

Dr. Russell: Right.

Dr. Boolbol: So, the explanation is well, I might just have to give this patient chemotherapy neoadjuvantly, then. Wouldn't you prefer we give her neoadjuvant endocrine if chemo won't benefit her? So, in my personal experiences, I've really not had trouble getting it approved after the peer-to-peer.

Dr. Russell: All right, we are now -

Dr. Boolbol: (1:03:03).

Dr. Russell: Yeah, thank you, Susan. There are many, many questions that are here that

we did not get to, and I apologize that we went on too long. You, if you would like to reach out to me for any questions about oncotype and these data that we shared, please feel free. Too, this recording will also be available afterwards to go back if we've completely confused you, or you'd like some data points to go back to. And, I can always be reached at my email address at crussell@exactsciences.com, if you have a specific question. And Susan's eminently findable throughout this meeting for any specific questions she has as well. So, I appreciate all of you spending the time with us at this symposium, and have a great rest of the American Society of Breast Surgery Meeting.

Dr. Boolbol: Tune in over the next few days for lots more information. Thank you.

[End of audio, 65:10]