

Program Title: Hormonal Therapies for Breast Cancer

Presented by: Support Connection, Inc.

Moderator: Marlene Stager, MS – Support Connection Peer Counselor

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Guest Speaker: Diana E. Lake, MD, Memorial Sloan Kettering Cancer Center, NY, NY

Dr. Lake is a medical oncologist with a practice that is devoted solely to the care of breast cancer patients. Dr. Lake's research interests involve all areas of breast cancer but focus mainly on the development of new therapies, prevention of cancer recurrence following surgery, and treatment of recurrent disease.

Working in conjunction with her colleagues on the Breast Cancer Medicine Service at MSKCC and as the liaison in breast medicine to Alliance for Clinical Trials in Oncology (a national clinical trials cooperative research group sponsored by the National Cancer Institute), she is involved in clinical trials to develop better hormonal therapies and improved approaches to treatment before surgery.

Dr. Lake is a past member of the National Institutes of Health (NIH) Scientific Review Committee, and has previously served on the NIH Cooperative Group Review and its Cancer Education committees and has received the Memorial Sloan-Kettering Cancer Center fellowship. She is a member of the NYS Health Research Science Board.

Topics:

- What are the different hormonal therapy options?
- What is the latest research?
- How have recommendations changed?
- Should I continue treatment for 5 years? 10 years? forever?
- Question & answer period.

NOTE: You may find it helpful to view and listen to the slides from this webinar (which are posted on our website and YouTube channel) while reading through this transcript.

Marlene Stager: Please remember, Dr. Lake is sharing her expertise. Any information from tonight or questions pertaining to individual concerns should be discussed with your personal doctor. It is now my pleasure to introduce Dr. Diana Lake. Dr. Lake is a medical oncologist with a practice that is devoted solely to the care of breast cancer patients. Her research interests involve all areas of breast cancer but focus mainly on the development of new therapies, prevention of cancer recurrence following surgery, and treatment of recurrent disease. Working in conjunction with her colleagues at Memorial Sloan Kettering Cancer Center and as a liaison in breast medicine to Alliance for Clinical Trials in Oncology, Dr. Lake is involved in clinical trials to develop better hormonal therapies and improved approaches to treatment before surgery. Dr. Lake, I turn it over to you.

Diana Lake: Okay. Thank you very much for the opportunity to meet with you guys and speak this evening. We have a tall order to give you an update of all of endocrine therapy. So, I think I'm going to concentrate mainly in early stage disease, because there are several important issues related to questions that patients often ask, and also will, however, mention a little bit about metastatic disease. Next slide, please.

So, I have no disclosures. Next, please. So, the objectives of today in the world of adjuvant hormonal therapy are, one, to discuss the issues of tamoxifen versus an aromatase inhibitor. Now, this mainly applies, we used to say, to the premenopausal women, because traditionally premenopausal women received tamoxifen and postmenopausal women receive aromatase inhibitors, although now I think we know it's just important to have endocrine therapy.

The duration of treatment is also something that I would like to address and it is less clear-cut with the aromatase inhibitors than it is with tamoxifen and, of course, the role for ovarian suppression. And, as I mentioned, I would discuss a word or two about metastatic breast cancer and endocrine therapy only because we're starting to look at some of those drugs with some of those combinations earlier in the treatment, so in the adjuvant setting. Next, please.

So, this is a slide that we always start out with, and you'll see lots of graphs and words in today's slides. They're not meant for you to memorize; it's just to illustrate a point. So, this is a slide that shows on two different sets of curves. One is showing the effect of tamoxifen on recurrence and then on the right-hand side is on the effective breast cancer mortality. You can see that in terms of recurrence, if you've been on tamoxifen for five years and then you evaluate patients at the 15-year point, there's really a gain of about 11% to 12% in terms of recurrence, so you have an 11% to 12% benefit in decreasing recurrences. And in terms of the overall mortality, you're really gaining about 9% to 10%. So, the use of endocrine therapy for five years, which was reported years ago, shows that there is a benefit for tamoxifen at that time as the main drug. Next, please.

There are -- with the advent of development in postmenopausal of aromatase inhibitors, we tried to look at that and to randomize or have clinical trials that address an aromatase inhibitor versus tamoxifen, and we started out only in postmenopausal women. So, to date there have been numerous combinations. There has been a direct comparison, where you can compare tamoxifen and an aromatase inhibitor, and there are about three trials there. You see ATAC looked at anastrozole, BIG looked at letrozole, and ABCSG looked at exemestane.

We looked at it at the switching point. In other words, you start out on tamoxifen; maybe after two to three years you switch over to an aromatase inhibitor or continue with tamoxifen, and then numerous trials which address that issue. The extended adjuvant trial, you look at someone who had been on endocrine therapy for five years, tamoxifen, or tamoxifen followed by an AI. And then at the end of five years they were randomized to placebo, because that was the standard of care. Nothing after five years or continuing on again with five more years of hormonal therapy. And then the BIG-98 trial looked at sequencing. It doesn't matter if you start out with tamoxifen and switch over to an AI, or can you start with an AI and switch to tamoxifen. And no matter what, all of these trials boil down to one central point, that an aromatase inhibitor at any point in a postmenopausal woman was better than tamoxifen alone. Next, please.

So, the Early Breast Trialists Group really looked at patients, and they found that at 20 -- excuse me, at 20 years, there's about a 21% recurrence rate, 7% of which were local recurrences or contralateral breast cancer, and 14% were distant recurrences. So, when you wonder, well, what's my risk of recurrence each year, it's somewhere about 1.5% close to 2% annually. Next, please.

So, there are numerous trials which then support the use of this extended adjuvant therapy. If we know that you have a 1.5% to 2% risk of recurrence annually, it would make sense to wonder what happens if I take endocrine therapy longer? So, with tamoxifen there's the aTTom trial and the ATLAS trial, and then there was the MA-17 and the MA17R, which went even beyond 10 years. And notice the effect here shows that there is a statistically significant greater impact after 10 years of endocrine therapy. So, clearly this data in all of these trials, both the MA-17 trial looked at aromatase inhibitors, the aTTom and ATLAS trials looked at tamoxifen showing that longer duration of therapy was better. Next, please.

So, the schema mentioning the MA17R was that patients were going to be on an AI for five years previous to the trial randomization. So, one could have been on tamoxifen if you were premenopausal for any number of years, usually up to five, but it could have been four to six. Then they were on an aromatase inhibitor of letrozole, and following this, after five years average of letrozole, patients were randomized to 2.5 mg standard dose for another five years or placebo. So, theoretically, one could have been on

hormonal therapy for 15 years, five of tamoxifen, five of letrozole, and another five of letrozole if you were in that group. So, that was called the extended adjuvant. And, again the whole basis of longer-term endocrine therapy is really based on the fact that patients with ER-positive breast cancer are at risk long term in contrast to ER-negative. Next, please.

So, the primary endpoint analysis was the five-year disease-free survival. And you see in the group that had letrozole for the extra five years versus the placebo, there was a 95% disease-free interval with letrozole, 91% placebo. That was statistically significant. Anything that is less than 0.05 is statistically significant. So, in this trial there was actually a 34% reduction in recurrences. So, that was good and that's what led to us now looking at extended adjuvant therapy defined as five more years of hormonal treatment after the first five. Next, please.

The next question, since we were doing so well with aromatase inhibitors, but remember, that was limited to the postmenopausal population, what about the premenopausal woman? Traditionally, a premenopausal woman receives tamoxifen, and that was the only option. So, there were two trials that ultimately combined their results in order to come up with some type of guideline. They were called the SOFT trial and the TEXT trial. The only difference is, the SOFT trial, randomized hormonal therapy upfront, that is, less than 12 weeks from surgery if you didn't have chemo. If you did have chemo, it was right after chemotherapy. Patients had ovarian suppression. The arms were ovarian suppression versus Tam, tamoxifen, versus ovarian suppression and an aromatase inhibitor, exemestane, versus the standard of care in a premenopausal woman with tamoxifen. And extended adjuvant, that is, treatment beyond five years, was really defined per the treating physician. The TEXT trial also randomized upfront. Everybody was randomized upfront less than 12 weeks from surgery. If patients had chemotherapy it was optional if they all started with ovarian suppression with the chemotherapy. Three arms were the same -- ovarian suppression/exemestane, ovarian suppression/tamoxifen. Patients were allowed to have a BSO, that is an oophorectomy after being on treatment six months, and then they too would be randomized per physician to extended adjuvant. Next, please.

So, what you found in the SOFT trial, low-risk patients, those who did not have chemo, node negative, no matter what you did, no matter which arm you were on, those patients do well. They could have been on tamoxifen, tamoxifen ovarian suppression, or ovarian suppression and an aromatase inhibitor. And you see here that their five-year distant metastatic-free survival, the time to having metastases within five years was all about the same. If we looked at the high-risk group, defined as those who received chemotherapy in the trial, then we knew that ovarian suppression versus aromatase inhibitor is better than tamoxifen. Ovarian suppression with tamoxifen was better than tamoxifen. But the difference between the ovarian suppression with the aromatase inhibitor being better than tamoxifen and ovarian function suppression better than tamoxifen, it's a greater difference with the AI, aromatase inhibitor. So, the real choices might boil down to ovarian suppression and an aromatase inhibitor versus tamoxifen. The AI was better.

In the really high-risk premenopausal woman, that's a woman who is under 35 who has node-positive disease and who received chemotherapy, you can see here that their five-year breast cancer survival with ovarian suppression and an aromatase inhibitor is 83%. The five-year cancer-free survival with tamoxifen is 68%, so there is a statistically significant difference, and that's a rule that we pretty much adhere to now. So, if you're a young premenopausal woman with high-risk disease who needs endocrine therapy, then this may very well be offered to you. Next, please.

This is just in graph form so that you can see the ovarian suppression in Tam versus Tam with a median follow-up of 67 months. The tamoxifen group had a slightly less disease-free survival than tamoxifen and ovarian suppression, and that's in the red. Next, please.

We talked about the analysis already, so we don't have to go into that. It really is just another way of saying the same thing. Next, please.

There is -- if you want to know ovarian function suppression with an AI being better than ovarian and tamoxifen is a 4% improvement in the disease-free survival, but notably there was no difference in the overall survival. So, in that particular trial you're not going to live any longer, but you may have -- but you would have a better -- you would have an improvement in your disease-free survival. Next, please.

So, the next trial that was most anticipated and really everyone was excited about, and that's the TAILORx trial, because we're going now to another question. We know how well patients do with endocrine therapy. We've touched on whether or not you should give endocrine therapy long-term, like greater than five years. We know that in postmenopausal women an aromatase inhibitor is better than tamoxifen, and we know that high-risk premenopausal women can be offered ovarian suppression, i.e., being made menopausal and then receive an aromatase inhibitor.

So, the next logical question is, well, if we can do so well with our hormonal therapy, does everybody really -- does everyone really need chemotherapy, because patients are getting a lot of chemotherapy? So, there was a test that was called the Oncotype DX, which I was not going into tonight, but I think you're probably all familiar, that this is a panel -- it's a 21-gene assay. So, your tumor is taken -- a biopsy or a sample of your tumor is taken and it's sent off for a genomic analysis, which looks at genes for estrogen, genes for progesterone, normal growth factors and other things, so 21 different genes. Depending upon the expression, this is all put into an equation and ultimately you come up with a number, and that number is called the recurrent score. And the number can range anywhere from zero to 100. And it divides breast cancer in those who are low risk for recurrence, intermediate risk for recurrence, and high risk, and the lower risk patients we know you can treat with endocrine therapy alone; the high-risk patients it's proven we need chemo and endocrine. But what we didn't know was what to do with that intermediate risk group. Do they all require chemotherapy or can we leave chemotherapy out in a subset of these patients? So, the TAILORx trial was a trial designed to answer that question. It stands for Trial Assigning Individualized Options for Treatment. Next, please.

The patients were all women with invasive breast cancer. They were between 18 and 75. The TAILORx was for node-negative patients. The ER and PR or ER or PR had to be positive in the local lab. The local lab also checked for HER2, so HER2 should have been negative, but there was not central testing for that. The other key thing is the tumor size in TAILORx. The cutoff was 5 centimeters for the larger size, so we didn't really look at very large tumors, like over 5 centimeters. And you were allowed to enroll on the trial if your tumor was under a centimeter, but if you had an intermediate to a high nuclear grade, so depending on how aggressive the tumor was. Also, all the patients who entered in the trial had to be willing to undergo chemotherapy. Next, please.

Again, this slide depicts what we just said. Arm A, low-risk group, endocrine alone; arm D, high-risk group, endocrine and chemo; and arm B and C was the experimental arm. Arm B, truly the experimental arm treating these patients with endocrine therapy alone, and arm C, the patients received the standard of care, which was endocrine and chemo. Next, please.

The endpoints were -- the primary endpoint was the invasive disease-free survival in the patients that had the intermediate score. That would mean distant invasive recurrence or local regional invasive, contralateral invasive, or any other second primary cancer, and obviously death. And then the recurrent scores that were between zero and 10, the endpoint here was the distant recurrence-free survival, and the relapse-free survival is something that was also looked at. Next.

So, the most common -- remember I said that patients had to be willing to accept chemotherapy if they were offered it, so the most common regimens were T/C, which is a very popular regimen in the country, and that's Taxotere/cyclophosphamide and others, especially on the East Coast, anthracycline-containing regimens of Adriamycin, Cytoxan and taxane. Next, please.

If we look at the primary endpoint of the invasive disease-free survival, the difference between arms B and C, endocrine alone versus chemo and endocrine, these lines are superimposed. Secondary endpoints, distant relapse-free survival, again, the lines are superimposed. Next, please.

If we look at all four arms, A, B and C, essentially they're going to involve endocrine therapy alone, endocrine alone, or chemo and endocrine. Those lines, the top ones here on the right, all superimposed. The line in pink represents arm D, and that is the high-risk patient defined as having recurrence score in this trial of 25 to 100. So, that tells you that we really -- and the risk of recurrence is about 13%, so then we have room for improvement in terms of the chemo status.

If we look at the nine-year event rates, then that's exactly what was published in June of this year and presented at the oncology meeting, and that is for the low-risk patient, nine-year event rates score between zero and 10, a 3% distant recurrence with endocrine therapy alone. This was initially reported three years ago in the *New England Journal* and the number has held. If your recurrent score is 11 to 25, again, there is no real significant difference. In other words, it's less than 1% difference in all of these endpoints. And, of course, if you look at the higher recurrent scores, there's a 13% distant recurrence despite chemo and endocrine therapy. Next, please.

So, the question that came up and that arose out of the TAILORx is, is there any subgroup in that intermediate group that might benefit from chemotherapy? So, the main thing that one looked at, again, it boils down to age. And what about women who have an intermediate score that are younger? They are under the age of 50, so they chose menopause as being 50 and people who are over 50, there is no chemo benefit at all in any of the endpoints that were looked at. But if patients who are under 50 having a score anywhere from 16 to 25, there may be a benefit. Next, please.

So, what it turned out was, again, 16 to 25, there is some chemo benefit perhaps in women under the age of 50. There were 9% fewer invasive disease-free events, including 2% fewer distant recurrences. And if your score was between 21 and 25, there is 6% fewer invasive disease-free recurrence -- excuse me -- 6% fewer distant recurrences.

So, I think the bottom line is, on the summary slides and results from the TAILORx, if your score is under 15, you're doing well, no chemotherapy benefit. If your score is between 16 to 25, these are all guidelines, and especially if your score is 21 to 25, there are fewer distant recurrences here, 6% to 7%, so you may benefit. If you're 16 to 20, you also may benefit. And I think patients having that score, between 16 and 25, need to sit down with their physicians and really discuss their thoughts and the physicians would discuss the data with the patient. Remember at all times that treatment with your doctor is like a partnership, so it's an ongoing discussion to review data and do what you think is best after you've been educated regarding the facts. Next, please. I think we've summarized that. Next, please.

So, this is just a slide to remind us, some of you may actually have participated in the TAILORx trial. So, we wish to thank you and all of the other volunteers and anyone who participates in clinical trials, because you're usually, you're actually helping science and you're helping both yourselves perhaps as well as other patients in future generations so that we can have and offer the best treatment to our patients. So, we thank you. Next, please. So, I want to say a word or two about the metastatic setting. Next, please.

The main drug that I'm going to talk about or the cycline, CDK4/6, or kinase inhibitors. Palbociclib was the first one, and it preferentially inhibits the growth of ER-positive cells. That's the bottom line from this particular slide. Next, please.

So, you see advertised on television, I'm sure, some of you may be on palbociclib. The other name for it is lbrance. It's an oral drug. It prevents cell cycle progression from G1 to S phase. You know, the cell goes through a cycle of growth. There's growth, there's rest, there's division and so forth, and so what this

does is it lets all the cells pile up, so after a gap they can't go on to the S phase. So, they're like cars going down the highway and you get a toll and the gate is down, you can't go, so everybody is piling up behind that gate, and that's what the CDK4/6 inhibitor does. And so in very small concentrations it was really able to have an effect on cells. Next, please.

And some of the trials to initially study this, or one of the trials, was a PALOMA 1. So, the PALOMA-1, and why everybody became very excited, in metastatic breast cancer first line, we would commonly go to an aromatase inhibitor if one hadn't had one before. And one of the drugs at the time, when this trial was starting that we looked at was letrozole. So, PALOMA 1 took the aromatase inhibitor letrozole as one arm, added on palbociclib and then wanted to know, is there any benefit in progression-free survival or events? And look what happened. With letrozole alone in the blue, the median progression-free survival was 10 months; with palbociclib added to letrozole, 20 months median survival. So, this was extremely exciting. The overall response rate was 43% with the combination versus 33% with letrozole alone. Next, please.

Side effects, because everybody is concerned about side effects that you expect here, there are some, and the major one is low blood count. So, if you look here, neutropenia grades 1, 2, and 3, much higher than someone who gets letrozole alone. Fatigue also more grade 1 and 2 and 3 than letrozole alone, and patients can also get arthralgias. So, certainly with the aromatase inhibitors, one of the big problems is joint pain and stiffness. You can get similar symptoms with the letrozole -- excuse me, with palbociclib. The important thing to note here is that about 40% to 45% of the patients actually required a delay in treatment or reduction in the dose, but the good part is the low white count is self-limited. So, it's not the same as the low white count that you have when you're on chemotherapy. Next, please.

The next step was to look at second line, so we commonly had letrozole as a primary and fulvestrant is a drug that's an injection and it destroys the estrogen receptor, and it was commonly used to second line metastatic disease. And, again, when we combined palbociclib with fulvestrant versus fulvestrant alone, median progression-free survival, 9 months versus 4, doubling, doubling the median progression-free survival. So, we see this in both first- and second-line treatments. Next, please.

Neutropenia is the same. It's not uncommon to have grade 3. You can get some grade 4. The nadir usually occurs weeks 3 to 4. We see it usually around week 2, that you can see at the end of week 2, which is why you always get a count check within the first two cycles on day 14. The duration of the neutropenia is short and it's rare but can happen that patients will get febrile neutropenia. Next, please.

This slide on the right will really list here the three kinase inhibitors. Palbo, the first to come out, ribociclib the second, and abemaciclib the last one and most recent. So, those are all the CDK4/6 inhibitors. Next, please.

The MONALEESA-2 study was -- and these trials do have odd names -- but MONALEESA-2 looked at ribociclib because the -- LEE011 is the -- was the research name. And, again, patients took ribociclib the same schema as the palbociclib, three weeks on, one week off with letrozole versus placebo and letrozole, and showing that there was clearly a benefit with the ribociclib. Next, please.

The characteristics of the two treatment arms were very similar. Next, please. Again, there was an improvement. As you can see here, the ribociclib and letrozole is better in terms of progression-free survival in contrast to letrozole alone. So, here, the second trial is also showing, it was 73% progression-free survival for the ribo versus 61% for those who did not receive it. Next, please.

Side effects are the same, a little nausea, and a little diarrhea with the ribo. The only other difference, it can elevate your liver function to a degree and cause some EKG changes, so that's why your physician may evaluate you for EKG changes. Ribociclib has also now been approved, next please, for use of tamoxifen.

We talked about the hematologic side effects, which are absolutely the same. The neutropenia, anemia, so you can get cytopenia. Platelet counts are less so. Febrile neutropenia occurred in 1.5% of this trial; in the other trial it was 1.9%, I believe. Next, please.

People always ask, well, what's the difference? This is a hard slide to read between the three inhibitors. They just have different side effects, but they're all quite effective. I'm going to -- next, please. Next, please. I think we talked about the main reason for reduction is really blood count, or in the case of ribo, the liver function. Next, please.

The bottom line is palbo is approved, AI or fulvestrant. With palbo, ribo is approved for an AI, and now I think also tamoxifen. The major side effects for everybody, neutropenia. You can get pulmonary emboli in palbo, so that's something to keep in mind, so thrombotic events. With ribo it's more cardiac changes, liver function changes. Next, please.

So, the other exciting trial is the MONARCH 2. So, the MONARCH 2 was abemaciclib, the third one, in combination with fulvestrant, and we're trying to see if that has a response, and it was studied -- next please -- in the exact same way. Patients were on abemaciclib with fulvestrant versus fulvestrant alone. Next, please.

We compared the PALOMA 3, which is palbo/fulvestrant versus abemaciclib and fulvestrant. Next, please.

And this is a key slide here. The median progression-free survival, remember how good it was with fulvestrant -- sorry, we have fulvestrant and abemaciclib median progression-free survival is 16.4 months, and fulvestrant alone is 9 months. Next, please.

The side effects as you can see are all manageable, and everybody benefited, no matter who you looked at, whether they had responded before to endocrine therapy, the metastatic sites, measurable disease, age group, race, performance status, abemaciclib and fulvestrant was better than the placebo arm. Next, please.

So, the conclusions were that abemaciclib plus fulvestrant is certainly effective treatment. So, you really have three different drugs that you can now give. Next, please. Next, please.

So, I mentioned the -- I mentioned those three drugs in the metastatic setting, because now we're beginning -- if something works in the metastatic setting, we look at it in the adjuvant setting. And so the PALLAS study is a study that is ongoing. In fact, it's going to close probably the beginning of November, first week of November, and this really takes patients who have early stage breast cancer and they're randomized to endocrine treatment, any endocrine treatment, plus palbo, versus endocrine treatment alone. The endocrine treatment is five years. You can go beyond, physician choice. The palbo is only for two years. We have no results, but this is an ongoing study. Next, please. Next.

So, we then began, the last few slides are starting to answer some questions that we all have, and one of them is how long should one stay on the extended adjuvant letrozole? So, the IDEAL trial actually looked at tamoxifen versus an aromatase inhibitor versus a combination of them all. And then they were randomized to letrozole versus letrozole -- excuse me, letrozole for two years versus letrozole for five years. So, it's two and a half versus five years. Next, please.

And what you see, if you're looking at the disease-free survival, the overall survival or the distant metastasis-free survival, there does not appear to be a difference at all between the two years and the five years. So, five years of an AI in the IDEAL trial was not necessarily better. So, this is one of the first trials that is beginning to show us, at least with metastatic -- excuse me, at least with postmenopausal

women on aromatase inhibitors it may be 10 years, or less than 10 years may be enough. So, we're not sure. And this, too, was recently reported. Next, please.

The DATA study was a study from the Netherlands, and, again, it tries to address the issues of three years of anastrozole versus six years, and patients received endocrine therapy, which was usually two to three years of tamoxifen and then they were randomized to three years of an AI or six years of an AI. So, for a couple of years or three years, everybody had the same treatment. And what they found here, there was absolutely no difference at all between the five years and the three years except possibly in women who had node-positive -- who had neoadjuvant chemotherapy. But perhaps longer aromatase inhibitors are better in the higher risk patients. Again, two to three years of tamoxifen, then they were on an AI, and they continued the AI, tried to look at three versus six years, maybe a difference in the patients who were high risk. Next, please. Next, please. Next, please. I don't need to go into all the details.

So, I think answering the question about extended aromatase inhibitors, there are several trials that show there is a benefit, MA17 and SABT, the initial exemestane trial, there is also some benefit but maybe not as great looking at the IDEAL trial, the DATA trial, there are subsets who will benefit. And then these last two trials, the SOLE trial, which really addressed whether or not you need continuous treatment. Next, please.

So, the SOLE trial addressed another issue. Adjuvant endocrine therapy, do we need continuous versus five years or can we have intermittent therapy, on for nine months, off, start again. Tried to address that issue and ultimately the -- next, please -- the disease-free and the overall survival area almost identical. So, the SOLE trial tries to answer that question. I do not recommend that you -- and I don't tell my patients to interrupt, either. I do not recommend having post aromatase inhibitor therapy. This is one particular trial I think you have to study this more, but it does leave credence to the fact that you're having a hard time with your aromatase inhibitor, you need to take a break and then restart with either another drug or a different schedule. You can do that or you have to interrupt the surgery, reconstruction surgery, that's okay, without any untoward effects. Next, please.

And the last trial, the ABCSG trial, which again looked at four to six years of endocrine therapy, Tam, AI, tamoxifen, then they were randomized to anastrozole for two years versus five years, showing that probably there is -- it's questionable -- next, please. If you look again at the disease-free survival, no difference; overall survival, no difference, short versus long. Next, please.

Secondary endpoints of contralateral breast cancer versus a second primary breast cancer, nothing that is statistically significant at all between the two. Next, please. But if you look at problems such as fractures, with longer-term aromatase inhibitor therapy there is a higher fracture rate, and this is something that's real and clinically significant. So, I think that needs to be taken into consideration. Next, please.

So, I think, again, we're just about finished. If we look to address the issue of extended adjuvant therapy and we're looking at hazard ratios, certainly after tamoxifen for five years, there is a significant benefit with extended adjuvant as demonstrated in the MA17, the B33 and the ABCSG trial after two years of an AI. There is a modest to no benefit in the MA17-R, the IDEAL, the DATA, the B42 trial. So, again, there may be subgroups who benefit. And if we look at intermittent AI, that's the same as continuous AI. There is only one trial that was one report at San Antonio. I do not think that that should change the current practice at this moment. Next, please.

So, I think the final thoughts are aromatase inhibitors are better than tamoxifen alone. Sequencing treatment, a Tam to an AI or you can start out on an AI, and this is important. Some of our patients will say I just can't tolerate it, so going back to tamoxifen is an alternative because you've at least been on some AI. The results of an extended AI are mixed. There are multiple trial designs. The largest benefit is seen after prior tamoxifen exposure, not prior aromatase inhibitor exposure. So, there is less or no benefit after that. The optimal duration of the AI is still unclear. We actually began to revisit this

ourselves. And in patients who are deemed to be sufficiently high risk, that is, positive nodes, poor risk features, perhaps there is a role for 10 years of the AI. And in the future, maybe genomic markers may help us to define which patients will derive more benefit. Next, please.

This is just a summary slide of all of the trials that we went through tonight. I think we went through -- next, please. We went through a large number of trials, but they just illustrate certain principles. One I think is the importance of an AI; two, there are high-risk patients that you should consider longer treatment, but the AI story is still to be determined. Certainly, ovarian suppression with an aromatase inhibitor is better than tamoxifen alone in your premenopausal high-risk patients. Next, please. Next, please. Next. And I want to thank you.

Marlene Stager:

Thank you, Dr. Lake, for a wonderful and informative presentation. We now have an opportunity for some questions.

Caller #1:

Dr. Lake, I've been on Arimidex, or I guess it's anastrozole, for nine years now. My question is, do we have research beyond 10 years? I've had prior cancer. I had leukemia and a bone marrow transplant back in '83, and then my breast cancer was in '09. I've had a lot of chemotherapy, full body radiation for the leukemia, and then for the breast cancer I did have chemo and radiation. I had 26 nodes that were cancerous. So, what happens after 10 years? Should I stay on it being a high risk? I've also had a third cancer, endometrial, but that was Stage 1.

Diana Lake:

Okay. There is no data at all. This is not an uncommon question. Personally, in my practice, I have a few patients who refused to stop the aromatase inhibitor. Now, as long as you understand that there is no data. The things that you have to follow, however, would be your bone density, and I know you've had a lot of prior therapy, so you may -- some of which may have affected your bones. So, your bone health is very important. Remember, that was shown in the ABCSG trial, that longer AI was associated with a higher fracture risk, that's one. And the other thing is cardiovascular risk, because aromatase inhibitors are associated with an increase in one's lipids, so that's something that you should discuss with your physician, what are your lipids, what is your bone health like, and make your decision. But there is no data of aromatase inhibitors greater than 10 years.

Caller #1:

Thank you.

Caller #2:

What do you mean by ovarian suppression? Do you mean surgery?

Diana Lake:

No. Ovarian suppression, there are several ways to do it. One is surgery, actually remove your ovaries, and the other is to give a medication that will shut down the ovaries so the ovaries will not produce estrogen.

Caller #2:

And what is that medication?

Diana Lake:

Lupron, for example, is one such drug, if you've ever heard of it.

Caller #2:

What's the name of the drug?

Diana Lake:

Lupron.

Caller #2:

Oh, Lupron, yes, okay. Thank you.

Online Question #1:

I know grapefruit is not advised if you are on tamoxifen. Is orange peel a risk? I've read some articles and seen some food lists that recommended avoiding tangerine, orange peels in tea, for example. Can you comment on that?

- Diana Lake:** I can't. I was not aware of orange peels, certainly was not aware of tea, but grapefruit, yes. Grapefruit, actually, interferes with a lot of medications, not just the breast medications. I suggest that you speak with a nutritionist, who asked that question, or your oncologist could connect you with a nutritionist.
- Online Question #2:** Have there been any studies on women who choose not to take AIs due to osteoporosis? I have had endometrial cancer two times and lobular breast cancer recently.
- Diana Lake:** So, if one has osteoporosis to begin with, I think you have several options, number one -- and you need endocrine therapy -- number one would be an aromatase inhibitor along with a drug, what we call bone-modifying agents. So, there was Zometa, zoledronic acid is one, and then the other, more modern drug is Prolia, which you may have seen advertisements on TV, which is denosumab. The Prolia is given one time every six months. So, you can certainly consider that. The other thing, and we're learning now, if you have severe osteoporosis, remember, all these trials show that it's just important that you have endocrine therapy. So, we're not as dogmatic, even though I made a difference between pre- and postmenopausal. The bottom line is, if you need endocrine therapy to be able to get it, and so therefore tamoxifen might be a good choice, and that is something you need to discuss with your physician because tamoxifen helps to maintain or slightly increase, that means improve, the bone density.
- Online Question #3:** And tamoxifen is even if you're postmenopausal?
- Diana Lake:** Yeah, that was the point that I was -- that's what I was just trying to say. Even though I made a point today and we divided everything into pre- and postmenopausal status, the important thing, and those are guidelines, but the important thing is that if you need endocrine therapy that you get it. And so, therefore, I would say if you need to have endocrine therapy, lobular carcinomas can respond to endocrine. They're very responsive to endocrine. I would go ahead and do it. But you would -- you might have to have a bone-modifying agent or tamoxifen.
- Online Question #4:** Most data discussed had to do with HER2-negative tumors. What AI and CDK 4/6 inhibitors are available for HER2-positive metastatic cancers?
- Diana Lake:** So, the CD 4/6 kinase inhibitors in HER2-positive breast cancer are, I think there are a couple of clinical trials to address that issue. That's not the standard of care. I think we have so many -- when you have HER2-positive breast cancer, you can really -- you have something to target, and that's the HER2 receptor. So, usually anti-HER2 therapy is included, or HER2-directed therapy. So, patients that are ER-positive, HER2-positive, and let's say we're talking about early stage disease, you've had your chemo, you've had your HER2-directed, we place those patients on aromatase inhibitors if they're postmenopausal. I think you could administer any endocrine therapy, meaning tamoxifen or an AI. There was one study in the 1990s which looked at neoadjuvant, I think it was letrozole was the drug, in patients who were HER2-positive. So, the aromatase inhibitors may be a little better in HER2, but the bottom line is you can administer HER2-positive patients who are also ER-positive any endocrine treatment.
- Caller #3:** Hi. I know this is may be a little off course, but what is the importance of vitamin D as far as breast cancer? I've been reading a lot about vitamin D would -- it would be very important for women that have had breast cancer to keep their levels up above normal with vitamin D intake. So, do you need vitamins? And then what if you can't take the amount of milligrams that they say you need to take in order to keep that D level up?
- Diana Lake:** I have a question to answer back. What is the vitamin D level that this article is quoting to you?
- Caller #3:** It said, I believe, that the blood test level for vitamin D would be 30, and that you should keep your blood level in the 50s, and in my case, let's say, if I were to take 5,000 units of vitamin D a day, that would maybe push me up into the 50s, but to me, I feel that that would cause toxicity.

Diana Lake: It doesn't -- we usually are not giving vitamin D in relation to breast cancer management, but vitamin D is part of bone health. You know, everyone used to be excited about vitamin D, thinking it also boosts one's immune system, but our recommendation is to give vitamin D to maintain a level above 30 along with calcium for one's bone health, especially if you're on an aromatase inhibitor. The prescription usually is exercise 30 minutes five days a week, moderate exercise, moderate defined as whatever raises your heart rate and makes you perspire. Calcium, you should take, it's preferable to take it through nutrition, like with yogurt, milk, but you can also take a supplement, and vitamin D, the average being 2,000 mg a day. But, again, that depends on what your vitamin D level is.

Caller #3: Thank you.

Diana Lake: Many people in North America are vitamin D-deficient.

Online Question #5: I was lymph node cancer-free with my IDC and am having a total hysterectomy. How long do I need to take an aromatase inhibitor? I can read that again. Node-free with infiltrating ductile carcinoma and having a total hysterectomy. How long do I need to take an aromatase inhibitor?

Diana Lake: Again, that's a variable question. Your nodes were clean, I don't know the size of your tumor, and that's something that you really have to discuss, because the only thing the hysterectomy -- I presume when you had the hysterectomy, your ovaries were removed. I hope that's what you're saying. So, if your ovaries were removed, you are now postmenopausal, whereas, before you were premenopausal. So, you just then become a node-negative postmenopausal woman. Depending on the size of the tumor and other features, at least five years. We don't know about the -- and that was the point I was trying to make. We don't really know if it's necessary to take an AI for 10 years. And, again, this is an ongoing discussion that you should have with your oncologist.

Caller #4: My question is, in terms of the AIs, is one better than another, or is it just a matter of tolerance?

Diana Lake: That's a nice question and everyone asks that. One is not better than another, in my opinion. There are two types of AIs. There's the steroidal based on chemical formation and nonsteroidal way of inhibiting. The nonsteroidals anastrozole, letrozole. They're an identical drug made by two different pharmaceutical companies. The other drug, exemestane, is a steroidal type, but it's not better than the others. Theoretically, if you're having difficulty tolerating one and you switch to another, you should have the same difficulty, but sometimes patients don't, and so we do switch.

Marlene Stager: Okay. I'd like to thank Dr. Lake again for so generously sharing her time, expertise, dedication and commitment to the breast cancer community, and thank you all for joining us tonight. Have a good night. Thank you very much, Dr. Lake.

Diana Lake: Thank you, you're welcome.