Medical Breakthroughs From SABCS

with

Dr. Naamit Kurshan Gerber
and
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Melissa Rosen: Thank you so much for being here tonight. I want to thank you for joining us for a really important conversation. SABCS may seem like just another entry into the breast cancer alphabet, but the annual San Antonio Breast Cancer Symposium in its 46th year hosts about 10,000 clinicians and scientists from all over the world and is the largest and most prestigious scientific gathering on breast cancer research.

The International Scientific Symposium allows for the important interactions and exchanges between basic scientists and clinicians devoted to improved diagnosis and treatment of breast cancer. And the information that is exchanged there each year directly impacts us as providers, as patients, as survivors. So thank you again for joining us for this really important conversation.

Before we begin, as always, I have a few housekeeping items to share. First, I want to thank our sponsors, Novartis and Gilead, for their generous support of this evening's webinar. This webinar is being recorded and will be posted on Sharsheret's website alongside a transcript for you to use as a resource. Participants' names and faces will not be in the recording. Of course, you also have the option to be anonymous during today's live webinar, the instructions on how to do that are in the chat box right now.

Additionally, we now have closed captions available. The instructions on how to activate that captioning is in the chat now as well and a reminder, we invite members of the Embrace community, those facing metastatic breast cancer to stay on at the end of the webinar for an intimate conversation with our speakers and with Bonnie Beckoff, our director of support services.

We received an incredible number of questions through our registration process and if there are questions that arise tonight, we will be monitoring the chat box, please put them there and we will add them to the list of questions that we will address during our Q&A session at the end of the webinar.

As a reminder, Sharsheret has been providing telehealth services to the breast and ovarian cancer communities for more than 20 years because cancer is so much more than just a physical experience. If you are interested in finding out more about Sharsheret's free, confidential and personalized services, please email us or visit our website at Sharsheret.org.

And as we move into the presentation, I want to remind you that as a national non-for-profit cancer support and education organization, we do not provide any medical advice. The information provided this evening by Sharsheret and by our speakers is not a substitute for medical advice or treatment for a specific medical condition. You should not use this information to diagnose or treat a health problem. As always, seek the advice of your physician or qualified

healthcare provider with any questions you might have about your own medical condition.

We are so fortunate to have our two speakers with us today. Dr. Natalie Klar is an academic breast medical oncologist at the Perlmutter Cancer Center at NYU Grossman School of Medicine. She received her medical degree from Albany Medical College where she graduated cum laude and was inducted into the Alpha Omega Alpha Honor Society. She attended her internal medicine residency at the University of Pittsburgh Medical Center. She has over five years of clinical and research experience in breast oncology and her goal is to personalize treatments based on her patient's tumor biology and immunologic infiltrates while keeping their cultural views and personal preferences in mind. Her clinical research interests include triple-negative breast cancer, immunotherapy and health equity. She has presented her research at many prestigious medical conferences including San Antonio. She has published original research and reviewed articles in Clinical Breast Cancer, the Journal of the National Cancer Institute, Breast Cancer Research Treatment and The Breast Journal. Dr. Klar, we are so happy to have you here today. Thank you very much.

Dr. Natalie Klar: Thank you for the introduction. I'm a breast medical oncologist at NYU and I'm going to review some of the medical updates from San Antonio.

To start out, I have no financial disclosures, but one of the studies I'm going to talk about is The POSITIVE Trial. I am one of the study authors on the trial.

An overview of the studies I want to discuss tonight: I want to discuss The POSITIVE Trial, which I am one of the study authors on. It’s a study looking at pregnancy after the breast cancer diagnosis and this is an update looking at the use of assistive reproductive technology.

I also want to discuss another study, the PREFERABLE-EFFECT study, which is a study looking at structured exercise programs in metastatic breast cancer patients and the impact on quality of life, fatigue and other cancer related outcomes. The third study I want to discuss are the updated results from the KATHERINE study. And this was a study presented several years ago, but they have an update in their results. And this is a study looking at T-DM1, which is also known as Kadcyla compared to trastuzumab Herceptin used in the adjuvant setting for stage two and three, and HER2-POSITIVE breast cancer.

And the fourth study I wanted to discuss was an updated result from the KEYNOTE-522 study, which is a study looking at the addition of immunotherapy pembrolizumab, also known as KEYTRUDA, in addition to chemotherapy compared to chemotherapy alone in stage II and stage III triple-negative breast cancer.

The first study I'm going to review is the POSITIVE study. This update is looking at fertility preservation and assisted reproductive technology in breast cancer for women who interrupted their adjuvant endocrine therapy. So the POSITIVE trial is a prospective international multicenter investigator initiated single arm trial. This study included women who have the diagnosis of hormone positive breast cancer and these women underwent their breast cancer related surgery, chemotherapy as indicated, radiotherapy as indicated, and then received at least 18 months and up to 30 months of adjuvant endocrine therapy. Then if these women chose to enroll in this study and were interested in a pregnancy, they paused their endocrine therapy for up to two years to allow time for conception delivery and/or breastfeeding, and then needed to resume their endocrine therapy at the two-year time point, and then to complete five to 10 years of endocrine therapy based on their decision with their physician. Then, these women are going to be followed for 10 years following that.

In terms of key eligibility, these were premenopausal women with stage I to stage III hormone positive breast cancer. These were women who wanted to become pregnant. These were women who were 42 or younger at study entry. These were women who had at least 18 months of endocrine therapy, but no more than 30 months of endocrine therapy before joining the study. And these were women who had no clinical evidence of recurrent disease.

So the primary endpoint of this study was breast cancer-free interval, and this was presented at San Antonio in 2022. The data showed that overall, at the three-year time point, there was no difference in breast cancer-free interval for the women who paused their endocrine therapy to attempt to have a pregnancy versus the women compared to the general population of women who usually do not pause their endocrine therapy for two years.

This presentation at San Antonio this year was looking at two things: menstruation recovery as well as use of assisted reproductive technology. And what they did was they collected information on the patients enrolled in the study. They were asked to keep a menstrual diary for two years. They were asked if they used any fertility preservation at the diagnosis of their breast cancer, and if they did, that information was collected. And if they used any assistive reproductive technology while they were on the study, that information was collected as well.

This study had 516 patients, 66% of the patients were 35 or older. 34% of the patients had a positive lymph node. 62% of the patients had prior chemotherapy. And 75% of the patients had not had a prior live birth.

In terms of menstruation, as some of you may know, when you receive chemotherapy, and 66% of the patients in the study had received prior chemotherapy, that can affect the ovary, so that can affect fertility and that can also affect the ability to continue menstruating. So a lot of times the

menstruations are interrupted. At the enrollment of this study, 53% of the patients had a amenorrhea, even though these are young women. The good news was 94% of the patients had a recovery of their menses. And at the six-month time point, it seemed that almost about 90% of the patients were having menses recovery. You can see on this graph that the green line was patients who received chemo with no GnRH and those had a lower rate of their menses recovering at six months. And GnRH you might know as Leuprolide or Goserelin, those are medications that sometimes are given with chemotherapy to protect the ovaries and prevent amenorrhea or early menopause from happening.

In terms of time to pregnancy, the good news was 74% of these women had at least one pregnancy. The biggest factor associated with having pregnancy during these two year time point was age. You can see the women under 35 at 24 months, 80% of them had a pregnancy. You could see in the blue dotted line, the women 35 to 39 were somewhere in the middle and the lowest rates of pregnancy were in the women who were age 40 to 42. But still at 24 months, 50% of those women were able to have a pregnancy.

Then, they looked at the data on using assistive reproductive technology. 51% of the patients did some form of fertility preservation at the time of their breast cancer diagnosis. 36% of the patients had ovarian stimulation for embryo or oocyte cryo-preservation, sometimes known as embryo or egg freezing. In terms of assistive reproductive technology, 43% underwent some form of assistive reproductive technology at enrollment. In this study, 16% of the patients had ovarian stimulation for IVF and 14% of the patients had cryo-preserved embryos transferred. And the data of using this technology with chances of pregnancy, as we discussed before, as age increased, the chances of pregnancy went down with the lowest rates of pregnancy in the older women in the study, the 40 to 42 year olds compared to the women under 35. The thing that made the chance of pregnancy the highest was actually using a cryo-preserved embryo compared to not using any assisted reproductive technology with an odds ratio you can see there of 2.41. And they have a little asterisk, and you can see 82% of the patients who had a cryo-preserved embryo transferred, had at least one pregnancy while on the study.

Then they looked at the use of this ovarian stimulation and this embryo oocyte cryo-preservation at the time of breast cancer diagnosis and if this increased the risk of breast cancer events occurring, and at the three-year time point, there's no significant difference in rates of breast cancer events occurring. You can see there's a difference of 9.7 versus 8.7, it's a 1% difference, but it wasn't statistically significant. And you can look at the graph here and you can see the blue line for the women who did the embryo oocyte preservation and the dotted line for the women who did not do it, you can see those lines are pretty similar. So there's not a big difference in terms of breast cancer outcomes at the three-year time point.

They then looked at the women who used assistive reproductive technology and ovarian stimulation while they were on the study and you could look at the two lines, the dotted line and the solid line and they looked fairly similar and there was not a big difference in the number of breast cancer events at the 24-month mark between these two groups.

Overall, the conclusion of this study is it's a large prospective study looking at fertility preservation and ART and patients with early stage hormone positive breast cancer who desire pregnancy, 90% of the women who had a amenorrhea resume their menses. Patients of young age was the main factor associated with shorter time to pregnancy. Embryo and oocyte cryopreservation at breast cancer diagnosis followed by an embryo transfer had the highest rates of pregnancy and was not associated, at least at the three-year time point, with worse prognosis from the breast cancer. There was no increase in breast cancer events for women who underwent IVF, but we need longer term follow-up. And this data is really important as we counsel our young patients about oncofertility and interest in how to stay fertile and have a pregnancy after they undergo treatment for their breast cancer.

And it'll be important to watch this data over time because right now we only have the data at the three-year time point and as we're discussing, these are very young women and 70% of them just had a baby. We don't want their breast cancer to reoccur at the three-year time point, nor do we want it to reoccur at the five, 10, 15, 20 year time point. So we're going to have to watch this data over time.

The next study I wanted to talk about is the PREFERABLE-EFFECTS study presented by Dr. May at San Antonio. And this looked at the effects of a structured exercise program for metastatic breast cancer patients and how it impacted fatigue and health related quality of life in these patients. This study had 350 metastatic breast cancer patients. They were either randomized to a nine-month structured and personalized exercise program that included aerobic training, resistance training and balance training. This program was twice a week for 60 minutes, or they were in a control group that was just their usual care and just general advice from their doctor that it's good to exercise. And you can see here in the graphs, the yellow-orange line represents the women who were in the exercise group and the exercise group patients had higher quality of life scores and lower physical fatigue scores compared to the women who were just in the general standard of care group.

The conclusion is that this structured resistance and aerobic exercise program resulted in beneficial effects on fatigue, health related quality of life and other clinically relevant outcomes in metastatic breast cancer. And hopefully there'll be more programs like this offered to patients as it seems to have a really good effect on helping patients with fatigue, quality of life, shortness of breath, pain, and some other symptoms that metastatic breast cancer patients have.

The next study I wanted to discuss was the updated results on the KATHERINE trial. The KATHERINE trial was a study in stage II and stage III, HER2-positive breast cancer patients. And this was a study that looked at the standard of care for HER2-positive breast cancer patients, which is receiving chemotherapy as well as HER2 antibodies such as trastuzumab Herceptin prior to surgery. And following that treatment, patients go to surgery and at time of surgery we can tell if patients had a complete response based on their pathology from their surgery, meaning no cancer is left or if they have residual disease, meaning there is still some cancer remaining.

For the patients who have residual disease, they're at higher risk for their breast cancer to come back. So this KATHERINE study looked at giving a newer medication at the time called T-DM1 Kadcyla for 14 cycles compared to giving the standard which was just trastuzumab Herceptin.

When the study was first presented back in 2018, they showed these graphs here and in terms of invasive disease-free survival at the three-year time point, if you had received just T-DM1, if you had received T-DM1, the invasive disease-free survival was 88.3% and if you receive trastuzumab, the invasive disease-free survival was 77%. And with this benefit, you can see the difference graphically too between the blue and the orange line. This was approved and this became kind of the standard for residual disease in stage II and II HER2-positive receiving Kadcyla T-DM1.

You can see here back in 2018 when they presented, they also looked at the overall survival, but the two graphs weren't very different, at least at this time point, and so they weren't able at that time point to see a significant difference in overall survival. So they represented the data this year at San Antonio and you can see here at the seven-year time point, the blue and the yellow orange line are actually still very separate and the difference is 80.8 versus 67.1 in invasive disease-free survival, which means that there's an absolute invasive disease-free survival benefit of 13.7% at the seven-year time point.

They then showed the data for the overall survival. And in terms of the overall survival, you can see at the seven year time point, we now see these two graphs, the blue and the orange starting to separate a little bit more. And you can see that the absolute overall survival benefit at seven years is 4.7%, which is a significant reduction in the risk of death by 34% with the T-DM1.

The conclusion is that there's a significant benefit at the seven-year time point for invasive disease-free survival with an absolute benefit of 13.7%. And now we're seeing a very significant overall survival benefit at the seven-year time point of 4.7%. So this is a med that we've been using for the past several years for our patients and this is good news to see that there's still lots of benefit years later after completing the treatment at the seven-year time point, and that the benefit extends to overall survival as well.

The last study I wanted to review is the updated results that were presented at San Antonio for the KEYNOTE-522 study, which is a study in stage II and stage III triple-negative breast cancer.

In this study the standard of care for stage II and stage III triple-negative breast cancer patients is receiving chemotherapy before surgery. In this study, patients either receive the standard of care chemotherapy before surgery or they receive the standard of care chemotherapy plus an additional immunotherapy called pembrolizumab or KEYTRUDA. And if they received the pembrolizumab before surgery, they also received the pembrolizumab after surgery.

This data was presented at the 36-month time point and they saw a difference between 84.5% and 76.8% in event-free survival. You can see the difference between the green and the brown lines on the graph. And this led to the FDA approval of pembrolizumab in this setting. And for the past year and a half two years, we've been using pembrolizumab based on this FDA approval and based on this EFS benefit. So the updated results were presented at San Antonio, and this is on the other side of the screen showing the 60-month update. And at 60 months we're seeing the graphs are still separate and you see 81.3 verse 72.3 with the same hazard ratio of 0.63.

They then showed some more data and they divided it by patients with different stages. So for the patients who had stage II disease and the patients who had stage III disease, we can still see the graphs are separate. And they looked at two different groups, the patients who their cancer completely went away at the time of surgery, calling PCR, and the patients who did not have a PCR and still had some residual cancer at the time of surgery. And you can see the lines are more separate for the patients who did not have a PCR, a difference on the stage II side of 69.2 versus 59.1 and a difference on the stage III side of 46.8 versus 38.2. However, what's interesting is even for the patients who the cancer completely went away, the PCR group, we are seeing a difference between the lines for the patients who received the pembrolizumab.

They then showed the same data for the patients who entered the study with a positive lymph node and the patients who entered the study with a negative lymph node. And as you can see, the graphs look pretty similar as well. And we see a benefit in both these groups.

So overall this data, this updated data shows that at the follow-up of five years we're seeing clinically meaningful improvement in event-free survival for patients who received pembrolizumab in addition to their chemo and this benefit is seen in the stage II patients and the stage III patients, this benefit seen in the node positive and the node negative patients. And interestingly, we're seeing the benefit in the patients who had the complete response as well as the patients with residual disease. So it's very interesting and we've been using pembrolizumab since it was approved a year and a half ago, two years ago based

on the previous data. But it's good to see that the data continues to show that all groups are benefiting from this medication being added to chemotherapy. And I think those were the studies I wanted to review for today. So I think we could move on to the next presentation and I'll take questions afterwards.

Melissa Rosen: Before you go, there was one question. There was one question that was very specific to one of the studies. The others that I noted were a little more general, but somebody asked about with the first study, "The cryo-preservation was always done before treatment in the POSITIVE study?"

Dr. Natalie Klar: I think the majority of the cryo-preservation was. Typically, we recommend, if you are receiving chemotherapy, there's a chance that that's going to impact your ovaries and your fertility, so typically we recommend if you're interested in a pregnancy and you are interested sometimes thinking about doing the cryo-preservation before you undergo chemotherapy. In the study they only talk about the rates of cryo-preservation being done before starting endocrine therapy and before chemotherapy, they don't talk about the rates afterwards. But yeah, that is an interesting question because sometimes in clinic we see patients who didn't have the opportunity, they were in a rush to get started on their chemo or other things. Sometimes there's also financial barriers as well.

Dr. Natalie Klar: I see in the chat someone just said, "Yes, they kind of lumped both the egg..." Because the oocytes that you were seeing, that's the eggs, so they lumped the embryos and the oocytes together in some of the data. And then other data though, when they talked about the highest rates of successful pregnancies, those were with the frozen embryos. And that has been known that embryos are a little bit more successful because it's a combined egg and a sperm and a full embryo, so they're a little less fragile and they're a little more successful when they go undergo the unfreezing process and implantation process of being successful.

Melissa Rosen: There are a lot more questions that came through, but they're a little more general. So we're going to save them for the Q&A. I want to thank you. Those are four hopeful studies, and we'll talk a little bit more about them shortly. But thank you very much.

We also have with us Dr. Naamit Gerber, who is the Vice Chair for Education and an associate professor in the Department of Radiation Oncology at the Perlmutter Cancer Center of the NYU Langone Medical Center. Dr. Gerber received her BA in the history of science from Harvard College and her MD from the Icahn School of Medicine at Mount Sinai. She completed her residency in radiation oncology at Memorial Sloan Kettering. Dr. Gerber specializes in the treatment of breast cancer and lymphoma. She's the co-leader for the Disease Management Groups for Breast Cancer and Hematologic Malignancies at the Perlmutter Cancer Center. In addition to her clinical practice, she's actively engaged in research that focuses on improving outcomes for women with early

stage breast cancer. She's authored over 50 peer review publications. Dr. Gerber also serves as the program director of the NYU Radiation Oncology Residency Program. Thank you for being with us and welcome to the screen.

Dr. Naamit Gerber: Thank you so much for having me. I really appreciate the opportunity to speak to all of you tonight.

Okay, so I'm going to go through a few studies from San Antonio. Here are my disclosures. I received research funding from Prelude and consultancies from Accuray. In order to place some of these studies in context, I'm actually going to start with the PRIME II publication, which came out in the New England Journal of Medicine just a little bit less than a year ago, which really sets the backdrop for the IDEA trial which was presented at San Antonio this year. And both of these studies are looking at the omission of radiation in early stage breast cancer patients.

We're then going to shift gears to talk about women who were treated with neoadjuvant chemotherapy similar to the paradigm of the KATHERINE trial that Dr. Klar just spoke about. And this was a trial that until San Antonio this year we knew nothing about its results. This was the first time we have results, so it's very exciting and I'll share those five year results with you.

And then finally I'm going to touch on a study that was presented at San Antonio that looked at outcomes in women with BRCA1 mutations based on the type of surgery they had.

Okay, so this is a slide which was from the Lancet 2011, which was really demonstrating this paradigm that when women have a lumpectomy, meaning they preserve their breasts, they do not have a mastectomy and then they get radiation, that radiation is not just lowering the risk of any recurrence, but it's actually improving the risk of breast cancer mortality, of dying from breast cancer and it's improving overall survival. And ever since the publication of this meta-analysis, this has really been the paradigm within radiation oncology and early stage breast cancer that when we give radiation after our lumpectomy, we're not just lowering the risk of recurrence but we're saving lives. But our field is always asking, are there women who don't need radiation? Are there women in whom they can still get a lumpectomy and still be spared radiation? And so for years we've been trying to identify a group of patients who might fall into this category.

One of the early trials that was done in this space, which was viewed as a success, was this study which looked at women 70 years or older with stage I estrogen receptor positive breast cancer. And these women were randomized to tamoxifen alone, this was before aromatase inhibitors. They all got tamoxifen versus tamoxifen and radiation.

What this study showed was that radiation, which is the women in blue are still doing better, but that the women who have the tamoxifen alone are still doing okay with only a 10% recurrence and that most of these women were thankfully not dying of their breast cancer and there was no difference in mastectomy free survival or overall survival. And so this study really sets the stage that maybe in women over the age of 70, if they're going to get five years of tamoxifen or an aromatase inhibitor, maybe they don't need radiation.

Then came the PRIME II trial whose 10 year results were published in the New England Journal just less than a year ago. And this lowers the age group to 65 years old. It included women with tumors up to three centimeters who were lymph node negative with hormone receptor positive breast cancer, negative margins. And very similar to the CALGB trial, they showed that radiation was still lowering the risk of a local recurrence, here's the blue line versus the red line, but it had no effect on overall survival or breast cancer specific survival. And that most of these women were not dying of their breast cancer, 13% of the deaths were due to breast cancer.

Interestingly, in the PRIME II publication, when they separated out the estrogen receptor positive patients into those who were strongly estrogen receptor positive versus those who were more weakly estrogen receptor positive, there was a higher risk of recurrence in those who are estrogen receptor low, showing that maybe we should not omit radiation in those women.

Then they also looked at the risk of recurrence in women who were not able to take five years of the endocrine therapy for whatever reason and so then the women who did not finish their five years of endocrine therapy and did not get radiation, the risk of recurrence was almost five times as high.

The takeaway from this publication is that perhaps we can lower the age to 65 for women who might not all need radiation, in these women radiation is still working though, it's reducing the local recurrence from 9.5% to essentially 1%. No difference on survival in this group of patients over 65. They had very few patients who had grade three disease or lymphovascular invasion. So this does not apply to all women with early stage breast cancer. It might not apply in women who are estrogen receptor low. It certainly is not applicable for who aren't able to tolerate five years of endocrine therapy. But radiation can be safely omitted in women 65 years or older with grade one or two estrogen receptor high cancers if they're going to tolerate five years of endocrine therapy.

We know that radiation is still working in this patient population and providing more than a tenfold reduction in local recurrence. We don't always know who's going to tolerate the five years of endocrine therapy. And then finally, we know that thankfully with shorter courses of radiation that we have now, as short is one week, maybe their women for whom radiation would provide a better risk

benefit ratio than endocrine therapy. And that's an area of ongoing study in the EUROPA trial going on in in Europe now.

This is very similar to this trial that was just presented in San Antonio, the IDEA trial. What was novel about the IDEA trial and what's novel about many of the ongoing trials right now in this early stage breast cancer space is they're lowering the age from 65 or 70 down to 50 and then they're using genomic markers to try to better select women who might not need radiation. So in this case, they're using the Oncotype score, which is a score, as many of you know, that we use for chemotherapy decision making. So women who have stage I breast cancer with a low Oncotype are being randomized. And actually this trial was a single arm, they got five years of endocrine therapy and no radiation. The mean age was 62. These were women generally with small tumors about a centimeter, low Oncotype scores, a mean of 11. A third of them had MRI. They were strongly estrogen and progesterone receptor POSITIVE. And very few grade three patients, only 3%.

At a median sample of 5.2 years, they had overall and breast cancer specific survival of 100% with five-year freedom from any recurrence of 99%. Two patients had recurrences before five years, six additional patients recurred later than five years, no distant recurrences.

They did look at compliance with endocrine therapy with tamoxifen, aromatase inhibitors. The patients who recurred before five years were taking endocrine therapy, but three of the six of the patients who recurred after five years were compliant and three of six were not compliant. These are the curves just showing the excellent outcomes in these patients. And these are some of the other ongoing trials which are looking at omission of radiation in women generally over age 50 or over age 55. Some are a little bit older, the PRIMETIME trial is 60, EUROPA is over 70. These are all stage I patients who are estrogen receptor POSITIVE, most are grade one to two and most are now using some form of biological selection, whether it's the Oncotype or the PAM50 score to really identify these lowest risk patients and are testing whether or not all these women really need radiation.

This is the DEBRA trial that we have open at NYU right now. A similar idea, age 50 to 70, recurrence score less than 18 and randomized radiation plus endocrine therapy versus endocrine therapy alone.

So just to conclude this part of the talk, this is very exciting work that maybe we don't need to give radiation to all of our patients. Right now we have published data for women 65 or older with small strongly estrogen receptor positive breast cancer. And again, the importance of us also looking at maybe can we deescalate endocrine therapy, which of course has its own side effects and give radiation in these women, which the EUROPA trial is looking at. And we need the results of

all of these prospective trials that are using biology to determine the benefit of radiation.

Okay, so now shifting gears to women who get neoadjuvant chemotherapy, and this is again sort of the first time we've seen results from this large trial that is an NRG, a National Cooperative Group trial.

So what this trial was looking at is we know that in women who have positive lymph nodes upfront that there's a small benefit of getting not just radiation to the breast but also radiation to the lymph nodes, meaning the lymph nodes that sit in the axilla, in the armpit above and below the collarbone. But when we started treating patients with chemotherapy before surgery with neoadjuvant chemotherapy and patients had positive lymph nodes before chemotherapy, but then at the time of surgery were found to have a complete response, we didn't know if those patients need radiation to their lymph nodes. We had no data in that space. And that was what this trial was trying to answer. So it's taking women who have positive lymph nodes, who get neoadjuvant chemotherapy and at the time of surgery have no cancer left in the lymph nodes. And it was randomizing those patients to either get regional nodal irradiation or no regional nodal irradiation.

Women who had lumpectomies in the no regional nodal irradiation still got radiation to their breast versus the breast plus the lymph nodes. And women who had mastectomies either got no radiation at all versus comprehensive radiation to the chest wall and the regional nodes. They accrued 1,641 patients. We have this open at NYU and we're accruing at NYU. The median followup time at the time of this report is five years.

This is the women in the trial. You can see a real distribution in age, young age, older age, distribution of race, clinical tumor size, a good representation of triple-negative, hormone receptor positive, HER2 negative, hormone receptor positive, HER2-positive. About 60% had lumpectomy, 40% mastectomy. Not all of the patients had a complete response in the breast, about 80% did they all had to have a complete response in the lymph nodes is the criteria for being on this trial.

You can see these curves are overlapping. There was no benefit of treating the lymph nodes in these patients. Similarly, there was no benefit looking just at local regional recurrence. You definitely see when you break down the numbers that in the regional nodal radiation arm there were fewer recurrences in the lymph nodes, it's eight versus zero. But as a statistical matter, there was no statistical difference between these groups.

Then when they looked at the subgroups, just to point out a few sort of interesting things, maybe a little bit more of a benefit in the mastectomy patients, maybe a little bit more of a benefit in the estrogen receptor positive

HER2-negative and less of a benefit in triple-negative, that was statistically significant. But all in all, for patients who present with biopsy proven axillary lymph node involvement and become lymph node negative after chemotherapy, regional nodal irradiation does not improve outcomes.

There are many advantages to neoadjuvant chemotherapy, you can shrink tumors, allow for less surgery either to the breast also to the axilla, maybe not need an axillary lymph node dissection. And now we can add another thing to that list that if women get neoadjuvant chemo and have a complete response, many of these women can be spared larger fields of radiation, or in the case of mastectomy, they can be spared any radiation at all.

Now I should note that we do not yet have the publication of this data and there will be tenure data. so we're not applying this in a black and white way in clinic yet. We're still talking to a lot of these patients, making very individualized decisions. But this is very exciting data that maybe some of these women can be spared the regional nodal irradiation.

Okay, and then finally, just to touch on this study that was presented on BRCA 1 mutations in surgery. This was a study whose goal was to look at the risk of contralateral breast cancer in women with BRCA 1 pathogenic variant. So not a variant of uncertain significance, but that it was known to be a pathogenic variant. Breast cancer stage I to III, they excluded DCIS or stage IV breast cancer.

This is a very large study. So it was 2,482 eligible participants from 26 centers in 11 countries diagnosed from 1995 to 2021 with a median follow-Up of nine years. About 42% of patients were less than age 40. And then this is the breakdown in the surgeries. So 34% had breast conserving therapy, so lumpectomy, 46% had mastectomy in just the affected breast and about 20% had a bilateral mastectomy.

When they looked at differences between the groups, you can see some slight differences. The bilateral mastectomy patients tend to be diagnosed later. The younger patients were more likely to get bilateral mastectomies. And then this is their outcomes, when they looked at contralateral breast cancer, they saw higher rates, not surprisingly in the patients who had either lumpectomy or unilateral mastectomy with the lowest rates in the patients who had bilateral mastectomy. When they looked at patients who died of breast cancer, this is unadjusted for other factors, we're going to get into a better analysis in a minute, but just looking just at the differences here, you see lower rates in bilateral mastectomy and then... I'm sorry, you see the higher rate of dying of breast cancer in the unilateral mastectomy with lower rates in bilateral mastectomy and in the breast conserving surgery arm.

But also very important to note that the bilateral mastectomy patients were more likely, so if you look here at the positive lymph nodes, unilateral

mastectomy patients were more likely to have positive lymph nodes and some other higher risk features. They also looked at other factors like who got oophorectomy, radiotherapy, chemotherapy and tamoxifen.

This was looking at contralateral breast cancer. I just showed the numbers, but to just show it on the graph, with the lowest rates in gray here from bilateral mastectomy and similar rates in lumpectomy and unilateral mastectomy. This was looking at breast cancer mortality with the higher rate in the unilateral mastectomy patients and lower rates in lumpectomy and bilateral mastectomy patients.

Now this is important because this is where they start adjusting for the other factors, so the fact that some women were coming in higher risk in the unilateral mastectomy arm. And here when they looked at all patients, they did not see any differences on multivariate analysis when they accounted for the other factors, meaning when they saw this higher rate of breast cancer death in these unilateral mastectomy patients that did not hold true once they adjusted for factors. And that was true both in women less than 40 and more and greater than 40.

Just to conclude this section, the most common surgery among women with BRCA1 mutations in this very large international cohort was unilateral mastectomy followed by breast conserving therapy and bilateral mastectomy. There is a higher risk of contralateral breast cancer when women undergo breast conserving surgery and unilateral mastectomy as opposed to bilateral mastectomy with no difference in mortality between the breast conserving surgery and the bilateral mastectomy. And then when they adjusted for other factors like age, nodal status and other treatments, they had no difference in breast cancer mortality with any surgery subtype.

I just want to thank Sharsheret for organizing this webinar and inviting me to take part. So many of my patients benefit from the services Sharsheret offers, and it's really so wonderful everything that you do. And I want to thank my research collaborators, my clinical team and all of the patients who have participated on these and many other clinical trials without whom we would never be able to advance our knowledge in our science. So we really appreciate participation. Thank you.

Melissa Rosen: Thank you so much. That was also a lot of very hopeful information. This is very difficult for the lay person to understand in general. There are a lot of questions and I am going to bring Dr. Klar up here as well. A lot of the questions focus specifically on determining earlier when a recurrence does happen. So some of these questions are study specific that you presented and some were just hoping you learned other things at the conference that you can share with us.

Are there any new and reliable markers to trend for disease recurrence? In other words, what type of surveillance should be happening? What about the new blood tests, are they accurate at this point? For people who have had bilateral mastectomies, perhaps had oophorectomies or hysterectomies, how are there ways for us to check to see if there are reoccurrences in other parts of our bodies? And I'm going to let you both decide who's going to talk.

Dr. Natalie Klar: I can start with this one. This is a great question, it comes up a lot. So for breast cancer, the screening guidelines for all the different subtypes of breast cancer for stage I, II, and III breast cancer is not to do systemic scans, so not to do CT scans or PET scans, and because that's the guideline, that means insurance companies might not also cover it. And not to do blood tests. There's the old-fashioned tumor markers you might've heard that are very non-specific. It's a lab test for CEA or a cancer antigen 27-29. Those are not very specific necessarily for breast cancer, but different types of cancer in general. And the guidelines are not to do these tests and to just do breast imaging, which is usually done by order, typically by the breast surgeon and based on your risk determined breast imaging. But like you said, if a patient's had bilateral mastectomies, it's just a clinical exam. And if you have a symptom you let us know, and if you have back pain, then we do a scan of the back, et cetera.

But of course we take care of young healthy patients and we want to catch disease earlier. So I think the question on, can we get a good test for this, is a great question. And there are some new tests and I think some people are alluding to them, which are called cancer tumor ctDNA, which is cell-free tumor DNA, and sometimes they take a sample from your breast cancer surgery or your biopsy and a sample from your blood maybe at the time of diagnosis and then they follow your blood over time to see if any of those cancer cells ever come back positive.

Right now in breast cancer, it's a little bit harder, there are been no large randomized studies to say exactly what to do for the data. There have been small studies showing that if it does become positive and then we scan a patient about 30% of the time we're going to find a spot that we then biopsy in its cancer, and 60% of the time we're not going to find anything. But if we follow that patient over the next several years, they're at higher risk for something popping up. So right now that's kind of where we are. And so most academic breast oncologists aren't doing this test routinely because we don't exactly know what to do with the information and having an extra test that can add stress and it's not necessarily clear what to do.

Melissa Rosen: So you're saying, we're still not there yet?

Dr. Natalie Klar: But the test is available and there probably are some doctors who are running it. I would say the best way to do this test is to do it in a randomized clinical trial. Right now at NYU, we don't have any opened. I think we're working to try to

have some, there might be other sites in the country that do have some of these randomized clinical trials. And other clinical trials, if patients enroll on a clinical trial for something else, sometimes this is one of the things that they're collecting in their blood tests and in their follow-up visits. And so hopefully in the coming years we're going to have more data on this. But right now, if you have friends or family who have colon cancer, right now they're making treatment decisions and using it. There's more data in colon cancer and other types of cancer.

Right now in breast cancer, it's a little bit unsure. And just because the test exists and it sounds really promising and a great idea, it's a little hard in this area where we don't exactly know what to do. So I would advise patients to maybe have ctDNA done in the setting of a clinical trial where it's controlled and it clearly tells the doctors what to do. But in the general setting, occasionally we'll do it on a case by case basis, but we're not generally doing it on all our patients.

Melissa Rosen: Okay. All right, maybe next year's update we'll have more information.

Dr. Natalie Klar: Yeah, hopefully.

Melissa Rosen: A couple of other questions. Any information shared about the clinical trials with regard to vaccines to prevent a diagnosis? I guess not. Okay. So we'll hope for that for next year too. This one is for Dr. Gerber specifically, which is, when will AI use in mammography become the standard?

Dr. Naamit Gerber: Yeah, great question. So it's definitely an area of emerging research. With the preliminary results, very promising in terms of the way that AI is improving diagnosis. And I think many radiology departments are already sort of incorporating elements of AI into their diagnostic protocols with radiology input. So I think it's happening and there's emerging research showing that it's helping with diagnosis.

Melissa Rosen: Thank you. A different type of AI, so are there any new drugs in the pipeline that might replace tamoxifen aromatase inhibitors with fewer side effects and less toxicity?

Dr. Natalie Klar: So there's some medications called oral SERDs, it's a class of medications. There was a medication approved within the last year or so, Elacestrant, but that is approved in the metastatic setting. So right now there's no newer meds in terms of the early stage settings. There's studies now when patients might hear medications like Abemaciclib is used in the early stage setting, but that's in addition to the endocrine therapy. And there's a medication called Ribociclib or Kisqali that also is right now only using the metastatic setting, but more data is coming out and that might at some point get approved to be used in addition.

But in place of those endocrine therapies, right now we don't have anything. However, some of these medications that are being used now, like I mentioned Elacestrant is and some of these other oral SERDs and other medications are being used in the metastatic setting, they're going to probably... We've had some studies opened at NYU being tested in the early stage setting, and so-

Melissa Rosen: Well, that's interesting.

Dr. Natalie Klar: However, nothing is without side effects. So unfortunately... And every patient's different, so there's a chance that maybe some patients do better on Tamoxifen versus on anastrozole and some patients might do better on these. But I think unfortunately it seems like all these medications will have some side effects for some patients.

Melissa Rosen: So as long as we're talking about aromatase inhibitors, any updates on the five versus 10 years of endocrine therapy?

Dr. Natalie Klar: I don't think there were any updates this year at San Antonio. What was interesting, actually last year they did a poll, they poll the audience sometimes with questions, and one of the polls last year, I think, at San Antonio was they were asking, "How often do doctors send any tests or any testing to make the decision of five years versus 10 years?" And it was an international crowd and it was actually pretty low percentage of doctors who answered and scientists there who actually were sending additional testing to determine five or 10 years.

So it'd be interesting if they polled the audience again if over the past few years if that's changed. There's certain tests that doctors can use. The Breast Cancer Index is one of them, and that's a test where it's a test on the tumor surgical sample, and you get results based on the tumor and genomics on whether or not they think there's a significant benefit of extending the endocrine therapy. So that's interesting that right now, at least when they polled two years ago, the majority of people weren't yet using the test. But that is an extra data point to help make that decision for the patients and their doctors.

Melissa Rosen: Thank you for that. Okay, somebody asked, with regard to the studies you were talking about, Dr. Gerber, "Did the studies look at photon or proton radiation therapy?" And before you even answer that question, can you explain the difference?

Dr. Naamit Gerber.: Sure. So most of the radiation that the vast majority of radiation oncology centers in the United States and in the world offer is photon radiation. Photons are just high energy X-rays, which are typically delivered with the linear accelerator, external beam radiation. Protons is also external beam radiation. It's a charge particle with protons. There are fewer proton centers throughout the United States. For breast cancer almost, I mean, not almost, all of these studies we're using photon radiation, so X-rays. There is an ongoing very large national

study comparing protons and photons for breast cancer for lymph node positive breast cancer, and we are awaiting these results. The main endpoint of the study is seeing if with protons we can lower the dose to the heart. Until this study results, the standard of care for breast radiation is photons. There is no indication at this point off of a clinical trial for protons, meaning that no one needs to get protons for breast cancer and we don't even know if they're beneficial yet.

Melissa Rosen: Okay, thank you.

Dr. Naamit Gerber: You're welcome.

Melissa Rosen: Two more questions, we're going to try and keep the answers real quick. Were there any conversations in San Antonio about treatments, any type of treatment, aromatase inhibitors, chemo, radiation, and the use of THC to manage side effects? No. Okay.

Dr. Natalie Klar: I don't think so.

Dr. Naamit Gerber: Not that I'm aware of.

Melissa Rosen: It was a good question. And somebody asked, and this is a great question to end with, somebody asked, "If we want to learn more about a particular study, where can we go to learn about these studies?"

Dr. Naamit Gerber: Yeah, that's a great question. So some of these studies are publicly available in their original form, but for someone who's not necessarily in the science world, it's sometimes is hard to read through the original results. San Antonio would have put out press releases, so if you can sort of find on Google the press release from San Antonio that often sort of has some commentary and is sometimes more in a lay language. And then there's also a publication called The ASCO Post, which is from the American Society for Clinical Oncology. And they'll often summarize major studies. And I don't know if they've already done it, but they'll often do it in addition to after San Antonio summarizing these studies. And again, there's some commentary, it's a little bit more of a lay audience. So those are just some of the more very reputable and scientific sources, but hopefully a little bit more digestible than just reading the original study.

Melissa Rosen: Amazing. We'll include that information in the follow-up email that goes out. I want to take a second to thank both of you very much for sharing your knowledge, your expertise with us. There was a lot of hopeful information here and it's clear that we're hoping for even more hopeful information next year.

They're not going anywhere yet, but I just wanted to take a second to share a little bit more information before we segue into our Embrace group. Again, those of you who are impacted by metastatic breast cancer who are planning on

staying on for this additional conversation, please stay where you are. And as the main part of the webinar concludes, Bonnie will begin the breakout session. So again, thank you to our doctors for joining us tonight. A lot of great information. Thank you to Novartis and Gilead for their support of tonight's program. Please take a moment to fill out the brief evaluation survey that's in the chat box right now, and you can click that and still listen to the rest of the webinar. And if you're staying for the Embrace breakout, that link will be given one more time.

Again, somebody just asked about a recording. A video recording of this webinar and a transcript will be available next week. And as soon as those are available, everyone who's registered will receive an email with a link.

Finally, I want to let you know that we have our annual genetics webinar scheduled for Tuesday, January 30th. This year's topic is Navigating the Conversation of Inherited Cancer Genes with Loved Ones. There's a link right now to register in the chat box if you're interested.

Again, please remember that Sharsheret is here for you and your loved ones. Sharsheret provides emotional support, mental health counseling and other programs designed to help you navigate the cancer experience or the pre-cancer experience. All are free and completely confidential and you can reach us at the email that I just saw pop up in the chat box. I'm also going to ask my colleague Bonnie to put the link to the evaluation in one more time. And thank you all for being with us tonight. Again, if you are staying on for the Embrace breakout, just stay put exactly where you are. And for the rest of you have a lovely evening. Goodnight.