Medical Breakthroughs from ASCO

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Elana Silber:

Hi, good evening. My name is Elana Silber and I'm the CEO of Sharsheret. I am really glad to see you all coming on the call. I see more coming on, but we're going to be mindful of everyone's time and get started. Just a reminder of where you are tonight, you are on Sharsheret's webinar, medical breakthroughs from ASCO with Dr. Ruth Oratz and Dr. Sharyn Lewin.

This call will be recorded, but you can participate anonymously by turning off your screen and no names will be posted in the recording when we put it on our website. If you have friends or family that couldn't participate tonight, we will archive this and we have people calling from all over the world that might be sleeping now, but they'll be accessing it tomorrow or soon after. We'll have this online for everyone.

Tonight's about medical breakthroughs and I wanted to remind you all that Sharsheret has a team of social workers and a genetic counselor that are on staff and available to provide mental health counseling and emotional support as we continue to navigate these most challenging times. But tonight, the focus is on medical breakthroughs from ASCO. ASCO is the top organization for medical oncologists and professionals. And the information that they provide sometimes could be beyond what we understand, the language or the jargon, it's hard for us. But bringing these top professionals here with us tonight, we can explain in layman's terms and things that can really help you understand what's new and what's best for you.

Again, nothing tonight is meant to provide you with specific medical advice, we still encourage you to reach out to your own healthcare professionals. And feel free to continue sending in questions, we have some before. I'd like to just also give a special thank you to the sponsors for tonight's webinar, which is the Siegmund and Edith Blumenthal Memorial Fund, Macrogenics, GSK and Merck.

We're going to start tonight with Dr. Ruth Oratz. Dr. Oratz is a medical oncologist at NYU Langone. Dr. Oratz specializes in treating people who have all stages of breast cancer as well who are those at increased risk of developing cancer. Dr. Oratz is also a very proud member of Sharsheret's medical advisory board and I'm going to turn the floor over to Dr. Oratz. Thank you.

Dr. Ruth Oratz:

Thanks very much, Elana. I'm delighted to be back with Sharsheret this evening. And as Elana said, we're really focusing on the presentations from this year's ASCO meeting. Things are a little bit technical and I'm going to be showing you the slides, which are actually from the meeting presentation. Don't get scared away by some of the words and the way it looks, I'll try to walk you through it and explain what we think some of the important breakthroughs were that were presented at this year's meeting, which was also a virtual meeting.

I'm going to start with advanced breast cancer and some of the developments that were presented, starting with triple negative breast cancer. That's what this TNBC is. This was a very important study, called the keynote study, which asked the question of whether or not adding immunotherapy to chemotherapy in the first line, meaning the very first treatment for metastatic disease of triple negative breast cancer was better than chemo alone. This is a randomized trial, chemotherapy with or without immunotherapy. And in this case, the immunotherapy drug that we looked at is called Pembrolizumab and that's also known as Keytruda.

In this trial patients also were stratified by whether or not their tumor had a particular marker, called PDL1, which gives us an idea of possibly how responsive that tumor will be to immunotherapy, how effective the treatment will be. In this study, in this randomized trial, we showed that there was a significant benefit to adding immunotherapy to chemotherapy in treating triple negative metastatic breast cancer. Particularly, if we do it right upfront, at the beginning of the metastatic disease.

In the next study, we're looking at results that are relevant to estrogen receptor positive breast cancer, ER positive. This is not triple negative, this is ER positive breast cancer. And again, this is looking at the efficacy of a new drug, this is a drug called Alpelisib or Piqray. And what we know about breast cancers that are hormone sensitive, that if we treat them with anti-estrogen drugs and now as a very common treatment, we add a CDK4/6 inhibitor. A drug like palbociclib, or Ibrance, ribociclib or Kisqali. You've heard those names. This study is asking the question of, can we use a new drug, called Piqray, after patients have already been treated with the other hormonal therapies? This is a very complicated slide, but it's really here just so you can refer back to it and ask your doctor the question of, would this drug, Piqray, be helpful in treating metastatic hormone receptor positive breast cancer? The answer was yes. We did see very good responses, but this drug is also a targeted therapy and in order for it to work, the tumor must have a mutation in PIK3C. It's a very, very specific subset of ER positive breast cancers, but it was an important study.

This is a third slide, which is looking at a very interesting question, also in metastatic breast cancer. And this is for all types of metastatic breast cancer, triple negative, HER2-positive, ER positive, any type of metastatic breast cancer. And here, we're asking the question, in women who present with a tumor in the breast and when we do the staging we find out that there is metastasis, does it make sense to aggressively treat the tumor in the breast? Or, should we just give systemic therapy by itself, without also adding, say surgery or radiation to the breast? And this was an important question because we really didn't know what to do and it was on a case by case decision, which of course, it always is. But this study actually randomized patients in this situation, what we call De Novo stage four breast cancer presenting with stage four disease. Should you or should you not address the tumor in the breast right up front. And what we showed in this study was, it did not make a big difference to do surgery or radiation or treatment, what we call local therapy. And that's actually important to know, because we wouldn't want to delay starting effective systemic therapy by addressing the local therapy first.

Now, this is not to say we would never do any kind of local therapy. Of course, if it's required for specific reasons, we would. But this is telling us we don't have to do it in every single case and we're not jeopardizing the outcome. A long term follow-up, in a very important study.

This next slide is addressing a specific type, again, of metastatic breast cancer. This is in patients who have BRCA mutations and we also looked at other mutations in the tumors, this is in metastatic disease. Very often we biopsy when there's metastatic disease and then do further analysis of that tumor, looking for mutations. I mentioned that PIK3C mutation, or the PDL1 expression, this helps us to decide whether or not specific targeted drugs will be effective in treating that type of breast cancer. Going beyond the general markers of estrogen and progesterone receptor and HER2/neu, but looking for these other pathways. One of those pathways is BRCA1 and BRCA2 and then there are other mutations that we find in the tumors, one of them is called PALB2. And what we did in this study was to use a drug and Dr. Lewin knows about these drugs and may mention them, the PARP inhibitors, which are very active in ovarian cancer, in patients particularly with BRCA mutations. But now, we are looking at breast cancer. The name of the drug in this study is Olaparib. And what we saw was that in tumors, now these are the tumors that had mutations in BRCA1 and 2, or in women who also had germ line mutations. Meaning, inherited mutations in PALB2. This drug had a lot of activity in the breast cancers in that setting.

For BRCA mutations and PALB2 mutations, the PARP inhibitor Olaparib really had very good overall response rates in metastatic breast cancer. Some of the other mutations like ATM and CHEK2, which are also common in breast cancer, did not have great responses to this drug. Again, important data for us when we're choosing drugs, we want to be able to target as specifically as possible for our patient, for the type of breast cancer and then also, looking for what other treatments she had. And interestingly, in

this setting, this agent, this PARP inhibitor was active in ER positive cancers, even if people have already received medicines like palbociclib and ribociclib. We were very pleased with this result as well.

Now, turning to HER2/neu positive breast cancer in the metastatic setting, again, another new drug which just was approved, tucatinib, showed excellent responses. This is again, a randomized trial where the patients were treated with the same backbone of treatment, trastuzumab or Herceptin plus capecitabine, which is Xeloda. Standard, very excellent therapy. And then, the patients either received tucatinib or did not, randomized trial. What we saw was that the patients who did get tucatinib, had a better overall result and especially in patients with brain metastases in HER2 positive breast cancer. Tucatinib really did a very good job at helping to control those brain mets, increasing the duration of response, the length of time that the therapy was effective and even improving median overall survival. A very exciting addition to our treatment for HER2 positive breast cancer.

I'm going to turn now from metastatic breast cancer to earlier stages of breast cancer and some of the breakthroughs that were presented at ASCO this year. Okay now, everybody wants to know what happens if I can't stand taking my tamoxifen or I can't stand taking that aromatase inhibitor. We do understand these drugs are difficult. And sometimes I think the hormonal therapy is even more difficult than chemotherapy, because it goes on for so long and the side effects can be very unpleasant. But this was a very, very important study, which looked at the outcomes in women who stopped taking their tamoxifen, or didn't take it for the full length of time, or didn't take the full dose and comparing that to people who did stay on. And the way they actually measured this was by doing blood tests and seeing what the levels of the drug were. It was not only on the patient's self reporting. And actually, more than half of the patients who didn't take the full dosage did report that to their physicians, but not everyone.

It was really by this biochemical blood assay. And what they found was that 16% of women in this study were not taking the full dose of their tamoxifen. And that this was associated with not as good an outcome. We do think it's really, really important to actually take the medicine. We know there are side effects and we'll work with you on that, but this is very important data to support that.

This study has already changed our practice in early stage HER2/neu positive breast cancer. As you know, early stage HER2 positive breast cancer is treated with chemotherapy and HER2 targeted agents like Herceptin and perjeta. In this trial, the question was, which chemotherapy do we have to give? Many of these patients are treated with an anthracycline, a drug like Adriamycin, Epirubicin. And in this trial there was a question of, well, what if we leave out that Adriamycin drug, the anthracycline drug or the Epirubicin drug? Because they have a lot of side effects and combined with Herceptin and perjeta, there may be more cardiac toxicity, more damage to the heart muscle. This was a very well run, randomized trial. Patients received either the anthracycline regimen, or the non-anthracycline regimen, which in this case was Taxol and carboplatin. And the result was actually identical. It was perfectly okay to leave out the anthracycline, to leave out the Adriamycin and patients did very well. There was no difference in the response rates, or in the overall outcome.

This was given in the neoadjuvant setting. That means the tumor was still in the breast. A patient came in, there was a lump in the breast. It was HER2 positive and she got the treatment with chemotherapy, Herceptin and perjeta and then went to surgery and saw what the result was. There was also ER positive and ER negative included in this. And no matter what subset it was, the outcomes were the same. Very important, we can leave out the Adriamycin safely.

This is a study that's relevant to triple negative breast cancer. Again, in that earlier stage setting. It's a little bit of a complicated study, but I'll try to walk you through. This was, again, patients who received standard treatment for early stage triple negative breast cancer, which is usually chemotherapy, surgery, radiation. And then they were randomized either to no additional treatment, what they had is the standard therapy, or continuing on a low dose of oral chemotherapy, capecitabine, again that's

Xeloda for a year. And what we're doing here is trying to find ways to make the outcomes better for our early stage triple negative patients. And this again, was a positive study, showing that if we give Xeloda, for one year following completion of that standard chemotherapy, improvements in the long term outcomes. Another very exciting, positive study that I think is going to be practice changing for us.

I'm going to stop here. There was a lot more information that was presented, but I think these are some of the highlights in advanced disease in early stage breast cancer.

Elana Silber:

Thank you, Dr. Oratz. I just want to remind everyone, if you have any questions you can type them into the chat and it's okay if you don't have questions either. A lot of them may have been addressed through the presentation, no pressure. But we will have time at the end if anybody has any questions. Thank you, Dr. Oratz. And we're going to turn the floor over to Dr. Lewin.

Dr. Sharyn Lewin:

Good evening everyone. Just give me one minute please.

Elana Silber:

Wait Dr. Lewin, did I not give you your intro? Let me give you your intro. We all know and love Dr. Lewin, but maybe not everybody knows who she is, let me remind you. Dr. Lewin is a gynecologic oncologist from Holy Name Medical Center and is an expert in gynecological oncology. She is on Sharsheret's medical advisory board as well, she serves as the Medical Director of the New Jersey based Holy Name Medical Center's gynecologic oncology division. Now a proper intro to Dr. Lewin, thank you.

Dr. Sharyn Lewin:

Thank you so much.

Elana Silber:

Apologies.

Dr. Sharyn Lewin:

No, no worries at all. Good evening everyone. It's such a treat to be here today. I have been a huge supporter of Sharsheret for many years, probably at least 15, hard to count. But it's been really amazing to watch and be a part of all the phenomenal support and educational programs, to say the least, that they have done for women and families. I decided to go ahead and just pull four of the sentinel papers and presentations that came from ASCO as well from Society of Gyn Oncology meeting, related to ovarian cancer. And these are four studies that really have changed the landscape of how we treat women with ovarian cancer. And I'm very excited to certainly take any questions during this part of the presentation or at the end. This slide just shows some of my disclosures, not only honorary speaker's bureaus, but research support that we receive at our institution.

What I'd really love to spend most of the time talking about are the role of PARP inhibitors for women with newly diagnosed ovarian cancer. And it's been so exciting to take care of women with ovarian cancer now really more than ever, because we have wonderful maintenance options for these women once they finish surgery and chemotherapy. I want to spend a little bit of time talking about two sentinel papers, they were highlighted at a big European meeting in the fall of last year, called ESMOE. And they were also discussed and presented new data from these trials at our Society of Gyn Oncology meeting

and they were also presented and discussed at ASCO. Really, the PARP inhibitors are for maintenance therapy for women with a newly diagnosed ovarian cancer, and have really changed the landscape of how we treat these women.

These slides are also from the meeting, they're a little bit technical as well, but I would like to walk you through them very carefully. The PRIMA study was a study that enrolled women with epithelial ovarian cancer, that's the most common type of ovarian cancer that we see. It was really for women with stage three of stage four disease. And these women had to have some form of residual cancer left after their primary surgery. Alternatively, these women could also have had chemotherapy first, which means neoadjuvant chemotherapy. These women were then randomized and this shows you the randomized schema. Once they finished surgery and chemotherapy, or chemotherapy and surgery, they were then randomized to something called a PARP inhibitor, which you see in the blue boxes, called niraparib, or they were randomized to placebo.

Prior to this trial, for women with advanced ovarian cancer, stage three or stage four, once these women would complete chemotherapy and surgery or surgery and chemotherapy, because that's the combination of how this disease is treated. Unless they were on trial or treated with something called bevacizumab or Avastin, the majority of women were actually. Based on PRIMA, we now saw that these women were stratified based on various different factors. What we essentially saw and don't get too bogged down with the numbers, is that women, all types of women with epithelial ovarian cancer or fallopian tube cancer, those women that have this PARP inhibitor as maintenance, it's an oral pill actually did much better. There was a much longer time for these women to have any evidence of cancer recurrence than women who were taking placebo, or not taking this PARP inhibitor. What they looked at was, here is the overall population of all women. And you can see the niraparib is on the blue line and the placebo is on the red line. Any time you see these curves, which have a big separation, it shows all of us that it's very statistically significant.

And then, when we actually looked at different populations in these women, there's a lot of discussion now about taking the tumor from surgery and testing it for something that's called homologous recombination. You may hear your doctors talk about HRD, whether the tumor has homologous recombination deficiency. It's basically a way that we repair DNA damage that can be present in the tumor itself. And you see there's a much larger separation of the curve for those women whose tumors expressed homologous recombination deficiency. And there was an even more impressive improvement in these women taking this PARP inhibitor, called niraparib over placebo. We see that the PARP inhibitors really tremendously benefit these women whose tumors have deficiencies in homologous recombination.

They looked at various different subgroups and the bottom line is that all women in this study really benefited from having this PARP inhibitor, niraparib, which is also called Zejula, for those of you that might be taking it or have heard of it. All different subgroups, based on different markers, had an improvement in having PARP as maintenance rather than placebo. And the patients that we saw the magnitude of benefit were much greater, certainly those women with a BRC mutation, also those that had homologous recombination deficiency in their tumor, this HRV. There was still a benefit in the women that had proficient homologous recombinations, they're just not as great as in these other subpopulations.

That study led to, really the recent FDA approval of niraparib for all women as maintenance therapy, who have had stage three or four ovarian cancer, once they had finished surgery and chemotherapy. That's been hot off the press and has completely changed the landscape for how we treat women after they have finished upfront surgery and chemotherapy. It is really impressive data, really groundbreaking and has completely changed how we're treating these women. Hopefully, we're actually curing a large

percentage of these women with maintenance therapy, which we were not able to do in the past. Again, like we said, we do see the magnitude of benefit is much greater in those women with a VRC mutation, or whose tumors express the homologous recombination deficiency. It's a big word, but it's basically genes in a pathway about how DNA is repaired.

There was a second study, called PAOLA, which was also presented and discussed, very similar. In this sense, this study was also a maintenance study. These women who were enrolled either, again, had stage three or four ovarian cancer of course, we also lump fallopian tube and primary peritoneal cancer into these groups as well. After these women had surgery and chemotherapy, they were randomized to a different PARP inhibitor, called olaparib, same one that Dr. Oratz mentioned before, with Avastin, bevacizumab. Or, they were given bevacizumab or Avastin alone with placebo, they did not have the PARP inhibitor. What's interesting too is that Avastin was continued during chemotherapy and then after.

Looking at the patient characteristics, most of the women had surgery first followed by chemotherapy. Although, about 40% had neoadjuvant chemotherapy, followed by an interval surgery. And the bottom line is, again, and you can see the blue line on top which is the PARP inhibitor olaparib with bevacizumab, versus the placebo with bevacizumab. The combination of the PARP inhibitor and Avastin really did much better and significantly led to a much longer time to be disease free. Again, extremely impressive and statistically significant data.

Then, when we were looking at patients that had tumor BRCA, which is what's called a somatic BRCA mutation, their tumor actually expressed the BRCA mutation. That's the graph you see on the left. There was a tremendous improvement in what's called progression free survival or the amount of time for disease to remain cancer free, in the patients that had the combination, the PARP inhibitor and the Avastin, versus Avastin alone. You can also see that was statistically significant as well in the patient that did not have tumor BRC expression.

Looking at various subgroups, looking at patients that had this homologous recombination deficiency in their tumor, followed by tissue BRCA. As well as those that had homologous recombination deficiency, but did not have tissue BRCA. And those that were negative for HRD, or homologous recombination. Again, you can see the magnitude of effect by the blue lines, there's such a big separation, was greatest in the patients that had either tissue BRC mutations or deficiencies in what's called homologous recombination for the combination of the PARP and Avastin, versus Avastin alone. Very impressive data and I will distill it down in a little more detail in one minute.

Really, the bottom line from these two sentinel studies, which as I mentioned again, were not only presented at ASCO, but at our Society of Gyn Oncology and ESMOE, this large European meeting, is that really frontline maintenance with PARP inhibitors is now a very impressive standard of care to be discussed. It's really important when women are diagnosed with ovarian, fallopian tube and primary peritoneal cancer, right when they are diagnosed that they undergo genetic testing. And that genetic testing is not only for a BRCA mutation, but it really needs to be a full panel test. And if women have been tested in the past for BRCA mutations and tested negative, they really should have an update test to look for the complete panel. But now, not only are we doing germline testing, but based on these two really sentinel trials that I mentioned, women also need to have their tumors tested for what's called HRD, homologous recombination deficiency. And that looks for various genes within the tumor itself that are deficient. And based on these two studies that I just showed you, we can see there is an impressive improvement and length of time before a recurrence happens, if women are then given a PARP inhibitor as maintenance.

This is really groundbreaking data, it has tremendously changed the way that we manage women with ovarian cancer. And it's actually really quite hot off the press, we're still in the process of educating

clinicians, discussing pathways and processes. But there are some toxicities that are associated with these PARP inhibitors. You may have heard of them, because they are FDA approved for women in the recurrent setting, who are at least partially platinum sensitive. Now based on the new FDA approval in the upfront or the new maintenance situation, I should say. It's for women who are newly diagnosed. Now PARP maintenance is actually a really wonderful option for women who either have a germline VRC mutation, now that's really based on the SOLO-1 data, which was presented about two years ago now. As well as the PRIMA data, which I discussed now, which is really for all comers with stage three and four disease. And now based on PAOLA, that was the study that added Olaparib to Avastin, we have many options for women who have ovarian cancer in the maintenance setting.

I think the biggest point is that it really is standard of care that women have germline panel testing and now they have tumor testing for HRD. Absolutely important. Hopefully this can be done within your physician's office that absolutely can so that women now, who are newly diagnosed with ovarian cancer are now eligible for PARP maintenance. Again, it's an oral pill that's taken. There are some side effects with these different medications, although most of us have become pretty familiar and comfortable managing them. You will see a lot of data regarding PARPs, not only in BRCA associated breast cancers, but also pancreatic cancer, prostate cancer. It's really a tremendous therapeutic option for patients that have BRCA mutations and in the ovarian cancer space. Those that have mutations in the tumor itself, for BRCA as well as this phenomenon called HRD, or homologous recombination.

Two additional ASCO studies that are very sentinel that I would love to talk about are the DESKTOP III trial as well as some of the overall survival data from SOLO-2. DESKTOP III was actually a phase three randomized trial that was presented which demonstrated an impressive improvement in survival for women who underwent a secondary surgery for recurrent ovarian cancer. Really, prior to DESKTOP III, we had just retrospective data, which means data that looks back to see what is the benefit when women have a recurrence of their ovarian cancer for doing surgery. It was definitely quite controversial in the United States, the role of surgery in the recurrent setting. But now, this is the first time that we actually have randomized phase three data that's actually the most robust clinical data that can be presented that showed an improvement in survival for women that had a secondary surgery. These women, once they had a recurrence, they met certain criteria. They were randomized to either surgery followed by chemotherapy, or chemotherapy alone. And the women that actually underwent surgery and had a complete resection of their cancer, had a significant improvement in their overall survival, which means the amount of time that they lived.

This actually is very much practice changing. People like me, who trained at Sloan Kettering, are very surgically aggressive programs, the Mayo Clinic for example, Irvine, have always been big proponents of secondary surgery, or what's called secondary cytroduction. But now, it's really been practice changing to have really excellent randomized data that shows us survival benefits for these women. An overall survival benefit, which is actually quite difficult to show in ovarian cancer. The majority of our studies have shown an improvement in the time for a recurrence to happen, but to actually ensure benefit in how long women live, is pretty amazing. And it's been very tough to do in ovarian cancer. I think the first time we've actually really seen it in a surgical trial is DESKTOP III. But we've also seen some impressive overall survival benefits in a study called SOLO-2, which I'm going to speak about next.

SOLO-2 was actually presented at SGO a few years ago. This also was a PARP inhibitor trial. But this was for women with recurrent ovarian cancer, who had at least two prior lines of chemotherapy and were at least partially platinum sensitive. Platinum sensitivity means that when you have a drug like carboplatin that's given, your cancer remains cancer free at least six months after finishing that drug. For these women that had at least to prior lines of chemotherapy, and were at least partially platinum sensitive, they were then randomized to either placebo or Olaparib, which is the oral PARP inhibitor as

maintenance. We actually have overall survival data to show that the women who received Olaparib, lived over a year longer than those that had placebo. The overall survival benefit was fantastic. And I think it all really gave us cause to see how important PARP inhibitor maintenance is for these women. Of course, SOLO-2 was a study that really wasn't rich with just patients with germline BRCA mutations, it's important to note that as well too. But this data was very exciting. And again, talks about the importance of PARP inhibitors in the recurrent setting.

There's two different areas of where you can use PARP inhibitors well now, which we've really changed the landscape of ovarian cancer, is to use PARP inhibitors from newly diagnosed women. And that's based on the PRIMA and the PAOLA studies that I just showed you. And it's also based on a study called SOLO-1, which was presented a couple of years ago now. Really based on all of this data, if you have a germline BRCA mutation, or you have a somatic BRCA mutation, which means the tumor itself has a mutation in BRCA or if the tumor is something called homologous recombination deficiency, which is a bit complicated explanation of what that is. All of these women definitely benefit from going on PARP maintenance once they finish chemotherapy. For those women who might have already been diagnosed and have completed their initial chemotherapy and surgery, if there is a recurrence, it can again be treated with platinum based chemotherapy. And if the disease is sensitive to that, women should also go on PARP maintenance as well too.

These are four of really, the most sentinel studies in our field right now that have not only changed the landscape for newly diagnosed women, but also really shown the importance of surgery as well as PARP maintenance in the recurrent setting. There were some other small trials discussed at ASCO too, but these were really the four most sentinel practices changing, if you will. And I think with that, I may actually just stop and see if there are any questions. I think the question part of these webinars are actually very helpful and robust for discussion.

Elana Silber:

Thank you Dr. Lewin. There were some questions that came in before, some are coming in on the chat, I'll just start with those. Someone wants you to explain what myChoice HRD testing is, Dr. Lewin.

Dr. Sharyn Lewin:

MyChoice HRD testing is actually the best assay to detect if the tumor has HRD. That was the assay that was utilized in those two studies that I just showed you, the PRIMA study and the PAOLA study. It's also been approved by the FDA, as a complementary diagnostic. Basically what happens is, a tumor on a slide, from your surgery or your biopsy is sent by the pathologist to a company that's called Myriad Genetics. And they basically look for these homologous recombination deficiency in the tumor itself. It's a complicated score of how they do it, but they look at three different things. I don't know if you want me to go into that level of detail, but it's looking at loss of heterozygosity, it's some called a GIS score, basically is what they determine. And there's a certain cut off, that if the tumor is at that particular cut off, the tumor does express HRD. I hope that answers the question, but that really is the best test on the market. The one that was used in both of those studies that I mentioned, to see if the tumor does have homologous recombination deficiency.

Elana Silber:

Thank you. There's a question for ovarian cancer, which PARPs help for patients that are BRCA negative, HRD negative and ER positive?

Dr. Sharyn Lewin:

Based on the PRIMA data that I showed you, the PARPs did show a benefit in patients that are BRCA negative and HRD negative, Zejula would be probably the PARP to use in that situation, it's also called niraparib. And that data, it's based on the PRIMA study that I just showed you, that did show a benefit for newly diagnosed women that are BRCA negative and HRD negative. Now really, when we're talking about ovarian cancer, we have to say what is the patient's BRCA status, that's very important that we know that. In addition, we also want to know if the tumor itself expresses a BRCA mutation, that's called a somatic BRCA mutation. And then we also want to know about this phenomenon called homologous recombination. And even though we know the PARPs work in all women with ovarian cancer, we know they work even better in those that have those factors that I mentioned, germline BRCA mutations, somatic or HRD.

Elana Silber:

Okay. Dr. Oratz, for early stage breast cancer, is the benefit only for tamoxifen or also for Arimidex?

Dr. Ruth Oratz:

Okay. The benefit is for the aromatase inhibitor as well as for tamoxifen. All of these hormonal therapies are very important for treating ER positive breast cancer. The study I was showing about adherence was addressing only tamoxifen, but the same is true for the aromatase inhibitors. Basically, if you don't take the medicine, it's not going to work.

Elana Silber:

Following up on that, further tamoxifen study, was the three year survival rate after the completion of five years of drug therapy or three years since diagnosis?

Dr. Ruth Oratz:

I'd have to go back to the slide, because I want to report that accurately. I did something crazy. Okay. It was from a median follow up of 24 months, which means about two years from when they tested the patients to see what their disease free survival was at three years from diagnosis. At the three year point.

Elana Silber:

Okay, great. There's a question, how is the Xeloda trial different from the CREATE-X trial?

Dr. Ruth Oratz:

I think that's referring to the other Xeloda trial. The study that I just presented was in women who had surgery and then chemotherapy and then were randomized Xeloda or no Xeloda, there was a benefit for Xeloda. The other's trial that I think you're referring to here is the neoadjuvant trial, where women presented with locally advanced triple negative breast cancer had their chemo and went to surgery. And then, only women who had some residual disease at the time of surgery, were given the Xeloda. But now, what we're saying is for almost every patient with early stage triple negative breast cancer, there is a benefit to getting that year of Xeloda after standard chemotherapy, not just the neoadjuvant with residual disease. It's extending an observation that we already had seen, and now applying it to even more patients who can benefit.

Elana Silber:

Dr. Lewin, there's a question about what percentage of ovarian cancer are positive for BRCA or HRD?

Dr. Sharyn Lewin:

That's a great question. Depending on what study you look at, up to about 20% of women with ovarian cancer have a germline BRCA mutation, 20%. A very high percentage, which is why all the national guidelines recommend that women have genetic testing, BRCA, or full panel actually as I mentioned is the best way to do testing. It's about 20%. Then, if you look at how many women have homologous recombination deficiency, it's about 50%. But BRC is within that 50%. If you think 20% have germline deficiencies, then all together HRD is about 50% and the BRC mutations fall within that. Homologous recombination is a way you repair your DNA, high definition way to repair double stranded breaks. And the BRC genes fall within that pathway. Altogether, counting the BRCA, about 50%.

Elana Silber:

And there's a question, in your experience have you ever seen a recurrence from an ovarian cancer, who's survivor after 20 years, if they were negative for BRCA?

Dr. Sharyn Lewin:

I personally have never seen that. I think I was writing back to that person privately, but it's extremely unusual to have a recurrence that long after initial diagnosis. But one should really have a new biopsy and just make sure it's really the same cancer, because that's a really long time to be cancer free. Looks like this person had surgery today, so I hope she is healing well. And surgery is definitely the right thing to do for someone who had that long of a disease free interval.

Elana Silber:

We have a question from someone who has early stage breast cancer, finished chemotherapy and has eight radiation treatments left and then will start tamoxifen. How soon after starting tamoxifen would she notice the side effects?

Dr. Ruth Oratz:

Side effects from hormonal therapy are very variable and very individual. It's really difficult for us to predict which side effects any given person is going to experience. Some of my patients start their medicine and really feel fine and they do very well with it and have minimal, if any change, in how they're feeling. There are other patients who feel a much bigger impact from the treatment. I think it depends on your age, whether you're premenopausal, or postmenopausal and where you are in that spectrum of menopause. Because, a lot of the symptoms associated with these treatments, particularly tamoxifen, are the symptoms of perimenopause. If you're in that age range of 45 to 55 and you're taking tamoxifen, it's going to amp up the symptoms that you'll already be experiencing with menopause. It's a little bit like asking the question: am I going to get cramps with my period? Everyone is very different, and at different stages in our lives, those side effects can vary. It's really hard to predict, start taking it and see how you do.

Elana Silber:

And someone asked a question, what is the standard, is it five years, is it 10 years? You talked about tamoxifen, stopping it before, but what is the recommendation?

Dr. Ruth Oratz:

The minimum duration of treatment is five years for tamoxifen or an aromatase inhibitor. There are now many studies which show a benefit for extended treatment, up to 10 years. But not everybody needs 10 years of treatment and we do have some tools which help us predict which patients will benefit the most from longer treatment, beyond five years. And that has to be made on an individual basis. We really make that judgment based on what we think the risk of a later recurrence is. Estrogen receptor positive breast cancers tend to recur later, rather than earlier. Whereas HER2 positive and triple negative breast cancers may see recurrences within the first five years of diagnosis. Sometimes, with ER positive breast cancer, recurrences can occur after five years, or even later. And it's in that subset of patients, at higher risk for late recurrence, that we feel longer duration of therapy is beneficial. You need to go over that with your doctor and make a determination about whether you should stay on longer or not. And that also would impact whether you should stay on tamoxifen, or switch to an aromatase inhibitor at some point, similar issue.

Elana Silber:

There's a question about someone who's read studies of adding testosterone to Arimidex that significantly helps with side effects. Is this something that's being studied? Have you heard about that?

Dr. Ruth Oratz:

Yeah, I'm aware of that data. And Dr. Lewin, you may about some of that data as well. It is not a standard therapy, it is not what we recommend and we are not giving testosterone with Arimidex.

Elana Silber:

Is Lupron recommended for premenopausal or early stage and then tamoxifen?

Dr. Ruth Oratz:

Again, we're talking about these questions of hormonal therapy, which are very important. Between a half and two thirds of all breast cancers are ER positive, most women with breast cancer are going to be on some of these drugs at some point in time. For premenopausal women, one of the options is tamoxifen, but another option is to lower the amount of estrogen that's being produced in the body. And we can do that by using medicines like Lupron, or triptorelin or Zoladex, which are called ovarian suppression drugs. These are drugs that block the message from the brain to the ovary, that says make estrogen, we shut that down. The ovaries stop producing or reduce dramatically the amount of estrogen that's coming out of them. And those medicines are given by injection, once a month or once every three months. In addition to that, we add either tamoxifen or an aromatase inhibitor. This is really a much anti-estrogen treatment, we're really lowering the estrogen levels dramatically in that premenopausal woman. This can also be achieved by removing the ovaries surgically and sometimes, that's indicated. But if we remove the ovaries surgically, we can't put them back in. With medicines like Lupron, or Zoladex, we have the option of stopping that ovarian suppression.

Dr. Ruth Oratz:

There are studies that show that in premenopausal women, if we add ovarian suppression, to tamoxifen or an aromatase inhibitor, we can get better results. Longer disease free survival, even some hint of an overall survival benefit. But again, not every premenopausal patient needs this treatment. It's really

based on what we think that risk of recurrence is and how much we want to suppress the estrogen pathway. A very individual decision and a complicated one. Please speak to your doctor about that.

Elana Silber:

And there are a lot of specific questions coming in. I know the doctors are seeing the chat and a lot of the questions that are coming in, we can also share with Dr. Oratz and Dr. Lewin and get back to you. But we do like to be mindful of people's times. If we did not get to your questions, the chat is saved, they will get to the doctor and we will get you information following the call tonight. I just wanted to thank Dr. Lewin and Dr. Oratz. Clearly the questions are coming in, the information you're sharing is really important. If it's needed, we will do this again, we'll bring you guys back. But I really want to give an opportunity for everyone going foward. I wanted to thank everyone for coming on the call and we continue to provide webinars going forward, there are a few scheduled in the week ahead. You'll start to see information coming up. I think there's a poll that may have popped up on your screen. If you're taking that, that would be great to let us know information about tonight.

Elana Silber:

Coming up next week, there is a webinar called love the skin you're in, before, during and after cancer. It's on Monday at 2:00 PM Eastern, 11:00 AM Pacific. And we encourage you all to join us on Monday night, July 27th. We're having a virtual streamed fund raiser for Sharsheret, but you can come as our guest. You just register at midsummermiracles.com. We would love for you all to be there, it showcases the work that Sharsheret is doing for the community and really gives us an opportunity to pay tribute to those women who really join together to support each other as we all go through this cancer journey. I want to wish everyone a good evening, good health and to stay in touch with Sharsheret, we're here for you every step of the way. Have a good night. Thank you.

Dr. Sharyn Lewin:

Thank you.

About Sharsheret

Sharsheret, Hebrew for “chain”, is a national non-profit organization, improves the lives of Jewish women and families living with or at increased genetic risk for breast or ovarian cancer through personalized support and saves lives through educational outreach.

With four offices (California, Florida, Illinois, and New Jersey), Sharsheret serves 150,000 women, families, health care professionals, community leaders, and students, in all 50 states. Sharsheret creates a safe community for women facing breast cancer and ovarian cancer and their families at every stage of life and at every stage of cancer - from before diagnosis, during treatment and into the survivorship years. While our expertise is focused on young women and Jewish families, more than 15% of those we serve are not Jewish. All Sharsheret programs serve all women and men.

As a premier organization for psychosocial support, Sharsheret’s Executive Director chairs the Federal Advisory Committee on Breast Cancer in Young Women, Sharsheret works closely with the Centers for Disease Control and Prevention (CDC), and participates in psychosocial research studies and evaluations with major cancer centers, including Georgetown University Lombardi Comprehensive Cancer Center. Sharsheret is accredited by the Better Business Bureau and has earned a 4-star rating from Charity Navigator for four consecutive years.

Sharsheret offers the following national programs:

The Link Program

- Peer Support Network, connecting women newly diagnosed or at high risk of developing breast cancer one-on-one with others who share similar diagnoses and experiences
- Embrace™, supporting women living with advanced breast cancer • Genetics for Life®, addressing hereditary breast and ovarian cancer
- Thriving Again®, providing individualized support, education, and survivorship plans for young breast cancer survivors • Busy Box®, for young parents facing breast cancer
- Best Face Forward®, addressing the cosmetic side effects of treatment
- Family Focus®, providing resources and support for caregivers and family members
- Ovarian Cancer Program, tailored resources and support for young Jewish women and families facing ovarian cancer • Sharsheret Supports™, developing local support groups and programs

Education and Outreach Programs

- Health Care Symposia, on issues unique to younger women facing breast cancer
- Sharsheret on Campus, outreach and education to students on campus
- Sharsheret Educational Resource Booklet Series, culturally-relevant publications for Jewish women and their families and healthcare Professionals

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