Jenny Stein:

Okay. So good evening. Thank you guys for joining us tonight. My name is Jenny Stein. I'm the Midwest Regional Director for Sharsheret, and I want to thank everyone for joining us for the latest in our webinar series, Highlights from ASCO 2024. For those who might not be familiar, ASCO, which is short for the American Society of Clinical Oncology, is the world's leading professional organization for physicians and oncology professionals that are caring for people with cancer. And tonight, we're privileged to be learning from two experts in this field. Dr. Deanna Gerber, from NYU Langone Perlmutter Cancer Center, and Dr. Yuan Yuan, from Cedars-Sinai Medical Center, both highlight the latest findings from the American Society of Clinical Oncology's 2024 Annual Symposium. We're grateful for tonight's webinar sponsor, Daiichi-Sankyo. And before we begin, there's just a few housekeeping items.

So our webinar is being recorded. It will be posted on Sharsheret's website along with the transcript. Participant's faces and names will not be in the recording. If you would like to remain private, you can turn off your video and rename yourself, or you can call into the webinar, we have put into the chat information on how to call into the webinar, if you need. And so you guys might have noticed that as you came in, everyone was muted upon coming into the webinar. We ask that you keep yourself muted throughout the presentation. We do ask that if you have questions, to put them in the chat box. You can either put them in the public chat or you can send a private message to the Sharsheret name. We've already received a ton of questions from you guys in advance, so thank you so much, and we will look forward to trying to answer as many as we can. We do ask if you do have a question, to make it as general as possible as we're not able to offer any specific medical advice.

As we move into the webinar itself, I want to remind you that Sharsheret is a national, not-for-profit, cancer support and education organization, and we do not provide any medical advice or perform any medical procedures. So the information that's provided by Sharsheret is not a substitute for any of your own personal medical advice or treatment for specific medical conditions, so you should not be using this information today to diagnose or treat any health problems. If you have any questions that are specific to your medical care, like I mentioned earlier, these doctors are not going to be able to advise regarding your specifics, and we would advise that you speak to your medical provider. And as always, we recommend that you seek the advice of your own physician or qualified health provider with any questions regarding a medical condition.

So in a moment, I'll introduce our presenters to you and then they'll both talk for about 15 or 20 minutes, and then we'll have time at the end for question and answer. So this evening, we are honored to be joined by Dr. Deanna Gerber, and later on this evening, by Dr. Yuan Yuan. Dr. Deanna Gerber is a gynecologic oncologist that specializes in minimally invasive laparoscopic and robotic assisted surgery at Perlmutter Cancer Center, which is part of NYU Langone Hospital in Long Island. She's also the newly appointed director of the High-Risk Genetics Program at NYU Langone, Long Island. So thank you so much, Dr. Gerber, and I'll turn it over to you now.

Dr. Deanna Gerber:

Thank you. Thank you for that great introduction. Let me share my screen. All right, can you guys see that? So I am honored and excited to share with you Updates in Ovarian Cancer Treatment from the ASCO meeting in 2024. So I wasn't sure if we were going to have an overview of what ASCO was, but Jenny did that wonderfully. So in terms of oncologic societies, ASCO is really remarkable. It was founded in 1964, every spring, it has a giant meeting in Chicago, and this year, over 40,000 people attended the annual meeting. For perspective, the gynecologic oncology annual meeting is very overwhelming for me, a lot of people, a lot of learning, and it's only 3,000 people. So this is really for [inaudible 00:05:05] way, way bigger, and it's the country's biggest cancer meeting. So jumping into the content, I just want to give some background on ovarian cancer.

Ovarian cancer is a complex disease. When we think about ovarian cancer, when we say ovarian cancer, the most common type that people are referring to is the high grade serous ovarian cancer. This is a cancer where, due to the lack of symptoms, the majority present at stage 3 and 4. There's really not many symptoms at early stage, and unfortunately, we only recognize that there's something might be off once it's advanced stage. So in general, the use of frontline treatments such as chemotherapy plus surgery is effective with almost all people going into a remission, however, about 80% of patients will recur in the first few years. So this point alone highlights the need for continued ongoing research and commitment of our scientific community to advancing this, and hopefully, making this not the case.

So when we think of ovarian cancer, like I briefly mentioned in the last slide, ovarian cancer is not just one disease. It used to be considered ovarian cancer, however, now we know that ovarian cancer can be split into many different histologies or subtypes. And so the majority of epithelial ovarian cancers are high-grade serous, and then there's other few ones, we'll be talking about clear cell at some point in a few slides. And then even more divided is the genetic subtypes. And so we are learning so much about the molecular profiles of certain tumors and the genetic profiles of people at risk for hereditary breast and ovarian cancer syndrome. So there's a lot to ovarian cancer, it's not just one disease. So when we think about treatment for ovarian cancer in the first-line setting, the treatment usually involves combination of surgery plus chemotherapy, the order of which varies.

There's several reasons why your doctor may recommend surgery first then chemotherapy. Sometimes, and it's becoming more popular in our country, now we do some chemotherapy, then surgery, followed by more chemotherapy, and that's called neoadjuvant chemotherapy. And you'll hear me talking about that a little bit later as well. And so this background is useful for thinking about the next study. So this study, it has a catchy name, it's the CARACO trial, it was a surgical study. And so the background for this study is that we know that lymphadenectomy, or lymph node removal, in primary surgery, so people undergoing surgery first before chemotherapy, if their lymph nodes are negative based on radiology or an exam, there's no benefit to removing those lymph nodes. If you ask someone 30 years ago if lymph nodes should be removed at the time of that surgery, the answer was yes, that is part of the cytoreductive surgery. But recently, we've learned that it's not beneficial.

So now, we want to know, does removing lymph nodes that appear normal benefit at interval surgery? So in these women who've had chemotherapy first then surgery, is there a benefit to lymph node removal? So this study was a prospective multi-institutional phase 3 trial. People with stage 3 and 4 with no suspicious lymph nodes seen on imaging or intraoperatively were enrolled into the study. During the surgery, the participants were randomized to lymph node removal versus no lymph node removal. And so the results of this study showed that lymph node metastases were diagnosed in 49% of the women with the lymph node removal arm. And again, these are women who didn't have any clinical evidence of cancer in the lymph nodes, and so this was an incidental finding of lymph node metastases. However, important to note is that the median survival did not differ between the women who had lymph node removal and those who did not. And not surprisingly, the participants who had the lymph node removal had more serious postoperative complications.

So what does this tell us? The conclusion of this study is that systematic lymphadenectomy, or lymph node removal, can be safely omitted with clinically negative lymph nodes. Though we were finding more lymph node metastases, it did not translate into an improved outcome or improved survival. And this is important because the surgical de-escalation allows to significantly reduce serious post-op morbidity. And so the next topic, the next few studies I want to discuss, this topic is really important. So when we think about treatment of ovarian cancer, once it's recurred, it all depends on when the recurrence occurs from the last treatment.

And so usually, at the first time, people will get a combination of chemotherapy involving... one of the agents will be a platinum agent. And so the time from occurrence from your platinum agent is how we determine if you're a platinum refractory, platinum resistant, or platinum sensitive recurrence. And that's based on this general timeline here. So less than six months from platinum agent is platinum resistant, and

more than six months is platinum sensitive. So this trial looked at the use of neoadjuvant elaborate for platinum sensitive ovarian cancer, and this is also actually titled the NEO trial. And so the background for this trial was that we know that certain people with platinum sensitive ovarian cancer may benefit from a secondary surgery, that's not routinely offered, it's just there's certain subsets of patients, women, who might be candidates for that.

So knowing that, you usually do a secondary surgery plus more chemotherapy, but is there a potential to deescalate therapy to use less toxic therapy with the use of olaparib? Olaparib is a PARP inhibitor which is really commonly used in ovarian cancer. It's been used for many years now and is now gaining some traction with breast cancer treatment as well. So I'm not sure if we'll hear about that in the next section as well. So this study was a phase 2 study. Preoperatively, the participants got six weeks of olaparib, and then had their interval surgery, and then postoperatively received six cycles of chemotherapy with olaparib maintenance versus olaparib alone. So no chemotherapy in these participants. And the results of this trial showed that the survival rates at three years was comparable between the arms.

And important to note that 31% of the participants in this trial did have a known germline BRCA mutation. A BRCA mutation is a biomarker for response to olaparib, and so that's helpful to know that the BRCA participants... the results of this trial may be specifically applicable to them. So the conclusions from this trial were that neoadjuvant olaparib followed by surgery was feasible and safe, and that olaparib alone after surgery was as effective as chemotherapy followed by olaparib, and was less toxic. Olaparib is an oral treatment, you do not need an IV for it. It's very well tolerated. And so this is a really exciting concept and exciting results. Another study I wanted to discuss is the BrUOG trial, and this is for clear cell ovarian cancer. And this is another subset of ovarian cancer that we know has poor response to our standard chemotherapy.

So those platinum agents we were talking about previously, clear cell ovarian cancers respond less frequently to these treatments, which highlights the need for research in this specific subset of ovarian cancers. So this trial was a randomized phase 2 study evaluating single agent nivolumab or in combination with ipilubumab in people with recurrent cancer. Both of those agents that I just said, the nivolumab and ipilubumab, are both immunotherapy. Immunotherapy is a general class of anti-cancer treatments that use your immune system to attack the cancer. And so this is one of the newer areas of innovation in cancer care. And so these two medications are used commonly in other cancers, but this is one of the big ones in ovarian cancer. So the results from this study showed an objective response rate of 14% with just the single agent nivolumab versus 33% with combination. That's more than double the response rate when you add the two medications together.

More impressively is for these participants who have a kind of cancer that's very hard to put into remission once it's recurred. Four people in this trial achieved a complete response, meaning, there was no evidence of disease on imaging on this treatment. The overall survival was improved with this combination treatment. However, not unexpected, there were more treatment related toxicities noted in the combination treatments. So obviously, if you use two toxic treatments together, you're going to have more side effects if you're using just one. So the conclusions from this trial were that immunotherapy demonstrated important, meaningful activity in people with previously treated ovarian clear cell cancer, and this warrants further study given the historically chemotherapy-resistant nature of the clear cell ovarian cancers.

So another study in the treatment of recurrence is this... looking at oral cyclophosphamide and bevacizumab. Both of these agents are routinely used in ovarian cancer. They're both listed in the NCCN guidelines for options for treatment for recurrent cancer. But this was based on really old studies, and so the authors of this trial wanted to really look into the safety and the efficacy to see if it actually works. And so the design of this study was a retrospective analysis of people with a recurrent ovarian cancer treated at a single institution with this regimen, this combination of oral cyclophosphamide plus bevacizumab.

And so the results of this trial, they identified 14 people with platinum sensitive ovarian cancer, and 86 participants with platinum resistant ovarian cancer. And interestingly, it was a heavily pre-treated group, meaning, the median number of previous lines of treatment was three, so they'd seen three different types of treatments previously. And the response rate in this study was 40%, with 4% complete response, so that's similar to the last study, and 36 partial response. So those are impressive numbers for recurrent ovarian cancer. And so the conclusions from this study were that bevacizumab and oral cyclophosphamide are well tolerated and active, with a response rate of 40% in those with recurrent platinum resistant high-grade ovarian cancer.

So shifting our topic into something that is really near and dear to my heart is survivorship. And so in the country, in all cancers, there's an estimated 17 million people who are cancer survivors. These rates will continue to rise, and that's because we have better signs, we're treating cancer better, we're getting more people into remission, we're treating recurrences better, we have an aging population, and so we're going to have more people who have had cancer in the past as our science gets better and as our aging population. But with that comes a huge responsibility of the medical community, we need to really take to heart, not just treating the cancer but treating the side effects that come with cancer, and also recognizing the things that... prevention, great screening, surveillance, these are all things that are important to our survivors. And so I just want to briefly talk about a few more studies that kind of touch on the survivorship aspect and not really the treatment.

So a hot topic of debate in gynecologic care is the safety of menopausal hormone replacement therapy. There was a big study that started in 2005 called the Women's Health Initiative that included tens of thousands of participants and really looked at the safety of using this hormone replacement therapy. So this specific study is a branch of the Women's Health Initiative. It looked at the use of menopausal hormone therapy, and the rates of developing ovarian and endometrial cancer. So this was a long-term follow-up of two specific branches of the Women's Health Initiative study that recruited over 20,000 post-menopausal women, between ages 50 and 79, without a prior history of cancer, breast cancer, at all, or any cancer, within 10 years. So women in this study were randomized to receive hormone replacement therapy versus placebo. The hormone replacement therapy, there was two different kinds, there was estrogen alone versus estrogen plus progesterone therapy. And the primary outcomes we were looking at were the development of ovarian cancer and endometrial cancer, and the related mortality.

So the results of this study were pretty noteworthy. So at the twenty-year follow-up, so this is a long-term follow-up, estrogen alone significantly increased ovarian cancer incidence and mortality versus placebo. However, estrogen plus progesterone did not increase incidence and mortality of ovarian cancer, and decreased endometrial cancer. So the combination seems to be safer. The breast cancer literature does show that progesterone may be the thing that increases your risk of these two substances. Progesterone is the one that increases your risk of breast cancer, but estrogen plus progesterone alone decreases your risk of endometrial cancer and does not increase your risk of ovarian cancer. So it's definitely a nuanced topic, and definitely want to discuss with your doctors. So the conclusions of this study were that estrogen alone significantly increased ovarian cancer incidence while the combination did not, and these findings inform decisions regarding menopausal hormone therapy use.

Another hot topic in all of medicine is the use of AI, use of artificial intelligence. And so can we use it in ovarian cancer? I think the answer is yes. So this study capitalized on the fact that we don't have good ways to define who's going to have a recurrence of their ovarian cancer and what really the prognosis is. So can artificial intelligence be used to help there? So this study looked at specific patient's data, DNA sequencing, drug response profile, and digital pathology profile of the patient's tumor that were input into a machine learning model.

The models were then used to classify survival at 2 and 5-year time points. The results of this study were really cool. So the AI models achieved a high prediction accuracy for both short-term and long-term survival cohorts. Interestingly, the molecular features predominantly drove the 2-year cohort top performing models, and digital pathology imaging was driver of the 5-year cohort. And so what this

shows is that machine learning models have superior prediction of short and long-term survivors, and that different aspects of the profile help identify the short and long-term cohorts and can definitely be used to identify people who may have recurrences and it can be definitely used as a clinical decision tool.

And this is important because it helps people plan for the future, know what's coming. Not that everyone wants that, but this is definitely something that's coming down the pipeline. And this is a really cool study as well. I find all of this really cool, obviously, it's what I do for a living. Circulating tumor DNA, this has been used in several other cancer types for a while. It's really relatively new to gynecologic cancers. And so the concept of circulating tumor DNA is that, see this woman here with a tumor in her ovary? I don't know if you can see my pointer. When that tumor dies or sheds with treatment, some of that DNA from that tumor will enter the bloodstream, and you'll be able to draw the patient's blood, and you'll have what we call circulating tumor DNA. With that circulating tumor DNA, plus the tumor, you can figure out how much DNA is in the blood, and make sure that it's the profile of the tumor you're wanting to track the recurrence of or the presence of. And so this is a really cool technology.

And so this study looked at, can circulating tumor DNA be used to assess if there's residual disease after your primary surgery in ovarian cancer? And so in general, we know that people who have a complete cytoreductive surgery at their first time tend to do better than those with residual disease. A lot of times, we think we're getting all the cancer, but we can't see it all, sometimes things are microscopic. And so is there a role for testing circulating tumor DNA to help us really predict how complete our surgery was? And so this was a perspective multi-center feasibility study. Blood and tumor samples were obtained. And the results of this study showed that there was a unique fingerprint generated for every patient. And then compared to the patients who had clinically no residual disease, those with residual cancer at the time of surgery had significantly higher circulating tumor DNA levels.

Also, those with a complete resection were noted to have a 97% decrease in median circulating tumor DNA levels from the day of surgery to 10 days post-op. So it drops off really quickly once you've done a complete resection. And so the conclusions from this study were that postoperative circulating tumor DNA levels differed substantially based on the residual tumor at surgery, and this may have clinical utility for evaluation in people with advanced cancer. So a lot of cool stuff. The conclusions here are that ovarian cancer is a complex disease. Less radical surgery with not removing lymph nodes does not compromise outcomes. Olaparib may eliminate the need for chemo in some. Combination Immunotherapy may be useful in certain cohorts of clear cell cancers. Cyclophosphamide and bevacizumab has good response in heavily pretreated patients. And combination hormone therapy may decrease risk of endometrial cancer. AI can help, and circulating tumor DNA might help as well. I think I ran over time, I did, and I apologize, but thank you so much. And I will be happy to take questions, I think, at the end. I will stop sharing.

Jenny Stein:

Yes, thank you so much, Dr. Gerber. Yeah. So we will take questions at the end. I see some in the chat, so thank you guys so much. We will try to answer as many questions as we can. But I do want to move on to introduce you guys to Dr. Yuan Yuan. Dr. Yuan is the Director of Breast Oncology Research at Cedars-Sinai Medical Center in LA. She specializes in the treatment and research of triple-negative breast cancer, and she currently is testing a new treatment to help the body's immune system fight cancer. So Dr. Yuan.

Dr. Yuan Yuan:

Thank you. Hi, everyone. You probably are in East Coast and it's quite late... the hours. I'm still in my clinic, just wrapped up. Let me share the screen. And Dr. Gerber, thank you for your wonderful talk because I had learned so much, and I found there's a lot of, I would say, very similar topics in breast cancer. So let me do perhaps... yeah, it's better. Okay. All right. So I only picked the two studies, there are so many of them, it's overwhelming, every ASCO. So hopefully, I'm not overwhelming you. So one study is focused on the really very practical question. So now we all understand, when we treat ER-positive

HER2-negative metastasis breast cancer, we now have frontline setting in this country, United States, we all give patients CDK4/6 inhibitor in combination with endocrine therapy. Typically, for postmenopausal women, we do aromatase inhibitor, but there are times we do fulvestrant, which is a selective estrogen receptor down-regulator.

So we have actually three drugs in this space. So there has been some much better understanding now to understand out of the three drugs, including ribociclib or Kisqali, palbociclib or Ibrance, or abemaciclib, which also had a commercial name called Verzenio. Out of the three, are they the same? Any differences? And how do we use these drugs? Can we sequentially use them? So say, if a patient come in, she already been treated with Ibrance for several years, now we found a bit more disease in the bones, perhaps maybe a new liver lesion, not overwhelmingly sick and still functions really well, the very valid question is to ask, can we treat her perhaps with the cousin drug? Can we treat her with abemaciclib or ribociclib? So recent data had shed some lights on it and then we continue to see new studies in this ASCO that gives us some of the update.

So you can see here that... I know I have a very sort of scientific wordy slides, but it's very straightforward. If you look at the so-called kinogram, this is on the right, so these are looking at the cell signaling pathways after treatment by the drug and look at which signaling path was impacted. Obviously, just by looking at it grossly, you can see there are some differences. For example, the abemaciclib apparently impacted multiple pathways. So there's multiple red dots here indicating beyond the CDK4, CDK6, there's other pathways being impacted. So that perhaps explains why abemaciclib is quite different, it has diarrhea. So the CDK1/9 was inhibited, and then the rival, or the palbociclib, seems to be somewhat similar. And interestingly, they have a high selectivity for CDK4 than the CDK6.

So that lays a foundation of perhaps now we are much better in understanding the efficacy. So these are the data extrapolated from large phase 3 trials. I know we're not supposed to comparing them, but we can't help to compare them, that give us a sense of which drug is better because you got asked by patients in the clinic. So if you look at these data, the winner appears to be, what's colored in blue here, which is ribociclib. And then this so-called hazard ratio, if it's shifted away from one and shifting down to the far left, that indicates better benefit. So you can see the somewhat differences, although there have some caveats interpreting each trial. For example, the PALOMA studies that seem to have a lot of patients had crossover or lost a follow-up. But this gave you a gross idea that out of this three CDK4/6 inhibitor, ribociclib appears to be the most potent one, and people or patients live longest on this treatment as a frontline therapy. So then the next question is, after the patient were treated with the first CDK4/6 inhibitor, can we switch?

So two years ago, there was a trial called MAINTAIN study. It's a phase 3 single center study switching endocrine therapy, and also switching patient largely from palbociclib to ribociclib and looking at how patient had performed. So basically, the control arm would be placebo plus switching endocrine therapy only. So there's no switch of ribociclib. So the patients who were included in this trial, and I know I went in straight forward to the final readout, but there was a table describing who they are. So 70% of the patient received Ibrance, or palbociclib as the first therapy, and they got switched over to ribociclib. And then such strategy had a benefit. I apologize for my slides, they're literally not being digested for you, but the progression-free survival in blue color is those patients who switched from aromatase inhibitor to fulvestrant and then also switched from palbociclib to ribociclib, or from Ibrance to Kisqali.

So these patients derived the benefit. It's a small incremental benefit, about three months, but it's there. So I think it matters because our patient would like to stay in endocrine therapy, not wanting to move fast to future next lines of therapy, and eventually, move on to chemotherapy. So this as always saw a second trial, it's called a postMONARCH study, with a similar idea, and it's actually interesting, presented by the same person who performed the earlier MAINTAIN trial. So Dr. Kevin Kalinsky presented, but in this study, they're largely looking at patients who were treated with the Ibrance or palbociclib and then switched over to abemaciclib. So this is very similar design. And this is a key takeaway, I like the way ASCO did this year, they give you the very much... the first slides give you the key takeaway. So the

postMONARCH trial in this trial basically showed there is benefit of continuing the CDK4/6 inhibitor, but switching the endocrine therapies from Ibrance to abemaciclib. So that's very similar to MAINTAIN trial that boosted our confidence in offer such gentle switch therapy, switch strategy for our patients.

And we don't have to really go into all this detail, but pretty much, very similar to the previous trial, taking patients who had hormone receptor-positive disease, and had disease progression previous CDK4/6 inhibitor, largely, Ibrance or palbociclib as an initial treatment, then switching over to abemaciclib, versus abemaciclib... sorry, the fulvestrant plus placebo, so not adding the abemaciclib. So obviously, maintaining the CDK4/6 inhibitor is a winner, just continuation of endocrine therapy, switching them from aromatase inhibitor to fulvestrant may not be so beneficial. So you can see the progression-free survival benefit is about six months here, somewhat similar to the previous study showed [inaudible 00:34:45]. We don't have to really go into all these weedy information, but literally, the take-home message is quite clear. So I'm going to leave some time for us to address your questions.

So I'm going to move on to the most exciting area that I'm sure some of you who follow the breast cancer treatment. Two years ago, we had this very exciting news, we used to divide breast cancer into three buckets, the ER-positive HER2-negative bucket, the HER2-amplified, HER2-strongly positive bucket, and the triple-negative. So now, this has been shaked up and redistributed. So two years ago, we learned data from DESTINY-Breast04, which, for the first time ever, showed cross-different old classifier of ER-positive disease, or triple-negative disease, as long as we find the tissue has a weak expression of HER2, which is defined by brownish stain by the immunohistochemistry between... 1+ or 2+, these are considered really the new classified HER2-low disease, which accounts for about 55 to 60% of all breast cancer, including a third of the triple-negative breast cancer. This is a groundbreaking news two years ago, and followed quickly by FDA approval of Enhertu. So this is a newer study looking at even more... I would say, in a more refined area, looking at DESTINY-Breast06 focused on ER-positive disease only, so we didn't have any triple-negative breast cancer included in the trial.

They asked literally two questions. One is, after patients travel through the journey of treatment, moved from previously endocrine therapy, now about to starting chemo. This is a big milestone. So they're asking first question, is that, is Enhertu better than conventional chemo, including capecitabine? So that's a very important question. Now, those of us who are familiar with ER-positive treatment, we understand quality life is so important. Are we eager to jump into intravenous chemo that may potentially cause hair loss, side effects, or shall we offer the least toxic but effective treatment? So in my heart, I felt capecitabine or Xeloda remained to be a really good choice. But this data may be changing my view, because now I see convincing data, although not overall survival benefit, but that's really shaping the current practice. So that's the first question. The second question is, they're smartly included very small amount of patient who didn't have a HER-2 low definition, but they're HER2-ultralow. So I'll come to this. What is HER2-ultralow... Do I have slides?

Okay, so ultralow are defined by very faint incomplete membranous stain, less than 10% of the cells, that in the past, before the data came out, they were classified as HER2-zero. So again, it's a really very important information. So every single patient should go back to ask their oncologist, "Did I have HER2-low disease? Did the pathologist report this data?" And that's definitely worth doing. Now, prospectively, moving forward, after we returned from ASCO meeting, we already jumped ahead, we talked with our pathology department, they already changed the practice, they should never report HER2-zero, they should report percentage, and especially, 2%, 3% matters, so those are HER2-ultralow patients. It's a newly discovered category. And then if you add them together, look at HER2-low plus HER2-ultralow accounts for up to 85% of all comers. So this is a really important news.

Now, this is again speaking for the patient population, what is the potential impact of this drug? Anyways, the trial is actually taken patient with hormone receptor-positive disease, HER2-low or HER2-ultralow, prior to endocrine therapy, but they cannot have prior chemo for metastatic disease, divide them into the Enhertu or T-DXd versus dealer's choice, the physician's treatment of choice including capecitabine, nab-pacitaxel, or regular paclitaxel. So quickly jumping into the conclusion here, you can

see a pretty phenomenal improvement of progression-free survival, improved from five months... or eight months to 13 months. So delta improvement is five months. Now, at this moment, the overall survival data is not yet out. So not yet causing any major... There's a trend toward better, but it's still too early, not enough inputs. So pretty much, this is the most important information, that I thought this is very much practice changing from this clinical trial, and it will shape our future discussion in clinic and standard-of-care.

I know the NCCN, the ASCO/CAP, which that defines how we should practice, and it will impact thousands of laboratories out there, and largely most of the academic center will usually do a good job in adapting quickly. But some of those patients who are being cared at community practice, some of the pathology labs may not adapt so quickly. I think a very important message is to ask your oncologist, discuss with them, asking, "Am I HER2-ultralow?" If this is ER-positive disease. So I'm going to stop here, but that's my last slide. We probably have one minute to talk about it. So this is literally the current modern 2024, the landscape or algorithms, how to treat ER-positive HER2-negative disease. So again, the HER2-negative... and be very careful nowadays how to say HER2-negative, including HER2-low, ultralow, or HER2-zero. So again, the frontline would be clearly endocrine therapy plus CDK4/6 inhibitor.

Now, we do have... in between the first and second line, we just learned the two trials, MAINTAIN study and postMONARCH, we can switch, we can perhaps prolong our stay in the CDK4/6 inhibitor space by switching from one to the next one, more potent one. And then depends on the PIK3CA mutation, ESR1 mutation, we have two PIK3CA or AKT inhibitors in this space, and then we also have PARP inhibitor for the BRCA2 or BRCA1 mutation carriers in this second line setting, then before we move on to chemo, we do have a very careful discussion based on the pathology feature and then based on the patient's desire, lifestyle, things... no one wants to lose hair, the ILD risk, there's a careful discussion right here. All right. So I'm going to give it back to the host. Thank you for your time, and thank you for the opportunity to discuss with [inaudible 00:42:31].

Jenny Stein:

Thank you so much, Dr. Yuan. So a lot of information that both Dr. Yuan and Dr. Gerber provided to us. And we have a bunch of questions that, hopefully, we can get through some of them. I just want to remind everybody though that the information that we provide tonight is not a substitute for medical advice or treatment of any specific medical condition, and you shouldn't use this to diagnose or treat any of your health conditions. If you do have questions, like I stated earlier, we do recommend that you talk to your doctor about your specific conditions. Okay. So a couple of questions. I'll start first with Dr. Gerber. There was some question regarding prophylactic surgery, hysterectomies, removing fallopian tubes, maybe removing an ovary, and wondering what the risk is of ovarian cancer if you've had a hysterectomy, and fallopian tubes removed but there's still one ovary, or if there's maybe both your ovaries are there, is there still this increased risk of ovarian cancer?

Dr. Deanna Gerber:

This is a great question. It's kind of like a hot topic in gynecologic cancer or gynecology completely. We believe... we know for certain people that ovarian cancer is actually fallopian tube cancer, it starts in the fallopian tube. We have a lot of reason to believe that ovarian cancer actually is fallopian tube cancer in most women. And so we believe that removal of the fallopian tubes will greatly reduce ovarian cancer, possibly eliminate it. However, we don't have that data yet. And so the person asking the question with one ovary remaining, it's hard to say what the risk... The risk of ovarian cancer in the general population without a mutation is really low, it's less than 2%, 1.7%. And so with one ovary left, I would probably quote the same risk, until we have more data, which it's definitely coming... It's going to be here soon.

Jenny Stein:

Thank you. Great. And while we're talking about just risks, a lot of questions have come out that were submitted before just on any new treatments, and this is really be for both you, Dr. Gerber and Dr. Yuan, about people who have a genetic mutation. Any new treatments for people with any type of genetic mutation that makes them more at risk for either breast or ovarian cancer.

Dr. Deanna Gerber:

I am happy to take this. So the BRCA mutations, the Lynch syndrome mutations, those are essentially biomarkers for activity in a lot of the new medications that we're using. The PARP inhibitors, which I talked about briefly, the immunotherapies, Lynch syndrome patients respond really well to those. And so there's a lot of new emerging data on people with these mutations. So that's why genetic testing is such a vital component of cancer care.

Jenny Stein:

Perfect. Great. Dr. Yuan, did you want to add something? Yeah.

Dr. Yuan Yuan:

Yeah. If I may add, I think we're largely fully aware about the BRCA1, BRCA2, that there's other genes, or less frequent, like PALB2 mutation. There's actually recent data showing that in PALB2 mutated patients, the PARP inhibitor, olaparib, works really well. Perhaps the progression-free survival even is better, a tad better than the BRCA mutated patients in metastatic breast cancer setting. But one biggest challenge we're calling for newer therapy is the patient who had progressed after the PARP inhibitor, I think that's an area of research. We currently conduct the trial, there have been plenty of data in a small phase 1, phase 2 setting, looking at combination of PARP inhibitor with immune checkpoint inhibitor in that setting. But it just felt like it's not enough, there need be new treatment.

Jenny Stein:

Okay. Thank you. And Dr. Yuan, this question's for you, I know we talked a lot about research if somebody is HER2-low or ultralow, but any new studies out there or research on the horizon for people with triple-negative breast cancer, particularly those that are metastatic?

Dr. Yuan Yuan:

Yes. So as we're aware, so nowadays, the neoadjuvant or early stage triple-negative breast cancer landscape has changed because we now have chemoimmunotherapy. But the same challenge here applies because the KEYNOTE-522 regimen uses, weekly, CarboTaxol, KEYTRUDA or pembro, followed by AC pembro. And then quickly, we're using this wonderful drugs, but if these patients who had treated with that regimen relapsed, it's forcing us to push forward the drug antibiotic conjugates, so the sacituzumab govitecan is the first one, used to be third-line treatment, now it's pushed up to first-line in that setting. And then if the patient had HER2-low disease, not ultralow, because ultralow data we talked earlier only applies to ER-positive disease, if the patient were HER2-low, then there's an option of Enhertu, otherwise, there's a lot of research now looking at a different type of antibody drug conjugates.

We have a phase 1 trial looking at the same Trk2 targeting with different payloads, or there's a HER3 targeting antibody drug conjugates with deruxtecan as a payload. So you'll see a lot of crowded antibody drug conjugates in the space. But there's still ongoing trials looking at CAR T-cells, looking at oncolytic viruses, but they're very early, very experimental. I think the most promising agent that we expect to see in the next couple year would be a different ADC, and then also ADC in combination with immune checkpoint inhibitor.

Jenny Stein:

Great. Thank you. Dr. Gerber, so there was some question, I know you talked about some chemotherapy regimens with the high-grade serous ovarian cancer. I'm wondering if there is any research out there on immunotherapies for people with a high-grade?

Dr. Deanna Gerber:

So there's a lot of research on the use of immunotherapy in ovarian cancer. The data is kind of mixed, and that is because immunotherapy relies on your body's ability to recognize something as other, it's using your own immune system to attack it. And so ovarian cancer doesn't have a high mutational burden, or the body doesn't recognize it as other as much. So we think that's why we don't get as robust of a response with immunotherapy in ovarian cancer. But there are some studies, there's the DUO-O study that showed that immunotherapy plus others... plus PARP inhibitor plus bevacizumab may be good maintenance.

Jenny Stein:

Great. Thank you. So Dr. Yuan, have there been any updates regarding treatment of breast cancer among men?

Dr. Yuan Yuan:

That's an excellent question. Not as far as I know, because the men's breast cancer are rare. And typically, when I was at NYU, I was doing my fellowship, we go to VA. So VA, I had quite a few male breast cancer. And then when men has breast cancer, most importantly is to rule out a familial disposition for genetic mutations, much higher percentage. And we follow exactly the women's cancer treatment route, based on the subtype. Not aware of a male breast cancer trial, it would be very difficult to adapt, it will be [inaudible 00:51:13] collaborations. Yeah.

Jenny Stein:

And speaking of collaborations, there was a question in the chat about if you guys collaborate with hospitals or institutions outside the US? What does that collaboration look like?

Dr. Yuan Yuan:

Go ahead.

Dr. Deanna Gerber:

The majority of the studies I actually talked about in my presentation were international studies. A lot of the large gynecologic cancer studies do require an international buy-in from institutions all over the world because these cancers, I guess when we think about it compared to breast, are relatively rare, they're not as common. And so to get the numbers we need, to get the data we need, it requires many institutions to collaborate to get us the big breakthroughs, and that often involves international stuff.

Dr. Yuan Yuan:

Yeah, absolutely right. So largely, most of these FDA approval drugs are registration trials globally. And as far as patient population, because earlier, there was a question regarding why young women's breast cancer rate or young patients cancer rate is rising, do we collaborate? It's an excellent question. So for us, we're at LA, we have Korean population, Armenians, and we also have a hot spots for Jewish population, so we are always interested in collaborating. For example, my colleagues collaborating with Seoul in Korea to look at those patients, and there's specifically environmental changes for immigrants. We also know there is impact, but I think we just lack of crystal clear understanding. I think we should call for more collaboration, if possible. Yeah.

Jenny Stein:

Okay. And this is a question either one of you, if you wanted to speak to, question about supplements working with an integrative medical physician, what are your thoughts about that in terms of preventing recurrence?

Dr. Deanna Gerber:

I feel very strongly about this topic. I am a western medicine practitioner, and I studied in med school here where we didn't learn any of these things, but the more I learned about cancer care, the more I realized that holistic alternative medicines are vital to cancer care. I think ultimately, your wellbeing, your holistic wellbeing, your healthy lifestyle, you're feeling less stress, you're feeling good, anything you can do to increase that will ultimately result in less recurrence in theory. And so I absolutely always encourage my patients to seek out all alternative methods.

Dr. Yuan Yuan:

Yeah, extremely complex. My patients come in, they were like, "Why? Why Cedars-Sinai does not have an integrative medicine." She was very unhappy about this. And it is very hard to do, because I often refer to Memorial Sloan Kettering website, if you type about herbs in the Google, there were leads to MSKCC's website, like they have herbal dictionary. But even that is not including everything. And every day, I got being asked with a new name, new drugs. I think it's just that we all felt a little helpless there. It's not enough research or enough funding to do those. But yeah, I think we're living our life, we have to probably get more answers. But it just needs probably a major approach, from government funding to academics, work together. Huge undertakings.

Jenny Stein:

One last question. I know, Dr. Gerber, you had mentioned about the circulating DNA, and somebody just put in the chat, if you could, again, just reiterate what you said about it, the questioning, "Is that a reliable source to predict reoccurrence?" And what are your feelings about using those types of tests?

Dr. Deanna Gerber:

So currently in ovarian cancer, it recently gained FDA approval for monitoring recurrence of ovarian cancer. The issue why this is not... why I'm not so gung-ho about recommending this to everyone for monitoring recurrence is because we have data, albeit it's old data, that shows that the earlier you detect a recurrence does not lead to better survival with ovarian cancer. And so is knowing about it when there's one circulating tumor... or not one, but low circulating tumor DNA in your blood before you're symptomatic, is that going to improve your outcome? And right now, the data says no. And so theoretically, yes, it could probably be used to detect recurrence, but will it lead to any meaningful outcome? It's hard to know.

Dr. Yuan Yuan:

Yeah. The biggest confusion here is that there has been plenty of data showing, before the imaging shows anything visible by eye, ctDNA could be there and be presently going up for 7 to 10 months. That makes people... I mean, tomorrow, I'm getting consultation, imaging shows nothing, the ctDNA is going up, and then the oncologist is asking what to do. So it is very hard because... and we also don't have a thousand drugs in the space available for patients. So we're trying to understand if you pull the trigger earlier, does that save life? Does that bring better benefit? So I think we still need to understand, but I think our patients in our visit room, they're asking a very good question, "How do you know I'm cancer-free?" So I think the last six months, I have drastically increased a lot more ctDNA, but I'm waiting to face the

scenario, like there's going to be difficulty. So every test is no perfect test, that's a problem. And the medical community is not ready yet to know what to do, that's a problem, a headache, we have.

Jenny Stein:

Well, thank you guys so much. We really appreciate, Dr. Gerber, you taking the time, and Dr. Yuan, you guys both taking the time and educating us this evening. I'm sorry we weren't able to get to all of your questions. But if you still have some questions, particularly specific questions, please, again, reach out to your medical provider, and they should be able to help answer your questions or steer you in the right direction. I'm sure so many of us tonight are more knowledgeable after learning from the two of you tonight. So thank you so much. We do ask that you guys take a moment to complete our brief evaluation survey that we're going to be putting in the chat box. These evaluations really do help inform our future programming. So we really appreciate you taking the time to complete that for us. And then finally, we'd love for you guys to stay connected with Sharsheret via our social media, where we post events that we are running, program updates, and different ways that you can get involved.

An upcoming program that we have is our 2024 Sharsheret Summit, which will be October 9th through November 10th. We're putting the website in the chat for you now. This summit brings together thousands of people virtually and in-person all across the country. And this is our marquee educational event. So if you're interested, please click on the link, learn more. You can join in our national virtual symposiums, the latest topics related to breast and ovarian cancer. You can attend or host an in-person education session, or an awareness raising program within your community, and learn about the latest screening guidelines and access the most up-to-date data and materials, which will have available in a digital resource packet. However you decide to participate, the Sharsheret Summit is the source for the latest information on breast and ovarian cancer in the Jewish community. I, again, wanted to thank our sponsor for today's webinar, Daiichi-Sankyo.

And please, never forget that Sharsheret is here for you and your loved ones. We provide emotional support, mental health counseling, and other programs designed to help navigate one's cancer experience. So all the services we provide are free and confidential. Our phone number, if you need, is 866-474-2774. We'll go ahead and put that in the chat, along with our email address, if you wanted to reach out to us that way. Our social workers and genetic counselors are available for each and every one of you. You're our priority, so please, never hesitate to reach out. And thank you guys so much for your time tonight.