From Podium to Patient: 2025 ASCO Updates in Breast and Ovarian Cancer Research

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SHARSHERET
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Devorah Silverman:

Good evening, everybody. Thank you for joining us tonight for our webinar, From Podium to Patient: 2025 ASCO Updates in Breast Cancer and Ovarian Cancer Research. My name is Devorah Silverman, and I am the Chief Operating Officer at Sharsheret. Welcome.

For those of you who may not be familiar, ASCO, the American Society of Clinical Oncology, is the world's leading professional organization for physicians and oncology professionals caring for those with cancer. The ASCO annual meeting gathers oncologists from all around the world to share the latest cancer research and discoveries, bringing together the best minds to shape the future of cancer care.

Tonight, we're privileged to hear from Dr. William Gradishar and Dr. Joshua Cohen, who will highlight the latest research that was presented at ASCO. We're grateful also to tonight's webinar sponsors, the Cooperative Agreement DP 240061 from the Centers for Disease Control and Prevention and to Gilead whose sponsorship is focused on tonight's Embrace post-webinar session.

Before we begin, a few housekeeping items. Tonight's webinar is being recorded and will be posted on Sharsheret's website along with the transcript. Participants' faces and names will not be visible in the recording. If you would like to remain private, you may turn off your video and rename yourself on your screen or you can call into the webinar. Instructions for how to do that are in the chat box now for both of those options. Closed captions are also available. The instructions about how to access them are in the chat now as well.

You may have noticed that all participants were muted upon entry. Please keep yourself on mute throughout the presentation. We received some questions in advance of the webinar and anticipate receiving more this evening. If you have questions, type them in the chat box, and please make sure to keep your questions broad as we can't offer specific medical advice. We'll do our very best to answer as many of your questions as possible.

As we move into the webinar itself, I also want to remind you that Sharsheret is an international nonprofit cancer support and education organization, and we do not provide any medical advice or perform any medical procedures. The information provided by Sharsheret and by tonight's speakers is not a substitute for medical advice or treatment for specific medical conditions. You should not use this information to diagnose or treat a health problem. If you have any questions that are specific to your medical care, we advise you to speak with your medical provider. Always seek the advice of your physician or a qualified health provider with any questions you may have.

As I mentioned, after we hear from Dr. Gradishar and Dr. Cohen, we will open up for questions and answers. And a special reminder for our Embrace community, which includes those facing metastatic breast cancer and advanced ovarian cancer, we hope you will stay on at the end of the webinar for an intimate breakout session with our expert speakers and Bonnie Beckoff, Sharsheret's Director of Support Services.

Now, onto tonight's speakers. Dr. William Gradishar is the Betsy Bramson Professor of Breast Oncology in the Division of Hematology and Medical Oncology at the Feinberg School of Medicine at Northwestern University. He is also the director of the Maggie Daley Center for Women's Cancer Care and the Robert H. Lurie Comprehensive Cancer Center. His research focuses on the development of novel therapeutics for the treatment of breast cancer.

He serves on multiple cancer committees and panels, including ASCO's Scientific Program Committee, the National Comprehensive Cancer Network, NCCN, Breast Cancer Guidelines Panel, and the NCCN Breast Cancer Prevention Panel. He also serves as a consultant to the Oncology Drug Advisory Committee of the FDA.

Dr. Joshua Cohen is a board-certified gynecologic oncologist and medical director of the City of Hope Orange County Gynecologic Cancer Program. He is an expert in the surgical cytoreduction of cancer and in the use of minimally invasive surgical techniques including robotic surgery. He values the opportunity to perform cancer surgery and to oversee systemic treatment, developing a personalized treatment plan for each patient. Dr. Cohen has led significant effort in gynecologic cancer research and completed the clinical research training program at the National Institutes of Health, as well as the Clinical and Translational Science Institute Certificate Program at UCLA Medical Center.

An investigator with more than three dozen peer-reviewed publications, Dr. Cohen leads studies designed to improve the quality of care and outcomes for patients facing gynecologic cancer. He joined City of Hope as an associate professor from the David Geffen School of Medicine at UCLA where he served as gynecologic oncology fellowship program director. Dr. Cohen is a fellow in the American College of Obstetrics and Gynecology and a fellow in the American College of Surgeons. Esteemed presenters, thank you for being with us. We'll begin with Dr. Gradishar. Welcome.

Dr. William Gradishar:

Thank you very much, and it's a pleasure to be with you, and let me just get my screen here. Are you able to see my slides?

Devorah Silverman:

Yes.

Dr. William Gradishar:

Okay. So thank you for the introduction and the opportunity to share just a snippet of what went on at ASCO. It's a huge meeting, there's lots of things presented, and we have limited time, so I thought I'd really focus my comments and discussion on three different areas of metastatic breast cancer and use them as a springboard perhaps to questions that'll follow.

So these are the three studies that I'm going to talk about, and I'll tell you why they're relevant, not necessarily for immediacy of being implemented tomorrow, but many of them will probably be a strategy we utilize very soon, and I'll explain why that's true. So three trials, one in hormone receptor-positive disease, one in triple-negative breast cancer, and one in HER2-positive disease, so each of the three silos of breast cancer, so to speak.

So let's start with SERENA-6. So this is a trial in patients with hormone receptor-positive disease. Now, it's first important to know that one of the drugs being tested is not available, and that's really not the major issue.

The major question that's being asked in this trial is if you have a patient with metastatic breast cancer, hormone receptor-positive, who's on endocrine therapy with the CDK4/6 inhibitor, and they're doing fine, they've been on the therapy for at least six months, if you detect something that's molecularly changing, even in the absence of anything clinically changing, so nothing is different on the way the patient feels, the scans look the same, but you find a molecular evidence of some changes in the tumor, what if you change the therapy at that point versus simply continuing it on with what you had started with? Will that impact on the overall outcome? And this is a strategy that's been employed in hematologic malignancies for a long time, but it's not something we typically do for most solid tumors.

So I'll tell you what the takeaways are right from the beginning, and that is the molecular abnormality that was looked for is what we call an ESR1 mutation, and this is a molecular abnormality that emerges under pressure of treatment. So if you biopsy patients when they were originally diagnosed with early-

stage disease and you were looking for this abnormality, you probably wouldn't find it. But as patients get treatment with, say, aromatase inhibitors or other endocrine therapy, these abnormalities, these mutations, emerge in up to 40% of patients. And this trial is going to, again, cutting to the chase, demonstrate if you change therapy, even in the absence of having evidence on CT scans, say, or bone scans, that the disease is changing, you may extend the duration of time the patient has without clinical evidence of disease progression.

Now, I mentioned already that ESR mutations are important. They happen, but they're not present at diagnosis. Fewer than 5% of patients have them. But as you get treated with aromatase inhibitors or CDK4/6 inhibitors with an aromatase inhibitor, which is more or less the standard treatment for patients with first-line therapy of metastatic disease and also being employed more commonly for early-stage disease, these mutations start to emerge.

And why are they important? Well, they're important because subsequent therapy with anti-hormonal therapy is often challenging because the tumors become resistant to endocrine therapy once an ESR1 mutation emerges, so that's why all these newer drugs are being developed. And the drug in this trial that's being tested, which isn't really the main question, is a drug called camizestrant. We're excited about this drug because it's a drug like fulvestrant or Faslodex, but you don't have to get a shot in your backside. You can take a pill, and it works particularly well in patients with ESR mutations.

Now, the way this trial was set up is patients had to be on their first-line therapy with an aromatase inhibitor and a CDK4/6 inhibitor for at least six months without evidence of disease progression. And at that point, they started doing what we don't typically do in patients with metastatic disease who are doing fine. They had started looking for ESR mutations and they had to screen 3000 patients to ultimately find 300. So a lot of screening, a lot of testing, to ultimately come up with 300 patients who were randomized in this trial. And the testing that was done is a blood test [inaudible 00:11:15], familiar with NGS testing and the platform that was [inaudible 00:11:20].

If you look at the design of the trial, I already alluded to it, patients with metastatic disease who had been stable without any evidence of progression were continued either on their initial therapy with an aromatase inhibitor and a CDK4/6 inhibitor, or at the time that an ESR mutation was detected, they were switched to the newer drug, camizestrant. So that was the switch without clinical evidence of disease progression, and they continued on a CDK4/6 inhibitor.

And again, if you look at the effect, I think a slide got eliminated here, but what the results showed is that progression-free survival, the time until the disease progresses, was improved by over a year in the patients who had an early switch, even in the absence of evidence of metastatic disease. And as a corollary of that, if you survey patients about how they were feeling, what their quality of life was, there was a significant prolongation in the time until they felt worse if you had an early switch, 23 months versus 6.4 months.

So what were the takeaways and what does this mean in terms of impacting on practice? Well, the first thing is the last bullet point: camizestrant's not yet available. It's an oral medication, we anticipate it will be approved, but it's not yet available. But the bigger question is if you start doing these molecular tests on patients, even in the absence of evidence of metastatic disease progressing, and you change therapy, might that improve the overall outcome?

And this trial, survival is immature, so we don't know that that impacted on survival, but the time until the disease progressed was markedly improved, not by statisticians, they get excited about two or three weeks if it's statistically significant, but this was clinically meaningful with an improvement of over a year. So it's a strategy that we might be using in the future sooner than we think.

The second trial is one in the triple-negative space, and I think most people are probably familiar with the constructs that are referred to as antibody drug conjugates. You have a targeting antibody for a specific antigen present in the tumor. It's usually linked to a cytotoxic drug like a chemotherapy drug. And the strategy is that you're going to more specifically target the tumor and potentially have less toxicity.

So one of the drugs we commonly use in triple-negative disease, ER, PR, HER2-negative disease, is called sacituzumab govitecan. In patients with metastatic disease who have what we call PD-L1 positive disease, the strategy we often use is combining an immunotherapy, a checkpoint inhibitor, with chemotherapy, and we usually reserve sacituzumab govitecan, commercially known as Trodelvy, until the second line or later lines of therapy. This is a question or this trial was asking the question, what if you move it up? What if you combine immunotherapy with sacituzumab govitecan compared to chemotherapy plus pembrolizumab?

And if you cut to the chase and want to just take away what was learned from this trial, we found that sacituzumab govitecan, the antibody-drug conjugate, when combined with immunotherapy, improved the time until the disease progressed. It was better than the standard which is chemo plus pembrolizumab. And this result may shift how we think about using this in triple-negative breast cancer, and we'll go through the data here very quickly.

So again, the patients that were involved in this trial were patients that had not gotten treatment for metastatic disease. They had triple-negative disease, and they were candidates for immunotherapy based on an assay we do that evaluates the tumor for something we call PD-L1 positivity, and there's a certain metric we use to determine whether a patient's a candidate.

So the patients either got what would be viewed as standard, chemotherapy, a taxane, or Gem/Carbo, two commonly used chemotherapy regimens, combined with pembro, or the antibody-drug conjugate, sacituzumab govitecan plus pembro, and the patients were treated until disease progression. And what was demonstrated in this trial was that if you look at the time until the disease progresses, patients who had sacituzumab govitecan combined with chemotherapy did better at each time point, six months, 12 months, and beyond, compared to chemotherapy plus pembrolizumab. And this represented basically about a 35% reduction in the odds of disease progressing at each time point.

So this was clinically significant again, and if you look in absolute terms, how much did it improve? It went from about just shy of eight months to a little over 11 months. Now, of course, we'd like to do much better than that, but nevertheless, that is a significant improvement in outcome. And survival at this point is too immature to say whether it impacts on survival, but clearly it moved the needle in terms of delaying the time until you had to change therapy to something else.

And the other endpoints that were evaluated were looking at what fraction of patients responded. It was a little bit better with sacituzumab and pembro versus chemo and pembro. And then if you were one of the patients who did respond, there was evidence that the tumor was responding, if you look on the right, the duration of that response is significantly greater, went from nine months to 16 and a half months. So if the tumor is responding to the regimen, the duration of that response was significantly greater.

So what does this mean on practice? Well, this may have a direct impact on what we elect to use in triple-negative breast cancer, rather than combining pembrolizumab, which is commonly used in these PD-L1-positive tumors. Rather than combining that with chemo, we may want to use sacituzumab govitecan.

It's important whenever you make a claim that something is better, that you also take into account what the side effects were. And in this case, GI symptoms were a little bit of an uptick in the sacituzumab

govitecan arm, a little bit more nausea, a little bit more diarrhea, but there were no unexpected toxicities, so this is something that I expect will likely be an option for patients very soon.

And the final one is the DESTINY-B09 study. And again, thinking about antibody-drug conjugates, in the HER2 space, we've had T-DM1 or Kadcyla, we've had trastuzumab deruxtecan for some time, and DESTINY trials, there have been numerous ones as the numbers suggest, and they've all demonstrated that trastuzumab deruxtecan is particularly effective not only in HER2-positive but HER2-low disease.

So this was a trial that was meant to ask the question, if you use trastuzumab deruxtecan as a first-line therapy, and again, we usually reserve it for later, will it have a significant impact on outcome? Keep in mind that the standard therapy in metastatic disease as a first-line therapy is what we call the Cleopatra regimen, and that combines Herceptin, pertuzumab and a taxane. And that has been the first-line therapy for quite some time for several years, and it clearly showed a benefit over just giving Herceptin. But now because all these trastuzumab deruxtecan trials were so effective, it became a natural question, what if you move the trastuzumab deruxtecan up as a first-line therapy?

So cutting to the chase, what did the trial show? And then we'll backtrack. It showed that if you combine trastuzumab deruxtecan with pertuzumab, you markedly improved the outcome. You increased the time until the disease progressed, and it represented a 44% reduction in the odds of the disease actually progressing with this regimen. And we'll get into what that actually means in practical terms.

So if you look at first-line therapy, in the Cleopatra regimen, and I'll just focus on the top of this slide, the observed median progression-free survival as a first-line therapy until the disease progresses is about a year and a half with Cleopatra. With the T-DXd and pertuzumab treatment arm in this trial, the median hasn't even yet been reached, so that really represents a marked improvement in outcome.

The trial looks like this. So these were first-line patients. Again, they had to not be chemo-resistant so to speak, so there had to be an interval from their prior therapy of at least six months before metastatic disease presented. They even allowed some patients that had asymptomatic brain mets to be involved, and they couldn't have gotten any other prior systemic therapy for metastatic disease.

Importantly, the three arms are Cleopatra, which is on the bottom, THP, or T-DXd plus pertuzumab, and the first, the top box is T-DXd plus placebo, and we're not really talking about that because that treatment arm was not reported in this trial. And it's important to understand what that treatment arm is going to do because it'll ask the question of how much pertuzumab adds, but there weren't enough events to allow that treatment arm to be discussed at the ASCO meeting.

So cutting to the chase, what did it show? If you look at the top-right-hand side of the slide, compared to THP, otherwise known as Cleopatra, T-DXd plus pertuzumab improved the outcome from 26 months to 40 months before disease progression. So that was, by anybody's measure, a significant improvement in outcome.

And you can look at the data in another way. What fraction of patients had progression at six months or 12 months or two years on the curves? And the fraction of patients who don't have any disease progression is significantly greater at each time point for T-DXd plus pertuzumab. Response rate was also higher on the left, and if you were a patient who responded, the duration of the response on the right was 26 months versus 39 months. So again, a significant and clinically relevant improvement in outcome, and I suspect that that will be something that we will be talking about when we discuss guidelines.

Again, survival is immature. We don't have enough analysis or statistical power to look at survival, but there's a slight trend at this early point suggesting that T-DXd will be better. We'll have to see.

Now, importantly, as I made mention a moment ago with sacituzumab govitecan, you always have to think about side effects, and one of the things with T-DXd that we always worry about is will you get

pneumonitis, which is a known side effect of trastuzumab deruxtecan? It's usually low-grade, but occasionally it can be life-threatening, and actually, a few patients have died, and that was also true in this study.

But compared to when this drug was first introduced five years ago, the number of patients who are having severe side effects has markedly decreased, and I think that reflects the fact that clinicians are very aware of this side effect. They back off on treatment if there are any sort of respiratory symptoms. So generally very safe, no effect on left ventricular ejection fraction or heart function either.

So what is the impact? Well, keep in mind in the Cleopatra regimen, which has been used forever now, oh, I don't want to say forever, but for several years, you get chemotherapy for roughly six cycles, and then you stop. If you're responding, then you just stay on the antibody, so the chemotherapy falls away.

The way this trial was designed is people just stayed on T-DXd plus pertuzumab sort of forever until the disease progressed, so one of the unanswered questions is whether you can get away with less of T-DXd than just staying on it forever, so we don't know the answer to that. We have immature survival data, but very compelling data from PFS, improved by greater than a year.

And the final nuance is there was a trial presented at San Antonio called the Patina Trial, so there are patients who are not only HER2-positive but ER-positive. And if they were getting the Cleopatra regimen and they were responding after six cycles, say, the chemo fell off, they continued on anti-hormone therapy, and a CDK4/6 inhibitor was added. And in that subset of patients with ER-positive disease and HER2-positive disease, the PFS, or progression-free survival, looks very much the same as what we see in this trial.

So again, there may be nuance about how we think about treating individual patients based on their markers, and we'll have to see how this plays out. But these results are exciting and represent I think another advance for patients with HER2-positive metastatic disease. So with that, I'll stop. Thank you.

Devorah Silverman:

Thank you so much, Dr. Gradishar. We really appreciate everything that you've shared with us, and we're going to turn now to Dr. Cohen.

Dr. Joshua Cohen:

Okay, great. Thank you all very much, and thank you, Dr. Gradishar. It's always so interesting to see what is taking place in other disease sites because there is some crossover, and it's certainly something, I always learn something when I see how something like breast cancer is treated because we can learn a lot of things from each other.

So just with that, we're going to talk about ovarian cancer, and I'm a gynecologic oncologist in Southern California with City of Hope, and wonderful to be here with all of you. No. These are older. I've served in an advisory fashion for a couple of companies in the past, nothing recently, and nothing that would impact the content of the discussion today.

So just a few things I do want to mention as we focus on some of the later trials that have been presented at ASCO this year. And similar to Dr. Gradishar, we'll say there's a huge amount of information that gets presented at ASCO, and it's really impossible to summarize all of it in 20 minutes in a meaningful fashion for anyone, and so I've tried to hit some of the highlights here.

But as we talk about these things, I know there's a very group of people that are listening currently across the country and who may watch this asynchronously later, so I really want you to think whether you're a patient or a family member, if this is something that you're taking to heart, where are you in

your treatment course, what type of ovarian cancer you have? Because that has a significant impact on whether some of this data is pertinent to you. Where you are in the treatment of chemotherapy.

For instance, the term platinum-sensitive or platinum-resistant, you'll hear me say this a few times during the presentation, meaning when was the last time that someone was given a platinum chemotherapy compared to when the disease recurred? Because that has implications for whether someone would benefit from additional platinum chemotherapy, which in many ways is the backbone of a lot of our treatments for ovarian cancer.

Have you received some more common medications that we do use for ovarian cancer? One such as bevacizumab or a class of drugs called PARP inhibitors. Also, are there any current medical conditions that you're impacted by or your loved ones are impacted by that may impact your ability to receive certain medications? Conditions such as autoimmune disease, kidney disease, liver disease, or second cancer may or may not make these studies applicable to you.

And then how many prior lines of therapy has one received? Meaning how many go-arounds of chemotherapy or other targeted agents? And are there any significant ongoing toxicities such as vision changes, which can happen with some of these drugs, or neuropathy, which is tingling in the hands of the feet, which can happen with some of these drugs? Because again, that may impact your ability to receive future drugs that treat these cancers.

And then what's your current activity during your day? Are you up and walking? Are you mostly in bed? Are you able to eat and drink on your own? And these are important things to think about because these all have implications for whether you would potentially benefit from these drugs as we better understand the toxicity of medications.

Also in the setting of clinical trials, I'm going to mention different phases, phase one, phase two, phase three, and I realize this is very confusing for patients and family members. And the simplest way I can break it down is that phase one is an early drug, meaning that it's a drug that we think is promised, but we're not quite sure what the dosing should be. We're not quite sure if it is actually going to be helpful, but we think based in the lab or based in other studies done in animal models, that there may be benefit for patients with ovarian cancer.

A phase two is a study where we know that there's some benefit on a dosing we've chosen. Now, we're looking to see what is that benefit? Is it something that's significant that we should really put it into a larger study and compare it to a standard of care treatment? Phase three is a larger study where we've actually shown that there's benefit, and now we want to better understand what that benefit is compared to the standard of care, similar to a number of the studies that Dr. Gradishar presented. Really, is this something that we should now use instead of the current standard of practice?

And then phase four is something that we don't often talk about it, but it's really a confirmatory study where the drug is now in use and we're looking for rare side effects that we may not otherwise see in a general population. And this is bore out not in cancer drugs, but actually in other drugs such as acid reflux drugs where maybe we didn't see this in a larger phase-three study, but after hundreds of thousands of people receiving these drugs, it's now apparent that there is a risk we need to be careful about.

Ovarian cancer is a misnomer. It's not just one drug or, I'm sorry, one disease. It's many different diseases. And that's why I want you to really think about what disease process that you're impacted by or your loved one may be impacted by, because we know that as we treat these cancers, we have to get really molecular. What do they look like on a DNA level and what do they look like under the microscope? And the most common ovarian cancers we treat, there's a term called serous: serous

ovarian cancer, high-grade serous or low-grade serous. There's also endometrioid, clear cell, mucinous, and carcinosarcoma. These are the most common types of epithelial ovarian cancer.

And I bring this up because a number of these studies focus on specific subtypes of ovarian cancer, and it's important to know which subtype that you may be impacted by. We also now believe we found the holy grail. The precursor lesion to high-grade serous ovarian cancer actually comes from the fallopian tube. It's called the STIC lesion, serous tubal intraepithelial carcinoma.

And for our BRCA1 mutation carriers, this is really our best chance to prevent cancer. Similar to when someone has a colonoscopy and we find a polyp that's not cancer but may become a cancer, this is where this cancer may start. It may start as a STIC lesion in the fallopian tube, and if we can remove these fallopian tubes early enough, we can prevent high-grade serous ovarian cancer.

I also want you to be familiar with the genetic testing that we're ordering. So as cancer doctors, when we order tests, we'll often say, "We're going to send your tumor for analysis and we're going to send you to see a genetic counselor." It's really important to understand that the DNA you have from your mom and your dad is in every cell in your body, but the DNA of the tumor may be slightly different, and that has implications for the disease and whether you'd benefit from a drug.

Some drugs require that it only be in the tumor, some drugs when they're approved require that you may have to have the mutation in your germline DNA, which is in every cell in your body. So really talk to your doctors about what germline testing or somatic testing means and what testing has already been sent.

So the first study I'm going to mention is a surgical study. So I'm a surgeon by training. I also do systemic treatments. I'm fortunate that I get to do systemic treatments for my patients, but this was a very large study that was presented to ASCO looking at the role of upfront surgery for ovarian cancer. So metastatic ovarian cancer, should patients receive initial surgery or should they receive chemotherapy first followed by surgery? And the term for that is neoadjuvant chemotherapy.

It was randomized. And the challenge with this study is that it was done at very specific cancer centers that are extremely high-volume with extremely high-volume surgeons, and this is not reality for most patients. Most patients get care in the community. And we talk about does this study mean that this is reality for me in Nebraska or reality for me in rural California, in Central California? It may not be, but in the hands of surgeons who do this every day in large complex cancer centers, this study was done to show is there benefit with upfront surgery or chemotherapy followed by surgery?

And what you can see here is that there actually was not a benefit in overall survival. The right side of the screen shows you that there was really no statistical difference for patients whether you had upfront chemotherapy or surgery first in that patients both had survival that was approximately 50 months, which is actually really good. And I want to say this number represents the fact that we've made significant progress in advanced ovarian cancer.

Where there may be some benefit in upfront surgery by an extremely qualified surgeon at a very high-volume center, there may be a benefit in progression-free survival for stage three patients with ovarian cancer. Progression-free survival means time that you don't have the cancer. It doesn't mean how long you're going to live.

What we did find though with upfront surgery is that there are some higher complication rates including 28-day complications, and this is the bottom of the left-hand side of your screen. So if you look at upfront tumor debulking, the 28-day complication rate was about 18% versus 12%. There was a higher chance of needing an ostomy. An ostomy is where when we resect cancer in the abdomen, we often will evaluate the intestine, and the intestine is often impacted. Sometimes we can remove the cancer and

leave the intestine intact, but sometimes we actually have to remove a portion of the intestine which may require a diversion, which is an ostomy.

There was a higher rate of ostomies needed in the upfront surgery group, 20% versus 8%. There was no difference in survival within 28 days of the surgery, so both sides lived equally in the short term. And when we looked at the progression-free resurvival, there was a small benefit for those who had upfront surgery. That did not translate into an overall survival benefit. The upfront surgery group had about a 54-month overall survival, meaning how long they lived, versus 48 months for the interval tumor debulking group.

And what I do want to say about the surgery, whenever you do the surgery, you should have a gynecologic oncologist involved in your care. And for those of you who may be newly diagnosed or family members, seek out a gynecologic oncologist to partner with your medical oncology team because that surgery makes a big difference for you. Whether it's the upfront surgery or the interval surgery, you want to have the best chance of removing all the cancer as possible. You want to have a team in place that's going to work with you and has done this before, and so I would say have an open dialogue with your medical team.

And to me, this study says, whenever you do the surgery, you want the best surgery possible. And likely whether you do the surgery initially or the surgery after three cycles of chemotherapy will not change how long you live as long as it's done by the right team.

This trial did not include a heated intraperitoneal chemotherapy, and that is something that we do offer our patients where we actually put hot chemotherapy into the abdomen for stage-three patients. And that is something that is a challenge with this study because the term HIPEC for heated intraperitoneal chemotherapy is now available to patients here in the US and internationally. Also, again, the applicability of a surgery that's done at extremely high-volume cancer centers may not be reality for most patients.

The next study I want to bring to your attention is an extremely important study that really represents a new drug category for patients with platinum-resistant ovarian cancer. So these are patients where they've had their upfront treatments and sadly the cancer's recurred, and we're looking for other options. And I mentioned platinum is the backbone of these treatments, but when patients are no longer responding to platinum, the tumor's growing, we need better options.

And this drug, this trial, represents that. It's called the Rosella Study. The study drug is called relacorilant, and it was given in combination with a chemotherapy called nab-PACLitaxel. The other name for nab-PACLitaxel is Abraxine. And relacorilant is a novel drug. It's a selective glucocorticoid receptor antagonist, or acronym, SGRA. And in the setting of platinum-resistant ovarian cancer, we know that patients express the glucocorticoid receptor, but it is a marker of poor prognosis.

So this drug binds that glucocorticoid receptor and we believe sensitizes it to chemotherapy, and so this drug was given in combination with Abraxine or nab-PACLitaxel, and you can see the development. This is a phase three. If you remember the phases I mentioned earlier, this is now really ready for primetime. So we did the phase one and twos, we saw response, we saw the dosing we wanted to use, and this was now the confirmatory, is there benefit?

And the exciting thing at ASCO 2025 is that there was benefit. And so for patients who were randomized to either the nab-PACLitaxel chemotherapy alone or the nab-PACLitaxel plus the relacorilant, we found a significant improvement in overall survival and an improvement in progression-free survival. And this is what these curves show. So the top-left corner of your screen shows an improvement in progression-free survival, and it's a modest improvement, basically seven months versus five months, but it is significant.

But the really exciting thing is the improvement in overall survival, and that was even more pronounced with a four-month benefit in overall survival. And the reason that this study is so important is that, again, not only does it represent a new class of drugs, it represents a new class of drugs in a group of patients that have received prior treatments where we often have very little to offer.

And the Rosella Study showed that the treatment drug really did not have more significant complications than the standard of care chemotherapy. And so the relacorilant plus nab-PACLitaxel was well-tolerated. There was some more episodes of neutropenia, meaning that your white blood cell count dropped and you needed support for this. There was a little bit more anemia. But really outside of that and diarrhea, there were no major safety signals.

And so the take-home from this study, this represents a new class of drugs for our patients with platinum-resistant ovarian cancer, it extended progression-free survival and overall survival, and the safety toxicity profile is favorable. So this really should be coming to you shortly. It will hopefully be approved in the near future for use in patients, and I would say if you're a patient with ovarian cancer, start talking to your medical team about relacorilant and whether you may be able to receive this.

We're going to move onto a phase two trial, so I just talked about a phase three trial in platinum-resistant ovarian cancer. I'm now going to talk about a phase two trial in clear cell carcinoma of the ovary. Historically, this is a rare subtype, but a subtype that is often chemoresistant.

And really, the exciting thing about this presentation from ASCO is that we saw activity with a combination of pembrolizumab and lenvatinib. This is a combination of immunotherapy, the pembrolizumab, and Dr. Gradishar mentioned this drug, in combination with another drug called lenvatinib, which is a tyrosine kinase inhibitor. It's an oral pill, it's a targeted agent. The pembrolizumab is an IV infusion, and we've been using this regimen in endometrial cancer for a number of years, but this was now applied to patients with clear cell carcinoma of the ovary.

And overall, the endpoints were objective response rate and progression-free survival. Patients had to have a clear cell cancer of the ovary, they needed to have already received at least one prior line of a platinum backbone treatment, and they could not have had prior exposure to lenvatinib or bevacizumab. And what we saw was a response rate of 30%, which again, in a population of patients where we're looking for new options for patients, this is exciting. It means one out of every three women who receives this drug, this combination, had a meaningful response.

And so this is something that if you are listening to this presentation and you have clear cell carcinoma of the ovary, this is data you can now talk with your medical oncologist or gynecologic oncologist about. And this is something that you may be able to receive in the very near future when we're looking for options in a setting of chemotherapy, which may have limited options.

So we looked at the study. 17 patients were alive and well with their progression-free survival at six months and a median follow-uptime of 10 months. The median progression-free survival on this regimen was 11 months. And really, again, a well-tolerated regimen given that we have a lot of experience with this drug, this combination of drugs. So exciting news for patients with ovarian clear cell carcinoma.

The first trial, we're going to change now to another large phase-three trial. We've really been looking to see how we can incorporate immunotherapy into the management of ovarian cancer. Ovarian cancer is a tough drug, tough cancer, in that it tends to be a cold tumor. There's cold tumors and hot tumors. Hot tumors mean that your immune system really responds, and it recognizes and attacks it. Cold tumors are tumors that the body's immune system just doesn't really seem to be able to identify and attack easily.

And ovarian cancer unfortunately is one of these tumors where we've really had a tough time getting immunotherapy up and going. This represents a large phase-three study where we were looking at the

role of adding an immunotherapy called dostarlimab to the upfront management of patients with ovarian cancer who were receiving a platinum backbone of carboplatin-paclitaxel, plus a medication called bevacizumab, which blocks new blood vessel growth, it blocks the receptor VEGF, and adding dostarlimab, and we continue to really hope for benefit.

In addition to this, we added a medication called niraparib, which is a PARP inhibitor. PARP inhibitors have significant data in the upfront management of ovarian cancer if someone has certain molecular signatures, and we were really hoping to see synergy with the niraparib and the dostarlimab in this group of patients.

And in summary, there was a very, very modest benefit in progression-free survival. Again, progression-free survival means time without the cancer, and that was in the group who received the niraparib plus the dostarlimab, and that benefit was approximately a month and a half. And I think if you asked many of us as cancer doctors, is it worth the toxicity of receiving essentially three maintenance drugs that you stay on for years at a time for that progression-free survival of a month and a half with no benefit in overall survival? Although it's statistically significant, I would argue it's not clinically meaningful.

And so I think this gives us more data that likely, unfortunately, this use of the combination of dostarlimab and niraparib is not really going to be viable for meaningful benefit in this patient population. And we're really starting to realize that the group of immunotherapies called checkpoint inhibitors are likely not going to be beneficial in the upfront management of ovarian cancer. It doesn't mean that they can't be used later on, and we have other combinations to incorporate, but at least in the upfront management of ovarian cancer, it does not appear that they're going to be a viable, useful option for patients.

So in summary, for this group, dostarlimab to first-line platinum chemotherapy with niraparib had a statistically significant but modest improvement in progression-free survival. We looked for signatures to see who would benefit more. And even looking at something called PD-L1 positivity, which is an immunotherapy marker, it was not translating into benefit, and there was no benefit in overall survival. So I think this is something that helps me better counsel my patients that we likely do not need to add this drug to their regimen.

Just in closing here, I want to mention another smaller study. And this looked at platinum-resistant ovarian cancer. So this is, again, a population of women who have been impacted by ovarian cancer and received platinum chemotherapy but are no longer responding to that chemotherapy backbone, and so we're looking for other options.

And this was a study looking at a new molecule called INCB123667, and it's a CDK2 inhibitor, so it blocks part of that the way that cells regenerate. It's called the cell cycle, so it actually puts the brakes on part of their regeneration process in the cell cycle.

And they looked at it in patients who have a CCNE1 amplification, which is a certain signature in the tumor, and what they found was that for patients who had this CCNE1 amplification, if they received this oral pill, there was benefit, that patients responded. This was a phase-one study, so they were looking for the right dose, they found the dose of 100 milligrams orally daily, and they found that 35% of patients who received this 100-milligram-a-day dose who had a CCNE1 amplification benefited. And that's really a big victory.

So this opens up a new pathway for patients with platinum-resistant ovarian cancer. This is something that's going to continue to be studied. It may not be available just yet, but I believe in the next year or two, this will be available for our patients with platinum-resistant ovarian cancer if they have a CCNE1 amplification. The way that we determine that is based on the molecular testing, and that goes back to my slide: know what testing has been done for you. Is it the germline, the somatic? What is your doctor

testing when they say we're sending you for genetic testing? Overall, it was a well-tolerated regimen and something that will go on for further testing in phase two and phase three.

So in summary, just to review some of the highlights from ASCO, the initial management of ovarian cancer should be conducted by surgeons who are at larger cancer centers if possible. And whether you receive surgery in the upfront setting or after three to four cycles of chemotherapy, really that's your best chance to have the best surgery and seek out the best team, meaning teams that have experience with this, gynecologic oncologists.

The HIPEC is more controversial, it was not included in this study, but something to talk about with your oncology team. Relacorilant represents a new category of drugs for treatment of patients with ovarian cancer. Now, we need to better determine when we should use it, But for platinum-resistant ovarian cancer patients, really a significant advance.

Antibody drug conjugates, which were discussed by Dr. Gradishar, which included trastuzumab deruxtecan are available for ovarian cancer patients. It was not really a highlight from ASCO, but something that I want to mention because it really is going to be an important part of how we treat patients in the future.

The meaningful use of immunotherapy and the management of ovarian cancer remains elusive, and the study that I did present shows that it's likely not going to be beneficial with the use of these checkpoint inhibitors in the upfront management of ovarian cancer. But we are doing some exciting things with CAR T-cell therapy, both at City of Hope and other larger cancer centers such as Northwestern. And I think you'll find that CAR T-cell therapy in the use of solid tumors, specifically ovarian cancer, will have a role in the future. And then lastly, patients with Cyclin E1 or a CCNE1-amplified tumor will now have hopefully access in the future to this new drug where there does appear to be a significant benefit upwards of 37% for those patients who receive treatment.

So in summary here, just to kind of keep things moving, meet with your medical team, advocate for yourself. It's okay to ask questions. It's okay to consider a second opinion. If you're getting care in a rural area or maybe you're seeing a doctor who's not as familiar with your cancer, it's okay to ask to be seen at an NCCN-designated cancer center. It's okay to ask, "Has my case been presented at a tumor board with other doctors, with medical oncologists, radiation oncologists, gynecologic oncologists?" All of us talking about you.

And there's always more than one treatment option. Whether that makes sense or not, if someone tells you this is the only option that you have or this is the only thing you should do, it's good to ask more questions. And reach out to your family and friends and reach out to amazing organizations such as Sharsheret for information as this, but also for support. So with that, I'm going to close and stop sharing my screen. Thank you.

Devorah Silverman:

Wow. Thank you so much, Dr. Cohen. Thank you so much, Dr. Gradishar. You've both shared a lot of really important information very clearly with us, so thank you. And we're going to try to maximize the next 10 minutes and ask as many questions as possible.

Before we begin with those questions though, I want to remind everyone that the information provided tonight is not a substitute for medical advice, and you should not use this information to diagnose or treat a health problem. If you have any questions that are specific to your medical care, we advise you to speak with your medical provider.

So the first question we'll ask, we'll ask of you, Dr. Gradishar. It seems that there are several new targeted treatments for different types of breast cancer, metastatic and also earlier-stage breast cancer. How will my doctor know which is the best for me?

Dr. William Gradishar:

Well, I think each patient is obviously different, and when we're thinking about what's the appropriate treatment, starting with metastatic disease first, we still differentiate the tumors in a given patient based on whether they're hormone-sensitive, HER2-positive or triple-negative.

And it's particularly true in the patients who are hormone receptor-positive that we have many different options because we start to see these mutations, PI3 kinase mutations, ESR1 mutations, AKT, P10. And we have drugs that are very specific to that, that are usually partnered with an anti-hormone therapy.

And as I was already mentioning, we're starting to see that we can combine antibody drug conjugates with immunotherapy and triple-negative disease, so we have to detect whether or not a patient has a PD-L1-positive status. That's another marker of whether you'd benefit from immunotherapy in the metastatic setting. And then in the HER2 setting, of course you have to determine if a patient is HER2-positive.

But very importantly, in the last, say, three years, actually, it's a very short time, what we usually called HER2 negative in the past, we now distinguish as being HER2-low or even ultra-low. And one of the antibody drug conjugates which we've talked about clearly works in that subset of patients. So understanding the features of the tumor on a molecular level are important, and that's starting to migrate into the adjuvant or early-stage setting, particularly with, again, hormone receptor-positive disease and HER2-positive disease where we look for these markers to help guide therapy.

And your physician and most oncologists, again, are going to be familiar with these nuances. But if you're looking for clinical trials, as Dr. Cohen already pointed out, sometimes it may be best to at least get an opinion from a high-volume center that has a lot of experience with the different subsets of given disease.

Devorah Silverman:

Right. Thank you. So relatedly, Dr. Cohen, if a new treatment sounds promising to a patient, how would you advise a patient to determine whether they can or can't get to be part of a clinical trial?

Dr. Joshua Cohen:

Yeah. And I think this is where it's having an open dialogue with your oncologist, but also reaching out to organizations such as Sharsheret to get more information. ClinicalTrials.gov is a very good website, and it's a publicly available website, ClinicalTrials.gov. And you can actually type in your disease type or your family member's disease type, and you can search by location, you can search by phases. It's really a well-done website. Thank you for putting that in the chat, Devorah.

And that's maybe where I would start. If you live in a rural area and you have a couple options to try to get to cancer centers, I would say start there, but talk to your medical oncologist or your gynecologic oncologist. And if you're not really hearing that they have an option there for you with a trial, ask them where you could go to at least talk about trials or new drugs because resources can be limited.

But I think the very first step is come in with a list of questions, talk to your oncology team. Ask them have they heard of this? What did they think? Get their opinion, because their opinion can be very important for you. But it's okay to look for clinical trials through ClinicalTrials.gov or support

organizations such as Sharsheret resources because, again, there may be a trial out there for you that your medical team just may not be familiar with.

And trials are not for everybody. But we're fortunate that when you work at a place with trials, there can be an option for someone to get access to a new drug where it may otherwise take two to three years with the FDA to get that approved.

Devorah Silverman:

Thank you. Okay. Dr. Gradishar, somebody's asking if it's safe to get pregnant using IVF after stage-one ER-, PR-positive breast cancer?

Dr. William Gradishar:

So that's an important question and obviously is something at top of mind, particularly in young patients who are survivors of breast cancer. And the collective data we have now is that by getting pregnant, you don't suddenly throw gas on a fire. So the outcome of patients who get pregnant with a prior diagnosis of breast cancer does not appear to be worse than any other patient, so I think that's reassuring.

And sort of as a corollary of that, if a woman is young and she, say, has hormone-sensitive breast cancer, and her doctor has told her, "Well, you need to be on anti-hormone therapy for five or seven or eight years," you start to push the timeline out to when you can get pregnant to a time and the age when it might be more challenging.

We also know that taking a break in antihormone therapy in order to get pregnant doesn't compromise the outcome with respect to breast cancer. So if you take nine months or a year off and then resume the anti-hormone therapy, outcome does not appear to be different.

Devorah Silverman:

Thank you. Okay. Dr. Cohen, people are reading that there are some clinical trials that are focused on pancreatic cancer vaccines and are wondering whether there's anything similar in the work for ovarian cancer?

Dr. Joshua Cohen:

Yeah. There are some vaccine trials that are in development, and I mentioned that ovarian cancer unfortunately tends to be, quote-unquote, a cold tumor. I would say they are out there. Is there a home run? There's not a home run. If you're looking for a trial and interested in it, certainly ClinicalTrials.gov is a good place to start, and you can type in vaccine trial and ovarian cancer, and you'll see what pops up. There's no large phase three studies that have shown significant benefit.

And I think we're all still figuring out with the immune system what we can use to take advantage of with ovarian cancer. We're all hoping there'll be a vaccine. There are studies, but there's nothing certainly near primetime that I would recommend. But I think if you look, you will find there will be trials that are available in the phase one or phase two that there's maybe some early promise. But you have to start somewhere. It doesn't mean it's not possible, it just means that we haven't found the right solution yet to a vaccine for ovarian cancer.

Devorah Silverman:

Dr. Gradishar, has there been any further study about how well the fast-forward radiation protocol is working out for patients in radiating breast tumor beds?

Dr. William Gradishar:

So there've been many different schedules of radiation that have been employed for patients with early-stage disease. One of the more common ones over many years, going back two decades, is you get five or six weeks of therapy, and then you get a boost to the bed where the tumor sat.

And since then, there have been efforts to try and abbreviate the duration of radiation therapy without compromising the risk of recurrence. And to date, those strategies have looked to be very similar in terms of outcome to those traditional ones where it was longer.

So we've started to very routinely used shorter schedules of radiation therapy, and again, not unlike drug therapy, the other part of this is what are the toxicities, what's the cosmetic outcome, et cetera? And there might be some slight trade-offs depending on the schedule.

So when a patient is being considered for radiation therapy, those are among the questions that you have to ask your radiation oncologist. Is the effect of the therapy the same regardless of how long the therapy is, how many times I got to go in and get it? And what's the cosmetic outcome? What are the long-term consequences? And for the most part, we try to use shorter schedules these days than we did in the past.

Devorah Silverman:

Great. I'm just going to try to get to a few of the questions in the chat box. Dr. Cohen, you mentioned the value of early detection for BRCA1 and 2 mutation carriers, and somebody's asking if early detection is also considered to be of comparable value for carriers of other mutations like PALB2 or BRIP1?

Dr. Joshua Cohen:

Yes. We have a cadre of genes now that we have recommendations for risk-reducing surgery, and we know that there are certain implications that come with that when we say risk-reducing surgery, whether it's removing the ovaries and the tubes or the fallopian tubes. There's really no guidelines that just say removing the fallopian tubes is beneficial, although we are studying that in BRCA1 mutation carriers specifically. Most of the guidelines that recommend surgery recommend removal of the ovaries and tubes. But yes, if you have a genetic predisposition, you should meet with a genetic counselor.

One of the most important things we can do as doctors in general is talk more about family history, and we know we're doing a poor job of offering genetic testing to the general population. So I would say know your family history. If you haven't had genetic testing and you have a personal history of ovarian and breast cancer or ovarian cancer and other family members with breast cancer, get genetic testing. Moms and dads can both pass it down. It's not just through moms. And if you test positive, meet with a genetic counselor, sit down with them, go through recommendations, meet with a cancer doc, because risk-reducing surgery can be lifesaving for you.

Devorah Silverman:

Right. Are there any promising studies that were discussed at ASCO or elsewhere for people who have triple-negative diagnosis and PD-L1-negative, Dr. Gradishar?

Dr. William Gradishar:

Well, there are a number of different antibody drug conjugates in development, and that's a path we're taking. And we're also looking at whether if you combine antibody drug conjugates with things like PARP inhibitors, which you heard from Dr. Cohen, or whether that would have some synergistic or additive effect combining them.

So there are a number of different strategies that are being evaluated. There's not one on the cusp of approval that has us all leaping up out of our chairs, but there are many things that are being looked at.

Devorah Silverman:

Right. There are some questions in the chat box also that perhaps you'll be able to get to in the Embrace breakout room or in the next couple of moments if you're able to see them, Dr. Cohen and Dr. Gradishar, and you'd like to respond, you can do so directly.

But at this point, I want to thank both of you, Dr. Gradishar and Dr. Cohen, for educating us so clearly, so comprehensively. You answered a lot of questions. And I know I speak for myself and I think for everybody here, we all feel much more knowledgeable than we did an hour ago, so thank you. Thank you again to our sponsors for this evening's webinar, the Cooperative Agreement 240061 from the Centers for Disease Control and Prevention and to Gilead.

I want to ask you to please take a moment to fill out a brief evaluation survey that my colleague has just put in the chat box. Evaluations really do inform future programming, so thank you for taking the time to share your feedback with us. You can click on the link now and still listen to the last few moments of the webinar. For those staying on for the Embrace breakout session, Bonnie will share the link again so that you can complete the evaluation after that concludes.

I'm proud to tell you that plans are well underway for our annual Sharsheret Summit. The summit web page will be launching shortly detailing a wide array of programming that we have scheduled during breast cancer and ovarian cancer awareness months.

But I do want to share a quick sneak peek. Two of our many scheduled webinars include the topics of managing scanxiety and exploring the reasons for the uptick in diagnoses in younger women. So stay tuned for more detailed information about those webinars and the entire summit.

Please remember that Sharsheret is here for you and for your loved ones. We provide emotional support, mental health counseling, and other programs that are designed to help you navigate the cancer experience. Everything we provide is free, completely private, one-on-one, and you can reach us at 866-474-2774, or by email, ClinicalStaff@Sharsheret.org. Our social workers and our genetic counselors are available to each of you. You are our priority, so please never hesitate to reach out.