Program Title: Treatment and Issues For Triple Negative Breast Cancer

Originally recorded on: May 14, 2020, 8 – 9 pm (NY time)

Moderator: Robin Perlmutter, LMSW- Support Connection Peer Counselor

Guest Speaker: Ayca Gucalp, MD, Assistant Attending, Breast Medicine Service, Memorial Sloan Kettering Cancer Center. Dr. Gucalp is a medical oncologist with a clinical practice dedicated exclusively to the care of patients diagnosed with breast cancer.

Dr. Gucalp's research activities are focused on the development of novel therapeutic strategies for the treatment of triple negative breast cancer (TNBC). She has a particular interest in evaluating the underlying biology of TNBC, with the goal of developing more effective and less toxic therapeutic strategies for the management of patients with this subtype of breast cancer. Dr. Gucalp has conducted several prospective therapeutic trials enrolling patients with TNBC, including a pivotal study establishing the potential role of anti-androgen receptor (AR) agents in the rare TNBCs that are AR-positive.

Program Description: This webinar addresses the following topics pertaining to Triple Negative Breast Cancer:

- Recent changes in standard of care therapy.
- The use of chemotherapy in patients who are found to have residual breast cancer.
- Post neoadjuvant therapy and the use of immunotherapy, both in the early stage and metastatic settings.
- Some of the novel treatment strategies that are under investigation for the treatment of patients with metastatic TNBC.

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

Robin Perlmutter: Welcome. I'm Robin Perlmutter, peer counselor here at Support Connection. I'd like to welcome you all to our nationwide webinar on treatment and issues for triple negative breast cancer with Dr. Ayca Gucalp. Remember that Dr. Gucalp is sharing her expertise, and any information from tonight or questions pertaining to individual concerns should be discussed with your doctor.

I'd like to now give a warm welcome and thank you to Dr. Gucalp for sharing her time and expertise with us tonight.

Ayca Gucalp: Thank you, Robin, for the introduction and the opportunity to speak tonight to the group about triple negative breast cancer.

Just a little bit about myself before we start. As Robin said, I am a breast medical oncologist. I work at Memorial Sloan Kettering. I exclusively take care of patients with breast cancer, and I also do clinical research. So the focus of my research is triple negative breast cancer and the development of novel therapies for the treatment of this subgroup of breast cancer. We'll focus most of tonight's talk on the advances in treatment that have changed the landscape of triple negative breast cancer management in the last few years.

So we'll start with some background information that may be familiar to many of you. Breast cancer is the most common cancer in women. It's estimated that approximately 276,000 new cases of breast cancer will be diagnosed in the US in 2020. Triple negative breast cancer represents

approximately 13% to 15% of all breast cancers, so about 55,000 cases a year.

Two things that are important to remember. One, while overall incidence of breast cancer has stabilized, breast cancer mortality has actually been decreasing in the recent years likely due to screening efforts and improved treatments.

And two, not all breast cancers are the same. It's very important for us to know which type of breast cancer we're facing. The prognosis is different. The treatment options are also different. The two biggest categories are the estrogen receptor-positive breast cancers and the HER2-positive breast cancers. The majority of breast cancers represented in blue are ER-driven and HER2-normal. The next group are the HER2-postivie breast cancers, regardless of whether they are hormone receptor-positive or hormone receptor-negative.

And finally, the smallest subset, and often unfortunately the most difficult to treat, are the triple negative breast cancers. Most simply put, triple negative breast cancer is defined by the absence of ER/PR and HER2 expression. I want to highlight the obvious weakness in this definition. Triple negative breast cancer is defined by what it lacks rather than by what it is.

So these distinctions actually help us guide choice in therapy. For estrogen receptor-positive breast cancers, we have many highly effective strategies that suppress estrogen production or block its activity. For HER2-driven cancers, several targeted therapies towards the HER2 receptor have dramatically improved survival outcomes for women with this subtype of breast cancer.

When it comes to triple negative breast cancer, the last few years have seen the introduction of more targeted therapies, or at least non-chemotherapy options for treatment. But the mainstay of therapy in this setting remains chemotherapy.

In the metastatic setting, we usually use single agents. There are some combination therapies that we use in the metastatic setting for triple negative breast cancer, and we'll talk about one particular conversation a little later tonight. But there really is no strong compelling data for combination chemotherapy for the management of triple negative metastatic breast cancer.

Treatment choices are often made from a constellation of factors. They include patient factors and considerations like performance status, other medical issues a patient may have, genetic status of the patient, any toxicities they may have from prior treatments, symptoms from their disease, as well as treatment feasibility and convenience and patient preferences.

There are disease-related factors as well such as the burden of disease, meaning how much disease there is, the tempo of the growth of the disease, the disease-free interval, prior exposures to therapy and potential resistances that may have developed. There are drug-related factors such as the activity profile of the drug, the toxicity profile of the drug and whether or not there are predictive biomarkers that may help make decision choices.

Also the timing of treatment is also very important. So obviously there are patient life events that impact treatment choices. Washout periods, so how long a patient's been off of a medication before they go onto the next one, particularly if they're going on to a clinical trial.
Also in this setting, trial availability is important, and the sequence in which patients receive chemotherapy is oftentimes very important.

So we discussed that breast cancer itself is very heterogeneous, but emerging evidence demonstrates that this diversity also extends to the triple negative subgroup itself. Evidenced by the identification of multiple biologically different tumors that have low expression of ER/PR and HER2, including the basal-like, caludin-low and luminal AR subtypes, to name a few. The development of agents that target these triple negative subgroups unfortunately has been difficult as testing for many potential targets is not standardized and remains variable, influencing the effective patient selection for treatment.

So what is new in the treatment of triple negative breast cancer? So before we talk about some of the newer agents that have been recently FDA approved for the treatment of triple negative breast cancer, I want to talk a little bit about the use of an older standard chemotherapy in a new way.

So capecitabine was first approved for the treatment of metastatic breast cancer -- sorry about that -- in 1998 in patients who had received prior therapy. It's an oral chemotherapy. But more recently, the CREATE-X trial was designed to test the use of this drug in early stage setting, particularly post-surgery if patients had received neoadjuvant chemotherapy, or chemotherapy prior to surgery.

So when a patient has chemo before surgery, the goal is to shrink the tumor to make the surgery easier and less invasive and ideally to make the tumor go away all together as women in this scenario tend to have better breast cancer outcomes. And while women with triple negative breast cancer generally have higher rates of what we call pathological complete response, or complete resolution of their tumor, often abbreviated in studies as PCR, it's not always possible. And until recently, for women with triple negative breast cancer, there was no actual further treatment after surgery if there was residual disease found at the time of surgery.

So the CREATE-X study was a randomized study in women who did not achieve a pathological complete response at the time of surgery. They were randomized to receive either oral chemotherapy with capecitabine for about 6 months, as well as standard of care therapy for the subtype of breast cancer, or standard of care therapy alone. The patients on this study had both hormone receptor-positive tumors and triple negative breast cancer. A majority had lymph node positive tumors, and the vast majority received chemotherapy that included medications like doxorubicin and paclitaxel.

So the trial met its pre-specified endpoint and was a positive trial. As you can see on the left, 5-year disease-free survival, so how long a patient lives without the disease coming back, was greater in the capecitabine treatment arm. So the capecitabine group is the curve in blue and the control group is the curve in red. In terms of overall survival seen on the right, so that's how long a patient lives in general, the study demonstrated a significant difference in favor of the capecitabine arm. So this was particularly pronounced among women with triple negative breast cancer. You can see here the disease-free survival curve on the left and again the overall survival curve on the right both favoring capecitabine.

The most common side effects for this drug include diarrhea and something called hand-foot syndrome, a side effect that's characterized by redness, dry skin, cracking and blistering of the skin predominantly involving the hands and the feet.

So most importantly, in conclusion, use of capecitabine after surgery improved how long people lived without the cancer coming back and then how long people lived in general. This study significantly changed management for patients with triple negative breast cancer after the

completion of neoadjuvant chemotherapy.

So now I really want to focus on some of the newer agents that are being studied for the management of metastatic triple negative breast cancer. In particular, during this talk we'll focus on PARP inhibition, immunotherapy drugs and antibody drug conjugates.

As we already know, the genes that you inherit impact your cancer risk. For example, there's an association with BRCA1 mutations and the development of triple negative breast cancer. But they can also have implications in the management of breast cancer. So women with BRCA1 mutations are more likely to be unable to repair DNA damage, leading to the development of cancer. PARP helps to repair DNA when it becomes damaged. And in cancer treatment, blocking PARP may help keep cancer cells from repairing their DNA damage, causing them to die.

The OlympiAD study was designed to test the hypothesis that treatment with olaparib, a PARP inhibitor, would be superior to the physician's choice of a standard chemotherapy in patients who had a germline BRCA mutation and had metastatic HER2-negative breast cancer and had received prior therapy in either the adjuvant or the metastatic setting. All patients had BRCA mutations, and they were randomized to receive either olaparib twice a day or a physician's pre-declared choice of standard chemotherapy with either capecitabine, eribulin or vinorelbine.

Patients were assessed every 6 weeks for the first 24 weeks and then 12 weeks thereafter and were treated until progression was confirmed. The primary endpoint of this study was what we call progression-free survival, or how long a patient lives without the cancer growing. The study was designed to also look at how long patients lived overall, how many patients had objective tumor shrinkage and how safe and tolerable the medication was.

So the confirmed objective response rate, meaning how many patients had objective tumor shrinkage, was higher in the olaparib group compared to the patients receiving chemotherapy. So 52% in the olaparib group and 23% in the chemotherapy group. So treatment with olaparib shrunk twice as many tumors than chemotherapy.

These Kaplan-Meier curves, or survival curves, depict the progression-free survival of patients treated with olaparib compared to those actually treated with chemotherapy. The median progression-free survival, so how long someone lives without the cancer growing, in the olaparib arm was 7 months compared to 4.2 months in the chemotherapy arm. So women lived longer without their breast cancer growing when they were treated with olaparib.

Looking at overall survival, women who received olaparib as their first treatment for metastatic breast cancer had improved overall survival. You can see on the left that in the first-line setting, overall survival was 22.6 months versus 14 months in the olaparib and chemotherapy arms, respectively. Unfortunately, overall survival benefit was not seen for patients treated in the second or the third-line setting.

This slide shows the side effects reported in greater than or equal to 20% of the patients who received treatment on the OlympiAD trial. Overall therapy with olaparib was well tolerated, and many of the side effects were considered mild.

In summary, olaparib therapy provided a clinically meaningful progression-free survival benefit compared to standard care chemotherapy in patients who had metastatic breast cancer and a

germline mutation in either BRCA1 or BRCA2. It was generally well tolerated with less than 5% of patients discontinuing treatment because of side effects, and overall had a lower rate of what we would call severe side effects compared to chemotherapy. OlympiAD was actually the first Phase 3 study in metastatic breast cancer demonstrating a benefit for a PARP inhibitor when compared to chemotherapy.

The EMBRACA trial looked to answer a very similar question about another PARP inhibitor called talazoparib. The EMBRACA study tested talazoparib as a single agent in patients with germline mutations and metastatic breast cancer and compared it again to physician's choice chemotherapy with either capecitabine, eribulin, gemcitabine or vinorelbine. As I said, it was a Phase 3 study randomized, and 287 patients were enrolled on this study.

You can see from these curves that talazoparib also improved how long women lived without their breast cancer growing. Patients who received talazoparib are represented by the blue curve, and the women who received chemo are represented by the green curve. The median progression-free survival in the talazoparib arm was 8.6 months compared to 5.6 months in the chemotherapy arm.

When we look at overall survival, it looks like there's a trend favoring treatment with talazoparib, but we'll need to wait longer before we can confirm that.

If we compare the toxicity profiles of the two drugs, we see higher rates of what we would call a hematological toxicity with talazoparib. So these are the effects on the number of the white blood cells, red blood cells and platelets a patient has. Gastrointestinal side effects such as abdominal discomfort or diarrhea were a little bit more frequent with olaparib, and hair loss was more frequent with talazoparib.

So next we shift gears to immunotherapy, which is an exciting area of research these days. For several years now, immunotherapy has actually been FDA approved for several cancers, but it's only recently that the use of immunotherapy with chemotherapy was approved for the treatment of metastatic triple negative breast cancer.

Our immune system actually has an on/off switch. If your immune system was on all the time, it would actually cause more harm than good. T-cells are a type of immune cell that recognizes and binds to foreign substances in the body. They're designed to recognize and kill tumor cells.

PD-1 is a protein found on these T-cells that helps to keep the body's immune responses in check. PD-1 acts as a type of off switch for T-cells. When PD-1 is bound to another protein called PD-L1, it helps to keep T-cells from killing other cells, including cancer cells. So PD-1 and PD-L1 work together to inactivate T-cells.

Some anti-cancer drugs called immune checkpoint inhibitors are used to block PD-1 or PD-L1. When these proteins are blocked, the brakes on the immune system are released and the ability of T-cells to kill cancer cells is actually increased. So antibodies to PD-1 or PD-L1 prevent tumor cells from inactivating T-cells.

The IMpassion130 trial was a Phase 3 randomized placebo-controlled study of nab-paclitaxel, otherwise known as Abraxane, plus atezolizumab versus Abraxane plus placebo in patients with metastatic or inoperable locally advanced triple negative breast cancer for first-line therapy. Atezolizumab actually binds a protein called PD-L1, which is found on the surface of cancer cells.

This drug may block the protein and help the immune system kill cancer cells. It's a type of monoclonal antibody and a type of immune checkpoint inhibitor.

Patients in this study were divided by their PD-L1 status, and the results were analyzed by these subgroups. 902 patients were randomized and 41% of those patients were actually PD-L1 positive in both arms. Patients who were deemed PD-L1 positive who received the combination of Abraxane and atezolizumab lived longer without their tumors growing. The progression-free survival overall was improved by 2.5 months. So 7.5 months in the combination arm and 5 months in patients receiving chemotherapy alone.

In the PD-L1 positive population, the difference in overall survival was much greater at an impressive 10.5 months with 54% of patients alive at 2 years in the combination arm of atezolizumab and Abraxane.

I realize now, I just want to take a moment to clarify the title of this slide. PD-L1 positivity in this study was actually assessed on the immune cells, not the tumor cells. So someone who was deemed PD-L1 positive in this trial had greater than 1% staining for PD-L1 on the immune cells in the environment surrounding the tumor.

So the number of patients with tumor shrinkage, and the length of that response otherwise known as duration of response, was higher in the group that received chemotherapy and immunotherapy. So based on the IMpassion130 trial, the FDA granted accelerated approval for the combination of atezolizumab and Abraxane for the treatment of patients with unresectable, locally advanced or metastatic PD-L1 positive triple negative breast cancer. This marked the first checkpoint inhibitor that was approved for the use in breast cancer.

Immunotherapy is now also being assessed in the early stage setting. Pembrolizumab, which was studied in the neoadjuvant setting in KEYNOTE-522, binds to a protein called PD-1 on the surface of T-cells. Pembrolizumab blocks PD-1 and helps the immune system again kill cancer cells. It's also a type of immune checkpoint inhibitor.

KEYNOTE-522 was a Phase 3 study. It was randomized and enrolled approximately 1,200 patients. The women had triple negative breast cancer that was locally advanced, meaning the tumor itself was either larger in size or involved several lymph nodes. And the patients were randomized to receive either neoadjuvant chemo, so chemo before surgery, with placebo or neoadjuvant chemo with pembrolizumab. The primary endpoint was pathological complete response, so whether the cancer was completely gone at the time of surgery, as well as event-free survival, how long a patient lived and remained free of cancer.

As you can see on this chart, complete response at the time of surgery was higher among women who received the combination in green of pembrolizumab as well as chemotherapy. There was a significant 13.6% improvement in what we call the pathological complete response rate with the addition of pembrolizumab to chemotherapy.

I think it's important to note, in comparison to the last study that we discussed, improvement in the pathological complete response rate occurred regardless of a patient's PD-L1 status, so regardless of whether they had that marker on the cell. Both PD-L1 negative and PD-L1 positive patients experienced improvement in this pathological complete response rate with the addition of pembrolizumab.

And at San Antonio, our big breast cancer conference in 2019, the investigators actually presented updated results from their analysis of the pathological complete response rates by patient subgroups. And I'm not showing this data here, but interestingly enough, results showed that patients with lymph node involvement of their breast cancer had a larger increase in the rate of pathological complete response compared with patients with lymph node negative disease. So essentially what this means is women who had higher risk tumors gained more benefit from the addition of pembrolizumab.

If we look at the most common side effects in these two large Phase 3 studies, what we can see is that the combination with a checkpoint inhibitor and chemo, the toxicity is largely dominated by the chemo agents. And the most common side effects are what we would expect from chemotherapy. You can see on these graphs, there are things like nausea, vomiting, hair loss, fatigue and low white blood cell count.

Across both studies, frequency of what we would call an immune-related side effect, so a side effect that's more similar to an autoimmune type of effect, were actually relatively low. Most frequently seen side effects included thyroid dysfunction, skin-related side effects and inflammation of organs such as lungs, colon and liver. There was one case of what we call myocarditis, so inflammation of the muscles of the heart, in these major studies.

There are several actually ongoing large Phase 3 trials investigating these two agents in patients with triple negative breast cancer in the neoadjuvant setting, in the adjuvant setting and in the metastatic setting. So hopefully we will have more information about these drugs in the near future and their uses for the management of triple negative breast cancer.

So I'd like to focus the last part of today's talk on a new category of drug under investigation in several cancers. This category is called antibody drug conjugates, or ADCs. And they are agents made up of a monoclonal antibody, so that's the top half of that Y, chemically linked through what we call a linker to an active chemotherapy agent, so represented by those red spikey areas towards the bottom of the Y.

And this is the mechanism by which these drugs work. So the monoclonal antibody binds to a specific protein or a receptor found on certain types of cells, including cancer cells. That's the one right there. The whole antibody drug conjugate is then internalized within the cancer cell where the cancer cell then degrades the linker and the active drug is released so it can cause cell death or what we would know as apoptosis.

So recent years have seen a number of antibody drug conjugates enter clinical studies across many cancer types, including triple negative breast cancer. We're going to focus a lot of the remaining of our time on a drug called sacituzumab govitecan, or otherwise previously known as IMMU-132. But other antibody drug conjugates such as LIV-1, DS-8201, which was recently FDA approved for actually HER2-positive disease is now being studied also in women with ER/PR HER2-negative tumors. And then most recently a drug called U3-1402 is also being studied in patients with triple negative breast cancer.

So I actually had to recently update my slides within the last week because very excitedly, as of

April 22, the FDA granted accelerated approval to sacituzumab for patients with metastatic triple negative breast cancer who had received at least two lines of prior therapy for metastatic disease.

As we've already mentioned, sacituzumab is an antibody drug conjugate of humanized anti-Trop-2. It's coupled with an agent called SN-38, which is an active metabolite of a very common chemotherapy called irinotecan. Trop-2 is actually expressed on greater than 90% of patients with triple negative breast cancer, so very commonly. And SN-38 is actually a much more potent drug than the standard chemotherapy, irinotecan.

The other good news is because antibody drug conjugates are a combination of an antibody as well as the active agent and don't become active until that active agent is cleaved inside the cell, you can actually export a higher drug to antibody drug ratio, allowing for more chemotherapy to hopefully enter the drug with less harm to surrounding cells.

The trial that led to this accelerated approval was a multicenter, single arm trial enrolling 108 patients with metastatic triple negative breast cancer. They'd received at least two prior treatments for the metastatic disease. And patients received sacituzumab on Days 1 and 8 intravenously for every 21 days. Interestingly enough, the population of patients enrolled on this study was what we call heavily pretreated. The median number of prior lines of therapy was five.

I think it's important to take a look at what we call this waterfall plot. You can see here that the individuals in red and blue had tumor shrinkage, where the women in yellow had stable disease. And it is very exciting to see a waterfall plot like this where a vast majority of patients either have stable disease, partial responses or complete responses, so tumor shrinkage.

The overall response rates of the overall number of people who had tumor shrinkage in this group was 34%. I think this is very important because of how heavily pretreated the population was. 41% of patients were on their third line of therapy, and approximately 60% of patients had four or greater lines of therapy in the metastatic setting. This response rate is particularly significant given that response rates with standard chemotherapy after first line can be as low as 10% to 15%.

In this swimmer's plot, you can also see that among those who responded to therapy, the responses were prolonged with a majority of responses lasting greater than 6 months and a good number of them lasting greater than 12 months. In this group, the median time that patients lived without their tumor growing was 5.5 months, which is again significant given how heavily pretreated this population was.

Side effects seen were similar to those with chemotherapy with the most frequent side effects being low white blood cell count, particularly low neutrophils, and gastrointestinal symptoms such as nausea, diarrhea, vomiting. Hair loss was also seen in this population with about 36% of people reporting some level of hair loss.

Based on these exciting results from the Phase 2, a Phase 3 randomized study of sacituzumab against treatment of physician's choice was designed and completed enrollment. Patients on this trial have all been enrolled completely, but we await the final results. The primary endpoint again was progression-free survival, so how long the women on the trial lived without their cancer growing.

So there are several targets that are currently under investigation that we didn't talk about for the

treatment of metastatic breast cancer, and hopefully in the next few years we'll see additional FDA approvals in this setting.

To summarize, triple negative breast cancer, it's a heterogeneous disease. Chemotherapy remains the mainstay for both early stage and metastatic triple negative breast cancer, although clearly there have been advances in terms of personalized treatments for patients. BRCA-associated triple negative breast cancer may be different, and treatment with a PARP inhibitor has changed the treatment of BRCA-associated cancers in the metastatic setting. We need to continue to work on personalization of breast cancer treatments, and particularly development of drugs like antibody drug conjugates, immunotherapy approaches and targeted therapies based more on the underlying biology of tumors.

So, many patients ask me what they can do. And I think some of the most important times -- most important things to focus on are knowing what your risks are. Early detection, as we talked about, has made a significant impact on mortality. And I know we didn't touch on it today, but maintaining a healthy lifestyle both in terms of diet and activity is very important. And finally, if possible, supporting ongoing research. Whether you yourself participate in the clinical trial or work as a patient advocate or navigator, there are lots of ways to support research in this setting.

So, it looks like we have a little bit of extra time, so I was going to actually go on and talk about some research that is very near and dear to my heart. It is the use of AR inhibitors in the management of metastatic triple negative breast cancer. The androgen receptor is similar to what we think of as the estrogen receptor or the progesterone receptor in hormone receptor-positive breast cancer, and 60% to 80% of all breast tumors are actually androgen receptor-positive.

Going in a little bit about -- I'm going to go back a slide. It looks like the mechanism by which androgens influence hormonal sensitivity and disease growth is not completely understood. And I think the main way that most people think about the androgen receptor is actually as the male hormone receptor because it's commonly thought of in the context of prostate cancer.

So, work that was done by my mentor and her lab colleagues when I was still a fellow actually looked to see how common this androgen receptor was in women with triple negative breast cancer. And what they were able to show from tumor samples on slides was that some triple negative breast cancers actually behave like hormone-driven breast cancers. And the main thing that was differentiating these tumors from other ER/PR and HER2-negative tumors was the fact that they expressed the androgen receptor. However, this didn't prove the function of the androgen receptor. We had to actually prove that the growth of these tumors were driven by the androgen receptor.

And so preclinical mouse and cell line tests were done to see whether or not if you block the androgen receptor, would tumor growth be decreased. And so I'm going to walk you through this somewhat complicated slide, but the most important thing is the top box, which goes to show a breast cancer cell line that was androgen receptor-positive, but triple negative. And when it was exposed to androgens, so male hormones like testosterone, that's the red line, the tumors grew. And if that drug was -- if the cancer cells were then exposed to both the male hormone as well as an anti-androgen therapy called flutamide, they were actually able to show a decrease in the growth of these cancer cells.

And so what we did and when I was a fellow was try and translate what we saw in cancer cells to

treating patients with ER/PR HER2-negative tumors. And so the first study that we did in this setting was of a drug called bicalutamide, which is a male prostate cancer drug. And we treated women with ER/PR-negative tumors that were androgen receptor-positive with the drug bicalutamide that was given as a pill daily.

So the primary endpoint of this trial was to see what the clinical benefit rate was, meaning how much tumor shrinkage or stable disease resulted from treatment with bicalutamide. And what we were able to show was that bicalutamide had activity in this population of women with androgen receptor triple negative breast cancer. While there was no clear tumor shrinkage in any of the patients, there were several patients that had stable disease for greater than 6 months. And if you look at the progression-free survival, it was about 12 weeks in this population that was also very heavily pretreated.

Interestingly enough, some individuals after our trial actually treated patients with bicalutamide, and they were able to show, and you can see from this case report, shrinkage of the tumor in this setting with the use of a drug like bicalutamide.

And I'm going to end here, but this is really not where the androgen receptor story has ended. There have been trials of novel and newer anti-androgen therapies that have actually shown tumor shrinkage. And we have actually now combined anti-androgen therapy with other FDA approved drugs for breast cancer such as palbociclib -- some patients may know it as Ibrance -- to actually show whether or not we can improve outcomes of women with the combination as opposed to bicalutamide alone. So that trial is actually completed and enrolled, and we're going to be presenting that at ASCO this year. So stay tuned to see the results of that combination therapy. So I'm going to stop here and I guess open it up to questions at this point.

So the first question is, "Is there a specific test for androgen status outside of FoundationOne genetic testing? PD-1, PD-L1 testing?" So I will tell you that at least for the androgen receptor, you've hit the biggest issue that has come up in the development of these drugs, which is there is no one standard test for assessing the androgen receptor. I think the one that has been the most developed was done during the trial of a drug called enzalutamide through a third party vendor using a specific antibody, and it's pretty much the one we've adopted for our ongoing clinical trials. But I will tell you that there are lots of different institutional tests that people do to assess for androgen receptor status, and it is reported on certain third party vendor testing platforms like Caris and FoundationOne.

In terms of the rest of your question for PD-1, PD-L1 testing, there is a specific PD-L1 test that was developed during the course of that study that we discussed of atezolizumab and Abraxane. It is the one that we use at Memorial Sloan Kettering, but I do think that there is some variability still in terms of PD-L1 testing as well. I hope that answers your question.

There is another question about how do you treat women with both ER-positive and triple negative metastatic breast cancer. And I want to make sure I understand this question. I'm assuming this means that if one patient -- one individual themselves had both estrogen receptor-positive and triple negative metastatic breast cancer? So I'm going to answer that.

I think ultimately if somebody has both an estrogen receptor-positive and triple negative breast cancer, oftentimes you treat them by what is most clinically active and what is kind of leading to the most volume of disease. So oftentimes, unfortunately, the triple negative component of a

breast cancer diagnosis is usually the more aggressive one, and so oftentimes it will probably dictate what treatments a patient's receiving. But if someone let's say had a triple negative tumor that was early stage and had been treated and their disease was -- their metastatic disease was estrogen receptor-positive, then the focus would then obviously be on the component that was estrogen receptor-positive.

So this question is somewhat personal, but we can kind of generalize it. "If you had genetic testing several years ago in the setting of a diagnosis of triple negative breast cancer, should genetic testing be redone, and are there new genetic tests available?" So I think that it is a very important question, and yes, I do think that women who had genetic testing previously should go back and re-meet with a genetic counselor and reassess their risk as it stands now and learn more about newer genetic testing platforms. There are several new genes that are actually being tested on these comprehensive platforms.

And our clinical genetics team often writes at the bottom of their consult notes that frankly, women with a diagnosis that may be associated with a genetic predisposition should reconsider at least genetic counseling every 5 years or so to assess whether or not there are new genes to be tested, or that the testing itself has just evolved and gotten more sensitive. So yes, I do think that it is worth at least meeting with a genetic counselor, again, if it's been several years since your initial diagnosis and testing because newer things are evolving all the time, newer tests.

"Does oligometastatic treatment tend to fall under the metastatic standard of care?" So, management of oligometastatic disease in breast cancer is very much an evolving field. I think for other cancers, particularly for example colorectal cancer, so colon cancer, the treatment of oligometastatic disease has been pretty longstanding, particularly as it pertains to liver metastases. That has not been so clear cut in metastatic breast cancer.

And I think there are several ongoing studies. I can think of a few at Memorial alone that are really focusing on management of oligometastatic with potentially more local interventions, allowing for either delaying certain systemic therapies like chemotherapy or allowing patients to remain on a treatment that had been working for the rest of the body other than one potential site. So yes, oligometastatic treatment does tend to fall under metastatic standards of care, but those standards of care, at least in terms of breast cancer, are really evolving right now and are an area of active research.

So this is a question about risk of recurrence years out. I'm assuming the question is more how does -- what is the kind of risk of recurrence in terms of timeline for triple negative breast cancer in comparison to estrogen receptor-positive breast cancers. So estrogen receptor-positive breast cancers, as kind of hinted at by this question, have the potential to have what we call delayed recurrences. So recurrences that happen 15, 20 years out from initial diagnosis generally because they are slower growing tumors.

That is very different than triple negative breast cancer. So I don't have this unfortunately figure on this slide deck, which I usually do when I give triple negative breast cancer talks, but triple negative breast cancers tend to have what we call a bimodal risk of recurrence. While the highest risk of recurrence is in the first 3 years, there is a second kind of smaller peak at around 5 to 10 -- sorry, 5 to 8 years, and then things tend to level off afterwards. And so unlike ER-positive breast cancers where while it's not common, there are definitely delayed recurrences at 15, 20 years out, those are less common for triple negative breast cancer which tend to level off kind of after that 5 to 8-

year mark.

Okay. So this is a question about this statement that I made. I think it's somewhere in the talk about lines of treatment. "What is a line of treatment? So is this counted by class or by agent? Example: Taxol for 8 weeks with a change to Abraxane/Tecentriq after receiving PD-L1 results." So, Tecentriq is the drug atezolizumab that I referenced in the trial -- sorry, in the talk tonight.

So I will say that this then becomes a bit of a semantics question, but line of therapy tends to be kind of the intended combination. So in the example that was given, the intention probably of an oncologist is always to give Abraxane and atezolizumab together as the first line of therapy, provided that you have those PD-L1 results. And so in this setting, I personally would probably consider the combination all the first line of therapy, even if someone started with another taxane or even Abraxane alone for a period of time.

I think it becomes a little bit more of an issue in terms of clinical trial enrollment. And sometimes in clinical trials they have to be counted separately. But from my point of view, kind of when I'm thinking about the management of my patients, I really think if I start someone on a taxane, whether it be Taxol, Abraxane alone until I get the PD-L1 results, and then I have the benefit of adding atezolizumab, I consider that all the kind of the first line of therapy.

Oh, somebody asking about Dr. Norton. Yes, Dr. Norton is still at Sloan. Very much active and very much an amazing member of our team. Each of us who end up becoming breast cancer oncologists spend probably at least 6 months or so with him during the last kind of year of our fellowship in his clinic. And it is definitely both a learning experience obviously from the point of view of learning about medicine, but also a great kind of world experience about being a medical oncologist. So yes, he is still there.

Robin Perlmutter: Okay. I think that's it, folks. So Dr. Gucalp, again, thank you so much for your passion, your dedication and commitment to the cancer community through your patients -- your commitment to your clinical practice and your tremendous involvement with research. So we are so blessed and grateful for all that you're doing for the cancer community, and especially deeply grateful for all that you're doing during this time as well in our world, so we just want to thank you. And I just want to also take the time to thank you all for coming out tonight to learn about this very important topic. Have a great night, everyone. Be well and stay safe. Thank you.

Ayca Gucalp: Good night.