Medical Breakthrough from ASCO

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Melissa Rosen:

Good evening, everyone, and welcome. Thank you for being here with us for Sharsheret's Medical Breakthrough Update from ASCO 2021. I want to thank everybody for joining us this evening. Tonight, we'll be learning from Drs. Tiffany Troso-Sandoval and Dr. Pamela Drullinsky, who will highlight the latest findings from the American Society of Clinical Oncology's annual virtual meeting from earlier this year.

We're grateful for tonight's webinar sponsors, AstraZeneca, Seagen, the CDC, and The Siegmund and Edith Blumenthal Memorial Fund, as well as our webinar partner this evening, Memorial Sloan Kettering Cancer Center.

Before we begin just a few housekeeping items, tonight's webinar is being recorded and will be posted on Sharsheret's website along with a transcript. Participant faces and names will not be in that recording. However, if you would like to remain private, you can turn off your video and rename yourself, or you can call into the webinar, and instructions for that are in the chat box now for both options.

You may have noticed that all participants were muted upon entry. Please keep yourself on mute throughout the call. But if you have questions, you can put them in the chat box either publicly or click on Sharsheret in the chat box to submit a question privately.

We have received many questions in advance of tonight's webinar, and we anticipate many questions in the chat box as well. We will do our very best to answer all those questions, but any questions not answered tonight will be addressed by email over the next week.

We recommend that you keep your screen on speaker view this evening. That will enable you to see the doctors' presentations. You can find this option in the upper right-hand corner of your screen.

As a reminder, Sharsheret has been providing telehealth services to the breast and ovarian cancer communities for almost 20 years, and the pandemic has not changed that. We continue to be there for each one of you every day.

As we move into the webinar itself, I want to remind you that Sharsheret is a national not-for-profit cancer support organization and does not provide any medical advice or perform any medical procedures. The information provided this evening is not a substitute for medical advice or treatment for specific medical conditions. You should not use this information to diagnose or to treat a health problem.

If you have any questions that are specific to your own medical care, the doctors may not be able to advise on specifics and they would then advise you to speak to your own medical provider. Always seek the advice of your physician or a qualified healthcare provider with any questions you have regarding a medical condition.

And now, this evening, we are so honored to be joined by two fabulous physicians, Dr. Tiffany Troso-Sandoval and Dr. Pamela Drullinsky. Dr. Drullinsky is a medical oncologist with experience in treating breast cancer. As a member of Memorial Sloan Kettering's breast cancer disease management team, she

works closely with her colleagues in pathology, radiology, radiation oncology, and surgery to provide comprehensive world-class care.

She is the medical director of Memorial Sloan Kettering Nassau located on Long Island. She also sees patients at the Evelyn Lauder Breast Cancer Center in Manhattan.

Dr. Troso-Sandoval is a board-certified medical oncologist with experience in breast cancer and gynecological cancers, such as ovarian, uterine, cervical, and vulvar cancer. She's a member of Memorial Sloan Kettering's breast cancer and gynecologic disease management teams and actively participates in conferences with other Memorial Sloan Kettering experts in these fields. We are going to begin this evening with Dr. Drullinsky.

Dr. Pamela Drullinsky:

Thank you so much for having this presentation. I'm just going to share my screen. Sorry, it's the same thing. I'm not ... Oh, here it is. Okay. Thank you again, everyone, for joining us this evening.

So, I'm going to speak about highlights from the recent two main meetings in oncology. One is called ASCO, the American Society of Clinical Oncology, and the other is called ESMO, the European Society of Medical Oncology. This is strictly about breast cancer.

So, we're going to speak about early-stage breast cancer, metastatic breast cancer, and some future research things that are going on. I have absolutely no financial disclosures.

So as most people are aware, breast cancer is not a new disease. The first recorded case was of Queen Atossa of Persia in 400 BC. So just to remind you that this is not a new problem.

A quick review of the anatomy of the breast, this is what the breast looks like. These little balloon things are called lobules, that's where milk is made, and the milk comes out the duct. So, cancers of the lobule are called invasive lobular cancer and cancers of the duct are called invasive ductal cancers.

Then just a quick review of what we call receptors. So, a normal breast cell looks like this. This is the nucleus, this is the cell membrane, and these little purple things are called receptors. I also call them little parking spaces.

So, women do express some estrogen receptors. That's why our breasts grow. But when breast cancer is estrogen receptor-positive, that means it mutates and you overexpress the estrogen receptor. So that means estrogen receptor positive. So that's what we're going to be talking about when I say estrogen receptor positive. HER2/neu looks the same. If you overexpress the HER2 receptor, you've got too many of these receptors are parking spaces. That's just a quick background.

So, looking at what's new in HER2-negative breast cancer, and this applies to both estrogen receptor positive and negative. So, this is brand new from the ASCO meetings. So, there is a trial called Olympia involving adjutant, which means after surgery, a drug called Olaparib, which is a PARP inhibitor ... And I'll talk to you about that in a few minutes.

But this was a phase three, double-blind, randomized trial involving almost 2,000 women. Again, HER2-negative. These women had either the BRCA1 or BRCA2 mutation, BRCA1, BRCA2, and were planned to have either chemotherapy before surgery, which is called neoadjuvant, or chemotherapy after surgery, which is called adjuvant.

You had to be eligible for this trial. At least four lymph nodes had to be positive and then chemotherapy was planned, or you had chemotherapy before surgery and then you did not achieve a pathologic complete response, which means at the time of surgery, there was no cancer leftover.

Patients were randomly assigned one-to-one, and they received one year of oral Olaparib or placebo. So basically, in patients with the germline mutation means that they've inherited either one of these two mutations, there is a problem, or an enzyme called PARP is upregulated. It means that it's overexpressed. When a cell mutates, instead of it dying, it continued to replicate, which is the opposite of what you would want to do. That's why cancer is at high risk in these two hereditary conditions.

So, the primary endpoint of this trial was invasive disease-free survival. The conclusion, and therefore it's now going to be used, is that the three-year event-free survival was 87.5% versus 80%, which is the placebo arm.

It was added to the NCCN guidelines just this month. The study was published in the New England Journal of Medicine.

Basically, this is what we call Kaplan-Meier Estimates. They're a little bit hard to see, but the invasive disease-free survival was about 8% better with the Olaparib for one year. The distant disease-free survival was about 7% better. The overall survival was also approved by about 5%.

Olaparib doesn't have that many side effects, but nausea is common, fatigue is common, anemia, vomiting, diarrhea, and occasional problems with blood counts. But, generally, compared to chemotherapy, it's well-tolerated. In terms of very serious side effects, they're equal between Olaparib and placebo.

So, moving on to triple-negative breast cancer. Basically, triple-negative breast cancer means that the three receptors that we check for breast cancer are not expressed, just like the picture I showed at the beginning. So that means estrogen is negative, progesterone is negative, and HER2 is negative.

So, triple-negative breast cancer accounts for about 15% to 20% of breast cancers. At diagnosis, most of them are considered aggressive, grade three, and highly proliferative means that they divide quickly. The majority are diagnosed 43% at stage two, which means lymph node involvement underneath the arm, or stage three with more lymph nodes underneath the arm, not distance spread.

Early occurrences with recurrence are common. Therefore, we usually give chemotherapy before surgery. Patients who achieve a pathologic complete response, which means that there is no tumor at the time of surgery, have a longer event-free survival and overall survival. So, there's a high unmet need for newer drugs.

This was just presented at ESMO, which is the European Society of Medical Oncology. This study is called KEYNOTE-522. It is a phase three study of neoadjuvant pembrolizumab and chemotherapy, so before

surgery, versus placebo and standard chemotherapy followed by adjuvant pembrolizumab, which means pembrolizumab after surgery in early-stage triple-negative breast cancer.

Basically, we have white cells in our body and there are several different types of white cells, including B cells and T cells. The problem with cancer is that it escapes our immune system. We don't recognize it as something that is ... That a mistake has been made.

So, this is supposed to represent a tumor cell. This purple thing is supposed to represent a T cell, which, again, is a type of white cell. Basically, the idea of these immunotherapy drugs, which there are several different types, but PD-L1 and PD-1, is to wake up the immune system, wake up our T cells to recognize the cancer and kill it.

So, the study involved 1,174 women between March of 2017 through September of 2018. You had to be over 18, you had to be in good shape. It didn't matter whether you were PD-L1 positive or negative, although that was assessed.

The way it worked is it was a two-to-one randomization. So, two-thirds of patients received chemotherapy, which involved carboplatin, Taxol, and Adriamycin and cyclophosphamide with pembrolizumab. Then you had surgery and then pembrolizumab continued for one to nine cycles or approximately 27 weeks. Then one-third of patients received placebo.

Basically, statistically significant and clinically meaningful event-free survival was seen, about 8% difference. Event-free survival by pathologic complete response was also improved.

Now the interesting part is that about 2% difference was seen in patients who responded with a pathologic complete response, but even in patients who did not achieve a pathologic complete response, there was an advantage to receiving immunotherapy, about 10%. Overall survival, it's early but it's trending toward positive.

In terms of treatment, the side effects in the chemotherapy were about equal. The main thing is that immunotherapy has completely different side effects from chemotherapy. They're more endocrinological related. So thyroid dysfunction is the most common. Thyroid dysfunction.

In summary then, this very important study, which is practice-changing, is called KEYNOTE-522. It was a prospective randomized, placebo-controlled phase three trial of the use of the first immunotherapy in early triple-negative breast cancer, both in the neoadjuvant setting and adjuvant.

At this point, we see a favorable overall response rate. The safety is consistent with the known drug side effects. Basically, it's important that a platinum is used in this combination.

So, moving on quickly, we're going to just go quickly through all the things that are new. So, in stage four breast cancer that's estrogen receptor-positive and HER2-negative.

So, one of the things that happens is when the estrogen receptor is blocked, unfortunately, we've got all these other things that can wake up. The most common is cyclin D1. So basically, what happens is cell cycle and then divide.

So, there are three commonly used drugs, Palbociclib, ribociclib, and abemaciclib, which inhibit this gene. They're called CDK4/6 inhibitors.

So, this was an update of a study in stage four breast cancer, estrogen receptor-positive and HER2-negative. They used two drugs, fulvestrant, which is a hormone receptor blocker, and ribociclib.

Basically, this is the first time in advanced breast cancer it was shown that ribociclib had an advantage in terms of overall survival, four years and five years, 53% versus 44%, and at five years, 46% versus 31%. It helped not only in the first-line setting, but it also helped second line. You see the blue curve is over the yellow curve.

The other thing is that it took longer for patients to receive chemotherapy. So, the more time that patients spend on hormonal therapy, the better the quality of life. So, this is a good sign that we can avoid chemotherapy for a while longer in patients with advanced breast cancer.

The side effects are well-known, but the main thing, just so everybody knows, are white counts, anemia ... Low white count is called neutropenia, anemia, and low platelets.

So, in conclusion, MONALEESA-3 remains the only randomized trial evaluating CDK4/6 inhibitors to demonstrate an overall survival benefit in postmenopausal women who are hormone receptor-positive, HER2-negative. There were no new safety signals noted.

So, one of the other questions that comes up often is how long do I take hormonal therapy after being diagnosed with breast cancer? So, most patients with early-stage breast cancer are recommended five years but depending on how many lymph nodes are involved or the size of the tumor, we often recommend 10 years of therapy. So how can we decide how long someone should take hormonal therapy after surgery?

So, the Breast Cancer Index or BCI, the question is: is there a prediction of benefit from extended aromatase inhibitors, meaning letrozole, Aromasin, and anastrozole in hormone receptor-positive breast cancer?

So BCI is an 11-gene expression molecular signature comprised of two functional panels. I will just show them like that. It is both prognostic for the risk of cumulative and late recurrences. Basically, they looked at women who had been on studies from the 1980s. This is a very big study, the NSABP B-42, and it looked at extended hormonal therapy. Basically, tissue was available from these women and that's how they used to test the results.

Basically, the relapse-free absolute benefit was 1.6%. This seemed to show a statistically benefit at about the four-year mark. So, if it was low, it confirmed that you only need five years of therapy. If it was high, it looked like it's possible that you could predict women that would benefit from 10 years of therapy.

So, the test has been added to the NCCN. There are still ongoing studies. But I think that if someone is having side effects or has questions, this is a tool that can be used by doctors now to decide how long someone should be on hormonal therapy.

Just moving on to some other updates. Basically, Oncotype is a test that's currently being used for a little bit over 10 years now. A study called TAILORx was started in 2007. I'm going through this a little fast because this is not new information. RxPONDER is a study that involved women with one to three positive lymph nodes. So, we currently do use these studies and this test to decide whether a woman needs chemotherapy or not. There's also MammaPrint. So, I'm just going to show you what else is being used with Oncotype.

So, this was from ASCO this year. Basically, a group called the West German Study Group is trying to use this test, the Oncotype, to decide what ... In one other scenario. So, the study is very complicated, so I'm not going to go through it, but I just wanted to show you what they presented at ASCO.

So basically, in women with recurrent scores of 12 to 25, which is the whole middle section, and you have N0, means no lift nodes, or just one to three positive lymph nodes, they used hormonal therapy before surgery. So, something that we don't use in the United States too much. So, the question is: can you avoid chemotherapy in certain situations? This is just one study looking at hormonal therapy in the neoadjuvant setting.

So basically, in patients who responded to hormonal therapy and have these scores, their cure rate, or at least the disease-free survival in five years, is quite good. 93% in responders. In non-responders, it's a little bit less, 3%.

So, one of the things that is ongoing in research is trying to see if hormonal therapy response before surgery can help some women avoid chemotherapy or not. Again, this is all investigational. It's just using the tools that are available to try to make some more predictions. I'll show you one more thing.

So, this was interesting. In women with quite a few lymph nodes, from four and more lymph nodes, if you responded to hormonal therapy, again, before surgery and your recurrent score was low, even with many, many lymph nodes, the cure rates were around 94%. So that's very assuring, and I think there'll be more studies looking at Oncotype in higher risk groups in terms of anatomy.

Then I'm just going to move on to ... Then a couple more things. So, in terms of HER2-positive and stage four breast cancer, one of the things that ... Now that things are working, Herceptin, which is trastuzumab, was one of the breakthroughs in the last few decades in breast cancer. So, the question comes, can we do something called de-escalation or using less chemotherapy?

So, this study was presented ASCO as well, trastuzumab plus endocrine therapy or chemotherapy as first-line treatment for metastatic cancer, in HER2-positive breast cancer only.

So, there was a one-to-one randomization. So, in women with advanced breast cancer, can you use hormonal therapy? Obviously, you had to be estrogen receptor-positive and HER2-positive, and Herceptin and avoid chemotherapy. So, this is a one-to-one randomization.

Women did about the same. So, this helps us decide that in women who are not in crisis and are just diagnosed with HER2-positive estrogen receptor-positive metastatic breast cancer, you can use hormonal therapy and avoid chemotherapy in combination with Herceptin. So, this was a very reassuring trial. Overall survival was about equal.

Then, finally, this is the last slide that I will present from the 2021 ASCO meeting, is we talked about pembrolizumab in the neoadjuvant setting, which is a PD-1 inhibitor immunotherapy. So, this trial entitled Durvalumab improves long-term outcome in triple-negative breast cancer. This was the results of phase two randomized trial called GeparNUEVO. It looked at this PD-L1 inhibitor, not PD-1. Again, trying to wake up those T cells so we can recognize cancer in addition to standard chemotherapy.

Again, so PD-L1 inhibitor added alone to chemotherapy is known to improve progression-free survival in metastatic breast cancer. So, when something works in metastatic breast cancer, you try to bring it on.

This was the trial. It looked at durvalumab versus placebo, chemotherapy and durvalumab versus chemotherapy, then standard chemotherapy and then surgery. Again, this is like the other KEYNOTE-522 that we talked about, but there was about an 8% improvement between the two arms. This included disease-free survival and overall survival, 91% versus 78% at three years.

In summary, durvalumab added to neoadjuvant chemotherapy in triple-negative breast cancer significantly improved overall survival and disease-free survival. So, we don't know what to do with PD-L1 inhibitors yet. KEYNOTE-522, again, was just presented and approved. And so, there needs to be more study in terms of other immunotherapies. So that's pretty much the latest in terms of ASCO and ESMO.

Melissa Rosen:

Thank you, Dr. Drullinsky. We are now going to hear from Dr. Troso-Sandoval.

Dr. Troso-Sandoval:

Okay. Can you see my screen? Yes? Okay. I see myself. Do you see my screen?

Melissa Rosen:

We're seeing you, Dr. Troso, not the PowerPoint.

Dr. Troso-Sandoval:

Okay, let's see. I'm having trouble getting them up. Does somebody want to ... There we go.

Melissa Rosen:

I have them up. So, if you tell me when you want to move to the next slide, just tell me next and I'll go ahead and control them.

Dr. Troso-Sandoval:

Okay. So, I can't move them. Okay. So, hi. My name is Tiffany Troso-Sandoval. I'm a medical oncologist at Memorial Sloan Kettering. I work with Dr. Drullinsky at the MSKCC Nassau site. I specialize now primarily in gynecological medical oncology. So, I'm treating ovarian, uterine, cervical, vaginal, vulvar cancers.

Tonight, I'm going to spotlight ovarian cancer updates from ASCO 2021. It wasn't a huge year for ovarian cancer, but there are a few very interesting things. I'll probably go over some other things that will be of interest for you as well. Okay, advance.

So, I just wanted to start with what is the initial treatment? As per Memorial Sloan Kettering, these are general guidelines, just so you can understand where I'm going when I explain some of the changes.

So basically, for stage one cancer, it's contained within the ovary. We usually will do upfront surgical staging and chemotherapy depending on the type of cancer. So high-grade serous is the most common ovarian cancer type that is very frequently seen with BRCA-positive mutations and is a more malignant subtype of ovarian cancer. So, anyone even with stage one cancer would usually be recommended to receive chemotherapy.

In stage two, again, a slightly more advanced stage, we do offer something called IMPACT, which is a test that looks at DNA, molecular profiling of the tumor, and genetic testing. This has become a standard of care for ovarian cancer.

Again, patients would be recommended to receive chemotherapy and possibly would be given maintenance PARP inhibitors. I'll get into that a little bit more. Next slide.

So, stage three and stage four cancers, the two options are we do an upfront surgery where the patient is hopefully going to get a complete gross resection. In other words, get all tissue out less than one centimeter of disease.

If for some reason, the patient is unable to do that because the disease is too advanced or they have fluid in their belly, for example, we may do upfront chemotherapy, which is called neoadjuvant chemo. The treatment is the same, drugs still, IV carboplatin, the Taxol, and sometimes we'll add bevacizumab or Avastin for higher risk patients.

Again, I'm going to get into the maintenance therapy a little bit later, but we do additional testing on this tissue, including looking for HRD. Basically, we're looking for patients that will receive benefit from a PARP inhibitor. Next slide.

So, again, now you see where we're going with this. We have the optimal treatment duration of bevacizumab combined with the carboplatin and paclitaxel in patients with primary epithelial, ovarian, fallopian tube, or peritoneal cancer.

So, the question here, next slide, is basically, how long do we need to use the Avastin? So, patients, for example, that have advanced disease, stage four disease, and we decide to use bevacizumab, and they have derived some benefit as has been shown in some of these studies. So, GOG-218 and ICON7 reveal that early and continuous use of bevacizumab for both 15 and 12 months, based on those two studies, in addition to the standard carboplatin and Taxol, improves progression-free survival.

So, the question is then is 15 good enough or would more be better? And so, the aim of this trial was to see if we prolonged the bevacizumab treatment for up to 30 months, would we have even better efficacy? Next slide.

So, this trial was basically designed where patients had advanced disease, stage IIB or IV, up to IV, and you could have either had some prior debulking surgery or had surgery later. But the key is that you can't receive bevacizumab, Avastin anywhere near your surgery. So if you were to receive neoadjuvant upfront chemotherapy first, we withhold the bevacizumab at least six weeks before surgery, because it will increase the risk of bleeding and decrease the healing rate.

So patients were randomized one-to-one to either receive the Taxol and the carboplatin with Avastin, bevacizumab. One arm got 15 months and one arm got 30 months. Next slide.

So we're basically testing the superiority of bev 30 months over bev 15 months. 900 patients were to be randomized over 30 months. But due to a low event rate, the study was closed after only 673 or 97% of the planned 697 events had been observed.

Basically, what that means is that there were so few people that were recurring in the period of time that was demarcated as the study that they had to stop it earlier to look at the results. Secondary end points were overall survival, safety, and tolerability as well. Next.

So basically the patient characteristics, just briefly just wanted to show everyone if they want to take a quick look at this graph here, is that it was evenly distributed. So patients were evenly distributed as to whether or not they had residual tumor after surgery or not, whether or not they had high-grade serous or a different subtype, what their performance status does in terms of how functional the patient was, as well as age. Next slide.

Also, again, just going through, the important part, I think, is the second half where they show you that the stages of the patients that were put on the trial were evenly balanced between the 15 and the 30. Next.

So I highlighted the overview of the adverse events. What is interesting is that they're pretty equal. Bev 15 months had 44 serious adverse events and 63 grade three to five, whereas bev 30 had slightly more, 46% and 68%. So not a substantial increase in toxicity with the additional months of bevacizumab. Next.

So we look at a primary endpoint, which is progression-free survival. So in other words, how long you're living without the disease continuing to grow or progressing. You can see here that we're going to focus mainly on the left side. But bev 15 had 24.2 months versus bev 30 had 26 months. This was not considered to be necessarily statistically significant.

The next one is a little more complicated to explain. It basically is looking at when they stopped event time versus continuing to follow the patients out after the study had completed. Next slide.

So subgroup analysis, they're looking at patients now that had no residual tumor. So they had a complete gross resection. In other words, they went into chemotherapy and received their Avastin, having had all their cancer removed. You can see between these two the progression-free survival was almost equivalent, 38.4 and 38.8. Next.

So now you have patients that have residual tumor or had stage four cancer. It had spread to another organ, south side of the pelvis and the abdomen. You see here that the bev 15 was actually a little bit higher than the bev 30, which seems a little counterintuitive. Next slide.

Overall survival, 54.3 versus 60, but this was not considered to be statistically significant. Next slide.

So the conclusions were that longer treatment with bevacizumab for up to 30 months was feasible, was not more toxic substantially, but that longer treatment with the bevacizumab for up to 30 months improved neither the PFS or OS. So overall did not help patients with progression-free survival or overall survival.

So, therefore, based on this study, the standard of care, which would be 15 months of bevacizumab remains the standard. Just to clarify how that works is patients will receive the Taxol, carboplatin, plus the Avastin. Then when they've completed their six cycles of Taxol and carboplatin, they will continue on with the Avastin for the completion of 15 months. Next.

So changing gears a little bit, everybody always wants to know about PARP inhibitors. So I'm going to give you a little bit of background and then some updates. Go ahead. Thank you.

So just briefly, I know Dr. Drullinsky touched on this a bit. Normal cells have two normal BRCA genes. BRCA genes help in repairing the DNA when it's damaged. A BRCA mutated cell, so, for example, a patient that has a BRCA mutation genetically or the BRCA mutation can arise only in the tumor and not be an actual genetic hereditary thing. So again, just to clarify, there's DNA of the tumor and we have DNA that's hereditary.

So in these DNA cancer cells that have a BRCA and you give a PARP inhibitor, that helps further inhibit single-strand repair of DNA breaks. So just looking at the slides that I have here, the BRCA mutated cells have one hit. Normal cells plus a PARP inhibitor in the third line have another hit, where if you have a BRCA mutation that you're born with or is in the tumor and you give a PARP inhibitor, the pill, you have a double hit. So it's much less likely or impossible for the cancer cell to repair itself and, therefore, it dies. That's the down and dirty of PARP inhibitors. Okay, next.

So what's very interesting here is that 50% of high-grade serous cancers have alterations in homologous recombination repair genes. So what does that mean? So basically homologous repair is what we were just talking about. It's repairing the single-strand DNA. What we know is that the BRCA 1 and 2 are part of that pathway.

But we've also found that there are other genes that are involved in this, and those are captured in what is called homologous recombination repair genes, HRR genes. I can't point, but basically this slide is showing you that there are other mutations that contribute to a tumor being deficient in homologous recombination in addition to BRCA. You could probably see in the lower right-hand side CDK12, RAD51, PTEN. You can go to the next. Thank you.

I'm not going to go through all of this. This was from last year. But basically wanted to just give you a quick overview of some of the trials that were looked at using PARP inhibitors in the upfront setting. In other words, the patient would have chemotherapy and then would go on maintenance therapy. There are different exclusion factors for the different drugs.

So as of the current state of the art, we have PAOLA-1, which looked at patients that had HRD-positive cancers. That means that the patient has either BRCA or HRD, meaning those other genes are present. I'm going to go through that a little bit more. This showed that the combination of bevacizumab with

olaparib, which is a PARP inhibitor, caused increased time to progression and improved median progression-free survival.

There was another study called PRIMA. Prima was very interesting in that it took all patients. So you didn't have to have a BRCA mutation and you didn't have to have HRD present. They looked at all comers, but then they broke it down.

Actually, this is an interesting point because a lot of people have a question about this. If you look in the center, under PRIMA, go down, HRD-positive. That includes BRCA patients. You have a 22.1 versus 10.9-month progression-free survival advantage.

HRD-positive patients which exclude BRCA, so in other words all those other genes but not BRCA, you still get a 19.6% versus 8.2 months progression-free survival advantage. But if you're HRD-negative and you get PARP inhibitor, they have an 8.1-month progression-free survival, and placebo is 5.4.

So this is the important point. In the HRD-negative, BRCA-negative cohorts, there is only a three-month improvement in progression-free survival for taking this niraparib for up to three years. As you can imagine, there are side effects. It's a medication and it has side effects and things that need to be controlled, that are not always pleasant for the patients. Next slide, please.

Just briefly again, same trends were displayed in the recurrent setting. So these were patients that had the QUADRA study, for example, on the right. The same drug, niraparib, was given to patients that were either platinum-sensitive or resistant, patients that had BRCA or HRD-positive, or unknown.

So the important point to look at here is the fact that patients that had platinum-resistant disease, even if they were HRD-positive, still had not a terrific response to the drug. This is actually an important point because it's often felt that patients that are platinum-resistant, meaning that they've received carboplatin in the past and have had progression of disease despite that, it's pretty much a marker of whether or not a PARP inhibitor is going to be effective. Next slide.

Just going over this quickly. Current FDA approvals for frontline. So olaparib, Lynparza, is available for maintenance following a complete or partial response to chemotherapy, if patients have a genomic or somatic BRCA mutation. Again, genomic is the genetic hereditary, somatic is the tumor DNA.

Second one would be olaparib in combination with bevacizumab. So for patients that had HRD-positive tissue, meaning those other genes aside from BRCA, can receive bevacizumab with olaparib. The test that we use for this is called Myriad myChoice, and that was FDA-approved as a companion diagnostic.

So there's also bevacizumab, which can be used alone as first-line treatment in combination with carboplatin and Taxol for advanced cancers. We just looked previously about how long we should be continuing that drug. 15 months is about the same as 30 months.

Then the last would be niraparib, which was approved as first-line maintenance following CR or PR to chemotherapy, with any advanced epithelial ovarian cancer. In other words, you don't have to have a BRCA, you don't have to have HRD. But, again, remember I showed you that there was only a very small, three-month difference, in patients that did not have BRCA or HRD present. Next slide.

So what about maintenance therapy for, this is my term, triple-negative ovarian cancer. So patients with triple-negative ovarian cancer are the patients that have genomic or hereditary BRCA-negative, or somatic BRCA-negative, meaning the tumor doesn't have BRCA either, and they're also HRD-negative. Next.

So just going back to ... It's just a different version of what you saw before. There's lots of HRD-deficient genes that we're looking at right now. Then we have these HR-proficient cancers. So these are the ones, again, no BRCA present in either the tumor or genomically and there is no HRD present. Next.

So this study was shown to utilize a new technique basically for advanced ovarian cancer. They're using homologous recombination proficient patients. Again, these are patients that are HRD-negative, BRCA-negative.

So this drug, ready, maintenance, gemogenovatucel. We're going to call that GEM from now on, and it was a phase IIB trial. This is a very interesting trial. Go ahead. Next slide.

So basically what they did was this was a personalized vaccine. They took some of the tumor that was harvested during surgery. They modify it with autologous tumor cells and then they basically give it as an injection. Then the tumor will respond and the T cells will be activated and we will collect ... There'll be antigen presentation and death to the tumors.

So, again, we're modifying the own tumor cells to be injected, to produce a response and T cell activation to kill the cancer cells. I actually went backwards on that, but okay.

So the study design, just quickly, they were randomized. Patients either received the vaccine versus placebo one-to-one. You had to have advanced stage disease, IIIB or IV, and have had to have had a complete response after first-line surgery, Taxol, and carboplatin.

So the treatment again was a vaccine. Sorry, go back one. That was given 12 doses. You got an injection every four weeks up to 12 doses. Then there was also placebo-controlled. Next.

So primary endpoint was recurrence-free survival. How long do these patients last until the cancer were to come back? Secondary end points were overall survival, safety/toxicity. Next.

So they did do some subgroup analysis because they were looking at HR mutation, including BRCA and HR-proficient. It's determined by myChoice by Myriad. That's the HRD testing. Next.

Just wanted to show you again that there was a predominance of patients that had had adjuvant therapy and patients that had ... There were still ... If you go to the bottom, frontline surgery residual disease status. So this is interesting. Patients had macroscopic disease, still residual cancer present, 34% and 25%.

So that's interesting because these are patients that often might not do quite as well if they had had upfront surgery without a complete gross resection. Next.

Just going over some of the adverse events. There was some injection site disorder, but as you can see, everything else is quite small. Interestingly, the connective tissue disorders is actually higher in the placebo, as are the nervous system disorders. That always makes you scratch your head. Next.

So looking at the recurrence-free survival and overall survival, you can see that in the bottom, if you look at the numbers, basically patients that had the GEM vaccine had an 11.5 months versus 8.4-month recurrence-free survival. So an improvement of about three months. Then in the overall survival, this has not been reached yet for the recurrence-free survival in overall survival. Next. Next slide, please.

So this was updated. These are homologous recombination proficient patients. Overall survival, updated recently, shows a hazard ratio of 0.4. So this is actually pretty impressive results. If you look at the graph on the right, you'll see that patients with two-year overall survival that received the vaccine, 92%, and at three years, 70% versus 55% and 40%. Next.

So conclusions, novel autologous vaccine specific for each patient. Excellent tolerability, ideal for maintenance therapy. Although it failed to meet the primary endpoint in all patients, but when they looked specifically in the HRP patients, the ones that were homologous recombination proficient, HRD-negative, these patients had encouraging results as presented. Next. Okay, next.

So one other interesting presentation was this particular drug, which is a folate receptor alpha-targeting antibody drug conjugate. This was given in combination with bevacizumab in patients with platinum-agnostic ovarian cancer, meaning that they don't care if there's platinum or not. Next.

So basically looking at ... This isn't the original slide. Basically, they were looking at this drug in platinum-resistant ovarian cancers in particular. So they showed that monotherapy with a folate receptor alpha agent showed that there was a high presentation of FR-alpha in patients present. Then with the bevacizumab you had a higher response rate. Let's keep going on this one.

So patients who had a non-platinum-based doublet with bev would be appropriate for this study. So these are patients that have been previously treated with Avastin. They were looking basically for the tumors that had high or medium presentation of this membrane receptor, FR-alpha. Next.

So just looking at the characteristics of these patients, again, you can see that if you go to the, one, two, three, number of prior systemic therapies, you can see that there are several patients, or 32% of patients, that had greater than three lines of therapy. Then they broke it down to whether or not the patients had FR-alpha expression that was either high or medium.

Then the other thing that is of note here is the platinum-free interval. In other words, how long had it been since patient had last received a carboplatin or cisplatin moiety? When they showed, it was less than six months, or six to 12 months, and greater than 12 months. Next.

So overall response rate for patients that are FR-alpha expression versus platinum status. So basically overall population, there was a 50% response rate. Not bad. Then when you break it down by FR-alpha expression, you saw that the patients that had high FR-alpha expression on their cells had an even higher response rate.

Then if you looked at patients that were platinum-sensitive versus platinum-refractory or resistant, sensitive patients are 69% and platinum-resistant patients, still 59%. So although it is better in the platinum-sensitive patients, everything is. To be honest with you, it's wonderful. It's most exciting that you've got a 59% response rate in patients that are platinum-resistant, because this is a harder group to treat. Less treatment options. Next.

Medium duration of response. This is just showing you that there was a pretty good duration of the response. So total population had 9.7. If you are high FR-alpha, you had 11.8 months. If you're platinum-positive, platinum-sensitive, then you had a 12.7. So it seems that platinum sensitivity and high FR-alpha are the optimal setting for this drug. But, again, you did get a response in platinum-insensitive drugs as long as there were high FR-alpha present. Next.

This is just a waterfall plot showing that 97% of patients demonstrated some level of tumor burden reduction. That's pretty exciting. They also showed that there was actually some very early responses. In other words, some of the patients had a very rapid initial shrinkage of tumor and then a durable benefit, meaning that it lasted. Next.

It was a very generally well-tolerated treatment. There were some hypertension and low white blood cell counts. Next.

Conclusions. The folate receptor alpha drug combined with bevacizumab in the broad population of recurrent ovarian cancer patients in need of more effective non-platinum-based therapies, there was a 64% overall response rate, 11.8-month duration of response, and a 10.6-month progression-free survival.

In patients that were FR-alpha positive with up to three prior disease, irrespective of platinum status, again the high FR-alpha patients that are platinum-sensitive, had the highest response rates. The high FR-alpha platinum-resistant still had a 59% overall response rate, 9.4-month medium duration of response and 9.7 months progression-free survival. These are impressive for platinum-resistant disease. Next. That's it.

Melissa Rosen:

Okay, thank you very much. We are now going to address some of the questions that have been both submitted in advance of this evening, as well as through the chat box. Dr. Troso-Sandoval, I believe this question is for you. Are there any advancements ... I know you did talk about some of this, any advancements in treating ovarian cancer that has reoccurred. So new treatments or procedures in radiology advancements for recurrence.

Dr. Troso-Sandoval:

Well, yes, that's part of what I just spoke about. Again, when you're looking at occurrence, you have to first define if the patient is platinum-sensitive or platinum-resistant, how long has it been since they last received a carboplatin, whether or not they're HRD or BRCA-positive. We'll also determine your treatment recommendations.

It's also very important in this day and age in the terms of molecular medicine. So having a DNA molecular profile of your tumor is very helpful in terms of defining targeted agents that would be useful.

Melissa Rosen:

Great, thank you. A question that came through the chat this evening. If a patient with a somatic BRCA mutation has an adverse reaction to ... And I apologize if I botched the name of this drug, olaparib. Like they have an allergy. Is it possible to switch to a different PARP inhibitor for maintenance therapy after ovarian cancer?

Dr. Troso-Sandoval:

So I've never seen a patient have an allergy, so to speak. I mean there are often side effects that need to be mitigated with these drugs. So, for example, Olaparib will frequently cause fatigue, some nausea. Those are the major side effects in the beginning.

What we often tell patients is to try and stick it through the first six weeks and any way that I can support them, I will. Normally, a lot of these symptoms seem to get better. They almost [takiflaps 00:52:41] on their own and seem to improve after six to eight weeks on therapy. If not, then we also will consider reducing the drug dose. So for adverse reactions, that's usually the way we'll go.

So the other drug that is still FDA-approved in this arena is also niraparib, which you certainly could switch to. Whether or not there's a cross-reactivity of allergies between those two, I don't really know the data on that. Again, I have never seen an allergic reaction to a PARP inhibitor yet.

But the niraparib I've found in practice tends to cause a little bit more thrombocytopenia or low platelet count. And so, I often find myself dose-reducing that drug much more frequently even than Olaparib. So in my hands at least, as well in some of my colleagues, the Olaparib is actually one of the easier ones to manage and mitigate the side effects.

Melissa Rosen:

Thank you. Many people had a question this evening about Lynparza, which was perhaps a very impressive result from ASCO this year. It's not covered currently by insurance, and patients were wondering if there are other options to access the drug currently.

Dr. Pamela Drullinsky:

Yeah, I think that's going to be an issue. But since the NCCN now has now endorsed it, and so has ASCO, I think insurance companies will slowly start moving toward approval. I would say to someone, if your insurance does not approve it, then I would appeal directly to the drug company on any drug that you can't get covered by insurance. Sometimes you can get assistance that way pre-FDA approval.

Melissa Rosen:

Great. Is there work currently on a vaccine potentially to prevent ovarian cancer?

Dr. Troso-Sandoval:

Not currently. At Memorial Sloan Kettering, they have looked at those. Really right now, they're primarily looking at therapeutic vaccines, like the one that we showed you, the GEM one. Basically, it's harder to prove a vaccine to prevent ovarian cancer until you have also proven that it is effective in treatment. As you can imagine, the time point, if you decided to try and create a vaccine that would help prevent the creation of ovarian cancer, it's very hard.

It's an endpoint to measure because you don't know if the patient actually would ever have ovarian cancer, how long that time would have been otherwise. It would just be based on statistics. There are studies that are out there, but right now the main thrust of research is primarily in therapeutic vaccines.

Melissa Rosen:

Okay, great. Then the same question would apply for Dr. Drullinsky. Is there a similar idea with a breast cancer vaccine?

Dr. Drullinsky:

No. That's the quick answer.

Melissa Rosen:

Okay. Thank you. There were some recent articles that might have suggested that there were some increased adverse risks to tamoxifen, potentially other cancers, I suppose. What are your thoughts on use of tamoxifen after initial treatment, but in premenopausal, early-stage patients?

Dr. Drullinsky:

Number one, get off the internet. Tamoxifen has been around 80 years. So it's interesting people come to both Dr. Troso and I with, "Oh, I just discovered this and this." There's no news with tamoxifen. It's been around 80 years.

Basically, in women who take tamoxifen for 10 years, there definitely is an increased risk for uterine cancer. It's about 1%. It's pretty rare, and that's not ovarian cancer, which is the sneaky one and complicated, as you can see by Dr. Troso's presentation. Uterine cancer is found very early and rarely in the metastatic setting and presents with vaginal bleeding.

So it's so rare that women on tamoxifen are not recommended routine ultrasounds of the uterus. So I would, again, get off the internet and not worry about secondary cancers when the benefit far outweighs the side effects.

Melissa Rosen:

Thank you. Thank you. I know that we had many, many questions that came in this evening, both in the chat box and submitted in advance. We will have an opportunity to address those via email later this week. But we are going to conclude this evening.

I want to thank Dr. Troso-Sandoval and Dr. Drullinsky immensely for educating us this evening. I know that you've answered so many questions, and I'm sure that so many participants this evening feel more knowledgeable after hearing your presentation and understanding the research that came out of ASCO this evening.

I'd ask you to please take a moment to fill out our brief evaluation survey that is right now linked in the chat box. Evaluations at Sharsheret really do inform our future programming, so we thank you for participating. We'd love for you to stay connected with Sharsheret via social media, where we post about events like these, program updates, and fun ways to get involved.

I again want to thank our sponsors for this evening, AstraZeneca, Seagen, the CDC, and The Siegmund and Edith Blumenthal Memorial Fund, as well as our webinar partner this evening, Memorial Sloan Kettering.

Please never forget that Sharsheret is here for you and your loved ones during this time. Sharsheret provides emotional support, mental health counseling, and other programs designed to help you navigate through your cancer experience. All of our programs are free and completely private.

Our contact information has again been linked in the chat box. Our social workers and genetic counselors are available to each and every one of you and you are a priority. So please never hesitate to reach out. We're all going to get through this together. Thank you so much for being here this evening and have a nice night.

Dr. Troso-Sandoval:

Bye bye. Thank you.

About Sharsheret

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

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

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

Sharsheret offers the following national programs:

The Link Program

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

Education and Outreach Programs

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

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