HIGHLIGHTS FROM ASCO 2023

Highlights from the latest findings from the
American Society of Clinical Oncology's Annual Meeting
with
Dr. Yuan Yuan, PhD, Director, Breast Oncology, Medical Director
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and
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Eve Kleinerman:

Good evening. My name is Eve Kleinerman. I am the Illinois regional director for Sharsheret, and I want to thank everybody for joining us this evening for the latest in our webinar series, highlights from ASCO of 2023. For those who may not be familiar, ASCO, the American Society of Clinical Oncology is the world's leading professional organization for physicians and oncology professionals caring for people with cancer. And tonight we are privileged to be learning from Dr. Yuan Yuan and Dr. BJ Rimel, two nationally recognized physicians representing Cedars-Sinai Cancer Center, who will highlight the latest findings from the American Society of Clinical Oncology's 2023 Annual Symposium. We are grateful to tonight's webinar sponsors, GlaxoSmithKline, Daiichi-Sankyo, Gilead, and AstraZeneca.

Before we begin, I just want to cover a few housekeeping items. The first of which is that tonight's webinar is being recorded and will be posted on Sharsheret's website along with a transcript. However, participants' faces and names will not be in the recording. But 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 both of those are in the chat box right now. You may have noted that all participants were muted upon entry. Please keep yourself on mute throughout the presentation. And if you have questions, put them in the chat box either publicly or you can message me, labeled as Sharsheret in the chat box, to submit a private question. We received many questions in advance of the webinar and we do anticipate receiving many questions in the chat box, and so we will do our very best to answer all questions tonight. But any questions that are not answered for you tonight on the Zoom will be addressed by email over the next week.

We recommend, for the best viewing, that you keep your screen on speaker view, which will allow you to see the doctor's presentations. You can find that option in the upper right-hand corner of your screen. As we move into the webinar itself, I do want to remind you that Sharsheret is a national not-for-profit cancer support and education organization, and we do not provide any medical advice or perform any medical procedures. This information, provided by Sharsheret, is not a substitute for medical advice or treatment for a specific medical condition. You should not use tonight's information to diagnose or treat a health problem. And if you do have questions that are specific to your medical care, the physicians on screen may not be able to advise regarding specifics and would advise that you speak to your medical provider. Always seek the advice of your physician or qualified healthcare provider with any questions you may have regarding your medical condition.

In just a moment, I'm going to introduce our presenters to you and they will give their presentations followed by a question and answer session. And after that, we will immediately begin our special bonus breakout program with our Embrace group for those who are facing metastatic breast or advanced ovarian cancer. Anyone facing advanced disease is invited to stay on for an intimate breakout session with Dr. Yuan and Dr. Rimel and a conversation that'll be moderated with Bonnie Beckoff, our Director of Support Services.

And now, this evening we are so honored to be joined by Dr. Yuan Yuan and Dr. BJ Rimel. Dr. Yuan Yuan is a Breast Medical Oncologist and Physician Scientist who specializes in Triple-Negative Breast Cancer and Breast Cancer Immunotherapy. Dr. Yuan currently practices at Cedars-Sinai Comprehensive Cancer Center, and is also working closely with the Cedars-Sinai Cell Therapy Team to bring first class immunotherapy treatments to patients with solid tumors, including breast cancers.

Dr. BJ Rimel began working at Cedars-Sinai Medical Center in August 2011 to focus on Gynecologic Oncology Clinical Trials. Dr. Rimel's research interests focus on barriers to clinical trial enrollment and use of digital processes to improve access and comprehension of clinical trials. Dr. Rimel is the Gynecology

Surgeon of the Cedars-Sinai Transgender Program. Dr. Rimel is also the Medical Director of the Cancer Clinical Trials Office. Both physicians' full bios are available on our website. And now I turn your attention to Dr. Yuan Yuan.

Dr Yuan Yuan:

Thank you so much, Eve. Let me share a screen. All right. Again, it's a great pleasure to be here tonight. And I'm so happy we're able to spend some time discussing ASCO updates. And I tend to speak too fast, but thankfully there is a breakout session. We can further clarify any questions if it wasn't clear. So the outline we're going to spend time on, mainly three trials, to discuss the early stage ER positive, may be potentially a breakthrough therapy, which will be the second CDK 4/6 inhibitor in the space. Then we'll discuss our exciting patritumab deruxtecan, which is a HER3 antibody drug conjugate. And then go over some of the mature data of TROPiCS 02. Then if we have time, we can talk about two ongoing studies happening in Cedars.

So for those who're familiar with breast cancer treatment, I think the CDK 4/6 inhibitor has been there since 2016, so the last seven years. It's moving now from the metastatic space to the adjuvant space. The idea behind that is that while patients are doing better and better in the metastatic setting, can we do this in our adjuvant setting to prevent breast cancer recurrence? There are some nuances about the three drugs, they're not exactly the same. So on the right-hand side, you see this pie chart, it's really looking at the mechanism of the drug. They don't even look similar. Especially this Abemaciclib or Verzenio, it tends to have a bit more toxicity. Patients can present with diarrhea. So you can see that it has a broader target. That being said, currently, abemaciclib is the only FDA-approved agent for high risk early stage breast cancer patients to take two years to prevent breast cancer recurrence.

So we do have some exciting new data coming out of this initial Johnston around 2020 trial, and further follow up really confirmed. Now we have four years of data. We're talking about patients surviving without a disease recurrence, so that's reconfirming the benefit. And how about the question? How about the next or other two? What are they doing? So in this ASCO 2023, it's the first time a long awaited phase three clinical trial is now studying the second CDK 4/6 inhibitor called ribociclib. Commercial name is Kisqali. So in this trial shown on this graph, patients were compared, it's a large study, 2,500 patients each arm. Ribo dose is a lower dose compared with metastatic setting. It's 400 milligrams daily, three weeks on, one week off, and also different from abemaciclib. This is three years of treatment. And then the control arm takes only an aromatase inhibitor. So these are the stage 2A or 3 patients who had ER positive for hormone receptor positive, HER2 negative disease. They have certain high risk features, including high Oncotype DX, perhaps other genomic profiles, or they are lymph node positive, or KI-67 over 20%.

So this trial, and then there's some granularity of the data. 27% of the patients were node negative. This is very important because the abemaciclib only applies for lymph node positive patients. So this is good and bad. So a high risk node negative patient now potentially will soon have this drug available if FDA approves it early next year. So I think that's an important distinction between ribociclib trial and abemaciclib.

And there is some more granular information regarding the toxicity, the reason for discontinuation. Granted, these are well tolerated treatments, but there are certain adverse events that led to the patients stopping the treatment. And this is the primary readout, invasive disease-free survival, meaning one would remain healthy without any recurrence of breast cancer. You can see that in such a short follow-up, three years, there's already a difference of 3.3%. It may seem to be relatively small, but that translated risk of invasive disease decreased by 25%. So hopefully in the future we'll see more follow-up

and eventually it will be overall survival data. And also translated the clinical trial data, highlighted in red is the risk of distant disease recurrence was decreased by 26%. So it's further helping these women to prevent metastatic disease.

Now the toxicity. The audience is familiar with this drug. It's an oral inhibitor, it's not a conventional chemo, but it does reduce the white cell count, especially since they're not trivial. In the metastatic setting, when patients were given 600 milligrams, there's a lot higher grade three events. Here it's reduced, but it's still not trivial. In addition, the table listed a number of toxicities. But the highlight is that it's reduced, comparing it with a metastatic setting. So not going into all the weedy discussion, the take home message from this trial is that the NATALEE trial supported ribociclib in a lower dose in combination with aromatase inhibitor as a potential new adjuvant treatment option for patients with stage two and three hormone receptor positive early stage breast cancer who face a higher risk of recurrence.

So currently, not yet FDA approved. And is this practice changing? So this is a very important question. After ASCO, we take this data home and then we see the patient next week and then we discuss them in the clinic. I, in fact, have patients who had completed two years of abemaciclib, and she asked me a question, "Can I switch to ribociclib and then do an additional year?" So there are a lot of interesting questions we may not have all the data to support, but certainly consider ribociclib in patients with high risk who missed the monarchE, which is an adjuvant abemaciclib eligibility criteria. So in order for us to understand a little better, we did this table to compare. So you can see that, definitely, these two trials cover similar populations. But granted, for those, for example the T2N0 nodal negative patient was not including the monarchE. The T3N0 patient was not including the monarchE, but now this is opening up the options for them. So these are welcome changes.

So we're going to move on to the really exciting area in breast cancer and beyond. This is called antibody drug conjugates. Here in the middle, it's just showing the structure of the drug. So the Y shaped antibody is in the middle and it's specifically designed and chemically bound or linked to chemotherapy drugs. So the yellow little spheres are the payload or the chemotherapy drug. So right now we have multiple agents already FDA approved and many to come. So for example, the ado-trastuzumab emtansine or T-DM1 was approved many years ago to treat HER2 positive or HER2 amplified breast cancer. And then we saw sacituzumab govitecan, now it's FDA approved to treat triple neg breast cancer, and also in hormone receptor positive previously chemotherapy treated population. Then what's in the clinical trial setting is this fam-trastuzumab deruxtecan or T-DXd, it's coming soon.

And then we have this exciting update from this ASCO, which is the HER3 antibody drug conjugates, we're going to go into detail in a bit. So this is again a different format, highlighting all the drugs available at this moment. And TROPiCS 02 is, in fact, what's in the middle, you don't see my cursors. This is blue, bottom left, down. This is the SN 38 payload. The antibody is a humanized anti-Trop-2 antibody. So what is Trop-2? Trop-2 over expresses on the surface of cancers. Especially breast cancer or in triple negative breast cancer, it's over expressed in 90%. In hormone receptor positive, over 80%.

So obviously, this differentiates the cancer cell with a normal cell so that it can naturally become a target. So the data initially came from an ascent trial showing in second line or third line setting, triple negative breast cancer patient, the drug definitely improves and controls the disease. There's overall survival and progression-free survival benefit that led to the very initial FDA approval. And then the TROPiCS 02 trial is actually looking at a different population. So can this drug benefit patients who are hormone receptor positive but went through often four or five lines of therapy, including multiple lines of hormone-based treatment? When they move on to chemo, eventually they may need something new. So this is a trial design for these patients who already progressed through multiple lines of chemotherapy.

And the final update, this is the recent ASCO update to show the overall survival benefit. Trial design. Very straightforward. And notice that these patients are relatively heavily pretreated. Beyond the conventional endocrine treatment, they also received an average two to four lines prior chemotherapy. So in total, over 500 patients were randomized to receive sacituzumab govitecan, commercial name is Trodelvy, versus physician's treatment choice, single agent chemotherapy. And the primary outcome is looking at progression-free survival. I want to draw your attention to this table on the right hand and the last row. Look at the median prior lines of therapy. You can see that they're relatively heavily pretreated, ranging from zero to eight lines of treatment, for example in the SG arm.

So this is the updated progression-free survival. You can see that these curves are separating at six months of time. 45% of the patients in the sacituzumab govitecan/Trodelvy or arm did not progress. And contra was 29% in the control arm. In the further follow-up, you can see the distinction at 18 months, 14% of the patients were stable with the new drug, versus conventional chemotherapy, only 4.7%. So that's a meaningful difference. And further subgroup analysis and the breaking down into overall survival. And actually the title, I apologize, it was a mistake, it's overall survival. You can see that the overall survival meets its primary goal, and the P-value is significant.

And then you may ask, does it really matter how high? So the edge score here is really talking about Trop-2. So we're now familiar with the HER2 expression, high low. So does the Trop-2 high low make any sense or make any differences? So this is to give us some ideas when patients have either low score versus high score. You can see that numerically, in the high score group, they appear to do better. But even in the low score group, there are small differences brought on by the drug. So I think at this moment of time, the FDA approval does not ask for Trop-2 testing. So we all do ER PR HER2 testing, but we don't do Trop-2 testing.

And response rate. I have to say, even in the sacituzumab govitecan arm, the response rate, 21%, is not super satisfying, but it's slightly better than the physician's choice arm. The toxicities, there is some breakdown of the detailed information I won't spend too much time on. And GI toxicity is not trivial from SG or sacituzumab govitecan. Diarrhea, nausea, vomiting, abdominal pain can be found. And clearly we need to pay attention to these symptoms. So the outcome in the conclusion is that the phase three TROPiCS 02 trial in hormone receptor positive, HER2 negative metastatic breast cancer continues to confirm the benefit and reduced risk of progression, and no new safety signals were seen. So I think it's worthwhile to bring this drug into discussion with the physician for appropriate patient populations.

So more exciting. Now we heard about HER2, Trop-2. What is HER3? What is HER? HER is a human epidermal growth factor receptor. There is actually a silent HER family including HER1, also called EGFR, it's talked about a lot in lung cancer. HER2 is famous for breast. And there's HER3 and HER4. So the HER3 is not a silent bystander, they play a very important role. They would form the teamwork or form these conjugates together with HER2 to help the HER2 signaling passing down the surviving signal.

So the reason this is becoming interesting is that, in the past, we didn't talk about it because there's no drug to target. Now, finally, we have the drug. So this drug is called HER3 antibody drug conjugates. So the antibody is called a patritumab, and the payload is deruxtecan. So this is very much the same payload as T-DXd, trastuzumab deruxtecan, the star drug last year. So this is a few trials already ongoing. And this ASCO, we saw a continuation of signals coming from a phase I/II trial, and really showing us the efficacy. And I was leading the trial at my previous institution with a robust enrollment. And we have really good patients coming out of this study.

So it's a complicated three-phase trial. But at this moment in time, we're seeing part A, which is a fixed dose. The drug is 5.6 milligram per kilogram, intravenously given every three weeks. And patients could

have hormone receptor positive or triple negative breast cancer. The only thing is that they cannot have previously antibody drug conjugates who, for example, patients with HER2 low disease already received in HER2, in this trial, they're not included. There are going to be tons of research questions in the future when we have several drugs FDA approved, how do we sequence them?

So coming back to the trial, the HER3 expression was studied. And you can see that over 60% of the patients have a high HER3 expression, over 75%, and they're relatively also heavily pretreated. Over 60% of the patients had received three lines or more prior chemotherapy. And efficacy data, and there's a lot of granularity of information. But the key message here is that, regardless of the HER2 expression level in the red box, you see a somewhat similar response rate. Focus on the PR, the second bullet point. So in HER3, over 75% of patients you see a 33% response rate. But even when the HER3 level is lower, you see the response. So this is, again, a recurring theme, that regardless of these receptor levels, they seem to be all effective.

Now, not enough information in this trial to draw too much conclusion of a triple negative versus ER-positive disease. So we need to stay tuned in for more information. Now, those who're familiar with T-DXd may ask a question, T-DXd has an FDA black spot warning regarding 10% of the patients developed a potentially life-threatening toxicity called ILD. What about this drug? So naturally, this is the first question. Now you can see that the right upper box showing that SAE ILD risk, only one patient in 60 patients totally accrued. So relatively low percentage. Although the number is too small here, the drug is very well tolerated.

I remember my first patient who went on to this trial, she came from a different institution. She was the one possibly masking this toxicity. Every time she comes in, no complaints, no hair loss, no nausea or vomiting. But if you look at the table here, 50% of the patients all have nausea. But the grade 3/4, severe nausea is very low. Fatigue, 6.7%. Diarrhea is 5% only. So again, I think the toxicity profile take home message is that it's very safe, very well tolerated. So the bottom line is that another ADC may get your attention. I think that's worthy of discussion for anyone who needs another novel treatment. It's time to discuss, perhaps seek these trials out.

So in the time I have left, I'm going to quickly talk about the algorithm for hormone receptor positive, HER2 negative metastatic breast cancer treatment. This is actively getting updated all the time, and you can see that the green, the first row is pretty standard frontline treatment CDK 4/6 inhibitor, first column. And then the second line, moving on. Now we finally have some, I would say, personalized or precision medicine driven approaches. We now have, if patients have ESR1 mutation, they can get oral SERD. If the patients were BRCA positive, which is near and dear to our heart, and Dr. Rimel will touch upon these patients. So the BRCA positive patients can certainly get olaparib or talazoparib.

If the patient's PIK3CA mutation, they have a specifically targeting alpha specific PI3K, alpelisib Piqray. And then good old everolimus is still there, and plays a critical role. And then they have two or three lines of options and can move on. And then if they have to move on to chemotherapy, then it's the space that they can either get standard care capecitabine or consider HER2 low treatment. You can see that the T-DXd in purple, fourth line, is there. Fifth line, sacituzumab govitecan. And more importantly, there are some interesting investigative drugs such as capivasertib. The rumor is that we may get approval later this year or beginning of next year. There's another drug targeting PI3K/AKT/mTOR. And stay tuned for all these red colors, they're investigational.

If I may, I'm going to take a really quick second to talk about two ongoing trials. I'm sure this group is super familiar with PARP inhibitors, it's sort of taking a second hit for this. Cells already carry a BRCA mutation, they're already defecting in BRCA DNA repair complex. And the PARP inhibitor has shown to

have a progression-free survival benefit in metastatic disease in patients who harbor this mutation. And the drug is currently already FDA approved to treat residual cancer after neoadjuvant chemo.

So what else is going on with PARP inhibitor? How can we leverage this drug? So we knew that from the preclinical experiments, It's a busy slide here, but the far left is showing that in the preclinical setting, PARP inhibitor is not only working on DNA repair mechanisms, it can also turn the immune cold tumor to immune hot, perhaps to help the immune checkpoint inhibitor to work better. So there's tons of evidence. And then there's two small trials, including durvalumab in combination with olaparib immune checkpoint inhibitor, and also niraparib, currently in the ovarian cancer space, FDA approved, in combination with PEMBRO that showed an interesting signal.

So at Cedars, my colleague Dr. Monica Mita has run a trial combining olaparib with pembrolizumab. She's still actively enrolling patients. But she opened it up a little bit more, not just limited to BRCA mutated patients. If anyone, through genomic testing, showed HRD, harmonics recombination defect positive, these patients would also qualify. And regardless of previous PARP inhibitor or immune checkpoint inhibitor treatment or not, there's perhaps a second opportunity to re-exercise this combination. So if there's an interest, let us know.

And I have worked with my colleague at City of Hope before joining Cedars. So looking at drugs that can turn an immune cold tumor to an immune hot. So we are repurposing this old drug called ivermectin, since the 1970s being used for parasitic treatment in Africa, worldwide for river blindness. So through aggressive NCI drug screening, preclinical mice models, we found that these agents can turn an immune cold tumor on the left into an immune hot. So after ivermectin treatment, you see these yellow dots are the T cells. So the cells initially were surrounding, they can't enter the center of the tumor, they can't take action. But now, after ivermectin treatment in this mice model, you see lots of tumor infiltration, and then you see the tumor actually getting so much smaller when we combine the ivermectin plus immune checkpoint inhibitor.

And after the tumor disappears, when you're rechallenging the tumor in the bottom right, when you're rechallenging this tumor with a mice patient, you find that the actual tumor cannot grow. So that is very interesting, intriguing. We were funded by Gateway Foundation to run this phase one clinical trial. We're actively looking for patients. So it's oral ivermectin plus the intravenously PD1 inhibitor called Balstilimab. So I'm going to stop here. Thank you so much. I hope I didn't talk too fast. Thank you.

Eve Kleinerman:

Thank you so much, Dr. Yuan. It was wonderful. And I'm now going to welcome Dr. BJ Rimel.

Dr. BJ Rimel:

Hi, thanks for having me. I'm going to share my screen, hopefully I get it right. Did it work?

Eve Kleinerman:

Yes. Perfect.

Dr. BJ Rimel:

Hooray. It's always the miracle part of the talk. So I'm going to give a very brief ASCO 2023 update. In ovarian cancer, we have, obviously we have a lot less patients, and so we have a lot less to talk about, especially as it relates to ovarian cancer. We had a very exciting trial come out this year that led to an FDA-approved drug. So I'm going to share that single trial, but try to hopefully break it down into its

pieces, talk about why this trial is important, what's different about it compared to some other clinical trials, and a little bit about the drug toxicity. And in all fairness, I got these slides from my very dear friend, Dr. Kathleen Moore, who is actually the principal investigator of this international trial.

So as Dr Yuan excellently mentioned, we have antibody drug conjugates. And these are really paradigm shifting new molecules. So as she mentioned, antibody drug conjugates are these amazing molecules that have both chemotherapy attached to a molecule that binds to a protein of interest. So anything that's expressed on a cell that you don't like, you can target this particular drug to that cell. And that's really where the magic is. And in GYN oncology, what we're seeing is that our treatments are becoming more individualized. We have PARP inhibitors for patients that have BRCA mutations or homologous recombination deficiency. We have immune checkpoint inhibitors for our patients with endometrial cancer that are MSI high or mismatch repair deficient. We have these new antibody drug conjugates that are really our new frontier, and they really allow us to target specific tumor antigens. So it's specific proteins that are hanging out on the cell surface membrane that allow us to unlock that cell and dump drugs inside.

So these are what they look like. As Dr. Yuan already mentioned, you have this Y. At the top of the Y, really where the binding sites are, they bind to the surface of the cell. The link is the thing that breaks off in the cell and dumps the drug inside. And the goal is that when you dump the drug directly into the cell, that you get less systemic toxicity. So hopefully what happens is cancer cells die and the patient feels better than they would on regular old intravenous chemotherapy, which isn't really targeted.

So onto the fun stuff, this is ASCO 2023's Phase 3 Mirasol study. Mirasol was combined with two, the European group as well as the American group. And the name of the drug is called Mirvetuximab soravtansine, or you can call it just Mirv for short, because otherwise it takes a really whole lot to say. This was for epithelial ovarian cancers and primary fallopian tube cancers. They look the same under the microscope, they all get lumped together. And they all, in this particular study, had to have expression of high folate receptor alpha. So the protein of interest, the thing that Y binds to, was folate receptor alpha.

So why did we do this study? Because unfortunately, for ovarian cancer, metastatic disease is very difficult to treat, and we have not been able to realize an improvement in overall survival for the last 30 years of research. And so we've not had a phase three study that demonstrated that. And this is the first time that's changed. It turns out that folate receptor alpha is expressed on most ovarian cancer cells and highly expressed in at least 35% to 40% of primary ovarian cancers of the epithelial subtype. And previous studies had demonstrated that this was true. Folate receptors are not new. We were super excited about it, and thus this study became a real thing.

So folate receptor as a targeted oncology, as I said, is not new. And if you are an ovarian cancer person, you know that these old drugs, pemetrexed used to be a big thing, and that's supposed to target folate. We use methotrexate, which is supposed to target folate. There's tons of things that we've used in the past, but none of them have been quite as targeted as this new agent. And so this research is really focused on using this particular highly expressed protein to find drugs to attach to it. So Mirasol is the study, the patient population is that they had to have recurrent endometrial cancer and they had, or pardon me, recurrent ovarian cancer and they had to have folate receptor high platinum resistant ovarian cancer. So the baseline, they were randomized between Mirvetuximab and the investigator's choice of chemotherapy. So the patients, some were BRCA positive, some were not. That wasn't required. But about 13% of the patients were BRCA positive. Most patients had a primary platinum free interval of less than 12 months. So they were mostly platinum resistant, and they were stratified by whether they had previously received different kinds of chemotherapies. And I think it's important to note that most of the patients in this study had received prior bevacizumab. Bevacizumab's brand name

is Avastin. Bevacizumab is an anti-angiogenesis antibody that is commonly used. And there were some questions about whether these patients would be able to have the same level of effect with this new drug because they'd previously seen a different antibody. And most patients have had three or more prior lines of therapy.

So what we see is our primary progression-free survival, the investigator's choice chemo, the median progression-free survival was only 3.9 months or about four months, which is not uncommon or unexpected. But with the patients that received the Mirv (Mirvetuximab Soravtansine,) which is that alpha folate receptor, they had an improvement in progression-free survival of five and a half months, 5.6 months. This doesn't maybe seem like a huge change, right, 3.9 months to 5.6 months? But you see that those curves separate and they stay separate, which means that really, even if they had to go off drugs, that progression-free survival benefit was still realized. But what's kind of even more important about that is the overall response rate. So what's really lovely to see is that overall response rate is really when we're asking, did the drug make the tumor go away? Did it make it go all the way, that's a complete response, or partially away, that's a partial response? Or did it just stabilize it, the cancer didn't grow, or did it progress, the cancer grew?

So in this study, what's really exciting is that of all the different kinds of chemo that were tested, none of them caused a complete response. So for those patients that received investigator's choice chemotherapy, there were no complete responses. The tumor didn't go all the way away. But for the new drug, the mirvetuximab soravtansine, it did. And so 5% of patients had a complete response, which is really radical and very exciting. Partial responses were almost 40%, 37% in stable disease, and 38%. So the clinical benefit, the amount of people that actually really benefited from this is really pretty exciting. And so the overall response rate is highly significant compared to the two arms.

You can really see this in what's called a waterfall plot. Waterfall plots look like waterfalls, they're supposed to. And basically the patients whose tumors respond are below the line, in this case they're orange or on the right side. And in the case of the investigator's choice chemo, they're blue. And what you can see is those patients whose tumors grew go above the line. And there are more people below the line, and that makes us really happy. So the more people we can get whose tumors shrink, the happier we are. And you can see that it seems to be a lot better with the mirvetuximab compared with the investigator's choice chemo.

So one of the things you have to do in a clinical trial is make sure you're right because bias obviously could make you think that a drug is better when it really isn't. And so they do this thing called BICR or blind independent clinical review. So they looked at all the investigators who put patients on the study and they said, did it really shrink? Was it really better? And so even with a blinded review of all of the data, they came up with pretty much the same thing. So 4.3 months for investigator choice chemo versus 5.9 months for mirvetuximab, which is almost exactly the same, which basically says that the investigators who were doing the trial did their best, and the blinded independent review people said that they agreed.

Okay, so here's where it gets very, very exciting. So overall survival. As I mentioned at the beginning, we've had 30 years of no improvement in overall survival in platinum resistant ovarian cancer, but now we do. Mirvetuximab demonstrated an improvement, a statistically significant improvement in overall survival between these two curves. So mirvetuximab, remember, is orange, and the investigator's choice chemotherapy is blue. And you can see that these curves are different. They separate and they stay separate, which means that it's a durable change in overall survival. So this drug seems to benefit some people, and the people that it benefits seem to live longer. And that is the whole goal. So you can see the

P value is really strong. And so how much longer did they live on average? They lived about three, four months longer.

Okay, remember I said that the bevacizumab question was, we don't know if patients that get the mirvetuximab are going to do as well if they've had prior bevacizumab or not. And so the investigators predetermined that they wanted to take a look at that question. So they had the statistical power to take a look and say, can I answer this question? So they divided people into people who've never had bevacizumab and folks who have. Folks who had never had bevacizumab had a better response, meaning a longer progression-free survival than those who did not. And we don't really know why this is, we can hypothesize a lot of things, but we just know that in this setting it's kind of interesting. So we're thinking about maybe we should use this drug before we move on to things like bevacizumab.

This is the efficacy summary. So, compared to the investigator's choice chemo, mirvetuximab demonstrated a 35% improvement in progression-free survival, with a hazard ratio of 0.63. If you're super into statistics, we could talk about that. We talked about how it improved the overall response rate. So the chance that the tumor would shrink is 42%, versus 16% with standard chemo. And there was a 33% improvement in overall survival, which is probably the most important point. This drug seemed to help people live longer, not just live longer without disease, but live longer. So that's exciting. We will learn more about this bevacizumab question as we do more experiments.

How safe was this drug? Well, it had some issues. So when we talk about how safe a drug is, we divide how bad the side effect is into grades, grade one being the mildest. Grade 3, 4, 5 being the worst. And basically we can say that this particular drug had some pretty significant side effects that made people feel pretty rotten. In fact, ooh, it's doing weird things, we know that 91 people had grade three or higher adverse events. But that's actually about the same as it was in the investigator's choice chemo arm because chemo also gives people some pretty ugly side effects. So it's really about the same. And then how many people had to turn off the drug because they were too sick? It was a little bit less actually in the mirvetuximab group compared to the investigator's choice chemo. So we're not seeing something that's so much harder to take than chemo. The effects are pretty similar.

So from a safety standpoint, we want to look a little bit at the main kinds of safety things that we saw. So we saw some of the classic problems with bone marrow counts, such as neutropenia, low white blood cells, anemia, low red blood cells, thrombocytopenia, and low platelets. We also saw some numbness and tingling in the hands and feet. That's called peripheral neuropathy, which is very common with these kinds of things. And alopecia, which is hair loss. Gastrointestinal, we saw some diarrhea, nausea and mouth sores, which we call stomatitis.

But we saw something new that everybody was a little bit sort of excited about in GYN oncology because we saw ocular toxicity. And for gynecologists, the eyeballs are very far from our normal organs of choice, and we were very distressed because we had to learn all of this new eyeball medicine that nobody knew about. So this is a very big deal for us. Keratitis or keratopathy, blurred vision and dry eyes were the main things we saw. So those are irritations of the eyes, dry, itchy, scratchy eyes, and even some vision changes. Thank G-d all the patients that had vision changes were able to have a complete reversal after stopping the drug. Very important.

Okay, so what does it mean that we had all this ocular toxicity? It means that we need to learn and to support our patients with some preventative eye drops. So what we learned was that we needed to give lubricating drops as well as corticosteroid drops. And so everybody who gets on this drug gets to see the eye doctor before we start to get a baseline exam, and then after cycle two. When needed, we made

dose modifications so that the eyeball stuff didn't get too bad. But very few people actually quit the drug because of eye toxicities, which I think is really important.

Okay, so what are the conclusions? We're in the home stretch, my friends. So the conclusions for this particular trial is that mirvetuximab soravtansine was the very first treatment to demonstrate an overall survival benefit in platinum resistant ovarian cancer in a phase three trial. This is very exciting for us. We know that it demonstrated statistically significant and clinically meaningful improvement in progression-free survival, overall response rate and overall survival compared to standard chemotherapy. And it gave us some different kinds of toxicity than we would expect to see with standard chemo. Some of it is better, little less neuropathy. Some of it is worse, now we have eyeball toxicity. And this is what we're seeing. It is the first antibody drug conjugate for ovarian cancer, and now the only FDA approved biomarker directed therapy for platinum resistant ovarian cancer.

So these are the kinds of practices changing in our world. We're doing a lot more of this now. We're giving a lot of this in our clinic because we understand it better and it really provides a brand new line of therapy for patients. So we're very excited. All right, thank you. This is a picture of the Michigan Beach shoreline, which is my happy place. And I look forward to all of your questions. And I'm going to stop sharing.

Eve Kleinerman:

Thank you so much, Dr. Rimel and Dr. Yuan Yuan. It has been so enlightening, and you both have taught us so much. We have received a fair number of questions for both of you tonight. But before we begin with the questions, I do want to remind everyone that the information that is provided tonight by the webinar, by both physicians, is not a substitute for any medical advice or treatment or for specific medical conditions. You shouldn't use this information to diagnose or treat a health problem. And if you do have questions that are specific to your medical care, the doctors may not be able to advise regarding those specifics, but they would advise that you speak to your own medical provider.

With that being said, I do want to jump in to some of the questions that we had for both of you tonight. And you can choose who responds to what appropriately. One question that came up, and I believe this was touched upon a little bit when discussing the BRCA positive patients. But are there any new maintenance findings for those who are BRCA negative but facing ovarian cancer?

Dr. BJ Rimel:

I'll take this, since it's an ovarian cancer question. So maintenance strategies for BRCA negative folks, that's what I heard. Okay, so for BRCA-positive people, obviously we have PARP inhibitors. For BRCA-negative people and homologous recombination negative folks, we have a bit of a conundrum. So we can give bevacizumab, which I mentioned is an anti-angiogenesis antibody, that is used in maintenance therapy and provides a median progression-free survival or more time without cancer of about three and a half months. Alternatively, we can give niraparib, which is a PARP inhibitor, which actually is still approved for homologous recombination deficient and BRCA negative patients, which provides a median progression-free survival of three and a half months. So you can kind of pick your favorite. You can also pick to do nothing. Some patients decide that three and a half months is simply not worth it, and the side effects are too great, they prefer to do other things. And we support that as well. But those are our two options for BRCA-negative homologous recombination deficient patients.

Eve Kleinerman:

Thank you so much. And I believe Dr. Yuan, this might be for you. We did get a couple of questions regarding dense breasts and screening. For those who are recommended to do screening, specifically let's say every six months, alternating various types of screening, but have been found to have very dense breasts, not only just dense breasts, are those screening modalities still going to be accurate for those types of patients?

Dr Yuan Yuan:

Great question. For those with dense breast tissue, I think most of the patients are screened with alternating mammograms with MRI. So MRI, regardless of how dense breast tissue is, it's actually probably the most beneficial test out there.

Eve Kleinerman:

That's great. And again, sorry Dr. Yuan, I believe that you did touch on this a little bit, but just to clarify. When we're talking about olaparib and those who are BRCA positive, are there any further survival statistics or information for those patients who are on that drug?

Dr Yuan Yuan:

Two settings. So for metastatic setting, the phase two, phase three trial did not show overall survival benefit. I don't believe there's any recent update. I think it really reflects the options they have, they probably go on to receive other treatments. And it's kind of difficult to tease out the overall survival benefit in these patients. But the bottom line is, if the drug is truly phenomenal like mirvetuximab, it's going to pan out. The signal will translate not only to progression-free survival, it will also translate to overall survival. But in our PARP inhibitor breast cancer trial, in the metastatic setting, we did not see overall survival benefit. But in the early adjuvant setting, for patients who underwent neoadjuvant chemo, had residual disease, this is actually only referred to triple negative or hormone receptor positive disease. So the HER2 positive BRCA positive is a unique entity no one had studied. But for those patients, there is an overall survival benefit of doing the one extra year of olaparib.

Eve Kleinerman:

That's great, thank you. And one consistent theme in many of the questions that we received is regarding some of the side effects that come from many of the drugs that are on the market. Was there anything that came out through ASCO that talked about new drugs that might be on the horizon that have lower levels of those side effects?

Dr Yuan Yuan:

It's a broad question, if I can tackle it. For example, Patritumab, the HER3 ADC we discussed earlier, it's the same payload of deruxtecan, but it's targeting HER2. It seems to have a lot less toxicities. Some of the toxicities are so challenging. I had a patient that I vividly recall who read about the TDXd, or trastuzumab deruxtecan information. She said, "I'm not going to get on it." I was like, "Why?" "Because there's a potential risk of ILD. It's scary." So I think, compared with that drug, the HER3 ADC seems to not have a major concern. And the mirv, it's challenging GI toxicity.

I think in the breast cancer world there's a lot of other ongoing trials, and each single one of them seems to have a unique toxicity. So the daiichi compound, one of them is Trop-2 targeting, but deruxtecan payload. It's called Dato DXD. And that drug is also unique. It's different from the other two deruxtecan

payload ADCs. So it can potentially cause oral mucositis, the patient can have mouth sores. So we don't understand, was it because the mucosa has an expression of Trop-2? But why are we not seeing it in sacituzumab govitecan? So I think we're still in the rudimentary phase of understanding the toxicity, but I think the trial data does give us different flavors of things. So that's why I think when we have all these tools available in the clinic, it will be a lot of personalized decision-making and discussing with patients according to their treatment history, their current symptoms or their wishlist. So there's a lot of wiggle space, I think. But in general, ADCs are not toxicity free. That's the message. Although they sound very targeted, very sexy, they are not spared of toxicities.

Eve Kleinerman:

That makes sense. And then for both of you, one question came in about what role molecular testing is playing in treatment decisions in both of your offices, in your facilities?

Dr. BJ Rimel:

So for ovarian cancer, the next generation sequencing is more limited, I think, than what's available in other cancers. We have certain things. But the issue for us is, it's BRCA, HRD, folate receptor. There's a couple of other NTRK mutations and other kinds of really spicy cool things. But beyond that, it's not a huge play, but it's more than it was five years ago. So I think that we're going to continue to see stuff happen over time.

Dr Yuan Yuan:

Yeah, if I may make a comment about breasts. We are far behind compared with lung, but we're making progress. We now have the liquid biopsy or tissue NGS, next generation sequencing. We can identify ESR1 mutations that we mentioned in our treatment algorithm. We have PIK3CA mutation driven drugs, HER3 mutation, HER2 mutation, and then the IHC level will have HER2 low. So I think we're getting a little bit better, but a lot of times, patients go through those tests, then come back without any actionable mutation. So just to bear that in mind, not everything we send will come back with a treatment solution. Sometimes they're very frustrating, we don't have that. So it's definitely making progress, compared with five years ago.

Eve Kleinerman:

Thank you. Well, that concludes our question and answer portion of the evening. And I want to thank both of you, Dr. Yuan Yuan and Dr. BJ Rimel, so much for educating us this evening. I know that you answered so many of my questions, and I am sure that many of our participants feel more knowledgeable after hearing your presentations this evening. As a reminder, in just a moment, we are going to begin our special bonus breakout room for the Embrace community for those facing metastatic breast or advanced ovarian cancer. Anyone who is facing advanced disease is invited to stay on for this intimate breakout session with Dr. Yuan Yuan and Dr. BJ Rimel and Bonnie Beckoff, Sharsheret's Director of Support Services.

Before you transition to that, if you can please take a moment to fill out a brief evaluation survey that's linked in the chat box now. We appreciate it. Evaluations really do inform our future programming, so we thank you for participating. And we'd love for you to stay connected with Sharsheret via social media where we post about events like tonight's webinar, as well as additional program updates and various ways to get involved. On that note, we would love to have you all join us for our 2023 Sharsheret's Summit, which will be this October, from the 13th to the 31st. This event, which is nationwide, both

virtual and with in-person programming across the country, brings together thousands of individuals virtually and in person in Sharsheret's marquee educational event. The link to explore the programming that we have available during that summit period is now being linked in the chat box as well.

I also want to, again, thank our sponsors for tonight's webinar, GlaxoSmithKline, Daiichi-Sankyo, Gilead, and AstraZeneca.

And please do not forget that Sharsheret is here for you and for your loved ones. Sharsheret is here to provide emotional support, mental health counseling, and other programs that are designed to help you navigate through your cancer experience. All of our programs are free and completely private and one-on-one. The contact information and where you can reach out to us has also, again, been linked in the chat box. Our social workers, our genetic counselors are available to each of you. And you are a priority, so please do not hesitate to reach out. And now we are going to transition into our Sharsheret Embrace breakout room.