**Program Title:** Advances in Ovarian Cancer Treatment
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**Guest Speaker: Thomas J. Herzog, MD**
Dr. Herzog is Deputy Director of both The Barrett Cancer Center & The University of Cincinnati Cancer Institute. He is also Vice-Chair of Quality and Safety for Obstetrics and Gynecology, University of Cincinnati College of Medicine. From 2004 to 2014 he was the Director of Gynecologic Oncology and the Physicians & Surgeons Endowed Professor of Clinical Gynecology and Obstetrics at Columbia University. He also was the Fellowship Director in Gynecologic Oncology for Columbia & Cornell Universities and New York Presbyterian hospitals.

Prior to 2004, Dr. Herzog was as an Associate Professor, and the Director of the Fellowship Training Program at Washington University in St. Louis. He has served as a Principal Investigator in a number of GOG trials with a special emphasis in ovarian and endometrial cancers.

Dr. Herzog has authored/co-authored over 270 peer-reviewed articles and lectures extensively nationally and internationally. He serves or has served on the editorial boards of Gynecologic Oncology, Obstetrics and Gynecology International, Hematology Oncology Times, and others. He is Co-Editor–in chief of Gynecologic Oncology Research to Practice.Dr. Herzog has been on the leadership council of the Society of Gynecologic Oncology, the Foundation for Women's Cancer, Board of Governors for the American College of Surgeons. In 2013, he was elected to the Board of the American Board of Obstetrics and Gynecology, and in 2014 to Council for the International Gynecologic Cancer Society. In 2015 he was elected to the Board of Director of Gynecologic Oncology Group Foundation.

**Topics:**

- The latest info on the development of drugs for advanced ovarian cancer
- Other novel chemotherapeutic agents in development
- Advances in immunotherapy
- PARP Inhibitors
- The role of molecular profiling
- Info from the Cancer Institute Survivorship Survey
- What do patients want?

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**Robin Perlmutter:** Good evening, everyone. I'm Robin Perlmutter, peer counselor here at Support Connection. I would like to welcome you all to our annual nationwide ovarian cancer webinar in honor of Ovarian Cancer Awareness Month. Remember that Dr. Herzog is sharing his expertise. Any information from tonight or questions pertaining to individual concerns should be discussed with your doctor. It is with my great pleasure that we have Dr. Thomas Herzog, Deputy Director of both the Barrett Cancer Center and the University of Cincinnati Cancer Institute. He's also the Vice Chair of Quality and Safety for Obstetrics and Gynecology at the University of Cincinnati College of Medicine. Dr. Herzog is a National Institutes of Health and American Cancer Society funded researcher with over 200 published manuscripts. Thank you, Dr. Herzog, for sharing your time and expertise with us tonight.

**Thomas Herzog:** Robin, thank you so much for having me. It's great to join everybody in the midst of Ovarian Cancer Month and certainly I look forward to getting through some of this material. I'm going to try to hit some high points and get into some deeper dives on some data. So if I'm losing you, they're in there but I'm going to quickly get out of that. But a lot of people are extremely informed about this disease and I don't want to do the totally superficial materials as well. So we'll do a little bit of both here so hopefully everybody has something - hopefully a little bit of something for everyone so to speak.

Let's start a little bit and talk about the natural history of ovarian cancer and unfortunately as many people on this call know, the majority of patients are diagnosed, a little over three-quarters are diagnosed

at stage III or stage IV meaning the disease is in the upper abdomen at the time of diagnosis. And with that we see an - we speak in terms of averages but of course that doesn't predict how any one person's going to do. For some people they go through that initial surgery and chemotherapy and the disease never comes back which is wonderful.

But for many others the disease does come back and it can either never responds very well to up front surgery and chemotherapy or indeed it comes back many, many years later or something in between. And so that's certainly a different experience for different patients that they go through in terms of the natural history and the timelines that we see. Nonetheless up to 70% of these patients will relapse and have advanced disease and then of course they're divided into platinum sensitive and platinum resistant depending on how long it's been since they were treated with platinum and responded and we then get into looking at a number of other treatments that can go down the cycle.

So, I think one of the things to really think about tonight is really where is our progress coming from. I think the next button that's depicted in this slide I think captures it well for me and that is clinical trials. Clinical trials have certainly played a major role in our progress and if we look over time here, not necessarily getting caught up in what the modality is but we have seen improvements in survival. So much so that we've now been able to push the five year milestone, we've been able to push the averages of those curves out beyond that for many, many women. That's wonderful news. What we want to do is cure more women with ovarian cancer is really the ultimate goal. Nonetheless we feel that some of the work we've done with looking at clinical trial endpoints has made a significant improvement in terms of the investment and the role of drug development in this space.

So we went a long time, really almost 16 years without any new approvals and then we had one conditional approval in 16 years and many people thought that was due to the fact that there was a misunderstanding to what the bar was for getting approval. And so we fleshed this out a lot with the FDA and with some of the regulatory authorities and I think we've been able to make some progress in this area and this progress I think has been very, very helpful in terms of the number of approvals we've had with now five approvals here in the last three to four years. So it's been much more productive.

I think many people understand how drugs are developed and before we dive into some of the things, I think it is important to understand this process in the sense that Phase I trials, of course are really with the goal of figuring out what the right dose is, Phase II is figuring out if there's any activity in a specific disease, and then Phase III of course is to see if it indeed is better than what the current standard of care may be. And then we can do additional work after approval to sort of hone in the best place to use the drug or the best dose and so forth. Those are the things that I think certainly makes a difference.

So I think one of the things that is of interest to the group tonight is how do we move to precision medicine where we give the right drug at the right time to the right patient. The real goal that's depicted on the slide is where we're able to interrogate the tumor such that the patient who's orange or blue gets the orange or blue pill and thereby has a better outcome. And so it sounds great. It certainly has garnered front page news - New York Times, Wall Street Journal, covers of Time magazine and others. But what is the reality and where do we stand right now?

Well, we are making forays into this area and I think these initial steps have been very successful but obviously we need to continue to do better. Certainly the first area that's been of great interest has been the whole concept of BRCA deficiency where we've been able to find that those patients who have a mutation, either germline or somatic, have a different outcome and in terms of the frequency in the population we feel that certainly if we include those with known HRD genes and so forth we're looking at well over 33% to 40%. If we take those folks out we're still looking at probably 25% to 30% that fall into this category. So that number continues to be important.

From a therapeutic standpoint we certainly will get into that in a little bit but from a prognostic standpoint you can see that the patients who carry these mutations do better. Why is that? We believe that's due to the fact that DNA-damaging drugs are very effective in being able to cause cell death in the cancers. And so they tend to live longer, respond to more treatments, and so forth. So that certainly makes a big difference as we move forward.

So as we look at this and as we look at this idea of moving to precision medicine and one of the things I think that you have to ask yourself is why have we - how have we gotten here and what else do we need to do? Because clearly we're not there yet. We don't have the orange pill in all cases that's going to be able to cure the orange tumor and I think that's important to understand. But we are making a lot of advances. And it's been - it's really been built on a multitude of platforms. Some of these are really due to the ability to do DNA sequencing at a cost that is a couple of log scales less than what it was even five years ago.

We're getting down now where we're very close to being able to do complete genomic sequencing for less than $1,000 right around the corner. So this is something that costs hundreds of thousands of dollars not long ago. This is something that's very exciting. We also have out of the sequencing comes a real burden of being able to interrogate big data. And so one of the big problems has been what do you do with all this data? How do you analyze it? And how do you tell what is really a true signal versus the background noise? And that's really been a big problem. So it's our ability to manage big data that I think has really played a major role in being able to do this.

So as we look at this, lots of different platforms that have been important and our understanding of molecular biology has improved. We have a better understanding of what these pathways are and do and what's relevant and what's not and where there are redundancies and where there are not and so there's a lot of things that have been very interesting. The development of the bio informatics as I said but also the development of biomarkers and companion diagnostics has played a big role, a better understanding of how doses and exposures change gene expression has played a big role as well. So there's been a number of things again that have really looked at how do we interrogate these tumors and how do we go after them?

Now one of the things that always comes up and certainly we'll touch upon some classes of drugs and we'll probably touch upon some individual agents, but with an audience like this there's a great interest in what's right around the corner. What is the next best thing? And I have to tell you, part of it being grizzled and old, I have seen a lot of things that were the next big thing.

And so my answer to that is always we just have to follow the process. And I understand the perspective. If you're sitting where I'm sitting versus where you're sitting, that can be very different in terms of what you say, what your demands are for trying to accelerate the process. And I completely understand that and I'm sympathetic to trying to do that and I've spent some of my career trying to do that. Because I do think the process is too slow.

The slide depicts what we consider the hallmarks of cancer and so out of this is really where most of the new compounds are coming. So certainly EGFR inhibitors you've heard a lot about. We're now spending a lot of time developing Cyclin-dependent kinases that can be inhibited with various drugs and these are responsible for evading growth and tumor suppression. So these look very promising.

We'll talk a little bit about some of the immune oncology agents that are out there. There's a lot of other different things, as you can see here, a lot of other different pathways that are certainly of interest. There at 7 o'clock you see the inhibition of VEGF with things such as bevacizumab or cediranib and those types of things. PARP inhibition we'll talk a little bit about. And you can see a lot these different things that are really being looked at in terms of how do we get to this individualized medicine approach.

So what are some of the pitfalls? So everyone gets excited about this but what are some of the barriers and what are some of the things we face? And I brought one of them up and that is that when we interrogate these genes we see so many changes in gene expression, so many pathways that are upregulated. What is the cause and what is the secondary effect? That is a really important principle as we go about trying to figure out what drug or what pathways need to be interrogated or changed to effect an outcome that's going to improve the condition of a patient with cancer. So it's not as straight forward as you would think. It's extremely complex. And it's an area that I think we're really starting to gain significant insights that will pay off significantly in the very near future here.

Immuno-oncology, one of the problems there is sampling. So we are so used to sampling - what? The tumor. So we sample what goes on in the tumor. We look for a viable tumor to sample and then we sequence that or we interrogate that. But that doesn't have anything to do with what's going on around the tumor. So a lot of the immune effects are actually what surrounds the tissue. So it becomes extremely important for us to get an idea of what's going on in the surrounding tissues are often referred to as the stroma.

And so that becomes very important but it's a new principle, to biopsy normal surrounding tissue around the tumor. These things are starting to become more important. Lots of ideas, lots of things out there. But how we validate them is really I think one of the things that's really important. We've certainly as I always say, cured cancer multiple times in mice, but we need to be able to do that in humans where there's an intact immune system. So this validation system is something that's really important.

Another problem is tumor heterogeneity. What is that? It comes in two forms, right? One is spatial meaning it's just where the tumor is. So if I take a biopsy from the ovary in a patient with ovarian cancer I may see genetic changes that are actually different than I would if I took it from the fatty apron that hangs down from the colon. You may see a very different type of gene expression pattern. The other thing is what about time? What if I took the biopsy of your tumor but now you had a recurrence, what if I took a biopsy from your recurrence? Would they be exactly the same? Well, many features would be the same but many would not. There's quite a bit there that one needs to consider in terms of really trying to put those together because I think that it can be challenging to necessarily assume that things are going to stay the same when we have good evidence that things do change significantly. So where possible, if we are trying to do something in a genetic sense, it’s better to get the most recent tissue that we can possibly get if that's possible. That's not always possible. Sometimes we rely on that original tumor.

I wanted to give you a little example of how we are personalizing some of this. We have a better understanding now that these tumors are very different based on cell type. So we know that serous and endometrial tumors tend to do a little bit better than those that are mucinous or clear cell for example and we know there are very different genetic mutations that are present.

So this is an example of a gynecologic oncology group trial where they said mucinous tumors in the ovary, treated like traditional ovarian cancer with agents like carboplatin and paclitaxel don't do as well. So maybe we should use a regimen that looks more like a colon cancer regimen. And indeed that's what was designed here. There's a real interest in doing this, not only with mucinous tumors but for example low-grade serous tumors where we think that the PI3 kinase mTor pathway as well as BRCA mutations are extremely important.

And so the FDA workshop that we did on behalf of the SGO listed all these trials that you can see on the left hand column that were all really aimed at some of the unique cell type that we see under the microscope. You see mucinous, you see low-grade serous, you see clear cell. And these are the ones that we struggle with because traditional chemotherapeutics are not nearly as effective. So we're looking at other agents, often taken from other tumors such as renal cell tumor in the case of clear cell carcinomas that have shown real promise and have been incorporated into clinical trials in terms of really where

we're going from here. So certainly very interesting as we move forward with these personalized medicines.

But really what are we trying to accomplish? Obviously we're trying to have a better outcome. We're trying to improve efficacy. The toxicities are different. I think the first glance of this was that we would potentially have less toxicity and in cases of these targets agents, there's a lot of unique toxicities that are different than chemotherapy but they are significant and for us to just say, well, they're targeted and therefore they won't affect the rest of the cells in the body is not accurate unfortunately.

Now hopefully we will get to targeted agents that are ever more targeted and do not effect normal cells but for right now we still see some changes. So while we get less myelosuppression, less neuropathy and hair loss we get things like hemorrhage or DVT or eye changes or bowel perforations. The list goes on and on. MDS and some other things that are extremely disturbing.

But nonetheless it's extremely appealing to try to hone in on what the underpinnings of a tumor are, try to attack that mechanism. That's really I think the most exciting part of what's going on in ovarian cancer right now. There's a tremendous amount of interest in this area. The challenges I think I've mentioned already.

So how does this play then? How do we look at this? These are a compilation of GOG trials. This was the GOG 170 series. These are a mixture of platinum sensitive and platinum resistant patients. So you can see the different types of drugs that are out there and I share this with you just to give you an idea of what we look at and what we're really looking for are two primary endpoints. One is the response rate and the other one is the percent that are progression free at six months.

And you can see the one that really kind of hit it out of the ballpark there was bevacizumab. I think most of you are familiar with this drug and have seen it used and so this led to a pretty big investment in terms of adding bevacizumab into a number of the trials here in the United States as well as worldwide and as well as the development of other drugs that inhibit new blood vessel growth. So these drugs are antiangiogenics. They keep new blood vessels from forming.

And you can see here I've grouped these by line of therapy. So GOG 218 and ICON7 which is a European trial were both frontline trials and AURELIA and OCEANS and now we have GOG213 are recurrent trials with AURELIA being platinum resistant, OCEANS being platinum sensitive and GOG213 being platinum sensitive. And the list goes on and on with different agents. So you have nintedanib, pazopanib, cediranib, trebananib, all of which have been developed in this area as well. You can see they have different targets.

Nonetheless one of the themes that we've seen with these agents has been an improvement in progression-free survival that's been statistically significant. And that's true whether we've been in the frontline setting or the recurrent setting. But we haven't necessarily seen that translation into overall survival with the exception of the GOG213 trial which was the borderline and the AURELIA trial was an improvement as well. But generally speaking it's been difficult.

Now part of that's due to crossover. It makes it harder than to really to show that difference because we treat with other drugs that are active. So it obscures the benefit that we might've seen when we divide into two groups, the second group that didn't get the experimental drug then gets another drug that's very good subsequently. It can catch up if you will in terms of survival or at least blur that difference to the point that we can't see it statistically. So those are some of the concerns that we see.

Nonetheless, in my mind we just need agents that are even more active that cause bigger changes in outcome so that we are able to preserve the overall survival effect. We do recognize though it is very challenging but extremely active agents have a good chance of being able to do that.

Now what about all this immuno-oncology talk? What is this all about? Well, as you know, earlier this summer there was approval for pembrolizumab for all micro satellite instability high tumors. What is that? These are tumors that have mismatched repair deficiencies and we're able to test that genetically. And it does include a small percentage of ovarian cancers and a very high percentage of endometrial cancers as well as cervical cancer. So this is an area that's gaining interest. It's an area that we're also very interested in with combinations. So PARP inhibitors along with these immuno-oncology drugs appear to be very promising. We'll talk a little bit about that.

But basically what we're doing with these checkpoint inhibitors is we're tricking the immune system into seeing the cancer as a foreign object. Well, you say, why would you have to do that? Isn't cancer foreign? It is but the cancer has already tricked the immune system into thinking that it's not. So that's really what's going on here is that cancer played a trick on your immune system, well, now we're playing a trick on the cancer and making the cancer identifiable to the immune system. So there's a lot of - we could spend 1.5, 2 hours going over some of the mechanisms involved with this and it's extremely interesting work but it gives you some idea of what's out there.

I'll give you a little overview of where we stand with these agents. One key area is blocking either PD-1 or PD-L1, the ligand. That's one way of doing this and that's again the cancers use that pathway to try to disguise themselves as normal. We unmask that disguise and then the immune system can see them, we rev up the immune system and there's a number of ways we can do that and then we bring in the cytotoxic T cells and the helper T cells and so forth and they're able to envelop the cancer and kill the cancer. And I have some of the agents that are down there whether you're going after the CTLA4 receptor or PD-L1, PD-1 pathway. You can see some of the different agents that you may have heard of that are in the small box at the bottom.

So lots of development in this area, most of the major pharmaceutical companies have at least one immuno-oncology agent or IO as we call them. So it's getting quite interesting as we move forward. Certainly, this is just to give you an overview and I'm not pitching for any of these. But just to give you a little bit of a taste of what's out there right now and where some of the approvals are and believe me, these approvals are changing so fast you almost have to update this every other month. Because there's so much going on in this area. But I wanted to give you a little bit of a flavor of what these agents are doing or what some of the more common agents that have been reported are doing in ovarian cancer.

And so we haven't seen wildly effective numbers in terms of response rate. However, we have seen some responses that have been interesting where we've had heavily treated patients who have responded to these agents in terms of not progressing. And so there's different - there's actually a different system used for measuring response, immune resist criteria that's used because many of these agents are what are known to be cytostatic meaning the cells don't grow but they don't necessarily - like chemotherapy often kills cells. Eventually the immune agents do that but it takes a lot longer.

And so one of the things you want to see is that they're at least slowing tumor growth down and of course they have a unique set of toxicities as well and can be related to inflammation of a number of vital organs including the lung, the liver, kidneys, the bowel and so forth. So certainly something that we need to learn in terms of how to manage these drugs in patients effectively. This particular slide is a busy slide again but it has a tremendous amount of information showing you some of the trials that are out there in different lines of therapy. So these are really taking patients that are after frontline therapy.

There's a number of trials looking at some of the agents there. For platinum sensitive recurrent, if you're recurrent with platinum resistant disease, there are a number of trials out there as well some in combination, some in single agent. But it just gives you an idea of the tremendous amount of interest that is going on right now in the immuno-oncology drugs in ovarian cancer. So very exciting times. As I said, this came out this past year with the approval of Pembro in this patient group. Again, some of the patients are exactly that, patients that really will have MSI high and could potentially be treated.

So let me get to the PARP inhibitors because I think this is a very interesting story and I want to spend a little bit of time on this as well. So one real interest has been how do we - we know that these patients who have these BRCA mutations have trouble repairing double strand DNA breaks.

One of the other phenomenon people have noted is that if you use a PARP inhibitor, of which there's almost 17 isoforms, PARP 1, 2, and 3 being the most active and PARP 1 and 2 specifically being the most active, we see that you actually can't repair your single strand DNA breaks. Remember, you're creating single strand DNA breaks every time you try to replicate. You have to nick the DNA so that it can unwind and then you get the replication fork to come along and so this is a process that's going on 24-7 every day. And in fact there's probably de novo cancers that are arising every day in every patient. That's why the immune story is so interesting because in many cases your DNA is able to be repaired properly or if it's not, your immune system often recognizes this cancer before it can disguise itself and therefore eliminate it.

And so that's why people are so interested in this interaction between the immune system and PARP inhibition. So this idea of using a PARP inhibitor in someone who already has a problem repairing DNA in their double strands is very interesting because if you have an accumulation of single DNA breaks, you get an accumulation of double strand breaks and if they're not able to repair those that results in cell death. And that would be cell death in the tumor. And so that gets into this concept of synthetic limpidity where you have two different pathways that you're targeting and that you're using to help one another in terms of outcome.

And so this is very important in terms of what one sees and indeed there's been a lot of interest in this in the last decade and there's been some fits and starts and then progress and then stops and so forth that have occurred in this field. It's been very interesting in the sense that there were some very interesting programs that were abandoned and then reclaimed and in some cases and others that were abandoned forever even though there appeared to be a tremendous amount of activity. So commercialization and pressure from advocacy groups and all kinds of different factors I think went into this in terms of finally getting to where we are today where we have multiple PARPs, where we have choices.

And so instead of really flashing through, which could probably be over 150, 200 slides I have now on PARP inhibition, I just try to do a summary slide that's fairly up to date. So if we look at this right now you have the big three with olaparib, rucaparib, and niraparib. Veliparib is being tested in frontline in the GOG setting and talazoparib is really being looked at mostly in breast cancer. So if we look at the big three in ovary, it's olaparib, rucaparib, and niraparib.

Now out of those, they all are approved in the US. I can safely say that likely they will all have very similar labels in the near future. Olaparib is approved for greater than third line treatment and just recently off of the study 19 and II date was approved for platinum sensitive maintenance. That's where that fits right now. Olaparib has spent time trying to convert from the capsules to the tablets. Many of you may know that there was a huge pill burden with the capsules with 16 a day. So it was very welcome to get to far less tablets that needed to be taken with better bio viability and so forth.

There's also a program to look at this with a VEGF inhibitor, cediranib. And all these programs are looking at combinations of PARP and other things. I didn't spend a lot of time talking about that in the slide but I do want to mention that. That's one of the things that's probably at the forefront right now. So the PAOLO trial, for example, is looking at olaparib with bevacizumab.

What about Rucaparib? Rucaparib is approved for greater than second line treatment. They just presented their ARIEL-3 data at ESMO this past week for any of you that happened to be monitoring what was going on in Madrid. So that data looked very favorable. They had a press release that came out Friday, I don't know, four to six weeks before. There was some new data that was presented but it looked

pretty good. I think that it doesn't look all that different than what we've see with the NOVA trial and with the SOLO-2 data. In my opinion it will likely get a label in that platinum sensitive maintenance setting as well and so they have a slightly different test that they do, looking at loss of heterozygosity. But they will likely get an approval across the board whether you have a BRCA mutation, whether you have homologous recombination deficiency or whether you don't have any of those.

And so what we see with these agents so far and has been very true with niraparib that I'll talk about in a second is if you have the BRCA mutation, your differences are very vast between the placebo and the PARP inhibitor. So very big differences, 20-some months versus 5 months essentially in terms of progression-free survival. Very impressive in the maintenance setting.

As you move to the genes that are like BRCA but not completely but they have problems repairing their DNA along the homologous recombination pathway, those are known as HRD genes. For those patients, they behave very much like BRCA but not quite as good. And then for those who don't have those genes nor do they have a BRCA mutation, we still see a benefit of PARP inhibition probably because there's other DNA pathways that we have not been able to identify yet that are in play with these PARP inhibitors and it makes a difference. So we're still seeing some good effects and those are good things. But nonetheless I think that as a whole, most thought leaders will tell you they don't see a difference, at least clinically, between these big three that I mentioned, olaparib, rucaparib, and niraparib.

Now, with niraparib, they have an approval not for treatment yet but they have another trial, the Quadra, that's looking at that and they do have an approval for all-comers, platinum sensitive maintenance, very much like we've seen recently with olaparib and what we'll likely see off the ARIEL-3 from rucaparib. They were originally using a genomic scaring test by Myriad and they found that even their all-comer population seemed to have a benefit although the magnitude of effect was smaller. And yet the FDA approved all-comers on that. So we might get into some questions on that and I welcome those but it's been very interesting to watch this. There's been a lot of guessing as to what the labels will look like as the FDA interpret the data and it's been a very interesting time for physicians in this space as well as patients because there's been a lot of changes just in the last year and that's good.

So what are other trials that are driven by integral biomarkers? Well, I just wanted to give you some idea. There's these things called umbrella trial and basket trials and so forth and really what we're looking at are different ways of doing clinical trials which is one of the themes I wanted to emphasize tonight. So we need to change the endpoints. We need to look carefully at what those are so that we can speed the efficiency and decrease the cost of these trials so we can get more done with less and get more patients involved in trials. And we also need to not worry so much that the cancer necessarily started in the ovary. As a clear cell of the ovary, maybe it should be in a trial with patients that have clear cell of the kidney, for example. And I talked about that earlier. Or mucinous tumors, they should be in with patients that have GI cancers that are of a similar stage or what have you or similar genetic changes.

And so I think that these are the things that are really exciting. I think many of you have heard of some of these trials that are here, the iSPY trial 1 and 2, an interesting trial in breast cancer. We now have the NCI-MATCH trial which ovarian cancer is part of. And I wanted to show you a little bit of data from the IMPACT 1 and 2 trial because I think it's very interesting, again, looking at being agnostic, meaning not caring as to whether the tumor started but rather what are the genetic underpinnings of the tumor. So the genetic underpinnings trump the location of where the tumor began.

So this is just to give you some idea. And this was done at MD Anderson but it give you some idea of the number of patients you need to enroll to actually find mutations that are targetable, that you have a drug sitting there ready to go that's FDA approved or at least is in a clinical trial that you can use for this particular patient. So there's a little bit of a spin down on that and we hope that becomes less and less as we develop more agents that are successful. But I just wanted to show you this data because I think it's really impactful. These are patients that received the MATCH therapy based on, they were able to find a

pathway or a gene that was overexpressed, for example, in the cancer, and they were able to target that versus if they just got regular run of the mill chemotherapy. They didn't find anything or they went on to get regular chemotherapy. There's a vast difference in survival there, the two survival curves, with the MATCH obviously being on top, doing much better. So those are the types of things that I think are really exciting.

So that really begs the question then, should I have my tumor tested? I'm not here to do any commercials tonight for that. Lord knows there's enough vendors out there who do this. I do think that it's the future and some will argue the future is now and some will argue the future was last week and others will argue the future is the future. We're not quite there and we haven't validated any of these in terms of showing improved survival in a prospective manner, although that's very difficult. We do have retrospective data and I've been part of some of those studies. I certainly have an interest in this. But I will have to admit that we have not validated this in a way that it needs to be validated.

As we continue to learn more and more about these pathways and these genes as well as develop drugs against these pathways and genes, we will get to a point, no doubt, where this will be a routine part of care. That could be as soon as the end of this year or it could be in two to three years. I don't know. It could be longer. But I will tell you it's certainly part of it. How many of these companies will still be around, I don't know. But it gives you some idea of the competition in this space for doing tumor testing and we could talk a little bit about that and what they're seeing. So there was not an overexpression, there was no vulnerability that they saw that would necessarily work.

Now, again, I have seen these types of reports and I have seen patients that have responded to therapies that weren't supposed to work and I've seen patients who didn't respond to therapies that are supposed to work. So to me we are at the very beginnings of this. We are very close to having something that I think is going to be very exciting but we just need to keep our head down and continue to do a little bit better in terms of developing more strategies that really get us there.

One of the last things that I wanted to talk about is that I don't think that we as clinicians have done a tremendous job of listening to patients. So there have been some good studies that have come out recently and I tout this one because I know it, not because I'm the senior author on it. But this was an interesting study and it was really fun to do but it was an eye-opener. Our goal was to try to figure out what do patients want out of a clinical trial endpoint. We always design these trials and we say, well, we want to set a difference of X and we want a hazard ratio which is basically how do the curves look different across the continuum to be Y and we want the medians, meaning at the 50% mark there.

How different are those? Half the patients are going to be at what versus what in terms of survival? Where on that survival curve? So we set these studies up to meet certain endpoints and thereby able to call it a positive study or a negative trial if it doesn't meet those expectations. And much of this dialogue goes on with the regulatory agencies. For example if it's a trial that is with the intent of trying to get an approval, for example.

So our goals here were to really look at the patient preferences in terms of efficacy, toxicity, quality of life and sort of putting those and trading those off as they often are, would you be willing to tolerate more toxicity if it resulted in more cure? Most people would. But would you be willing to tolerate more toxicity, a lot more toxicity, if it only gave you an extra 6 weeks of progression and then you'd go on to something else? A lot of people said no, I don't think that's a great idea.

So it was interesting to look at what people wanted. So we were looking at those tradeoffs as we moved through this and what we really found was that whether it's overall survival or progression-free survival, we really set the benchmark really too low because we were trying to find the sweet spot and we were asking - what about one month? What about two months? What about three months? Four months? Five months? And really almost everybody wanted more than five months. The majority of the patients said

that was really the beginnings of what they thought was significant to them or meaningful. And that was a minimum which is important.

Of course you'll say, of course. They're patients. They'd rather see five years instead of five months. Of course we understand that. But when they're looking at a trial and when they're thinking about a trial they would go on, for example, and we'd say we're thinking this trial, this investigational product in this trial is going to give you an extra six months, is that enough? It appears that may be. But if it's 3.5 or 4 months it appears that it's not with the majority of patients. So we certainly need to dive into this deeper but it is interesting in terms of how we look at it.

What about toxicity? What's unacceptable? And the only thing that I was a little bit surprised was that nausea wasn't higher up there. For me, I'm a weekend warrior. I have pain and do things like that so I understand that concept. Memory loss, certainly disturbing. Infection, disturbing. Hospitalization, very disturbing. Those were the ones that really stood out. I was surprised nausea wasn't a little bit higher, for me anyway, maybe you just get used to it but for me when I'm nauseated I just can't do anything effectively and it's just ruining my entire quality of life. It will be interesting to hear from you folks.

We asked about a preference for progression-free survival of 3 to 4 months, no difference in overall survival, and absolutely no toxicity. So you'd gain several months and you'd have no trade out in toxicity or you could gain 5 to 6 months in overall survival - and we did a lot of these tradeoffs, this is just to give you an example of some of the things we came up with to try to figure this out. But you had toxicity and the toxicity was three times neurotoxicity of normal. So you had probably grade two to grade three at least neurotoxicity. Of course a lot of patients said they don't like either of those. Understandably. But the majority would take the overall survival and toxicity and we know from other studies it depends on context, right?

So we know that patients who are in the frontline setting where a cure is very much at the forefront of the thought process because we know we're going to have a high chance of curing a significant percentage, that becomes very important. If we are looking at patients who are in the recurrent setting, especially if it's been many, many lines of therapy, we've come to the realization unless there's a major breakthrough, which there could be, we're probably not looking at a cure, but we're looking at trying to prolong life with the best quality of life for as long as possible. So we know from other studies that that's certainly important. But it's interesting to put some of these scenarios out there and see how they play off one another.

We did some ranking, some log ranking in terms of what people find most important. To give you some idea here, in terms of cure, living longer, feeling healthier were the big ones. Response. I think response often get missed, drug companies and clinicians, when they're interpreting clinical trials. So when you think about your visit, when you come in, really what I'm trying to figure out is whether you're responding or not. I don't know what your progression-free survival is. I don't know what your overall survival is. Because those are all things that are going on in the future.

But I can tell you if you're responding. And that's the kind of - you feel good, I feel good visit. I always tell the story, my shortest visit of the day is my nurse comes in, tells me that Mrs. Jones has 16 complaints and I'm going to be in the room for about 40 minutes just hearing the complaints before we get anywhere and then I go in and say, hey, your CA125 fell from 682 down to 87 after just two cycles. I say, how are you feeling? She goes, great. Is there anything I can do for you? Nope. She just wants to get right to chemo. She doesn't want me messing around with anything. She doesn't want me changing any doses. She certainly doesn't want to change the regimen.

So it's very inserting in terms of what patients want. But response rate is something that we often don't take into account because that's in real-time. And I think that's an important thing. I think the main thing

we wanted to bring out of this is we really need to bring the patient's voice into the context of all this and I think that for me is really what I learned from all this moving forward.

In conclusion, I didn't get into a lot of the individual drug development programs because literally I could spend about two to three hours going through drugs that attack P53 now, some CDK inhibitors, the list goes on and on and on. But honestly many of those are going to be busts. So for me to sit here and talk about all those I think is frustrating. I'd rather talk about the principles and classes of drugs that I think are going to be promising moving forward. I do think we're in a much better spot now in terms of turning out drugs that are going to be effective than we have been probably ever because of all the convergence of the technologies that I talked about.

We're understanding how the individualized care, we're able to recognize some of these unique drivers, and I think that's important. This whole idea of sequencing and systems biology and combining all this type of information is really going to make a difference as we move forward. And I think it's really exciting that we're able to even get the regulatory agencies which have traditionally been very staunch in their stance to be more proactive in terms of looking at how to approve drugs in ovarian cancer.

And so we need to continue to improve these trials because the most important resource that we have is patients. Patients are by far our most important resource. We can't waste that on something that's not likely to work. We have to have trials that are at least as good as the standard of care but hopefully provide a number of great options for our patients. So smaller trials that are smarter, looking for bigger differences. That's what are patients are telling us. That's the voice of the patient that we need to be looking for these bigger differences.

Robin, I'm going to turn it back over for some questions if I could?

**Robin Perlmutter:** Terrific. Thank you. We have a question in the chat.

**Thomas Herzog:** Do you want me to take that, Robin? I see it. Is that the rucaparib question that you're seeing?

**Robin Perlmutter:** Yes.

**Thomas Herzog:** Okay. Great. So the question basically boils down to toxicity with Rucaparib in terms of renal function. All the PARP inhibitors have a little bit of that. Rucaparib certainly does. And that's where they actually - so some of it - it's interesting that one of the carriers for creatinine is interfered with this so it artificially elevates the creatinine. So some of that's a real effect and some of it's more of an artifact. So that needs to be followed over time to make sure the course of the actual kidney function itself is not deteriorating. So it is something that you can see over time but generally not - it's something generally patients don't have to come off the drug for. Occasionally, yes, but usually not. So that's the good news.

**Robin Perlmutter:** Thank you. There's two more questions in the chat.

**Thomas Herzog:** So, the questions about breast cancer that was treated last in 2014. Would drugs like raloxifene and tamoxifen be counter indicated? Again, there's a lot more to your history that one would need and Robin will tell you I can't give out individual advice here. That's something you need to speak with your physician about because things like what the ERPR status is, the tumor was or what stage that tumor was, all kinds of things go into that. But in general, no. You should be able to take those drugs. But again, that's giving you a general answer for that.

Next question, with people surviving longer, are you seeing more brain tumor metastasis? Yes. The question is are we seeing a change in the pattern of recurrence over time. And the answer is yes. I've seen recurrences with ovarian cancer that I never saw before in the last ten years. Mostly good news, right because these patients are living decades and so while many patients 20, 30 years ago died in 3, 5 years

for sure, now we have patients that are living well over 10 years, 15 years and so on and we do see differences in some of those recurrences.

One of them that we do see is a slight uptick in the number that have brain metastasis. In fact we have two people on the service right now I believe that have involvement of brain on our service at - where I am. So I think that's something that we normally would not have seen and we're getting better at taking care of those patients as well. One of the patients this is actually her second recurrence in the brain and neurosurgery thinks they've got a very good shot of reoperating and having a good outcome. It is different but it's a good problem to have. If we can change and keep going, I'd like to see what recurrences look like at 30 years if we could do that.

Next, a patient says grateful to report no side effects at all from olaparib monotherapy in the 12th month. That's wonderful. CA125 dropped down to normal after cycle one and thanking me for a great webinar. This person is obviously very nice and very intelligent. Very nice at least. The point here that's very interesting, and I saw recent data with olaparib in this setting is there were I think 13% of patients that were on the drug for over five years and up to 40% of those were BRCA wild type, meaning they did not have a mutation. So for some people, these PARP inhibitors work for not months, they work for years and again I don't want to sell false hope for someone else that has a different experience and I've had patients that look like they might be in the former category and they're doing really well and I've had patients that didn't do very well on the PARP at all. So it's not for everyone but it is a great new class that we're very excited about because it offers options and we like having options for patients.

**Robin Perlmutter:** Okay. Thank you. Anyone have a question by phone?

**Caller 1:** I have a question. Can I?

**Thomas Herzog:** Sure. Go ahead.

**Caller 1:** So my question is if someone like myself, so I'm - I started having ovarian cancer in '05, had it three times and I've been NED for five years. I had Avastin and all kinds of things. But I've been off medication for almost four years. Is there anything - I know I'm in a lucky cohort of people who have been, are surviving- I'm actually a former patient of yours from New York. But anyway, yeah, I mean, I'm just walking around without a net. Is there anything going on for people like me or do we just kind of take care of ourselves and do the best we can? They had to take me off the Avastin and I was on Cytoxan for many years, like seven or eight years and eventually they wanted me off that as well. I don't know. Is there anything else?

**Thomas Herzog:** You've not been on a PARP inhibitor, right?

**Caller 1:** No.

**Thomas Herzog:** I'd predict that you'd do very well on a PARP inhibitor. So for me, I think probably really close surveillance as I know you're doing. And at the first hint I would get you on some form of platinum, knock the tumor back down and then put you on PARP maintenance. You're likely to have a response and the long-term response is extremely high.

**Caller 1:** So it would just be for now just screening, nothing proactive or intervention?

**Thomas Herzog:** We occasionally are able to eradicate all disease even after not a normal pattern. Normally our best shot's up front but occasionally I've had patients like you that were able to do that after a couple of rounds of chemo, we were able then to get rid of all the disease that we weren't able to get rid of in prior cycles. It's not the norm and I certainly don't want to give the impression to everyone else out there that's the norm but it does happen and that's why we keep fighting.

**Caller 1:** Okay. Thank you.

**Thomas Herzog**: I'm glad you're doing so well.

**Caller 1:** Thank you very much.

**Caller 2:** I have a question about metformin.

**Thomas Herzog:** Yes?

**Caller 2:** The outlook for metformin potential for all of us taking (inaudible).

**Thomas Herzog:** Yeah. There are some trials looking at that and we think there's a little bit of an interaction between metformin and the immune response and some other pathways that are very exciting. Yet I've seen other data in some cohorts where the data's been not that impressive. So I think we need to identify who's going to benefit from it. I have no doubt that there's going to be a subset of patients who are going to do well but I think we need to flesh that out yet.

**Caller 2:** Thank you.

**Robin Perlmutter:** Okay. I believe this concludes our webinar. I just want to take the opportunity to thank you, Dr. Herzog, for this wonderful and very comprehensive and enthusiastic presentation.

**Thomas Herzog:** Thanks, Robin, for having me.

**Robin Perlmutter:** We look forward to future webinars and thank you so much for all you do for the ovarian cancer community.

**Thomas Herzog:** Thank you, it's much appreciated.

**Unidentified Speaker:** Thank you so much, Dr. Herzog.

**Unidentified Speaker:** Thank you.

**Thomas Herzog:** Good night, everybody.