SEQUENCING OF TREATMENTS FOR PATIENTS WITH OVARIAN CANCER

Laura Doherty, FNP-BC, AOCNP®, Women & Infants' Hospital of Rhode Island/Brown University
Katina Robison, MD, Women & Infants' Hospital of Rhode Island/Brown University

MODERATOR Welcome back, everyone. Our next talk is entitled Sequencing of Treatments for Patients with Ovarian Cancer. Please join me in welcoming Ms. Laura Doherty and Dr. Katina Robison of Women & Infants' Hospital of Rhode Island.

DR. ROBISON Thank you so much. We are very delighted to be here. We are grateful to have been invited to come today and talk with you about an area that we actually think is incredibly exciting. I think we probably get the benefit of talking about something that has a lot of new findings recently, even as recent as last week.

We're going to talk today about the sequencing of ovarian cancer treatments, but what we're going to really do is we want to go over a little of the history of ovarian cancer and treatments and maintenance and where we've been and where we're coming. We really want to focus a lot today on PARP inhibitors, what's the data behind the PARP inhibitors, the efficacy, the safety, give you some tools to use in your own clinics, and then discuss the options of first-line therapies, as well as maintenance therapies. And, finally, touch on some of the new exciting trials that are going on currently looking at some of the combination therapies with PARP inhibitors and some other targets.

We have no financial disclosures.

For the purposes of the talk today, we're going to be using the term ovarian cancer to refer to ovarian fallopian tube and primary peritoneal cancers. As we all know, ovarian cancer remains a major problem. And while only 20,000 women are diagnosed every year, we're still seeing over 14,000 deaths from ovarian cancer. This makes it the leading cause of cancer-related deaths from GYN malignancies, but the fifth leading cause of cancer-related deaths for women of all cancer types.

And why is that? Well, the majority of women will respond to upfront treatments, which is great, but we also know the majority will also recur, with nearly 80% of women recurring at all stages of all diagnoses. And these recurrences happen typically within the first 2 years. And then we see the next recurrences getting shorter and shorter and shorter time between those, meaning that most women are living on some type of treatment for the remainder of their lives.

Only 30% or less of women at any stage of ovarian cancer diagnosis are actually cured of this disease, which is not good enough. And why is that and what have we been doing to make this better? Well, we've been trying to have more drugs, and the FDA has approved over the last 40 years a number of different drugs for treatment of ovarian cancer.

But you can see when you look at the gray – these are all the treatments – you can see that paclitaxel and carboplatin, which are still our mainstay of treatment, were basically approved by the FDA nearly 30 years ago and that's still what we're using every day. But when you look at the blue boxes—these are

the maintenance therapies—this is where we're saying, "Can we leave women on something that may benefit and may change the overall survival? Are there any types of those?" You can see it wasn't until the last 2 years that the FDA approved any of this.

It wasn't for lack of trying. There's been lots of investigation on what kind of maintenance therapies we could use for women with ovarian cancer. But, unfortunately, the clinical benefit was just not there. With the exception of the taxanes and using paclitaxel for 12 months was a bit of a clinical benefit that was seen. And when you look at the data from GOG-212, we, in fact, saw that there was the improvement of progression-free survival. But what was really difficult is that we also saw an increase in grade 3 and 4 adverse events, particularly the neuropathies. And the hair loss was persistent, making it not an ideal drug for using in a maintenance therapy.

So, why now in the last 2 years are we seeing four drugs be FDA approved for the use of maintenance? What's different, what's changing? Well, we're getting smarter, we're understanding the genetics of ovarian center. We're really being able to determine what it is both in the woman and in the tumor that makes ovarian cancers tick. So, when we look at the genetics of ovarian cancer, we have a number of genes that we know are frequently mutated, both germline, meaning that it's inherited, and somatic, meaning that it's in the tumor itself.

And when we look at these, we also see that many of the genes that are frequently mutated in ovarian cancer, they happen to regulate DNA repair. That's important because that helps us have a target for therapy. So, let's think about

that. Let's go back to our basic biology classes where we think about DNA repair. And what does this mean? And in cancer, this is really important to all of us.

We all remember that the DNA – there's two strands and, basically, I always think of them like two sentences that are backwards and they need to match up perfectly. And whenever you have a problem, either something's missing, you have something deleted, then our own cells typically every day have something in them that repairs those. When those go wrong, that repair doesn't happen and now damaged cells continue to survive and proliferate, which is a problem.

When we look at the different types of DNA repair, one of the areas that we hear about a lot and the enzymes that are talked about frequently in ovarian cancer, as well as breast cancer, are the *BRCA* genes. And that's because these code for an area called homologous recombination. Homologous recombination is our cells' own ability to repair double-stranded DNA breaks. And so, we typically have breaks every single day and our cells repair those. When you have a deficit in one of these repair enzymes, such as *BRCA1* and *BRCA2*, then you have what's called homologous recombination deficiency, otherwise known as HRD frequently when we talk about that. And this will become important in this talk.

What's also really important is *BRCA*, the breast cancer susceptibility gene. Why do we talk about it all the time? Well, that's because somebody has inherited some type of deficiency in that BRCA enzyme pathway. But there's also tumors that have a defect, and so for this talk I want to clarify some of these

terms because when we look at the studies and the evidence behind them, we really want to make sure that we're clear what each of these means to make sure that you can take home the important things.

So, a germline mutation in the *BRCA* will be looked as we all have a little "g" in front of the "*BRCA"*, and that means a woman inherited that. A somatic mutation will have a little "s" in front of it and that means that the tumor had it, but it was not a germline, not inherited. And then, finally, wild type means that there was no deficiency at all, it's a normal functioning *BRCA* gene. If you see "*BRCA"* with just the mutation, that will refer to both germline and somatic. And that's important when we review some of the data behind these studies that we're seeing.

The other term I think is important as we start to look at some of this literature is the loss of heterozygosity. This is one of those terms that we are starting to see come up a lot. We're also testing for this sometimes in tumors, so it's important to understand. So, the loss of heterozygosity. Heterozygosity is a good thing in our bodies, right? We want to have two sets of genes, which most of us do, and we inherit those. It's like having a spare key for your house; you have a backup in case something goes wrong.

When you see the term "LOH low," that means you have both sets. When you see the term "LOH high," that means you lost that spare key; you don't have both sets, you don't have a backup. These women often exhibit something that looks like *BRCA*, often referred to as a *BRCA*ness. And you will see some of this term in some of the studies as well.

So, the other really important pathway in DNA repair—and this is important for treatments—is the single-stranded break repairs because that's where you see the PARP enzymes. The PARP enzymes fix the DNA single-stranded repairs. So, how do PARP inhibitors work? This is important to understand first so that we can understand the evidence behind using them. It actually makes a lot of sense. So, if you have a single-stranded DNA break like we do in this talk, you see the little PARP enzymes binds it, fixes it, goes down, DNA is repaired, cell lives. You add a PARP inhibitor, now that cells get a double-stranded break because it hasn't repaired.

But in a normal, healthy cell, you still have the ability to repair through homologous recombination and, again, the cell lives. Now, you have a cell that has a homologous recombination deficiency, whether that's inherited—a germline—or somatic, and whether it's in the *BRCA* gene or in one of the others, this cell now dies.

So, imagine we give a woman a PARP inhibitor and she has a *BRCA* mutation, now that cell dies and doesn't survive. That was the basis in the lab of why this was thought that it would work. In fact, it does work and the FDA has now approved three PARPs for the use and maintenance and treatment in different ways. In the remainder of this talk will go through how to use them, what they're approved for, and what's the science behind that.

Olaparib was the first to be approved and this was approved for women in treatment initially who had had at least three prior lines of a chemotherapy and also had a germline mutation. Germline, not somatic. Rucaparib, on the other

hand—also approved for treatment—at least two lines and any type of *BRCA* and mutation—germline or somatic—all three have been approved for the use in maintenance therapy and this is in the recurrent setting. They've all been approved currently just in the recurrent setting for maintenance. You've had to have complete or partial response to the prior therapy.

So, let's look at the proof and the evidence behind using these. It's great that the FDA approved them, but when you're talking to women in the clinic, you want to know what can I tell them about their survival advantage? What can I tell them about the data behind this? Is it worth using? Let's first think about what it takes to get FDA approval, and let's also think about which phases of trials are important.

So, let's remember that all that lab stuff happened in the preclinical phase, but then when we see a good evidence, we want to make sure first and foremost in a phase it's safe. Phase 1s are about safety and numbers are small. In a phase 2, we want to know that it has some efficacy, that there is actually a benefit. And then, finally, in phase 3, you're comparing it to the gold standard, which in many cases of maintenance is a placebo because a gold standard is not leaving women on something. And then it makes it to the FDA.

So, first, we're going to talk about treatment, which ones have been approved for the treatment using PARP inhibitors. Which PARP inhibitors can we use for treatment? So, remember, these are only treatment currently in the recurrent setting. And olaparib has been approved for women with a germline mutation, at least three prior lines. And you'll hear me saying this over and over

again because we always have to keep thinking about it because there are little differences and it's important.

Study 42 was the main study that was the background for this; it was a phase 2 study looking at women who had a germline *BRCA* mutation and they had to have had at least three prior lines. And what we saw was a 34% overall response rate with a progression-free survival of 6.7.

Now, I want to remind everyone progression-free survival is often the endpoint we're talking about in these trials. And while overall survival seems so much better to most of us, it is really challenging in ovarian cancer trials when women receive many lines of treatment after the particular study they're in to see overall survival benefits because there's so many factors you have to control for it. So, progression-free survival has been considered a very acceptable alternative. If you look at this overall response rate of 34%, it kind of doesn't sound great, but when you think about this population who's heavily treated prior, this is actually a good overall response rate.

Rucaparib is also approved for treatment, at least two lines, and any type of *BRCA* mutation, germline or somatic. There were two studies that led to this bring approved by the FDA, the first being Study 10. The second part of Study 10 was a phase 2 expansion and this was among women who were platinum sensitive, having two to four prior lines of treatment, and they had a *BRCA* germline mutation. We saw a nearly 60% overall response rate in this particular trial.

ARIEL2 was one of the big trials that was done; it was a phase 2. There is still a part two that is ongoing and has completed recruitment, but we do not have the results for it yet. But, in the part one, this was women who were platinum sensitive, having received at least one prior line. And what was interesting about this study is that as you can see here, they did look at the *BRCA* mutations, all of them—meaning germline and somatic—and we saw that the progression-free survival was 12.8 months. But, they also look at LOH high separately. So, remember, that was the last of the heterozygosity; these were the ones who had the *BRCA*ness and, in fact, saw an advantage over the LOH low. So, treatment with PARPs currently is only for recurrent setting and the only two that are approved olaparib and rucaparib.

Let's move on to maintenance therapy. Maintenance is really important for a lot of reasons. One of it is that we are now saying, "Okay, we treated you with all this chemotherapy and now we want to leave you on something else indefinitely." It doesn't always sound great, so there's a few things we have to really think about and be smart about as oncologists to make sure that this is the right thing for our patients.

First, it needs to be effective treatment. Second, the adverse events can't be very much. You want it to be something that women can go out and live their lives normally and you want to make sure they're having a good quality of life. And, finally, convenient. Because going back and getting an infusion in the infusion center where you were getting treated for your cancer all along isn't

super ideal. It's not convenient and it's hard to get back to a regular life. So, obviously, oral medications are really desirable.

The FDA has currently approved a number of medications for the maintenance, as we saw. We'll touch on bevacizumab because it's been FDA approved, as well, which is a VEGF inhibitor. And then we will talk about the three parts that have been approved and some of the data behind those.

Let's talk about first the use of bevacizumab in frontline maintenance; currently, the only drug approved by the FDA frontline maintenance. The NCCN put forward guidelines stating that we should consider this as an option. And when we look at the NCCN guidelines from 2018—which my guess is we'll actually change in 2019 and we'll talk about that in a second—they do also talk about pazopanib, which is a tyrosine kinase inhibitor. So, women who have not received bevacizumab in upfront treatment can be considered to use this tyrosine kinase inhibitor.

The progression-free survival benefit was 5 months, and this is something that has not been FDA approved and in clinical practice is not used routinely. If a woman has received bevacizumab with her upfront treatment, then considering leaving her on bevacizumab for an additional year to 2 years depending is something to be considered. And this is largely based on GOG-218 data, wherein this study we saw that women who were on bevacizumab upfront and who remained on it had an improvement in the progression-free survival compared to the women who received just bevacizumab upfront with no maintenance or

standard chemotherapy with paclitaxel and carbo and no bevacizumab. There was no difference seen in the overall survival.

Hot off the presses last week – I think this is probably the most exciting thing I have seen in my years of practicing oncology – is that now the *New England Journal of Medicine* published the results of SOLO-1 saying that frontline use of olaparib as a maintenance might be something we should all be doing every day.

SOLO-1 was a large randomized controlled trial with women who had a stage III or IV ovarian cancer. Women were then randomized to either receive olaparib maintenance after their treatment with a platinum for 2 years or a placebo. And what we found and the reason this is being published so quick is that we all know survival curves and we all see them, right? This separation in a survival curve to see is extraordinary and super exciting.

And what they have found is that while we have not even met the maturity yet for progression-free survival, the women in the placebo group progression-free survival was 13.6 months. We don't know what the median progression-free survival is yet in the olaparib group, but what we do know is that at 12 months nearly 90% of women were still progression-free and that was in the olaparib group. But, at 48 months, almost half of the women remained progression free; they have no cancer yet. That is a huge number, which is very different. We are seeing nearly a 3-year benefit currently. I think we will be getting a lot of information. The FDA was at our site this week and I think we will be seeing an FDA approval for this drug very, very quickly.

Now, let's talk about maintenance in the recurrent setting. The antiangiogenics have been looked at in the recurrent setting for maintenance many times and I think many of us use them in this way. Again, bevacizumab is the one that we use primarily largely based on OCEANS, GOG-213, as well, because we see improvements in the progression-free survival when we leave them on bevacizumab afterwards. We have also seen cediranib used, which is a VEGF inhibitor, as well, and you can see that we also see a benefit in progression-free survival.

But, what about the PARPs? What's the evidence behind PARPs and maintenance, and are these something we should be choosing first, and how do we decide those things? Which Laura will touch on. Olaparib has been approved for maintenance therapy in women who had a platinum-sensitive ovarian cancer with or without a *BRCA* mutation. And this where it varies a little bit from the frontline treatments and the recurrent treatments.

So, in the maintenance setting when we looked at Study 19, we saw this was a phase 1 – women who were platinum sensitive and they either had a germline mutation or did not. You did not have to have a germline mutation in order to be in this study. And we saw that there was an 8.4 month compared to a 4.8 month. And I think about it as like you have almost a double in the progression-free survival among this group. It was even greater for those who had a *BRCA* mutation with 11.2 months. There was no change in overall survival seen for the non-*BRCA* mutated, but there was a 2-month advantage and an overall survival for the *BRCA*-mutated patients.

SOLO-2 was a phase 3 study and this, again, is looking at olaparib versus placebo in women who were platinum sensitive who had a germline mutation and at least two prior lines. And women with a germline *BRCA* mutation had a very significant advantage in progression-free survival: 19.1 months compared to 5 months. So, usually we'll say it's nearly 20 months, so you potentially could be close to 2 years without needing to go back on another chemotherapy, which is a long period of time compared to 5 months.

Rucaparib similarly is approved. Again, remember, all three are approved for the same things in the maintenance setting. Rucaparib ARIEL3 was the large study. It was a phase 3 trial, platinum sensitive, greater than or equal to two prior lines of chemotherapy. But what was interesting about ARIEL3—and this is important for us to remember when we are really thinking about which patients are best to be using which PARP inhibitors—is that in ARIEL3 while they looked at the *BRCA* mutation patients and we saw a 16-month progression-free survival – and this, again, is germline and somatic – they also looked at women with other homologous recombination deficiencies, so not *BRCA*, so the other, the RAD51s. And what we saw was that there was also a significant progression-free survival advantage. We also saw in those without any genetic mutations—so, the *BRCA* wild type and LOH low, so normal cells—there was still an advantage over placebo.

And, finally, niraparib. Niraparib, the large study for this was the NOVA trial. And in the NOVA trial was a phase 3 trial looking at platinum sensitive, again, had at least two prior lines, and, again, you need a complete or partial

response in order to stay on a maintenance. When we looked at germline *BRCA* mutations compared to all others – what they did in NOVA initially – and saw, again, a very significant improvement at 21 months versus 5 months for those who had a germline mutation. We saw an advantage for everyone else, as well. So, when they broke down the everyone else and said, "What's the advantage for those who don't have a germline mutation?" Again, they saw an advantage for every group; those who were HRD positive, those who had somatic mutations, and those who were HRD negative. But, who really benefited and who looked quite similar, actually, to the germline mutation were those with somatic mutations, meaning that really germline and somatic mutations really seem to have the same benefit in most of these studies.

So, to summarize, there's a lot of data in this, but FDA has currently approved bevacizumab for frontline maintenance. It is the only drug for frontline maintenance, although I think it was reasonable to offer your patients olaparib and I would anticipate that to be FDA approved very soon. And then we see bevacizumab and all three PARPs are approved for maintenance therapy in the recurrent setting.

Now I'm going to let our lovely Laura—who's my nurse practitioner in clinic and we work together all the time really trying to think about our patients—get down in some of the nitty gritty about what we see every day and some tools to help you with managing that.

MS. DOHERTY Thank you, Dr. Robison, for sharing with us the data that supports the use of PARP inhibitors in clinic. I think it is really useful when

you're counseling patients to have some of those numbers in the back of your head to really give them concrete ideas of how much time these maintenance therapies will give them.

I'd like to talk about some case studies and what are the side effects we see with these PARPs and, also, talk a bit about some of the exciting combination treatment options that are in the pipeline.

So, one of the first things we think about with starting a maintenance therapy is timing. Bevacizumab is typically started, it's continued with a 3-week interval dosing, so if the patient was on a cytotoxic medication with bevacizumab and they're in remission, then those medications are stopped and we continue every 3 weeks with the bevacizumab infusion. Our pharmacy has platelets of 75,000 and an ANC of 1,000 as our parameters for starting the bevacizumab.

PARP inhibitors are a little bit different because typically they're not something that the patient's been on with their therapy, so we do need to make sure that there has been resolution of toxicity before the patients are started on PARP inhibitors. We want to see platelets above 75,000, hemoglobin about 10, white blood cell count above 3,000.

Oftentimes, just by nature being eligible for a PARP inhibitor, the patients had at least two prior lines of therapy and it's likely there can be some heme toxicities from that. So, I'd say in clinic we probably see patients start within 4 to 8 weeks after completion of their treatment regimen. And our protocols actually will give us about 12 weeks to start the patient on a PARP inhibitor.

One of the other things we think about is pharmacology. Niraparib is actually just a once daily dosing; olaparib and rucaparib are twice a day. And when we first started with olaparib, we had 50 mg capsules and they were dosed at 400 mg BID, so the patients were taking a lot of pills. Those are getting phased out and now the indications that we talked about are for tablets and that's usually just two or three tablets twice a day for olaparib. In rucaparib, you can see there's a couple of different dosing options—the 200, 250, and 300—but it would be 600 BID.

When we're thinking about comorbidities that the patients have when we're selecting a PARP inhibitor, patients with any renal impairment, they will need a starting dose modification with olaparib and patients on a CYP3A inhibitor will also need a dosing modification.

What adverse events do we see with these PARPs? What did we see in the studies, and what do we see in the clinic? So, across the board we see anemia; that is a class affect with olaparib, rucaparib, and niraparib. Niraparib we tend to see some pancytopenia and it's pretty significant. Pretty much half the patients are going to experience some toxicity and about a quarter are going to experience a grade 3 or grade 4. And we do see some with rucaparib, as well.

A lot of GI issues with the PARP inhibitors. Again, that's kind of across the board. Decreased appetite, nausea, vomiting, diarrhea. And then with rucaparib and niraparib, abdominal pain, and distention. We see upper respiratory tract infections with all of the PARP inhibitors, we see shortness of breath with rucaparib and niraparib, and we also see pneumonitis with olaparib, which is not

on the side, but it is something to be mindful of when you're counseling the patient before you start the medication and also when you're seeing them regularly in your follow-up visits. We see some rashes with rucaparib and niraparib, and the big thing we see with the PARP inhibitors is fatigue.

We see some change in taste, we see headache with niraparib. And unique to olaparib, we'll see some myalgias and musculoskeletal pain in about a fifth of the patients. So, overall, you can see more than 20% of our patients are experiencing some toxicities with these medications.

You'll see here the CBC correlates with what we were just discussing, certainly a decrease in hemoglobin, a decrease in platelets with rucaparib and niraparib, and a decrease in the ANC with rucaparib and niraparib. And for chemistries, we actually see an almost guaranteed increase in creatinine on patients with taking rucaparib. We'll see an increase in ALT and AST and even cholesterol in these patients. And so, we'll see about 35% of our patients who have a CBC or chemistries that have changed.

The big thing that we need to counsel our patients on is the risk of myelodysplastic syndrome and acute myeloid leukemia. It's about 1.5% or less and it is across the board for the PARP inhibitors, so that is why it is really so important to wait until their hematologic toxicities have resolved from their prior therapies. And we're starting with monitoring with a CBC to asses for that. And then with niraparib we're actually doing weekly CBCs for the first month, which makes sense because we can see some pancytopenia with niraparib, so we followed that patient really closely.

If we see that there is prolonged hematologic toxicity, then we take a break from the PARP inhibitors and we continue to monitor the CBC weekly. If it's been 4 weeks, they haven't been on the PARP and they still have a toxicity, then at that point they do need to see a hematologist for further evaluation. If MDS or AML is confirmed, then we discontinue the PARP inhibitor.

So, what are some of the strategies we have for managing the adverse events we see in clinic? Well, diarrhea; certainly, we saw that's a big side effect of these medications. But I can tell you in clinic I haven't seen it be too much of an issue for patients. For most patients, it does respond to an antidiarrheal. Always in this population we're making sure that it's not an infectious cause, but I would say we don't see hospitalizations or patients seem to come in for IV repletion and it typically is managed well.

Nausea and vomiting is a big one. Patients are counseled extensively on this when we start them on the PARP inhibitors. We send them home with at least two different kinds of antiemetics, they're counseled to call us if they're home and they're nauseous and they're vomiting. We don't want that, we want to do a better job. We have so many ways to manage this now, it shouldn't be affecting their quality of life. And, certainly, because it's an oral medication, it's really important that they're able to keep it down.

Cancer-related fatigue. This is multifactorial, as we all know. The patients by nature of being eligible for PARP have had multiple lines already; they're probably deconditioned from that. We try when we see patients in our survivorship visits to really emphasize getting regular exercise and trying to

combat the chemotherapy-related fatigue with regular exercise; we stress that at every follow-up visit. But, nevertheless, it's very easy to get deconditioned on these regimens, so we'll send patients to physical therapy, we'll assess for untreated anxiety and depression and see if we can do a better job with that and, perhaps, that will help their energy levels.

We'll assess for their sleep habits and counsel on better sleep hygiene, but, you know, sometimes no matter what you're doing, the patient's still going to be fatigued. And oftentimes, we'll have some good luck with referral to palliative care, which is certainly appropriate in this patient population. And I've seen some patients started on low-dose stimulants and they actually do really well and they're able to get up and get out of bed and play with their grandkids and it's like a gamechanger. I think most of these really are manageable side effects and they don't affect the patient's quality of life.

And that was also found in the NOVA analysis where they noted that patients on niraparib and placebo, there was no difference in quality of life also noted during the SOLO-2 trial. And this graph shows us that in the maintenance therapy trials that assess for quality of life, there was no clinical effect. And if you remember when Dr. Robison was talking about the important reasons, the important things we think about when we're thinking about maintenance, we want this drug not to affect the patient's quality of life.

So, I'd like to talk about a case study that I think brings in a couple of things that we learned today. The patient's name is KM. She's a 42-year-old woman; she's a high school teacher; she's a mother of two young children; and

she loves to run. She presented to us with a stage IV high-grade serous ovarian cancer back in March of 2016. Her CA125 was 7,300 at diagnosis. This is a very good marker for her. We did not know her *BRCA* status at the time.

She was treated with neoadjuvant chemotherapy, carboplatin, and paclitaxel. She had three cycles, had a great response to the treatment, and she underwent an interval optimal debulking TLH BSO omentectomy in August of 2016. She then had three additional cycles of adjuvant carboplatin and paclitaxel and at completion of treatment, her CA125 was six. She had a complete response.

At the time, she was declining genetic evaluation; she thought perhaps in the future. So, that was 2016. What if she was a patient now presenting now with new disease? What have we learned that we could offer her for maintenance therapy at this point?

Well, we know bevacizumab would have been an option. We would have started her on bevacizumab during her frontline treatment. We also know based on the results of the SOLO-1 trial, the olaparib would most certainly be an option for her if we had her *BRCA* status.

But, in 2016, we didn't have those options, so we saw her in surveillance. And her CA125 started to rise; a CT showed recurrence of pelvic disease in November of 2017. She was platinum sensitive. And just a refresher on platinum intervals, platinum sensitivity means that you have gone over 6 months from the completion of our platinum treatment before you recur. We'll see patients who are platinum resistant, so they recur before that 6-month period. And then

patients who are platinum refractory who actually either progress during treatment or don't respond to platinum therapy. So, platinum sensitivity is certainly a good thing for this patient.

So, she started on carboplatin, gemcitabine, and bevacizumab initiated in December of 2017. And this was per the OCEANS trial that we saw Dr. Robison review earlier. If you remember, there was an additional 4 months progression-free survival for patients who were on this regimen and continued on bevacizumab afterwards.

So, it was a tough regimen for her; she had pancytopenia, she required a growth colony stimulating factor, she required multiple transfusions of packed red blood cells and platelets. It was a rough go and it was significantly affecting her quality of life. She ended up discontinuing treatment after the fifth cycle for prolonged thrombocytopenia. Fortunately, her CA125 had normalized and her CT showed no evidence of disease at the time. She did get her genetic evaluation during the second-line treatment and she was found to be *BRCA* positive, *BRCA1*.

So, what do you think about maintenance for this patient? We have a couple of options now. She's been on bevacizumab with her second-line treatment, so she is eligible for bevacizumab moving forward. She's also *BRCA* positive, which we know conveys a significant benefit for maintenance with a PARP inhibitor.

So, we had this discussion with her and the decision was made to keep her on the bevacizumab, as she was already on it, and she did have such a hard

time with hematologic toxicities with her second-line treatment. So, she started on the single-agent bevacizumab and, unfortunately, her CA125 started to rise after her first cycle, so right before cycle two her CA125 increased and we knew that she was brewing a recurrence. So, we sat down again and we talked about, "Maybe this is time to think about the PARP inhibitor for you." Her values had recovered and she had been about 8 weeks out from when she completed her treatment.

So, a PARP inhibitor for patient KM. Which PARPs are appropriate in this setting? Well, as we learned, olaparib, rucaparib, and niraparib all have indications for maintenance after the second treatment. But what toxicities are we concerned about when we're selecting which PARP? Well, with all of the hematologic toxicities she had, we would steer clear of niraparib and rucaparib just for that reason and so, we ended up going with olaparib 300 mg BID.

Her CA125 normalized and she's tolerating the regimen incredibly well. She has no hematologic toxicities; her nausea is well managed with antiemetics, as needed; her fatigue improved after the first month; and she is working full time, she's caring for her children; she's running again; and she's doing yoga. And we are now 5 months out and she continues to do well.

So, I'd like to talk a bit about some of the PARP inhibitor trials that are in the pipeline, some very exciting stuff. Dr. Robison talked about SOLO-1 and those results. We're also looking at retreatment with maintenance, so patients who were on olaparib, progressed, treated, now in remission, do they benefit from going back on olaparib? That's the OReO study. We have frontline

maintenance with niraparib in the PRIMA study. We've also got a lot of combination approaches that are coming and these are really exciting. PARPs with DNA damaging agents, PARPs with immunotherapies, PARPs with antiangiogenic agents.

So, what's the rationale of combining these? Well, with the antiangiogenic agents the hypoxia that they cause may induce a *BRCA*-like phenotype, so patients who might not respond to PARPs as well as the *BRCA*-mutated patients, if you also give them a VEGF inhibitor, theoretically we would see them respond similar to a patient who's *BRCA* mutated.

Immunotherapy. Well, we know that the PARP causes DNA damage and we know that the more damaged that the cells are, the easier it is for the immune system to see them. And if we're taking the brakes off the immune system with an immune therapy and we're damaging the cells with the PARP inhibitor, the hope is that the immune system would be able to find those cells easier. And then with the chemotherapy, we're increasing the DNA damage by using two DNA damaging agents.

This graph just also shows us that combining a PARP with a taxane gives us a similar *BRCA*ness phenotype that we talked about with the antiangiogenic agents.

So, just a summary of a couple of trials that are out there. We see olaparib paired with cediranib in several studies looking at it as treatment, looking at is as maintenance. We have olaparib combined with chemotherapies, we have rucaparib with chemotherapies, and we also have olaparib, which we haven't

talked about, but it's not FDA approved, but it is a PARP that we're seeing in studies. Currently, they're using it as frontline treatment with carboplatin and paclitaxel and then as a maintenance. We don't have any results of that yet.

The immunotherapies. We've got olaparib with CTL4A blockades; we've got olaparib with PD-L1 inhibitors; we've got niraparib with PD-L1 inhibitors; and then we're seeing actually some combinations of three or four different immunotherapies, antiangiogenics, PARP inhibitors, and regular chemotherapy. So, we're trying to figure out the right combination and so far, so good.

We have some preliminary results that look very good from the TOPACIO/KEYNOTE-162 trial. This was a phase 1 and 2 study of niraparib and pembrolizumab in patients with recurrent ovarian cancer. At the time of the data cutoff, there were 62 patients enrolled; 62 were valuable for an initial response assessment. This was a difficult-to-treat population; 50% had platinum-resistant ovarian cancer, 29% were platinum refractory. So, if you remember, they didn't respond or progressed through platinum therapy. Over half had seen bevacizumab, and almost a quarter were platinum ineligible.

So, what did we see? We saw an overall response rate of 25% and we didn't see a difference in the *BRCA*-mutated patients versus the *BRCA* wild type. And when we're talking about the thought that perhaps an antiangiogenic agent or an immunotherapy combined with a PARP might give us better responses, we're seeing that.

Platinum status did not matter; we saw a 23% response rate in platinum resistant patients and a 24% response rate in platinum refractory. The durable observable response was 9.3 months with nine patients remaining on treatment.

The adverse events we saw were expected with niraparib: anemia and thrombocytopenia. You'll see here, actually, that it's a 200-mg dose. And when we were talking about dosing, I said that it's 300 mg for niraparib, but we're seeing in trials and some of the protocols I can think about in our clinic that they're starting a lower dose with niraparib when they're coming it with other medications. And we've also seen some weight-based dosing.

So, how does this compare to what these patients would be receiving without these trials? Well, for patients who are platinum resistant, standard of care would be doxorubicin with bevacizumab, and patients only respond about 5 to 18% of the time. So, a 25% response rate is much better for these patients. Platinum-refractory patients have an even lower response rate. And we just saw 25%.

And historically, PARP inhibitors only give us response rates about 5 to 10% in patients without *BRCA* mutations who have platinum-resistant disease and anywhere from 0 to 14% in those with *BRCA* mutations, but who have platinum-refractory disease. And we see in this particular population, as well, only 10 to 15% response to anti-PD-1 antibodies. So, overall, it's good and I think we're moving in the right direction.

I'd like to just recap what we hope you were able to take home from the talk today. Recurrence treatment. If you're looking to treat a patient with a PARP

in the recurrent setting, if the patient has had at least three prior lines and is germline *BRCA* mutated, then they can be treated with olaparib. If they've had at least two prior lines and are either germline or somatic mutated, they can be treated with rucaparib.

Maintenance in the frontline setting. If the patient received bevacizumab with their frontline treatment, they are eligible for continuation of bevacizumab in the maintenance setting. If they have a *BRCA* mutation and they've received their frontline treatment, we fully expect olaparib to be FDA approved soon for maintenance in that patient population. Patients who have a recurrence and they've had two or more prior lines of treatment regardless of *BRCA* status are eligible for olaparib, rucaparib, and niraparib in maintenance.

So, what are our conclusions? The treatment landscape for ovarian cancer is rapidly changing. As you can see, when Dr. Robison had that nice timeline graphic – you know, our first drugs were approved – what we're using now for frontline was approved in the '90s – there really wasn't too much until 4 years ago and now we've got all these new targeted therapies and indications for them.

Focus on the molecular biology of the tumors and development of targeted treatments to exploit these molecular changes. It's certainly the direction that things are going for ovarian cancer.

Tumor testing is essential for these patients, so getting genetic evaluation, getting tumor tissue testing is very important. Frontline maintenance is now an option with bevacizumab and we expect olaparib in the near future. There is

FDA-approved treatment options for maintenance in the recurrent setting, which include bevacizumab, olaparib, rucaparib, and niraparib, with improved progression-free survival and no impact on quality of life. We expect combination targeted therapies for treatment in the future.

So, the big take-home here is that there is a lot of hope for these patients and I don't think that's something that we had even just a few years ago. So, we'd love to answer any questions you may have.

FEMALE Thank you so much for that. And thank you for the summary because I work in GYN oncology, too, and I know I always say maintenance. Sometimes we forget that we're not talking about upfront, we're talking about after the patient has had a recurrence and then we're going to use it for first relapsed maintenance.

So, right now the only maintenance drug that is FDA approved is bevacizumab. My question to both of you is what percentage of your patients do you see bevacizumab or do you wait for it in a recurrent setting?

DR. ROBISON I would say we probably typically don't use it. I think the use of it upfront – you need to have been on it upfront – and I think the majority of our patients aren't because most are, honestly, on trial I would say where we are using a lot of the combination therapies, which I think are probably going to be more promising. So, if I have the option of a trial versus putting them on, then I don't. I think the ones who – when we don't have a trial or don't want to be on a trial, then I think I will often consider using it and then – but, I have to think about it right at the beginning and putting them on it.

FEMALE Thank you.

DR. ROBISON And I think that's also something we didn't highlight. I really think there are so many trials right now available that are really exciting and interesting for these women. And so, every time you're having a patient come into your office and you're seeing them with a diagnosis, I think it's really important to really like look which trials do we have at our center? Which trials are out there opening up? Because you're getting a lot of these opening and closing. But, I mean, in, you know, the 16 years I've been doing this and seeing this, I've seen so little improvement until the last year or two. And I think that really is encouraging and I think clinical trials right now are super important.

FEMALE I'm not in ovarian cancer, but is there any role for IP chemo any more and more debulking than just one time?

DR. ROBISON So, I think that's - I will probably take this, I'm guessing, right?

MS. DOHERTY Mm-hmm.

DR. ROBISON That is a hugely debated topic. And then you can add HIPEC into that mix now, too, which is even more, you know, the heated intraperitoneal chemo and I think you will get 100 GYN oncologists and probably 90 opinions.

Again, I think that there was great data for IP; there has been studies that have followed that question it. Those studies are murky because of the addition of things like bevacizumab, so when you gave IP with bevacizumab versus IV, we no longer saw the benefits. There was also the same idea with giving it, you

know, dose dense paclitaxel and, again, no benefit if given with bevacizumab. So, there's a lot. These studies were designed in such ways that there were so many little differences that it makes it tricky to pick the very best, which is, again, why I often opt for a clinical trial when able.

I think HIPEC – there was a *New England Journal of Medicine* article published within the last, what, 6 months or year about HIPEC in the women who have had neoadjuvant and using it at your interval debulking. And, again, there is a lot of debate about that currently, but I think those are things that are going to be added in. What's going to be interesting is how do you take this amazing maintenance, you know, data from SOLO-1 and now where do you put these other things? Like is it still beneficial to do HIPEC if you put them on olaparib and their *BRCA* I don't think would have those answers.

So, I think there's a lot to be determined which is the best. And I don't think we, unfortunately, know quite yet.

FEMALE So, if I understand correctly, olaparib has now been approved like just recently for frontline maintenance?

DR. ROBISON Not approved yet, but the FDA literally was at our site all week. Because that *New England Journal* came out last week. And we happened to be one of the top recruiting sites for it, so we knew the data a little before, so we were able to get it in to you guys. And literally the publication came out. And so, while it hasn't been approved, I would 100% be comfortable personally, and, in fact, every patient I saw like right now who's finishing

treatment or even finished a little – like within the last few important – I'm like, "Do we know their *BRCA* mutation status?"

And the interesting thing is in SOLO-1, it was all-comers with *BRCA* mutation, although only two women had a somatic mutation. The rest were all germline in the group of 300 plus. And so, you know, I still think it's that question, is genetic testing enough or should we be doing, you know, tumor testing for everybody, as well? And I think, you know, then you talk about insurance coverage and all the things that go around those.

But, FDA approval will certainly make insurance coverage of olaparib easier. I do think you could go to an insurance company with that article and argue pretty strongly that it's appropriate to put the woman on it.

FEMALE Mm-hmm. So, is your plan, you know, once this is official that you'll use that instead of the bevacizumab?

DR. ROBISON For anybody with a *BRCA* mutation, that would be what I would do in practice for sure.

FEMALE Mm-hmm.

DR. ROBISON I mean, I think that is such a tremendously bigger difference. And it'll be interesting, right? It's kind of like breast cancers in a lot of ways. I mean, it will be interesting to see – this was only 2 years; nobody knows how long should you keep women on it. You know, what's the overall survival advantage? Could we see more cure rates? Like I think there's a lot of potential. People are incredibly excited about this, as you can imagine.

FEMALE For the *BRCA* testing, do you have to have tissue?

DR. ROBISON Yes. Well, so, if you do a germline test, obviously, no, but, yes, for a tumor. But, most of the time most centers will keep your tissue, so we never rebiopsy our patients in a recurrent setting. And I would say that we are standardly sending tumors for testing in the first recurrence and now I'm shifting to high-risk patients sending it upfront for testing.

FEMALE Just to clarify, I think you mentioned that in germline you use blood?

DR. ROBISON Blood, yeah.

FEMALE And then in somatic, you use tissue?

DR. ROBISON And you want to know both and so, there's an argument about using, you know, the germline knowing germline matters for you as a person and for your family, when it comes to the therapies. Now we're probably saying that it's maybe slightly less important than we thought it was because the somatic mutation in the tumor itself really seems to also be – you know, have a better response, as well. But, it is a conversation we have with patients about both all the time.

FEMALE I want to tag off of our earlier session on cost. And I want to direct this to you. So, whether you're using rucaparib, olaparib, or niraparib – and I don't work for any of the drugs companies – but we tend to use the online specialty pharmacies. Have you had any issues with cost? And I will say that because I've had zero copays, $50 copays, and I've had patients that have had $5,000 copays. And my industry reps have been very helpful, but there are some patients that literally cannot get this drug for $50 a month.

DR. ROBISON Yeah.

FEMALE I want to know if you've had any barriers with that.

MS. DOHERTY I think we have. We typically direct them – we have some personnel who handle trying to get things approved, so I don't know what they're paying and I don't know what they end up paying. But it is something that on a regular basis we're having to send to our financial people to help them with. But it's probably along the lines of what you're experiencing, I would think.

FEMALE And my last question – I promise to turn this over – with side effect profile, you had mentioned that the niraparib, there's a higher incidence of thrombocytopenia, so, you're evaluating your patient with a prior hematological toxicity or blah, blah, blah. But, I'm hearing out in the community that even though the starting dose FDA recommendation is 300 mg – 3 100-mg pills – is the starting FDA dose, some of the clinics are starting at 200.

DR. ROBISON Yes.

FEMALE Can you address that and what you guys do?

MS. DOHERTY Yeah. And I think we saw that even in studies where they had patients on a 200-mg dose of niraparib and we have patients weight-based now in some of our protocols for niraparib. So, I would think most patients end up on a reduced dose. Do we start them on a reduced dose? I don't know how many patients I've started on niraparib.

DR. ROBISON Yeah, I was going to say, I think niraparib isn't necessarily our first choice often because of that. So, I don't start them – certainly, if I was considering starting somebody on it who had had hematologic

toxicities, I would consider starting at the lower dose. And I think we will probably see that dose being optioned. But we have seen weight-based a lot in the new studies, which is interesting.

FEMALE Yeah, so I have a question about side effects with the PARP. Do you see neurotoxicity?

MS. DOHERTY No, I haven't.

DR. ROBISON Yeah, I mean, in general, no, we haven't seen - I can't – it's always right – there's the tricky part because everybody has been on taxanes and platinums and have some baseline toxicity. I haven't seen anybody come in saying, "Oh, it's worsening." Or years later after treatment who have none, I haven't seen that be a problem, nor do I see it in most of the studies reported.

MS. DOHERTY Yeah, I think I have seen change in taste, but I didn't see any data about –

DR. ROBISON Yeah. But, it's definitely not something that comes up, which is great.

FEMALE And then what about frequency of pneumonitis; do you see that?

MS. DOHERTY It was less than 1% for olaparib.

DR. ROBISON And the SOLO-1 data just came out on that, too, which was the same. So, it's rare, but important. I think we are – are we still okay? Okay, good. Yeah.

MS. DOHERTY Oh, we're over. Well, thank you so much for spending this hour with us; we appreciate it.

DR. ROBISON We really appreciate your time.

MODERATOR Thank you, Ms. Doherty, and also Dr. Robison.

[END]