

Cancer Conversations

Episode 3: The Latest in Ovarian Cancer Research and Treatment

Announcer:

Welcome to Cancer Conversations, a podcast series from Dana-Farber Cancer Institute. In this episode, from September 2014, Dr. Ursula Matulonis, Dr. Susana Campos, and Dr. Panos Konstantinopoulos discuss the latest treatment options for ovarian cancer, as well as answer questions about side effects and new clinical trials.

Dr. Matulonis is a medical oncologist and the Medical Director for the Gynecologic Oncology program in the Susan F. Smith Center for Women's Cancers at Dana-Farber. Both Dr. Campos and Dr. Konstantinopoulos are also medical oncologists with the Gynecologic Oncology program in the Susan F. Smith Center.

Dr. Ursula Matulonis:

I'm going to get things going. These are actually questions that have been sent in by you, the audience, and we're going to go through them one by one, and then we got a few extras this morning. Number one, Dr. Campos, the question is: Is there more than one type or subtypes of ovarian cancer? And are all ovarian cancers treated the same way?

Dr. Susana Campos:

Now, I think that's an excellent question. There are many types of ovarian cancer, and we traditionally categorize them into high-grade serous carcinoma or serous carcinoma, endometrioid, mucinous, and clear-cell. But over the course of the last several years, what we've identified is, even within the serous adenocarcinoma that we're subdividing or partitioning out—the high-grade and the low-grade—and the question is quite important because we're starting to understand some molecular alterations that might guide us in terms of treatments individually. I think that's a very good question, one that we kind of still struggle with in some subtypes of ovarian cancer.

Traditionally, they're still treated with platinum and taxanes, but there's been some research specifically in the mucinous type of ovarian cancer as to whether or not we really should be adhering to the carboplatin and taxol, or perhaps employing a G.I. regimen. There's an ongoing clinical study that I think recently just closed that may shed some light into the equation.

Dr. Ursula Matulonis:

Yeah, that's good. I'm going to let Panos chime in here, too, but I think it's really important that the audience understand that I think in ovarian cancer, we really need to do a better job of improving how we're treating women, and one of the (I think) very exciting next steps in clinical trial development has been exactly what Sue just said, sub-splitting out the different histologic subtypes of ovarian cancer. You would never think about treating breast cancer in one way anymore, so it just doesn't make sense to think about ovary cancer as just one cancer.

So, certainly, as Sue mentioned, high-grade serous ovarian cancer is the most common type of ovarian cancer. We treat it with platinum. Panos, do you have any thoughts about high-grade serous? It's certainly an area of laboratory interest to Panos.

Dr. Panos Konstantinopoulos:

Yes. High-grade serous cancer is a very heterogeneous type of cancer. We now know there has been a lot of analysis, both in terms of the DNA, the protein, and the RNA of these tumors, and we know that there are different subtypes of this high-grade serous. There are tumors that may have (50% of them, actually) defects in a DNA repair pathway called [inaudible 00:03:12] combination with genes like BRCA1 and BRCA2 are involved. There's another 20% of tumors that actually have a specific

alteration called cyclin E amplification. These tumors usually don't respond well to platinum chemotherapy, and we're trying to figure out other approaches that we can target them. There's another 2% to 3% of tumors that have mismatched repair defect.

So, we're trying to understand tumors better so that we can potentially treat them in an individual manner. I have to say, here that here at Dana-Farber we have embarked on this initiative, trying to genotype the tumor of every patient for 275 different genes and get an individual report. With this, we can potentially identify for each patient the appropriate treatments and streamline them into appropriate clinical trials that we could offer them what we call the "personalized treatment" for each patient and for each patient tumor.

Dr. Ursula Matulonis: That's great – more to come on that. Sue, I was recently diagnosed with ovarian cancer, and I'm trying to wrap my head around all the terminology. Can you explain what the CA 125 number is and why doctors track it?

Dr. Susana Campos: The CA 125 is a protein antigen on a tumor, and it's specific in ovarian cancer; however, it can actually be elevated in, for example, certain types of uterine cancer. But it is a marker – a serum protein that we actually measure at the time of diagnosis. In some cases, the tumor marker is elevated in individuals with ovarian cancer. More often than not, it is, but there are times when individuals can have ovarian cancer, and that CA 125 is normal.

I think it's important to know that that level is never 0. In a normal individual—an individual without a malignancy, say—it's somewhere between 0 and 35. But it is, too, a tracking device. If elevated at the beginning of treatment, we track it every single time the individual comes in for chemotherapy. What we hope is that we see a nice decline in that CA 125.

I think we all agree that we spend a lot of time talking about the CA 125 in that, it is a test that is not a good screening test, and I know there are many questions out there: Why not use this as a screening tool? It is quite nonspecific and nonsensitive. For example, young women who are menstruating, pregnant, have a urinary tract infection, or any kind of pelvic inflammation can cause that increase in CA 125. It's important to note: as we're tracking that CA 125, it could be a little bit blurred, so we often counsel patients not to get too apprehensive if it goes up or down by a couple of points; it's simply the trend of the CA 125. But the hope is indeed that the marker normalizes at the conclusion of therapy. It is basically a tracking device.

Dr. Ursula Matulonis: Yeah, that's a good point. All of us are going to talk a little bit about screening—although I wish we had better screening tests—but also new therapeutics and the MUC16 protein that's stuck onto ovarian cells, that [inaudible 00:06:42] CA 125, and now we should have medications and drugs that are targeting that MUC16 prior to being [inaudible 00:06:48] from this. [inaudible 00:06:50], Sue, that's perfect, thank you. Panos, What other biomarkers are used by Dana-Farber for ovarian cancer progression, besides CA 125?

Dr. Panos Konstantinopoulos: The majority of the time, as Sue mentioned, the CA 125 is the tumor marker, biomarker, bloodmarker that we use. There are occasions where we could, for certain types of ovarian cancer (like the mucinous type) where we could follow other biomarkers like the CEA (the carcinoembryonic antigen) or the CA 99 (which is the cancer antigen 99). There's another [inaudible 00:07:26] called 84, which has been FDA-approved, actually, for following to track progression of disease, but this is not used very frequently.

But there are many occasions where there's actually no blood biomarker that's elevated in patients with ovarian cancer. In that situation, we have to follow them with imaging studies, like CT scan or sometimes, depending on the scenario, PET scans.

Dr. Ursula Matulonis: Yeah. I think HE4 probably what this individual is driving at. I don't use it. Do you use it, Sue?

Dr. Susana Campos: No. You know, there are indications in terms of when an individual presents with an ovarian mass, and sometimes that's used, compounded with the CA 125, to try to help the surgeon determine: could this be malignant or nonmalignant? I think different institutions use it differently. We haven't here used it too much. The CA 125 will dictate, will tell the story.

Dr. Ursula Matulonis: Yeah, exactly. And, obviously, for women who have granulosa cell tumors, we use [crosstalk 00:08:31]. That's the other biomarker we use.

Dr. Susana Campos: Right.

Dr. Ursula Matulonis: OK. Panos, this is a biggie (this is directed towards Panos, but I'm going to let Sue chime in, too): What are areas researchers are focusing on the most with regards to ovarian cancer treatment?

Dr. Panos Konstantinopoulos: I think that the biggest area of investigation right now in ovarian cancer is trying to understand the different molecular pathways that drive ovarian carcinogenesis, because if we understand the different pathways, then we could potentially develop therapies that we could target these pathways.

So, there is a lot of excitement right now about targeting DNA damage repair pathways. Many times, ovarian cancers are defective in terms of their ability to repair DNA. We have drugs that are actually directed against these DNA repair pathways. There's a lot of research on various signaling pathways that are frequently activated in ovarian cancer (for example: the MAP-kinase pathway and the PI3K pathway), and we actually have a lot of clinical trials in our institution that target these particular pathways.

There's a lot of excitement about targeting blood angiogenesis, which is tumors forming new blood vessels. We have a lot of drugs that are targeting new blood vessel formation. There are a lot of drugs [inaudible 00:10:15] drug and a lot of research that is targeting cell proliferation, B53 mutations, which are also commonly expressed in ovarian cancer, particularly the high-grade serous ovarian cancer, which 100% is associated with B53 mutations.

I think the biggest area of research right now is, again, understanding that not all ovarian cancers are created equally, and that there are several different pathways that are driving these different diseases, and that we should treat these different diseases based on the particular molecular pathway that's been responsible in these cases.

Dr. Ursula Matulonis: Right. I think that's a good lead into the fact that ovarian cancer is not necessarily a one-mutation type of cancer (like EGFR-mutation lung cancer), or even over-expressing cancer (like HER-2 breast cancer), and I know that our group has really taken the premise that maybe we should start targeting various pathways.

Dr. Susana Campos: Right.

Dr. Ursula Matulonis: Sue Campos has run two trials now that actually have combined drugs of different pathways (specifically of antiangiogenic drugs and EGFR inhibitor, plus an antiangiogenic, plus a PI3-kinase inhibition), and that's definitely been a theme that our group has really started to study. Do you want to chat about those, Sue?

Dr. Susana Campos: Yeah. These are the studies that we have done. I think what I've gotten even more interested in is we can find these mutations, but what are the mutations that actually drive the cancer pathway?

Dr. Ursula Matulonis: Right.

Dr. Susana Campos: And we've spent a lot of time, and patients have been amazing in terms of participating in these clinical trials, in terms of clinical trials with drugs that block new blood vessel formation. We're at a point where we see people responding brilliantly, and we're at a point where we don't see people responding...

So, the question is: who are these individuals that indeed do respond? I know you've done a lot of work with the angiogenic signature, so we can give the drug to the individuals that do but perhaps save some collateral toxicity.

Dr. Ursula Matulonis: Right.

Dr. Susana Campos: I was interested in the American Society of Clinical Oncology meetings this year, where there were two very important abstracts presented in terms of individuals who got this drug called bevacizumab: Who are those individuals that did respond, maybe responded better, responded poorly? I thought that was intriguing at [inaudible 00:12:53] this year.

Dr. Ursula Matulonis: Yeah, absolutely. I think there's a lot going on about we have all these different medications, although we need more targeted therapies in ovarian cancer, but bevacizumab has been the one that's been studied a lot, but it has toxicities. We want to choose our patients carefully, who go into trials and receive that drug. Dr. Campos, are there any treatments available that are easier on the body than standard chemotherapy?

Dr. Susana Campos: You know, there are different types of chemotherapy. Chemotherapy has notorious side effects, and we try to finesse the side effects using supportive elements, sometimes even utilizing chemotherapy in a different fashion. We've started to use chemotherapy, instead of an every-three-week session, perhaps a weekly session. Patients have responded in some cases—not all, granted—but in a very, very nice light.

Dr. Ursula Matulonis: Good. Panos, there are a couple of questions about specifically PARP inhibitors, and updating the audience (again, as quickly as we can) and then also about immunotherapy.

Dr. Panos Konstantinopoulos: We have very, very good evidence that the immune system plays an important role in controlling malignant progress in ovarian cancer. Actually, about 10 or 12 years ago, investigators showed that if you look at patients' tumors, if these tumors included specific lymphocytes—specific immune cells that actually could potentially kill the tumor—these patients actually did better, and lived longer. So, there is no question that the immune system plays an important role in ovarian cancer progression. The question is: How can we harness the immune system?

There have been a lot of approaches in terms of trying to stimulate the immune system to attack the tumor. For example, there have been vaccine approaches. There have been approaches, for example, that try to target the immune system against CA 125 protein that's been produced, but these approaches so far have not really produced very good results.

However, recently, we're very, very excited about these drugs called "immune checkpoint inhibitors," which, as Ursula mentioned, they have been FDA approved in diseases like melanoma. These drugs are pembrolizumab or ipilimumab. There is this theory that the tumor cells actually put a break in the immune system that's not allowing the immune system to fight the tumor, and what these drugs do is they release the break so that the immune system can fight back the tumor.

We're very excited about these immune checkpoint inhibitors in that there are now clinical trials in our institution where we're asking the question of whether these drugs, which have had such a great activity in other tumors, like melanomas and renal cell cancers, whether we can see similar activity in ovarian cancer, and that's a work in progress right now.

Dr. Ursula Matulonis: Yeah, OK. I'm going to come back to you on that. Sue, a big question: Are there mechanisms yet to reverse platinum-resistant cancer? And what ways have been attempted to try to reverse that platinum resistance and make the cells once again platinum sensitive.

That is actually a very, very important area in terms of clinical research. In BRCA mutation carriers, there can be reverse mutations that can make patients again susceptible to certain chemotherapeutic agents. I think this is your specialty, so...

Dr. Panos Konstantinopoulos: Yeah. Essentially, as Sue mentioned, one of the ways that this happens is [inaudible 00:16:32] that tumors may have BRCA mutations, which cause DNA repair defects, and they're platinum-sensitive, and then this DNA repair is reverted, and that can lead to platinum resistance. There are clinical trials that we have now that are using ATR inhibitors or NTM inhibitors, which, through our Phase I program, could potentially reinstate platinum sensitivity. Ursula recently ran a clinical trial of a drug called SGI-110 in combination with carboplatin that was actually an agent that could potentially reverse platinum resistance, and we're waiting to see what the results of this study are. The most important thing here is to understand how platinum resistance occurs, and there are multiple different mechanisms. In this situation, we should target those mechanisms so that we could potentially revert that. The other thing is that, even if a tumor becomes platinum-resistant, that doesn't mean that there may be other drugs that we can use, and we have clinical trials that we will be talking about that could potentially be of big use for platinum-resistant tumors.

Dr. Ursula Matulonis: Right. And certainly, we have a new fellow who has joined our group, Elizabeth Stover, who works at Levi Garraway's lab here, who is going to work on platinum resistance and trying to reverse it.

Dr. Susana Campos: That's a great question.

Dr. Ursula Matulonis: It's great to have a targeted MD/PhD working on that. This is a quickie, and I'm going to answer this one because it's easy: Is there a connection between ovarian cancer and HPV? The answer is no. HPV causes cervical cancer and head and neck cancers. Sue, When is the best time to consider a clinical trial? If you join a clinical trial right away, does that mean you may be using drugs you cannot use again in the future?

Dr. Susana Campos: That is an excellent question. In clinical trials, I think, at every interaction with your clinician you choose and, as a team, delegate your therapy, you should ask the question: Is there a clinical trial for which I am eligible? Oftentimes, we have clinical trials more in the recurrent setting. There are Phase I, Phase II, and certainly Phase III clinical trials.

Let's give you an example in the recurrent setting. You should always ask the question: What do I have at my disposal? There are numerous standard therapies: What clinical trials could I use at this

time? It's about organizing and tailoring the therapy to the individual so that, at the end of the day, as we treat this disease, you always have as many options as you possibly can.

As I said, at every encounter when you're about to change therapy, ask the questions: Am I eligible for a clinical trial? And there will be times when a standard therapy is more practical, and there will be times when a clinical trial should actually be considered, so it's quite important.

As you pick a clinical trial, it's not that it eliminates certain things, but there is a notion that they have eligibility criteria for clinical trials, so oftentimes, they'll say you cannot have more than two or three prior lines, so this is very important to work with your clinician and say, "How do I position my choices so that I have more choices as years pass?"

Dr. Ursula Matulonis: Right. That's a really good point, because some of the clinical trials we have open are very early on in the treatment of ovarian cancer. Yet, with some other trials, you can have received a number of different lines of therapy.

What Panos was referring to before is our onco-profile mapping that we do on all patients who walk into Dana-Farber. It really can give us some new hints or clues about what potential clinical trials are available if there's an AKT mutation or a PI3-kinase mutation, so it gives us a lot of information. Sue, another question for you: For someone who has been diagnosed with Stage I ovarian cancer, what is the risk of cancer of recurrence? And what is the chance after 5 years?

Dr. Susana Campos: When you think about ovarian cancer, we often talk about epithelial ovarian cancer, which is 90% of the ovarian cancers. Overall, a Stage I 5-year survival rate, if you were to Google it, is 90%, and I think it's important if [inaudible 00:20:47] specific to look at different types of Stage I. You have Stage IA, Stage IB, and Stage IC. Take, for example, a Stage IC. According to the literature that exists recently, it's about 85% 5-year survival rate. Now, let's talk about different types of ovarian cancers, like stromal types of tumors, where a Stage I is a 95% 5-year survival. We always measure in 5 years, and is there a magic of 5 years, a line in the sand? It tells us about the biology of the disease. I think it's very hard to give statistics after 5 years, but obviously, if people haven't recurred in the 5 years, the likelihood of them recurring in Stage I is quite low, and it's quite reassuring.

Dr. Ursula Matulonis: Yeah, that's great. Panos, My mother was diagnosed with ovarian cancer, and I was genetically tested, but results did not show BRCA 1 mutation (she was BRCA 1 and 2 negative). Are there other genes that could cause ovarian cancer? That's certainly a very appropriate question, given the New England Journal PALB2 story on breast cancer.

Dr. Panos Konstantinopoulos: Absolutely. There are other genes that are involved, although 90% of familial/hereditary ovarian cancer is caused, actually, by BRCA 1 and BRCA 2 mutations. There are other genes that have been involved in hereditary ovarian cancer. For example, there are the mismatched repair genes that are involved in that so-called Lynch syndrome, which causes familial clustering of tumors, like colon cancer, uterine cancer, and ovarian cancer. The genes include MSH2, MLH1, and MSH6, and sometimes PMS2. There is also some data about rarely some genes called RAD51C and RAD51D that have been shown in some ovarian cancer families. Ursula mentioned the PALB2 story, which has been found to be associated in patients with breast cancer.

In our institution here, we have this next-generation sequencing platform that is looking at 25 different familial cancer genes, so every patient we refer here for genetic counseling talk to them about this myriad 25-gene panel testing that includes all these genes that I mentioned (the mismatched repair genes as well as the RAD51C/RAD51D/PALB2 that Ursula mentioned, and of course, BRCA 1 and BRCA 2), so we get a comprehensive answer about whether those genes may be involved. And I want to mention also that, in many cases, even when there are families that have a lot of ovari-

an cancer, we're not able to find a gene, and that doesn't mean that there is no hereditary disposition. It may very well be a gene that we don't know about that we haven't figured out, and there may very well be a hereditary predisposition even in that case that we're not able to find. So, even if a test is negative—particularly in the setting of a positive family history—that should not definitely give us the false reassurance that there is nothing going on, so this patient should follow up with their genetic counselor and discuss ways to potentially prevent and screen for this disease.

Dr. Ursula Matulonis: Good. Sue, What options do ovarian cancer patients have if they have refractory ovarian cancer? And you might want to define for the audience what that means. And how successful are these options?

Dr. Susana Campos: Understood. There are considerable choices to actually be had. We often think of refractory as individuals who progress while they're on their induction therapy of a platinum-taxane. Other people defined it within 3 months after completing therapy. I suspect that maybe in that question there is also the concept of resistance disease, which is if an individual progresses in less than 6 months after finishing their carboplatinum and taxane, and they're resistant—so, refractory and resistance.

Dr. Panos Konstantinopoulos: There are standard options, clearly. There is liposomal anthracycline. There is topotecan. There are many standard therapies, but this really is the category of individuals that really should be seeking clinical trials, whether they be in Phase II clinical trials or whether they be in Phase I clinical trials. One of the studies that I think has been so illuminating in the last year has been a study called the "Aurelia Trial," which I think we're going to start to learn a little bit more about, and in this particular trial, patients have been treated with bevacizumab, which is avastin, and chemotherapy. But in that core group of individuals, bevacizumab and taxol really outperformed. That combination really outperformed taxol. These were, in essence, in patients who we defined as resistant. If you go back to the study, they're almost refractory because they're within the 3-month period.

There are many options, but individuals who find themselves in that situation should ask the question again—standard therapies and "What are the clinical trials?"—so they can really explore what's out there for them. There are options, and people shouldn't feel as though their back is against the wall, because there clearly are options, yeah.

Dr. Ursula Matulonis: Right, right. Do you want to mention the Cyclin E story in those patients with platinum-refractory disease?

Dr. Panos Konstantinopoulos: We start to know that some of these patients that have platinum-refractory disease have this Cyclin E-amplification—it's 20% of the patients. We're trying to figure out ways, and there are some Phase I clinical trials that we have in our institution to target these particular patients who have this alteration and have this platinum resistance and platinum-refractory disease.

Dr. Ursula Matulonis: Great. We have a lot of questions. Panos, I'm going to ask you the question... And this is more along the PARP inhibitors, because I asked you about immunotherapy PARP inhibitors. You gave a great answer on immunotherapy, but I wanted to have you speak specifically about PARP inhibitors but also your work on Hsp90. The question is: Are there drugs that have been found to have a significantly different effect for BRCA-positive versus BRCA-negative patients?

Dr. Panos Konstantinopoulos: Patients who have a BRCA mutation (who have a "BRCA-positive," as we call them), they have a defect in a specific DNA repair pathway called homologous recombination. In other words, they cannot repair DNA damage well. There are specific drugs that actually cause DNA damage that these tumors cannot repair, and these drugs are PARP inhibitors. That's one example. Other drugs are platinum. Actually, platinum is a drug that causes DNA damage that is repaired by homologous recombination. Doxil is another drug that could potentially...

These drugs seem to have a very, very good response, particularly in patients who have BRCA mutation. That doesn't mean that these drugs don't work also well in patients who are BRCA-negative, but they seem to work very, very well in patients who are BRCA-positive. There are also some other drugs that have been found in the laboratory. For example, there's a Phase I study of this drug called sapacitabine, which is a nucleoside analog we have in our institution that seems to work very well in patients who do have this BRCA mutation.

It's important also to underscore that there are other ovarian cancers that, despite the fact that they don't have BRCA mutations, they may also have defective homologous recombination, and they still may respond very well to PARP inhibitors, to platinum, to Doxil and all these drugs. So, even if you're BRCA-negative, that does not mean that you may not respond to drugs that we know work very well in BRCA-positive patients. It's actually one of the challenges in ovarian cancer, to try to identify which are these patients who, despite the fact that they don't have a BRCA mutation, may actually respond very well to these drugs.

Dr. Susana Campos: Dr. [inaudible 00:28:35] study that she presented to the American Society of Clinical Oncology really did highlight that. Our colleague utilized two drugs, cediranib and olaparib, and interestingly enough, even BRCA-negative mutation individuals responded brilliantly—actually, better! So, getting to your point, absolutely.

Dr. Panos Konstantinopoulos: Absolutely.

Dr. Ursula Matulonis: Sue, hot off the wire: Can you comment on ways that women can prevent ovarian cancer?

Dr. Susana Campos: Ways to prevent ovarian cancer: Listen to your body. Communicate your symptoms. I know we take a history every time an individual comes in. Oftentimes, patients are very distraught because they've had symptoms that they think have lasted for a little longer than they should, and the symptoms are, in essence, symptoms that are very not unique to women. In terms of abdominal bloating, early [inaudible 00:29:18], these things can happen in women all the time, but if there is a constellation of symptoms, a grouping of symptoms, present them to your physician. Address the question. Even though ovarian cancer is not as common as breast cancer, it does occur. Present them to your individual and ask the question, "Should I have an ultrasound? Should I have a gynecological examination?" CA 125 is not the answer at all times.

I think one of the key factors (especially when talking to your primary care physician) is to be very, very concrete with your family history. At times, this really clues in a physician as to the fact that this may be an individual from eastern European descent that may be more likely to have ovarian cancer. Take time to have a detailed history. Family history is important.

There is literature also in terms of the oral contraceptives, and we learned this over the years that oral contraceptives can decrease the risk of ovarian cancers. A woman has to be mindful they also have side effects, so talk very cautiously with your clinician.

Dr. Ursula Matulonis: Sue, also, a question from Andy, hot off the wire: What are some promising therapies for clear-cell cancers, which are usually resistant to chemotherapy?

Dr. Susana Campos: Absolutely. This has been one of the thorns in our side, has been the clear-cell histology, that [inaudible 00:30:31] histology we talked about. Actually, we have colleagues here and at MGH that are working very closely with clear-cell and actually looking into antiangiogenic therapeutics for clear-cell carcinoma of the ovaries, so that still is there. And again, molecularly profiling these tumors allows us to understand which genetic aberrations

exist, and that is really the launching pad to maybe a particular trial, whether it be antiangiogenic inhibitors or other inhibitors that fit mutations that we find.

Dr. Ursula Matulonis: Yeah, I think our [inaudible 00:31:02] has been, to me, really important with the clear-cell cancers.

Dr. Susana Campos: Absolutely, yeah.

Dr. Ursula Matulonis: I mean, probably more often than not, I will find PIK3CA mutations.

Dr. Susana Campos: Exactly.

In 25%.

Dr. Susana Campos: Especially clear-cell.

**Dr. Panos
Konstantinopoulos:** Yeah, absolutely.

And for those women who show resistance to platinum, I tend not to go right to Doxil or another chemotherapy, but I try to get them onto a clinical trial.

**Dr. Panos
Konstantinopoulos:** Yep.

Dr. Ursula Matulonis: Panos, do you have any thoughts about that?

**Dr. Panos
Konstantinopoulos:** I think that PIK3CA mutations are 25% of these clear-cell tumors, and I think that's great.

Dr. Ursula Matulonis: Right.

**Dr. Panos
Konstantinopoulos:** We're trying to understand clear-cell ovarian cancer from a molecular standpoint better now. There is this these [inaudible 00:31:42] mutations that about 50% of these patients have, and we're trying to find specific vulnerabilities that these patients have. I think that there's more definitely to come, but in the meantime, I think antiangiogenic agents such as Sue mentioned and PIK3CA/PI3K pathway targeted approaches are the best ways to proceed at this point.

Dr. Ursula Matulonis: Yeah. And I think, again, anecdotally, women who respond to agents that involve the PI3K-kinase pathway that I've seen have the best responses to having clear-cell cancer. I mean, I think it's—

Dr. Susana Campos: There's been a lot of preclinical work suggesting that.

**Dr. Panos
Konstantinopoulos:** Absolutely.

Dr. Ursula Matulonis: Sue, a question about nutrition: Can you speak about the role of nutrition in cancer development and how to eat after treatment to minimize the risk of recurrence?

This is a question that comes up all the time in our clinical visits. The effect of nutrition remains a little bit vague, but if you look in the literature, there are some kind of bullet points that I think we can share with individuals. There are some studies suggesting decreasing your intake of meat, especially red meat. There's some literature regarding the risk of milk and perhaps the hormones that exist in milk. That's been a theory that's been out there for some time.

I think the theory that stands now is that a person who actually has a diet that's rich in vegetables, fruits, grains, complex grains... Actually, this could be beneficial to a patient with ovarian cancers. I always try to tell my patients, "You're not just an individual that has ovarian cancer; you're an individual that has to maintain her heart, her lungs, her liver, her colon. It's important just to have a diet that substantiates that. I always think that a protein-based diet, complex carbohydrates, minimizing sugar intake... That doesn't mean you can't have your cake if you want it sometimes, but be very mindful. It's not just about the issue of ovarian cancer; it's you as a whole individual.

Dr. Ursula Matulonis: And Sue, another question for you: What are some of the symptoms of ovarian cancer recurrence? Would it just be an elevated CA 125? Or are there other signs I should be looking for?

Dr. Susana Campos: That's a very important question. People become very fearful after undergoing and taking the investment in chemotherapy. Oftentimes, if the marker was elevated to begin with, we will know before you have a symptom. It will be a rising CA 125. Let me just mention the fact that if the CA 125 goes up one month, it doesn't necessarily mean it's going to continue to go up; it's the trend of the marker that we follow.

There are times when an individual will present to us with either increasing abdominal distention. Oftentimes, we hear about changes in bowel habits. They're easily tired. They get full very easily, perhaps shortness of breath. It can be a little bit of everything.

We always tell people, "Understand how you feel now. If you have a symptom, just present it. Let us decipher it."

Dr. Ursula Matulonis: Yeah. No, I think that's smart. I think just listening to your body and us listening to patient symptoms, we really pick up a lot just by talking.

Dr. Susana Campos: A lot, yeah.

Dr. Ursula Matulonis: Sometimes a physical exam doesn't always clue you into what's going on. Panos, an important question: Can you discuss neuroendocrine ovarian cancer? And I'm actually going to put in there "small-cell ovarian cancer." What's currently known about this disease and its treatment? Is there such a thing as neuroendocrine ovarian cancer of the G.I. type? If so, what does it mean?

Dr. Panos Konstantinopoulos: So, neuroendocrine tumors are rare tumors. They're only 1% or 2% of ovarian cancers, and the most common ones are the small-cell, which are the high-grade neuroendocrine tumors, which are usually one of two types. There's the small-cell hypercalcemic type, which is associated, actually, with elevated calcium levels. There's been, actually, some genetic discovery that shows that there is a specific

gene that's mutated for these tumors.

These tumors usually involve women who are in their early age (usually age of 20 to 40). Usually they are quite aggressive tumors. They tend to present not only in the ovaries, but they present with metastatic diseases in other places very, very early. And usually, we follow the same principles in terms of management of these tumors with surgery, if we can do surgery, and after surgery, obviously, the chemotherapy. We use a specific regimen, not exactly the similar regimen we use for the regular ovarian cancer, but similar regimens. These are the small-cell cancers, neuroendocrine tumors, but there are these low-grade neuroendocrine tumors—the so-called carcinoids.

I don't know what this patient is referring to. Usually, there can be primary ovarian primary ovarian mucinous carcinoids, which look like G.I. tumors, or they can be carcinoids that are metastatic to the ovary, originating from the G.I. tract, like from the colon or the appendix. Frequently, there can be an appendiceal primary carcinoid that has spread to the ovary, or a small-bowel carcinoid that gets spread to the ovary. These are tumors that are low-grade. They're not like the small-cell neuroendocrine high-grade tumors.

We actually have a special clinic here at Dana-Farber for these carcinoid tumors that we see, and they have a special management, which usually, depending on their presentation, they can involve either local approaches (for example, radiofrequency ablation, depending on if they involve the liver) or systemic therapy with drugs like [inaudible 00:37:22] that can be used in that case.

These low-grade carcinoid tumors can be associated also with a so-called "carcinoid syndrome," because they produce certain substances that can cause various types of reactions. It's a very, very big umbrella of different rare tumors that need specialized treatment clearly.

Dr. Ursula Matulonis: Yes, I agree. I also wanted to follow up on the small-cell because it's a very rare variant. Sue, do you have any comments on small-cell? I mean, I think we've all seen...

Dr. Susana Campos: Yeah.

Dr. Ursula Matulonis: It's typically in very young women.

Dr. Susana Campos: Yes.

Dr. Ursula Matulonis: With the kind of hypercalcemic small-cell cancer type. What are your thoughts about how best to manage those women?

Dr. Susana Campos: It's to know what all options are available. I think it's fair to say that we have had a handful of individuals with small-cell, and they are difficult malignancies. They can be aggressive, so understanding what they are at time-zero is important, and [inaudible 00:38:27]. Obviously, we're going to treat these individuals with the conventional therapeutics, yes. We're going to profile the molecular.

Dr. Ursula Matulonis: Yep.

Dr. Susana Campos: But also, know that we've gotten to a point, in the past decade that we've worked, that even high-dose chemotherapy has been brought into the equation.

Dr. Ursula Matulonis: Absolutely.

Dr. Susana Campos: So, it's understanding what it is, what it can do, and picking your team very early in the upfront.

Dr. Ursula Matulonis: I would agree. I've certainly, just because of the truly aggressiveness of this cancer, thought about high-dose chemotherapy [crosstalk 00:38:55] mutation, which is really the only time that I've ever thought about that in cancer.

Dr. Susana Campos: Indeed, yeah.

Dr. Ursula Matulonis: No, true. Panos, do you want to speak about the molecular alterations that have been found recently in small-cell cancer?

Dr. Panos Konstantinopoulos: So, there was a gene called SMARCA4 that has been found to be associated in the majority of patients with small-cell cancer of the ovary of the hypercalcemic type, and they're also both somatic, which means "acquired mutation," but they're also germline, so they're families. Actually, this tumor, the small-cell ovarian cancer of the hypercalcemic type sometimes can run through certain families, and there are germline mutations, inherited mutations, genetic alterations of this particular gene that can run in families. Obviously, that has important implications.

But as Ursula and Sue mentioned, I think that these are very, very aggressive tumors, and obviously, knowing this is a very recent discovery, knowing this gene, we could potentially try to identify specific vulnerabilities of these tumors so that we could potentially identify therapies that go beyond the chemotherapies that have been mentioned.

Dr. Susana Campos: Yeah.

Dr. Ursula Matulonis: Right.

Dr. Susana Campos: And I think it's important to know that if someone is diagnosed with a rare tumor, unfortunately, there are times when people feel: "Is there a clinical trial for me? It's so rare—is there active research going on?" And there actually is—even national organizations, such as NRG has a rare tumor committee that takes these tumors that are rare and really tries to dive into them and tries to answer some questions with different chemotherapeutic agents in molecularly defined situations.

Dr. Ursula Matulonis: Yeah.

Dr. Susana Campos: So, even though you have a rare tumor, it's not that people are not interested.

Dr. Ursula Matulonis: Yeah, and I think now, more than ever, there's been better collaboration and cross-referencing with folks like us who see women with ovarian cancer.

Dr. Susana Campos: Right.

Dr. Ursula Matulonis: Translational scientists as well as basic scientists. So, the speed of the technology has really increased. The price of examining genes has dropped, and we're definitely getting more information, so I think it's a really exciting time.

I'm just going to go through these questions. Panos, this is a question that I'm not exactly sure what it means, but I'm going to ask it because it's on our list: Is there any research that is helping us pinpoint or reasonably estimate when the onset of cancer was? I'm actually going to expand that question to another realm: WHERE the onset of cancer was, given what we've learned in the past few years?

Dr. Panos Konstantinopoulos:

This a great question that Ursula actually expanded. As Sue initially mentioned, there are different types of ovarian cancers. There are the so-called high-grade serous ovarian cancer, and with this tumor, we now have some evidence that it may actually originate not necessarily in the ovarian tissue but actually in the fallopian tube tissue. Usually, there is a very clear precursor lesion that's called "serous tubal intraepithelial carcinoma," which is present in the fallopian tube, and usually, this tumor spreads inside the abdomen to the ovary and elsewhere. Usually, these tumors stand to spread quite fast. We cannot clearly say how long it took. In many cases, it could be, actually, a few months that

Dr. Ursula Matulonis: this may happen, so it's very, very important to try to identify these precursor lesions, but we're not ready to do that yet.

There are also the other types of ovarian cancers—the so-called low-grade serous ovarian cancers—which usually have precursor lesions that these are the borderline ovarian alterations, and these tumors usually have a longer period of progression and longer period of how they develop.

To answer that question, I think that how long this ovarian cancer has been depends on the type of ovarian cancer. It depends on where it originated from. It's not easy, and I know many women ask the question: "How long did I have it inside? Why didn't I pick it up? Why didn't my primary care physician pick it up?" And I have to say that, in many cases, it's just the nature of this disease that it just spreads so quickly, and automatically, people present with advanced disease, even at very, very early and very quickly, and that is, unfortunately, how it is, and it's really nobody's fault. No physician's fault, no patient's fault; it's just how this tumor sometimes behaves.

Dr. Susana Campos: I agree.

Dr. Ursula Matulonis: We have time for one more question, and then we're going to wrap up, because I want to hear what everyone is really excited about in the ovarian cancer field. Sue, the last question, and I think I know what this question is: Can tumor-freezing treatment be used in ovarian cancer or other cancers in the pelvic area? Is that successful?

I'm actually going to rephrase this question, because I think this is what that means: If somebody has an isolate recurrence, is it possible to treat that isolated recurrence with something besides surgery?

Dr. Susana Campos: Absolutely. These are a few cases, but they do exist, so if an individual recurs and there is an isolated lesion, we often look to a multidisciplinary approach. We reach out to our surgical colleagues and ask the question, "Can these be resected, number one?" We reach out to our radiation oncology colleagues, "Can this be radiated?"

But we also use tools of interventional radiology to understand whether or not these tumors could be cryoablated, and I've had several cases where these are isolated liver lesions that come back years after, and we're able to have the patients undergo cryoablation, and we've avoided chemotherapy. We've avoided radiation therapy. We've avoided surgical intervention. It's case by case, I agree.

Dr. Ursula Matulonis: Yeah, absolutely.

- Dr. Susana Campos:** But oftentimes, we'll refer our patients to our interventional colleagues with the Brigham to address this question specifically, so the answer is yes—in selective cases. The answer is absolutely yes.
- Dr. Ursula Matulonis:** I think cryoablation, radiofrequency ablation, and the radiologist will pick what best therapy to use, depending upon where the spot is, how big it is, and how safe it is to do it.
- Dr. Susana Campos:** Absolutely.
- Dr. Ursula Matulonis:** All right, quickly, before we wrap up—and I want to thank the audience today: Dr. Campos, what are you most excited about in the field of ovarian cancer right now?
- Dr. Susana Campos:** I'm excited about the fact that things are changing and that we're now longer committed to simply chemotherapy of carboplatinum and taxol. As Panos said, we're molecularly profiling these tumors. We're learning which genes actually turn on a tumor, and there's a whole category of drugs that we're starting to utilize—that we have utilized—and really tailoring the therapy to the individual. I think we've been doing this for many years, and I think what's the most exciting thing is that if you had asked us 10 years where we were and to know where we are today, it's so much more exciting today because there are so many resources, and people can have fruitful lives with ovarian cancer.
- Dr. Ursula Matulonis:** Great. Panos?
- Dr. Panos Konstantinopoulos:** I agree with Sue. I mean, I think that we have to strive to get to individualized, personalized therapy in ovarian cancer, similarly to what is happening with other cancer types. I think what I feel is an exciting field is that we are starting to understand better now platinum and PARP inhibitor resistance and trying to find approaches to overcome this. This is something that I have also been involved with my laboratory efforts to try to understand this. So, I think we live in exciting times in ovarian cancer research. There are a lot of novel drugs that are being developed, and I think that there's a bright future for our patients to fight this difficult disease.
- Dr. Ursula Matulonis:** Yeah, and I'm certainly very excited about different combinations of therapies, because we know and understand the genetic and genomic complexity of ovarian cancer. Sue talked about antiangiogenic agents. Panos talked about PARP inhibitors, immunotherapy drugs. Well, you know what? We're going to start to combine these therapies together, because sometimes one drug just doesn't work by itself, and it only makes sense that we combine these therapies because they really will tackle different innate problems in the cancer that really drive this tumor along.
I want to thank everyone in the audience. Dr. Sue Campos, thank you so much for being here, Dr. Panos Konstantinopoulos, and a good day to you all!
- Dr. Panos Konstantinopoulos:** Thank you very much.
- Dr. Susana Campos:** Thank you.
- Dr. Ursula Matulonis:** Thank you.

Announcer:

This has been Dana-Farber's Cancer Conversations featuring Dr. Ursula Matulonis, Dr. Susana Campos, and Dr. Panos Konstantinopoulos of the Gynecologic Oncology Program in the Susan F. Smith Center for Women's Cancers at Dana-Farber. To download more episodes and learn about other cancer podcast series, visit Dana-Farber.org/podcasts.