**Program Title:** Advances in Ovarian Cancer Treatment  
**Presented by:** Support Connection, Inc.  
**Moderator:** Robin Perlmutter, LMSW – Support Connection Peer Counselor  
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**Guest Speaker: Douglas A. Levine, MD - NYU Langone Perlmutter Cancer Center**

In addition to his clinical practice, Dr. Levine is the Head of the Gynecology Research Laboratory, where he studies cancer prevention, precision medicine, and rare tumors with unmet needs. He serves as the translational scientist on many national clinical trials determining what genomic alterations are associated with response to targeted therapies. He discovered universal mutations in SMARCA4 that drive small cell carcinoma of the ovary, hypercalcemic type. Dr. Levine has an outstanding level of expertise and leadership in ovarian and endometrial cancer research and a deep commitment to women’s health.

Dr. Levine has been very active within the NIH-sponsored Cancer Genome Atlas project (TCGA). He serves as co-chair of the ovarian, endometrial, and uterine carcinosarcoma disease working groups. He is a member of the Scientific Advisory Committee of the Ovarian Cancer Research Fund, the Clearity Foundation, and the Honorable Tina Brozman Foundation. He has authored or co-authored more than 200 peer-reviewed articles and two textbooks.

Dr. Levine has received funding from the National Cancer Institute, the Department of Defense, Stand Up 2 Cancer, and the Gynecologic Oncology Group. He has been awarded the American Congress of Obstetricians and Gynecologists Mentor Award, served as co-chair of the American Association for Cancer Research Special Conferences on Ovarian Cancer, received the 2013 Foundation for Women’s Cancer Excellence in Ovarian Cancer Research Prize, is the Assistant Dean of the Department of Defense Ovarian Cancer Academy, and was recently appointed as translational science co-chair of the NRG Oncology Corpus Committee.

**Topics:**
- The newest info on the development of drugs for advanced ovarian cancer
- The most current FDA approvals for ovarian cancer
- Information presented at the most recent national conferences
- A question & answer period

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**Robin Perlmutter:** Please remember that Dr. Levine is sharing his expertise, and any information from tonight or questions pertaining to individual concerns should be discussed with your doctor. It is with my great pleasure that we have Dr. Douglas Levine from NYU Langone Perlmutter Cancer Center. In addition to his clinical practice, Dr. Levine is the head of the Gynecology Research Laboratory, where he studies cancer prevention, precision medicine, and rare tumors with unmet needs. He serves as a translational scientist on many national clinical trials determining what genomic alterations are associated with response to targeted therapies. Dr. Levine has an extensive list of credentials including work with the NIH, Ovarian Cancer Research Fund, Clearity Foundation, American Association for Cancer Research, and the Honorable Tina Brozman Foundation. Thank you, Dr. Levine, for sharing your time and expertise with us tonight.

**Douglas Levine:** Thank you. Good evening to everyone on the East Coast, and good afternoon to anyone on the West Coast. Great. So, I was asked to discuss advances in the treatment of ovarian cancer, which I'll do over the next 30 to 40 minutes. And, again, thank you all for joining us this evening. And the outline will be basically to discuss some of the latest developments in surgical trials, the medical trials, cost-effectiveness, and a review of PARP inhibitors and their use in the maintenance setting, and then we'll take some questions and possibly give some answers.

So, just a few bits of background before we get started. Many of you who have been with us for a while know that one of the latest bits of development that we’ve learned in the past 5 to 10 years is that ovarian cancers are not one disease, they’re many diseases. They come from different sites of origin, they come from different cellular origins, and they have very different genetic makeups. I like to say that the diseases in the ovary are as different as the diseases that occur in the chest. For example, you wouldn't
think that breast cancer and lung cancer are really one disease just because they both can occupy the chest, and ovarian cancers can come from the fallopian tube, they can come from endometriosis, they can come from the ovary, and they're very different diseases. We've learned a lot about each of these diseases, and in the pie chart on the right side, it sort of shows some of the genetic defects that we've learned about in the most common type of ovarian cancer called high-grade serous carcinoma, the type that is often what you read about when you read about ovarian cancer. It's the most aggressive and it's the one that usually presents at advanced stage, and we know a lot about that type of ovarian cancer.

The next slide here shows a depiction of where these cancers come from, and, as I mentioned, we do think that high-grade serous carcinoma originates at the end of the fallopian tube, or at least most of the cases do; there's always some exceptions.

The next two most common types are called clear cell carcinoma and endometrioid carcinoma, and we think that those grow out of something called endometriosis, which can develop through a retrograde menstruation where endometrial cells can implant into the pelvis, and that's very common. And every so often that endometriosis can turn into clear cell or endometrioid carcinoma. And so those are the most common types of ovarian cancer. And tonight we'll mostly be talking about high-grade serous carcinoma because it's the most common and it's the most aggressive.

This next slide, really, is just a reminder for me to remind everyone that genetic testing is very important. All women with ovarian cancer or first-degree relatives of someone who had ovarian cancer should be tested for mutations and BRCA1 and 2. These are called germline mutations that can be inherited, and these can be tested with a blood test or a saliva sample. They are generally covered by insurance, and there is protections against medical insurance discrimination. This testing is very important because it can guide treatment. We have a number of drugs called PARP inhibitors, which work quite well in women who carry BRCA mutations and have ovarian cancer. And probably more important and most important is that BRCA-associated ovarian cancer is almost completely preventable if we do identify everyone who has a BRCA mutation or mutations and a few other genes. At the right time we can do a risk-reducing surgery, which will mostly eliminate the risk of cancer in those people. And BRCA mutations may account for up to 20% of ovarian cancers, and if there’s about 22,000 cases of ovarian cancer every year, we can reduce that by 4,000 cases right away, today, if we were able to identify everyone who had -- who carried a BRCA germline mutation, or a mutation that's inherited from their parents. And so it's very important for cancer prevention.

It's also important that when we do identify a patient or a woman who has ovarian cancer and has genetic testing and is found to have a mutation, we then offer testing to all of their first-degree relatives, so those people can (1) figure out if they're at risk, and only 50% of those people will be at risk because there's only a 50% chance that you'll inherit a mutation from one of your parents. And then if they are at risk, we can discuss what preventative options are available, including birth control pills. And if they're not at risk, that's a reassuring sign that I would imagine is good to know.

So, again, I'm sort of belaboring the point, but everyone with ovarian cancer should be tested for mutations in BRCA1 and 2, and we're pretty good at doing that nowadays -- not perfect, but pretty good. But we're not quite as good at making sure all family members get tested, and that really requires a collaboration between patient and provider.

So, I think my last introductory slide is just that the general treatment of advanced ovarian cancer is to start with an aggressive surgical procedure to try to remove all cancer that is visible to the naked eye. We can do this about 50% of the time, and about 75% of the time we can remove all large-volume cancer, and that's good and that's helpful. And then it's only helpful because we follow it with chemotherapy. That typically consists of carbo and Taxol, or some type of taxane and some type of platinum agent given in combination. And most patients will go into remission after that treatment, and then frequently that will be monitored with either a CA-125 blood test that's really designed to monitor cancer; it's not designed to
screen for cancer. And for about half the patients or so, cancer will come back at some point, and it will be treated again with either surgery or chemotherapy, and some of the studies that we're going to discuss will shed light on what that proper treatment is.

The one caveat is that traditionally we always thought that surgery was the best initial treatment, and there were some studies to suggest that maybe chemotherapy should be given before surgery to make the surgical operation easier. And that's an area that's been very controversial in our field, and there have been some studies that I'll go over to suggest that maybe that's true or maybe that's not true, and as of today we still don't quite have the right answer.

And so that leads to the first study that was presented at one of our national meetings in early June called the American Society of Clinical Oncology, or ASCO. And this was a study from Japan, where they were comparing upfront surgery or initial surgery compared to neoadjuvant chemotherapy. So, neoadjuvant chemotherapy means that you give chemotherapy first, and then you do surgery later, usually after three or four cycles of chemotherapy. That's in contrast to primary surgery, or initial surgery, which technically is initial surgery followed by adjuvant chemotherapy. So, adjuvant chemotherapy is when chemotherapy is given after some other treatment, like surgery, and neoadjuvant chemotherapy is when it's given before.

And so this trial comes in the background of a few other trials that I mentioned. So, these trials that you see here, called the EORTC trial and the CHORUS trial, were done in Europe and the United Kingdom, respectively, and they did not show any difference in giving chemotherapy first or doing surgery first. However, in all of the studies there was a selection bias, and the outcomes of the entire study were really not that good. And we weren't sure if they were not that good because it was only sort of the difficult cases that were put onto the study, or if the surgery done in the studies was not so great. And so these studies were hard to interpret, which led to a lot of controversy in our area. And so the Japanese clinical trial group took patients with advanced cancer and randomized them to have initial surgery or initial chemotherapy, and that's what's depicted on this slide. And their goal was to prove that neoadjuvant chemotherapy was not worse than debulking surgery. And I'm not 100% sure that's the right question to ask, but we'll get back to that in a few minutes.

And so they tried to accrue 300 patients. They needed to do this to show that there was no difference between surgery and chemotherapy. They actually did enroll 300 patients as planned, and you can see here they are pretty much evenly divided between the two arms of the study. And as expected, patients had stage 3 and stage 4 disease, which is shown here.

And then this is an interesting slide about the surgical outcomes. And so their initial surgery actually took less time than when they did surgery after chemotherapy, which doesn't really make a lot of sense. Usually it takes more time to do surgery initially. And then if you look at this number -- I'm not sure you can see my cursor here, but 37% of the time, when they did primary surgery, they could remove all cancer that was more than 1 centimeter, and they could do this 60% to 80% of the time after giving chemotherapy. This 37% number is a little bit on the low side, so another problem with this study. But when they did this, they showed, as expected, that when all the cancer was taken out, patients did much better. That's not new information, but when they put this in comparison between the arms, they could not show any difference between surgery first or chemotherapy first. But the one good thing that is shown at the bottom of the slide as far as overall survival is that all patients on this study did much better, almost twice as well, as in the United Kingdom trial, and at least 50% better than in the European trial. And so it was gratifying to see that this is a good group of patients who have a survival of what we expect in general, but still they could not show that the chemotherapy was not worse than the debulking surgery. And so it was sort of a negative study without showing differences between the two groups. But, again, not 100% clear this is the right question, and so they are concluding that chemotherapy cannot always be a substitute for initial debulking surgery.
Now, this is very different from a paper presented only in poster form at our ASCO meeting by the -- an Italian group of investigators from Rome. This group of surgeons launched what’s called the SCORPION trial. And the unique thing about this is the Italians are known to be very good surgeons, and so the investigators here are well known to us as a profession, and we know that they’re very aggressive and they’re very good surgeons. So, what they did here is they only took patients who had what they called a high tumor load, and that was determined by doing laparoscopy, where you look inside the belly with a camera and patients had to have a score of 8 or above, which means they had to have a high burden of cancer. And so these were not easy operations. These were real, bona fide, major surgical operations. And they did this, and what you can see here, there is a lot of data here, but I'll just call your attention on the right side. You can see here that between 47% and 45%, which is over 90%, so 93% of the time they could take out all the cancer that was more than 1 centimeter. So, that's contrasted to the Japanese study, which is only done 37% of the time. So, this is more than, you know, twice as good, and that's just a reflection of this group of Italian surgeons who are known to be very good surgeons. And so that was gratifying.

Most patients had what we call upper abdominal disease, which means extensive cancer. And then when we looked at their outcomes, they also failed to show a difference between surgery versus chemotherapy. This is only a poster; it's not a finalized study. We don't have the full report, but they conclude, at least based on the data to date, that new adjuvant chemotherapy followed by surgery is not better than doing surgery alone or doing surgery first.

You've heard me say a couple of times that I'm not sure this is the right question, because most of us would believe that surgery is better. And so the question we'd like to answer is, is surgery first better than chemotherapy first, or are they equivalent? We’re not trying to prove that chemotherapy is better. We think chemotherapy might be worse. So, we either have to prove that they are equivalent or that surgery is better. And the way you design trials really depends on what question you’re trying to answer, and I’m not 100% sure that either of these studies were necessarily asking the right question. But so far, and particularly this early data from the Italian group, suggests that for patients who have a high burden of cancer, that maybe surgery is not better than giving chemotherapy first. However, with all the data that's available today, the controversy still continues. If you ask 10 different GYN oncologists, you'll get 11 different answers. And it really speaks to the fact that these types of treatments have to be individualized, and every patient is different and every cancer is different, and where the cancer is located and where the surgeon is located both play an important factor in what is best for both the patient and for the situation.

So, moving away from initial surgery, the next trial, which is an American trial from the Gynecologic Oncology Group that has been renamed the NRG Oncology Group, was asking two questions. This was a randomized Phase 3 trial called 213, and the background here is whether bevacizumab is helpful in treating recurrent cancer. That’s the drug that targets blood vessels, and whether surgery is also beneficial for patients when cancer comes back. This is in the background of something called the DESKTOP III study, again, a European study. The Europeans often do trials before the Americans can get their act together and do the trials, possibly due to regulatory issues that we have in the United States to protect patients and doctors. But this study is from a German investigator group, and they showed that when you also take patients that meet certain criteria and you do surgery versus no surgery. In this study doing surgery did lead to a better progression-free survival, which is how long it is until the cancer comes back, but they do not have a measure yet of what’s called overall survival.

So, with that as background, the first question was, does the addition of bevacizumab lead to an improvement in overall survival for platinum-sensitive recurrent ovarian cancer? That's when the cancer recurs more than six months after the last platinum-based chemotherapy treatment.

And so this is a complicated schema that I will skip and just jump to the results here. There was a small benefit to receiving bevacizumab. Here it was on the order of about five months, and in this pink box
here it's really a borderline statistical significance depending, really, on how you do the analysis. And this is basically what every study with bevacizumab shows, is that there is about a four- to six-month advantage. This is almost the first study that shows what's called an overall survival advantage rather than a progression-free survival advantage. And so bevacizumab works. It works pretty much whenever you give it. It works a little bit, so it works three to five months, which is good but not great. And there is no right way, you know, when to give bevacizumab. At my center we usually don't give it initially; we usually give it when a cancer returns.

But the other question was, should surgery be performed for recurrent disease? And that was the question where basically patients who were surgical candidates were randomized to surgery versus no surgery. And that's the eligibility. There were about 450 patients -- I mean, 485 patients enrolled in total. We had trouble reaching the accrual in the United States, so we reached out to our Korean colleagues. The Korean and the Japanese both have excellent clinical trial groups, and the Korean clinical trial group put on almost half the patients onto the study.

And so about 60% to 70% of the time all cancer could be removed, and the main findings were that there was no benefit to surgery when performed for recurrent ovarian cancer compared to not having surgery. A couple other analyses showed there was no benefit in progression-free survival, but keep in mind, only 60% to 70% of people could have all the cancer taken out, which was the goal of the surgical operation. That led people to say, well, what if you could take out all the cancer? And here you can see this top red line is when all the cancer is removed, and the blue line is when all the cancer could not be removed, and there seems to be a benefit certainly in progression-free survival when all the cancer could be removed, and that's not something new.

But on this final slide what I'll show you is that for progression-free survival, when all the cancer could be removed, there was a benefit compared to not doing surgery at all, keeping in mind that all the cancer could only be removed 60% to 70% of the time. And this did not lead to a benefit in overall survival.

And this was pretty well tolerated, but it does lead to the conclusion that what we call secondary cytoreduction was not associated with an improvement in outcomes in general. There was a benefit when all the cancer could be resected. And so this will lead to a little more controversy. I think most of us are still recommending secondary cytoreduction in certain circumstances, but those recommendations are a little more limited in light of this randomized trial that was recently reported. Again, keeping in mind this paper has not been published, and the reason I keep mentioning that is that the data is not really finalized until the manuscript or the paper is accepted for publication. Because at that point there is a very rigorous analysis of all the statistics to make sure there were no mistakes. And we all make mistakes and sometimes we can make very important mistakes in clinical trials, and so just before something gets published, it's -- the analysis is done just about as rigorously as possible to minimize the chance of any errors in the data. And that's really when the results are considered finalized.

So, moving on a little bit to targeted therapies. This slide is just an overview of something called synthetic lethality, and that's the concept behind PARP inhibitors that are now FDA approved in many situations for ovarian cancer, and now recently for breast cancer. Basically, cancer cells undergo damage, particularly when they're subjected to chemotherapy, and they have different ways to repair that damage. And repairing that damage is good for the cancer cell but not good for the patient. So, the cancer cells want to survive and we don't want the cancer cells to survive. We want the cancer cells to die and the patient to survive. And so some of the ways by which cancer cells repair DNA damage is by using a protein called BRCA, BRCA1 or 2, and another protein called PARP, and those are responsible for two different types of DNA damage. Now, if you have a BRCA mutation or receive a PARP inhibitor, one type of DNA repair will be eliminated, but the cancer cell has alternative mechanisms and the cancer cell will still survive. But if you give a PARP inhibitor to a tumor that is deficient in BRCA1 or 2, now the cancer cell cannot survive, and that's precisely why the PARP inhibitors work so well in the context of BRCA mutations. And that's what's shown on the bottom left on this graph. It's what is called a waterfall plot, and when the bars go
down, that means the size of the cancer is going down. And here you can see in BRCA1 and 2 carriers, a lot of the patients, which is each bar, are experiencing tumor shrinkage. And on the right side, here the bars are showing patients with and without BRCA mutations, and this leads to the point that some tumors even without BRCA mutations will have a response to PARP inhibitors. And so that’s the basis for a lot of the PARP studies that have been done. But now we’re moving on to do PARP studies in combination with other drugs to expand the arena of patients that will benefit from PARP inhibitors.

So, this was an early study looking at a PARP inhibitor and a mTOR inhibitor. An mTOR is responsible for different types of cellular growth, and if you inhibit mTOR, certain pathways will not be activated, which can lead to cell death or death of the tumor cells. And this study was done in endometrial cancer, in ovarian cancer, and in breast cancer. It was done out of MD Anderson Cancer Center.

This is the same slide that I showed before about how PARP inhibitors work. And you can see here the patients were pretty much evenly distributed between those with the different types of cancer that I mentioned. And the remarkable thing is that even in the -- for the ovarian cancer patients I’m just showing here, many had platinum-resistant disease, which is obviously more difficult to treat, and most of them did not have BRCA mutations. And so this is not a group that you would necessarily think would be sensitive to PARP inhibitors, but, in fact, when you add the mTOR inhibitor to the PARP inhibitor, 20% of patients will respond, which is probably a little bit higher than expected. And that was the same basically across all of the arms. For ovarian cancer, in particular, there was a 20% response rate. Now, that’s not great, but it is about twice as high as you would expect for platinum-resistant ovarian cancer without BRCA mutations. So, that was promising, if not great. We’d certainly like to do a lot better and need to do a lot better, but that’s a good start for a unique combination that was pretty well tolerated.

However, a slightly more exciting study combined a PARP inhibitor with an immune checkpoint inhibitor. So, neratinib is a PARP inhibitor that we just talked about, and pembrolizumab is one of several immunotherapies that works through a mechanism called immune checkpoint blockade, and it really prevents the cancer cells from hiding from the body’s own immune cells and the body’s own immune system. And so this is a study led by investigators from Dana Farber Cancer Institute, another fine cancer center in Boston. And here it was only for women who had platinum-resistant or refractory ovarian cancer. So, this was a very -- these are very challenging tumors to treat, usually not with BRCA mutations. And in this study the idea is that activating -- creating DNA damage may sensitize the PARP inhibitors, but it may also activate the immune system. And using an immune checkpoint inhibitor will allow the immune system to recognize the cancer cells, and that’s the rationale behind the combination of a PARP inhibitor with an immune checkpoint inhibitor.

And so there was an initial phase and then a more extensive testing phase of the study. The study is called TOPACIO, and 60% of patients had previously received bevacizumab. There were about 60 patients on the study altogether. Many of the patients had -- as required, most patients had platinum-resistant or platinum-refractory cancer, and most patients did not have a known BRCA mutation.

And what you can see here is there was a 25% response rate. Again, for platinum-resistant cancer that’s not bad. It’s almost bordering on good. I don’t say that too enthusiastically, because it’s still, you know, relatively low, but I felt it’s better than we had been doing, and so you have to start somewhere and go from there. And so this is a very promising study. And you can see from this waterfall plot that the patients who responded is a combination of patients with BRCA mutations and without BRCA mutations. And so that’s fairly promising.

And another very fascinating thing is that it really didn’t matter if you had a BRCA mutation or not. The response rate was about the same, which suggests that the combination is doing something completely different than the PARP inhibitors are doing by themselves, and so that’s exciting for future studies. And this is also a fairly well tolerated treatment. And so this will go on for additional testing.
The last main treatment study here is specifically an immunotherapy study. And this is a pretty important study, because patients frequently come in and say, you know, can I get immunotherapy, because we've heard of so many great responses to immunotherapy in general in many other types of cancer, including lung cancer, colon cancer, brain cancer, melanoma. There's lots of really great responses from immunotherapy. So, a lot of patients say I want to receive immunotherapy. And so this is a study that, again, was measuring the response in patients who have recurrent ovarian cancer. They had two groups based on number of prior treatments. As patients get more treatments, it gets more difficult to be successful with those treatments, and so there was a stratification for the number of prior lines of treatment.

And they also measured the expression of something called PD-L1, which is really the immune checkpoint blockade protein. And they used a score called a CPS, combined positive score, which basically counted the number of cells that express PD-L1, with the idea that if you express more PD-L1, you'll have a better response to these checkpoint inhibitors. And so, again, the only thing to note on this slide is that a number of patients did have platinum-resistant or relative platinum-resistant disease, which is an important factor here.

But the response rate was only 8%, and so that's very low. That's not really a great response rate even in the earlier group. It was actually more responsive in patients who had more lines of prior therapy. There were over 350 -- there were 375 patients in the trial. This was a huge trial, and the response rate was not great. However, for the people who did respond, the median duration of response or almost the average duration of response was eight months, and that's not bad in this type of population with lots of prior treatments. That's actually pretty good. And so there's a small group of patients who did okay, but the overall response rate is quite low, 8%. It's not that much better than we get with, you know, other types of chemotherapy. So, this is the reason why, if you go to your doctor and say I'd like to get immunotherapy, I have high-grade serous ovarian cancer, he or she might say, well, we don't really recommend it. Because so far the single agent response rate, when we give immunotherapy by itself, it doesn't work that well. It does work for a small number of patients, but it does have some serious toxicities. There's about a 1% risk of death from immunotherapy. There can be very toxic side effects that was just reported recently in the New England Journal of Medicine. And so it's really a careful balance. And so in general, this by itself is not the most promising and most exciting drug. In contrast, again, to the trial I presented previously, where a PARP inhibitor with an immunotherapy drug, that worked much better, at 25% compared to 8%.

This is the waterfall plot. And this is the conclusions that I basically just mentioned, except for the fact that it did seem that when the tumors expressed more PD-L1, that was associated with a slightly higher response rate. So, theoretically, that could be a biomarker that could be used in the future to assess response.

The last part here really asks the question as to how much does all this cost? You know, cost is one factor. It may not be the most important factor, but certainly people who approve these types of drugs often ask that question. And so this group of investigators did some modeling. And just as an example, basically, most drug costs go down over time, and so you can argue that the price of drugs is really, you know, arbitrary and relative, and we can all make our own opinions as to why drugs are priced the way they are, and I won't pass any judgment on that right now. But this does show that the price of Taxol has come down, you know, many, many fold, from almost $1,000 a dose to $150 a dose. And, in fact, no one really wants to do clinical trials of Taxol anymore because for the drug companies it doesn’t pay, and so therefore they don't want to study Taxol so much. And we do have better drugs than Taxol nowadays, but it's a very inexpensive drug, and that's good because we use it a lot and it's quite effective.

So, these guys, this group of investigators compared a number of trials using a number of different drugs, including the PARP inhibitors, bevacizumab, which targets blood vessels, pembrolizumab, which targets the immune system, and paclitaxel. And here on the right side, when you consider the cost of the drug
and the risk of complications, you can see the overall cost, and you can see basically PARP inhibitors are the most expensive drugs right now. Bevacizumab is less expensive, and Taxol is really the least expensive drug based on how it's given, the drug cost, the pretreatment costs and the toxicity costs. And so they considered both response and complications in their analysis, and this is basically the outcome in the top right. These are the most effective and the most expensive drugs.

Bottom left is the least effective, least expensive drugs, and the bottom right is kind of the best of the -- it's the most effective and the least expensive. And so, in fact, bevacizumab and paclitaxel are much more cost-effective than the PARP inhibitors. And this is somewhat informative when you're, I guess, thinking about healthcare delivery. For an individual patient I think there's many considerations that have to be thought about. And so, basically, because the PARP inhibitors cost a lot of money to get started because of the BRCA testing, and because they work so well, people take them for a long time, and that's really why they have become very expensive.

And so just in the last couple of minutes, I just want to highlight a couple of things, going back to the BRCA mutations that we talked about. Again, it's important for cancer prevention to identify as many people as we can with BRCA mutations. This lovely waterfall is a picture to remind us about cascade testing. This is a cascading waterfall, and it's very important that when someone is found to have a BRCA mutation that all of their first-degree relatives are tested so we can give them proper counseling regarding cancer prevention.

One thing that is kind of tricky is when to give PARP inhibitors. So, on the bottom right here, there's two scenarios, and the real question is, do you give PARP inhibitors in what's called the maintenance setting? When someone has completed chemotherapy, is now in remission, should they take a PARP inhibitor to keep them in remission as long as possible, until the cancer comes back and then switch to something else? Or should they not take the PARP inhibitor and keep that remission going on its own as much as possible, and then start the PARP inhibitor when the cancer does come back? There's reasons to do both approaches. I'll just say that PARP inhibitors are very well tolerated for many people; on the other hand, they also have side effects for many people. And in one study, about a quarter of the patients on a PARP inhibitor needed to receive a blood transfusion, and that's kind of a big side effect. Instead of doing nothing and not being tired and not having an upset stomach, you could be at the beach or you could be taking a PARP inhibitor.

So, obviously if the therapy works we want to give it to people, but the real question is -- it certainly does work, there is no question about that -- but the real question is, do you give it early or do you give it later on?

These are basically the three PARP inhibitors that are now FDA approved for the maintenance setting after platinum-sensitive recurrence. So, that means that cancer has come back, the first time usually. It's been treated with platinum. It's gone away again, so it's gone back into remission, or the cancer is responding, but typically it goes back into remission or there is a pretty good response. And then what you can see in all these numbers is that you give a PARP inhibitor in this situation to someone who has a BRCA mutation, the benefit is about 10 to 15 months, which is really great. I mean, that's a whole year, which is great. If you give it to someone who doesn't have a BRCA mutation and doesn't have any problems with DNA repair, they really don't work that well. They work very minimally, and that's another controversial area, is whether PARP inhibitors should be given to everyone or they should only be given to patients who have BRCA mutation or a tumor that has something like a BRCA mutation. And these are questions that we don't know all the answers to, and a lot of this comes down to judgment and having a careful conversation of risks and benefits, and basically the priorities for individuals.

And so my last slide sort of just talks -- takes us all the way back to initial diagnosis, and there have been lots of great clinical trials that I've put on the past couple of years. I wasn't going to talk about all of them today, but some of the current controversies that we really have no answer to is should chemotherapy be
given directly into the belly? So, we used to think that intraperitoneal chemotherapy or chemotherapy that goes right in the belly was great, and it probably is great for some patients and probably is not necessary for some patients.

The second figure here shows the question about whether Taxol initially should be given every week, on a weekly basis, or should be given every three weeks? And we don’t have a great answer to that. I think it depends probably whether or not you are receiving bevacizumab at the same time, and there probably is a benefit to giving paclitaxel every week.

And the final graph on the right talks again about bevacizumab, when should bevacizumab be given? Should it be given initially or later on? In Europe it's given a lot of times initially; in the US it's usually given later on. But these are all controversial areas and, again, if 10 different people gave you 10 different answers, unfortunately that would be very reasonable. So, we don't have all the answers. We're continuing to work on the answers.

A few of the take-home points for tonight is just that neoadjuvant chemotherapy is not superior to primary debulking surgery or cytoreductive surgery. Secondary cytoreduction may prolong progression-free survival, but it does not seem to have a benefit to overall survival and has to be used selectively. Combining PARP inhibitors with other agents is very promising. Using immunotherapy by itself is less promising. Drugs are expensive and that’s a consideration. And here at the NYU Perlmutter Cancer Center we have many Phase 2 and Phase 3 clinical trials for ovarian cancer, endometrial cancer, and cervical cancer.

A lot of the data that I presented tonight was worked on by others. Probably all of it was work done by others. I don't think I played a role necessarily in the studies that I talked about. My research involves a lot of preclinical work and cancer prevention and rare tumors, and things with precision medicine. And so I thank all the speakers who contributed the slides to the public domain and anyone who I stole slides from.

And, finally, it does take a big group, but this is my clinical group here at NYU. This is my laboratory. We just built a brand-new hospital that opened a few months ago. It's all single-bedded rooms, the first single-bedded room hospital in New York City. It has a beautiful view of the East River and Empire State Building. But all this work really takes a village, both of the doctors, the scientists, and most importantly, the patients. And, really, I think most of us, particularly in my group, we really consider this to be a partnership and we're working together, patient and doctor, to try to have the best outcome for each individual person, and as a group, trying to expand what science can do to help patients overall. So, thank you again for listening and joining us tonight, and I'd be happy to take any questions.

Caller #1: -- my wife here, who has stage 4 ovarian cancer, and I got the impression that the early trials in immunotherapy, or the actual FDA-approved immunotherapy, but that 8% figure is not promising. And yet a lot of us have been holding our breath waiting for something big to happen in that area. Is anything big going to happen in immunotherapy for ovarian cancer?

Douglas Levine: So, that's a very good summary. And immunotherapy has been very exciting for many types of cancers, including for some, endometrial cancer; it has not yet been very exciting for ovarian cancer. It has a lot of potential, and what we're trying to figure out now is why is it that immunotherapy does not work as well for ovarian cancer as it has worked in other cancers. There are some really great people doing some really great work, and that's where the combination therapies come in. So, going from 8% to 25%, I mean, that's a threefold improvement with the combination with PARP inhibitors. So, that's one promising -- and, again, that's in a population of people who have received many lines of therapy, so you could imagine if we gave it earlier, it would probably work even better. So, I don't think we're going to see the big immunotherapy advance in the near future. I think it's going to take a lot of work with
combination drugs, both targeting different aspects of the immune system and putting it together with other types of treatments.

**Caller #2:** Dr. Levine, one thing that you didn’t mention was that if there’s a BRCA mutation that’s somatic, the germline blood testing is not going to show up and you need to have your tumor analyzed, and the Clearity Foundation does that.

**Douglas Levine:** Right. So, a couple of things there. So, we were talking about prevention. I was talking about BRCA mutation most in the context of prevention, in which case it is only the blood test BRCA mutations of the inherited. One is called germline mutations. But you’re completely correct, about 5% to 10% of tumors will have what’s called a somatic mutation, which is just in the tumor. It’s not inherited; it can’t be transmitted to children. But it does result in a response to PARP inhibitors, and so we do have tests to do that nowadays. Clearity Foundation actually doesn’t do the testing. They can help people get testing. They are also extremely helpful in interpreting the testing. The testing -- doing the testing nowadays is actually not that difficult. Interpreting it is really hard for both patients and doctors, and so the Clearity Foundation can be very helpful in interpreting those tests and letting you know what the important questions are to ask, and also contributing to their research to try to figure out how to combine the results with the proper treatments. So, very good point. So, somatic mutations are different than germline mutations. They both result in response to PARP inhibitors, but only germline mutations can be inherited.

**Caller #3:** Dr. Levine, as someone who is a garden-type variety, got no -- anything exotic (inaudible) BRCA, what do you know about durvalumab and its being studied?

**Douglas Levine:** Durvalumab is another immune checkpoint blockade inhibitor by another company. It is one that has had slightly more promising results but not -- I wouldn’t certainly call it a homerun. So, it’s just another immunotherapy being tested, and it probably also is being tested by -- with other combinations. There was one report for durvalumab about a year or so ago. I haven’t seen anything lately reported in ovarian cancer, but I’m quite confident there are ongoing studies.

**Caller #4:** Dr. Levine, can you talk a little bit about aromatase inhibitors and getting those in. (Inaudible) primary peritoneal. I’ve been on just about, I think, everything you’ve mentioned and then some, and now I’m on Avastin maintenance and they want to add in a aromatase inhibitor.

**Douglas Levine:** Sure. So, the main sort of breakthrough or new knowledge with aromatase inhibitor is actually in low-grade serous carcinoma, which I didn’t talk about at all. So, low-grade serous carcinoma is a pretty rate type of ovarian cancer. It can affect younger people. It can come back over a long period of time. But about two -- I think it was about two years ago, maybe three years ago, David Gershenson of MD Anderson has really been one of the experts and leaders in this particular area, reported on a very large retrospective series of women who were treated for low-grade serous carcinoma and then after the treatment as a maintenance therapy, like what we’re talking about, some took an aromatase inhibitor and some did not. And those that took the aromatase inhibitor seemed to have the cancer stay away for a much longer period of time. And so now for low-grade serous carcinoma, this is becoming a standard of care that many of us are using.

For high-grade serous carcinoma, it’s much less clear how effective an aromatase inhibitor is. It’s not a bad treatment. You know, a lot of cancers do express estrogen receptors, which is one --

**Caller #4:** (Inaudible)

**Douglas Levine:** Yeah, so, again, a lot of high-grade serous carcinomas will express the estrogen receptor. It doesn’t mean that the estrogen-targeting drugs work that well. And so that's one of the shortcomings of some of the molecular testing platforms, like you mention, is that they’ll do a test and it will seem like a drug should
work, but that has not been tested in the clinical trial. And so it does make a logical sense, but there aren’t studies to show, you know, if you took an aromatase inhibitor versus a placebo, how much better would it work? Now, it may work, and so people try that, and you’re trying that and I certainly hope that it does work, but we don’t have data to suggest that just based on the estrogen receptor positivity in high-grade serous carcinoma, because there’s so many other things going on, that the aromatase inhibitors are highly effective. Having said that, we often use them when people have a little bit of cancer coming back, maybe the CA-125 is going up, but there is no clear evidence of disease. Maybe in combination with something else, like you’re doing, that would make sense, but we just really haven’t done those trials.

Caller #4: My number is up but still normal and now they want to put something else in to possibly quell it.

Douglas Levine: That’s really why clinical trials are so important. So, whatever happens to you hopefully will be great, but we don’t know if that’s just the natural history of your particular cancer or is it because you actually took the aromatase inhibitor. And if someone else didn’t take it, would the marker go up just as quickly or just as slowly? And that’s really why it’s so important for us to conduct and for patients to help us run clinical trials, so we know these answers. Because, as you know, aromatase inhibitors have side effects, they give you joint pain. You know, they’re pretty well tolerated, but some people have to stop them. And if they’re ineffective, you wouldn’t want to take it, but we really won’t know that unless a clinical trial is performed.

A chat question is when do you think CAR T-cell therapy will have a receptor that is useful in ovarian cancer? So, I think this is a question about CAR T-cell therapy. So, CAR T cells are chimeric antigen receptor T cells, and these are really engineered T cells that can be designed for a specific tumor. And these actually have been very promising, but they’re very difficult to make and we can’t make them in large quantities yet. And they haven’t been extensively tested, but there’s some very promising results from a very small number of patients. This is a completely different type of immunotherapy than what was -- than what we’ve been talking about with the checkpoint blockade. That’s why all immunotherapy is not the same. This type of immunotherapy is very tricky and complicated, but so far it has been promising. Can we get it to work for everyone? Can it be safe? There is certainly some toxicity.

There’s a couple of trials going on. University of Pennsylvania has been some of the leaders in this area, as has Memorial Sloan Kettering is just getting their program up and running in the clinical side for ovarian cancer. They’re doing a lot of stuff in other cancers. And so these are great studies. I’d encourage anyone to go on them if they’re eligible. It’s a lot of work, it’s a lot of blood transfusions and things like that, but there has been some promise to CAR T-cell therapy so far.

Robin Perlmutter: Do you have some more questions, folks?

Caller #5: Dr. Levine, I was wondering, I’ve heard about maybe a just beginning trial, but molecular profiling for ovarian cancer. I know they’ve done it for breast cancer. Do you know anything about that?

Douglas Levine: Well, that’s sort of what we’ve been talking about throughout. So, even just testing the tumors for BRCA mutations, that’s a form of molecular profiling. We now can measure 300 or 400 genes at the same time and develop a molecular profile.

For high-grade serous carcinoma the truth is that we often don’t find useful targets, and so we do that for our patients and it’s often -- most of the time covered by insurance. The important thing now is to find those somatic BRCA mutations, because that makes PARP inhibitors very effective. And so I think pretty soon at diagnosis, everyone is going to have germline and somatic testing for BRCA mutations and a few other things because of a new study called SOLO I that’s going to be reported probably next month, that has already been reported vaguely as being positive. And that’s really using a PARP inhibitor for initial maintenance therapy. And if that truly is positive, a lot of people with BRCA mutations will get a PARP inhibitor almost right away after finishing initial treatment. And so I think early on, as soon as people are
really diagnosed and on chemotherapy, we're going to be doing germline and somatic BRCA testing and probably molecular profiling at the same time.

**Caller #6:** Doctor, do you need a live tumor in order to do molecular testing?

**Douglas Levine:** You don't need a lot, but you need some, and so every so often the testing will fail because of not enough tumor available. Certainly, anyone who has had a major operation has more than enough tumor. It is a little tricky to do off a biopsy specimen, like a CT-guided biopsy or a needle biopsy. That can be tricky. It often will work, but sometimes it will fail. Sometimes, if you really want to have it done, you could have a repeat biopsy, and if you're doing a biopsy just for that purpose, usually we can get enough tissue.

**Caller #6:** But you have to have cancer, not in remission?

**Douglas Levine:** You're only doing the profiling of the cancer, but you can use a specimen that was collected previously. So, if you had cancer at some point and it was removed, there is a specimen somewhere that can be profiled. If you're actually in remission, you know, usually we don't recommend doing the -- I don't recommend doing the profiling in remission because you're not going to use that information. And both the test and the tumor can change over time, so the tests we're doing nowadays is very different than what we were doing a year or two ago. And so it makes most sense to do the test when you're going to use that information for treatment.

**Caller #6:** What is the target that is being attacked? Is it what Star came up with two summers ago?

**Douglas Levine:** I'm sorry, could you repeat that?

**Caller #6:** When they do the CAR T targeted therapy, what's the target that the T cells are attacking?

**Douglas Levine:** There's many different targets and people are making different types of CAR T cells that do target different things that are on the tumors. So, CA-125 is a target, WT1 is a target. You can also make sort of your own targets through something called adoptive T-cell therapy, where you actually can hit the tumor cells and mix them with the T cells, and then that cancer will target your own tumor, which is possibly one of the most promising approaches that's coming up.

**Caller #7:** Doctor, you mentioned about the disease keeps changing, so with each recurrence, it's not the same disease?

**Douglas Levine:** Right. So, what happens is early on the disease, when there is a lot of cancer, the disease is very heterogeneous, and there's lots of different, what I call clones. And there's lots of different mutations and different parts of the tumor. And what the chemotherapy does, it basically selects for the bad stuff. So, the good stuff gets -- the good cancer cells die, and I say they're good because they're dying and we want the cancer cells to die, so they're behaving. And so the chemotherapy will kill all the cancer cells that are easy to kill. But then there's a small number that are resistant or that will hide from the chemotherapy, and then over time that small population will grow back, and then that will now become the dominant population. So, if you give the same drug right away, it's not going to work because the cancer cells that have survived are the ones that have survived from that chemotherapy drug. And so that's why you have to give a different chemotherapy drug to target the cells that are already hiding from the first chemotherapy drug. Then if that second drug works, maybe all those cells will die, but now the ones that grow back might be sensitive to the first drug. And so we do recycle some drugs over time because the cancer population can change under what's called selection from the chemotherapy agents.

**Caller #7:** So, if I have tumor tissue stored from a surgery -- (inaudible - background noise).
Douglas Levine: Just to finish up, one person was asking about when to send the tumor specimen. So, we don't know how much the cancer changes and we don't know whether the important things are changing, and so it makes sense to send the test when you're ready to use it, because sometimes people have a second operation. It probably doesn't make sense to have a biopsy just for that purpose, because the bits that change that are going to affect the treatment are probably pretty limited. So, we can use previous tumor specimens when needed.

Caller #8: So, again, I have one really important question, Doctor, and if you choose not to answer, I understand. We talk about a lot of treatments, percentages, trials, etc. We don't talk about cure. When you look down the road, are we talking years, decades or never?

Douglas Levine: If I think I understand your question, are people being cured and when will they be cured? So, advanced ovarian cancer is hard to cure. It's not impossible, though. I do talk about cure with my patients. We know a lot of factors that are associated with what I call long-term survival, okay? So, we know that if you live five years, that does not equal being cured, and that's a good thing, because a lot of people are living five to ten years now, whereas, a decade ago that was not the case. So, I'm quite confident that people are living longer and better with ovarian cancer. Longer is pretty self-explanatory; better, I mean that the treatments are better tolerated now than they used to be. So, people are living longer and better, and that's good, but not good enough. I do think that if you live 10 years without your cancer coming back, there is a very good chance you're cured. And we published a paper about 10-year survivors maybe a year or two ago, and we found that of the people who were alive 10 years after a diagnosis, about half of them never had a recurrence and half of them had one or more recurrences. And so there's definitely some patients with advanced stage ovarian cancer who are cured today, and we have some idea as to who is more likely to be cured from advanced ovarian cancer.

Early-stage ovarian cancer is much more curable, and I'd almost say early-stage ovarian cancer is highly curable. But since advanced stage ovarian cancer is so -- is difficult to cure -- not impossible, but difficult - - some of our biggest advantages will come from prevention. So, if we prevent ovarian cancer, no one has to worry about being cured because you won't get it. And so it's going to be a combination of efforts. It's going to be better prevention; it's going to be better treatments. We may see some cures with some combinations. I really don't know if that's going to happen in three years or 30 years. And I also think there's a possibility that we're working on other methods of early detection so that we can detect the cancer at an earlier stage when it's more curable. That's also very difficult. But the biggest benefit right now is in prevention, where we can prevent cancer from women who are at high risk and possibly others who never have to get cancer and don't have to ask that question.

Caller #8: Thank you, Doctor.

Robin Perlmutter: Okay. Dr. Levine, I'd like to thank you for this great presentation, your passion, dedication and commitment to the ovarian cancer community, and to all of you folks for coming out tonight and taking the time to become educated on this very important topic. Have a great night, everyone.