Program Title:
Overview of Therapies and Immunologic Strategies for Ovarian Cancer

Presented by:
Support Connection, Inc. (*With funding from The HERA Women's Cancer Foundation http://www.herafoundation.org.)

Originally Recorded on:
September 23, 2014, 8 pm - 9 pm (NY time)

Guest Speaker: Dr. David Spriggs, MD, of Memorial Sloan Kettering Cancer Center:
- Head of the Division of Solid Tumor Oncology and Winthrop Rockefeller Chair of Medical Oncology
- Received his MD at University of Wisconsin School of Medicine
- Completed residencies at Presbyterian Hospital (New York); The New York Hospital/Cornell Medical Center, and Fellowships at Harvard Medical School; Dana-Farber Cancer Institute; Brigham and Women’s Hospital
- Board certified in Medical Oncology; Internal Medicine
- In addition to the daily care of women with gynecologic cancers, runs clinical trials testing new, targeted drugs, and oversees a small research laboratory looking for answers to questions such as why certain tumors resist drug treatment and how genes can affect the development of tumors.
- Serves on committees for the National Cancer Institute and plays a role on the editorial boards of such publications as Investigational New Drugs, Gynecologic Oncology, and Clinical Cancer Research. Is the associate editor of the Journal of Clinical Oncology. Has authored (or co-authored) more than 150 journal articles on such topics as ovarian cancer biology and the results of clinical investigations, from the earliest stages of drug development to randomized phase III trials.

Topics:
- The latest information in the development of drugs for advanced ovarian cancer
- Advances in immune therapy
- Question and answer period

Robin Perlmutter: [In progress] -- topics. Remember that Dr. Spriggs is sharing his expertise, and any information from tonight or questions pertaining to individual concerns should be discussed with your own doctors.

It is my great pleasure that we have Dr. David Spriggs of Memorial Sloan Kettering Cancer Center. He is the head of the Division of Solid Tumor Oncology, Winthrop Rockefeller chair of Medical Oncology. In addition to the daily care of women with gynecological cancers he runs clinical trials, testing new targeted drugs, and oversees a small research laboratory looking for answers to questions such as why certain tumors resist drug treatment and how genes can affect the development of tumors. Thank you so much, Dr. Spriggs, for sharing your time and expertise with us tonight.

David Spriggs: Okay. Thank you, Robin, it's great to be here. So, what I am going to do tonight is I'm going to talk a little bit about some current topics in the management of ovarian cancer. I'm going to talk a little bit about personalized medicine, a little bit about some of the new medications that have been introduced particularly as it relates to presentations that were done this year at the annual ASCO meeting in Chicago in June (inaudible) of the future of immunologic strategies for ovarian cancer. So, I am (inaudible) entire Gynecologic Oncology Service at Sloan Kettering which includes 11 medical oncologists who care for a variety of patients over the past several years [and our surgical colleagues] as well. So, could I have the next slide, please?

So, what we're going to be talking about today is, we're going to talk about new drugs, most of which at this point are investigational, which is to say that you won't be able to get these drugs outside of a clinical trial because they have not yet been approved by the FDA. And so the clinical trials can be difficult to identify. On the slide here you see the clinicaltrials.gov site that is maintained by the National Library of
Medicine and has a variety of clinical trials. It can be a little overwhelming when you start out, but it is the best and generally one of the most up-to-date sources for information about clinical trials and where these clinical trials are being performed across the United States, in fact, North America and Western Europe as well. Next slide, please.

So, I think that this is an important point here, is that before you travel to a distant site to enroll in a clinical trial, since clinical trials all have limitations in terms of who is eligible to participate in these clinical trials. I think it is really important to make sure that your primary oncologist speaks with a study coordinator to make sure that indeed you are not making the trip for no good reason and the study is still actively accruing and there are spots on there for the treatment of additional patients. And then, of course, not all the cancer centers are covered by all insurances, and so you do have to make sure with your own insurance carrier that the insurance that you have will cover those aspects of the clinical trial that will be billed. This will not, of course, include the new drug, but will include a variety of safety and other testing that goes along with the clinical trial. Next slide, please.

So, I want to start out with a few comments about precision medicine, and this idea of precision medicine or personalized medicine has gained a lot of popular traction in the course of the last several years as we've gone into the genomics era. And you can see in the slide here that historically we talked about the histologic type of cancer, which is on the far left-hand side, where you see a woman's open abdomen and the microscopic slide down at the bottom on the left represents how an ovarian cancer might look under the microscope.

And through the modern technologies, including gene expression, transcriptomics, where you look at the RNA version of the gene, and proteomics, where one can actually examine the critical proteins, have all been miniaturized and integrated into small chips about the size of transistors that now allow the characterization of a variety of the DNA, RNA and proteins associated with a specific cancer. And the goal there is to identify what is called actionable mutations, where there may be approved drugs which would target those mutations or alternatively drugs that are in clinical trials that might have been designed to target those mutations, although they may or may not do so. So, it is a large process that is really, I think, just coming into its own. Next slide, please.

And so this began with The Cancer Genome Atlas, which was originally the idea of Dr. Harold Varmus, who is now the Cancer Center director, Dr. Eric Lander, and one of the earliest cancers that were examined under The Cancer Genome Atlas was serous ovarian cancer. And it had about 450 different patient tumors that were identified and they were able to use these signatures (inaudible) in the prior side really begin to break it down into four subgroups which thus far have not actually turned out to be treated differently but are genetically and expression-wise different, and have different characteristics. Next slide, please.

And one of the goals of an analysis like this is to identify what we call the drivers of the cancer, that is, the mutations in the cancer which have been altered and lead to the cancer's uncontrolled growth and metastases. And certain cancers, like non-small cell lung cancer or melanoma have turned out to have a small number of critical drivers that appear to cause the growth of cancers, whether it's melanoma or lung cancer, in the majority of patients with these diseases. But cancer is a disease of mutation, and so there are many other mutations which have come to be called passengers, where the mutations are coming along for the ride. But attacking those passenger mutations doesn't actually do any improvement in the growth rate of the cancer or for the patient. Next slide, please.

So, the interesting thing about ovarian cancer is compared to many of the other cancers that have been subsequently tested in The Cancer Genome Atlas endeavors, there really have been a very small number of drivers that have been able to be identified. And so ovarian cancer has not really been able to capitalize on the transcription trend genomic revolution. Essentially, all of the tumors will have a loss of the tumor suppressive gene p53, and many will also have secondary silencing of another gene, OPGML. But a third or up to a half will have loss of (inaudible) related to the BRCA1, BRCA2 genes (inaudible) related to familial
ovarian cancer and [lung] cancers. But not all of these cases will turn out to be familial, but changes in the BRCA1 or BRCA2 gene, or some other gene in that pathway are commonly associated in about 50% of all of ovarian cancer. Next slide, please.

There are a few, what we would call actionable targets for testing ovarian cancer, and these are being looked at right now. One that is probably the most familiar to the audience is the homologous DNA repair, HRD, which is the key target for the PARP inhibitors, which are particularly effective in tumors that lack the BRCA1 or BRCA2 (inaudible). There are other genes that low-grade serous cancers, MAP kinase and the hormone receptor pathway, estrogen receptor, progesterone and androgen pathways. In clear-cell cancer, angiogenesis seems to be the key driver, whereas, in endometrioid cancer it looks as though p10 and -- loss of p10 and the gene PI3-kinase are associated with these genes. There are other mutations that can occur but they tend to be quite rare and isolated, and thus far are far too rare to really be associated with therapeutic (inaudible). Next slide, please.

And the transcriptomics, or the idea that you can measure the RNA from these tumors and get some kind of a prediction as to how the cancer will behave and whether or not therapy or a particular kind of therapy might be useful is still in its early days. The most validated signature is the Oncotype DX, which is commonly used for the decision-making in adjuvant chemotherapy breast cancer, but there is not any kind of similar trial available, or similar assessment available in ovarian cancer. And so at this point it remains something that there is a lot of interest in in the research community but not one that has been settled on and can really be used to identify who needs therapy and what kind of therapy might be appropriate. Next slide.

Okay, so now l am going to turn to targeted therapies and I'm going to talk again about the PARP therapy and one of the, I think, most interesting trials that were presented at the ASCO meeting this year. Again, I want to emphasize that these drugs at this point are all investigational drugs and would only be available for patient use in the context of a clinical trial, where we try to identify exactly who might benefit from these drugs. Next slide, please.

So, and there are a large number of clinical targets out there, and you see some of these specific genes. For example, c-kit is an important gene in the GIST tumors and in chronic myelogenous leukemia. FLT3 is common in acute leukemias of various sorts. MET and RET are other oncogenes. eGFR is commonly seen in the context of lung cancer, and the ERBB2 is another name for HER2, the principal target for Herceptin.

So, you see there are a large number of targets on the surface of the cell, which are the ones identified there in sort of a yellowish. And then inside the cell, the cancer cell is a whole other area of targetable genes that you see in the blue and the pink, and it just helps us think about these as being on the surface or internally, but there are a lot of possible targets. Next slide.

Now, one of the things that is happening in the context of cancers in general is the idea that cancers may not all be according to type, but may be according to genetics. And so one might find, for example, that breast cancer and gastric cancer and some lung cancers all share an increase in the HER2 surface receptor, which is the target of Herceptin and T-DM1. And so while you would think that breast cancer, lung cancer, gastric cancer would require different therapies, if they are driven by the same driver, oncogene mutation, then what you find is that you are able to use a single drug across many diseases. And this has led to a different trial concept, the idea of a basket trial, where you are looking at recurrent actionable alteration in any solid tumor as opposed to limiting the entry to these trials, specifically to a histotype-like lung cancer. Like melanoma in the lower line, you see that over half of those cases of melanoma are characterized by mutations (inaudible), whereas, most of the other cancers have a complex (inaudible). Next slide.
And so I think that the truth is that there are many different targets, and you can see in the portfolio at Sloan Kettering right now you can see all the different targets in the Phase 1 and Phase 2 clinical trials that were available at the end of 2003 -- I'm sorry, 2013. Next slide.

So, at the end of the summer there was a summary of some of the most interesting presentations at ASCO specifically related to GYN, and these were talks given around the country. I'm just going to hit some of the high points from that ASCO presentation of 2014. These are the kinds of things your oncologist heard when he or she was in Chicago in the first week in June and went home with additional information about where the new drugs are going to be coming from. Parenthetically, this is the 50th anniversary of the American Society of Clinical Oncology, which is in some ways quite astonishing that 51 years ago there were so few oncologists in the United States that cancer therapy was not even a specialty that had its own organization. Next slide, please.

So, we talked a little bit about the personalizing therapy and those slides were taken from my colleague, Dr. Kohn, Elise Kohn was asked to talk about personalized therapy. And then I just want to talk for a few minutes about the combination of cediranib and olaparib, which I think was one of the more surprising outcomes of the ASCO meeting. Let's go to the next slide.

So, this was a randomized Phase 2 trial comparing the efficacy of a combination of the PARP inhibitor olaparib, which is a PARP inhibitor that has been around for the longest period of time and was really brought in clinical trials in the 2007-2008 time frame, along with another drug which is also a pill that appears to act against the formation of new blood vessels. So, like Avastin or bevacizumab, cediranib is an anti-angiogenic drug, and the study compared a combination of two drugs with the PARP inhibitor alone. So, let's go to the next side, please.

And this is the background of these two drugs. Cediranib is the newer drug. It's an oral inhibitor, a tyrosine kinase, and the tyrosine kinases are the enzyme activity that is associated with receptors, in this case for the vascular endothelial growth factor. And so it has some side effects, as all of these drugs do, particularly diarrhea, high blood pressure and fatigue, which are all fairly characteristic of this whole class of drugs, and had a relatively modest improvement rate by itself, somewhere in the neighborhood of 17% improvement rate with only about a 5.5 month duration of response on average.

And then the olaparib is the drug that is the lead, I think at this point, PARP inhibitor. Its side effects include many of the same things, that is, nausea, some fatigue and some low blood counts. It also has a response rate which can be as high as 40% or 50% in patients with mutations in the BRCA1 or BRCA2 genes, but about half of that in the context of patients who do not carry that mutation. It was a little more durable in terms of response rate, somewhere in the seven- to nine-month range. Next slide, please.

This is a study where in preclinical models the idea was to see whether or not there was overlap and whether or not they were particularly good together, and they show in this slide on the upper panel on the right, you can see that the bar graph on the far left shows that they are essentially the same in the absence of treatment. But when you combine the PARP inhibitor and the inhibitor VEGFR, on the far right you can see that there is a dramatic drop-off in the ability of those cells to grow, with the black bars, whereas, the controls without treatment continue to be roughly the same.

So, I think that it is also probably true because of the sensitivity to PARP inhibitors seems to be increased when cancer cells are starved of oxygen. And there may also be secondary relative genetic alteration as well. Next slide, please.

And you can see that when the two were put together, you see what -- this has become a familiar presentation of the results, a so-called waterfall plot, where on the left side you see patients who had their tumors grow. And you can see the largest rate of growth is on the far left was somewhere in the neighborhood of 10%. As you go left to right you can see that many of these patients had a substantial
decrease in the overall size of their tumors and compared to the number of patients that had tumor growth there was a much bigger effect. And so in this early, early phase clinical trial, so-called Phase 1 trial, there was an overall response rate in ovarian cancer of about 45%, which was significant and generated the interest in doing the study. Next slide.

So, the study was to compare the time between the start of treatment and when cancers began to get worse, looking at the combination compared to the PARP inhibitor alone. And it was restricted only to high-grade serous ovarian cancer and only patients who had not become platinum-resistant. And in addition to looking at the time before worsening, they looked at overall survival, they looked at response rate, and of course they looked at the side effects and the effect of those two drugs together. Next slide, please.

And the study was simply this. It was a randomized study and, of course, both arms got some active treatment. The one arm got the PARP inhibitor, olaparib, in the standard dose at 400 mg twice a day. And the other arm, the lower arm in that little graphic shows that they got less olaparib, that is, only 200 mg twice a day, but also received cediranib. So, one of the principles of combining these drugs is you see that you can get the full dose of both drugs in order to get patients to be able to withstand the toxicity of such treatment. Next slide, please.

We have already talked about this. They had to have high-grade serous or endometrioid histology, that they were sensitive to platinum in either epithelial cancer, tubal cancers or primary peritoneal cancer. Patients who previously received a PARP inhibitor were, of course, generally prohibited as were patients who received antivascular treatments, like bevacizumab. But there was no other limit on the number of platinum-based therapies. Next slide.

And everybody knew what they were getting, it was randomized, so half the patients got one and half the patients got the other. They did try to make sure that the patients with known BRCA mutations were equally divided among the two arms, and there was a targeted accrual of 90 patients. So, the goal was to get 90 patients and there was no subset analysis planned. Next slide, please.

Enrollment was completed in May with 44 patients getting cediranib and 46 getting olaparib, and the first analysis was done in November, when about 50% of the planned event, in this case it was the cancer getting worse again, had occurred. All of these clinical trials are monitored by a data safety monitoring board to make sure that if there is a clear difference between the two arms in any randomized study that patients are protected, that the study is stopped, the blind is broken, and anybody who can benefit from the better arm has an opportunity to receive that arm. The DSMB, which was through the Dana Farber Cancer Institute, found that it was so unequal that it was time to stop the study and so that the results were reported early. Next slide, please.

This is just a comparison of the patient characteristics, and the whole point of this table is to stay that they matched up. There is very little difference between the two arms, and so the study valuation can be considered to be statistically adequate. Next slide, please.

And here is the most important graphic here, and what this is what's called a Kaplan-Meier curve. And basically when someone had their cancer get worse, a little tick mark, the whole curve moved down, and so you can see that the blue line where the single agent, olaparib, the PARP inhibitor, was being given, dropped off much more quickly than in the combination study, even though they were getting a lower dose of the PARP inhibitor. And the red line shows you that there is a substantial difference, and so that difference turns out to be highly statistically significant and the average time to having cancer progress was nine months receiving olaparib and it was almost twice that, 17.7 months in the combination study. Next slide, please.
Not only that, but it also had a better response rate in terms of overall tumor shrinkage, and usually these things all go together and it's really not surprising. Next slide, please. Back one, thank you.

And what you can see here is that there is one counterintuitive result here, and that is for the patients who had BRCA mutations in their germ line, there is really very little effect. And it's really only in the patients who didn't carry the BRCA mutation that the cediranib seemed to give a substantial advantage in addition to the olaparib. It just goes to show you, I think the average impact of olaparib is much greater than the impact on a specific patient for cediranib. Let's go on.

There were side effects, and one of the things that is important, of course, to think about with all these clinical trials is side effects are common. If you look here at the combination arm, you can see over here 34% of these patients had grade 2 high blood pressure and almost 40% had grade 3. So, putting the two together does certainly give more side effects, gave more diarrhea, patients were more tired, so it was -- when you take two drugs you get more side effects. And one of the unfortunate problems with targeted therapy is it is targeted but it's not perfectly targeted, and in some ways the side effects are just as onerous as chemotherapy, they are just different. Next slide.

So, when you did the combination there were more side effects. More patients had to stop altogether, but there were also a substantial number, over 70% of the patients ended up having to have the doses of the drug reduced in order to tolerate the medication. So, this may not be the right dose, but it is quite clear that the two drugs together do seem to be beneficial. Let's go on.

Then I just want to share another study that was done looking at clear-cell cancers, and this was done in Japan. Now, this is a Phase [2] trial and it was done because the Japanese have an almost -- let's go one more slide. So, in Japan what you see is, look at the red triangle and you can see the clear-cell cancer, or CCC, is much more common in Japan than it is in the United States or Western Europe, about three times more common. And there was a great deal of interest in Japan in exploring the clear-cell cancer question because it is a common disease. And they had some preliminary information to suggest a different drug, that is, irinotecan, or CPT-11, might be beneficial in that context. Next slide, please.

And so they were able to look at the effects in an early Phase 2 study, and you can see that having clear-cell cancer was much less favorable than a classic serous cancer. And you can see the yellow lines in these proportions surviving in the Kaplan-Meier curve really do suggest that clear cell is a much more difficult disease for patients to tolerate. Next slide.

This is the randomization, and again it's done at multiple centers simultaneously, and half the patients got the classic carboplatin and paclitaxel, and the other half got CPT-11 and cisplatin based on the pilot studies done in Japan. Next slide, please.

And these patients were all followed for two years. You can see it's a very large study, and when it is all said and done, the results are very similar. And so in the context of a clinical trial, I included this one because it has -- the outcome is equal but not superior, so that not every clinical trial results in improvement. Interestingly, very few clinical trials result in a decrement in outcome and those are stopped very early. Let's skip along, please. Next slide, and again.

So, let's spend the last few minutes talking about immunologic therapies. And immunologic therapies have an intuitive appeal to both patient and doctor. We would like to believe that the body's own immune system can and does control the development of cancer and that somehow when a cancer actually presents at a clinical level, it has to do with some kind of failure of the immune system. And if you go to the health food stores, essentially every shelf is packed to the gills with various pills and liquids and so forth that are all touted as immune-stimulants, which of course they are allowed to do under the current laws in the United States because there is no way to really measure immune stimulation, and so that is one of the problems.
So, there are three -- we have a program project grant, or a large research program in the context of ovarian cancer at Sloan Kettering, where we are looking at different ways to try to approach the immune treatment of ovarian cancer. And the categories here include an antibody therapy program that is run out of my laboratory; a vaccine program, which is run by Dr. Paul Sabbatini and Jedd Wolchock; and the beginning of a cellular therapy program, which is really run by Dr. Renier Brentjens and Roisin O'Cearbhaill. Let's go to the next slide, please.

First of all, the MUC16 antibody strategies, MUC16 is the parent molecule that is recognized in the CA-125 test that many people with ovarian cancer will have done on a regular basis, and because it is so unique to ovarian cancer represents a nice target for antibody treatment. And not only for treatment but also for radiodetection using PET scan, for example. Next slide, please.

And this is what the cartoon looks like, and you can see that it is a very complicated molecule. It is very large and it has both parts down at the bottom which is stuck to the cell membrane on the outside (inaudible), and then a large molecule, which is released. The high levels of CA-125 do appear to be weakly associated with worsening cancer, and the function of why MUC16 does that is not really well understood. Next slide, please.

When one looks at what happens when MUC16 is expressed, it turns out that many genes, including invasion genes and genes that are associated with metastases do seem to be up-regulated, and so fibronectin, a [metalloproteinase]. proteins and so forth do seem to be increased when MUC16 is artificially introduced into noncancerous cell lines. In this case it's a mouse fibroblast line. Next slide, please.

And the way this probably happens is that the MUC16 has many sugars on the cell surface. And the presence of those sugars on the MUC16 gene essentially trap growth factor receptors, like epidermal growth factor and others on the cell surface and cause persistent stimulation inside the cancer cells so that the cancer cells are promoted to grow and invade. And you see this with the galectin, which is a protein which binds sugars and hooks these receptors on the left to the MUC16 on the right. Next slide, please.

And when you block the ability of those sugars to bind, what you get is you get to have a significant loss of invasion and the invasive properties of metastatic cancer. And so the goal is to create antibodies which can mimic the loss of those sugars and inhibit the growth and the invasion of MUC16. Next slide, please.

We now have some antibodies that we are just beginning to test that will actually take the purple line there and turn it into one of the lower lines below based on the fact that we are able to block the MUC16 sugars on the cell line. And these are being developed in conjunction with a commercial company in California, Eureka Pharmaceuticals. Next slide, please.

They also have the ability to image, and what you can see here along the top is you can see that a PET scan of a mouse with a tumor onboard can show clear localization of that tumor with the MUC16 present. But on the left-hand side where there is no MUC16 on that tumor there is no localization at all. Next slide, please.

Okay, and then the second program that I want to just touch on is the vaccine program. Next slide, please. Dr. Paul Sabbatini and Jedd Wolchock are creating a vaccine-based program for patients in second or third remission, looking at the ability to target specific antigens including the MUC16, the CA-125, as well as another antigen, which is an antigen mostly expressed in the fetus, the NY-ESO-1 or WT-1. So, these are well validated clinical targets and the vaccines are being created to try to create post response to those targets. Next slide, please.
And this trial is now completing and we should have the results in the next two or three months. But this is a trial run through the Gynecologic Oncology Group where we looked at vaccination versus immune stimulation with a simple adjuvant. And 164 patients were entered and we are waiting to see the results as to whether or not the vaccination really can change the time before the cancer comes back in patients who have had two or three prior relapses. Next slide, please.

And this is done with a single multivalent vaccine done by a wizard chemist at Sloan Kettering, Sam Danishefsky, who represents the chemist interest in oncology, and he has helped us make this vaccine. And we hope that we will have these results, and this could turn out to be a pretty exciting program. Next slide, please.

WT-1 is another antigen targeting. Let's just move on. And then the CA-125 MUC16 target is also being tested. Next slide, please. So, one more.

And this is the clinical trial that will be opening this spring looking at second and third remission, testing the patients and then choosing the vaccine based on the expression of the tumors antigens that are present on their particular cancer. Next slide, please. And next slide. Let's just skip that, we're running a little short on time.

And I just want to end with a little bit of information about this autologous modified T cells that Renier Brentjens and Roisin O'Cearbhaill are doing. Next slide, please.

And the idea here is to introduce a modified receptor to the T cell that is focused on a target like CA-125 or MUC16 in a specific cancer so that every T cell, which are the immune-killer cells, is now focused on hitting that antigen and it gives a much greater signal. There have been some terrific responses in leukemia/lymphoma, and we are very anxious to get this program started again, roughly in the first quarter of 2015.

So, I promised that I would stop in time to have some questions, so why don't we stop the lecture now and, Robin, if you would like to moderate the question-and-answer period, I think we could go to that.

Robin Perlmutter: Sure, I am happy to. Thank you so much, Dr. Spriggs. So, if you could type in your question. If you're on the Web and you can type them in, that would probably be the easiest way and then I could read them to Dr. Spriggs and he can respond. If you are only on the phone and you don't have access to your computer, then I'm going to ask you to, if your last name begins with A through L, if you have a question, please speak, and we'll take one at a time.

Unidentified Participant: How do you find out about the antigen vaccine trials at Sloan?

David Spriggs: Well, I think that, again, the best way is to probably have your oncologist call directly. Because these trials have fixed number of patients, they do tend to open and close. As you might imagine, people are very anxious to participate in the vaccine therapy just because of the intuitive appeal of those treatments, in spite of the fact that so far none of them have shown to be -- to have any real impact. So, I would have your oncologist speak with Dr. Paul Sabbatini, who runs the Sloan Kettering vaccine programs, and Paul would be able to help your medical oncologist decide whether or not there would be something that would be suitable for you to participate in. One of the key problems is that these investigational therapies require a lot of -- they must be done at the site that is sponsoring it, and so it would require treatment for all the vaccines at Sloan Kettering.

Robin Perlmutter: Next question? Okay, we'll move on to M through Z. Anyone with the last name M through Z that has a question?
Unidentified Participant: I may just want to ask about that trial. If all the treatment has to be done at Sloan, would that include the satellites?

David Spriggs: That is a very good question and the answer is that our satellite system has not had the infrastructure to do all of those studies previously. And although we are at this point where we are trying to get some of those studies up and running in the network sites, it varies from study to study. So because if there is a specific storage issue, if there is specific blood drawing and so forth that might be required, many of the network sites are really not set up to do that kind of work. So, it varies from study to study.

Unidentified Participant: Okay.

Unidentified Participant: For the T cell work that you are doing, do you need tumor for that?

David Spriggs: No. Because the -- you would need to have an elevated CA-125, which is the biomarker that our first program is going to be targeting, and that study will be submitted to the FDA this fall. It has already passed the recombinant DNA technology board, and so we would anticipate that that study in conjunction with a company called Juno, which has invested heavily in the technology, will be ready to go probably in February or March, is what we are projecting right now.

Robin Perlmutter: Okay. Here is a question for Dr. Spriggs from the Web. Ovarian cancers tend to mutate over time. Are original or old tumor samples valid for the vaccine trials?

David Spriggs: The answer is that we are at an early stage of testing, and -- for example, the MUC16, because it's a CA-125 antigen, while it may mutate, the CA-125 indicates that the cancer is still present, and that the antigen is still present. NY-ESO-1 or WT-1, we would like to have the most recent tumor tissue available for testing, but since we can't assure a patient that her participation is going to necessarily be beneficial, it's very hard to ask patients to undergo a biopsy in that context. So, we are using archival tissue excepting the fact that mutations do occur and it will be an imperfect surrogate of where we are at the time when the patient might start on treatment.

Robin Perlmutter: Thank you. When utilizing CA-125, what about those who have a very low CA-125?

David Spriggs: Those with a low CA-125 are not going to be benefited by immune strategies which really target that specific gene product. And so we would want to be looking at other strategies for those patients, because that is part of the personalized medicine strategy is you want to be sure that a patient has the potential benefit because they have targets that you are going to be testing. And so a low CA-125 would indicate that those patients probably would not have a high probability of benefiting and would be better off on other treatments.

Robin Perlmutter: Thank you.

Unidentified Participant: How does this vaccine therapy differ that Dr. Sabbatini is doing than what he was doing, say, I don't know, five or six years ago?

David Spriggs: Well, I think that the answer is five or six years ago Dr. Sabbatini was doing single epitope vaccines, and so as the field has matured he has continued to put more and more different antigenic targets into the vaccine. And so while he was doing one target at a time in the, more like 10 years ago, it is now six or seven targets.
The second change that is occurring is we are really moving away from vaccines that generate antibodies, like a tetanus shot, to vaccines that really are much more likely to activate the T cells. Because the field has really begun to move so that we are more and more convinced that antibodies are great but they don't have the same kind of profound long-lasting effects that activating T cells will. And so you have a whole different strategy for immunization that goes with T-cell activation. And so we are more likely to be using proteins rather than sugars in order to do the immunization to get that kind of a response.

Unidentified Participant: I am in Philadelphia and Dr. June is doing [chimeric] stuff, I think. But he requires a lot of tumor, your tumor, in order to get the T cells. So, is your system different than his?

David Spriggs: Our system would be different. We are harvesting the T cells through a leukapheresis and then transforming them outside the body, growing them up and then giving them back. Dr. June at times has been isolating -- I may be wrong. Dr. June has -- I think that Dr. Coukos is using the -- has set up the program for the live tumor, which is then killed. It's an autologous tumor vaccine at the University of Pennsylvania. I'm not aware that Dr. June is actually doing any ovarian cancer stuff, because he has been doing leukemia, on lymphoma things very much like Dr. Brentjens has been doing here at Sloan Kettering and up in Boston. I think that the program for autologous vaccine does require live tumor or tumor immediately at the time it is taken out, and the tumor is then -- a denatured process and then used as an autologous tumor vaccine.

Unidentified Participant: So, Sloan has ovarian as an area focus, whereas, I think you are right, Penn has been looking at the lung cancer and skin cancer.

David Spriggs: Yeah, I think melanoma and leukemias, there is a lot to be done and no center can do everything, and so you end up -- I sort of kidnapped Dr. Brentjens and told him that he ought to stop wasting his time on leukemia and pay attention to ovary cancer. And so we've been able to -- with the antibodies that we generated we've been able to convince him that this is an area worth exploring, and he has become quite enthusiastic about it. But there are people looking, for example, at mesothelioma, there are people looking at prostate cancer. Same strategy, different antibodies, different targeting, but no place can do everything and it just happens that this is something where our investigators have been more interested in going forward with the ovarian cancer targeted.

Unidentified Participant: Thank you.

Robin Perlmutter: We have time for a few more questions.

Unidentified Participant: To do these vaccines antibodies do you need to be cancer-free? Is it done as maintenance or is it done as a therapy for active cancer?

David Spriggs: The vaccine studies that Dr. Sabbatini has been doing we believe are going to work best in remission, and so those patients without cancer are the ones that are most likely benefiting. They are the ones that we are putting on those trials right now. Because the chimeric T-cell antigen strategies are even newer, one of the things that we are anxious to do is we are anxious to test those. And we believe that they should be powerful enough that we should be able to see tumor shrinkage even in patients with established visible tumors, because that is certainly what happened in lymphoma, for example. So that the initial clinical trial for the CAR T cells will require some measurable tumor, so it will be a different group of patients entirely.

Unidentified Participant: And this is, you think -- did you say February when it was going to start?
David Spriggs: Yeah, I think it's a little iffy, but I think that is hard to imagine we're going to get it done before the first of the year, and I always build in a little bit of flexibility in terms of when these things really get started.

Robin Perlmutter: Okay. We have a question: Is the olaparib/cediranib pairing still investigational or has it been FDA approved?

David Spriggs: So, the answer is it is still investigational. There are no FDA-approved PARP inhibitors available today. At this point there are no approved PARP inhibitors and so anyone getting a PARP inhibitor will be getting it on a clinical trial. I think that within a couple of years they will be commercially available.

Unidentified Participant: Just asking a question about if you were BRCA positive and your CA-125 started to elevate, then you would have to go on a trial to get a PARP inhibitor?

David Spriggs: Yeah. There are a variety -- I think there are at least five in commercial development right now, and so many of them are in the final stages of testing. So, they are Phase 3 trials with only a couple of prior treatments. So, unfortunately, the patients who have been treated for ovarian cancer for several years and may have gone through several different chemotherapies will not immediately be able to access those drugs in most cases.

Now, I think that once the data becomes more clear, there will be -- before the drugs are actually approved there will probably be what they call a compassionate program where patients with a certain BRCA mutation who have progressive cancer will be able to get it while the company is going through the final steps of drug approval. But we are not close to that at this point. I think it is at least a year away.

Unidentified Participant: Can I just ask one more thing about recurrence? If you were, say, four years out and you begin to have recurrence, would it be the same kind of cancer? I mean, if everything is taken out of you --

David Spriggs: Well, of course, that's one of the common misconceptions is just because your ovarian cancer comes back in your lung, you don't have lung cancer. And so I think that, yes, it's almost -- it is very likely to be the same kind of cancer, but after four years I think it would be prudent to biopsy that cancer and make sure it's the same. And we also see people who have second cancers, and even though their uterus, tubes, ovaries have been taken out, they can have cancer arising in the peritoneal covering, and that can happen 20 years later. And so, again, the question is should you treat that cancer as recurrent cancer or is that a new cancer and the patient should receive the same treatment perhaps she received 10 years ago? It's a little tricky but I think by and large you can tell with biopsy. And the longer the time is between the first cancer and the second apparent, the more likely a biopsy is going to be required in order to really know.

Unidentified Participant: Okay, thank you.

Robin Perlmutter: ARIEL3 and NOVA are two PARP inhibitor trials that are open but with one-third randomization.

David Spriggs: Yes.

Robin Perlmutter: I guess that's your question. Yes? Okay. And then the second one is -- oh, sorry, go ahead.

David Spriggs: That is the requirement that is currently being imposed by the FDA in order to get these drugs approved, and so two-thirds of the patients will receive active drug and one-third will receive a placebo, and that is made very clear on the consent form. And it is a difficult circumstance, but most of the drugs that we use
today have been approved through those same kinds of randomized, placebo controlled trials and that the two-thirds/one-third really maximize the number of patients who will receive active drug.

Robin Perlmutter: Okay. And last question: There was an issue awhile back that the company making Olaparib decided to quit making it. Can you comment on its availability and how it may affect our ability to get it in the future?

David Spriggs: Are you talking about Olaparib?

Robin Perlmutter: Yes.

David Spriggs: Yes, okay. Olaparib didn't -- they didn't stop making it, but they spent over a year and a half reformulating it because it was in big, greasy, nasty pills that people had a hard time taking. And so they needed to reformulate it so that the active drug was going to be in a more attractive form and people were not going to have as much trouble swallowing the pills. And that is one of the hidden disadvantages. Nobody likes IV, intravenous chemotherapy, but oral chemotherapy, sometimes you end up with a large number of pills or a big nasty pill, and that can be hard to take, too. So, that was the delay. That has ended and they are now actively doing clinical trials with the reformulated olaparib, so I don't think that is relevant any longer.

Robin Perlmutter: Okay, thank you. And, folks, that is our webinar tonight. Dr. Spriggs, I just want to thank you again for being on tonight and giving such a fantastic presentation. And, folks, for all of you who joined us this evening, I hope you enjoyed this and we thank you for joining us and look forward to having you again. Thank you so much, everyone.

- END OF TRANSCRIPT -