Prostatepedia[1]

[1]expert insight + advice

Immunotherapy

Prostatepedia_January [2019] Volume [4] No. [5]

In this issue....

The goal of this issue is to capture the current state of the art in immunotherapy of prostate cancer. We live in a time when immunotherapy is making major contributions to the treatment of many malignancies. The Nobel Prize was recently awarded for the discovery of checkpoint inhibitors that have revolutionized the treatment of melanoma. Chimeric antigen receptor T (CAR T) cell therapy represents a major advance in the treatment of B-cell lymphoma.

"Immunotherapy is making major contributions to the treatment of many malignancies."

Unfortunately, immunotherapy has not yet had such a dramatic impact on prostate cancer treatment. The Provenge (sipuleucel-T) vaccine has been approved for prostate cancer treatment because it results in a modest improvement in the survival of patients with advanced disease. The checkpoint inhibitors have not shown useful activity in prostate cancer, although a small group of patients have had dramatic responses. The current situation may be best summarized by saying that immune response to prostate cancer can be demonstrated in patients, but various factors appear to limit cancer cell kill.

In this issue, we feature conversations with investigators who are doing interesting research on how to overcome factors limiting the effectiveness of immunotherapy in prostate cancer.

Dr. Charles G Drake talks about the state of immunotherapy in 2018 and looks ahead to what we can expect to happen in 2019.

Dr. James Gulley talks about why the initial trials with the prostate cancer vaccine ProstVac didn't prove as promising as we'd all hoped. He also outlines a number of prostate cancer vaccine clinical trials looking for patients.

Dr. Julie Graff discusses clinical trials—both completed and those looking for patients—that combine Keytruda and Xtandi.

Dr. Fatima Karzai tells us about clinical trials at the National Institute of Health that combine PARP and PD-L1 Inhibitors.

Dr. Bruce Brown, Chief Medical Officer of Dendreon, discusses a clinical trial that looks at using sipuleucel-T in men on active surveillance.

Each conversation this month includes information on clinical trials that are recruiting prostate cancer patients. If you think you may be a fit, please don't hesitate to contact the investigator.

Charles E. Myers, Jr., MD P1

ISSN: 2381-4020

Prostatepedia is published in Charlottesville, Virginia by Rivanna Health Publications, Inc.

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Charles G. Drake, MD
Immunotherapy: Looking Ahead to 2019

Dr. Charles G. Drake is the Director of Genitourinary Oncology, Co-Director of the Cancer Immunotherapy Program, and Associate Director for Clinical Research at the Herbert Irving Comprehensive Cancer Center, New York-Presbyterian/ Columbia University Medical Center.

He spoke with *Prostatepedia* about the current state of affairs for immunotherapy for prostate cancer and what he anticipates happening in 2019.

Over the past year, we've looked at early data from several anti-PD-1-based immunotherapy combinations. In 2019, we'll be looking to see more results from these combination studies, to see which combinations will actually work in patients. It's pretty clear that although PD-1 blockade has some activity, it doesn't have a lot of activity. The idea is if you combine PD-1 blockade with some of the more standard therapies for prostate cancer, you might get more activity.

One of the more interesting combinations is PD-1 blockade plus a PARP inhibitor like Lynparza (olaparib). PARP inhibitors have activity in prostate cancer, particularly in patients who have mutations and proteins that repair DNA; these mutations are called called homologous repair defects. These patients have a good response to PARP inhibitors. A combination of PD-1 plus PARP inhibitors is being tested both in patients *with* the mutations and in patients *without* the mutations. What has emerged in other diseases likes ovarian and breast cancer is that if one blocks PD-1 and treats with a PARP inhibitor, sometimes it looks like it doesn't matter if the tumor has those DNA repair mutations or not. There are ongoing trials combining several of the anti-PD-1 / PD-L1 agents like Keytruda (pembrolizumab), Opdivo (nivolumab), and Imfinzi (durvalumab). All these drugs will be combined with PARP inhibitors. The question is whether that combination will lead to objective responses similar to what has been seen in other tumor types. Interesting early data from the NIH group suggest that the PARPi / anti-PD-L1 combination is active.

The second interesting combination involves PD-1 / PD-L1 blockade with hormonal therapy. We showed a while ago that hormonal therapy seems to at least temporarily block tolerance to prostate tumors in murine (mouse) studies. A vaccine plus hormonal therapy can lead to improved responses. The idea is that by giving initial hormonal therapy with immunotherapy, or adding an immunotherapy when you switch hormonal therapies, you will get better responses.

One randomized Phase III trial already tested this combination. The study enrolled patients who were on Zytiga (abiraterone) and then randomized them either to Xtandi (enzalutamide) or the combination of Xtandi (enzalutamide) plus a PD-L1 blocking antibody called Tecentriq (atezolizumab). I'm on the steering committee for that trial. Those patients were pretty healthy in general, though, and so it's probably going to take a couple of years until we read out whether the combination leads to an improvement in survival.

Other PD-1 or PD-L1 blocking agents will be combined with hormonal therapy as well. At Columbia, we're doing a really great trial called Magic-8. We're giving anti-PD-1 in combination with the first hormonal therapy. This is for patients who have had surgery or radiation, who have evidence of a rising PSA, and have a fast doubling time. They will get the anti-PD-1 Opdivo (nivolumab) plus hormonal therapy with degarelix for a short course. Patients will first get two doses of immunotherapy—a prime and a boost. A month after that, they will get the combination of immunotherapy plus hormonal therapy with degarelix. They only get four months of hormonal therapy and then we stop everything to see if they can recover their testosterone and not have a PSA relapse.

To enroll in Magic-8, patients have to have had primary therapies, so they had to have either surgery or radiation. Then they have to have a PSA that's rising quickly, with a PSA doubling time less than 12 months. Immunotherapy, as you know, is not without risk, so this trial is not for everyone. Patients have to have a reasonable indication that their recurrent prostate cancer is aggressive. They have to have a testosterone level greater than 200, so that their cancer will respond to androgen ablation. One thing that's a bit different from other trials is that we don't care if the patient has radiographically detectable metastases or not. If they have metastases, we're asking them to agree to get a biopsy because we want to try to understand in which patients this combination works. Their PSA also has to be reasonable. It has to be more than 2 but less than 50.

This trial is open and accruing. If anyone reading this is interested in participating, he can contact me at cgd2139@cumc.columbia.edu. It's worth pointing out that I was involved in a similar trial with Provenge (sipuleucel-T). In that trial, there were some patients who got Provenge (sipuleucel-T) plus initial hormonal therapy who were able to enjoy a long period of time during which they had their testosterone recover without a PSA relapse. So hormone therapy plus immunotherapy is an exciting combination. Our current trial focuses on early stage disease, where it makes some sense that immunotherapy might have a better chance of working because of the patients' relatively limited tumor burden.

We talk a lot about the side effects from these immunotherapeutic agents. What do you think the impact of these side effects will be as you move them earlier in the disease state?

Dr. Drake: Some physicians who don't have a lot of experience with these drugs treat them very lightly. With anti-PD-1 monotherapy, about 15 percent of patients will have a grade 3 or 4 adverse event later. Most of these side effects can be managed with steroids. The ones we see commonly are skin rashes, (dermatitis) and sometimes inflammation of the gut, which is colitis. Often we see thyroid abnormalities. Some patients need to be treated with thyroid hormone replacement.

There are some side effects that can be very dangerous. We've seen patients get a single dose of anti-PD-1 and develop irreversible type 1 diabetes. That's because their immune system gets activated and kills the beta cells that make insulin in the pancreas. It's reported in the literature and it can happen in any of these trials. A lot of people look at the overall numbers and think that these drugs are great and that they're completely safe. That's partially true – they great, and they are generally fairly safe, but they're powerful immune drugs.

It's also worth noting that some patients can develop immune-related adverse events that can last. In my experience, some of the skin events like dermatitis wax and wane throughout patients' lives. Some of these adverse events can be serious. It's very rare that we see something we can't treat with steroids but it's not out of the question. That's why we insist men have a fast doubling time in the trial I just spoke about. Patients had to have a doubling time less than 12 months. Those patients on average will have metastatic disease within about 18 months. These are patients who are in danger from their cancer. Whenever a patient enrolls on a trial, they need to sign an informed consent document. But whenever anybody signs a consent form, they all think it's not going to be me. All these things are rare, but they're not unheard of. Patients need to be aware.

The combination that's shown efficacy in other cancers is the combination of immunotherapy with chemotherapy, surprisingly, and in most cases one sees at least an additive effect. This has been shown in lung cancer and a couple other tumor types. It is being tested in Phase III trials in bladder cancer. We always think of the chemotherapy as being immunosuppressive; it kills immune cells and causes neutropenia. It turns out that maybe it's not that bad. So there are a couple of trials that combine anti-PD-1 with chemotherapy in prostate cancer, although results haven't been presented publically as of yet.

Some of these data are probably going to get presented at ASCO GU in 2019, in particular it could be that the combination of immunotherapy plus chemotherapy–probably Taxotere (docetaxel) in prostate cancer, is additive. That would

be exciting because there are patients who have rapidly growing disease or visceral disease who, we think, really need chemotherapy. Their response rate to chemotherapy is good—about 40 percent, but if we could get that to be either a higher response rate or a more durable response, we would be excited and that would be great news for patients.

To be frank, I was quite surprised when standard doses of chemotherapy was shown to be additive with PD-1 blockade in lung cancers. In my lab, we studied the combination of immunotherapy and chemotherapy for a long time. When we studied this combination in mice, we'd get an answer that suggests you have to give a lot less chemotherapy and you have to give it very carefully. In humans, most of the trials just give standard chemotherapy at standard doses with immunotherapy. Again, in lung cancer and other cancer types, the combination works. Maybe this will work in prostate cancer. That would be exciting.

To me, those are the big things in immunotherapy for prostate cancer at the end of 2018 and heading into 2019: combinations of immunotherapy with PARP inhibitors, with hormonal therapy, or potentially with chemotherapy.

This one last concept I should mention. There are these molecules called bi-specific T-cell engagers, or BiTEs. These are very small molecules. They have two arms. One arm is an arm that grabs the tumor. Commonly they target PSMA or maybe B7H3. There are a couple of these. The other arm is an antibody that grabs T-cells. The idea is that these small bi-specifics or BiTEs have one arm that latches on to the tumor and the other arm that grabs any T-cell that is floating by. It doesn't have to be a specific T-cell; it just has to be in the neighborhood. This arm grabs a T-cell and drags it over to the tumor. What is fascinating is in that dragging-over process these constructs activate the T-cells so that they can kill tumor cells. There is a drug like this called Blincyto (blinatumomab), which has been approved for acute lymphoblastic leukemia.and is quite effective. It's in the ballpark of chimeric antigen receptor T-cells. These drugs are being tested for prostate cancer by a number of different groups in Phase I trials. If they work, it would be very exciting. These are immune drugs.

Do you have any thoughts for men considering joining prostate cancer immunotherapy clinical trials?

Dr. Drake: Men need to be aware that clinical trials have fairly strict entry criteria in terms of which drugs you can be on and which you can't be on. They're generally oriented towards fairly standard therapies. If patients are on nonstandard therapies, they need to come off them before they go on a trial.

The second thing is that a lot of patients come in at the wrong time. The time to look for a clinical trial is before something happens or right when you're going to switch therapies. For example, say your prostate cancer is progressing and it's pretty clear that you should go on chemotherapy. If a man is interested in a clinical trial, it's really not a great idea to just start the chemotherapy. It's a good idea to start looking for the clinical trial before that time. In other words, if you're smart, it's better to be proactive and say I'm on Xtandi (enzalutamide) or Zytiga (abiraterone). It's working. These are good drugs, but when they stop, I want to try something outside of the box. I want to try, say, chemotherapy plus immunotherapy.

If you start looking a month or two ahead of time, then it's much easier. You can meet the principal investigator, and they can say, "We love you, but you're on Avodart and if you're on Avodart, you can't go on this trial. If you want to go on this chemotherapy plus immunotherapy trial, maybe it's a good idea to taper off that Avodart now. When you progress, then we'll try to get you on this trial."

Patients need to understand that getting on a trial is a process. It's a little bit cumbersome sometimes. And it takes some time. Many of these trials, especially the Phase I trials, have waiting lists. If a patient comes to Columbia looking for one of these bispecific trials when they're doing very poorly and need to start a new treatment quickly, this is very tough for us.

It typically takes somewhere around three to four weeks to get on a trial. As patients think about that, it's a good idea to budget that into their projections. You just can't walk in and say, "I'm a great candidate for your trial. Sign me up." I'd love to sign you up. Let's sign an informed consent. Let's do the screening labs. Let's make sure you qualify. I'm probably making it sound unappealing, but it is a process, and the longer lead time and the more that patients think about it ahead of time, the better off they are.

The other thing men might want to think about is randomization. For example, let's say a man enrolls on a trial that randomizes them to chemotherapy versus chemotherapy plus some sexy immunotherapy and he goes on the trial and gets randomized to the standard chemotherapy arm. Their initial reaction is often to be disappointed. But men should know that if they get standard chemotherapy on a trial, we have study staff who act like the police. They're the study nurses. They make absolutely sure that we give chemotherapy entirely according to protocol, that men get followed-up according to protocol, that patients get imaged according to protocol, and that we do labs according to protocol. As you might imagine, that close follow-up leads to patients on the standard arms of randomized trials doing better than they would have otherwise.

The message about planning ahead is a good point. Most of the time, we just point patients to www.clinicaltrials.gov.

Dr. Drake: Although clinicaltrials.gov is a terrific resource, sometimes the trial descriptions are less than fully complete. So, it can be really hard, even for me as a physician, to look at a trial description and figure out if a patient has a good chance of qualifying or not. Usually, there is a coordinator for a clinical trial at an individual institution who can talk to you on the phone for 10-15 minutes to get a basic idea if you're going to qualify.

Thank you for the chance to talk with the readers of *Prostapedia* about my favorite subject in the world, immunotherapy, and for the chance to hopefully help some of your readers learn a little bit more about clinical trials and how they can join. Pp[1]

James Gulley, MD
Prostate Cancer Vaccine Clinical Trials

Dr. James Gulley is the Head of the Immunotherapy Section and the Director of the Medical Oncology Service at the National Cancer Institute's Center for Cancer Research in Bethesda, MD.

Prostatepedia spoke with him recently about ProstVac and open prostate cancer vaccine clinical trials.

"To me the ultimate machine is the human body."

Why did you become a doctor? What was it about medicine that drew you in?

Dr. James Gulley: I think this has to go back to my high school biology teacher. His name was Vernon McNeilus. He was a retired orthopedic surgeon who just found a way to instill inspiration and that sense of curiosity about life. He drove us to really be excited and interested in science and in biology in particular. I had decided that I wanted to do something in science or medicine, but there was no way that I was going to go spend all that time to become a doctor. I'd been in school long enough. One of my friends decided he was going to go into medicine. I said if he can do it, I can certainly do it.

Then it actually evolved even further than that because during my stint in college I got the opportunity to do a summer research program. I decided I liked research, so I applied to MD/PhD programs and got accepted into two. I decided to go to Loma Linda.

What is it about medicine that keeps you interested?

Dr. Gulley: I think the thing that really drives me is how fascinating it is to understand how things work. I've always been fascinated in what makes things work. As a little boy I would take things apart trying to figure out what made them work and then put them back together again. If something was broken in the house, my mom would just give it to me and I'd tinker with it and get it to work again.

To me the ultimate machine is the human body and one serious puzzle is to figure out ways to bring back health from sickness. Not just a puzzle for curiosity's sake, but because of the effect that cancer can have on families, to uncover ways to effectively treat cancer. I think it's truly something that I have seen patients who were close to death who have had remarkable and prolonged clinical responses. That, to me, begs the question that if we can do it for some people, then why can't we do it for all people? That is what I am passionate about.

Are there any patients you've had over the years whose cases changed how you see your own role or the art of medicine?

Dr. Gulley: I've had several patients that have been exceptional responders; that really has changed how I view things. One of my more recent exceptional responses from this past year is a retired army surgeon who has advanced metastatic castrate resistant prostate cancer. I have been treating him since 2005. He was initially treated with radical prostatectomy. It turned out that he had a high Gleason disease. He had radiation therapy, but he had recurrence of his disease, unfortunately. He was treated with hormonal therapy, with chemotherapy, with Provenge (sipuleucel-T), and Xtandi (enzalutamide).

He came to me last year having had multiple therapies including other experimental immunotherapies. He was clearly not doing well. His PSA was going up very quickly with a doubling time of less than a month. His symptoms were getting substantially worse. He articulated to me that even going to church every week was becoming difficult: one week he was able to sing the songs and the next week he was too tired to sing. Then the next week he was almost too tired to stand up.

We were able to enroll him in a study combining a vaccine with checkpoint inhibition. When we gave him that combination, his PSA dropped dramatically. It has now gone to undetectable. His lesion in his bladder, which was causing local symptoms so that he had to have a chronic indwelling Foley catheter, shrunk away. When we biopsied it there was no evidence of tumor there. He has some lesions that are seen on bone scan, but I'm not sure if that represents viable tumor or not.

He is now over a year out from when he started treatment. His energy level hasn't been better since before he was diagnosed. He is out doing everything he wants to do. To me that is amazing. It is amazing we can see responses like that.

From a scientific standpoint, of course, I was stunned to see this and wondered could he have micro-satellite instability that leads to lots of mutations. It turned out that he had micro-satellite instability in his cancer, suggesting that the immune system was able to see his cancer much more readily, so all we need to do is allow those immune system cells to be functional with the Opdivo (nivolumab).

We also had one other patient that didn't have micro-satellite instability with this combination who also had a really nice 90% or so drop in his PSA. It's not undetectable, but he hasn't had the immune checkpoint inhibition for well over a year now. He's just on vaccine alone because he had some bleeding in his urine from the checkpoint inhibitor. To me, having responses like that changes my outlook. It says the immune system, even in patients with prostate cancer, can be harnessed to attack the tumor. We just have to figure out ways that we can make this more applicable to all patients.

There's still the possibility that immunotherapy for prostate cancer can become a viable treatment option. We just need to find the right combination and the right patients to use it in?

Dr. Gulley: Yes. I would say that immunotherapy is being used in prostate cancer and used effectively with Provenge (sipuleucel-T). However, I would say I want disease to shrink away reproducibly with immunotherapy. That doesn't happen currently with Provenge (sipuleucel-T) as a single agent. Are there other ways that we can use immunotherapy so that patients who are symptomatic from large tumors get better from the therapy? This is the paradigm change. I do think that Provenge (sipuleucel-T) definitely has a place. I think we need to be able to find a way to treat patients who are more advanced and to shrink down disease, not just improve survival.

There is another vaccine that was under investigation called ProstVac. Can you tell us a little about that vaccine and whether or not it has been effective?

Dr. Gulley: ProstVac is a pox viral-based therapeutic vaccine that has the genes for PSA, as well as three different human T-cell co-stimulatory molecules. What that means is that the vaccine is something that we can give that can train the patient's immune system to recognize and attack cells that make PSA. Normal prostate cells or prostate cancer cells can make PSA. There are cancer patients who have had their prostates removed. The only cells left behind that would express PSA are the cancer cells.

There are two basic viruses that are used. One is vaccinia for the initial vaccine. It's a really good jolt to the immune system. All the subsequent boosting vaccines are given with fowlpox that again contain the same genes for PSA and co-stimulatory molecules. That can continue to boost an immune response.

There were initial studies done with this agent that showed that it was safe to give in patients with advanced cancer and that when given it could generate immune responses to PSA in those patients. If you took cancer cells with the immune cells from those patients, those immune cells could recognize and kill those cancer cells that make PSA.

We then did additional studies looking at this activity, including one randomized Phase II study that was double-blinded. 125 men received vaccine versus placebo. In that study, we found that there was no difference in progression-free survival, but there was an improvement in overall survival, which was our secondary endpoint.

This is very similar to what was seen with Provenge (sipuleucel-T). So we followed this up with

a larger study to confirm whether or not these findings are correct. We embarked on a 1,200-patient study that over enrolled. There were 1,297 patients enrolled on that study. We presented the results at the conference of the American Society of Clinical Oncology in 2018: there was no improvement in overall survival with the vaccine.

I should mention a little bit about the trial design. There were three arms in the study: one group received the vaccine plus GM-CSF. This was used in the Phase II trial and showed an improvement in survival. GM-CSF, or Granulocyte-macrophage colony-stimulating factor, can further boost immune response. We don't know if it is required for the vaccine or not. Interestingly, because of the difficulty in getting this outside of the United States and because we didn't know if it was needed or not, we did one arm with GM-CSF and another with no GM-CSF. The third arm got a placebo. The placebo vaccine was just comprised fowlpox vector.

What we saw in that study, which showed no improvement in survival, is that we don't really have a clear explanation of what happened or why we saw a difference in the Phase II study. It could be that the Phase II study was just under-powered and the results we saw were based on chance. (I'm just going to lay everything out here.) It could be that the vaccine *was* effective and that it did generate immune responses, but that those immune responses did not translate into improved survival for a variety of different reasons.

First, multiple agents have been approved since the initiation of the drug; Zytiga (abiraterone), Xtandi (enzalutamide), Jevtana (cabazitaxel), Xofigo (radium-223), and Provenge (sipuleucel-T) were all approved after that study was designed. It's possible that when these agents are used afterwards they delete out any treatment effect. If you look at the overall survival

"I want disease to shrink away reproducibly with immunotherapy."

data from Xtandi (enzalutamide) and Zytiga (abiraterone), you'll see huge improvement in survival in the post chemotherapy setting. In the pre-chemotherapy setting it's very difficult to see an improvement in survival. In fact, there was no statistically significant improvement in survival with Zytiga (abiraterone) in the pre-chemotherapy setting, suggesting that that could be another explanation for why an improvement in survival just wasn't seen. The lines are really overlapping.

Finally, it could be that the vaccine was generating an immune response. That immune response went to the tumor, but those cells were held in check because of regulation of PD-L1 or something like that. It turns out that when you have activated T-cells that recognize a tumor, they make gamma interferon and cause the other T-cells there to recruit other cells, but that gamma interferon will cause up-regulation of PD-L1. (PD-L1 is a stop sign to T-cells.)

As soon as the T-cells see that stop sign, then they stop everything and they can't do anything while that's there. If you come in with an immune checkpoint inhibitor and block either the PD-1 or the PD-L1, you basically cover that stop sign and those T-cells go back to work.

Perhaps that is what's going on. We did a study in the neo-adjuvant setting where we gave a ProstVac vaccine to patients undergoing surgery. We did see immune cells getting into the prostate, but often not into the tumor, so it may not just be the PD-L1. There are other things excluding the T-cells from the tumor, for example there may be no HLA-A2 expression. Maybe there is up-regulation of TGF-beta. These are still things we're grappling with, things we're trying to understand. We're also trying to come in with other clinical studies to address these different aspects of what might be going on in the tumor microenvironment to lead to a better outcome.

You're still looking for explanations.

Dr. Gulley: Correct. There are ongoing studies looking at ProstVac in men with a biochemical recurrence. There are ongoing studies in active surveillance—with patients who don't need treatment.

There are ongoing studies in combination with other agents, like ProstVac and Opdivo (nivolumab). We've looked at that combination in men with metastatic disease. I mentioned earlier two of the twelve patients had good responses. Ten of them didn't. We're trying to understand that better, so we're taking it into the neoadjuvant setting. We've enrolled one out of the seventeen patients we need to understand a combination of a vaccine plus Opdivo (nivolumab). We're getting biopsies and comparing that with the prostatectomy specimen

to see if there is an increase in immune cells. Do we get more of an increase in immune cells from that combination than we get from the vaccine alone? How do we improve upon that?

If a man reading this is interested in joining a trial, there are multiple options for him to consider?

Dr. Gulley: Absolutely. We also have other vaccines besides ProstVac that we're testing in prostate cancer.

There is another study at Washington

> *"There are ongoing studies looking at ProstVac in men with a biochemical recurrence."*

University that looks at ProstVac plus a neoepitope-based vaccine. It turns out that if we have mutations like the patient with microsatellite instability prostate cancer, the immune system really can recognize that as being bad and foreign. What a lot of people have tried to do is understand which mutations patients have and which mutations their immune system might see and then develop vaccines specifically for that mutation in that given patient.

At Washington University, in collaboration with Dr. Russell Pachynski, we are doing a study that looks at the immune responses. Dr. Robert Schreiber is also involved in this study and really is the science behind the neoepitope-based vaccine for the trial. The Prostate Cancer Foundation funds the study.

We're working with BMS, who is supplying Yervoy (ipilimumab) and Opdivo (nivolumab) for this study. We'll give patients ProstVac and then they'll get the neoepitope-based vaccine. We're hoping to get good immune and clinical responses.

Anyone who is interested in participating should contact Dr. Russell Pachynski, the clinical lead at Washington University, at rkpachynski@wustl.edu.

Are there any other clinical trials that you'd like to highlight?

Dr. Gulley: I do want to highlight our Quest study. In this study we're using a vaccine that targets a gene called brachyury. Brachyury is over-expressed in prostate cancer and bad-acting prostate cancer cells. This vaccine is similar to the ProstVac vaccine with the pox viral vectors and the co-stimulatory molecules. But instead of PSA, it targets brachyury. Brachyury is a gene that is involved in drug resistance; it's involved in cancer metastasis spreading and in stem cell-like properties. It basically takes a cancer cell and makes it worse. It makes a cancer cell really difficult to kill. We're targeting this from an immune standpoint. We're then combining it with four different additional pathway blockades. We're blocking PD-L1 with an antibody. That antibody has on its tail two receptors for TGF-beta that serves to vacuum up, if you will, all the TFG-beta that they see. They can grab on to any of these proteins.

TGF-beta is involved in multiple things. It is involved in the biology of tumors, making it easier for them to spread. It increases fibrosis and makes it harder for drugs to penetrate or cells to penetrate. It increases the new blood vessel growth into the tumor so it can help feed them. Most importantly, it really blocks an immune response and can prevent immune cells from getting into the tumor. By eliminating that from the equation, you can make the playing field much better for immunotherapy.

In addition, we add in IL-15 or interleukin-15, which can really boost good immune cells like T-cells and NK-cells. Then finally, we add in a pill that decreases the activity of the IDO. IDO is an enzyme that is up-regulated in tumors that leads to starvation of T-cells by depleting the essential nutrients for those T-cells to work. All of this can set up an immune response to be more active and hopefully be able to eliminate tumors.

Anyone interested in this trial should contact me directly at gulleyj@mail.nih.gov. We are actively enrolling. The current group of patients we're enrolling will get two agents targeting three pathways. Then in the next group, we're going to add another agent. In the final group, we'll add in the fourth agent.

Are there any other trials that you think patients may find interesting?

Dr. Gulley: We have another trial for men with biochemical recurrence. We're looking at two vaccines along with this same agent that blocks PD-L1 and TGF-beta. There is one final trial that looks at combining an antibody that blocks PD-L1 with a PARP inhibitor. We've seen really good responses with that combination.

Any final thoughts for men about either ProstVac, the enrolling clinical trials you've spoken about, or immunotherapy for prostate cancer?

Dr. Gulley: I would like readers to understand that we are in an extremely exciting time in the development of cancer immunotherapies. We're showing deep and durable responses across a wide range of different cancers. We are not seeing that yet in prostate cancer. However, we now have combination approaches that are ongoing that we hope will bring prostate cancer fully into the realm. We are already seeing unprecedented responses in patients and we're learning from those patients what is driving those responses. We hope to be able to use that knowledge to expand the proportion of patients responding.

The only way we can do that is through clinical trials. We need to try different approaches and then learn from who responds which pathways lead to resistance and which pathways lead to response. We can then design future studies based on those responses. If we just do this in a physician's office where we're not getting biopsies and not understanding what's going on, we are not going to make the progress that we need to make to really turn prostate cancer into a disease that even in the advanced setting can be cured.

Everyone with advanced prostate cancer should consider joining a clinical trial. If you are interested in clinical trials at the National Cancer Institute, after you are enrolled on study, we will pay for you to fly here for your visits from anywhere in the United States. We will not charge you or your insurance company for any of the studies, scans or laboratory tests that we do here. Pp[1]

Julie Graff, MD
Combining Keytruda and Xtandi

Dr. Julie Graff is a medical oncologist at Oregon Health & Sciences University.

Prostatepedia spoke with her recently about her continuing work on combining Keytruda (pembrolizumab) with Xtandi (enzalutamide).

Why did you become a doctor in the first place, and what keeps you at the table now?

Dr. Julie Graff: I told my mom when I was six that I would become a doctor. Then, as I went through school, including high school, I became very interested in science and thought maybe I would become a scientist and work in a lab.

When I got to college, I did a lot of inorganic chemistry research. At the same time, I started doing hospice volunteer work. I worked with a lot of patients with cancer. I had such a strong connection with them, and I enjoyed my work with them so much that I would try to combine my love of science with my love of patients: I went into medical school.

Even as an undergraduate, I felt like I would be an oncologist because those patients, the ones fighting cancer, were very special to me. Also, there's so much research to be done in the field.

In medical school, I did genetics research. When I was interviewing for residencies, I looked for places with good oncology programs.

How did you end up working with prostate cancer?

Dr. Graff: When I was a first-year resident at Oregon Health & Science University, I found Dr. Tom Beer who was, in my thinking, one of the busiest, most productive people I'd met. I approached him to see if we could do some research together. He gave me my first research project. We presented the data at a meeting, and then we published the results. It was very satisfying.

When I applied for my fellowship, I asked him to continue as my mentor with the idea that I was eventually going to study breast cancer. I thought I could learn a lot about clinical research and prostate management, which includes some things similar to breast cancer, and then branch off. After doing clinic work with him and meeting many patients, I enjoyed prostate cancer work so much that I continued on.

Have you had any patients whose cases have changed the way either you see the art of medicine or how you view your own role as a doctor?

Dr. Graff: There certainly have been. I've always been interested in helping people with the life they want to lead. People have such strong opinions coming to appointments. Sometimes you feel like you have a great treatment for some patients, but they're not interested. They're more interested in their quality of life. Something that you find to be not that toxic, they're appalled at. On the other side, you'll meet people who are maybe more frail and will have a tough time on the treatment, but will do anything to get as aggressive a treatment as they can. It's just interesting to me to see that.

I do have one story, though. One of my patients when I first started in my career had metastatic gastric cancer. He was in his 80s. Before he came to the exam room, I was frantically reading about his case, thinking about treatments, and worrying about the HER2 status of his tumor. Then he walked into the room and said he didn't want any treatments. We spent the rest of the visit talking about his life. I just really appreciated that and would never want to force someone to go in a treatment. I always try to remind people that they have a choice. That man really opened my eyes.

Are you saying that there is the path you would suggest as doctor just looking at the case and the science, but that that can change when you meet the actual person and find out what his wants and needs are?

Dr. Graff: Exactly.

What are Keytruda (pembrolizumab) and Xtandi (enzalutamide)? How and when are they used in prostate cancer patients?

Dr. Graff: Keytruda (pembrolizumab) is an intravenous antibody to PD-1 or programmed death 1 on immune cells, in particular T cells. When that protein is present, it can interact with tumor cells that have PD-L1 and through that interaction the tumor cells turn off the immune system. We consider it a checkpoint inhibitor.

We've known for a long time that in some cancers T cells, which are the part of the immune system that can kill cancer cells, are present in the tumor and yet they're not actually killing the tumor. Over the decades we've learned that some of those cells, not necessarily T cells but immune cells in the environment, are actually helping the tumor grow. We've also learned that some of them are trying to fight the tumor, but they're being turned off by the tumor.

Keytruda (pembrolizumab) can block that negative signaling, thereby activating the immune system. It was first approved in melanoma and has received multiple subsequent approvals. So far we don't have great markers for knowing who will benefit from the drug and who won't, but we are working on that.

Xtandi (enzalutamide) is a drug that binds to the androgen receptor, which is inside the prostate cancer cells, and prevents it from interacting with androgens or male hormones. In that fashion, it leads to some cell death and helps people live longer. It's been FDA approved since 2012 in the post-chemo setting, and now it has been approved in the pre-chemotherapy setting. It used to be approved only in metastatic disease, and now it's approved in non-metastatic castrate-resistant disease. It's being applied in different stages of the disease.

What is the rationale behind combining these two agents?

Dr. Graff: In studies where checkpoint inhibitors like Keytruda (pembrolizumab) are used alone, there's not a lot of tumor activity. There's certainly not a good rationale to use Keytruda (pembrolizumab) by itself in prostate cancer. Maybe as time goes on we'll find that perhaps 2 out of 100 patients have certain mutations that make the Keytruda (pembrolizumab) alone helpful, but we're not yet there.

There wasn't a great reason to use Keytruda (pembrolizumab) by itself, so we began to think about combinations. Xtandi (enzalutamide) was felt to upregulate PD-L1 on dendritic cells, in particular when people became resistant to the Xtandi (enzalutamide), so that was one initial reason.

Castration therapy may reinvigorate the immune system. When you're maturing as a child, you have a thymus gland behind your sternum that helps create new T cells. As you go through puberty, that gland shrinks and becomes inactive, so you don't make new T cells.

It looks like maybe the thymus increases again during castration therapy; there's a hypothesis that you're creating new T cells.

There is also a reason to think about Xtandi (enzalutamide) in particular. It's helping in those two regards.

Also, if you used Keytruda (pembrolizumab) in combination with chemotherapy, you would be at risk of killing a lot of immune cells with the chemo itself. If you used Keytruda (pembrolizumab) in combination with Zytiga (abiraterone), which is like Xtandi (enzalutamide), you would have to use prednisone, which would perhaps dampen the immune response. When our study was designed in 2014, it made a lot of sense to combine Keytruda (pembrolizumab) with the Xtandi (enzalutamide).

What have studies revealed about the combination? Is it effective? What kind of side effects do patients experience?

Dr. Graff: We did a Phase II study looking at 28 patients with metastatic castrate-resistant prostate cancer whose cancers were progressing on Xtandi (enzalutamide). We added 4 doses of Keytruda (pembrolizumab). We saw 5 responded in that group of 28. That's only 18%, but when they responded, they responded spectacularly.

The most extreme case was a gentleman who started out with a PSA of 2,500 that went down to 0. He had big, bulky liver tumors that just shrank away. He must be two and a half, almost three years

out from treatment and he's still in complete response. His case is extreme. But when we *do* see responses, they're spectacular.

If those five patients had only had a dip in their PSA or something less impressive, the study wouldn't be as important as it was. Then we had four other people who had very durable responses as well. That's the benefit part of the study.

But there are known side effects with each of these drugs. With Keytruda (pembrolizumab), when you stimulate the immune system you run the risk of the immune cells killing or attacking healthy tissue. For example, a patient on Keytruda (pembrolizumab) could develop autoimmune hepatitis where the immune cells are attacking a healthy liver. There are some bad sides to stimulating the immune system.

In our study, we did see some of those side effects. In these 28 patients who were treated, we did have patients who had autoimmune toxicities in which their own immune cells attacked healthy tissue. We had four patients who had thyroid dysfunction, which is a fairly well recognized side effect of Keytruda (pembrolizumab) that is easy to manage with thyroid medicine. We had a couple people with colitis, which happens when the immune system attacks the colon; that has to be managed with high-dose steroids and sometimes biologic drugs that GI specialists use. We saw side effects that we would expect from Keytruda (pembrolizumab) and we saw some side effects that we would expect from Xtandi (enzalutamide) such as fatigue. Since these patients had already been on Xtandi (enzalutamide) for a long time, we did not observe worsening of the Xtandi (enzalutamide) side effects with the addition of Keytruda (pembrolizumab). We mostly just saw those Keytruda (pembrolizumab) side effects.

Any follow-up studies planned?

Dr. Graff: We got funding from Merck to add another 30 patients on to that study. Those 30 have already been enrolled and treated. For those patients, we insisted on a biopsy. For the first 28 patients, we asked them to get a biopsy if they had a tumor that could easily and safely be biopsied. In the next 30 patients, we required that they have a biopsy. We have now a nice array of tissue from these 58 patients and we're working on getting the results. We have some multiplex stains and hope that the paper can come out next year.

We've also just got funding from Prostate Cancer Foundation for another study. People don't do as well on drugs like Keytruda (pembrolizumab) if they received antibiotics in the prior few months before taking the drugs.

There seems to be a very strong connection between what's in your gut microbiome, particularly in the colon, and how you respond to these drugs. There are now multiple studies showing that if you get antibiotics beforehand, that isn't good for your response to the drug.

Having a limited diversity of bacteria in your gut is not good for response. Certain bacteria predict a response and resist it. When you look at the studies that name certain types of bacteria, it's not consistent. I can't say every study showed that bacterium X was associated with response.

What we are doing is treating 32 veterans with this combination of Keytruda (pembrolizumab) and Xtandi (enzalutamide) and then dividing them up into responders and non-responders. We are then taking a fecal sample from the responders and giving it to the non-responders and then retreating with Keytruda (pembrolizumab). It's kind of wild, but we want to see what the relative contribution of the microbiota of the gut adds.

Interesting.

Dr. Graff: I'm excited to see what happens.

We got $1 million from Prostate Cancer Foundation. The clinical trial is not yet open. Unfortunately, there are a lot of steps you have to take before it can be opened, but we're working on it.

Any more thoughts on this particular combination and the promise it may hold?

Dr. Graff: I would say that there a lot of trials underway looking at the combination. Of note, one of my colleagues just opened a study for Veterans with aggressive localized prostate cancer. All patients will receive Xtandi (enzalutamide), Keytruda (pembrolizumab) and androgen deprivation therapy (such as Lupron) before getting a radical prostatectomy. Different companies have launched their own trials looking at their respective PD-1 or PD-L1 inhibitors in combination with Xtandi (enzalutamide). I think in the next maybe two years we'll have an answer as to how effective it really is. Pp1

Fatima Karzai, MD
Combining PARP and PD-L1 Inhibitors

Dr. Fatima Karzai is the Director of the Prostate Cancer Clinic for the Genitourinary Branch at the National Cancer Institute. She's keenly interested in developing novel strategies for harnessing the power of the immune system for hormonally driven cancers, particularly in advanced prostate cancer.

Prostatepedia spoke with her about a clinical trial she's running that combines PARP inhibitors and a class of immunotherapeutic agents called PD-L1 inhibitors in men with advanced prostate cancer.

Why did you become a doctor? What is it about medicine that keeps you interested?

Dr. Fatima Karzai: I decided to become a doctor at a very young age. I've always wanted to help people. When I was younger, I thought that being a doctor was the best way to do that. I really enjoy patient interactions, so that's why I'm a clinical researcher and I see patients on clinical trials. I find that it's the most rewarding experience to be able to interact with patients. It's always been a goal of mine to be able to help people in this manner. I think oncology was best suited for me to do so.

What are PARP inhibitors and PD-L1 inhibitors? How do they work, in which patients are they used, and how effective are they?

Dr. Karzai: PD-L1 inhibitors are members of a group of drugs called checkpoint inhibitors that have been developed for the treatment of cancer. PD-L1 is a protein that is present on the surface of cells. In cancer, PD-L1 on the tumor cells interacts with another protein on a person's white blood cells, which are immune cells that help fight cancer. This PD-L1 protein prevents the immune system from attacking the tumor cells. A PD-L1 inhibitor blocks that ability of the tumor cell to suppress our immune system, which can help our immune system kill cancer cells. They've been successful in certain cancer types like lung cancer and bladder cancer.

PARP inhibitors are a type of targeted therapy. We all have DNA in our bodies; when it becomes damaged, our bodies know how to repair it. Many things can cause DNA damage: exposure to UV light, radiation, or substances in the environment. There is an enzyme in cells called PARP. PARP helps repair DNA when it becomes damaged. By blocking PARP in cancer cells, we can keep cancer cells from repairing their damaged DNA, which causes them to die. PARP inhibitors work very well in a subset of patients whose tumors harbor something called "DNA damage repair mutations." These mutations can occur in the tumor itself or it could be something that a patient is born with. PARP inhibitors were initially studied in ovarian cancer and breast cancer. We're starting to use them more in prostate cancer.

What is the rationale between combining the two agents for prostate cancer?

Dr. Karzai: We wanted to expand the use of PARP inhibitors. Like I mentioned before, right now they're used in patients with these specific mutations. We're trying to figure out if we're able to get this class of drugs to work in patients without these mutations if we combine them with another drug. Historically, PD-L1 inhibitors have not been that successful in prostate cancer, so we decided to put these two drugs together to see if there is any additive or synergistic mechanism that could help patients with advanced prostate cancer.

For more information …

About NCI-supported clinical trials, visit https://www.cancer.gov/about-cancer/treatment/clinical-trials/search

What have the studies revealed about the combination?

Dr. Karzai: We are still accruing to the study. We've looked in-depth at the first 17 patients and seen deep and prolonged responses in men with castrate-resistant prostate cancer with the combination, in men who have these germline or somatic DNA damage repair abnormalities. We're now adding additional patients to the study to better define the activity and to help us evaluate the biology more.

You said you're still looking for more patients?

Dr. Karzai: Correct.

Tell us a little bit more about eligibility criteria and who men can contact if they think they're a fit.

Dr. Karzai: We are looking for patients with advanced prostate cancer—i.e. the prostate cancer has gone outside the prostate and is in either the soft tissue, organs, and/or bones. We would like to have these patients previously treated with either Zytiga (abiraterone) or Xtandi (enzalutamide). We think patients who have progressed on these two treatments might be more amenable to our combination. We allow previous chemotherapy, so if a patient has had Taxotere (docetaxel) or some other chemotherapy, they would be eligible. We are looking for patients who are still able to perform their activities of daily living and would be willing to participate in our trial and travel.

Some of our patients are local, but many come from across the United States. We even have some international patients.

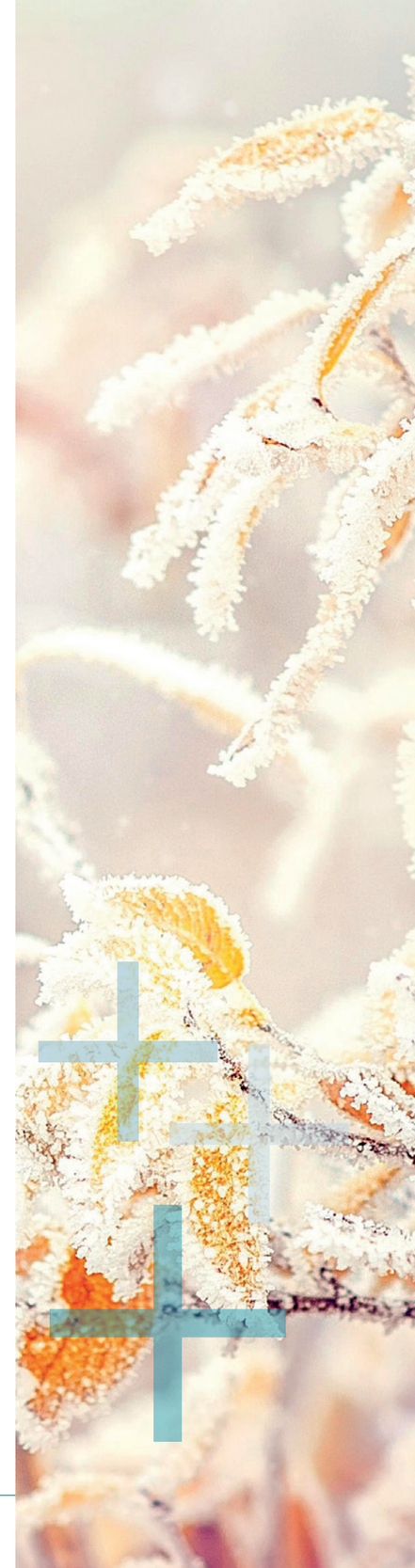
You help defray the cost of travel for some of your clinical trial participants, don't you?

Dr. Karzai: We do. Once a patient is on one of our protocols, then we reimburse flights in the United States. We also have a stipend for meals and hotels.

> *"We reimburse flights in the United States. We also have a stipend for meals and hotels."*

Any further thoughts on this particular combination or other combinations that you think may hold promise?

Dr. Karzai: Even though this type of immune therapy hasn't been very successful thus far in prostate cancer, I still think that we need to do more studies and research to be able to find the subset of patients that it might work in. Immunotherapy is very exciting. We shouldn't count it out in prostate cancer yet. The first vaccine that was FDA-approved in cancer was actually for prostate cancer. I think that the whole realm of immunotherapy is still open and could provide benefits for our patients. I am happy to see any patient for a consultation —those with newly diagnosed disease or those who are more advanced. We have clinical trials that span that spectrum of prostate cancer. Pp



Clinical Trial: PROVENGE® + Active Surveillance

Urologist Dr. Bruce Brown is the Chief Medical Officer of Dendreon, makers of the prostate cancer therapeutic vaccine PROVENGE (sipuleucel-T).

Prostatepedia spoke with Dr. Brown about a trial they're running that will evaluate the effectiveness of sipuleucel-T in reducing disease progression in men on active surveillance.

What is the thinking behind your trial that looks at sipuleucel-T in men with lower risk non-metastatic prostate cancer?

Dr. Bruce Brown: As you know, PROVENGE, which is Dendreon's product for metastatic castrate-resistant prostate cancer (mCRPC), has been approved since 2010. It's been prescribed to over 30,000 men and has been found to be effective and safe. But that is in a small population of prostate cancer patients – men with metastatic disease that has spread and who have already failed some treatments. When we looked at the whole prostate cancer landscape, we asked how we can potentially get this treatment to more prostate cancer patients who may benefit? In the United States, about 180,000 men a year are diagnosed with prostate cancer. Over 80% of those men have localized disease. That is much different than the current indication for PROVENGE. Of that 80%, more than 50,000 will go on active surveillance. Active surveillance is a treatment option for localized disease that hasn't spread.

There are three main treatment options when you are diagnosed with localized prostate cancer. First is active surveillance, which we'll discuss. There is also radical prostatectomy, which removes the prostate, and radiation therapy to the prostate as well as the tissue outside the prostate. Obviously, radiation therapy and radical prostatectomy have some side effects.

Active surveillance is exactly how it sounds. You "actively" monitor patients, meaning the cancer is not treated but closely observed. You repeat biopsies. You repeat blood tests. You repeat physical exams. The thought is that a lot of prostate cancer patients don't progress and their disease doesn't change: it doesn't spread or metastasize. Their risk of dying of prostate cancer is fairly low. They might do just fine for years without the need for more aggressive treatments that may result in life-altering side effects.

We focused on this active surveillance population. Of men who go on active surveillance, about 10% a year will progress and go on to further treatment. We wondered if there was a way for sipuleucel-T to delay or prevent their disease from progressing and needing other treatments. They could go on sipuleucel-T and be spared the side effects of surgery or radiation therapy.

At a high level, that's why we're doing this particular trial. But what medical evidence did we have that our drug might be beneficial in this setting? We have several studies that looked at treating men with earlier-stage disease with sipuleucel-T. These studies weren't in our labeled indication that we sell commercially. We have evidence that the immune response in men with earlier disease was even greater than in men with advanced disease. That gave us some inkling that the patient's own immune system will mount a bigger response when sipuleucel-T is given earlier.

That makes sense because immunotherapies work best when the burden of tumor is lower, which would be the case in early stage disease. Immunotherapies also work better when a patient's own immune system is more robust. Again, as you progress through any disease, especially cancer, your immune system is able to mount less and less of a response the further along you go. So we have evidence that our drug mounts more of an immune response in earlier disease.

We also did another trial where we gave sipuleucel-T to patients with localized disease. Two weeks after they received their last dose of sipuleucel-T we removed their prostate. Then we looked at those prostates and we saw that the immune cells had migrated into the prostate and surrounding tumor cells. It showed us that things were happening from our drug because that doesn't happen in patients who don't get our drug.

Again, our drug was causing the immune cells to start doing their work – moving to the tumor, and then hopefully at some point, although we didn't see it in the trial because we didn't follow them long enough, to start doing something to those tumor cells. It made us feel better about the fact that by treating patients with sipuleucel-T early, the immune cells would migrate to the tumor.

What can patients expect to happen during the trial?

Dr. Brown: We are looking for patients who have been diagnosed with prostate cancer within the last 12 months. We're looking for certain patients that fit into roughly a low or intermediate risk category, based on their biopsy results. These patients don't have spread of disease, but again, they may progress over the years. These are patients who have been newly diagnosed, whose biopsy fits these particular characteristics, and who are considering active surveillance and perhaps want to be on a treatment that doesn't involve surgery or radiation therapy.

If a patient decides to enter this trial, he will be randomized. That means he will be put into one of two groups. We will enroll approximately 450 patients—two-thirds of the patients will be treated with a normal dose of sipuleucel-T, which is three treatments two weeks apart. One-third of the patients will not receive sipuleucel-T; they'll continue to be followed per the active surveillance protocol.

Both groups of patients will follow predetermined study visit follow-ups, which involve blood tests, physical exams, and subsequent biopsies. Our primary endpoint is based on the follow-up biopsies, to see how many in each group have biopsies that get worse.

How long are you planning on following these men?

Dr. Brown: We will do the first biopsy between 12 and 18 months after they are randomized into the trial and then we'll do a second biopsy between 33 and 39 months. Each patient will be followed for at least three years.

If someone who is reading this is interested in participating, who should he contact?

Dr. Brown: He can visit ClinicalTrials.gov or contact (800) 772-3125. When prompted, please enter study code number: 170101 (do not hit the #, hash or number key). Expect a brief silence until an available agent answers. In the event an agent is not readily available, you will be directed to a voicemail box.

Are there any associated fees?

Dr. Brown: No. Patients don't pay anything to participate in the trial. Pp1

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