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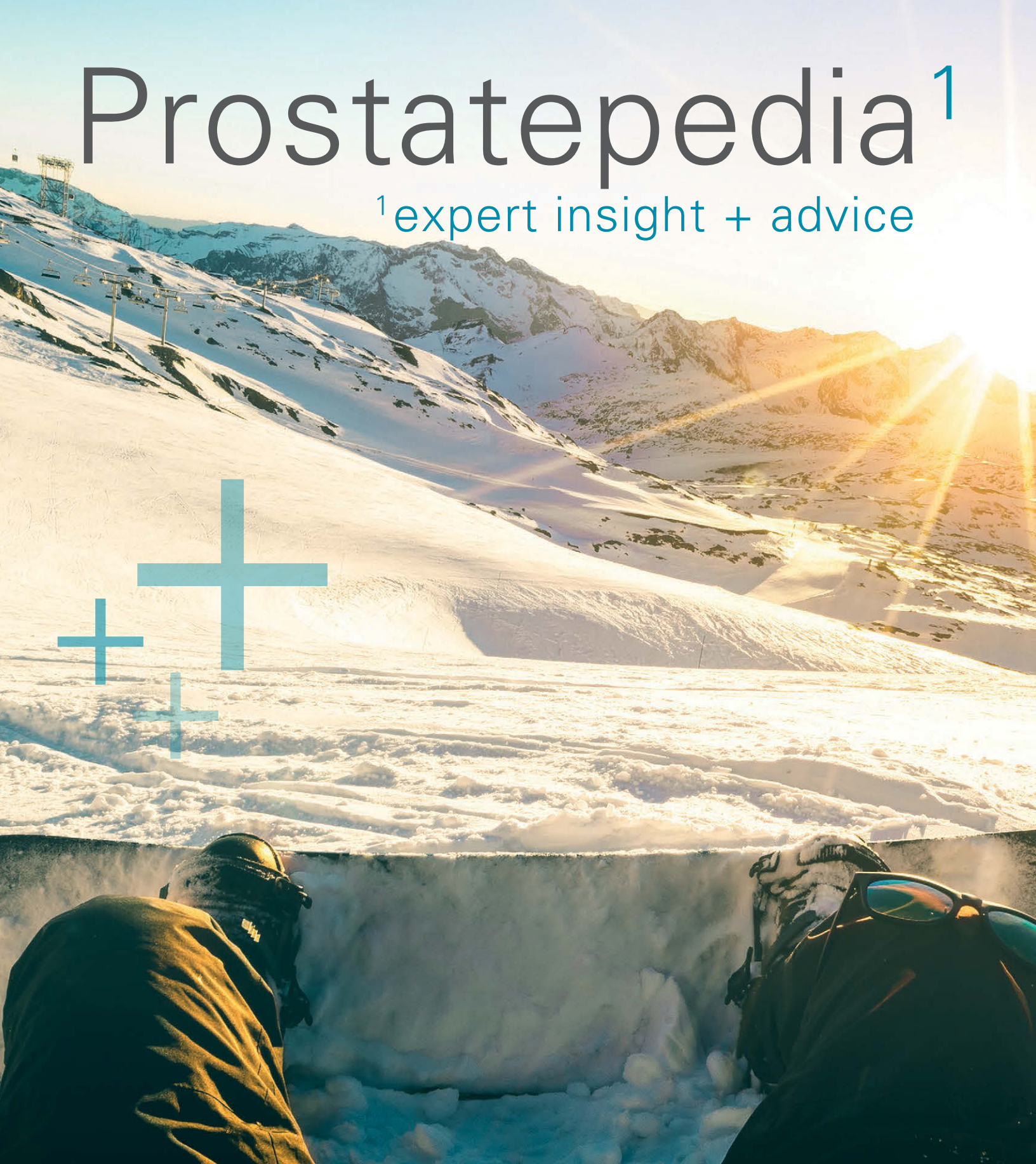


Immunotherapy

Prostatepedia_January [2018] Volume [3] No. [5]

In this issue....

Every January we publish an issue on immunotherapy. If you compare our January 2017 issue with this year's conversations, I am sure the advances in the science behind immunotherapy will excite you. While we only have one FDA-approved immunotherapy called Provenge (sipuleucel-T), the future looks promising.
As Dr. Tomasz Beer points out in his conversation, we're at an interesting intermediate stage in immunotherapy development. We know that various immunotherapy approaches like vaccines, checkpoint inhibitors, and CAR T-cell treatments can control a variety of cancers, but we don't yet have an immune-based treatment that has a consistent, major impact on prostate cancer survival or even quality of life.

I'd like to highlight several important themes in this issue. First, evidence continues to suggest a favorable interaction between hormonal therapy and various forms of immunotherapy. Second, there is continued interest in combining immunotherapy with radiation therapy. This offers the hope that immunotherapy might open the door for more effective multimodality treatment.

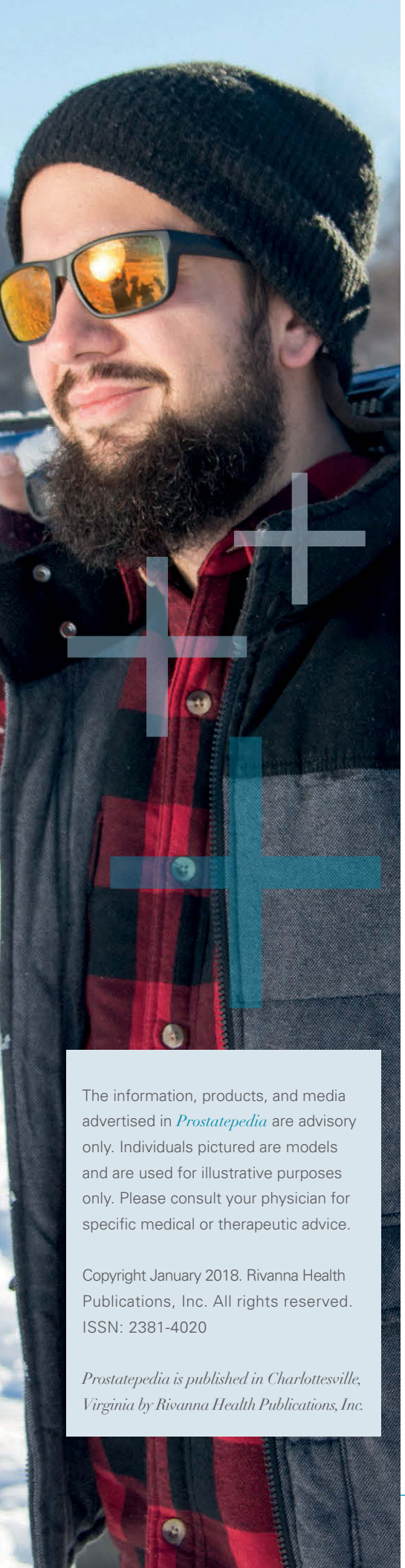
The emergence of CAR T-cell treatment for leukemia and lymphoma has been very exciting; patients with very advanced disease are entering remission. It will be interesting to see this approach applied to prostate cancer. Also note that major funding for CAR T-cell trials in prostate cancer comes from the Prostate Cancer Foundation (PCF), a nonprofit, and not the United States government. This is a trend I noted last month.

There have been some notable disappointments. The randomized trial testing the Prostvac vaccine failed to meet the requirements for FDA approval. It is still possible that this vaccine might prove valuable in patients with less advanced prostate cancer.

Also, the available checkpoint inhibitors continue to show only modest activity. It may well be that CTLA-4 and PD-L1, the two checkpoint proteins currently targeted, are not the only checkpoint proteins produced by prostate cancer. For example, earlier this year, investigators from MD Anderson Cancer Center showed that Yervoy (ipilimumab), an agent that targets CTLA-4, triggers production of another checkpoint protein protein called VISTA.. It may well be that prostate cancer can block immune response in a variety of ways and that we need to inactivate each of these defenses.

Even with these difficulties, immunotherapy offers potential benefits that warrant the attention it is receiving. One of the benefits is that the immune response can evolve over time to match the evolution of the cancer cell population's resistance. In the laboratory, immunotherapy also offers one of the most robust means of attaining durable and complete remissions.

Charles E. Myers, Jr., MD Pp1



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Guest Commentary
Charles Drake, MD

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 frames this month's conversations on immunotherapy.

This is a fascinating time for immunotherapy in prostate cancer.

For the first time, we have a randomized, Phase 3, 800-person trial combining immunotherapy with hormonal therapy. This trial looks at Tecentriq (atezolizumab), a Genentech agent. Patients with metastatic castrate-resistant disease who have progressed on Zytiga (abiraterone) are randomized to Xtandi (enzalutamide) alone versus Xtandi (enzalutamide) plus Tecentriq (atezolizumab). Although there are not a lot of Phase II data supporting this regimen, this is a bold trial concept that could lead to immune checkpoint blockade being FDA-approved for some patients with metastatic castrate-resistant prostate cancer (mCRPC).

On the other hand, in some quarters there is still a lack of enthusiasm for PD-1/PD-L1 blockade in prostate cancer. This lack of enthusiasm is based on older data from the original Opdivo (nivolumab) Phase 1b trial, which included 17 patients with mCRPC. We also didn't see many objective responses in the anti-CTLA-4 (ipilimumab) Phase 3 trials. This lack of response led to the idea that combination therapies will be needed to go forward. This is not unique to prostate cancer.

Combinations range from immunotherapy-immunotherapy combinations, which are mostly in Phase 1 and 2 trials, to immunotherapy-hormonal therapy combinations, one of which is in Phase 3. In addition, Dr. Doug McNeill has done some nice work combining anti-PD-1 with DNA vaccines. Dr. James Gulley and his colleagues at the National Institute of Health tested similar combinations using anti-CTLA-4 plus ProstVac VF. Other combinations include combined immune checkpoint blockade. Dr. Emmanuel Antonarkis at Johns Hopkins University is leading a trial combining CTLA-4 plus an anti-PD-1 in high-risk (ARV7 splice variant) patients. A second, larger trial of that same combination is being conducted at MD Anderson Cancer Center.

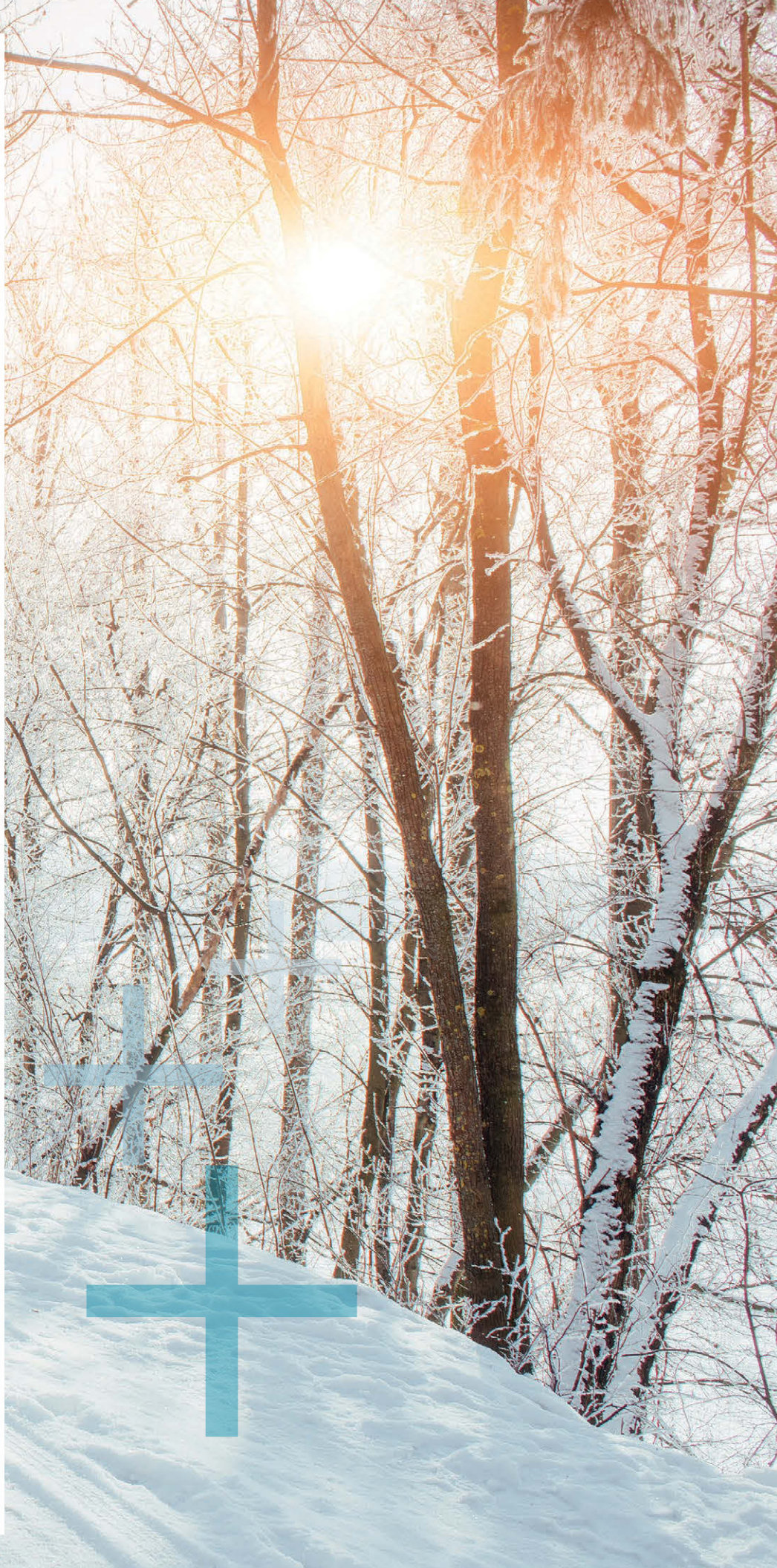
In her conversation, Dr. Naomi Haas talks about the idea of using adoptive T cell therapy, either in the form of chimeric antigen receptor T cells (CAR T-cells) or in the form of adoptive T cell therapy. I think that is a fascinating therapy that hasn't been brought forward in force in prostate cancer. Dr. Haas and her group launched a trial of PSMA-targeted CAR T-cell. There is a lot of enthusiasm in the field about that trial. It's worth noting that Dr. Susan Slovin at Memorial Sloan Kettering Cancer Center has also been doing groundbreaking work in adoptive T cell therapy. I think it's an exciting time for those therapies.

The success of drugs focused on patients with DNA mismatch repair mutations—PARP inhibitors—has led to the idea of combining immunotherapy agents with them. The folks at National Cancer Institute (NCI), particularly Dr. Ravi Madan, have generated fascinating data on those combinations. This work is moving forward at the NCI and in larger trials combining PD-1 blocking drugs with agents like Lynparza (olaparib) and Zejula (niraparib). The early data generated by the NCI group are quite exciting. We'll see how this shakes out either with other agents or in larger datasets. Overall, it is very interesting.

I've been working on immunotherapy for prostate cancer since 2000.

We went from irrational optimism about vaccines alone to a bit of depression when some of the large vaccine trials weren't particularly successful, and as they continue to be unsuccessful as monotherapies. Also, Dr. Tomasz Beer, Susan Slovin, and myself all had cautious optimism about CTLA-4, which very nearly achieved its primary endpoint in a randomized Phase 3 registration trial. That has given way to guarded optimism that we'll eventually figure this out.

Finally, I'll add that there are plenty of clinical trial opportunities for prostate cancer patients. But many times, patients jump into the next therapy after one therapy fails, and they do not take some time to carefully consider their clinical trial options. In my experience, prostate cancer patients sometimes seem a bit stunned when they learn that they're progressing. This is totally understandable. But for many patients, a very reasonable option is to think carefully about which trials might be available to them. One information source is www.clinicaltrials.gov, but simply bringing up clinical trials with their treating oncologist is a great first step. Pp[1]



Tomasz Beer, MD
Immunotherapy for Prostate Cancer

Dr. Tomasz Beer, the Deputy Director of the Oregon Health & Science University Knight Cancer Institute, specializes in prostate cancer oncology. Dr. Beer was selected as one of six top scientists to take part in a research dream team that joins together world-class institutions to study treatments for advanced prostate cancer.

Prostatepedia spoke with him recently about immunotherapy for prostate cancer.

How and why did you become a doctor?

Dr. Tomasz Beer: I originally wanted to be an engineer. Then I decided to major in biomedical engineering and was drawn to the biomedical sciences. My parents were both scientists, so I thought by becoming an engineer I was rebelling against them, which is kind of laughable.

In college, I didn't love the engineering classes, but I did like the biological science classes. I began to consider medicine. I went to Johns Hopkins University where about 20% of the undergraduate class was pre-med. And because a lot of my friends were pre-med, it was pretty easy to consider it as a major. I ended up volunteering at Johns Hopkins and at one of the local hospitals in Maryland. I really loved both of those opportunities.

Between my commitment to biological sciences and the joy I got out of being in a healthcare setting, I decided that was what I wanted to do for a living.

In your mind, is there a divide between patient care and research, or do they go hand-in-hand?

Dr. Beer: Most of the research that I do is clinical, which means experimental therapeutics. That is woven deeply into the fabric of my clinical practice. When patients come see us, they have all the ordinary standard-of-care options, and then potentially they have additional treatment options through clinical trials. It's not much of a shift; it's part of the fabric of what we do and it's pretty well integrated.

What is immunotherapy and how is it used in prostate cancer treatment?

Dr. Beer: Our immune systems are capable of controlling, or maybe even eliminating cancer. Immunotherapy provides some sort of treatment or intervention that helps engage the immune system in that task. There are a number of different ways to do that. While we've been working on immunotherapy for several decades, it's still in its infancy. We don't have a full and complete understanding of how the immune system works and how to manipulate it to our advantage.

"While we've been working on immunotherapy for several decades, it's still in its infancy."

We know enough now that cancer treatments that rely on the immune system continue to become a reality for patients and to make a difference. We're in that transition period between preliminary and developing opportunities to deliver reliable treatments.

How does it work? In an antigen-specific approach, we develop a vaccine or some other way to activate the immune system against a particular antigen (a protein made by a cancer cell) that is unique or predominant to the cancer.

Another approach is to activate the immune system more generally, and by doing that, hope that the immune system distinguishes between our own antigens and the cancer's.

These approaches are therapeutic. These are not the sorts of vaccines that we think of in terms of the prevention of infectious diseases, where we vaccinate ourselves when we're healthy to build up immunity before an infection. Right now, immunotherapy means treatment for an established cancer.

So then these vaccines don't prevent cancer: this is a type of treatment.

Dr. Beer: Yes. For example, the vaccine against HPV infections is a conventional antiviral vaccine for a viral infection, and because the virus leads to cervical cancer, it's also a cancer prevention strategy. That is a different way to use the immune system to fight cancer.

Immunotherapy is therapeutic cancer vaccination.

Why are some forms of immunotherapy more effective for different kinds of cancer? What is it about prostate cancer that makes it more susceptible to that kind of approach?

Dr. Beer: First, we don't have a full understanding of these distinctions. Second, just because there are treatments for one disease and not another doesn't necessarily mean that prostate cancer is more susceptible.

Dendreon, the company that developed the vaccine for prostate cancer, focused on prostate cancer and did not have the resources or bandwidth to try the same thing for other cancers extensively. It's sort of an accident of history in the case of Provenge (sipuleucel-T).

That particular vaccine targeted a prostate cancer-specific antigen called PAP, so it wouldn't have worked in its normal form against other cancers. One could take a similar approach with an antigen that was specific to other tumor types, but it just hasn't happened yet.

With immune checkpoint inhibitors —the most contemporary form of therapy—we think that some cancers are more susceptible because they have more abnormal antigens. The cancers with higher mutational burden seem to respond better to these agents and it's probably because they're more different than normal cancers with pure mutations.

"The approaches are varied."

There are also other factors. For instance, melanoma or kidney cancers have traditionally been thought of as more susceptible to immune interventions because there are rare patients whose native immune systems were successful against them. But we don't know if one cancer is more susceptible to immune therapy than another or for what reason. We're still learning about that.

Would looking at genomics tell you who might respond and who won't?

Dr. Beer: Prostate cancers that have microsatellite instability, which is a genomic abnormality that is a consequence of having a DNA repair defect, seem to respond at a higher rate to PD-1 inhibitors.

There are many caveats to that. First of all, that conclusion is based on a very small number of patients. Secondly, there are patients without microsatellite instability who can respond to these agents at a lower rate. We don't fully understand the genomic predictors of response to PD-1 inhibitors. We don't have such tools for Provenge (sipuleucel-T) or other immune therapies, which so far are being deployed without genomic patient selection. We may as we learn more.

Let's talk about the three broad categories of immunotherapy: vaccines, checkpoint inhibitors, and chimeric antigen receptor T-cells (CAR T). How do those work? How do we know when they're working?

Dr. Beer: Unfortunately it was announced a couple of weeks ago that the vaccine Prostvac failed its clinical trial. That was a big disappointment to the field. We haven't seen all the data yet, but we expect to learn more in the coming months.

In general, vaccines attempt to select either a specific antigen, or sometimes a number of antigens, by using dead cancer cells or something like that to essentially induce an immune reaction in the human body. The approaches are varied.

In the case of Provenge (sipuleucel-T), we incubate some immune cells with an antigen from prostate cancer along with an adjuvant outside of the body and then we reinfuse those cells. It's not as simple as just a vaccination in a traditional sense.

How do we know these things work? For now, studies that show a survival advantage are necessary. If we see interventions that delay cancer progression or improve quality of life, that would be good evidence as well. Because these vaccine products haven't shown classic cancer responses so far, we really rely on large long-survival trials.

Checkpoint inhibitors are very different. They are antibodies

to specific molecules on the surface of the immune cells. Essentially, they activate the immune system and unlock tolerance, which is the state where the immune system does not attack prostate cancer because it thinks it's not foreign and not worth attacking. By interrupting those checkpoints, we activate the immune system and give it a second chance at recognizing cancer as something to get rid of.

"Immunotherapy is still new in prostate cancer treatment."

There are many checkpoint inhibitors. The most common are CTLA4 and PD-1, and they're all under study.

Unfortunately, the CLTA4-targeted checkpoint inhibitor Yervoy (ipilimumab) did not succeed in two large Phase III clinical trials for prostate cancer. I was the lead author on one of those and was intimately involved. The next generation of checkpoint inhibitors is moving forward. There is a lot of interest in these agents.

CAR T-cells are really new. A couple of CAR T-cell products were recently FDA approved for hematologic malignancies but not for prostate cancer.

As far as I know, experimental use of CAR T-cells to treat prostate cancer is extremely rare. It will be tried in many cancer types, including prostate.

The idea behind CAR T is that we genetically modify the T-cell receptor. The T-cell receptor defines what the T-cells attack. We create artificial

T-cells designed to tackle the cancer, or an antigen on the cancer, and then we put those artificial T-cells back in the human body. It's a very exciting strategy that has significant promise. A lot more work needs to be done.

Couldn't these agents—Prostvac or Yervoy (ipilimumab) have an impact as part of a combination of agents? Perhaps they just aren't useful when used alone.

Dr. Beer: That is a possibility. One could imagine combinations of multiple checkpoint inhibitors, which is tried in other tumor types. One could imagine combinations of a checkpoint inhibitor with some sort of an antigen-specific vaccine. One could also imagine combinations of those agents with more conventional cancer-killing drugs that, by virtue of killing cancer, may spill antigen and make the immunogenic processes more effective.

Those are questions that are being asked in smaller clinical trials. Bear in mind that the things we've talked about are so crazy new that, while Yervoy (ipilimumab) failed, everything else like PD-1 inhibitors has only been studied in tiny clinical trials so far. Larger trials are just now getting underway. CAR T-cells are very new.

What kind of side effects do patients experience with these immunotherapies? I've heard that they can be onerous.

Dr. Beer: Absolutely. I wouldn't want anybody to think that because it's the immune system, it's safe and easy like a flu shot. The checkpoint inhibitors can, and often do, overshoot a bit: when they activate the immune system, we get autoimmune side effects or immune-related adverse events. These can include inflammation in various places in the body. Inflammation causes diarrhea in the colon, hepatitis-like conditions in the liver, hormonal abnormalities from the pituitary gland, pneumonitis in the lungs, and skin rashes —all related to an overly stimulated immune system. When that happens, we provide immune-suppressive therapies to counteract it.

CAR T-cells are extremely toxic. These are very high-risk therapies. People are routinely expected to end up in the intensive care unit for a number of days with a sepsis-like syndrome: low blood pressure, high heart rate, swelling, etc. These agents are not to be taken lightly.

But we know how to manage these side effects. We don't just say you're going to get really sick, so we'll just cross our fingers. We know how to counteract the immune storms and how to manage them. The vast majority of patients are able to get through the treatment and recover from the side effects. When all is said and done, if they've benefited from the treatment, we're able to manage the toxicities.

Is there anything else you think patients should know about immunotherapy for prostate cancer?

Dr. Beer: Immunotherapy is still new in prostate cancer treatment. Provenge (sipuleucel-T) is available and offers some benefit, but it's not a large and compelling benefit. We're not curing people yet.

Other agents are largely in clinical trials. I don't want to create the impression that these agents are widely available today and making a difference left and right in the lives of patients. But we do see a lot of promise, and we're excited about that.

Do you think Provenge (sipuleucel-T) is not used as much as it should be because there is no real way to tell if it's working?

Dr. Beer: There are several factors that keep Provenge (sipuleucel-T) from wide use. Foremost, it's difficult to tell if an individual patient is benefiting. And when there is a benefit, it's modest in size. When first developed, the only alternative to Provenge (sipuleucel-T) was Taxotere (docetaxel). Now we have six life-extending treatments that compete for patients. The makers of Provenge (sipuleucel-T) would make the case that there's room for everyone and that all these agents should be used sequentially. I don't disagree with that, but in practical reality, a lot of folks end up on one of the competing agents. That has put some pressure on usage.

Finally, Provenge (sipuleucel-T) is fairly complex to deliver. Competing products are a prescription of a pill while Provenge (sipuleucel-T) requires multiple cell collections and reinfusion on a tight schedule. For some people, that's a barrier.

What would you say about using Provenge (sipuleucel-T) earlier on in the disease progression?

Dr. Beer: That's challenging. I would really encourage people to use treatments in ways that are proven to work. It's hard to get behind the use of Provenge (sipuleucel-T) in a setting in which we have no idea what it does. The agent is quite costly and it's not free from side effects. I'd advocate for clinical studies in that setting. I don't advocate the use of agents like these where there is no evidence to support it.

There is a lot of promise in immunotherapy. I just want to balance that promise against the reality for patients who need a treatment today. We're really just getting going with these treatments. I urge a bit of caution about the reality of today, but there's lots of hope for the future. Pp1

Ravi Madan, MD
Combining Immunotherapies

Dr. Ravi Madan, the clinical director of the National Cancer Institute's Genitourinary Malignancies Branch, focuses on immune-stimulating therapies. In particular, he's interested in how we can combine these approaches with other therapies to improve patients' lives.

Prostatepedia spoke with him about which immunotherapy combinations he feels are the most promising.

Why did you become a doctor?

Dr. Ravi Madan: I was always interested in science in school. Medical oncology seemed like an opportunity to practically apply science in a meaningful way on a daily basis and actually impact people's lives. That was really my driving force.

What is it about immunotherapy that interests you?

Dr. Madan: For years, we attempted to target cancer, which is a diverse and heterogenous biological entity, with therapies that were very limited or very focused. With immunotherapy, though, we finally have a treatment that is dynamic and can evolve within the patient. This gives the immune system a chance to activate itself and personalize the immunologic attack against that person's specific cancer cells, creating a form of personalized therapy for that patient's cancer. We've never really had this opportunity before, and we are only scraping the surface of what immunotherapy can do for people with cancer.

What kinds of immunotherapy are available now and what is still emerging?

Dr. Madan: There is an FDA-approved therapeutic cancer vaccine called Provenge (sipuleucel-T) that is available in the United States, Europe, and some other parts of the world.

Provenge (sipuleucel-T) is a therapeutic cancer vaccine derived from a patient's own immune cells. These immune cells are removed from a patient and then exposed to a target protein. Those immune cells are then reinfused back into the patient after that immune-activation phase. The goal is that those activated immune cells will seek out and destroy prostate cancer cells; this has been shown to increase survival in men with advanced prostate cancer, or what we call metastatic, castration-resistant prostate cancer.

Another strategy that is more common throughout the broader medical oncology field is something called immune checkpoint inhibitors. These are approved for and have demonstrated efficacy in many cancers. They help limit regulatory mechanisms that have the potential to turn off immune cells. Sometimes the cancer cells themselves are the ones turning off the immune cells that are trying to recognize and kill them.

On their own, unfortunately these agents have not proven efficacious in prostate cancer. However, several combinations, including some combinations with vaccines, have demonstrated some preliminary evidence of a greater impact than when we just use immune checkpoint inhibitors alone. Several of these combination studies will be very interesting to watch in the near future.

Which combinations do you think appear most promising?

Dr. Madan: There are multiple strategies of interest, but one strategy combines a vaccine with immune checkpoint inhibitors. Our group at the National Cancer Institute, as well as one at the University of Wisconsin, has demonstrated some preliminary evidence that this combination may have an impact. There is also ongoing research looking at combining Xtandi (enzalutamide) with an immune checkpoint inhibitor. In preliminary

data, that combination seems to have an impact in a subset of patients.

Why aren't you looking at Zytiga (abiraterone)? Is there something specific about Xtandi (enzalutamide) that makes it a better combination partner?

Dr. Madan: I'm not aware of any specific studies looking at a combination of Zytiga (abiraterone) and a checkpoint inhibitor, though I wouldn't be surprised if there are some going on. There is some clinical data that suggests that after treatment with Xtandi (enzalutamide), immune cells may have a higher expression of PD-1, which may create a stronger rationale for the Xtandi (enzalutamide) combination.

In addition to the vaccine combinations, there is a strong rationale to combine immunotherapies with other antiandrogen therapies, including standard androgen deprivation therapy as well as forms of radiation, including definitive radiation.

There are also multiple trials combining immunotherapy with chemotherapy.

Do you have any thoughts for prostate cancer patients considering joining an immunotherapy clinical trial?

Dr. Madan: Patients considering clinical trials should understand the rationale behind the clinical trial and make sure it coincides with the personal treatment strategy they developed in conjunction with their physician. If there's an overlap between those two things, then patients are very comfortable throughout the clinical trial process.

It's also important for patients to understand that some trials may have a placebo. If that's the case, patients should feel comfortable with the implications of getting a placebo

and should certainly discuss it with their doctor.

Now, many immunotherapy trials, including many we've done here at the NCI, often involve a standard therapy in combination with immunotherapy. In those trials, there is no placebo, so it's also important for patients to realize that the opposite can be true: not every trial has a placebo.

Patients coming on a study should understand the potential side effects so that they can be vigilant and communicate anything that comes up to the study team. In this way, patients can ensure their own safety.

Most of the patients on these immunotherapy clinical trials have had multiple other treatments. Doesn't that impact any kind of immune response they might have?

Dr. Madan: It can. That's something we're looking at.

That actually gets to the last point I want to emphasize. I think that oftentimes patients feel that clinical trials are what you do when nothing's left and there are no more standard options.

But clinical trials are available for all stages of disease. Here at the NCI, we have studies for newly diagnosed prostate cancer patients to those with biochemical recurrence to those with early metastatic disease. All of these patients have other standard therapies available to them. Sometimes the trials combine immunotherapy with standard options in ways that allow patients the chance to do something before standard therapy, to potentially get an additional treatment in the short term while still knowing that they can use standard care down the line.

Clinical trials aren't just for people who have exhausted all their options. At every point in your disease process ask your doctor, "Are there trials that I should be considering in addition to these standard options?"

Do most patients find out about clinical trials through their doctors?

Dr. Madan: Yes and no. It's always good for patients to ask their doctors about trials. But honestly, there are so many trials available that is it hard for their doctor to know every trial appropriate for their particular situation.

I've often referred patients to www.clinicaltrials.cancer.gov, because you can get a lot of information about ongoing clinical trials in your region.

Are you saying that patients should find out about potential trials and then ask their doctors about them, rather than waiting for their doctors to bring them up?

Dr. Madan: Absolutely. I think it's reasonable to ask your physician, "I understand this is my standard option, but are there any clinical trials that I should also consider at this time?" The perfect time is when a patient is starting a new therapy or the therapy they're on is no longer as effective. That's the time to ask this. If you're on a therapy that's working, you should always really consider staying on that therapy for as long as it works.

Even as early as those in the active surveillance bucket?

Dr. Madan: Yes. As I said, there are prostate cancer trials at every stage of the disease, from active surveillance all the way through metastatic disease.

Is anybody looking at immunotherapy in men on active surveillance?

Dr. Madan: There is an ongoing study conducted in multiple academic centers around the country looking at a therapeutic cancer vaccine Prostvac in patients on active surveillance.

Prostvac, not Provenge (sipuleucel-T)?

Dr. Madan: Correct. This is with the experimental therapeutic Prostvac, not the standard agent, Provenge (sipuleucel-T).

Is there anything else prostate cancer patients should know about immunotherapy?

Dr. Madan: Patients should really be optimistic. There is a lot of innovative research underway in prostate cancer immunotherapy. Hopefully this research will lay the foundation for the future and immunotherapy will one day play a very important role in prostate cancer treatment.

But that goal cannot be achieved without patients taking part in clinical trials. I can't tell you how wonderful it is to work with patients on our studies here at the NCI. These are truly remarkable people who often tell me, "If this trial helps me, that's great, but I'm really taking part in this study so that you can learn to help others tomorrow." I never cease to be amazed by these patients. They are sincerely selfless individuals hoping for the best for themselves, but also giving of themselves to future patients. It is an honor to get to know them and work with them. Pp

Douglas McNeel, MD, PhD
Prostate Cancer Vaccines

Dr. Douglas McNeel is a Professor in the Department of Medicine at the University of Wisconsin-Madison and Director of Solid Tumor Immunology Research within the UW Carbone Cancer Center. Dr. McNeel focuses on prostate immunology and the development of antitumor vaccines as a form of prostate cancer treatment.

Prostatepedia spoke with him recently about immunotherapy for prostate cancer.

> *"For a therapy to work for cancer it would have to be adaptive."*

Why did you become a doctor?

Dr. Doug McNeel: My father was a biologist and my mother was a medical technologist. I grew up thinking that I would probably do something in a science-related field. In college, I studied both music and chemistry and fell in love with both.

One summer I did research in a chemical research laboratory and really liked it. The following summer I had an internship at Washington University doing medically oriented research and just absolutely fell in love with it. I knew that was what I wanted to do. I decided at that point that I wanted to become a physician-scientist.

What is it about studying immunotherapy that brings you back to the table? What is it that you find so fascinating about it?

Dr. McNeel: I ended up studying immunotherapy by accident, frankly. I was working on a PhD in a cancer-related area. I was on an oncology rotation during medical school. The whole field of cancer just felt more at home to me. There were a lot of unanswered questions. A lot of medicine involves: when a patient has *this*, you do *that*. But there are still a lot of still unanswered questions in oncology. I thought that was more of a fit for me.

During that training, I did a rotation at the Fred Hutchinson Cancer Research Center in Seattle, Washington. I ended up doing my internship, residency, and fellowship training there. At that center, there is a very strong emphasis on immunology with bone marrow transplantation. That is where I became interested in immunology.

I then realized that cancer is a changing event, like infections: infections and cancers adapt to whatever you throw at them.

Most of our other treatments, like chemotherapy or radiation therapy, are static. They don't change. It just made sense to me that for a therapy to work for cancer it would have to be adaptive. There has to be an immune approach to it.

Can you give us an overview of vaccines for prostate cancer: which are available now and which are still in development?

Dr. McNeel: If a person has prostate cancer, he usually has surgery or radiation therapy to remove the cancer. These initial therapies cure a majority of patients, but about a third of the time, the disease comes back or resurfaces. We can usually detect the recurrence at a very early stage with a PSA blood test.

Our original thought was that the point of recurrence is the time to intervene, to create a tissue-rejection response.

You can't really do without a normal kidney. The same is true of the liver. But you can do fine without a prostate. So if we can create a rejection-response to remove any prostate tissue, whether it's cancer or not, that would be okay.

That was our original thought. The idea with vaccines is to teach the host to generate an immune response that will recognize and destroy cancer cells.

But this is a challenge to treat existing tumors with vaccines. With infectious disease vaccines—what we normally think of when we talk about vaccines—we get an immune response that then protects you later on. We call them prophylactic vaccines. But we don't treat active infections with vaccines. We treat them with therapies that target the bug directly or infuse in an immune system like an adoptive therapy approach.

With cancer, we see the same kinds of hurdles. What we know from animal models is that there are a number of cancer vaccines that can protect animals from cancer, but to get the best response against existing cancers, you have to start when tumors are small and barely detectable. That has been a challenge in pushing those vaccines into human trials.

We're also learning that when you generate an immune response by means of a vaccination, the cancer can put up a big barrier very quickly to fight against it. Our thought process on vaccines is currently in the midst of changing given that kind of information.

A number of cancer vaccines have been studied over the years. Most of the effort has not produced anything, because we have been looking at vaccines alone, usually in patients with more advanced cancers.

There has been one exception. Provenge (sipuleucel-T), which is a vaccine targeting a protein called prostatic acid phosphatase, was approved in 2010. In this approach, patients have blood removed and their antigen presenting cells are spun out. Then the target of the vaccine, this prostatic acid phosphatase protein fused to an immune-modulating drug, is put together in the lab in the culture dish. The education of the immune system takes place in the lab, if you will. Those cells are then shipped back and infused back into the patient two or three days later. That process is cumbersome, but the approach was shown to be effective.

"Our thought process on vaccines is currently in the midst of changing."

One large trial led to its FDA-approval. But there were other supportive Phase III trials showing that people who got the vaccine versus those who got a placebo vaccine did better and lived longer. It was a challenge rolling out Provenge (sipuleucel-T) because we don't see PSA declines with it. We also don't see changes in the tumors on scans, but we know that men with advanced prostate cancer, in general, live longer if they get that treatment.

Prostvac is an approach that has been in Phase III trials up until recently. Unfortunately, the Phase III trial was deemed to not have met its primary endpoint in September 2017. It did not show that people lived longer. It's unclear if Prostvac will be developed or not.

Prostvac is a viral vaccine. There is one virus that encodes PSA and then a separate virus. People are immunized with one virus coding the PSA and then boosted with the separate virus. The idea is to use viral vaccines to focus the immune response on the target protein PSA.

What about DNA vaccines? How do they work?

Dr. McNeel: DNA is very much like a virus in that you can use DNA encoding a target and administer it directly into the skin or muscle of a person or an animal. It will be taken up by antigen-presenting cells. The gene encoded will be presented to the immune system and you can generate an immune response to that target. This is very much like a viral vaccine. It's taken up by the same kinds of cells and presented in the same way. You get more of a cellular immune response, as opposed to protein vaccines that we usually use for viral and bacterial vaccines: they generate more of an antibody response.

We believe DNA vaccines generate the "right kind" of immune response for attacking cancer cells. However, they're generally weaker than some other kinds of vaccines. They don't generate as potent an immune response as some of the viral vaccines. However, they have fewer safety concerns—they're not infectious agents. And they are more specific: A viral vaccine might encode several hundred irrelevant viral proteins including the one target you're interested in, but a DNA vaccine only encodes the agent you're trying to target. Thus, they're a bit more specific.

At this point, it's unclear whether one type of vaccine is better than another because the reality is that apart from Provenge (sipuleucel-T), we don't have any other examples of vaccines that have been FDA approved.

However, we believe that vaccines will best be used in combination with other things. It may be that

the cheapest and easiest vaccines may be the preferred vaccines. If vaccines are going to be used in combination with other agents, you can't spend hundreds of thousands of dollars on one therapy and then hundreds of thousands of dollars on another. That's an advantage that we think DNA vaccines may have because they're simpler and easier to manufacture.

Which combinations do you think look the most promising? And just because Prostvac alone didn't help people live longer, couldn't it be useful when combined with something else?

Dr. McNeel: Absolutely. I think there is evidence that it will probably be useful in combination.

Which combinations do you think look the most promising?

Dr. McNeel: Our group has been studying combinations of vaccines in the laboratory. We know that combining several with DNA vaccines works. They can provide an antitumor response. If you implant a tumor in an animal and then immunize the tumors, the tumors don't go away but they do grow more slowly.

We've begun asking what is going on in the tumor that provides this resistance. We found that the major pathway is that tumors upregulate (or increase) a molecule called PD-L1. If it's a very potent immune response that's being stimulated, the T-cells that are elicited express high levels of PD-1.

We've found that you can block that when you immunize using an antibody like Opdivo (nivolumab) or Keytruda (pembrolizumab). At least in mice, if you combine a DNA vaccine with mouse versions of antibodies that block the same molecule blocked by Opdivo (nivolumab) or Keytruda (pembrolizumab) than you get a better antitumor response and eradication of the tumor in some cases.

We've started trials looking at that combination. We've reported results in early abstracts at several scientific meetings. We found that the same thing happens in people. If you give a vaccine and then follow it with anti-PD-1 therapy, you don't see much of an effect. But if you combine them, give the vaccine and anti-PD-1 therapy at the same time so that you block the PD-1 that is upregulated with vaccination, PSAs decline. We've seen decreases in tumors on CT scans. That PSA decline is something we rarely see with vaccines alone. We haven't seen very many with PD-1 blockade alone either. We think that combination really makes a lot of sense.

> *"It's unclear whether one type of vaccine is better than another."*

What are the side effects of these treatments like? When you combine these agents are the side effects amplified?

Dr. McNeel: With most types of vaccines, we see very little in the way of side effects. For 48 hours, patients will have some flu-like symptoms. They might have mild fevers, some joint aches. There may be redness and swelling at the site of immunization. That's really about it.

The side effects of combinations really depend on whatever the other agent contributes. Our study looks at DNA vaccine with Keytruda (pembrolizumab). To date, we have not seen toxicity that wasn't a known side effect for Keytruda (pembrolizumab) alone.

In general, side effects from these therapies are much better than, say, chemotherapy. We want to move these therapies earlier and earlier in the course of disease to potentially avoid the need for hormonal therapies.

Do you have any thoughts for men interested in joining an immunotherapy clinical trial?

Dr. McNeel: I think patients should join a trial if they're interested.

For men with very early recurrent prostate cancer, there have been several clinical trials for patients with early-stage prostate cancer that have seen very similar effects. There were vaccine trials at Memorial-Sloan Kettering Cancer Center over a decade ago in men with just a rising PSA. They found that a number of people had a slowing of the rate of rise of their PSA. Several subsequent trials have found similar findings.

If a patient can find a clinical trial looking at vaccines in an earlier stage of disease, it's worth taking a look at. But the standard is to not do anything except consider hormonal therapy or wait until the disease has metastasized. But I think it's an opportunity to do something proactive. It's unlikely to have adverse effects. And the reason for participating is not only to help advance the field, but also with hope that individual patients will benefit by getting access to exciting approaches that are early in development.

But while we think that these vaccines might work by themselves in people at a minimal stage of disease, the

effect will be greater in combination. That's what we're finding in men with later-stage disease. If a patient can find a trial using some of these vaccines in combination with other immune-modulating drugs, it might make sense to consider it.

What is the process of getting a vaccine like Provenge (sipuleucel-T) like?

Dr. McNeel: This treatment is prescribed by a physician. If prescribed, you would go to either a hospital or a Red Cross and be hooked up to a machine called a leukapheresis machine that they often use for collecting blood products. You get hooked up to that machine. It takes about two hours of blood going out of one vein, spinning through the machine to collect the cells that they want. The rest of the blood is infused back in the other arm through another IV. That product is then shipped across the country. They do their manufacturing and then they ship it back. You come back three days later to have those cells infused back into your body.

Is that process painful?

Dr. McNeel: No. It's not painful at all. They just sit and an IV pole hangs. It takes about an hour to infuse in. Sometimes people get infusion-related reactions. They might get chills and fever. It's not so common.

What about some of the other vaccines in clinical trial right now?

Dr. McNeel: They're all different. Prostvac is just a vaccine drawn up in a syringe in the pharmacy that is injected under the skin, like how you get a flu shot. DNA and peptide vaccines are given the same way: an injection under the skin or into the muscle.

Painful at all?

Dr. McNeel: No. They might sting a little bit.

One company is looking at a DNA vaccine in which the injection goes into the muscle and they then apply an electric current to it called electroporation.

Why do they do that?

Dr. McNeel: They've demonstrated that they get better penetration of the DNA vaccine into the muscle cells. They see a stronger immune response if they do it that way. I've heard some patients say that it can be painful. But I think that's the worst of it. In general, there aren't many problems with the actual injections.

Do you have any thoughts for community urologists and medical oncologists who may be reading this?

Dr.McNeel: Provenge (sipuleucel-T) is still out there. It's an approved therapy and certainly something for patients to talk to their doctors about. Again, this is a treatment approved for patients with more advanced prostate cancer.

Nothing is really approved for patients with earlier stage prostate cancer, but there are a lot of clinical trials going on around the country that patients can look into.

Do you think Provenge (sipuleucel-T) is still underutilized?

Dr. McNeel: It's probably underutilized. There was a lot of excitement and enthusiasm that if Prostvac met its endpoint in Phase III trials it might supplant Provenge (sipuleucel-T). But that is not the case. There may be a resurgence of Provenge (sipuleucel-T) as a result. We'll see.

This is an exciting time for patients. We're seeing effects happening. We're seeing real effects from immune-based therapies for a number of diseases.

There has been a lot of enthusiasm for these checkpoint inhibitors like Opdivo (nivolumab), Keytruda (pembrolizumab), and Yervoy (ipilimumab). When they work, they work really well. But to date, they haven't worked very well for prostate cancer. An occasional patient will respond, but it's pretty rare. Even for diseases where they do work, really only about 20% of patients respond to them.

What we're finding is the reason these checkpoint inhibitors work is that they need to have the immune cells present to recognize the tumor. For some diseases, like prostate cancer, you just don't have a lot of these immune cells in the tumor ready for the checkpoint inhibitors to work on. There are lots of thoughts on how do we get these immune cells into the tumor: maybe we use hormonal therapy, chemotherapy, or radiation therapy. Vaccines are a simple way to do it. That's why we think these vaccines work in combination with checkpoint inhibitors. Vaccines can generate these T-cells and then make these checkpoint inhibitors work. That's why we're really hopeful about the combination approach.

It's an exciting area for patients to participate in clinical trials. Pp1

Saul Priceman, PhD
Engineered T-Cell Immunotherapy

Dr. Saul Priceman is an assistant research professor in the T-Cell Immunotherapy Program at City of Hope in Duarte, California. His expertise is in T-cell biology and cancer immunotherapy. He's currently developing chimeric antigen receptor (CAR)-based T-cell immunotherapy primarily for breast, prostate, and pancreatic cancers.

Prostatepedia spoke to him about CAR T-cell therapy for prostate cancer.

How did you come to be doing immunotherapy research?

Dr. Saul Priceman: After college, I started to work at a biotech company called Amgen. I worked on a cancer drug for three years and then realized I needed to get a PhD so I could make the most impact in my field. I got my PhD in molecular and medical pharmacology from the University of California, Los Angeles (UCLA). Pharmacology is the study of drugs and how they interact with the body, but mostly as it relates to disease and to therapy.

At UCLA, I got interested in studying the immune system in cancer patients. I wanted to really understand what is going on with the immune system as cancers progress. As you probably can appreciate, a couple weeks after getting a virus or bacterial infection, it's your immune system that eradicates it from your body. If it doesn't, your body would likely go haywire and require immediate intervention. Your immune system is also critical for vaccines to work and is why you have lifelong protection following vaccination.

> *"A paradigm-shifting idea has emerged."*

I also got obsessed with autoimmune diseases. Your body knows what is self and what is not self. When you have autoimmunity, your immune system attacks your body. That was interesting to me. And actually a lot of what we learn in the context of cancer with respect to your immune system, we learned from studies of infectious disease and autoimmunity.

The final piece was that over the last few decades a paradigm-shifting idea has emerged: from before you're even born until the day you die, you probably get hundreds of cancers. It's just that your immune system blocks that cancer from growing so that you don't ever become symptomatic. The cancer you deal with is the one cancer that gets around your immune system and grows. That idea was intriguing to me.

Your immune system plays an essential role in your body's ability to fight everything. It's the reason why we can live 100 years without succumbing to a plethora of different things that can attack your body, including cancer.

Would you call cancer in general a failing of the immune system?

Dr. Priceman: Not really. Cancer is really many different things that occur in sequence, or simultaneously, that are likely the root cause. I wouldn't claim that cancer is one thing. But I certainly think cancer is an immune disorder. In a lot of cancers, including prostate cancer, viruses can play an important role in the initiation of that cancer. Cervical cancer, for example, is nearly 100% virus-mediated. So whether your cancer is virus-mediated or not, the immune system plays an essential role in the initiation and progression of that cancer.

I was interested in that idea, but it seemed as if almost nobody else was really interested in this when I got to UCLA.

I went to a virus gene therapy lab and asked the principal investigator of that lab if I could study the immune system and cancer. She said, "I don't know anything about that, Saul, but I'll support whatever you do." For the next four and a half years, I did just that. Together, we made an impact.

I then went to City of Hope National Medical Center, which was pioneering tumor immunology and immunotherapies. I ended up studying how the immune system affected autoimmune disease, obesity, insulin resistance, and cancer in my postdoctoral work. I did well in that area.

And then I realized T-cells are "it." If you are going to fight an infection properly, or fight cancer properly, you have to engage the T-cells. T-cells are a specific type of immune cell, that are often called the soldiers of our immune system—the fighters that rid us of infections or cancer. I moved into another group at City of Hope to develop chimeric antigen receptor (CAR) T-cell therapy for cancer. The T-cell receptor is a protein on the T-cell that engages another immune cell, a virally-infected cell, or a cancer cell to ask: "Who are you? What are you doing here?" If that other cell is not doing the right thing, the T-cell kills it. That process is messed up in cancer. That group was engineering those T-cells to recognize cancer cells as a threat. I got very interested, and that is what I do now. I develop, with a large group of researchers, CAR T-cell therapy for multiple cancers, including prostate.

Where are we in the development of CAR T-cell therapy for prostate cancer?

Dr. Priceman: CAR T-cells are FDA approved for two diseases, which just happened in the latter part of this year. We have CD19-directed CAR T-cells for a B-cell malignancy, whether that is lymphoma or leukemia. These reengineered T-cells go after cells that express the protein CD19, which is expressed on the vast majority of B-cell leukemias or lymphomas. This therapy is now putting patients that are refractory to multiple lines of other therapies in complete remissions, an almost unheard of feat, and changing the landscape of treatment options for these patients.

At City of Hope, we also have clinical experience treating gliomas or glioblastomas that are aggressive brain cancers with similar CAR T-cells. We locally deliver CAR T-cells to the brain for those patients. We're first in the world injecting CAR T-cells intraventricularly, which is a specific route of delivery that will bathe the central nervous system with those CAR T-cells, so we can attack multifocal brain disease instead of just one site—but still regionally localized in the brain.

Four years ago, with Prostate Cancer Foundation funding, we started to ask, "Couldn't we get these same responses in prostate cancer?" They gave us a million dollars and two years to make that a reality.

We actually just published a paper in *OncoImmunology* this month on the development of a prostate cancer-specific CAR T-cell. We are going through the regulatory process now and will hopefully start our clinical trial by mid 2018.

How exactly does the approach differ in prostate cancer?

Dr. Priceman: The target protein is very different. It's overexpressed in prostate cancer in the majority of patients. One of the benefits of targeting our CAR T-cells to this protein is that it is also expressed in pancreatic, bladder, and other solid cancers. We're trying it first in prostate cancer, but we also think that we can make an impact in these other diseases eventually. The target is called prostate stem cell antigen, but that is a little misleading because it is expressed in some nonprostate cancers.

Is CAR T-cell therapy for prostate cancer used in conjunction with other therapies or alone?

Dr. Priceman: The biggest challenge for prostate cancer—and this applies to other cancers like pancreatic–is that they're immunologically "cold." This means that if you slice the prostate tumor in half and look at the different cells in the tumor, you'll find very few T-cells. There is almost no immune response happening in these tumors. Some people argue that this is because prostate cancer is lowly mutagenic, which means that there is a low mutational burden in that tumor and that is possibly why there's no immune response going on. The immune system doesn't see anything incorrect in prostate cancer so it doesn't fight. That's one argument.

The other argument is that there is a massive ongoing immune suppression in prostate cancer. The idea is that even if there is an attempted immune response the suppressive activities happening in the tumor shut it down at every angle.

Either way, prostate cancer is immune-cold. Even if we make the best CAR T-cell in the world—and I do think CAR T-cell therapy will have a impact in this disease—the challenge will be that a lot of those T-cells may not get into the prostate tumor to have an effect.

We will then combine CAR T-cells with other therapies. The go-to

combination will be checkpoint inhibitors. If there is an immuno-suppressive pathway, we'll want to put the brake on that to allow CAR T-cells to get to and attack the tumor.

My group and I have ideas for developing other rational combinatorial therapies to improve CAR T-cell efficacy in prostate cancer, which we will clinically evaluate in the next few years.

What about combining with hormonal therapy?

Dr. Priceman: Yes, that's a great idea and we're doing that, too. In addition to checkpoints, hormone ablation therapy can increase the immune infiltrate in cancers, so we think combining that with CAR T-cells will improve the CAR T-cell infiltrate and efficacy.

Radiation therapy, which is common practice for prostate cancer, can also impact the immune microenvironment in tumors in a beneficial way. We are also doing preclinical studies on using radiation therapy to improve CAR T-cell efficacy..

What are CAR T-cell therapy side effects like?

Dr. Priceman: They can be severe in some situations. We're grappling with how to engage the immune system without having a rampant toxic effect on the patient. We're doing that in many ways. I can't go into detail on all of them, but we are very cognizant that CAR T-cell therapies can have side effects that we want to reduce without jeopardizing the therapeutic benefits.

We don't know what those side effects will be in our prostate CAR T-cells, but they're largely clinically managed in other cancers. They're not manageable in a small percentage of people, but in the vast majority,

they *are* clinically manageable. Oftentimes these side effects don't interfere with the beneficial, therapeutic effects of the CAR T-cell, but we'll just have to meet that challenge in the clinic. That's the point of this Phase I clinical trial.

Would there be a synergistic effect to these side effects when you combine immunotherapies?

Dr. Priceman: Not necessarily. They shouldn't be synergistic. But regardless, there are different ways to manage that: we can lower the doses of checkpoint inhibitors. (We're not trying to use the checkpoint inhibitors alone, so we don't necessarily have to use the doses used as monotherapies.) Another option is to use checkpoint inhibitors locally. We're looking at all of this preclinically.

"Exercise will most likely become a required part of patient care."

Do you think we're a few years away from CAR T-cell therapy being available to prostate cancer patients?

Dr. Priceman: Yes. It's right around the corner. We hope we make an impact and can make this type of treatment available to all prostate cancer patients one day.

Do you have any advice for those considering joining a CAR T-cell clinical trial?

Dr. Priceman: Do it. If anything is groundbreaking and revolutionizing therapy for late-stage, advanced, refractory prostate cancer, it will be immune-based therapies. Checkpoint inhibitors alone have not worked in prostate cancer, for the most part, although in certain patients and in certain combinations, they are working. But we think CAR T-cells plus a checkpoint inhibitor *will* work. I really do think CAR T-cells will change the landscape of available therapy.

Is the delivery process as difficult as the Provenge (sipuleucel-T) process?

Dr. Priceman: No, Provenge (sipuleucel-T) is likely more difficult to produce. In fact, the CAR T-cell world has a great success rate in manufacturing cells, especially for solid tumors. CAR T-cell manufacturing is easier in terms of where we get the T-cells, how we engineer them with the CAR, how we expand them, bank them back, and complete the quality control and release criteria. I think in most cases it's simpler than a vaccine-type approach, which is what Provenge (sipuleucel-T) is.

Is there anything else patients should know about CAR T-cell therapy for prostate cancer?

Dr. Priceman: The more patients we treat with immunotherapy, the more we understand why it's working and why it's not working. We can then go back to the lab to improve the therapy. It doesn't happen overnight, but that's the bench-to-bedside cycle.

I really do think that in the future immunotherapy will absolutely change the ballgame for prostate cancer patients. We're almost there. The responses that we're getting in leukemia and lymphoma are so staggering and exciting. And these are heavily pretreated, heavily refractory patients. I think it's only a matter of time before those kinds of responses are attainable in prostate cancer. Pp

Susan Slovin, MD
CAR T-Cell Therapy Clinical Trials

Dr. Susan Slovin is a medical oncologist specializing in prostate cancer immunology at Memorial Sloan Kettering Cancer Center in New York City.

Prostatepedia spoke with her recently about immunotherapy for prostate cancer.

Why did you become a doctor?

Dr. Susan Slovin: I wrote my first research paper for the journal Mycologia as an undergraduate at Barnard College. It entailed the rediscovery of a fungus that was isolated from the Cresskill River in New Jersey and had not been seen in over one hundred years. It implied that there was early pollution within the river and lead to an intense study of the level of pollution of the New Jersey rivers and water supply. I recognized that I was good at research and elected to pursue a research career first. However, I realized after obtaining my PhD, that I needed a medical degree to facilitate my work, which was highly translational.

For that, it became necessary for me to have better insight into diseases, and hence, my desire to get a medical degree so that I would be able to extrapolate work that I was doing in the laboratory into the clinical arena. I went to medical school late after having had a successful research career that included a laboratory at Thomas Jefferson University funded by two R01 NCI grants with several postdoctoral fellows under my aegis. I started medical school at 33, finished at 37, completed an internal medicine residency at 40, and a hematology/medical oncology fellowship at 43. The rest of the math no one has to do, but the reality is that I've been fortunate to have excellent preparation in my academic life for what I like to do right now, which is translational medicine.

Going to medical school late was tantamount to being a late bloomer; sometimes it takes years to realize that you are doing what you were destined to do.

Do you think that background gave you a different perspective?

Dr. Slovin: I most certainly had a different kind of perspective. I'm used to the blue book exam, and in the blue book exam you write things, you think about things, and you have a different mental mindset than my colleagues who were doing multiple-choice tests. Your brain is wired differently as a PhD.

What is CAR T-cell therapy in the context of the clinical trial you've been running?

Dr. Slovin: My career goes back probably 40 years when immunotherapy meant that you tried to devise a variety of different platforms to influence the human immune response so that it recognizes and fights cancer. We didn't have the same level of sophistication in understanding the inner mechanisms of the immune system we do now, and frankly, in the 1970s, we were just identifying that there were two cells that governed the immune system, B- and T-cells. The world, unfortunately, has become checkpoint-centric much to my dismay. I believe that people think that checkpoint inhibitors are synonymous with immunotherapy. There are other immune treatments that continue to be investigated, but may not be easily exportable into clinical practice due to their uniqueness and complexity in development. This is, in fact, the case with CAR T-cell therapy. CAR T-cells (chimeric antigen receptor T-cells) are another platform whereby we engineer a patient's immune T-lymphocytes (a white blood cell that is known to fight the cancer cell) to treat their cancer. We've been focusing on patients with metastatic prostate cancer to the lymph nodes and/or

bone tissue who have failed other therapies but have not had chemotherapy before. They essentially have had multiple hormonal therapies.

We are using the body's immune system in a different way than checkpoint inhibitors.

The body has two cell types: first, we have B-cells, which produce antibodies. Antibodies are proteins in the blood that fight infection or recognize molecules that don't belong there. And second, there are T-cells, which are white cells involved in immune surveillance and tumor cell killing. In other words, they scavenge the body looking for molecules that don't belong. Molecules that don't belong include foreign cells, bacteria, and viruses. And, remember that cells also go to the bathroom and they leave behind waste products that may be foreign to the immune surveillance cells. These cell products, along with cells that die as a result of radiation or chemotherapy, provide novel antigens or molecules that may never have been seen before by the immune system and may invoke the immune system to respond and protect the body.

The immune system does not react against things that don't pose threats to it. But the use of CAR cells takes advantage of the fact that T-cells are the largest cell population in the body and that they are the ones involved in effecting an anti-cancer response.

T-cells are part of the CAR therapy approach called *adoptive cell transfer*. It's a little different from what's been done with Provenge (sipuleucel-T), which is, ironically, the first autologous (self-derived) immune cell product used for the treatment of a solid tumor for prostate cancer. What's ironic about that is that here we are in the world of prostate cancer for which we have an approved immune-based therapy but which appears to be minimally responsive to the more widely and successfully used checkpoint inhibitors.

Unlike Provenge (sipuleucel-T), which stimulates the patient's dendritic (antigen-presenting) cells, adoptive cell transfer uses only a particular population of the patient's immune cells to treat their cancer, mainly their T-cells.

"We are using the body's immune system in a different way."

CARs are approved in two indications: acute lymphocytic leukemia and lymphoma, but as yet have not been demonstrated to have antitumor efficacy in solid tumors. They are formed by engineering T-cell receptors, which graft a molecule with particular specificity onto an immune effector cell (T-cell). Typically, these receptors are used to graft the specificity of a monoclonal antibody onto a T-cell (for example prostate-specific membrane antigen [PSMA]) with transfer of their coding sequence facilitated by retroviral vectors. The receptors are called chimeric because they are composed of parts from different sources. The upshot is to be able to develop an "armored CAR," that allows the T-cell to seek out cells that express that same molecule and therefore will ultimately engage the cancer cell that expresses the molecule and kills it via a variety of mechanisms. These include the recruitment of other cell populations and soluble serum factors such as cytokines. In toto, these cell populations also signal to one another to seek and destroy what may be considered foreign to the body. While there are limitations to the technology, we take the T-cell and change or engineer its receptor to express other molecules that recognize a wide range of proteins on the cancer cell. As such, when the T-cell receptor notices that protein, it will immediately follow the cancer cell and bring with it the remaining part of the T-cell to try to affect the cancer.

You can put anything on the surface of that T-cell, any particular kind of molecule, and use it to identify the cancer cells that harbor that molecule.

In prostate cancer, we have PSMA, a molecule that is overexpressed on the surface of prostate cancer cells as they become more resistant to therapy. Our group has used PSMA as a focal point for CAR therapy. We've been learning a lot about how to use these cells. It's a very costly enterprise, and it has not proven perfect yet in the world of prostate cancer. We were able to complete a 12-patient trial looking at CAR T-cells' ability to track to cancer cells with PSMA on their surface. We know that these CAR cells can migrate to the cancer cells and persist at the site of disease, but they can be unstable and not proliferate sufficiently to continue to interact with the cancer.

Most of what we've done in this field can be credited to the preclinical and clinical work of Drs. Michel Sadelain and Isabelle Riviere.

Sadelain is the head of the genetic and cell engineering facility here at Memorial Sloan Kettering. A lot of his preclinical studies in mice showed that you could engineer T-cells and direct them to human prostate cancers that had been placed inside of the mice. Not only do the mice live

longer, but also these cells migrated to the tumor, persisted, and cured many of these animals. Hence the translation into what we're doing now.

This technology is probably the best example of translational research that was done at the preclinical level and is now in men.

We know that giving these cells is safe. With all CAR technologies, whether in solid tumors or blood-based cancers, a major issue is cytokine release syndrome (CRS). This syndrome means that there are inflammatory proteins that show that the cells are activated. It does not necessarily mean that you're causing an antitumor response—it just means that the immune system is activated. We've been fortunate that this has been self-limited and does not last more than 24-48 hours. A patient starts to get chills or a fever. We treat people with antibiotics and fluids, but for the most part, this goes away on its own.

CRS is different in hematologic malignancies. People are in the intensive care unit. We have to recognize this syndrome early on when patients may have minimal symptoms because if not noted sooner, low blood pressure, shock, and death could occur in these patients. Fortunately, this technology in prostate cancer has fast become an outpatient treatment, whereas sometimes hematologic patients require longer in-hospital care.

There is a lot of promise in CAR T-cells. Our last few patients, and particularly the last patient, had indications that the cells could migrate to a large lymph node in his chest. The lymph node has been relatively stable. His PSA has been slowly rising, but what we have found with immunotherapy is that in spite of rises in PSA, which panic most people, the cancer stays

"It's a little different from what's been done with Provenge."

stable for quite a while. We continue to monitor patients with imaging to see how they do. While the success of CAR T-cells in prostate cancer has not been reached, we have learned that not every virus used to make these cells results in a stable cell. Sometimes the cells don't grow in the body as they should, or they may not make it into the site where the tumor is because they're just not as robust as they should be. We are currently involved in finding different viral vectors that are more robust and need a lower dose of cells on a per-kilogram basis to have an antitumor effect.

Hopefully, we'll get the next trial up and running soon, within the next few months.

"Our group has used PSMA as a focal point for CAR therapy."

This is cutting-edge technology. Every immunotherapy out there has associated side effects. Many people just assume that because there are advertisements out there claiming that somebody lives longer on a particular immune therapy, that it is in fact for all people and that it is a great drug. But that particular drug doesn't necessarily serve every person. We see that with checkpoint inhibitors: only about 25% of people respond while the side effect profiles have been heavy. People can become grievously ill on the checkpoint inhibitors in spite of their success in several solid tumor malignancies. Quality of life can be impacted.

Are the side effects of CAR T as severe?

Dr. Slovin: They're different. Cytokine release syndrome could be serious and result in severe hypotension and shock requiring massive-volume resuscitation and intubation. The checkpoint inhibitors can cause equally significant side effects that could put somebody in the intensive care unit. We've seen people with myasthenia gravis (neuromuscular disease). We've seen severe colitis. Prostate has the worst endocrinopathies that we've seen compared with other solid tumor malignancies. Patients may have profound fatigue due to hypophysitis (inflammation of the pituitary gland) to the point that they can't even get out of bed.

We must respect any kind of immune treatment that affects normal homeostasis of the immune system. It sounds so easy when we talk about it, but the reality is that we are changing the normal homeostasis of the body and the body may or may not like that. That's why one has to be circumspect, not only in trial design but in carrying the treatment forward into the clinic.

What else should patients know about these upcoming CAR T trials?

Dr. Slovin: There will be more trials for immunotherapy in prostate cancer. Treatment responses take much longer with immunotherapies than with other drugs. But these will offer opportunities for cutting-edge science and treatment. Pp

Clinical Trial: Naomi Haas, MD CAR T-Cell Therapy

Dr. Naomi Haas is the leader of the kidney and prostate cancer programs at the University of Pennsylvania Health System in Philadelphia.

Prostatepedia spoke with her about her Phase I chimeric antigen receptor (CAR) T-cell therapy for prostate cancer clinical trial.

Why did you become a doctor?

Dr. Naomi Haas: I always wanted to be a veterinarian, but I was invited to apply for a BS/MD medical program. In that program, you complete both college and medical school in six years. I have a competitive spirit, so I decided to apply.

To my great surprise, I was accepted.

I went into oncology because I have a lot of cancer in my family—on both my father's and mother's side. I was very afraid of cancer. I felt like the more I learned about cancer, the more I would somehow be able to help my family and myself.

What is it about caring for patients that brings you back to the table?

Dr. Haas: I'm very interested in both patient care and research. During my oncology fellowship, I spent a lot of time in the lab. I was really interested in answering critical questions about how cancer works and why drugs work in certain ways. I wasn't very good at making pretty things in the lab, though.

My clinical talents seem to be in taking care of patients. I enjoyed patient interaction. I eventually left the lab, but I do feel as if that lab experience made it much easier for me to talk to devoted scientists who dedicate all of their time to lab work.

What is the thinking behind your clinical trial?

Dr. Haas: Patients are interested in approaches that could potentially allow them to live for very extended periods of time without a lot of side effects. The prostate cancer field has evolved very quickly. We have a lot of new agents that we didn't have even three or four years ago.

One of the things that has come out of the University of Pennsylvania is that Dr. Carl June is doing a lot of CAR T trials in different solid tumors—including prostate cancer.

This particular immunotherapy trial we're discussing collects patients' T-cells and exposes them to a virus that has a target in it. We then give these cells back to the patients to train their bodies to attack the cancer.

It's a very attractive approach. We started developing this clinical trial over five years ago. At the time, a lot of the therapies didn't include some of these small molecule pill-type therapies that patients could take. We were interested in developing nontoxic approaches for patients that would hopefully incorporate into their immune system and would work for a really long time.

"I was very afraid of cancer."

Can you walk us through the details of the trial?

Dr. Haas: Patients first have testing to see if their cancer expresses the same kind of targets that we're making in the CAR T trial. They have to have a biopsy of their tumor, which shows that their prostate cancer expresses a protein called prostate-specific membrane antigen. PSMA is similar to PSA, but this protein is secreted on the *outside* of the prostate cancer cells. It's on the membrane, so it's much more accessible to treatment. It might bring down cells that a PSA target might not otherwise do.

"It's a very attractive approach."

So, patients first undergo testing of their tumor. If they have at least 10% expression of PSMA, then they're a candidate for the trial.

They then undergo a process called *apheresis*: an IV is put in their arm and their blood comes out into a machine. This machine removes some of the T-cells—the immune cells—from their bloodstream, but their blood is at the same time returned to the body. They're not really losing a lot of blood. We're just pulling some of the T-cells, the T-lymphocytes, out of their bodies.

Then we infect those T-cells with an inactivated HIV virus. This is the same virus that causes HIV, but we remove the bad stuff so that it can't cause HIV in patients. We put two targets within this inactivated virus: PSMA and TGF-beta.

TGF-beta is an immune marker present in a lot of the lymphocytes. In prostate cancer, the lymphocytes hang out near the prostate cancer cells, so we felt that if we targeted both we would have a better chance of hitting the tumor with our target and not hitting other parts of the body that we didn't want to harm.

Once these cells are infected with this CAR T, they are grown in culture. We make volumes of these T-lymphocytes with this antivirus with PSMA and TGF-beta in it.

The process takes about three weeks. Then we give it back to the patients through an intravenous line over about half an hour. It's just a one-time treatment.

We then follow people very closely over a number of days, weeks, and months. We make important measurements, such as how much the T-cells expanded in the blood. We also do another tumor biopsy to see if the CAR T has reached the tumor.

"We're looking for patients who haven't had anti immunologic therapies."

We follow scans, blood tests, etc. to make sure that: 1) the patients aren't having side effects; and 2) to see whether or not we can prove that the CAR T has incorporated into their bodies and that it's doing its job.

We're in the very early stages of this clinical trial. We're looking first at a low dose of CAR T and are planning look at higher doses and then multi-doses because we think patients might need more than one dose to offer an effective therapy. We're also looking at CAR T in combination with immune adjuvants. Sometimes we give a little dose of Cytoxan (cyclophosphamide) or a little dose of fludarabine with CAR T to make the body have an even bigger immune response.

Do patients need to be in the Philadelphia area to participate?

Dr. Haas: They do. We have had people come from far away, though they have to commit to staying within an hour of our hospital for the first two months. The reason for that is if they were to get a side effect or they were to get sick, we would want them to be admitted to Penn because we know the drug, and we want to make sure that they get the proper workup and proper care.

What types of side effects do you anticipate?

Dr. Haas: We've treated one patient and will be treating another two in the next month. The most serious side effect that we would anticipate is something called cytokine release syndrome (CRS), which is flu-like symptoms: high fever, shaking, chills. That's a very common side effect for CAR T-cell therapy for leukemia, which was FDA approved in October 2017. We're not seeing as many side effects so far in the solid-tumor CAR Ts, but we don't have a lot of patients enrolled yet in this particular trial.

If this is a Phase I trial, you're still figuring out what the side effects might be, correct?

Dr. Haas: Safety, yes.

What type of patients are you looking for?

Dr. Haas: We're looking for patients who haven't had anti-immunologic therapies, so they can't have had Provenge (sipuleucel-T). They can't have had Yervoy (ipilimumab) or Opdivo (nivolumab) because we're not sure how those things will affect the CAR T-cells. We might allow these patients in the future.

We don't want people to be too heavily pretreated. We're asking that they've at least received one standard therapy, so they have to have signs that their prostate cancer has been getting worse on standard hormone therapy. Not just a rise in PSA: there has to be something that we can see on scan that is getting worse. They have to also have tried one of the new oral therapies like Xtandi (enzalutamide) or Zytiga (abiraterone). They are allowed to have had prior chemotherapy, but we ask that they not have a lot of treatment. Right now the trial is limited to people who've had three or less of those sort of more extensive therapies.

We're also not allowing Xofigo (radium-223) at this point because during the trial we're going to have to use some conditioning therapies like Cytoxan (cyclophosphamide) or fludarabine, which potentially can make cell counts low. We're afraid that if they have too much chemotherapy up front or too much Xofigo (radium-223) they may not have the bone marrow reserved and could have side effects. We're being relatively cautious.

Is there anything else you think patients should know about this trial?

Dr. Haas: The trial is fully funded by the Prostate Cancer Foundation. We're very excited about that. The trial is supported entirely by donations, so it's quite unusual in that respect. It is all outpatient therapy, but it is pretty labor intensive.

In the United States today, only 4% of the adult population participates in clinical trials. Clinical trials are how we move the field forward; I strongly encourage patients to participate in some kind of clinical trial. It could be a questionnaire. It could be a drug treatment. It could be looking at their tissue. This is how we help ourselves. Patients help themselves while helping other patients. Pp1

How To Get Involved…

For more information, email Dr. Haas at Naomi.Haas@uphs.upenn.edu.

Monica Bryant: Cancer + The Law

Monica Bryant, a cancer rights attorney, is part of the four-woman team behind Triage Cancer.

Prostatepedia spoke with Ms. Bryant about legal and employer issues facing prostate cancer patients.

How did you come to start Triage Cancer?

Ms. Monica Bryant: I am an attorney by trade. As long as I can remember, I've had an interest in the law and how it can either oppress or empower people. I started off working in the United States Congress. I worked first for a senator and then for a House of Representatives member.

Then, I found myself in Chicago looking for a new job. I was looking for an area in which I could use my legal expertise to help people. The fates collided and I started at another organization and about five and a half years ago, my colleague Joanna Morales (our CEO) and I started Triage Cancer. We didn't think the world needed another nonprofit, but we saw a gap in services and felt our unique expertise could help.

That is why Triage Cancer was created. When someone gets a diagnosis, there is so much information they have to learn. So much of it is self-education. We want to give people all the information we can so that they can triage what they need to deal with now and what can wait till later.

Triage Cancer's mission is to provide education and resources on all types of cancer survivorship issues: from health insurance to employment, finances, fertility, and sexuality.

We provide this education in a number of ways. We host a Speakers Bureau of experts from around the country and in Canada. When a hospital, support group, or another cancer organization puts on an educational event and they're looking for expert speakers on a particular topic,they can reach out to us and we will match them with the most appropriate individual.

That matching is based on a number of factors. It could be about a specific topic. Or perhaps they're looking for someone to speak to a particular audience, say of young adults, seniors, caregivers, or healthcare professionals. We try to match the speakers closely to the requestor's needs. We've had some really good success with it.

Could a man reading this who runs a support group contact you to arrange a speaker for his group?

Ms. Bryant: He could certainly ask. We have people who run various self-support groups that ask for speakers. Sometimes we have larger groups.

It all depends on speaker availability. Some speakers will only speak if there's an honorarium and some will only speak if the group is local to him or her. Every figure has his or her own criteria. But we want people to ask because the worst that we could say is we don't have anyone.

We also match people with other resources. If we can't provide a speaker for a support group, maybe there's a webinar we're hosting that could be useful. We've had support groups host viewing parties for webinars.

In what other ways do you provide education?

Ms. Bryant: At Triage Cancer, we host in-person conferences and webinars. We do three in-person conferences a year. This year, we're going to be in Ypsilanti, Michigan; Reno, Nevada; and Lewiston, Maine. We try to pick places without other big cancer education conferences. More information can be found at http://triagecancer.org/conferences.

Are webcasts of these conferences available after the event?

Ms. Bryant: No, not for the in-person conferences. We try to keep them intimate. There's no set number, but we want them to be interactive. We want people to be able to ask questions in a casual environment. If we start webcasting, we're concerned that it would change the tone of the conference. We are looking at other ways to make this digital content reach more people. That's in our five-year plan.

But we also have a webinar series: we try to host one webinar per month. The topics run the gamut. I would say the most popular tend to be around health insurance issues, especially in the United States. For example, we hosted one in August 2017 that was about the appeals process when a health insurance company denies a service or claim.

Are these webinars available online?

Ms. Bryant: They are. And you can visit www.triagecancer.org/webinars to see the upcoming webinars as well.

We record and post all of them online. We will take them down if there's an update later, but we keep a library of all the topics up there.

On October 18, 2017, we hosted another webinar about how to pick an insurance plan. That's something that comes up quite often. When someone has an employer-sponsored plan, and they're given more than one option, they don't necessarily know how to choose the best plan for them.

We hear that also from people who have Medicare and may have plan options. We also hear that from people trying to purchase insurance

in the individual market because there are a lot of factors. Health insurance status and adequacy of a health insurance plan have a direct correlation to health outcomes.

What are some of the other issues you cover?

Ms. Bryant: Employment issues are an important topic that comes up frequently. Joanna and I have expertise in legal issues, so we generally speak on those topics. We want to empower people to recognize that the law is a tool that they should use for their benefit. We don't simply advocate that people sue their employers, but we want to get to people before there is an issue.

For example, in the United States, we have a law called the Americans with Disabilities Act (ADA). One of the things that the ADA provides for people with a cancer diagnosis is something called a "reasonable accommodation." For someone who may be suffering from either long-term or late-term side effects and who wants to work through treatment or return to work after treatment, a reasonable accommodation allows them to get some assistance to remain in the workplace. The average American doesn't necessarily know about that.

They usually don't need to know about it, right?

Ms. Bryant: Right. Or they're into their treatment, they haven't accessed reasonable accommodations, and then their job performance suffers, so they are let go. We see such a scenario often where people feel they've been discriminated against. But when we peel back the layers, it's not necessarily discrimination, it's that their job performance has suffered, and they haven't accessed the benefits that might be available for them.

We want to give people this information so that they can go to their employer empowered and access resources available to them, keep their jobs, and keep being the valued employee they want to be. People shouldn't suffer as a result of not knowing what's out there.

What kinds of financial issues do people experience?

Ms. Bryant: That's an issue across the board. We look at finances in the broadest terms possible because we know that it's not just about medical bills, even though that is obviously a huge factor.

The issue starts with the health insurance piece. If someone doesn't have an adequate health insurance plan and their out-of-pocket costs are skyrocketing, that's going to have a direct impact on their finances. If someone isn't accessing workplace protection so that they can continue to work, that has a direct impact on finances.

We find that a lot of people think very narrowly about finances, focusing only on financial assistance for copays. While that's definitely an important part of the conversation, we want people to think more globally. That way, we can avoid some of the pitfalls.

Are finances more of an issue, for example, for people who have prostate cancer? Or are these mostly issues people who aren't working or who are on fixed incomes face?

Ms. Bryant: We see financial issues from all different types of people, from all walks of life. Even people who would probably describe themselves as middle-class prior to a diagnosis tend to suffer what has now been termed the financial toxicity of a cancer diagnosis.

If someone can't go to work, works for a small employer, and doesn't have access to the Family and Medical Leave Act (FMLA), they lose their jobs. Even if they have access to the FMLA, it's unpaid leave.

For individuals who have lower incomes or who might not have a job that offers health insurance, financial toxicity tends to be more severe. We see this severity in younger adults because they tend to have smaller savings and be less secure in their careers. But it really isn't limited to any particular segment.

Even if someone is middle class (and I'm not sure how we define that anymore) and has an employer-sponsored health insurance plan, if they're out of work for more than 12 weeks they could lose their job. Then they have to figure out what to do for health insurance. If they don't pick an adequate plan, they can exhaust their savings and tap into retirement. Maybe they can't pay their mortgage. It can snowball very quickly if someone doesn't understand how to use all of the different parts of the system.

We talk about finances in a global manner because there are so many pieces to the puzzle and each piece is important.

Disability insurance is another very important piece. And very few people understand what disability insurance even is and how it can be useful after a diagnosis.

I'm sure most people don't really understand what it is until they actually need it. And then it's too late.

Ms. Bryant: Right. And in this country, if you don't have disability insurance prior to your diagnosis, it can be very challenging to get once you have a preexisting condition.

That makes sense though, doesn't it?

Ms. Bryant: I would like to see some more options for folks when they're a number of years out of treatment, especially since so many people worldwide are diagnosed with cancer and since it has become more of a chronic disease. Healthcare industries need to adapt to this change.

That's especially true with prostate cancer. Most men who have prostate cancer can have it for 10 to 15 years. They die with prostate cancer, rather than of it.

Ms. Bryant: Right. So to deny disability insurance for 15 years to people after they've had that diagnosis is extreme.

Are there other issues that come up specifically for prostate cancer patients?

Ms. Bryant: Many people request conversations around intimacy and sexuality. That's a hot-button topic because it's challenging to talk about.

One of the experts we have in that area says it's harder for men to talk about those issues than for women to talk about them. We get a lot of traction when we offer content around intimacy and sexuality.

Conversations about nutrition and exercise are particularly well received, as well, because people acknowledge that we can improve overall health, but there's a lot of misinformation out there. The internet is both a wonderful thing and a horrible thing at the same time.

With so much information out there, how do you vet what's good information and what isn't?

Ms. Bryant: Exactly. It can be really challenging to figure out what's reputable. I think that a lot of people who participate in those sessions, either

in our conferences or in our webinars, appreciate that the presenters not only have expertise in nutrition or exercise, but that they really come at it from a perspective specific to cancer. It makes it just a little bit easier to digest information when you know it's a reputable source.

You also have a lot of other resources available on your site. Can you talk a bit about that content?

Ms. Bryant: We are in the midst of a website redesign. At the moment, the Resources tab contains several types of resources for patients, survivors, caregivers, and health care professionals.

The state and international resources are specific to the contact information for relevant agencies. We want to make it easy for people who need information to find it in one spot. It's all location-specific information. If your state has these programs, you can find the contact information for agencies such as the Comprehensive Cancer Control Program, the State Disability Insurance Program, and Fair Employment.

Under Quick Guides, you'll find materials that we have created at Triage Cancer. These cover a host of different topics. We've broken them out by topic area: advocacy, employment, and insurance issues. These are designed as snapshots of a particular topic, so they're no more than four pages long. They're written in very plain, digestible language. They're useful for both the patients and the healthcare professionals who work with them.

There are a lot of Quick Guides, so someone might download several to get all the information they need. But we never want it to be so overwhelming that they stop reading.

We hear from a lot of healthcare professionals who say they're asked questions that they don't necessarily have the time or expertise to answer. Healthcare professionals, support group leaders, or anyone can go to our website, download the Quick Guide, print it off, and hand it to someone as a starting point.

We're really excited about another online tool called www.cancerfinances.org. We think of it as a choose-your-own-adventure tool.

CancerFinances.org has different modules, but people can go there for answers to a series of questions. Based on the answers to their questions, they will get targeted information relevant to them. Right now, we have health insurance, disability insurance, and financial resources available.

Again, these are complex topics, so we are constantly trying to find new ways to present the information so that it's accessible.

If someone is looking for individual insurance in the marketplace, CancerFinances.org will only give the information about that and not necessarily about Medicare or vice versa.

If someone is looking for more information on a particular topic and can't find it, we have a list of our partners. We believe very strongly that we are a community; with so many great resources and organizations out there, we don't have to reinvent the wheel. Pp1

TRIAGE CANCER

Merel Grey Nissenberg: Advocacy Groups Meet

This October 13-15, the 13th Annual Meeting of the National Alliance of State Prostate Cancer Coalitions (NASPCC) met in Washington, DC on Capitol Hill. State prostate cancer organizations, including state coalitions, associations, foundations, and consortia were represented by at least one leader. Invited guests and sponsors also attended.

The first panel on advanced prostate cancer covered new treatments for advanced prostate cancer and appropriate clinical trials. After a detailed Q & A session, a second panel on genomics and genomic testing met. The presentations included information on markers.

Then Dr. James Gulley, lead Prostate Cancer Researcher at Building 10 of NIH spoke about immunotherapy. Dr. Gulley will return at next year's meeting.

In the third panel of the day, the prostate cancer coalitions of Georgia, Arkansas, New Mexico, South Carolina, and California presented. Mr. Tom Kirk, an invited member of the Executive Committee of NASPCC and Vice President of the California Prostate Cancer Coalition, moderated the panel. The five state leaders discussed awareness and education programs in their states and expressed a willingness to help other state coalitions as needed.

> *"The five state leaders discussed awareness and education programs in their states."*

At lunch, Dr. Michael Zaragoza, President of the Delaware Prostate Cancer Coalition, talked about the current proposed United States Preventive Services Task Force guidelines for PSA testing.

The group later heard Dr. Ashley Ross, a Urologist/Oncologist from Dallas and formerly of Johns Hopkins, discuss important advances in diagnosis and treatment. Dr. Ross's discussion included genomic testing, early and advanced prostate cancer, and the 2017 results of clinical trials.

Attendees also heard from Mark D. Vieth, Coordinator for the Defense Health Research Consortium (DHRC), who spoke about the urgent need to keep the Congressional Directed Medical Research Program (CDMRP) in place. NASPCC is a signatory of the letter asking that the CDMRP remain in place, and NASPCC joined the DHRC by vote after this year's Annual Meeting.

The group then heard from panelists who discussed new products and advances benefiting patients with prostate cancer. These included CyberKnife and hydrogel spacer for men undergoing radiation therapy for prostate cancer. A company offering free genetic testing at various centers in the US also spoke.

The group elected its 2017-2018 officers: Merel Nissenberg of California, President; Johnny Payne of South Carolina, Vice-President; Donald Lynam of Kentucky, Treasurer; and Jan Marfyak of New Mexico, Secretary. LaTanya Patton of Missouri is again Director-at-Large. These five officers comprise the Executive Committee, along with Tom Kirk as Invited Member.

The 2017-2018 Board of Directors are the officers named above along with Robert Johnson (Wyoming), Alvin Chin (Virginia), Paul Kradel (West Virginia), Mary Anderson (North Carolina), Dave Hulbert (Minnesota), Ira Baxter (Tennessee), Michael Zaragoza, M.D. (Delaware), and Sanford Jeames (Texas).

Saturday evening NASPCC held a cocktail awards reception.

"The meeting concluded with an open discussion on participating state prostate cancer organizations, co-branding issues, and goals."

Robert Johnson of Wyoming gave a talk entitled "Why We Are Here," and then Dave Hulbert of Minnesota talked about his journey as an advanced prostate cancer patient. The group presented two awards: the Georgia Prostate Cancer Coalition won Most Outstanding State Prostate Cancer Coalition of 2017, and Kathy Meade of Virginia received a service award. Guests included the Chief Counsel for Senator Roy Blunt (Missouri) and the Executive Director of the Vietnam Veterans of America. Merel Nissenberg received a surprise crystal award of appreciation.

On the last morning of the meeting, Tom Kirk gave a detailed discussion on "The New Workplan" adopted by the Board on July 18. Andrew Chesler of CancerCare also spoke about a number of emotional and physical issues facing prostate cancer patients and caregivers, which was very helpful in addressing a topic often overlooked at prostate cancer meetings.

The meeting concluded with an open discussion on participating state prostate cancer organizations, co-branding issues, and goals. The group is especially grateful to Tiffany Razzo, who served as staff during the meeting.

Next year, the group will meet October 12-14. Pp[1]

XTANDI takes on advanced prostate cancer while you take on what matters to you.

Talk to your doctor and visit XTANDI.com/info

Please see Important Safety Information for XTANDI on the next page.

ONCE-DAILY
Xtandi®
(enzalutamide)
40 mg capsules

ONCE-DAILY
Xtandi®
(enzalutamide)
40 mg capsules

Talk to your doctor and visit XTANDI.com/info

Who is XTANDI for? XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body. (This is a type of advanced prostate cancer.)

Important Safety Information

Who should not take XTANDI?

XTANDI is not for use in women. Do not take XTANDI if you are pregnant or may become pregnant. XTANDI can harm your unborn baby. It is not known if XTANDI is safe and effective in children.

Before you take XTANDI, tell your healthcare provider if you:

- Have a history of seizures, brain injury, stroke or brain tumors.
- Have any other medical conditions.
- Have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form of birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See "Who should not take XTANDI?"
- Take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works. You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

How should I take XTANDI?

- XTANDI is four 40 mg capsules taken once daily.
- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.
- If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure. Your healthcare provider will stop XTANDI if you have a seizure during treatment.
- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

The most common side effects of XTANDI include weakness or feeling more tired than usual, back pain, decreased appetite, constipation, joint pain, diarrhea, hot flashes, upper respiratory tract infection, swelling in your hands, arms, legs, or feet, shortness of breath, muscle and bone pain, weight loss, headache, high blood pressure, dizziness, and a feeling that you or things around you are moving or spinning (vertigo).

XTANDI may cause infections, falls and injuries from falls. Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see the Brief Summary on the following page and the Full Prescribing Information on XTANDI.com.

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QUESTIONS ABOUT XTANDI?

Call 1-855-8XTANDI (1-855-898-2634)

PATIENT INFORMATION
XTANDI® (ex TAN dee)
(enzalutamide)
capsules

What is XTANDI®?

XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body.

It is not known if XTANDI is safe and effective in children.

Who should not take XTANDI?

XTANDI is not for use in women.
Do not take XTANDI if you are pregnant or may become pregnant. XTANDI can harm your unborn baby.

What should I tell my healthcare provider before taking XTANDI?

Before you take XTANDI, tell your healthcare provider if you:

- have a history of seizures, brain injury, stroke, or brain tumors
- have any other medical conditions
- have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form of effective birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See "**Who should not take XTANDI?**"

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XTANDI?

- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.
- If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure. Your healthcare provider will stop XTANDI if you have a seizure during treatment.
- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

The most common side effects of XTANDI include:

- weakness or feeling more tired than usual
- back pain
- decreased appetite
- constipation
- joint pain
- diarrhea
- hot flashes
- upper respiratory tract infection
- swelling in your hands, arms, legs, or feet
- shortness of breath
- muscle and bone pain
- weight loss
- headache
- high blood pressure
- dizziness
- a feeling that you or things around you are moving or spinning (vertigo)

XTANDI may cause infections, falls and injuries from falls. Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XTANDI?

- Store XTANDI between 68°F to 77°F (20°C to 25°C).
- Keep XTANDI capsules dry and in a tightly closed container.

Keep XTANDI and all medicines out of the reach of children.

General information about XTANDI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XTANDI for a condition for which it was not prescribed. Do not give XTANDI to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about XTANDI. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about XTANDI that is written for health professionals.

For more information go to www.Xtandi.com or call 1-800-727-7003.

What are the ingredients in XTANDI?

Active ingredient: enzalutamide

Inactive ingredients: caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, black iron oxide

Marketed by:

Astellas Pharma US, Inc., Northbrook, IL 60062
Medivation Inc., San Francisco, CA 94105
15I074-XTA-BRFS

076-1977-PM

This Patient Information has been approved by the U.S. Food and Drug Administration.

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