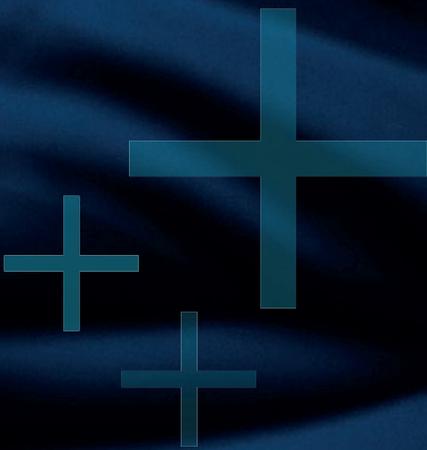


# Prostatepedia<sup>1</sup>

<sup>1</sup>expert insight + advice



## Immunotherapy

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# *In this issue...*

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**This month we're talking about advances in prostate cancer immunotherapy. The interviews are informative and lucid—quite an achievement as cancer immunotherapy is quite complex.**

One important takeaway is that Provenge (sipuleucel-T) is much more effective when the tumor burden is low. In my experience, this treatment is often offered when metastatic spread is too extensive for optimal effectiveness. Perhaps cost is one reason. Provenge (sipuleucel-T) is about \$90,000. Many patients face 20% copays, which mean out-of-pocket fees of \$18,000.

My major interest in immunotherapy is how it might complement other prostate cancer treatment modalities. While there are patients who experience dramatic responses in terms of tumor kill, this happens in only a small minority of patients with currently available immunotherapies. Still, there are clinical settings in which immunotherapy might have a major impact.

One promising role for immunotherapy may be in the establishment and maintenance of cancer dormancy. When dormant, a cancer persists, but doesn't grow or spread. Clinically, this situation is most useful when

the volume of cancer is small or micrometastatic. Cancer dormancy is a very active area of research; the literature is extensive.

Broadly speaking, there are three mechanisms for establishing cancer dormancy. First, the ability of the cancer to form new blood vessels has been blocked. Second, the machinery for cancer proliferation has been blocked. Third, dormancy can be established and maintained by ongoing immune attack on the cancer cells. It is this third mechanism that I think best fits the immunotherapeutic tools we currently have. While this approach has not been extensively studied in prostate cancer, it has been extensively investigated in other malignancies. (See *Cancer Research* 74: 6750, 2014 for a review.)

There are two clinical settings where immune dormancy might have a major impact. First, in PSA-only recurrent disease after initial surgery or radiation, patients have residual cancer that is too small to be seen with currently available imaging technology. Second, in patients with metastatic disease who have dramatic responses to hormonal therapy or chemotherapy. Newer therapies have significantly increased the proportion of patients who experience these dramatic responses. For example,

in the PREVAIL trial, patients with metastatic disease progressing on LHRH agonists like Lupron (leuprolide) were randomized to placebo versus Xtandi (enzalutamide). Just under 20% of patients entered a radiologic complete remission. Similarly, in the CHAARTED trial, 27.5% of the men on Lupron (leuprolide) and Taxotere (docetaxel) had a PSA less than 0.2 ng/ml at six months. I think these results identify two situations in which systemic treatment can cause a dramatic reduction in cancer volume and a test of immunotherapy-induced cancer dormancy would be reasonable.

Immunotherapy remains an exciting area of prostate cancer research that may well complement existing treatment options. This line of research offers a promising path to durable remissions in advanced prostate cancer.

*Charles E. Myers, Jr., MD*

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# Susan F. Slovin, MD, PhD

## Immunotherapy for Prostate Cancer



**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.

*How did you come to focus on prostate cancer?*

**Dr. Susan Slovin:** I came to prostate cancer rather serendipitously. I became a fellow at Memorial Sloan Kettering Cancer Center well before I found out that my brother, father, and father-in-law developed prostate cancer.

I was enjoying my rotation on the genitourinary oncology service, which focuses on all malignancies of the bladder, prostate, and kidney. At that time, the chief of my division, Dr. Howard Scher, talked to me about how important it was to expand the group. He also started to talk to me about a career in this particular area, as I was the only woman there. It was a new area. I was the first woman in the group and the first to become a full professor. It has been nothing but a joy to be a part of something that started out as a prostate group of two men and one woman to become a group of over 25 people, including women.

I just wish that my family members who had prostate cancer could have benefited from some of the newer therapies that are now approved.

*What is immunotherapy for cancer?*

**Dr. Slovin:** I've been in the immunotherapy field for close to 35 years. It has always been a challenge to explain my work to people because immunotherapy seems to take on different meanings for different people.

In general, when we talk about immunotherapy, we're talking about doing something to use the body's own immune system to fight bacteria or cancer—treating something that is foreign to the body. For many years, people have been trying to develop strategies to enhance the body's own immune system, sometimes in not very healthy ways.

Cancer patients, in general, are thought to have some sort of immunologic dysregulation—meaning that there is something inherently defective with their immune system but that they are, by and large, relatively immunologically intact. Relatively immunologically intact means they can fight off pneumonia, an infection, or a virus and do very well. If you believe that cancer is an immunologic

problem, meaning that the cancer cells escape our normal regulatory system of surveillance—our immune surveillance, then there is something wrong, we have just not been able to exactly identify the causative factor.

We're now broadening our experience with immunotherapies. For a long time, we wanted the body's own immune system to fight the cancer, but we have now developed other therapies to induce the body to generate an anti-tumor effect. The body does not de novo figure out how to do that: there is something that is lacking such that the body is unable to direct specialized immune cells to fight the cancer.

For many years, we studied vaccines, which were isolates of the markers present on tumor cells. We would grind up a tumor and then try to isolate various fractions out of that. We would try to determine if there was anything the body could react against—what we called antigens. Antigens are molecules that sometimes are part of the body, but may reflect an altered self, meaning that something has changed as the malignancy or cancer occurred.

The long and short is that, after 40 or more years, we've never really been able to come up with a vaccine that

could actively treat cancer. We tried different preparations to enhance the immune system and rev up certain populations of cells like B-cells, which produce antibodies, or T-cells, which are often the cell population involved in immune surveillance and the killing of tumor cells. But these preparations have not been optimal.

That is our reason for looking at other approaches, among which have included using a patient's own cells that have been altered in some way to try to get them to recognize these molecules, or using a new group of drugs called checkpoint inhibitors.

But people who have cancer shouldn't walk around thinking, "Oh, my god. My immune system is shot to hell." It's not. It's just that a different part of the immune system is being used. It is still protective and still functional, but again, there is something missing that we don't understand.

*Are different cancers more or less responsive to immunotherapy? How does prostate cancer fit into that spectrum?*

**Dr. Slovin:** You've asked the million-dollar question: is prostate cancer an immunologically targeted organ? That question merits a lot of discussion. A lot of that has to do with our own understanding of why certain solid tumors are more responsive to certain drugs than others.

Other solid tumors like kidney and bladder cancers are thought to be somehow immunologically driven. Why do we think that? A kidney cancer patient could have a very large primary cancer in his or her kidney with metastatic lesions in the lungs. If you remove the primary tumor, which means removing the kidney, those lung lesions disappear. That is example number one.



We find example number two in bladder cancer. Treating cancer within the bladder with bacillus Calmette-Guérin (BCG) vaccine, which is tubercle bacilli (TB), generates an inflammatory response in the bladder. After several weeks to months of treatment, the bladder cancer can go into remission.

We see a third example in melanoma. Sometimes an unusual skin lesion can suddenly turn from dark brown to black indicating that it is abnormal; the same spot can turn pink, which is more or less self-cure. This is extraordinary.

We're not sure about the exact mechanisms, but these three examples give us the impetus to look at immunologically driven malignancies.

Why are some tumors more responsive than others? To date, there have been a number of different vaccines in melanoma, bladder cancer, kidney cancer, and even prostate cancer. Even though these vaccines are capable of generating an immune signal, meaning the patient generates antibodies against the immunogen, invariably there does not appear to be a correlation with a biologic change in the tumor's behavior.

You can have very high levels of antibodies or even T-cell reactivity suggesting that there is recognition of the molecule, that the immune system understands it and is reacting to it. But there is a significant disconnect: there doesn't seem to be a change in the biology of the cancer, meaning the cancer doesn't go away.

Even though you have a high antibody response suggesting the immunotherapy is working robustly—whether it is a vaccine or a checkpoint inhibitor—if the cancer doesn't go away and

doesn't get smaller, then you have to assume that this immunotherapy is not really doing what you would hope it would do.

Now, there are some data suggesting that it can sometimes take weeks to months before an immune response occurs and that sometimes the disease can look worse before it looks better. This delay in response may be due to what we call inflammatory, or immune, cells getting to the site of the tumor to attack and only then does a patient go into remission.

People often think other malignancies are more robust in their response to immunotherapy because some may have more genomic alterations or mutations than others. They have a greater number of what we call hyper-mutations, meaning they have abnormalities in their genome suggesting some sort of instability and that these are the malignancies that respond to immunotherapy. Still, there are some malignancies that will respond in spite of the mutational burden.

We're not quite sure why some cancers respond and others don't. It may be completely independent of these mutational burdens, but that is what we're using right now as one plausible explanation.

#### *What about checkpoint inhibitors?*

**Dr. Slovin:** Checkpoint inhibitors are not vaccines. I put them into a very different category than immunotherapy. Checkpoint inhibitors are a unique class of drugs that function as "breaks" to the immune system's ability to spontaneously react in a manner that could be detrimental to the patient. Essentially, checkpoint inhibitors prevent the body from reacting to self-molecules that may





lead to autoimmunity like in lupus or rheumatoid arthritis. Instead, our body tries to prevent any sort of encounter with a molecule that is of lesser importance. Unless it is critical to maintaining the integrity of the patient's immune system, these checkpoint inhibitors regulate how we respond.

The first checkpoint inhibitor, CTLA-4 (cytotoxic T-lymphocyte associated antigen 4), was discovered by Dr. James Allison. An antibody was directed to CTLA-4 and used as therapy; it was found to be very powerful in melanoma and now has FDA approval.

There is another pathway called PD-1, or programmed cell death protein 1, for which two drugs were generated. Both have been FDA approved in melanoma as well as in non-small-cell lung cancer, head, and neck cancer.

#### *What about Provenge (sipuleucel-T)?*

**Dr. Slovin:** Prostate cancer does not have a lot of genomic instability, or these hyper-mutations. Immunotherapy for prostate cancer started to explode with the approval of Provenge (sipuleucel-T), which was the first treatment done via a patient's own cells.

Cells are obtained via an apparatus called a leukapheresis machine, which removes the mononuclear, or white, cells. These cells are then sent to a separate laboratory where they are co-incubated with a protein, (prostatic acid phosphatase) which has been genetically coupled with a growth factor called GM-CSF (granulocyte-macrophage colony-stimulating factor). After a 48-hour turnaround, these cells are reinstated or re-infused into the patient as three separate infusions, one every two weeks.

Sipuleucel-T was the first immune therapy ever approved for a solid tumor. It opened up the door for researchers to start looking at other immunotherapy modalities. Sipuleucel-T is relatively nontoxic. It conveys a survival benefit. But its robustness in generating a significant anti-tumor effect is less, at least compared with some of the other therapies that are out there. Why? We don't know. It does not have immediacy of action, meaning we can follow the patient for three, six, even nine months and not see the cancer change, even though there is a survival benefit. Imaging with bone and CAT scan does not show shrinkage of the tumor, but nevertheless, there is a survival benefit.

There is a lot we still don't understand about prostate cancer. Unlike a lot of these other cancers, prostate cancer is largely directed toward bone. When there are a lot of cancer cells in the bone, sometimes there is not a lot of room for immune cells to get in there and do anything.

#### *What are chimeric androgen receptor T-cells?*

**Dr. Slovin:** There are other therapies we are trying to adapt for prostate cancer. Among them are chimeric androgen receptor T-cells (CAR T-cells).

CAR T-cells are essentially T-cells that have been genetically altered to become like an armored car—a tank, if you will, which can carry different kinds of guns. You can hook it up to any antibody you want so that it can be directed to a specific molecule on a cancer cell. There are CAR T-cells directed to molecules that are present on leukemia cells. There are CAR T-cells directed against prostate-specific membrane androgen (PSMA), prostate stem cell antigen, and a variety of different constructs.

This has been exceptionally successful in the hematologic malignancies and it's still in its infancy in prostate cancer, although we've had some experience following patients who've received these therapies and have shown that in an occasional patient, these cells can live in the peripheral blood for at least 10 days or more. Again, because of some concerns about how they're produced, we haven't really hit upon the best construct yet, but it is extremely promising. CAR T-cells have been exceptionally successful in acute lymphocytic leukemia, for example—much more than had been anticipated.

*What about combining various forms of immunotherapy or combining immunotherapy with another treatment like radiation or chemotherapy?*

**Dr. Slovin:** Everyone has been relatively impressed with the single-agent action of some of the checkpoint inhibitors, but unfortunately combining checkpoint inhibitors with Provenge (sipuleucel-T) alone doesn't seem to be as robust. That has given forth the idea of combining two different kinds of checkpoint inhibitors.

Why not give chemotherapy with a vaccine, or chemotherapy with Provenge (sipuleucel-T), or give other biologic agents together? The rationale is not always that strong. We don't always have preclinical models to substantiate it.

Sometimes, it's a matter of sitting down and looking at the way the immune system is constructed and then going back to ask what can we do to facilitate our therapy's ability to recognize the antigens associated with a tumor?

There are several preclinical papers suggesting that if you give radiation,

you can release tumor antigens into the bloodstream making it easier for drugs to seek them out as targets. Antigen, or tumor cell antigens, in particular, can be released by radiation because radiation promotes cell death. When you have necrotic cells, those antigen cells are all necrotic cells.

Other things that can do this would be chemotherapy or freezing cells (called cryotherapy). All of those therapies facilitate cellular products and antigens in the peripheral circulation.

Releasing antigens is the easy part. The hard part is determining the timing of when to give the different therapies. It may be that the right way to do it is to give radiation or cryotherapy or chemotherapy 24 hours before you give the immune drug, but we really don't know. That remains a prevailing problem ongoing clinical trials are addressing. Timing and dosing seem to be critical. We don't want people to have untoward toxicity. We want people to have the lowest acceptable dose possible that will still provide a significant anti-tumor effect and is safe.

*What is the thinking behind combining Provenge (sipuleucel-T) with Xtandi (enzalutamide) or Zytiga (abiraterone)?*

**Dr. Slovin:** There are two reasons: first is cellular kill. Androgen receptor blockade prevents transcription of the message to make the cells grow.

There is also a school of thought that you can modulate the immune system with Zytiga (abiraterone) or with Xtandi (enzalutamide). There is some preclinical data by the Hodge Group at the National Cancer Institute suggesting that Xtandi (enzalutamide) does have an immune-modulatory effect in some preclinical models. In fact, the Hodge Group actually

shows that when we combine Xtandi (enzalutamide) with a vaccine and/or radiation in animals, they had improved survival.

But often what happens in animal models does not necessarily translate to man. That has been a major issue.

What is the thinking driving all of this? Sometimes we have absolutely no data to drive our thinking. When Taxotere (docetaxel) first came on the market, everybody added to it every known prostate cancer drug in the hope that its effect would be improved. We try to make a rationale based on preclinical work, but sometimes it just takes expertise to say, "Well, if this drug targets one pathway and that other drug targets another, maybe if we combine them we will have a complementary synergism, or at least some additiveness that would not otherwise be there if we were to think about it in a more rational manner."

I wish it was straightforward, but it isn't. Sometimes we come up with a reason based on what we think is doable.

*(Provenge) sipuleucel-T is the only immunotherapy available to patients outside of a clinical trial, correct? Is it routinely combined with Xtandi (enzalutamide) and Zytiga (abiraterone)?*

**Dr. Slovin:** Provenge (sipuleucel-T) has been FDA approved for use in men who are castration-resistant and are either asymptomatic or minimally symptomatic. The package insert does not contraindicate combining, so if the patient wants to go on Provenge (sipuleucel-T) and his doctor feels that there is a component of more active disease, there is nothing to stop them from combining, but we don't have any preclinical or clinical work suggesting that this is the right thing to do.

Most of what we base our work on, particularly the National Comprehensive Cancer Center (NCCC) guidelines, is really based on Level I data. We are looking at Phase III clinical trials to provide the impetus for what we do.

One has to be very creative in making combinations, but one has to also be very careful if this combination is not something that has been in a clinical trial to support its safety. Doctors really are liable for the care of their patients if the combination is detrimental.

### *Because toxicities could overlap?*

**Dr. Slovin:** That's right. But you might not know about it until you do it. By and large, Provenge (sipuleucel-T) is relatively well tolerated. There have been some fever and chills and an acute reaction during the infusion.

Xtandi (enzalutamide) itself has great efficacy. How do you know what adding the Provenge (sipuleucel-T) does, if anything?

That is one of the dangers of using these combinations outside of a clinical trial. You don't know how the drugs work with one another. There may be absolutely no benefit to adding Xtandi (enzalutamide). If the patient's PSA goes down, is it the Provenge (sipuleucel-T) or the Xtandi (enzalutamide) or both? I already know with a tremendous amount of certainty that Xtandi (enzalutamide) is going to bring it down.

### *I thought Provenge did not lower PSA?*

**Dr. Slovin:** It does not usually do so. There have been one or two case reports showing a decline in PSA. All I'm suggesting is that if you gave Provenge (sipuleucel-T) along with Xtandi (enzalutamide) and the PSA goes down, I will bet you dollars to nickels it is the Xtandi (enzalutamide)

and not the Provenge (sipuleucel-T). That has been one of the major issues in promoting Provenge (sipuleucel-T).

It has lost some popularity as a result of the fact that nobody knows *when* it is going to work or *whether* it is working. There has been some data suggesting that there is a change in the immunologic milieu in the newly diagnosed. If you give Provenge (sipuleucel-T) before prostatectomy, you can actually see changes, but we really don't know how those changes correlate to systemic effects down the line. How beneficial is it going to be?

### *Are there clinical trials looking at giving Provenge (sipuleucel-T) before prostatectomy?*

**Dr. Slovin:** That was already done in several Phase I trials, mainly looking for safety and to see if they can find any immunologic target or signal on which to build other trials.

### *Is Provenge (sipuleucel-T) expensive?*

**Dr. Slovin:** It is \$93,000. I believe Medicare covers 80% of it.

Some patients are extremely nervous about their PSAs. Urologists will very often encourage people to use Provenge (sipuleucel-T) if they have no evidence of disease and a rising PSA. There has been no data to suggest Provenge (sipuleucel-T) is beneficial to this patient population. I think it's more psychological—we're doing *something*, as opposed to just watching, but we really have no data to support it.

Patients like to see something going on. If they don't, they're not happy.

### *They're just nervous.*

**Dr. Slovin:** Exactly. You know what PSA stands for? Promotes Stress and Anxiety!

### *PSA and imaging are pretty much the only outward signs we have of what the cancer is doing, correct?*

**Dr. Slovin:** That is correct. Unless someone happens to be symptomatic, you would be monitoring the scans every three to four months depending on the pace of the disease and the PSA doubling time. But you're right, imaging itself is now taking on a completely different tone with these new molecular targeting agents.

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

**Dr. Slovin:** There are a lot of very good clinical trials coming out. There is some new data that just came out on pembrolizumab, an anti-PD-1 checkpoint inhibitor, showing complete responses in a very small number of patients. It is extremely encouraging.

But the concern is that everybody will jump on the bandwagon just because one drug shows responsiveness in one cancer. People sometimes misguidedly think that every treatment will be broadly applicable to every solid tumor.

I've been in this field for a very long time. I'm extremely encouraged at the novelty and continued enthusiasm everyone has for vaccines and/or immunotherapy. I am proud to say that I am no longer alone in promoting immunotherapy for prostate cancer. We've made so many strides. I continue to be very hopeful for immunotherapy for the prostate. I think we will ultimately find the right combination, but it will take time. 

# Padmanee Sharma, MD, PhD

## Immune Checkpoint Blockade



**Dr. Padmanee Sharma is a genitourinary medical oncologist and immunologist deeply involved in immunotherapy research at the University of Texas MD Anderson Cancer Center in Houston.**

*Prostatepedia* spoke with her recently about immune checkpoint blockade for prostate cancer.

*How did you come to focus on prostate cancer immunotherapy?*

**Dr. Padmanee Sharma:** Years ago, when I was enrolled in my MD/PhD program with my PhD work focused on immunology, immunotherapy was not really working in oncology. But I was fascinated by T-cells because they are incredibly powerful: they can recognize bacteria or a viral infection and clear them out of the body. They do a great job of recognizing what does not belong in your body. The question remained as to why T-cells weren't able to eliminate cancer.

I went on to do internal medicine and oncology work at Memorial Sloan Kettering Cancer Center (MSKCC) with my mentor, Dr. Dean Bajorin. While I was at MSKCC, I developed an interest in genitourinary medical oncology that led to work in bladder and prostate cancers.

*What is immunotherapy for cancer?*

**Dr. Sharma:** Immunotherapy for cancer refers to getting your own immune cells—your T-cells and B-cells—to eliminate the cancer. But, the question of how to unleash the immune response against cancer is one that has been researched and thought about for many years, with many different ideas tested without a lot of success. But, the reason for limited success was that we didn't really have a basic understanding of how T-cell responses were regulated. That took years of basic science research. T-cells have an *ignition switch*, which is the T-cell receptor. T-cells have a *gas pedal*, which is a CD28 co-stimulation. Those two things together get the T-cells moving, but T-cells also have a brake pedal. The *brake pedal* is CTLA-4 (cytotoxic T-lymphocyte-associated protein 4). It was the first brake that was identified. Once the T-cells get going, they then engage that brake because they don't want to keep going forever.

In cancer, if the T-cells get turned off by the brake before they can eliminate the entire tumor, then the immune response is insufficient and the tumor continues to grow. In the 1990s, Dr. Jim Allison's work showed that if you blocked that brake (CTLA-4) with an antibody

(anti-CTLA-4), which is this new field of immune checkpoint therapy, we can allow T-cells to operate longer. After blocking that brake, we started seeing the first set of patients whose disease went away with immunotherapy. Today, we have identified many more brakes. CTLA-4 was the first, but now we know of many more brakes, including PD-1 (programmed cell death protein 1) and PD-L1 (programmed death-ligand 1). Blocking those also lead to anti-tumor responses in the clinic.

*Are some cancers more or less responsive to immunotherapy?*

**Dr. Sharma:** Some studies have shown that tumors with higher mutation loads have more antigens, which means that there are more things for the T-cells to recognize as foreign, or as not belonging to the body, and that that allows for better immune responses against them. Those high-mutational-load tumors are eliminated more easily. Melanoma, lung, and bladder cancers have high mutational load.

Prostate cancer, on the other hand, has fewer mutations. Many think that because prostate cancer has fewer mutations, it doesn't attract enough of a T-cell response to lead to eradication with immunotherapy.

We are doing a lot of research in this area at MD Anderson. Our understanding is that, yes, high-mutational-load cancers do tend to have more T-cell infiltration. Before you start any treatment, prostate cancer doesn't have many T-cells infiltrating into the tumor, or not as many as in melanoma, lung, or bladder cancers. But it may be possible for us to think of combination therapy strategies, such that one treatment allows T-cells to get into prostate cancer and then a second treatment blocks the relevant brakes on the T-cells.

We did a clinical trial in which we gave anti-CTLA-4 therapy to patients. We could see that the treatment enabled T-cell infiltration into the tumor, but we also found brakes such as PD-L1 and VISTA (V-domain immunoglobulin suppressor of T-cell activation). That is the issue in prostate cancer. It is not that we can't get the T-cells in there. The T-cells may not need a hundred antigens to infiltrate into tumors, and it may be possible to get T-cells into tumors with a few antigens, but then we have to block compensatory or adaptive brakes that may become expressed as the immune response changes in the tumor. The yin and yang of the immune response means that each time we change a positive aspect of the immune response, such as driving T-cells into a tumor, we may also affect a negative aspect of the immune response, such as increasing expression of more brakes. Prostate cancer does have some antigens that the T-cells can potentially recognize, but there may be other inhibitory pathways that regulate immune responses in prostate cancer. We've not run clinical trials yet that test whether we can give combination immunotherapy strategies to increase T-cell infiltration and block compensatory inhibitory pathways, but we hope to start those types of trials soon.

We propose that it may well be important to block multiple pathways. In prostate cancer, we may need not just a monotherapy strategy, such as only anti-CTLA-4 or only anti-PD-1, but perhaps a combination of two, or a combination of other inhibitory pathways identified.

*What about combining checkpoint inhibitors with hormonal therapy, radiation, or chemotherapy? Is that done?*

**Dr. Sharma:** Yes, that is done. Our trial combined anti-CTLA-4 with an older hormonal therapy Lupron, or leuprolide acetate.

Recently, there was data reported from a small clinical trial that patients who had had Xtandi (enzalutamide) responded to anti-PD-1 therapy. [See page 18 for a conversation with Dr. Julie Graff about that trial.] They will be expanding that trial to look at larger numbers of patients to see if that is, in fact, true.

I do think that combination therapy is going to be very important. Radiation therapy is combined with immune checkpoints in other tumor types. We're looking to see if that combination can be expanded into prostate cancer.

There was a Phase III clinical trial looking at radiation therapy and anti-CTLA-4 in patients with metastatic prostate cancer. Although we had some patients who did very well and responded, the p-value on that trial was .053. It didn't meet the statistical significance of less than 0.05. It was 0.053. It was deemed a failed trial, but we actually learned a lot from that trial: that yes, some patients responded to the combination of radiation and anti-CTLA-4. Trying to understand who those responders were will be very important.

*Does the emerging field of genomics inform immunotherapy approaches to prostate cancer?*

**Dr. Sharma:** There has now been a lot of data published, especially from the Stand Up To Cancer Dream Team led by Dr. Arul Chinnaiyan and Dr. Charles Sawyers. They've done some phenomenal work that was recently published showing that there are mutations that can be identified in prostate cancer patients. Some of these mutations may be targetable by small molecule inhibitors or some of these mutations may be recognized by T-cells. We are still trying to figure out whether these different mutations in prostate cancer are being targeted by the immune system after treatment with immune checkpoint therapy. The immune system may be able to target these types of mutations that occur in multiple patients or possibly, the immune system may target mutations that are unique to each patient. We're still trying to identify these unique mutations, which may not act as driver mutations, but may be able to generate effective immune responses. If we identify appropriate mutations to target, perhaps we can treat these mutations with a personalized medicine approach such as personalized vaccine strategies in combination with immune checkpoint therapy. The field of genomics has also shown us that patients who have mutations in genes that regulate DNA repair may have more mutations and, as I discussed earlier, more mutations may lead to expression of more antigens to initiate T-cell responses. There are some patients with prostate cancer who have these types of mutations in DNA repair pathways and they may be the patients who respond best to immune checkpoint therapy. Many studies are ongoing to address these issues and we'll learn a lot as the data emerge.



*What about side effects? If you're combining multiple forms of checkpoint inhibitors or checkpoint inhibitors with other modalities, is there an additive effect?*

**Dr. Sharma:** Immune checkpoint therapy definitely has a different side effect profile than chemotherapy or hormonal therapy. We have to be wary about toxicities; patients need to be monitored carefully. If we recognize these toxicities early enough, we can treat them. We have more knowledge about these toxicities now since we've done more trials and used the agents more. We are definitely able to recognize them better. We just need to spread that knowledge to the rest of the prostate cancer community. Right now, academic centers have more experience with these agents than local communities.

As we gain more knowledge about what these toxicities are and learn how to recognize them, it is much easier to treat them early enough so that they don't become severe. If we can treat these toxicities earlier, we can resolve most of them and possibly continue treatment.

*Most of these immunotherapies are being tested in the later stages of prostate cancer. Is there any talk about using them earlier?*

**Dr. Sharma:** Most of the time, when we start new therapies, we test first in later stage disease because there are potential side effects and toxicities that we may not know about. You don't want to give those side effects and toxicities to patients with earlier stage disease who have a very high likelihood of being cured.

As we get more and more data and as we get better at treating, managing, and even mitigating toxicities, we move drugs into earlier stages of disease.

Again, in earlier disease stages, patients have better survival outcomes. You don't want to give potentially life-threatening toxicities to those patients. You have to weigh the risks versus the benefits.

Immune checkpoint therapy has certainly been shown to provide incredible benefit in patients with metastatic disease. It is now being moved earlier into stages of disease where patients have a high likelihood of relapse in order to decrease the probability of relapse. If we treat earlier, it is possible that we will generate a memory immune response. For example, we don't administer the polio vaccine while you have polio. Instead, we give the vaccine to generate an immune response, so that if you're ever exposed to the polio virus, the memory immune response that was generated with the vaccine can reject the virus and get rid of that infection before you get sick.

Hopefully, if we treat with immune checkpoint therapy in an earlier stage disease, we can get an immune response that leads to *memory response*. If a few cancer cells relapse later, the memory immune response can eradicate those cells before they form a large tumor.

So yes, we are moving immune checkpoint inhibitors into earlier disease stages. As those clinical trials complete, we'll have more data.

*Then this is just the natural evolution of drug development? You start testing an agent in later stage patients and then gradually begin testing it earlier?*

**Dr. Sharma:** Exactly. I think it makes sense ethically to test agents first in patients with later stages of disease who may not have other treatment options in order to avoid introducing





potentially fatal toxicities to patients with earlier stages of disease who have available therapies with proven benefit.

*Is there anything else you think patients should know about immunotherapy?*

**Dr. Sharma:** For years people have always thought of cancer treatment in terms of gaining a few weeks or months in terms of survival, with the subsequent thought that everyone eventually dies because we're not really making their cancer go away completely, or we're not really engaging the immune response to keep the cancer under control. But now, with immune checkpoint therapy, we have survival of 10 or more years, and, in my opinion, even cures. We're not just extending life by a few more months; 20% or more of patients are living 10 years or more, and some of these people can be considered cured of their disease. But, unfortunately, 20% is still a small group of patients and we need to do better, we need to make it 100%.

There is this possibility of real, durable survival so that you can live a normal life. Cancer is not a death sentence in the same way it used to be. We need to start thinking of cancer as a chronic disease that people can live with, like high blood pressure. People live with high blood pressure. You may not really *cure* high blood pressure but you can treat it and keep it under control with medications. Maybe we can do that with cancer, as well. But, more importantly, as we learn more and develop novel treatments, maybe we can cure even more patients with cancer.

PP



# James Gulley, MD, PhD

## Immunotherapy



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

*Prostatepedia* spoke with him recently about immunotherapy for prostate cancer.

*How did you come to focus on prostate cancer immunotherapy?*

**Dr. James Gulley:** I started my training in Southern California at Loma Linda University in cancer immunotherapy. I worked with a prostate cancer cell line and started to get interested in prostate cancer. I then went on to Internal Medicine training at Emory University and then came to the National Cancer Institute (NCI) for my fellowship in Medical Oncology. By the time I finished my fellowship, I was quite sure I wanted to do immunotherapy for prostate cancer.

I became involved with Dr. Jeffrey Schlom, who had developed prostate cancer vaccines in his laboratory. I helped take those vaccines into the clinic in a series of clinical trials that showed: first, the vaccines were safe; and, second, they generated good immune responses.



*"I tend to classify things into two groups when we're talking about immunotherapy."*



Later, we started to do combination studies and then eventually a large randomized Phase II study. We finished enrollment earlier this year for a larger randomized Phase III study in prostate cancer.

One of the things that drew me to prostate cancer was that it was the number one cancer in men and the number two cause of cancer mortality. While I was still doing my training, apart from initial hormonal therapy, nothing really impacted outcomes in men; there were just minimal changes. Our treatment didn't impact survival.

I wanted to take this common disease and find even better treatments. Over the last six years, we've had multiple different agents approved for prostate cancer, which has really been wonderful for our patients. A lot of these agents have improved

survival, but haven't led to the elimination of disease in a substantial proportion of patients. We still have room to improve but are certainly in better shape than we were six years ago.

*What is cancer immunotherapy?*

**Dr. Gulley:** I tend to classify things into two groups when we're talking about immunotherapy.

There are agents like vaccines that can stimulate an immune response. When most of us think of vaccines, we think of the flu shot—things that prevent disease. But there is a slightly different class of agents called therapeutic vaccines, which are vaccines used to treat diseases already there. The idea is the same. You're getting the immune system to recognize and attack a given target. Vaccines are one strategy to stimulate an immune response.

There are various different proteins that have been used to stimulate an immune response. These natural proteins, like Interleukin 2 (IL-2) and GM-CSF (granulocyte-macrophage colony-stimulating factor), are found in our body.

There are also cellular therapies, which are immune cells normally

found in patients. We can take these cells out of the patient's body, train them to be riled up against prostate cancer cells, and then infuse them back into the patient.



*“Vaccines are one strategy to stimulate an immune response.”*



The other class of agents is more a facilitator of the immune response. These agents allow immune cells to work better within the tumor microenvironment and include things like immune checkpoint inhibitors. Immune checkpoint inhibitors have gotten a lot of press recently and are approved for multiple cancers, including kidney cancer, bladder cancer, melanoma, and lung cancer.

Molecules like TGF-beta (transforming growth factor beta) or IDO (indoleamine 2,3-dioxygenase) can also cause the immune cells not to work at the tumor level. Both can shut down a good T-cell response within the tumor microenvironment.

*What is the rationale behind combining various classes of immunotherapy?*

**Dr. Gulley:** A lot of this work has been done in cancers like melanoma. There is a particular immune checkpoint inhibitor called ipilimumab. It blocks a signal on the T-cell that would normally tell that T-cell to turn back off. It can drive that T-cell to stay active for a longer period of time.

Combining ipilimumab with another checkpoint inhibitor allows that T-cell to work better within the tumor

microenvironment. The response rate in melanoma with either of these checkpoint inhibitors alone is relatively low—in the 20% range or less with ipilimumab and 35-40% range with nivolumab. When we give both agents in combination, we reproducibly get 50% or more patient response.

That combination has given us pause, though, because the number of side effects also goes up.

*What kind of side effects?*

**Dr. Gulley:** Side effects we see with anti-PD-1 or anti-PD-L1 antibodies are generally relatively mild compared to the side effects we see with anti-CTLA-4 antibodies. With anti-PD-1 or anti-PD-L1, we see some immune-related side effects in organs.

The thyroid or adrenal glands may not work well or the liver enzymes may go up. The immune system is



*“The other class of agents is more a facilitator of the immune response.”*



now activated temporarily against those organs. We treat this by stopping the anti-PD-1 antibody. If needed, we treat with steroids.

We see much the same thing with anti-CTLA-4, except we may see it more frequently and with more intensity. There is more likelihood of things like colitis, or inflammation of the colon, which can lead to diarrhea. Sometimes the combination of the two agents can lead to an increase not only in the severity of events but also in the number of events.

Certainly, there have been deaths related to immune checkpoint inhibitor use. However, compared to chemotherapy, there are relatively fewer deaths and fewer side effects with most checkpoint inhibitors, especially the newer checkpoint inhibitors like PD-1 and PD-L1 agents.

The more interesting combinations don't just combine two checkpoint inhibitors, but rather combine a way to stimulate the immune system (such as a vaccine or cellular therapy) with an anti-PD-1 or anti-PD-L1 agent—something that allows the T-cells generated to work better at the level of the tumor.

There are a number of ongoing studies, including one we just opened at the NCI that combines these two agents.

Sometimes, if you give the anti-CTLA-4 antibody ipilimumab at much lower doses in combination with normal anti-PD-1 antibody doses, you get good responses without having a lot of side effects.

We also have a study in which we combine a vaccine we developed here at the NCI with low-dose ipilimumab—just 1 milligram per kilogram—and a standard nivolumab dose. (Previous prostate cancer trials looked at 10 milligrams per kilogram of ipilimumab.)

That particular trial just opened. We'll first treat patients with metastatic disease, but then we'll treat three different groups of patients with localized disease undergoing surgery. Those groups of patients will be treated with: 1) a vaccine; 2) a vaccine and ipilimumab; and 3) nivolumab, a vaccine, and ipilimumab.

If one of your readers is interested in joining the trial, they can contact our clinical group at 301-443-6211.



*Is anyone combining various forms of immunotherapy with treatments like hormonal therapy, radiation, or chemotherapy?*

**Dr. Gulley:** Historically, we have used standard-of-care agents based on their ability to kill cancer cells. We haven't studied the impact of standard-of-care agents on the immune system or the impact on the tumor cell in an immunologically relevant manner.

Chemotherapy, hormone therapy, and radiation therapy can all kill tumor cells, but they don't all kill tumor cells in the same way. Some of these therapies can kill tumor cells in such a way that makes it easier for the immune system to make an immune response to them. As a clinician, I think that is an interesting and important phenomenon and is part of a spectrum of things the anti-tumor agent can do to tumor cells called immunogenic modulation.

Chemotherapy, radiation therapy, and hormonal therapy can also all change the way a tumor cell looks to the immune system to make it easier for the immune system to recognize or kill it. This becomes very important for cells that aren't completely killed by the standard-of-care agent. The chemotherapy shines its spotlight on the tumor cells so that the immune system can go in and take care of them. We're finding some very nice potential combination agents.

We just published a paper earlier this year on combining our vaccine PSA-TRICOM with a radionuclide called Quadrimet (samarium-153 EDTMP). See *Oncotarget*, July 28, 2016, to read the article. We treated patients with Quadrimet (samarium-153 EDTMP) alone or with Quadrimet (samarium-153 EDTMP) plus vaccines. Patients treated with the

combination therapy had a doubling in progression-free survival. They also had better immune responses and better PSA decline.

Based on that, we are looking to combine immunotherapy with Xofigo (radium-223). We just finished preclinical work showing that we get much the same type of changes within the tumor that make it easier for the immune system to recognize or kill.



*“Therapeutic vaccines train the body’s immune system to recognize and attack those tumor cells.”*



*Is there any thought to using these various forms of immunotherapy earlier?*

**Dr. Gulley:** Patients historically have been treated with experimental therapies when they have failed all standard therapies. I completely endorse that strategy for chemotherapy.

However, when you're dealing with immunization therapies, we require an active, engaged immune system. An active, engaged immune system works better if there is not a lot of negative regulatory influence within a large tumor burden. I think it is then incumbent upon us to use immunotherapy earlier, especially when we also have a low likelihood of side effects.

It makes complete sense to use these therapies, especially well-tolerated vaccines, earlier in the disease process.

We're doing a study looking at a vaccine alone in newly diagnosed patients who are candidates for active surveillance. These patients have low-volume Gleason 6 tumors. We're doing a randomized study of vaccines versus placebo to see what kind of immune response we get within the tumor from routine biopsies. We're quickly enrolling that multicenter study. It is sponsored by the Division of Cancer Prevention at the NCI.

*How many patients are you enrolling?*

**Dr. Gulley:** Right now this is a relatively small 150-patient trial. We just extended it from 90 patients to 150 because it was enrolling so quickly. The trial is open at a number of centers in Southern California, Arizona, and here at the NCI. Patients can contact 301-443-6211 if they are interested in participating.

*Is there any thought to using immunotherapy in men who are thought to have potentially aggressive disease based on the results of genomic tests?*

**Dr. Gulley:** I don't know anybody who is doing that yet.

But there is actually some very interesting data coming out on Keytruda (pembrolizumab) and Xtandi (enzalutamide) in patients failing Xtandi (enzalutamide).

Dr. Julie Graff published a paper earlier this year in *Oncogene* on that combination. She gave an update of her data at the Prostate Cancer Foundation meeting in the fall of 2016. Five out of 28 patients responded. That is an 18% response rate, which I would argue is exactly what we see with PD-1 inhibition in lung cancer. I don't know if it's the combination with Xtandi (enzalutamide) or if it's the genomics. Dr. Graff and her group are working

on enrolling more patients and doing genomic studies on all patients.

At least one of those patients had microsatellite instability and, therefore, probably a lot of mutations. Those mutations could lead to antigens that are novel to the immune system and therefore much easier for the immune system to identify and attack. Maybe that is why that particular combination works.

We don't know exactly, but there are larger studies looking at it. Merck has its Checkpoint 365 study; one of the three arms will combine Xtandi (enzalutamide) with Keytruda (pembrolizumab).

### *It's a whole new world.*

**Dr. Gulley:** It is very exciting. Provenge (sipuleucel-T), a therapeutic vaccine, arguably was the first modern-era immunotherapy for any cancer. It was approved for prostate cancer, which we should always remember. By itself, Provenge (sipuleucel-T) doesn't cause big decreases in PSA. It doesn't change a man's symptoms, and it is only really indicated for minimally symptomatic or asymptomatic patients. But it does improve survival. That is a great start.

We should capitalize on the groundbreaking work with Provenge (sipuleucel-T). We know it generates T-cells. The question is: are those T-cells able to do what they need to do at the tumor level?

There is interesting retrospective data suggesting the earlier you use Provenge (sipuleucel-T), the better off you are. The idea is the earlier the vaccine gets your body's immune system engaged in fighting your cancer, the more likely you are to have a better outcome.

In the Phase III study, those patients that had the lowest quartile of PSA had a 13-month improvement in survival compared with those who had the placebo. This was associated with a 50% decrease in the risk of death. I think you're going to see us using immunotherapy earlier on, especially well-tolerated immunotherapy.

You're going to see us saying, "If this is what we get with a vaccine alone, how about adding in an immune checkpoint inhibitor? How about if we add other things that can allow those T-cells to work at the level of the tumor?" Maybe we're going to be able to find patients with very low amounts of disease or just at high risk for recurrence, and perhaps wipe out the cancer completely. These are things we have to study carefully.

But I do think that is the direction we are moving in.

### *Do you think the fact Provenge (sipuleucel-T) doesn't affect PSA scares patients? Many patients obsessively track their PSA levels.*

**Dr. Gulley:** I think patients often reflect what their doctor tells them. If their doctors are very concerned about PSA and make treatment changes at the drop of a hat based on the PSA, I think the patient then also becomes very focused on PSA. To me, it is most important to treat the patient. I hate to focus on the numbers. I prefer to focus on the patient.

We cheat a little bit when we're using these hormonal therapies, because they stop the production of PSA, even though they don't necessarily kill all the tumor cells. We're equating a decrease in PSA with improvement in outcome or improvement in shrinking of the disease. Usually, they do go hand in hand. Usually, PSA is a good marker for us to use. If PSA goes down, that is usually a good thing.

More importantly, with Provenge (sipuleucel-T), we have an improvement in survival that is much more important than changes in PSA. It is also well tolerated. Those are two good things that have formed the base. Now let's figure out ways we can get this done cleaner and better: by adding in other therapies or using it earlier on, etc.

### *Is there anything else that you think patients should know about immunotherapy?*

**Dr. Gulley:** As we look toward the future, the most important thing is that many of my patients really like the idea that we now have ways to get their body's immune system engaged in helping fight their cancer.

Second, when we think about therapeutic vaccines, we can think of them like the old adage that says, "If you give a man a fish, you feed him for a day, but if you teach him to fish, you feed him for a lifetime." Therapeutic vaccines train the body's immune system to recognize and attack those tumor cells. That immune system response could be around for a much longer period of time. Even if you don't see a decrease in PSA right away, that immune impact could potentially be with the patient for the rest of his life.

Third, I think that the true benefit will come once we figure out how to stimulate a great immune response and how those immune cells can work at the level of the tumor. Then we will have agents working hand in glove to lead to optimal immune responses. One potential strategy will be combining vaccines with immune checkpoint inhibitors for other molecules that can modulate the tumor marker environment to make it easier for the immune system to recognize and kill cells. [Pp](#)

# Julie Graff, MD

## Xtandi (enzalutamide) + Checkpoint Inhibitors



**Dr. Julie Graff is a medical oncologist at Oregon Health & Sciences University and VA Portland Health Care System.**

*Prostatepedia* spoke with her recently about her work on combining checkpoint inhibitors with Xtandi (enzalutamide).

*How did you come to focus on prostate cancer?*

**Dr. Graff:** I decided to go to medical school when I was very young. When I was in college, I studied math and did hospice work. As a hospice volunteer, it was my job to sit with patients while their caregivers got a break. I met a lot of people who meant a lot to me in the process. Some of the patients had cancer. I decided then and there that I wanted to work with cancer patients.

I was a math and chemistry minor. I loved to do research. I wanted to work with people and do research. I went to medical school in Washington, D.C., where I got to do genetics research.

Then I came out to Portland, Oregon, to complete my post-medical school training. I did a residency in internal medicine and a fellowship in hematology/oncology. In that process, I met Dr. Tomasz Beer (see *Prostatepedia* October 2016).

He is a senior prostate cancer researcher and has been a wonderful mentor to me.

I didn't originally think I was going to go into prostate cancer research, but Tom is such an inspirational person. Once I got started on that track, it was easy to continue. I really enjoy the patients and the research.



*“Unlike a bacteria that clearly is not you, cancer is you, so the immune system sometimes gives it a pass and lets it go.”*



*What are checkpoint inhibitors?*

**Dr. Graff:** One way to think about cancer is to consider that cancer develops because your immune system has let you down. There are cells that are part of the immune system circulating around your body all the time looking for things that shouldn't be there, like bacteria and viruses.

We think they can look for cancer, too. Cancer is a little tricky because it develops in a cell that belongs to you. Unlike a bacteria that clearly is *not you*, cancer is you, so the immune system sometimes gives it a pass and lets it go. We're learning that one of the ways that happens is the cancer cells themselves can express proteins on their surface that turn the T-cells off when the T-cells come to clear the cancer out. T-cells are one type of immune cell that help kill cancer cells.

It is important to control T-cells, because if they are out of control, you can get autoimmune illnesses in which your immune system attacks your body. (Crohn's disease and lupus are well-known autoimmune diseases.)

One of the ways cancer escapes the immune system is by expressing something called PD-L1 (programmed death-ligand 1) proteins. These PD-L1 proteins are on the cancer cells' surface. When a T-cell comes to kill a cancer cell, it's programmed cell death protein 1 (PD-1) binds with the PD-L1 on the cancer cell's surface, which turns off the T-cell. But there are also antibodies that interfere with that interaction called PD-1 inhibitors. They coat the PD-1 on the T-cell and stop the T-cell from being turned off by the cancer cell.

These PD-1 inhibitors are currently used as therapies in other cancers. PD-1 inhibitors such as Opdivo (nivolumab) and Keytruda (pembrolizumab) are currently FDA approved for melanoma, non-small cell lung cancer, and kidney cancer. There is also a PD-L1 inhibitor approved for bladder cancer.

We know that they work. When they work well, the cancer shrinks. We also know that PD-1 inhibitors are pretty well tolerated.



*“We need to work together to figure out why these combinations work and in which patients they are going to work so that we can tailor therapies.”*



The thought was that this type of therapy didn't work in prostate cancer. There was a study of Opdivo (nivolumab), which is currently FDA approved, in 17 prostate cancer patients. None of them had an objective response. That study was a turnoff to everyone in the field, signaling that these drugs may not work in this particular cancer.

There is also another pathway, called the CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) pathway, that interferes with the interaction between the antigen-presenting cells and T-cells, a different part of the immune response. There are two big studies now in prostate cancer showing

that they do not improve survival, either. Many, therefore, thought that checkpoint inhibitors won't work in prostate cancer. There were a lot of theories about why that might be.

I then had the idea of combining a PD-1 inhibitor with an androgen receptor antagonist Xtandi (enzalutamide). I got funding to treat 28 patients with that combination; we found real activity.

*Why do you think you found activity?*

**Dr. Graff:** There are a few potential explanations.

One explanation is that Xtandi (enzalutamide) may help the immune system work better. There are tests suggesting that may be true. One investigator at the National Cancer Institute (NCI) took two different kinds of prostate cancer cells, treated them with Xtandi (enzalutamide), and then did a separate test to see if T-cells could kill them. He did find that when you treat the prostate cancer cells with Xtandi (enzalutamide), the T-cells worked better against them. He looked specifically at different proteins to try to figure out why. But that is still a little bit of an open question.

There is another reason why Xtandi (enzalutamide) might be special. A different study showed that men with prostate cancer resistant to Xtandi (enzalutamide) had upregulation of PD-L1. There might be some synergy between Xtandi (enzalutamide) and PD-1 inhibitors.

*You treated 28 patients with Xtandi (enzalutamide) and a PD-1 inhibitor. What about using Zytiga (abiraterone)?*

**Dr. Graff:** I have not looked at Zytiga (abiraterone), but yes: could the same be true? Why just this combination? Some people are wondering about Lynparza (olaparib), which is a PARP

inhibitor that has been shown to work when prostate cancer has certain genetic mutations.

The other thing about hormone therapies is that they can sometimes lead the thymus to regenerate. The thymus is a part of the body located behind the sternum that is very active when we're younger. When we hit puberty, the thymus tends to involute or shrink down. T-cells are named T-cells because they mature in the thymus.

It is possible that through hormone manipulation, we generate new T-cells, but I don't know that anyone has shown that.

*What is the next step? Looking at this combination in larger groups of patients?*

**Dr. Graff:** Yes. We have a nod from Merck to enroll 30 more patients.

In prostate cancer, when there is only cancer in the bones, it can be hard to biopsy. In those first 28 patients, we said they didn't have to have a biopsy if there was nothing safe to biopsy. But for this next 30 patients, we're going to require a biopsy. We need to know who responds.

In those first 28 patients, we only had five responders. That is a small number—about 18%. If the responses hadn't been as good as they were, we may not have continued looking, but they were almost 100% responses. Real responders.

If 18% of men with prostate cancer in the world respond like that, we need to find out who they are and what it is that is making them respond. That is the goal of the expansion study.

We also need to test whether or not Keytruda (pembrolizumab)



can work on its own. Does it require Xtandi (enzalutamide)? If it does require Xtandi (enzalutamide), does the cancer have to have already progressed on Xtandi (enzalutamide)? Or could we use Keytruda (pembrolizumab) upfront?

*By upfront, do you mean earlier in disease progression?*

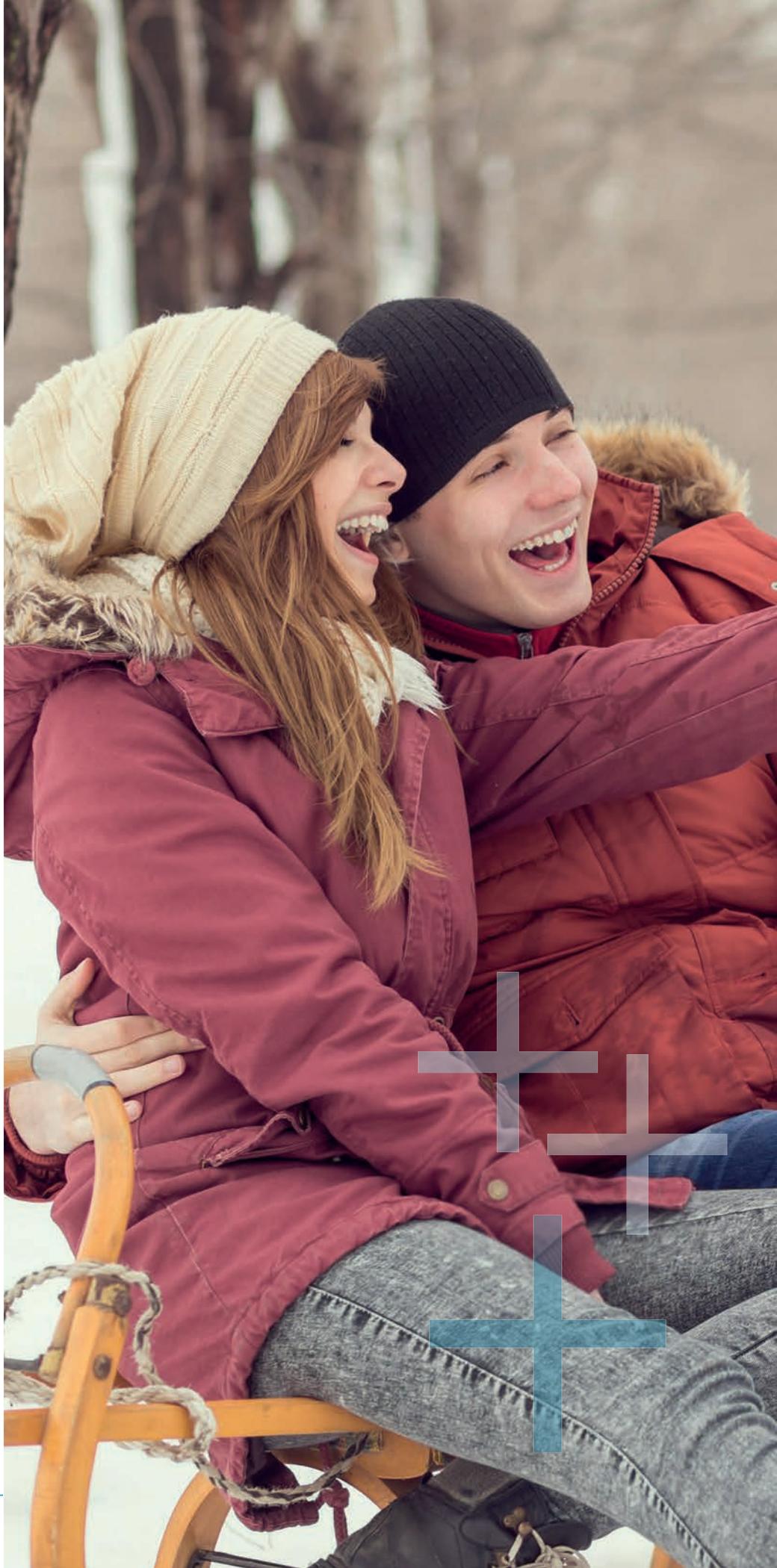
**Dr. Graff:** Yes. I think metastatic disease is important, at least at this stage. Castration resistance may be important, meaning the cancer is no longer responding to just turning off the testicles. Maybe Keytruda (pembrolizumab) doesn't require Xtandi (enzalutamide) resistance; maybe it could work upfront.

*Which combinations do you feel are the most promising?*

**Dr. Graff:** My study suggests that combinations can be really effective. In that earlier study, there weren't any responses with Opdivo (nivolumab) alone. I think combinations are really important. Which combinations? We're just going to have to try various combinations to see which make the most sense. Zytiga (abiraterone) is a possibility, but it requires prednisone, which could be immunosuppressive. Zytiga (abiraterone) may not be the optimal partner.

One of my colleagues at NCI is combining Opdivo (nivolumab) with Lynparza (olaparib), that PARP inhibitor I mentioned earlier. Maybe that is a better combination.

Radiation has also been of interest, because once you kill cancer cells in the tumor, proteins are released into the blood stream. That can help ramp up the immune system. One has to also consider what additional toxicities are being added through these combinations, though.





*Particularly with radiation?*

**Dr. Graff:** Exactly.

*Some are combining Xtandi (enzalutamide) with Provenge (sipuleucel-T) to drive the PSA down. Do you think that is, in part, because patients are nervous when a treatment doesn't lower PSA?*

**Dr. Graff:** There are people in the community who use Provenge (sipuleucel-T) in combination with Xtandi (enzalutamide) and Zytiga (abiraterone) in part to help the patient feel better. But I don't think there is great data showing that that combination is any better than just using Xtandi (enzalutamide) or Zytiga (abiraterone) alone.

When we started our study, we asked, "Is PSA response a good endpoint? Maybe these immunotherapies aren't driving down the PSA or shrinking the cancer; they're just keeping it more at a steady state."

But PSA turned out to be a fine endpoint. The Xtandi (enzalutamide) was already failing the patient. The PSA was going up despite Xtandi (enzalutamide). Adding the Keytruda (pembrolizumab) brought the PSA back down and shrank the tumors. It turned out that the Xtandi (enzalutamide) alone *didn't* bring the PSA down, but the immunotherapy plus Xtandi (enzalutamide) did.

*Is there anything else you think patients should know about your study?*

**Dr. Graff:** There is real hope out there, but we're not done yet. There is a temptation for patients and doctors to use Keytruda (pembrolizumab) or one of the other PD-1 inhibitors off the shelf and not in a study.

But I think that is the wrong answer. We need to work together to figure

out why these combinations work and in which patients they are going to work so that we can tailor therapies.

I want patients to feel hopeful that there is work underway that can make a big difference in their lives and hopefully shrink their cancers, but also not to get carried away with these results. Don't assume this is a one-size-fits-all approach, because it isn't.

*Don't rush out and ask your doctor to prescribe?*

**Dr. Graff:** Exactly.

*Is there any area of research you've got your eye on?*

**Dr. Graff:** There are all sorts of things right now in prostate cancer. We're seeing PARP inhibitors start to become the standard of care for patients whose cancers have certain DNA repair defects. We're seeing some new radiation treatments like Actinium that lead to profound responses in cancer.

I'm also excited about results from the NCI on combining Lynparza (olaparib) with PD-1 inhibition.

We're learning that combinations are really important. The same is true for testicular cancer: a combination of chemotherapy can be curative. Maybe if we find the right combination of the six treatments that improve survival in metastatic castration-resistant prostate cancer, we can cure a certain fraction of patients.

*You're using genomics to pinpoint which combination is appropriate?*

**Dr. Graff:** Yes. We're trying to better characterize the tumor and even better characterize the patient. <sup>FP</sup>



# Clinical Trial: Dr. Lawrence Fong, MD Prostate Cancer Immunotherapy

**Dr. Lawrence Fong is the co-leader of the Cancer Immunotherapy Program at the University of California, San Francisco.**

*Prostatepedia* spoke with him about immunotherapy and about several prostate cancer immunotherapy clinical trials for which he is recruiting.

*How did you come to focus on prostate cancer immunotherapy?*

Dr. Lawrence Fong: When I was a medical student at Stanford University, I really was struck by the immunology courses. There were some professors who were interested in cancer immunotherapy. In the 25 years since medical school, cancer immunotherapy has been an area of interest and focus for me.

I became interested in prostate cancer during my fellowship and focused on medical oncology. Prostate cancer is such a common disease, but it is also a disease where I thought I could really make a difference.

*What is immunotherapy for prostate cancer?*

Dr. Fong: Immunotherapy uses treatments that energize a patient's own immune system to target cancer. This is a very different way of thinking about cancer therapy.

Historically, we've thought about treatments like chemotherapy or hormonal therapy or radiation therapy that try to kill the prostate cancer cells directly.

With immunotherapy, we're at least one step removed. We're giving a treatment that doesn't directly target the prostate cancer. We're giving a treatment that gets the immune



*"We're relying on a patient's own immune system to do the heavy lifting."*



system to attack the prostate cancer. In many ways, we're relying on a patient's own immune system to do the heavy lifting in targeting the prostate cancer cells.

*Are some cancers more or less responsive to immunotherapy? Where does prostate cancer fit into that spectrum?*

Dr. Fong: Prostate cancer can clearly respond to immunotherapy, it just responds in a different way. Our first FDA-approved cancer vaccine,



Provenge (sipuleucel-T) was FDA approved to treat prostate cancer. FDA approval was a significant milestone.

The challenge is with the newer wave of immunotherapies called immune checkpoint inhibitors. Immune checkpoint inhibitors include the anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) or the anti-PD-1 (programmed cell death protein 1) antibodies that are being FDA approved across many other cancers. Those immune checkpoint inhibitors have not been shown to improve survival in prostate cancer.

But we *do* have a cancer vaccine for prostate cancer that improves survival. It is just that the immune checkpoint inhibitors, which are revolutionizing treatment in so many other cancers, have lagged a bit in prostate cancer.

*Why do you think that is?*

Dr. Fong: Our initial studies with Yervoy (ipilimumab), the anti-CTLA-4 antibody FDA approved for melanoma, showed that prostate cancer patients can often have very dramatic responses: Yervoy (ipilimumab) can lower the PSA from very high to near undetectable levels. We see tumors shrink. These responses to Yervoy (ipilimumab) can last for many years. This is very different

from the duration of response we typically see with other treatments in metastatic castration-resistant prostate cancer.

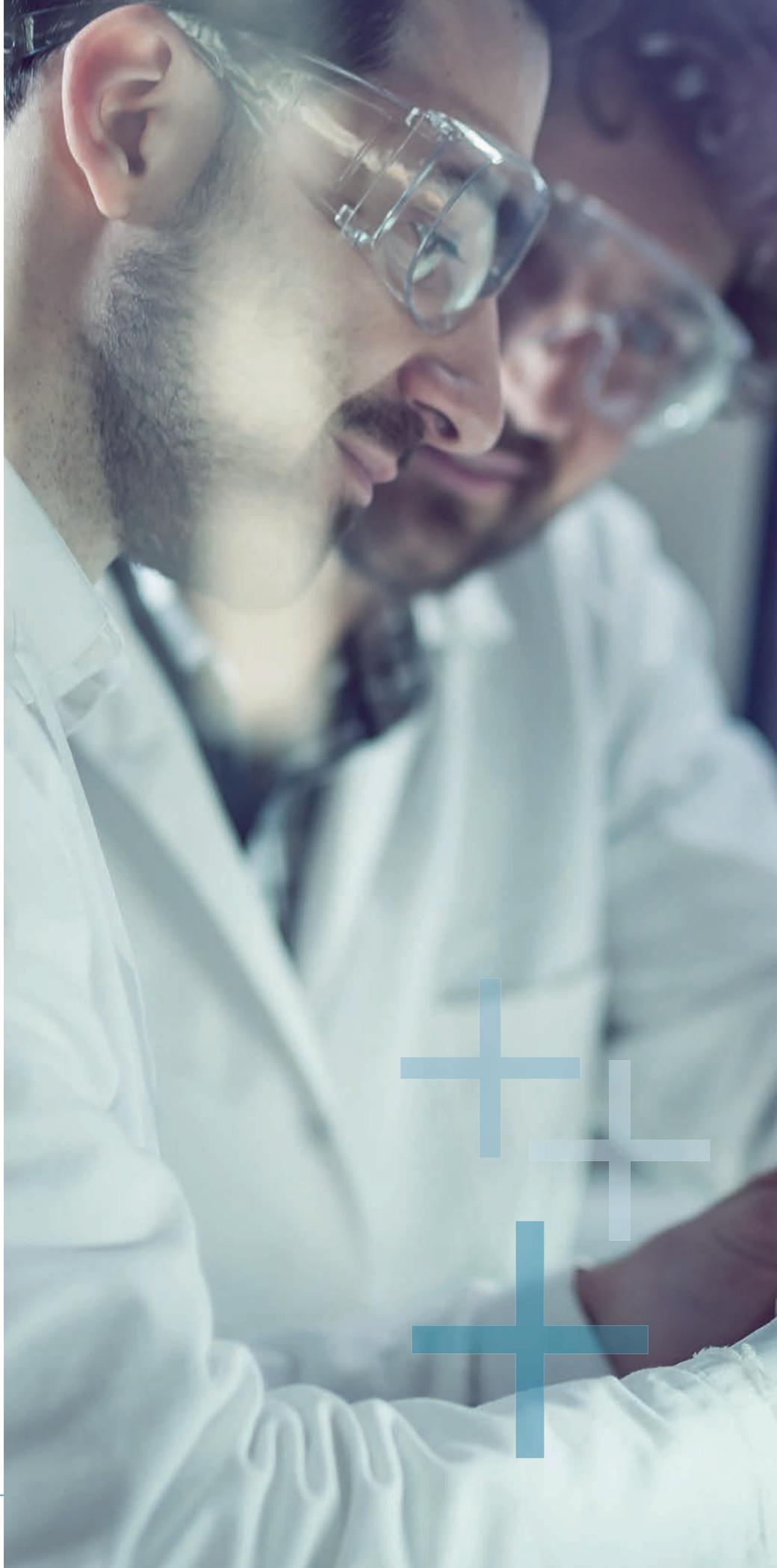
The challenge is that the number of patients who respond to those treatments is low—less than 10% respond or have those dramatic responses. The challenge is that if you try to treat hundreds of men with these immune checkpoint inhibitors in a randomized clinical trial, those who benefit get diluted because they are relatively infrequent. As a result, the Phase III clinical trials with Yervoy (ipilimumab) did not show any survival advantage.

The key will be in patient selection and developing combination therapy. Patient selection is really about identifying which men are going to respond.

When we talk about combination therapies, we need to think about ways we can combine these immune checkpoint inhibitors with other immunotherapies or with conventional therapies for prostate cancer to increase the frequency of men who benefit.

*Aren't you recruiting patients for a trial that combines Provenge (sipuleucel-T) with delayed or intermediate CTLA-4 blockade?*

**Dr. Fong:** We know that the cancer vaccine Provenge (sipuleucel-T) primes the T-cell immune response. We find that that immune response may not be as vigorous as we'd like it to be. When we gave Provenge (sipuleucel-T) to men with localized prostate cancer and then looked at their prostate tissue, we saw that the immune system was going to the prostate tissue, but that the immune cells were not going all the way in to the center of the tumors.





We wanted to enhance the Provenge's (sipuleucel-T) activity. We combined Provenge (sipuleucel-T) with the immune checkpoint inhibitor Yervoy (ipilimumab).

The thinking was that the vaccine steps on the gas and directs, or steers, the immune system toward the prostate cancer. By then giving Yervoy (ipilimumab), we release the brake to allow this immune response to really take hold and attack the prostate cancer more than we would see with Provenge (sipuleucel-T) alone.

*What should patients expect if they enroll in the trial?*

**Dr. Fong:** This trial is for men with metastatic castration-resistant prostate cancer. If one of your readers is interested in this clinical trial, he would need to come to the University of California, San Francisco (UCSF) to be screened. He can get his Provenge (sipuleucel-T) locally, but would need to come to UCSF to receive the Yervoy (ipilimumab). Yervoy (ipilimumab) is given every four weeks for four total doses. We then follow the patient. We could potentially give additional treatment down the road to those who respond.

*Can you talk a bit about which other types of combinations are being explored—two vaccines versus a vaccine and checkpoint inhibitor or two checkpoint inhibitors?*

**Dr. Fong:** We're exploring the combination of Yervoy (ipilimumab) with Prostavac, another cancer vaccine, along the same lines of the Provenge (sipuleucel-T) and ipilimumab trial that we just talked about.

We are also talking about ways in which we can use other immunotherapies to treat prostate cancer. For instance, we have a study

that looks at a drug that blocks adenosine receptors. The thinking behind that trial is that within the tumor microenvironment, the adenosine that is released by tumor cells turns off the immune system. We now have drugs that block that pathway. So we're studying those new drugs in combination with an anti-PD-L1 (programmed death-ligand 1) antibody. We're looking at a number of other immunotherapy combinations.

There is a long list of different targets we can hit with drugs to enhance an immune response. One approach we're taking now gives these immunotherapies prior to radical prostatectomy in men with localized prostate cancer. The standard of care for men with localized prostate cancer is surgery. Our studies are administering combinations of immunotherapies prior to that surgery. We will then look at the prostate tissue to see how a patient's immune system is being stimulated directly at the tumor site. In that way, we hope to guide the most potent immunotherapy combinations.

*Is anybody looking at using immunotherapy even earlier, say in men on active surveillance?*

**Dr. Fong:** We'd love to move immunotherapies into that setting. That is one of our reasons for doing these neoadjuvant clinical trials. If we can show that we're inducing an immune response within the prostate tumor, then the next step is to administer the immunotherapies to the active surveillance patient. We haven't gotten there yet.

*What about side effects? When you combine forms of immunotherapy, does it amplify side effects?*

**Dr. Fong:** Some of these combinations don't amplify the side effects, but others



*"We're exploring the combination of Yervoy with Prostavac."*



do. A prototypical example is in melanoma. Yervoy (ipilimumab) and Opdivo (nivolumab), an anti-PD-1 antibody, are now FDA approved for melanoma. The combination clearly leads to much higher response rates. At the same time, we see that 70% of patients receiving that combination treatment develop immune side effects. We're now removing two brakes on the immune system. Unfortunately, you can get side effects in which the immune system impacts tissues like the colon (and leads to colitis or diarrhea), the lung, the endocrine glands, the thyroid, the pituitary, or adrenal glands. When that happens, we have ways of treating it and dampening the immune response, but those potential side effects really do increase with some of these combination treatments.

*What about combining immunotherapies with other modalities like hormonal therapy or radiation?*

**Dr. Fong:** There have been trials combining Provenge (sipuleucel-T) with both Zytiga (abiraterone) and Xtandi (enzalutamide). Those studies show that you can combine those treatments without really impacting the effects of Provenge (sipuleucel-T).

There is some rationale in using hormonal therapy to enhance an immune response. The thinking is that through hormonal therapy you can enhance the response to Provenge (sipuleucel-T). We have a clinical trial that combines hormonal therapy with another anti-PD-1 antibody called

Keytruda (pembrolizumab) with radiation therapy. The thinking, again, is that by leveraging treatments like hormonal therapy and radiation therapy we can enhance the effectiveness of an immunotherapy, in this case, an anti-PD-1 antibody. That trial is underway. Those interested should call (415) 353-2051.

We also have a clinical trial combining an anti-PD-L1 antibody with Xofigo (radium-223). We will use an FDA-approved treatment for prostate cancer to deliver radiation therapy to the sites of prostate cancer in the bone. What we're hoping to do is kill cancer cells to release proteins in those cancer cells. The immune system can then take up those proteins and educate the T-cells to attack those proteins, thereby attacking the prostate cancer wherever it might be in the body.

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

**Dr. Fong:** The key is working on these different combination therapies. For a long time, people thought prostate cancer would not respond to anti-PD-1 antibodies, but we now have some evidence that a small proportion of patients can respond.

One of our goals is to figure out who those individuals are, but also to think about which combinations can make that treatment effective for more patients. There will be significant progress on both of those fronts over the next couple of years. PP

### *How To Get Involved...*

Patients who are interested in participating should call [415-476-3496](tel:415-476-3496) for more details.



# Darryl Mitteldorf

## Mobile App Tracks Side Effects



**Darryl Mitteldorf founded Malecare, a national men's cancer support and advocacy organization.**

*Prostatepedia* spoke with him recently about Cancergraph ([www.cancergraph.com](http://www.cancergraph.com)), a mobile app that tracks symptoms and side effects.

*How did you become involved in prostate cancer advocacy?*

Mitteldorf: In the 1990s, I was working abroad as a refugee resettlement social worker. In 1997, my dad was diagnosed with prostate cancer. I returned to the United States to help care for him. Though he lived in one of the greatest cities in the



*"Cancergraph is a mobile app for your iPhone or Android device."*



world, New York, there were no prostate cancer support groups. So I started one for him. From that one support group, Malecare grew into one of the world's most important patient advocacy organizations. As more and more psychologists and social

workers volunteered with us, we grew into a national organization offering prostate cancer support groups in the United States and then, ultimately, around the world in partnership with other country-specific patient organizations.

*What kinds of programs and services does Malecare offer?*

Mr. Mitteldorf: From working with thousands of prostate cancer patients, we learned how to optimize patient program design and psychosocial support in other male cancers, like testicular cancer and male breast cancer. While about 95% of our work is still focused on prostate cancer, about 5% includes testicular and male breast cancer. We were the first organization to start a male breast cancer support group and a male breast cancer support group network.

In the early 2000s, we developed access to healthcare and disease awareness projects for underserved communities, such as gay men diagnosed with prostate cancer. We saw how important our work was to the LGBT community. We were the first organization to offer an LGBT cancer survivor support group. We then understood the need for an organization to provide

both support and advocacy for LGBT cancer survivors and, in 2005, formed the very first LGBT cancer survivor support and advocacy program, the National LGBT Cancer Project.

In 2007, we started two additional programs. Twice As Many is focused on African-Americans, who die of prostate cancer at 2.4 times the rate that white men do in the United States and Europe.

The second program focuses on what has become the hallmark of Malecare: advanced-stage disease. We became one of the first organizations to understand that advanced-stage prostate cancer has its own unique cohort of men. One of the phrases we use is: "Men don't die from prostate cancer. They die from advanced-stage prostate cancer." We developed a dynamic program led by Joel Nowak for men with advanced-stage disease. That has been an extraordinary contribution to the world of psycho-oncology.

Malecare is also known for its research unit, which has produced numerous peer-reviewed journal articles, abstracts, and conference presentations. Malecare even has a patent on a nuclear medicine device and a method to reduce secondary tumor formation from external radiation

therapy, including IMRT (intensity-modulated radiation therapy) for prostate cancer.

You can see most of our work via our website, [www.malecare.org](http://www.malecare.org), including links to our online support groups and ways to sign up for in-person groups and patient advocacy initiatives.

### *What is Cancergraph?*

**Mr. Mitteldorf:** Cancergraph is a mobile app for your iPhone or Android device.

Cancergraph is our solution to reducing the difficulty cancer survivors have in recalling which symptoms and side effects they experience between doctor appointments. For typical patients, there are several weeks to months between appointments. When patients sit in the oncologist's office, they're challenged to remember each time they vomited, each time they had a hot flash, where and when their aches and pains were, when things were going well, and when things were really going badly. It's impossible to remember. And very few people are good about keeping a written diary.

Cancergraph allows you to instantly record what is going on at any time of day or night, no matter where you are. You can input up to five of 200 symptoms and side effects relative to 119 cancer types and all available treatments and medications. It takes less than 90 seconds to set up and less than three seconds to use. Cancergraph is currently used by thousands of prostate cancer patients, and they are using it well.

For example, if you were to experience nausea in the middle of the night, after you go to the bathroom, you press one button on your iPhone or Android to record the time, day, severity, and your location of a particular side effect or symptom. (Location is important



*“You can input up to five of 200 symptoms and side effects relative to 119 cancer types”*



because altitude may impact particular side effects. Also, where you experience a side effect is important: in your home, in a specific room, away from home, in transit, or on the way to an occasion.)

It takes more effort to clean up after your nausea than it does to use Cancergraph to record your nausea.

You don't have to tell the app the time of day or day of the week.

It knows. You don't have to tell the app where you're standing: you just tap what you're experiencing and you're done. The app generates everything.

And it's fun to use. You watch the app create the graph. You toggle any of the different symptoms or side effects to see relationships between them at different times of day. The more data you put in, the more fun it becomes. You can enjoy your life while creating data that will extend your life.

### *How do you send the data to your doctor?*

**Mr. Mitteldorf:** Once you are ready for an appointment, you either email the report to your doctor or print the report yourself and hand it to your doctor.

By creating a graph and a dataset your doctor already understands, Cancergraph makes your doctor-time more useful, and, most importantly, more about you. You control all of your data, all of the time. You can delete everything, anytime, anywhere.

We'll soon offer a web-based version of Cancergraph, where de-identified data generated by tens of thousands of Cancergraph users will create real-time, rigorous reporting on how medications and treatments affect patient quality of life. There are many similar-sounding websites, but none are based on real-time data.

Now, imagine if your doctor could understand what you were going through 24 hours a day, seven days a week—whenever he or she wanted to check in on you? You may not call your doctor to say you're experiencing severe pain, but the app may tell him or her for you—with your permission. Your doctor could then contact you to say, “Come into the office tomorrow morning because your medication isn't working.” Cancergraph is working on that with an anticipated Fall 2017 release.

Health doesn't take place in your doctor's office. It takes place in your life. The ability to examine you *while* you are living your life will be a complete game changer. Today, we can only do this in a hospital setting or under a clinical trial with a lot of patient intervention. But to do this without interfering with your life? That is an entirely new way to do medicine.

### *Is Cancergraph available for iPad and tablet?*

**Mr. Mitteldorf:** Cancergraph is optimized for smartphones because that is what most people have in their pocket or on their bedside table, but it does work on iPad and Android tablets.

### *Is Cancergraph free to download?*

**Mr. Mitteldorf:** Yes. It is entirely free. Just go to the iPhone App Store or the Google Play Store for Android and download it for free. Cancergraph is financed entirely by donations to Malecare. 



# Patients Speak

## Using Provenge

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*Todd Seals (www.toddseals63.blogspot.com) is a prostate cancer survivor.*

*Prostatepedia* spoke with him recently about his prostate cancer journey and his experiences with the prostate cancer vaccine Provenge (sipuleucel-T).

*How did you find out you had prostate cancer?*

**Mr. Seals:** I was 42 years old. I thought I had sciatica. I had quite a bit of pain going down my glutes and right leg. I had been going to a chiropractor. Then I started urinating blood. I knew something was wrong, so I went in for a urinalysis.

Nine months before the urinalysis, I was diagnosed with pneumonia and



*“I didn’t know anything about prostate cancer.”*



I went in for a chest x-ray. They said, “We noticed a spot that is probably a pulmonary nodule. They’re really common. It’s probably nothing to worry about, but you should have it checked.” All I heard was, “It’s a pulmonary nodule. It’s nothing to worry about.” I never had it checked.

When I told that story to my doctor after he got my urinalysis results, he sent me in for a chest x-ray. My lungs looked like swiss cheese. Both lungs were covered with lesions—small tumors two to five centimeters in diameter.

I then had a PSA test: it was 3,216.

I went to work the next day. My doctor called me at work. I was a couple hundred feet up on a catwalk when he said, “Mr. Seals, I don’t know how to tell you this, but you have cancer.”

He told me to come in. He gave me a Lupron (leuprolide) shot and started me on Casodex (bicalutamide) that day. From what I understand, it isn’t common practice to start both of those drugs. (You usually start Casodex first.) But I didn’t know anything about prostate cancer. I thought it was an old man’s disease. My grandpa had it. He lived 30 years with prostate cancer and died of something else. I always thought prostate cancer was the good cancer. That was a mistake.



To put it mildly, it was a really bad day. I'm a hick from the sticks. My town has 400 people. This is a logging and mill area. There are a lot of clear-cuts where they cut down all the trees and replant.

I drove out to the middle of a clear-cut the day after my diagnosis and I started telling God what an asshole he was. I was just yelling and crying. That went on for about an hour. I sat there for the longest time. I listened to the birds and watched the sunset. A black bear comes walking up the end of the road. He stopped about 25 feet away, looked at me, and then he wandered on. He wasn't in any hurry.

I used to be a youth leader in my church. Then I joined a rock band. In times of crisis, we reach out and a lot of us reach out to God. I dusted off my Bible, opened it, and read two verses. Psalm 103:2-3: "Bless the lord, O my soul...He who forgives my sins and heals my body of all its diseases."

After that, my doctor set me up with a urologist and an oncologist. The next few weeks were a whirlwind: CAT scans and bone scans and biopsy. You know the drill.

My Gleason scores came back 3s and 4s. I was a 7. My oncologist said this is not the most aggressive. He said, "We're going to treat you. We're going to do what we can for you."

During that time period, I used to go to sleep at night wondering what it was going to feel like to die. I made peace with it. It's weird, but cancer changed my life in a lot of ways and I would say 85% of it was for the better. I'm a better person. I'm a better friend. I'm a better husband. I'm a better father. I know how precious life is. I enjoy life now. I really live my life. I figure one of these days, I'm going

to come sliding through the gates of heaven all banged up and say, "Damn, that was a hell of a ride!" That's my plan.



*"I'm a better friend.  
I'm a better husband.  
I'm a better father."*



Two weeks after my initial PSA, and two weeks after starting Lupron (leuprolide) and Casodex (bicalutamide), my urologist wanted to do another PSA test. He couldn't believe my initial PSA was that high; he hoped it was a mistake. It came back at 2,900 or something. It had already fallen a couple of points in just a couple of weeks. It dropped pretty quickly.

At the time, I was in a new relationship with my now-wife. I told her, "You didn't sign on for this. I understand." She wouldn't hear any of it.

I got my PSA checked every month. Every month it dropped. It continued dropping and dropping. After a year, it reached undetectable levels.

They rescanned me. My chest was clear. Before treatment, I had bone metastasis, lymph node metastasis, and lung metastasis. My oncologist had speculated that I probably had brain metastasis because things were happening to my vision, but they never did a brain scan so it was unconfirmed. Do you remember black and white TVs? Remember how when you'd shut the black and white TV off, the picture would shrink down to that little dot in the middle and then just disappear? That is what my vision was doing.

It would just contract and contract and contract until I could only see a pinhole of light. That would last about 45 minutes and then it would go away.

On my one-year anniversary, I went to see my oncologist. He said, "It's been a year. Because it's been a year, I'm going to tell you now what I wouldn't tell you then. I didn't think you'd be here." He said, "You were really sick. I'm amazed by your result."

*How was it suggested that you go on Provenge (sipuleucel-T)?*

**Mr. Seals:** I was on the night shift. (I have continued to work. I work 50 to 60 hours a week.) When I work the night shift, there is not very much to do. I had a lot of downtime to search the web.

I was diagnosed in 2006. In 2007, they were shooting for FDA approval of Provenge (sipuleucel-T). Because all I did was search the web about prostate cancer, I was in the know about it. I was really excited. I cried when it didn't receive FDA approval. They went for another Phase III clinical trial. I was following it the entire time. I knew that once I became hormone refractory, I wanted to go on Provenge (sipuleucel-T). It made sense to me to have my immune system firing on all cylinders, doing what it could to help fight this disease. For me, in my heart, Provenge (sipuleucel-T) was my next treatment of choice.

I was on hormone therapy for three and a half years before my doctor said we're going to give you a break from the hormones to see what happens. I took a yearlong vacation from hormonal therapy.

At the end of that year, my PSA had risen up to about 10 or 11. I asked



if we could try an old treatment—diethylstilbestrol (DES). We did. That was a big mistake. I went from a no-cup to an A-cup and then to a B-cup. I had to have my chest radiated. That only lasted about six months. Then I went back on Lupron (leuprolide) and my PSA continued to rise. A CAT scan revealed the lung nodules were starting to come back.

I told my doctor I wanted to use Provenge (sipuleucel-T). At first, he was all for it, but the oncology board disagreed. They said I couldn't have Provenge (sipuleucel-T). I was crushed for about 10 minutes, then I decided to fight.



*“There are too many patients and not enough doctors.”*



Why did they deny me Provenge (sipuleucel-T)? I had a lung metastasis, but the Centers for Medicare and Medicaid Services (CMS) had just taken away the lung metastasis exclusion. I was no longer excluded because I had that one nodule in my lungs.

My oncologist said, “You’re too young. It’s not going to work for you. There is new scientific evidence.” He pointed to an article by Marie Huber that compared the treatment to a faulty placebo. He told me it wasn’t going to work; I was going to die. It was ugly. We would have screaming matches on the phone. This went on and on. I filed appeal after appeal after appeal.

I’m not afraid of chemotherapy. When the time is right, I have no

qualms about doing chemotherapy, but the time wasn’t right.

I was adamant that I was going to get Provenge (sipuleucel-T). I appealed all the way to the Washington State Insurance Commissioner.

In the meantime, I had a plan B. I found a doctor in Las Vegas named Nicholas Vogelzang (see *Prostatepedia* May 2016 for an interview with Dr. Vogelzang) who said he would prescribe. I contacted the patient assistance people at Dendreon, the makers of Provenge. Nick was going to prescribe once my appeal process had been exhausted; patient assistance would then kick in. We made an appointment for the last week of April 2012.

Two days before we were supposed to leave for Las Vegas, the Washington State Insurance Commissioner ruled in my favor.

In the meantime, because I wasn’t going to go on any other treatment until I had Provenge (sipuleucel-T), I watched my PSA double every six weeks. By the time I got Provenge (sipuleucel-T), my PSA was up to 100.

We kept the appointment with Nick. We spent four days in Las Vegas. We had a ball. The rest is history.

I had the first leukapheresis on May 1 and finished Provenge (sipuleucel-T) on June 3.

*What was the process of getting Provenge (sipuleucel-T) like?*

**Mr. Seals:** It had ups and downs. In most aspects, it was the easiest treatment I’ve done. There was really only one hiccup: the Red Cross nurse wanted to make sure I was comfortable while I was going through the pheresis process, so she turned the blood heater





up so I'd be nice and warm. I've been on Lupron (leuprolide) for five years. I had hot flashes from hell. I thought I was going to die right there. They almost aborted the pheresis process because I was freaking out, but as soon as she turned the blood heater off everything calmed down. That was the only hiccup.

The pheresis process took almost four hours. The hardest part was that I had to hold my arms still with a needle in each one. I couldn't move my arms. I just sat there and watched movies and talked to my wife and my mom and dad.

I never experienced any other side effects than the fatigue after my first infusion. I slept for 24 hours. I think part of it was stress. My wife kept checking on me to make sure I was breathing. (She's a nurse.)

This probably isn't scientific, but I literally felt better after the first infusion. I know it doesn't work like that. Maybe it was positive thinking, but I felt better.

I got 17 side effect-free, progressive months. I probably could have gotten more. My PSA was rising slowly prior to treatment—doubling every six weeks. Post-Provenge (sipuleucel-T), my PSA continued to rise, but it took four months to rise 40%, so the treatment slowed progression.

I've now been on Zytiga (abiraterone) for 36 months. My scans are clean. My PSA is less than 0.05.

*Do you have any advice for men considering Provenge (sipuleucel-T)?*

**Mr. Seals:** Don't take no for an answer. If your doctor won't prescribe it, find a doctor who will.

Don't be afraid of a second opinion, even if you trust your doctor.



*“When people hear they have cancer, they either put on their gloves and step into the ring or they grab a shovel and dig a hole in the backyard.”*



It's important to be your own advocate. Doctors don't have time for us. They're overwhelmed. There are too many patients and not enough doctors. And they certainly don't have time to research everything coming down the pipeline. Educate yourself.

*If you hadn't done all that research you might not have known about Provenge (sipuleucel-T)...*

**Mr. Seals:** Exactly.

On my wedding day, I promised Amanda 30 years. That's a big promise. Provenge (sipuleucel-T) is part of the reason I believe I'm going to make it.

Hope is the most powerful weapon in our arsenal. I grew up in the 1970s. I was a tweener when Richard Nixon declared war on cancer. For the next half a dozen years, all these cancer movies came out in which the star always died at the end. I grew up believing that if you had cancer, you died. We have to change that message. We have to instill hope.

When people hear they have cancer, they either put on their gloves and step into the ring or they grab a shovel and dig a hole in the backyard. You can fight this disease. It doesn't have to be a death sentence. 





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

**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.

**FIND OUT HOW YOU CAN  
FIGHT BACK.**

**Talk to your doctor and visit  
[XTANDI.com/info](https://www.xtandi.com/info)**

### 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](http://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](http://XTANDI.com).**

**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.

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XTANDI is not for use in women.

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**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](http://www.Xtandi.com) or call 1-800-727-7003.

**What are the ingredients in XTANDI?**

**Active ingredient:** enzalutamide

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

**Manufactured by:**

Catalent Pharma Solutions, LLC, St. Petersburg, FL 33716

**Marketed by:**

Astellas Pharma US, Inc., Northbrook, IL 60062

Medivation Inc., San Francisco, CA 94105

14L082-XTA-BRFS

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

Revised: August 2015

# Prostatepedia<sup>1</sup>

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#### WHAT IS ZYTIGA® (abiraterone acetate)?

ZYTIGA® is a prescription medicine that is used along with prednisone. ZYTIGA® is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

#### IMPORTANT SAFETY INFORMATION

##### Who should not take ZYTIGA® (abiraterone acetate)?

Do not take ZYTIGA® if you are pregnant or may become pregnant. ZYTIGA® may harm your unborn baby. Women who are pregnant or who may become pregnant should not touch ZYTIGA® without protection, such as gloves.

ZYTIGA® is not for use in women or children. **Keep ZYTIGA® and all medicines out of the reach of children.**

##### Before you take ZYTIGA®, tell your healthcare provider if you:

- Have heart problems
- Have liver problems
- Have a history of adrenal problems
- Have a history of pituitary problems
- Have any other medical conditions
- Plan to become pregnant (**See “Who should not take ZYTIGA®?”**)
- Are breastfeeding or plan to breastfeed. It is not known if ZYTIGA® passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA® or breastfeed. You should not do both. (**See “Who should not take ZYTIGA®?”**)
- Take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZYTIGA® can interact with many other medicines.

##### If you are taking ZYTIGA®:

- Take ZYTIGA® and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA® one time a day. Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA® or prednisone without talking to your healthcare provider first.
- Take ZYTIGA® on an empty stomach. **Do not take ZYTIGA® with food.** Taking ZYTIGA® with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA®.
- Swallow ZYTIGA® tablets whole. Do not crush or chew tablets.
- Take ZYTIGA® tablets with water.
- Your healthcare provider will do blood tests to check for side effects.
- Men who are sexually active with a pregnant woman must use a condom during and for one week after treatment with ZYTIGA®. If their female partner may become pregnant a condom and another form of birth control must be used during and for one week after treatment with ZYTIGA®. Talk with your healthcare provider if you have any questions about birth control.
- If you miss a dose of ZYTIGA® or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.

##### ZYTIGA® may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia), and fluid retention (edema).**

He spent 35 years fighting dangerous fires.

RETIREMENT WON'T CHANGE WHO HE IS.  
NEITHER WILL

**ADVANCED PROSTATE CANCER.\***

IF YOU THINK YOUR TREATMENT OPTIONS ARE LIMITED, THINK AGAIN.

\*ZYTIGA® is a prescription medicine used along with prednisone to treat metastatic castration-resistant prostate cancer, a type of advanced prostate cancer that is resistant to medical (eg, hormonal) or surgical treatments that lower testosterone and has spread to other parts of the body.

...talk to your doctor to see if ZYTIGA® is right for you.

once-daily

 **Zytiga**®  
(abiraterone acetate)  
250 mg tablets

Tell your healthcare provider if you get any of the following symptoms:

- Dizziness
- Feel faint or lightheaded
- Confusion
- Pain in your legs
- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems.** You may develop changes in liver function blood tests. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA® and during treatment with ZYTIGA®. Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - Yellowing of the skin or eyes
  - Darkening of the urine
  - Severe nausea or vomiting
- The most common side effects of ZYTIGA® include:
  - Weakness
  - Joint swelling or pain
  - Swelling in your legs or feet
  - Hot flushes
  - Diarrhea
  - Vomiting
  - Cough
  - High blood pressure
  - Shortness of breath
  - Urinary tract infection
  - Bruising

- Fast heartbeats
- Headache
- Muscle weakness
- Swelling in your legs or feet

- Low red blood cells (anemia) and low blood potassium levels
- High blood sugar levels, high blood cholesterol and triglycerides
- Certain other abnormal blood tests

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 ZYTIGA®.**

**FOR MORE INFORMATION, ASK YOUR HEALTHCARE PROVIDER OR PHARMACIST.**

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ZYTIGA® can interact with other medicines.

You should not start or stop any medicine before you talk with the healthcare provider who prescribed ZYTIGA®.

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

Call your doctor for medical advice about side effects. You are encouraged to report negative side effects of prescription drugs to the FDA.

Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088 (1-800-332-1088).

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Horsham, PA 19044 USA  
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**PATIENT INFORMATION**  
**ZYTIGA® (Zye-tee-ga)**  
**(abiraterone acetate)**  
**Tablets**

Read this Patient Information that comes with ZYTIGA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**What is ZYTIGA?**

ZYTIGA is a prescription medicine that is used along with prednisone. ZYTIGA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

ZYTIGA is not for use in women.

It is not known if ZYTIGA is safe or effective in children.

**Who should not take ZYTIGA?**

Do not take ZYTIGA if you are pregnant or may become pregnant. ZYTIGA may harm your unborn baby.

Women who are pregnant or who may become pregnant should not touch ZYTIGA without protection, such as gloves.

**What should I tell my healthcare provider before taking ZYTIGA?**

**Before you take ZYTIGA, tell your healthcare provider if you:**

- have heart problems
- have liver problems
- have a history of adrenal problems
- have a history of pituitary problems
- have any other medical conditions
- plan to become pregnant. See **“Who should not take ZYTIGA?”**
- are breastfeeding or plan to breastfeed. It is not known if ZYTIGA passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA or breastfeed. You should not do both. See **“Who should not take ZYTIGA?”**

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZYTIGA can interact with many other medicines.

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

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

**How should I take ZYTIGA?**

- Take ZYTIGA and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA 1 time a day.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA or prednisone without talking with your healthcare provider first.
- Take ZYTIGA on an empty stomach. **Do not take ZYTIGA with food.** Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA.
- Swallow ZYTIGA tablets whole. Do not crush or chew tablets.
- Take ZYTIGA tablets with water.
- Men who are sexually active with a pregnant woman must use a condom during and for 1 week after treatment with ZYTIGA. If their female partner may become pregnant, a condom and another form of birth control must be used during and for 1 week after treatment with ZYTIGA. Talk with your healthcare provider if you have questions about birth control.
- If you miss a dose of ZYTIGA or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.
- Your healthcare provider will do blood tests to check for side effects.

### What are the possible side effects of ZYTIGA?

#### ZYTIGA may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema).** Tell your healthcare provider if you get any of the following symptoms:
  - dizziness
  - fast heartbeats
  - feel faint or lightheaded
  - headache
  - confusion
  - muscle weakness
  - pain in your legs
  - swelling in your legs or feet
- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems.** You may develop changes in liver function blood test. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA. Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - yellowing of the skin or eyes
  - darkening of the urine
  - severe nausea or vomiting

#### The most common side effects of ZYTIGA include:

- weakness
- joint swelling or pain
- swelling in your legs or feet
- hot flushes
- diarrhea
- vomiting
- cough
- high blood pressure
- shortness of breath
- urinary tract infection
- bruising
- low red blood cells (anemia) and low blood potassium levels
- high blood sugar levels, high blood cholesterol and triglycerides
- certain other abnormal blood tests

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 ZYTIGA. 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 ZYTIGA?

- Store ZYTIGA at room temperature between 68°F to 77°F (20°C to 25°C).

### Keep ZYTIGA and all medicines out of the reach of children.

### General information about ZYTIGA.

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

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

For more information, call Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or go to [www.Zytiga.com](http://www.Zytiga.com).

### What are the ingredients of ZYTIGA?

**Active ingredient:** abiraterone acetate

**Inactive ingredients:** colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

**Manufactured by:** Patheon Inc. Mississauga, Canada

**Manufactured for:** Janssen Biotech, Inc. Horsham, PA 19044

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