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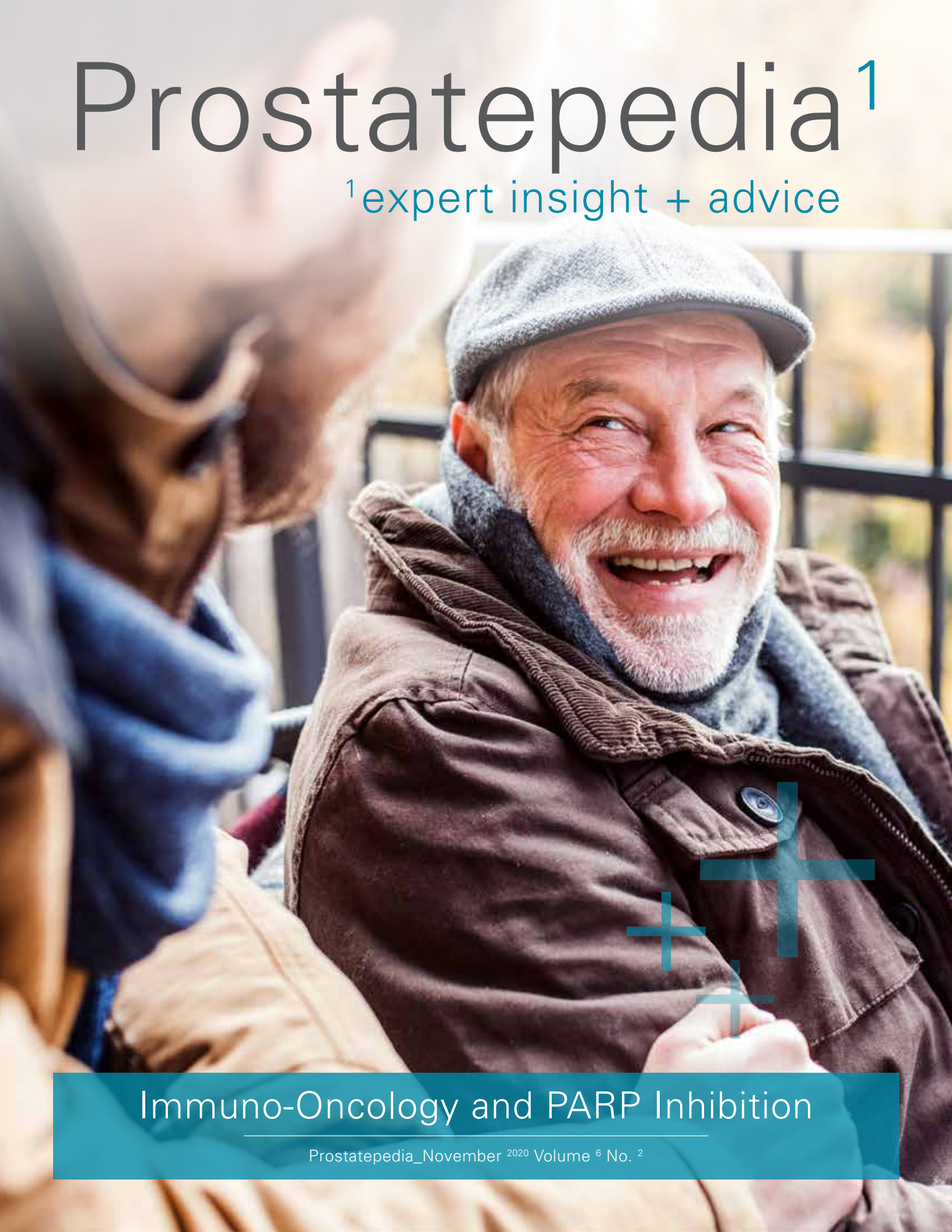

Immuno-Oncology and PARP Inhibition

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In this issue....

Three topics dominate this issue: the current status of the Provenge (sipuleucel-T) vaccine, the status of other immunotherapy techniques under development, and the use of poly ADP ribose polymerase (PARP) inhibitors. Behind these specific topics, this issue illustrates how the treatment paradigm has been shifting. Prostate cancer treatment selection has traditionally been done without knowledge of the specific molecular characteristics of a given patient's cancer. The revolution in molecular biology increasingly allows a clinician to test for these molecular changes and then tailor the treatment to the patient and his cancer. These techniques are also providing other benefits. We now know some of the mechanisms that allow prostate cancer to evolve resistance to existing treatment options. This knowledge then leads to new drug development or new approaches to immunotherapy. One example of this is the new generation of antiandrogens, starting with Zytiga (abiraterone acetate) and Xtandi (enzalutamide).

PARP inhibitors are a new class of drugs that are a direct outcome of research on molecular changes that have a profound impact on prostate cancer biology. This story starts with the discovery of gene mutations associated with familial breast cancer: breast cancer type 1 and type 2 susceptibility proteins. These are abbreviated as BRCA-1 and BRCA-2. These two proteins are involved in DNA repair, and when they are inactivated by mutations, DNA repair is less efficient, leading to a greater likelihood that cancer-causing mutations will develop. In cells with BRCA-1 or -2 mutations, some residual DNA repair does take place using the PARP. This allows sufficient DNA repair for the cancer cell to survive. If PARP is also inactivated, the cancer cell dies. This led to the development of drugs to inhibit PARP. These drugs proved to be more useful in BRCA-1 or -2 mutant ovarian rather than breast cancer and are now standard in the treatment of ovarian cancer.

Studies have shown that men who inherit mutationally inactivated BRCA-2 are at increased risk of developing prostate cancer. These cancers tend to be very aggressive, rapidly becoming resistant to hormonal therapy and are associated with short survival. BRCA-2 mutations are relatively uncommon in men with newly diagnosed prostate cancer, but they become more common as the cancer progresses through standard treatments. Clinical trials have shown that PARP inhibitors have useful activity against prostate cancer that has mutations in BRCA-2 and other DNA repair mutations. As a result, PARP inhibitors are now approved for the treatment of prostate cancer.

As discussed by several interviewees, there are reasons to think that combining PARP inhibitors with immunotherapy might prove beneficial.

This issue also contains information about which patients are most likely to benefit from Provenge (sipuleucel-T). In general, patients with less extensive disease and a slower prostate-specific antigen (PSA) doubling time tend to do better.

Finally, a range of potentially new approaches to immunotherapy of prostate cancer are discussed. If you fit the eligibility requirements, you might want to consider entering one of the clinical trials.

Charles E. Myers, Jr., MD

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Andrew Armstrong, MD
Immunotherapy Today

Dr. Andrew J. Armstrong is Professor of Medicine and Surgery and Associate Professor in Pharmacology and Cancer Biology at the Duke Cancer Institute.

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

Can you tell us about Provenge (sipuleucel-T)? What is it and what is it used for?

Dr. Andrew Armstrong: Provenge (sipuleucel-T) has been around for a decade and is a cellular product. It's like a treatment vaccine. A prostate cancer-specific protein called prostatic acid phosphatase (PAP) is used to immunize a patient against his own cancer, which commonly expresses PAP. The patient has blood drawn, and then these immune cells are stimulated outside of his body by PAP, which, when combined with an immune stimulant called granulocyte macrophage colony-stimulating factor (GM-CSF), revs up the antigen-presenting machinery that is in the immune system to present those antigens to the T cells in his body once it's reinfused, like a blood transfusion. Those T cells can then engage the cancer directly. It's a complicated process that happens over a short amount of time. The bottom line is that patients with metastatic prostate cancer can live longer when they receive this immune therapy. The magnitude of the survival benefit associated with Provenge (sipuleucel-T) is the same as the

"The bottom line is that patients with metastatic prostate cancer can live longer when they receive this immune therapy."

magnitude of the survival benefit that you see with chemotherapy and newer hormonal inhibitors. Provenge (sipuleucel-T) remains the only FDA – approved immunotherapy in prostate cancer available broadly in the United States, unlike immune checkpoint inhibitors which only work in a small subset of men.

Is the process painful or difficult for patients?

Dr. Andrew Armstrong: It's not painful. It involves going to a Red Cross center, where you donate the blood through a peripheral vein, which takes four to five hours. The blood is run through a pheresis machine, and most of the blood is simply returned to the patient. But the white blood cells, those immune cells, are filtered out. About 1% of the circulating white blood cells are taken from the patient during that pheresis procedure. It's a negligible effect on the patient's white blood cell count, so it's not an immune suppressive treatment. You're donating some white blood cells, but you get them back three days later.

Those white blood cells are flown down to a laboratory. The laboratory then expands the white blood cells, mixes them with PAP-GM-CSF, and then they're flown back to the center where the patient receives the infusion in a treatment room, which takes an hour. It's not a particularly toxic therapy. There's little in the way of pre-medications or side effects when you're receiving it. Much like a blood transfusion, some patients will have low-grade fevers and chills. It's rare, but it can happen. But most of the time, those resolve within 12 hours and the patient feels the same. One

of the biggest risks of Provenge (sipuleucel-T) is that some patients don't have very good intravenous access and have to get a central catheter.

Was there any delay in the delivery of Provenge (sipuleucel-T) during COVID-19?

Dr. Andrew Armstrong: Since patients were afraid to leave their homes, patients were often getting virtual visits during the peaks of COVID-19. During that time, there was a period where it was not advisable to go to Red Cross centers, or even your doctor's office if it could be avoided. We didn't stop prostate cancer care during COVID-19, but there were certain patients that could safely defer things like Provenge (sipuleucel-T) for a few months. Now, the safety precautions put into place in hospitals and Red Cross centers reduce the risk of COVID-19, but there remains some ongoing risk until this pandemic ends.

Does Provenge (sipuleucel-T) increase survival?

Dr. Andrew Armstrong: Yes, based on two randomized trials which led to the USFDA approval in 2010. It's an immunotherapy and does not suppress the immune system, it activates it. It doesn't predispose to any bacterial infections like chemotherapy does, but it improves survival to the same degree. Having a catheter can raise the risk of infection, however, so precautions are needed for these men.

When is it used, and in which men?

Dr. Andrew Armstrong: It's most commonly used before chemotherapy. In men who have hormone resistant or castration resistant disease, their disease is progressing despite

hormone therapy since they have metastatic disease. A common question is, "I have localized disease, can I get Provenge (sipuleucel-T)?" The answer is no, but an ongoing trial called ProVent is studying this immune therapy in very early localized prostate cancer to see if this can be effective at reducing the need for surgery or radiation. Currently, Provenge (sipuleucel-T) is only approved for men with metastatic disease whose disease is progressing despite hormone therapy.

Another common question is, "Can I get it at the same time as Zytiga (abiraterone acetate) or Xtandi (enzalutamide)?" Yes, we have shown that this is safe, and you see a similar immune response whether you're taking it concurrently with these other androgen receptor (AR) inhibitors; however, Prednisone use may lower the immune response somewhat, and avoiding immune suppressive medications during Provenge (sipuleucel-T) is recommended.

We try to give Provenge (sipuleucel-T) by itself, if possible, with ongoing androgen deprivation therapy (ADT), and then move on to one of these AR inhibitors. Or, if you have a patient who is rapidly progressing and needs an AR inhibitor, you give the AR inhibitor and you can still give Provenge (sipuleucel-T) once the patient has had a good response to therapy. Because Provenge (sipuleucel-T) does not reduce prostate-specific antigen (PSA) or provide disease control in the short term, using an AR inhibitor concurrently in some men can be helpful, while still offering the long-term survival benefits of Provenge (sipuleucel-T).

Is it ever combined or sequenced with chemotherapy?

Dr. Andrew Armstrong: No. Chemotherapy like Docetaxel (taxotere) or Jevtana (cabazitaxel) is immune suppressive and was explicitly excluded in the phase III impact study that led to the FDA approval of Provenge (sipuleucel-T). However, Provenge (sipuleucel-T) can be given in some select men who have completed chemotherapy and are off immune suppressive medications.

What can you tell us about the data related to Black men and Provenge (sipuleucel-T)?

Dr. Andrew Armstrong: The Provenge Registry for the Observation, Collection, and Evaluation of Experience Data (PROCEED) of over 1,500 patients across the United States was established as a requirement by the FDA to be inclusive of Black patients and to track the safety and long-term efficacy of Provenge (sipuleucel-T). From the PROCEED registry, we published a paper that compared Black men to White men who had metastatic castration resistant prostate cancer and were treated with Provenge (sipuleucel-T). Matched for the same PSA level, we showed that Black men survive more than one year longer compared to White men, which is a very interesting finding. This benefit in Black men was observed in the original IMPACT phase III trial, but needed confirmation.

We adjusted for all sorts of other patient and tumor characteristics that might explain that result, but the improved survival in Black men stood up statistically in our model. It made us think that there could be a difference with other immune therapies by race and ancestry. Now, we're looking at how to explain the longer survival by Black men over White men and whether we can learn from that and improve the

response to immune therapy based on that biologic understanding. We do not know if differences in outcome may be related to race-related differences in immune responses, in tumor biology, in exposures, in patient factor, or in access to care or subsequent treatments, but we are exploring all of these possibilities.

Does that mean you would choose immunotherapy over other options when treating Black men with prostate cancer?

Dr. Andrew Armstrong: I look at Provenge (sipuleucel-T) as being complementary to existing therapies rather than replacing them. I'm offering Provenge (sipuleucel-T) to all men who meet the criteria for it, and there is a survival benefit regardless of race. But it is particularly important for Black men to receive this treatment since the magnitude of the survival benefit is even greater than what we'd expect with chemotherapy. It doesn't replace other therapies like hormonal therapy or chemotherapy since Provenge (sipuleucel-T) doesn't cure prostate cancer and the disease continues to progress despite this therapy. These men still need to go on to other therapies. But it might factor into your decision of which treatment to give first, and in preference to others.

In our practice in Durham, North Carolina, about 25% of our men with prostate cancer are Black. Provenge (sipuleucel-T) is an important treatment for those patients who are eligible. It's not the only treatment they'll get, and we follow national guidelines to offer all proven therapies in additional to a large portfolio of clinical trial options. But we want to make sure that we're not excluding patients based on race. Black men

are disproportionately affected by lethal prostate cancer, so it's good news that survival is better with this treatment.

Are you looking more closely at genomics and genetics in immunotherapy in response to that information?

Dr. Andrew Armstrong: We are. There are already some clues as to which patients with prostate cancer have extraordinary responses to immune checkpoint inhibition. These are the programmed cell death protein 1s (PD-1s) like Keytruda (pembrolizumab) and Opdivo (nivolumab). The FDA has approved these drugs broadly in patients who have microsatellite instability-high (MSI-H) prostate cancer, 3% to 6% of all patients. Some of those patients have hereditary types of prostate cancer with colorectal cancer, also known as Lynch syndrome. For others, it's unique to their tumor, so tumor testing using next-generation sequencing (NGS) panels can be helpful. We have also recently published some data on other genomic alterations in prostate cancer that may help the immune response, such as CDK12 and LRP1B.

"We're looking at how to explain the longer survival by Black men over White men and whether we can learn from that and improve the response to immune therapy based on that biologic understanding."

This past year, we have studied two potential other subsets of prostate cancer that might respond well to immune therapies. One is a genetic type called CDK12, where that gene is deleted in 6% to 7% of prostate cancers. It's not hereditary, it's just in the tumor. We have two multi-institutional studies in the *Journal of Clinical Oncology, Precision Oncology (JCO PO)* that came out this year. These large, multicenter studies showed that this subgroup of patients had a better response to these immune checkpoint inhibitors, at a rate of about three to four times that of unselected men with metastatic prostate cancer. This work is now undergoing prospective validation in clinical trials of immunotherapy, but this early data suggests that CDK12 altered metastatic prostate cancer is a unique subtype that is immune responsive.

The second one that we've identified is a gene mutation called LRP1B. We showed that when patients have this gene mutated or deleted in their cancer, they have a better response and survival with immune checkpoint inhibition. That was true not just in prostate cancer, but all solid tumors as we reported at this year's American Society of Clinical Oncology (ASCO) 2020) in June. This gene is altered in 6% to 7% of patients with prostate cancer but is actually more commonly altered in lung cancer and many other solid tumors. Altogether, there are some unique genetic subtypes of prostate cancer that we already know could respond better. What the field is trying to understand is how you might broaden that impact to a much bigger list of patients. When you just use a PD-1 inhibitor broadly, it only works 6% to 7% of the time. The field is doing clinical trials to look at different combinations like chemotherapy and immune checkpoint, poly ADP ribose polymerase (PARP) inhibitors and immune checkpoint, and AR inhibitors and immune checkpoint. These are large phase III studies, a tremendous investment in science to understand which of these combinations might turn out to be the best. Within those studies, we're going to learn whether there are subgroups defined by certain mutations that have an even better outcome.

A final alteration found in some men is the tumor mutation burden (TMB), which adds up the number of alterations identified. When TMB is high, it makes the tumor more foreign to the immune system. The immune system is able to recognize it, and with these immune therapies, the outcomes appear to be better. The FDA has granted a broad approval to Keytruda (pembrolizumab) for solid tumors that have TMB above 10 to get this therapy. Prostate cancer doesn't tend to have a lot of mutations in it, unlike melanoma or lung cancer, but it's an important subset for the testing, and not all of these tumors meet other criteria like MSI high disease.

Tell us more about the PARP inhibitors and the immune checkpoint inhibitors.

Dr. Andrew Armstrong: PARP inhibitors just received FDA approval this summer. Lynparza (olaparib) and Rubraca (rucaparib) are approved for prostate cancer. They're only approved for men who have certain mutations, like the BRCA2 gene. Lynparza (olaparib) has a broad full approval based on improved survival in men with

homologous repair deficiencies, either inherited or acquired in the tumor, and indicates now the need for testing in all men with metastatic prostate cancer. These DNA repair defects in many cases predispose to a great response to PARP inhibition that can be durable in some men for longer than a year. These patients might respond well to the immunotherapies as well given that PARP inhibition can lead to higher mutational rates and recognition by the immune system. There's some preliminary data that the combination with PARP inhibitors has a higher response rate, but only randomized studies will prove that. There is an ongoing phase III trial called KEYLYNK-010 testing whether combining Keytruda (pembrolizumab) with Lynparza (olaparib) improves survival over second line hormonal therapy in men with metastatic castration resistant prostate cancer. This trial is open to men irrespective of their genotype.

We're also planning to launch a chemo immunotherapy clinical trial, which will have a combination for neuroendocrine disease of chemotherapy and an immune checkpoint strategy. That strategy is commonly done in lung cancer, and it works beautifully, resulting in better survival. More to come on that later!

Are there any other trials that you've got your eye on?

Dr. Andrew Armstrong: One to look out for is the VISION study. This is an immunotherapy. It uses an antibody that binds to prostate-specific membrane antigen (PSMA). Instead of it just being a passive immunotherapy, it's loaded with a warhead of Lutathera (lutetium Lu 177 dotatate), a radioactive particle. When I'm communicating with patients, I call it a "smart bomb." It's not a dirty bomb like chemotherapy, which broadly attacks all rapidly dividing cells and can result in hair loss, marrow suppression, nausea, and other side effects. It goes right to where PSMA is, which is the tumor. It's safe and well-tolerated with a good quality of life. There can be some reduction in platelets and dry mouth and dry eyes, but overall it is tolerated well by patients. The VISION phase III trial is testing six doses of this therapy compared to the best treatments that we have in this more refractory group of patients. We'll probably hear about that study's results next year.

Is there anything else you want to call attention to for patients?

Dr. Andrew Armstrong: There are a lot of novel immunotherapies. Seeking an opinion at an academic medical center if you have castration resistant or metastatic disease is important since you're going to see a wide range of options, whether it's one of these combination trials or other innovative immunotherapies. It is important to ask to have your tumor and your DNA sequenced for mutations that may open the door to trials or proven therapies and which may impact you and your family in terms of cancer risks.

When along the prostate cancer journey does it makes sense for a man to start talking to his oncologist or urologist about entering a trial like this?

Dr. Andrew Armstrong: Right away. Usually, community oncologists and urologists are capable of managing standard of care, but we have clinical trials open and available for men across all different disease states. If you never seek out a second opinion, you'll never hear about these options. The treatment landscape and all the decision making is much more complicated than it used to be.

And if a man enters one of these trials, is he still cared for by his local doctor in addition to the study?

Dr. Andrew Armstrong: There are many different patterns of collaborative care. I have patients that live several hours away who still get their hormone shots with their local doctor. If there's a medical emergency, it's good to have somebody on call locally. But the clinical trial itself is usually done at the center.

You had to use a lot of telemedicine and change the way you were approaching patient care during the height of the pandemic. What part of those changes do you think you're going to retain going forward?

Dr. Andrew Armstrong: Patients like some aspects of telehealth where they can go to their local lab and then have a phone call or a video visit with their doctor, particularly if there's not a lot going on. They don't have to miss as much work. They don't have to sit there waiting for as long. It's certainly safe with COVID-19 and social distancing. The video visits are here to stay for some patients. For others, it may not be appropriate. When they're getting active treatment and coming in for scans, they do often need to be seen in person, and it is much easier to have complex discussions with patients and their families in person.

Are you seeing more people reaching out to you from afar for a second opinion?

Dr. Andrew Armstrong: No. 80% to 90% of my patients are in person. It's much easier to communicate and get to know a person in real time. Pp

David Penson, MD
Prostate Cancer + Immuno-Oncology

Dr. David Penson MD, MPH, MMHC is Professor and Chair for the Department of Urology at Vanderbilt University.

He spoke with *Prostatepedia* about immuno-oncology for prostate cancer.

How does Provenge (sipuleucel-T) fit into the immunotherapy arena today?

Dr. David Penson: The field itself has accelerated at such a rapid pace. Just 15 years ago, there was no immunotherapy for prostate cancer at all. The first drug in that class was Provenge (sipuleucel-T), which was a cancer vaccine. Since then, we've seen a number of other agents, poly ADP ribose polymerase (PARP) inhibitors, drugs which are not personalized and work differently. We've started to harvest the immune system to fight cancer, either by slowing the immune system down, slowing down different parts of the cascade, or using the body's own immune system to fight the tumor, which is how Provenge (sipuleucel-T) works. It's an exciting time in prostate cancer research and prostate cancer treatment. These drugs are game changers.

There are some differences between the PARP inhibitors and Provenge (sipuleucel-T). PARP inhibitors are slowing down certain chemicals involved in the immune response and improving survival through that mechanism. Unlike Provenge (sipuleucel-t) which is made from the patient's own cells, the PARP inhibitors are off-the-shelf drugs. The drugs work well, and now they've been approved in the most advanced prostate cancer. Some of them work better than others in different patients. Some patients have different genetic predispositions and different genetic mutations, which make them respond better to some drugs than others.

Provenge (sipuleucel-T) is a drug that harvests the body's own immune system to fight the cancer directly. The patient undergoes leukapheresis which activates the immune cells with antigens against prostate cancer and puts them back into the patient. Provenge (sipuleucel-T) is well tolerated, often better than the PARP inhibitors, since it's more personalized.

We find Provenge (sipuleucel-T) to be helpful in patients who have newly diagnosed castrate-resistant prostate cancer, and who are early in that phase. Provenge (sipuleucel-T) is used earlier in the process since you're recruiting the patient's immune system to fight the cancer. You don't want to do it when they're on death's door. You want to do it earlier on so they have those additional antibodies to fight the cancer.

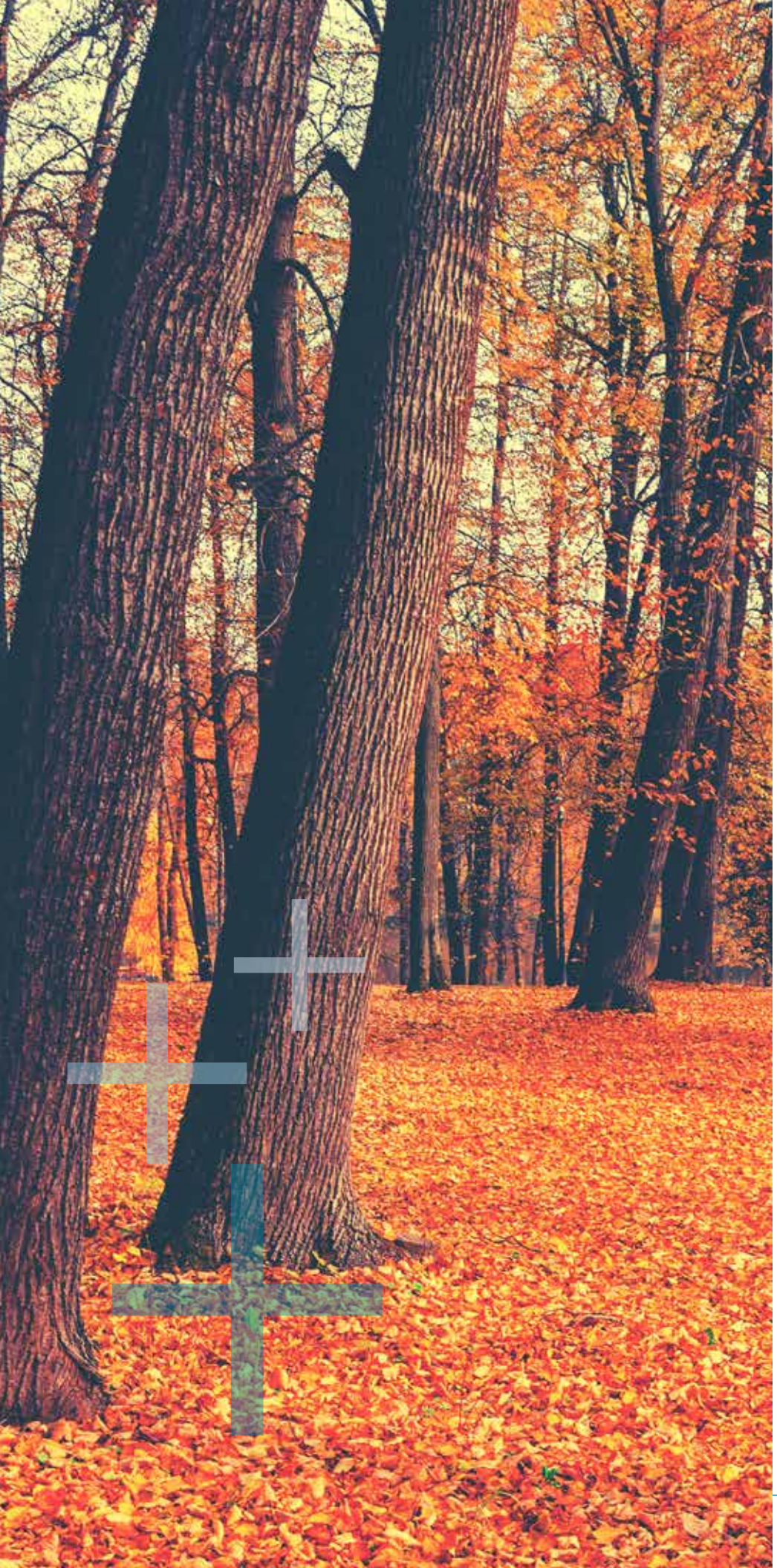
There is some work going on now with Provenge (sipuleucel-T) in active surveillance but it's only FDA-approved in the hormone-resistant stage, and that's where I use it.

How is it being explored for use in active surveillance?

Dr. David Penson: There is a study looking at randomizing men who are on active surveillance and localized disease to Provenge (sipuleucel-T) versus placebo. We'll have to see what it shows. No one is routinely giving Provenge (sipuleucel-T) in the active surveillance setting, and payers wouldn't pay for it.

There is no impact on prostate-specific antigen (PSA) from Provenge (sipuleucel-T). How does the lack of some demonstrable impact on the cancer play out with patients?

David Penson: It makes patients nervous. It has been a barrier to people adopting the use of the agent since people want to see that PSA drop right away. That being said, we know it has an effect on survival.



"It's an exciting time in prostate cancer research and prostate cancer treatment. These drugs are game changers."

The body needs to activate the immune system in response to the agent. The body needs time to make more antibodies and more killer cells to kill the cancer. That takes a few months. During that time, PSA is going to go up. What I often tell patients is, "Look, we're going to give this a try. We know it has a survival benefit. You need to sit tight with the PSA. Unless it's going through the ceiling, we're going to be okay."

Patients have to realize that, while they feel a whole lot better about having their PSA drop, no one ever died of an elevated PSA. They die of prostate cancer. What really matters is survival and symptoms, and Provenge (sipuleucel-T) does well there.

Do you think that men sometimes focus too much on PSA?

Dr. David Penson: Yes, I discourage patients with any level of prostate cancer from getting it tested more frequently than quarterly, except in certain rare circumstances. That gives you a chance to see what's really happening, particularly earlier in the castrate-resistant setting. If you are checking your PSA all the time, you will give yourself more anxiety than you will any benefit from prostate cancer treatment.

Most patients get a response to the first agent. These drugs take time to work, even when they affect the PSA. You've got to give yourself a little time.

What is the Registry of Sipuleucel-T Therapy in Men With Advanced Prostate Cancer (PROCEED)? What were the findings, and how did those findings impact how you approach certain men with prostate cancer?

Dr. David Penson: There's a lot of data in PROCEED. We're looking at men receiving Provenge (sipuleucel-T), their overall survival, their symptom-free survival, and the side effect profile. They're just starting to scratch the surface of what they can do with PROCEED since they've been collecting data for some time.

The study that has had the most impact from PROCEED looked at differences in survival between African-American and White men. The finding was that African-American men who received Provenge (sipuleucel-T) had a considerably longer median overall survival benefit, about nine months.

Why did that happen? There are a lot of hypotheses. There are biological differences, genetic differences between people. There are genetic differences between all people, and there may be genetic differences associated with race that influence outcomes.

When you look at these differences, they may affect the way the immune system responds. We do genetic testing in many patients now, for not just germline testing, but somatic testing too (looking at mutations within the tumor itself) to see if that patient is a better candidate for one PARP inhibitor versus another. The genetic makeup of a patient is going

to affect their response to the immunotherapy.

Provenge (sipuleucel-T) is a reasonable option in men who have castrate-resistant prostate cancer, regardless of their race or their ethnicity. It works better in men who have slower PSA doubling times. There's some data that shows the earlier you get it, the better, and that's why men with lower PSAs may do better. But if I'm seeing an African-American patient with a low and/or slowly rising PSA, I can tell them comfortably, "This agent is going to work for you. It may actually work better for you than the White guy coming behind you."

Do you think the value of PROCEED is going to be the number of clinical trials it spawns?

Dr. David Penson: It's going to give us real world evidence about clinical effectiveness. It's going to allow us to look at subgroups who may or may not respond to the drug better than others. It's also going to give us a good look at the side effect profile. There are a lot of questions about the efficacy and the side effects of Provenge (sipuleucel-T) since it's the first drug of its kind. PROCEED will answer a lot of those. It's a great place to do these other analyses, these trials, by looking at different groups and seeing how they respond.

Is the side effect profile muddied by the number of other agents men are on either before or after Provenge (sipuleucel-T)?

Dr. David Penson: To some degree, yes. But if I have a patient who has been on Xtandi (enzalutamide) for example, and I add Provenge (sipuleucel-T), if they were going to get a side effect from Xtandi (enzalutamide), it's likely that they would have gotten it earlier when they were on the Xtandi (enzalutamide) alone. If they get Xtandi (enzalutamide) and Provenge (sipuleucel-T), and they get an unexpected side effect, that's useful information. It tells me I don't want to mix those two drugs together. They're both safe drugs, and they've been mixed together. They're fine. I'm just using that as an example.

The earlier trials were for Provenge (sipuleucel-T) and for these drugs, but you can't beat real-world data.

Do you have any parting thoughts for men with prostate cancer about immunotherapy?

Dr. David Penson: This is something that patients should discuss with their urologist, with their medical oncologist, and they need to become educated consumers. For men with advanced disease in particular, even though the internet can be a bit of a jungle, they should still be learning things, learning about new trials and new agents, and asking their doctors about it. The worst thing that happens is the doctor says, "I don't think that's the right fit for you," or, "I didn't know anything about that. Let me get back to you on it." If your doctor is offended that you did some homework, maybe you don't want that doctor. There is no right answer, even in this space. What drug should we do first? What drug should we do second? We don't know. Having an informed patient helps deliver the best care, particularly in the immunotherapy space, which is advancing at a blistering pace. It's an incredible time. Pp

Evan Yu, MD
Immunotherapy Approaches

Dr. Evan Yu is the Medical Director of Clinical Research Support at the Fred Hutchinson Cancer Research Center and the Clinical Research Director of Genitourinary Medical Oncology at Seattle Cancer Care Alliance in Seattle, Washington.

He spoke with *Prostatepedia* about approaches to immunotherapy in 2020.

Where do we stand with Provenge (sipuleucel-T) compared to emerging options in 2020?

Dr. Evan Yu: Prostate cancer is one of the solid tumor types that does have an FDA-approved immunotherapy. Provenge (sipuleucel-T) is an autologous cellular immunotherapy, more like a vaccine. You're making activated antigen-presenting cells that educate your immune system to target prostatic acid phosphatase (PAP), which is highly expressed on prostate cancer cells. Specifically, those antigen presenting cells educate your B and T cells to create antibodies, and also to induce cell-mediated immunity for the T cells to kill cancer cells, respectively.

The challenge with Provenge (sipuleucel-T) is that it seems to work well for a certain subset, the asymptomatic, minimally symptomatic, early metastatic castration-resistant prostate cancer patients with low prostate-specific antigen (PSA). Provenge (sipuleucel-T) likely takes effect later and helps slow the disease down. It's not one of those things where the graph goes up with the tumor growth and then it shoots down. It goes up, starts to attenuate the growth curve, and then levels out.

"For patients who have alterations in some of these DNA repair genes, the early retrospective data shows that they also respond to standard prostate cancer therapies."

Other autologous cellular immunotherapies, like PROSTVAC, haven't shown a survival benefit. It's possible there was some statistical underpowering there. The amount of other subsequent therapies might have led to that being negative in the randomized phase III trial. This emphasizes that clinical trial design is just as important as the efficacy of the drug.

When it comes to checkpoint inhibitors, cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibition, Yervoy (ipilimumab), looked like it had activity, but it didn't show an overall survival benefit in a couple of randomized controlled trials. It doesn't have a lot of promise on its own, maybe in combinations or with select patient populations down the road. In terms of other checkpoint inhibitors, programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1), early data with Opdivo (nivolumab) and Bavencio (avelumab) didn't look very promising.The data with Keytruda (pembrolizumab) in the post-chemotherapy setting and then the PD-L1 high setting, which were unique populations, showed small response rates in unselected patient population in the 5% to 10% range.

A couple other strategies are combination therapy and biomarker selection. The latter includes patients with mismatch repair alterations,

microsatellite instability (MSI), and hypermutation. There is a broader approval for Keytruda (pembrolizumab) across all tumors for patients who harbor those alterations. An active area of investigation is with patients who harbor CDK12 mutations. That leads to focal tandem duplications, which are highly immunogenic, even more immunogenic than hypermutation. That is an active area of exploration with ongoing studies.

Combination therapy has some promise. There are a lot of combinations that are ongoing right now with immune oncology agents, including Imfinzi (durvalumab) with Lynparza (olaparib) and Keytruda (pembrolizumab) with Lynparza (olaparib).

If you give a poly ADP ribose polymerase (PARP) inhibitor, even if the patient doesn't have a DNA repair gene alteration, it can lead to cytosolic accumulation of DNA fragments. This can activate the STING pathway, which can increase interferons and immunokines in general. You might get more T cell immune recruitment to the area. Since PD-1 and PD-L1 antibodies work by directly inhibiting the ability for cancer cells to turn off your T cells, it makes sense to combine a PARP inhibitor with an immune oncology agent. That's the theory and rationale behind combining Keytruda (pembrolizumab) and Lynparza (olaparib).

The KEYNOTE-365 study combines Keytruda (pembrolizumab) with different FDA-approved prostate cancer therapies. Lynparza (olaparib), in the post-Taxotere (docetaxel) setting for metastatic castration resistant prostate cancer in unselected patient population, showed an impressive soft tissue response rate. For full disclosure, I'm the principal investigator of that study, so I'm a bit in the weeds. But it's over 20% measurable tumor response rate on the waterfall plots.

The confirmed response rate was not that high, but RECIST 1.1 confirmed response doesn't take into account bone metastases. If you're responding in soft tissue and you get a new lesion on bone scan, it could be progression, or it could just be healing since healing sometimes looks like a new lesion on bone scan. That would not be a confirmed RECIST 1.1 response, and that could have happened a lot on the study. Of course, there could be a differential response in soft tissue and bone, and this combination regimen might work better for patients with soft tissue measurable disease. Hence, the response rates reported from this trial overall might be more robust than anticipated.

Biomarker data from these studies has not all yet been performed and reported. For example, we need to understand better what the exact mutation rates for DNA repair genes are as well as tumor mutational burden (TMB) and microsatellite instability (MSI). That data is forthcoming.

When do you anticipate having more definitive information on efficacy of these combinations?

Dr. Evan Yu: For the randomized phase III trials, the reporting of the results will be event driven, so it depends on accrual and it depends on when they reach those survival events. The randomized phase III trials with Keytruda (pembrolizumab) with Lynparza (olaparib) in prostate cancer should be the first one to read out because it's the latest stage disease and has dual primary end

points of overall survival and radiographic progression free survival.

Can you explain more how and when PARP inhibitors are used?

Dr. Evan Yu: PARP inhibitors are an interesting class of agents. They inhibit a protein called PARP that is involved in repair of DNA after a cell experiences DNA damage. This protein is especially important for cancer cells that experience DNA damage, when an additional DNA repair protein is mutated or altered.

Relevant to this point is the fact that 23% of men with metastatic castration-resistant prostate cancer will have a gene mutation in one of the key DNA repair genes. In most of the studies, there's a panel of 15 or 16 known DNA repair genes involved in homologous recombination, with BRCA2 being the most common and the most important one in prostate cancer. But BRCA1, ATM, CHEK2, and CDK12 may have importance as well. There are a lot of different gene mutations that are important for DNA repair.

Whether cancer cell or normal cell, DNA repair mechanisms are important since DNA gets damaged all the time. Every cell doesn't ultimately become a cancer cell since you have a lot of checks and balances in place. One of those are different methods of DNA repair. There's homologous recombination repair, there's single strand break repair, there's mismatch repair, there's nucleotide excision repair. Most of the genes we have talked about are working via what's called homologous recombination repair, and that is a very high-fidelity pathway.

The way that these drugs work is that if you have one impaired DNA

repair mechanism, oftentimes your cells can still balance out DNA repair with some of these other repair mechanisms. Synthetic lethality requires taking out two different nodes. If you have one mechanism impaired, the cell might be able to survive. If you're able to impair another mechanism, you might then get cell death, or what we call apoptosis. If you give a PARP inhibitor to somebody who already has a mutation in a homologous recombination repair gene, you're now taking out the ability for single strand break repair, to couple with an already challenged DNA repair situation. That eventually leads to double strand breaks and widespread apoptosis.

That's why PARP inhibitors work for patients who already have these DNA repair gene mutations, whether that mutation was inherited or whether it developed spontaneously (somatically) over time in the tumor. In summary, PARP inhibitors, by inhibiting single strand break repair, should work better in a patient that already has problems with homologous recombination repair.

Can you highlight some trials focused on PARP inhibitors?

Dr. Evan Yu: In the study with Lynparza (olaparib), we've seen data from the PROfound trial showing both an overall survival and a radiographic progression-free survival benefit, especially for the BRCA1, BRCA2, and ATM cohort. Rubraca (rucaparib) also received accelerated approval in prostate cancer for patients with BRCA1 or BRCA2 alterations in the post-chemotherapy setting, but we have yet to see the randomized phase III data. There are also ongoing combination studies with Talzenna (talazoparib) and Xtandi (enzalutamide).

Zejula (niraparib) is also being studied up front in combination with Zytiga (abiraterone) in the MAGNITUDE trial.

The eligibility criteria vary from trial to trial. Some trials are genetic selection based, based on homologous recombination deficiency genes, and others are unselected combinations. Generally, combination studies are unselected studies, meaning that they're already in combination with an efficacious agent in metastatic castration resistant prostate cancer since there might be some additional synergism, even in a setting where a DNA repair gene alteration is not present.

Do you have any advice or thoughts for men about immunotherapy, immuno-oncology, or PARP inhibition?

Dr. Evan Yu: Although I have great enthusiasm for all of these approaches, my parting shot is to generate some caution. For patients who have alterations in some of these DNA repair genes, the early retrospective data shows that they also respond to standard prostate cancer therapies. Therefore, we should feel confident when we alter patient therapy based on a DNA repair gene mutation that the likelihood of response to the agent is high, because the downside is that we could have missed an opportunity to treat with other potential efficacious agents. When you think about patient selection, testing is incredibly important. My belief is that our field needs to spend a lot more time understanding the basic biology and optimizing the details of our companion diagnostcs to understand who will respond well to these new drugs and who won't respond well to these new drugs. A lot of the assays that are out there just say, "Hey, there's a mutation in gene X. Consider treatment with a PARP inhibitor." But there are a lot of questions about that mutation. Is that gene truly predictive for response to a PARP inhibitor? Is that specific mutation really that important? Have both alleles of that gene been lost, and is that necessary for that specific gene? The questions go on. However, the knee-jerk reaction for the treating physician is to be excited to tell the patient, "You should receive this new treatment option." But if we give that new option to a patient who was never destined to respond to it and the patient missed an opportunity for an unselected, yet efficacious prostate cancer therapy, I'd be concerned about that.

Would you suggest men seek a second opinion in this situation?

Dr. Evan Yu: If you have a significant potentially life-threatening disease, it's always a good idea to seek a second opinion.

What would you say to men interested in joining clinical trials?

Dr. Evan Yu: It's always my top recommendation. I'm biased since I'm a researcher. I work at an academic medical center, and I perform clinical research for a living. You have to take my recommendation with a grain of salt. However, if you think about it, everything we know today about every treatment you've received for your prostate cancer was learned through clinical trials. We wouldn't know what we know, and we wouldn't have the currently available therapeutics if previous patients hadn't volunteered to enroll on clinical trials. Hence, we must be grateful for the contribution of all those patients and families.

Think about why you want to go on a clinical trial. Your number one reason to go on a trial is to be altruistic. Future patients with prostate cancer will benefit from that information, regardless of the ultimate results of the trial. A very important secondary reason to go on a clinical trial is you might get lucky and receive a treatment that's highly efficacious, that may benefit you before that agent is commercially available.

When do you think men should start asking about clinical trials?

Dr. Evan Yu: Immediately. With cancer, immediately.

Even newly diagnosed men should start asking?

Dr. Evan Yu: Absolutely. It depends on the situation. Not every man should go on a clinical trial, but every man should at least ask and consider it. For example, with newly diagnosed, high-risk, localized prostate cancer, we're not curing the majority of patients. Your doctor may say, "Here's what we ought to do." But unless you ask for statistics or unless that doctor is incredibly comprehensive, you may not get the complete picture. It's hard for health care providers in a busy clinic to sit down and give people the bad news that there may be only a 30% cure rate. And if we're only curing a smaller percentage of patients, we need clinical trials to identify what new treatments, and what kind of intensification of treatment we need to cure more people. Pp1

Saul Priceman, PhD
Immunotherapy: BiTE's, CAR T, and more

Dr. Saul Priceman is an assistant professor in the Department of Hematology and Hematopoietic Cell Transplantation at City of Hope in Duarte, California. His expertise is in T cell biology and cancer immunotherapy.

He spoke with *Prostatepedia* about innovative approaches to immunotherapy primarily for prostate cancer.

What are bi-specific T-cell engagers (BiTEs)?

Dr. Saul Priceman: A BiTE is two binding entities that together force T cells, the "soldiers" of your immune system, to be in close proximity to a target cell (virus infected) or a tumor cell. Simultaneous to that, they're activating the T cell by saying, "There's something you want to kill, and here it is."

How is it being used against prostate cancer today?

Dr. Saul Priceman: Provenge (sipuleucel-T), which is a dendritic cell-based vaccine for the treatment of prostate cancer, was the first FDA-approved cell immunotherapy for any tumor type. Prostate cancer has always remained high up on the totem pole in terms of tumor types for immunotherapy development. It's also high on the totem pole for BiTEs. There's one target leading that effort called prostate specific membrane antigen (PSMA). There are a number of companies and academic entities that have developed PSMA-directed BiTEs. They are in early-phase clinical trials. They seem safe, and they're showing interesting antitumor responses.

There's another one called six transmembrane epithelial antigen of the prostate 1 (STEAP1), which is another tumor target that allows BiTE development to target prostate cancer. That is also in the early phases of clinical development.

Are there any clinical trials that you want to call attention to for patients?

Dr. Saul Priceman: Amgen is leading the effort with PSMA, and they've also started an effort with STEAP1. They also have the only FDA-approved hematologic malignancy BiTE targeting CD19, Blincyto (blinatumomab). They are in multi-center early phase clinical trials in treating patients with a PSMA BiTE.

What's the side effect profile like with those?

Dr. Saul Priceman: The PSMA is expressed in the salivary gland. In targeting PSMA, there have been some toxicities associated with that. The side effects are not strong in the context of PSMA BiTEs. Cytokine release syndrome (CRS) is a by-product and a side effect toxicity associated with immunotherapies. That's something that happens with PSMA BiTEs.

Where are you with chimeric antigen receptor (CAR) T cell therapy?

Dr. Saul Priceman: We started our first trial last year in patients with prostate cancer, targeting a protein called prostate stem cell antigen (PSCA). We've treated six patients. We are excited about it. We are now treating our seventh patient, so we are in the early stages of the trial, along with a few other academic institutions that are developing other CAR T cell strategies for prostate cancer.

PSCA is not unlike PSMA, but it's a different target. We are the first to treat a prostate cancer patient with CAR T cells targeting PSCA. PSMA-directed CAR T cells have been in trial for many years. There are a couple institutions and companies that are developing PSMA-directed CARs. We're actively trying to understand the safety profile and what types of efficacy we're seeing using both of these targets.

What's the advantage of targeting PSCA?

Dr. Saul Priceman: We're one of two places that are building PSCA-directed cell therapies. Based on what we're seeing already, we are excited about it. It's early, but we are definitely looking forward to continuing this trial, expanding on it, and building out other combinations with it.

We picked PSCA prior to developing any data. We generated a package full of preclinical data to support the target, to support the CAR T cells. We optimized a potent CAR T cell. In hindsight, we definitely chose the right target in PSCA for patients with prostate cancer. We were sponsored and supported by the Prostate Cancer Foundation. They continue to support us through the trial, and we are lucky to have their partnership in this program.

Do you have any advice about CAR T cell therapy for men with prostate cancer?

Dr. Saul Priceman: We just started developing CAR T cells for patients with prostate cancer and putting them into patients with prostate cancer to learn about the safety profile and whether there's activity of the CAR. It's a promising arena for us because of Provenge (sipuleucel-T) since there's evidence that immunotherapy can work and improve patient survival. We're building on that experience, and now the field is trying to develop CAR T cells and BiTEs.

We're still treating patients with advanced disease. These are patients with metastatic castration-resistant prostate cancer. They've gone through the gamut of therapies, particularly hormone therapies, androgen-blocking therapies, and chemotherapy. These are heavily pretreated patients. We are looking forward to moving it more up front, since we are cognizant that there are possible changes to PSCA, PSMA, and other antigens that we're targeting in later stage disease, but we need to get safety tackled first. We have to show it's safe before asking questions of efficacy.

Do you have a feel for how early you might want to end up using the strategy?

Dr. Saul Priceman: There have been thoughts that you would inject the CAR T cells into the prostate of a patient with early diagnosed disease. We're not there yet, but I envision it could be early. If it's safe, and you can show targeting with minimal toxicities, why would you do anything else? This is a one and done, you're not coming in every month. You're not coming in every couple weeks. You're not seeing those toxicities accumulate and happen in each step. You're getting infused with one cell therapy, and you're done. You go home and let the work happen naturally. That's our thought. It hasn't happened yet, but that's the hope.

What are oncolytic viruses?

Dr. Saul Priceman: Oncolytic viruses are viruses that we use to infect a tumor cell to cause lysis or death of that tumor cell. That's what a virus does typically do. It gets into the host cell, uses the host cell's genomic machinery to make more of itself, and then it ultimately lyses and pops that cell, spreading thousands of new viruses around to infect neighboring cells in the body. Biologists deleted a couple critical genes in viruses that would force the virus to use things that tumor cells, and not normal cells, use as replicative machinery. These modified viruses are called oncolytic viruses.

Use of oncolytic viruses are in the early stages as well. Amgen's leading the only FDA-approved oncolytic virus, T-VEC (talimogene laherparepvec), a herpes simplex virus that's been genetically modified for use in treating metastatic melanoma. Oncolytic viruses kill cells, but in doing so, they can also elicit an immune response since viruses are seen as foreign to the body. They kill a tumor cell, resulting in antigenic release, which makes the immune system say, "Oh, that's different. I'm going to go after that." In addition to virus antigens that the immune system should see, they will start to recognize tumor antigens that they previously didn't recognize.

You can also engineer viruses to deliver genes of interest into the tumor cell since the virus has to get into the tumor cell and integrate into the genome in order to make itself again. We can force viruses to deliver genes that we want introduced into the tumor. The virus does the dirty work, it delivers the gene of interest. For example, you can force genes that heighten the immune response in tumors, or deliver genes that force tumor cells to die more efficiently than with just the typical virus lytic cycle. People are investigating oncolytic viruses not only as single agents, but also as rationally designed combination approaches.

We just published an exciting example of this in the journal *Science Translational Medicine*. We demonstrated a novel combination of oncolytic viruses and CAR T cells. The FDA has approved CAR T cells targeting CD19,

which is expressed on the surface of leukemias and lymphomas (blood cancers). But unfortunately, nothing as promising to date has been developed for solid tumors, like prostate cancer and others. To change that, we made an oncolytic virus and put the CD19 gene into the virus and infected tumor cells. The CD19 was integrated into the genome of tumors, and CD19 was then presented on the cell surface. When we gave CD19-CAR T cells that would otherwise be ineffective against colon, pancreas, ovarian, prostate, and triple negative breast cancer, they began targeting those tumors infected by the virus. It's an example of a "universal" strategy, where independent of the type of tumor a patient has, this combination may offer a treatment for them.

Which of those combination approaches seems the most promising?

Dr. Saul Priceman: The combination of oncolytic viruses and cell-based therapies, like CAR T cells, are extremely promising. Because you can engineer both agents in multiple ways, it brings about innovative combinations that can be tailored to any given cancer type.

What are the side effects like with these oncolytic viruses alone and in combination?

Dr. Saul Priceman: Oncolytic viruses started out as local, intratumoral injections, and that's what T-VEC (talimogene laherparepvec) is approved to be. It's not approved to be given intravenously, but recently people have shown some safety around systemically administering oncolytic viruses. There are groups testing regional administration, intraperitoneal injection, to treat patients with peritoneal carcinomatosis, which is often

a late stage event in ovarian, colon, and pancreas cancers. We're also investigating doing that in the brain for patients with primary brain tumors and metastatic brain tumors. There are companies now testing systemic delivery of oncolytic viruses since they've developed viruses that have such profound tumor selectivity that they're able to inject it systemically and feel confident that it will be safe and accumulate only in tumors.

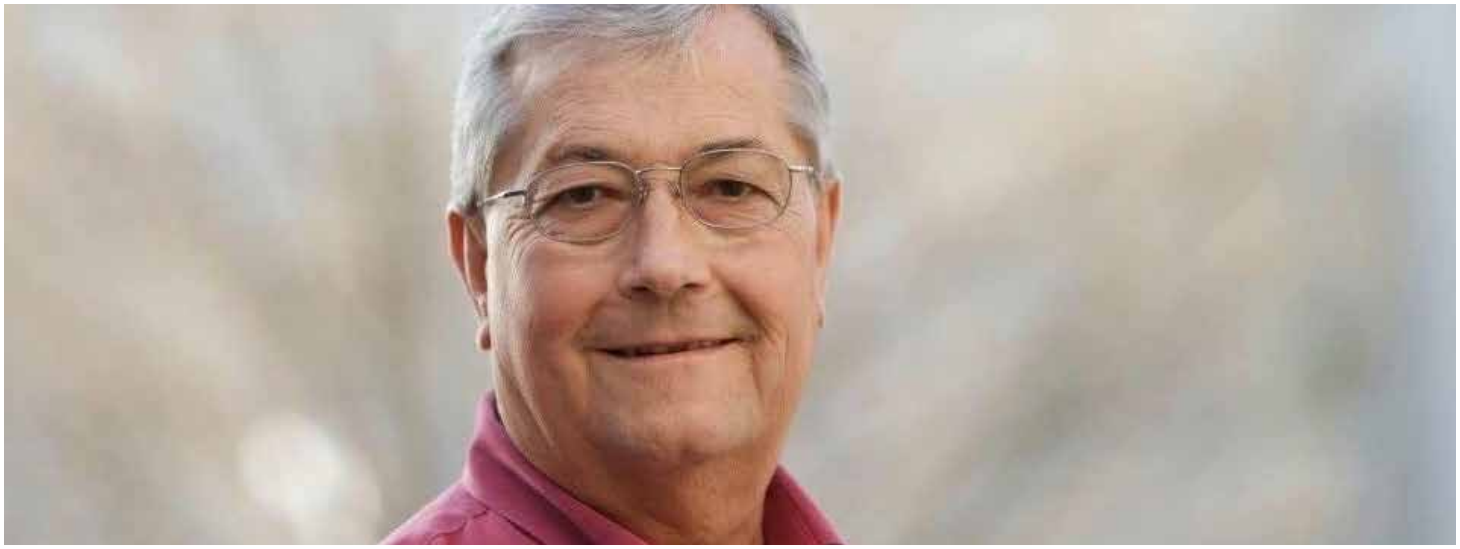
Do you have any last comments for patients about these immuno therapy strategies?

Dr. Saul Priceman: It's an exciting opportunity for patients to be involved in early trials, where there's an indication that the trial therapy is safe with the potential to improve patient outcomes. We have to treat more than a couple of patients to understand the therapeutic profile. Prostate cancer patients have been willing to do that. It's helping us understand whether these therapies work. It may feel like it's a long process, but are definitely moving new therapies quickly into early phase testing in patients.

If someone is interested in joining such a trial, how can they get in touch?

Dr. Saul Priceman: They can always connect with me by email or call City of Hope and get through to my office phone. If it's an active trial, I can direct them to the clinical coordinators that would be part of the enrollment process, or I can connect them with my clinical partners. I'd be happy to connect people if they reach out. I'd encourage them to also browse clinicaltrials.gov and find new trials in their area that they're eligible for.

Patients Speak
My Experience with Provenge



Rollie Swingle talks to *Prostatepedia* about his prostate cancer journey and his experience taking Provenge (sipuleucel-T).

What was your life like before you had prostate cancer?

Mr. Rollie Swingle: Prior to being diagnosed, I had no symptoms, I was asymptomatic. I led a normal life. I was working long days in our business every day. I was physically active and active in our community. I'd be in the gym on the treadmill and doing different exercises. I had no symptoms.

In 2002, we moved from Tracy to Elk Grove. I hadn't seen a doctor for two years. So I said, "I'd better get a doctor." And I went to a doctor at the UC Davis Clinic in Elk Grove. My doctor did a digital rectal examination (DRE). He informed me that, "Something's not right with your prostate. It's very firm. I want you to go see this particular doctor." It was a urologist at the UC Davis Comprehensive Cancer Center, Dr. Chris Evans. The same day I saw the urologist, he said, "You have to see this medical oncologist," Dr. Primo Lara. They did the prostate-specific antigen (PSA) test. It was 298. They decided to do a biopsy, and it came back 4/5-5/4, very aggressive. A bone scan showed that the cancer had metastasized to my spine, my ribs, and my pelvis. The prognosis was not good. We immediately started treatment programs with the UC Davis Comprehensive Cancer Center. That was January of 2004. My very first treatment was in a Southwest Oncology Group clinical trial with Zoladex (goserelin acetate). After Zoladex (goserelin acetate), for a short period of time, they introduced Casodex (bicalutamide). The Zoladex (goserelin acetate) worked great, and after I was introduced to Casodex (bicalutamide), the PSA elevated.

They stopped the Casodex (bicalutamide) and left me on Zoladex (goserelin acetate). That continued to work well for

a long time. Since then I've been on 11 different treatment programs over 16 years, everything from standard of treatment to several clinical trials, research projects, immunotherapy, chemotherapy, and the most recent treatment I started in August of 2019 was Xofigo (radium-223).

It was six infusions, four weeks apart, a six-month program. It worked incredibly well. My PSA went down to 6.6, the lowest that it had ever been since I was diagnosed. And the lesions on my bones were not as prominent. That treatment ended in February of 2020. Three months later, I had a PSA and it went from 6.6 to 7.3, no big shakes there.

Three more months later, it did elevate to 19. However, the bone scan showed no changes. The lesions were still not as prominent and nothing new. I've never had a new lesion since I was diagnosed and I've had no pain, I'm asymptomatic.

Now I'm on watch and wait, and I go back next week.

At what point were you prescribed Provenge (sipuleucel-T)? What was the experience like, and what are your thoughts about prevention?

Mr. Rollie Swingle: I was prescribed Provenge (sipuleucel-T) in February of 2012. It's three sessions over a nine week period. Since I had chemotherapy prior to Provenge (sipuleucel-T), my veins were pretty fragile. They couldn't do the blood draw through veins in my body. They had to put a port in, and we had a problem with the port. The first session was fine. During the second session, the blood started to coagulate in the port , and they had to flush it out. When they came to the third treatment, it started coagulating right away. They decided, "We've got two sessions of his blood. We've altered the white cells. We're fine with that." So I only actually had two out of the three, but it worked incredibly well.

"They did the prostate-specific antigen test (PSA). It was 298. They decided to do a biopsy, and it came back 4/5-5/4, very aggressive. A bone scan showed that the cancer had metastasized to my spine, my ribs, and my pelvis. The prognosis was not good."

Talk to me about that, because I know there's no impact on PSA.

Mr. Rollie Swingle: No, but my PSA went down drastically. I'm an odd duck. It is not supposed to affect your PSA. Mine dropped drastically, but as my oncologist said, "You're one of those people with your body chemistry, you react this way to these things." My PSA went down. At the time I did Provenge (sipuleucel-T), a lot of the doctors weren't excited about it since there wasn't a way to measure it, measure how it was working, unless the guy kept living.

It worked for a long time afterwards, too. Those altered cells, those white cells, just kept working in my body for a long time.

What therapy did they put you on afterwards?

Mr. Rollie Swingle: After Provenge (sipuleucel-T), I didn't do anything until a clinical trial in 2013 with Zytiga (abiraterone acetate) and Prednisone. I was on it for 21 months. I was showing good results. The trial was a double blind. Neither the clinical trial personnel nor my doctor knew if I was getting the medication or a placebo. At the end of my time on the trial, we were informed that I was on the placebo

They were amazed to find out that I was on the placebo.

How did you find out about the clinical trial?

Mr. Rollie Swingle: I'm constantly being offered treatment programs by UC Davis. When I went on Xofigo (radium-223), Dr. Lara sat with my wife and I, and we went through five different possible treatment programs I could have gone on at that time. We eliminated them all except for Xofigo (radium-223).

Do you think that's because you have let your doctors know that you are open and interested in clinical trials or because of UC Davis's approach?

Mr. Rollie Swingle: Both. They call me the poster child at the Cancer Center because I've done a lot of things. I've done TV interviews, I've got posters. They had two big billboards, one coming in from Davis on I-80 and the other one on I-80 near Roseville. They had my picture with Dr. Lara promoting clinical trials.

How did you get involved in this type of advocacy?

Mr. Rollie Swingle: When I was diagnosed with active prostate cancer, I was given two options. One was no option, and my life

expectancy would have been quite short because of the type of cancer. The other was get involved with UC Davis, they told me they could extend my life. I'm an open book. I'm one of these people that wants to share, I want people to know what's out there, and I just got involved. They started asking me to do things. And I said, "That's not a problem. If I can help, I'll do it."

What do you get out of being an advocate? Do you feel like you're helping other men the way you were helped?

Mr. Rollie Swingle: When I was diagnosed, there wasn't much out there as far as mentoring. At UC Davis, Dr. Marlene Von Friederichs-Fitzwater started a program called Peer Navigator. I got involved with that in the very beginning. Peer Navigators mentor newly diagnosed prostate cancer patients. We're currently in limbo since COVID-19 has had an effect on it. There were also a lot of changes in its structure before that point. They're reorganizing it. I am also co-facilitator for the advanced stage and recurrent prostate cancer group for the greater Sacramento area Us TOO Prostate Cancer Support Group.

Even during COVID-19, a lot of the mentorship could be done through phone and video conferencing., couldn't it?

Mr. Rollie Swingle: Yes. Since May, I've gotten five new patients. We use GoToMeeting. Our group is for men and their significant other. We have around 30 people on the video conferences twice a month. It's been wonderful.

Are you considering keeping the virtual support groups going? For some people, it might be easier to attend those kinds

of meetings than getting off work or leaving your home environment and driving all the way to the hospital or wherever.

Mr. Rollie Swingle: There's a group of five advisors, and we're going to have another meeting soon to determine if we'll continue with the video conferencing and the in-person since there are some people that they have difficulty reaching. We meet at two different places, either at UC Davis or at Mercy San Juan Medical Center.

We don't want to lose that personal contact. When we have the meetings in person, we'll sit for two, three hours. You talk and it's important to them. You can't beat the one-on-one, face-to-face interaction.

What advice would you give to other men?

Mr. Rollie Swingle: In general, most of the people that either are newly diagnosed or those that have recurrent disease, I just tell them my story. I start telling them about my PSA level and all the different treatments I have gone through, and that alone gives people hope. From the support group, they realize, "That guy over there's had 25 years since he was first diagnosed. And this one over here is 18." They had PSAs that were 200, 300. We had one guy with a PSA of 5,000 come in here.

Now he's an advocate. He's doing well. That's what I get out of it, seeing someone that feels like they have no hope discover that there is hope.

I encourage them to research, to ask their doctors. Cancer facilities like UC Davis get a lot of the latest treatments available. They get the clinical trials, they get the research projects.

Smaller centers may not have as much opportunity. Doctors at these clinics quite often advise their patients, "Go to UC Davis or some other facility that has much more advanced programs." When they come, we work with them. I give them my phone number, I give them my email, and I say, "Anytime you want to call if you have any questions, or you just want to talk. We'll do that."

The newly diagnosed people, when they come to our meetings, generally don't have a lot of information about their situation. They were just diagnosed and they're out there floating around. They come into our meetings and you start giving them information and you give them websites, you give them different things to look up, and you encourage them to do research. They usually come back, and they're in a different mode right away.

People die from prostate cancer, but not as many die as they used to. The numbers I had when I was first diagnosed were very advanced, and the prognosis was not very promising. Because there was not a group that I could turn to to discuss my situation, it made it a very difficult time in our lives.

Thanks to the tremendous staff and programs at UC Davis Comprehensive Cancer Center, I have had wonderful treatments that have extended my life. Pp[1]

Patients Speak: My Experience with Immunotherapy

David Rothschild spoke with *Prostatepedia* about his prostate cancer journey and experiences with Provenge (sipuleucel-T).

What was your life like before you had prostate cancer?

Mr. David Rothschild: I was teaching in a culinary arts program in high school. I was married, happy, active, had good routines. I was diagnosed when I was 55, and it was devastating.

I was diagnosed digitally first, by my primary care physician and prostate-specific antigen (PSA) rising. A urologist verified with a biopsy and sent me to a radiation oncologist who said, "Because of your relatively young age, and the numbers aren't that high, I think you're best off with radical." This was in 2000, we didn't know what we know now. It became a rush job. I had a radical prostatectomy, and shortly thereafter they called me into the office and said, "Your life's never going to be the same." They told me that it had metastasized. There were positive margins, seminal vesicle involvement, and it's only a matter of time before it shows up.

When we left the doctor's office, I came home and what'd I do? I cooked. That's what I do. I cook when I'm depressed, I cook when I'm happy. So I came home and I cooked with tears streaming down my face. I'm sure it was a salty dinner. I've always had a supportive wife. I've been lucky in that regard. But I was devastated.

How did you pull yourself out of that?

David Rothschild: I continued to go to the gym. I go to the gym, to this day, three days a week. Well, I don't go to the gym anymore. I call it the gym, but it's in my house now. It's too dangerous. I live in Arizona and we're a hotspot. I do a stationary bike three times a week and do some stretches and do a bit of strength training. That's always been good to raise my spirits. I was lucky enough to find a support group, and I met with them once a month. It was

helpful to talk to other guys who were in the same boat, maybe even further advanced than I was. I was a Gleason 9.

Do you still go to the support group?

Mr. David Rothschild: I don't. That support group disbanded, which is so sad. I went for the better part of 15 years.

It dwindled. Men don't like to talk about it. To this day, it's a little better, but it's tough. You go to some of the online support groups, and there are women talking about their fathers, or women talking about their husbands. Men don't want to talk about it. I've always been verbal, so I don't have any problem talking about it. I'll share. In fact, I've been a mentor for quite a number of years now for other men through an organization called Imerman Angels.

Have you thought about starting the support group again on your own?

Mr. David Rothschild: I have. I met with the CEO twice, and she said, "We're going to put this back together, and you're going to help it." It never happened, the numbers didn't support it. By the end, we had two or three guys in the support group.

Let's talk about immunotherapy. Did you have Provenge (sipuleucel-T)?

Mr. David Rothschild: I had three of three treatments, and it was in a blood bank. The first time went well, and I had no problem with it. I had an eBook. So that was fine. The next one and the one after, they got progressively slower. I could hear the worry in their voice that it was going to coagulate and this wasn't going to work. That made me feel more nervous.

"Men don't want to talk about it. I've always been verbal, so I don't have any problem talking about it. I'll share."

But it all worked out. I had three treatments and then three infusions back at the oncologist's office three days later.

It was boring, but not at all terrible.

What kind of impact did it have on your cancer?

Mr. David Rothschild: I have no idea. My cancer has always been notated by a PSA rise, and Provenge (sipuleucel-T) has no consequence on PSA.

There's no observable impact. I never had any signs of prostate cancer, from day one. I never felt any different before or after. My life has always been the same, other than my sexual life going down the tubes. I continue my life as it is. I didn't find any difference in the Provenge (sipuleucel-T) treatment, before or after it.

Did you go on to have other treatments after the Provenge (sipuleucel-T)?

Mr. David Rothschild: Yes. I've got a good team now. I've fired a number of oncologists who I felt were talking down to me. I'm not a doctor, but I do my research, I'm a smart man. I've been dealing with this for 20 years, so I can't stand being talked down to. You have to keep trying until you get one that you feel good about. I'm currently with a good team: an oncologist, a radiation oncologist, a urologist, and my primary care physician.

Did you go through insurance to have the Provenge (sipuleucel-T)?

Mr. David Rothschild: It was all done through the oncologist's office. I was approved in December, and I started Provenge (sipuleucel-T) in September of 2014. I never had a problem with insurance. When I retired, it was covered through my teaching. To this day, I have a good insurance program.

Do you have any thoughts for other men who are considering Provenge (sipuleucel-T)?

Mr. David Rothschild: I have mixed feelings. I've read the research, and research says it gives you three or four more years. Three or four more years is a good chance for me. That's a long time. At my age, like I tell my wife all the time, I can't waste this COVID-19 year. You can't waste the time. If I have gained three years, that would be wonderful.

Would I recommended it? Only if insurance pays for it. It's $100,000. If you have to pay that out of pocket, and you see no signs that it's making you any better, you can't know that you're going to live longer. It's tough. There are other immunotherapies out there now.

Any other advice that you have for men, just general advice for other men with prostate cancer?

Mr. David Rothschild: Always bring somebody with you to the doctor's office. I know when I first started, I only heard what I wanted to hear, and it was all bad. My wife would say, "That's not what he said." Always take somebody with you

to have another set of ears. Keep every single doctor's record, every single test. Request every record. They're yours, that's important.

As far as the Provenge (sipuleucel-T), the oncologist's office makes good money off of it, so of course they're going to push it. There's motivation for them to offer it. Do I also think there's potential for longevity? I do. So, like I said, I have mixed feelings.

And there's also no way for you to tell whether it was the Provenge (sipuleucel-T) or the treatments you had after that's contributing the most to your survival, right?

Mr. David Rothschild: Exactly. For years, they couldn't find the cancer. They finally found it on a number of scans, years later, when the scans got better. They found that it was one lymph node on the iliac chain, and that it had launched to golf ball size. They did Stereotactic Body Radiation Therapy (SBRT), which is an intense, focused beam. The PSA rose again, and then one year to the date almost, they did it again. They zapped it again. Then, I started Provenge (sipuleucel-T). After Provenge (sipuleucel-T), I went on to Xtandi (enzalutamide).

What was the SBRT like? Did you have a lot of side effects?

Mr. David Rothschild: No, I never had side effects. The SBRT was five days. I didn't have bowel problems, which I understand other people have.

Do you have any side effects from Xtandi (enzalutamide)?

Mr. David Rothschild: Minor. Like all the guys on Xtandi (enzalutamide) will tell you, they're lethargic. I exercise, and that takes away the lethargy. I don't nap. I come out of the nap and I feel awful, so I don't nap.

What kind of exercise do you do?

Mr. David Rothschild: It's mostly cardio. In 1988, I was running on an indoor track. I live in Arizona and most of the year, you can't run outdoors, it's too hot. When my knees got bad, I went to the stationary bike, and I've been doing a stationary bike for many years now. I do an hour on the stationary bike and watch some TV show or news. No, I can't watch the news now. It's too depressing.

What's the plan going forward? Are you going to stay on Xtandi (enzalutamide) for a while?

Mr. David Rothschild: They've let my testosterone rise a bit, from undetectable to 250. My doctor said, "I'm not concerned about that. I'm only concerned about PSA. We can live with a 250." At 250, I feel stronger. I feel like I have more stamina. It's not great, but it's better.

My last doctor's visit was a telehealth visit, I don't feel comfortable going into his office. I did one visit to a doctor's office. I went into my primary care physician for a physical, and I asked him to do my oncologist's blood work as well, so they shared results. He could see my PSA and my free testosterone and he said, "I've had people on Xtandi (enzalutamide) a long time." I always ask him, since my PSA has been undetectable for years, "How do I know I still have cancer?" He says, "You don't, you don't." I ask, "Well, what if I came off of Xtandi (enzalutamide) for a while?" He says, "I wouldn't advise it. It would be hard to get you back on the right track. I'm concerned that this thing would start to rage in you." I trust the doctor. He's always being conservative. But you also have to be your own advocate. Doctors aren't gods. Pp

PROVENGE®
(sipuleucel-T)

Think more about special occasions.
Think less about cancer.

PROVENGE is a personalized immunotherapy that activates the immune system to help fight advanced prostate cancer and has been proven to help certain men live longer.

Learn more about the power of personalized immunotherapy at PROVENGE.COM

INDICATION

PROVENGE® (sipuleucel-T) is a prescription medicine used to treat certain men with advanced prostate cancer. PROVENGE is an established cellular immunotherapy and is customized to each individual by using his own immune cells.

IMPORTANT SAFETY INFORMATION

Before receiving PROVENGE®, tell your doctor about any medical conditions, including heart or lung problems, or if you have had a stroke.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on the following pages.

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PROVENGE®
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IMPORTANT SAFETY INFORMATION, (cont'd)

Tell your doctor about any medicines you take, including prescription and nonprescription drugs, vitamins, or dietary supplements.

The most common side effects of PROVENGE include chills, fatigue, fever, back pain, nausea, joint ache, and headache. These are not all the possible side effects of PROVENGE treatment.

PROVENGE is made from your own immune cells, which are collected during a process called leukapheresis. The cells are processed, returned, and then infused back into the patient through an IV (intravenous) infusion about 3 days later. This process is completed in 3 cycles, about 2 weeks apart. Each infusion takes approximately 1 hour and requires 30 minutes of post-infusion monitoring.

PROVENGE infusion can cause serious reactions. Tell your doctor right away if you:

- Have signs of a heart attack or lung problems, such as trouble breathing, chest pains, racing or irregular heartbeats, high or low blood pressure, dizziness, fainting, nausea, or vomiting
- Have signs of a stroke, such as numbness or weakness on one side of the body, decreased vision in one eye, or difficulty speaking
- Develop symptoms of thrombosis which may include: pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, shortness of breath, chest pain that worsens or deep breathing
- Have signs of infection such as a fever over 100°F, redness or pain at the infusion or collection sites

Tell your doctor about any side effect(s) that concerns you or does not go away. For more information, talk with your doctor.

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

Please see additional Important Safety Information on the left side of the previous spread and Brief Summary of Prescribing Information on the opposite page.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary is designed to help you understand treatment with PROVENGE (pronounced PROH-venj). The more you understand your treatment, the better you will be able to participate in your care. This Brief Summary does not take the place of talking with your doctor or healthcare professional about your medical condition or your treatment. If you have any questions, speak with your doctor.

What is PROVENGE?

PROVENGE is a prescription medicine that is used to treat certain patients with advanced prostate cancer. PROVENGE is made from your own immune cells.

What should I tell my doctor before getting PROVENGE?

Tell your doctor about all your medical problems, including:

- heart problems
- lung problems
- history of stroke

Tell your doctor about all the medicines you take, including prescription and nonprescription drugs, vitamins, and dietary supplements.

How will I get PROVENGE?

Since PROVENGE is made from your own immune cells, your cells will be collected approximately 3 days before each scheduled infusion of PROVENGE. You will need to go to a cell collection center for this collection. The collection is called "leukapheresis" (pronounced loo-kuh-fuh-REE-sis). Your collected cells are sent to a manufacturing center where they are mixed with a protein to make them ready for your infusion.

You will get PROVENGE in 3 intravenous infusions (put into your veins), about 2 weeks apart. Each infusion takes about 60 minutes. Following each infusion, you will be monitored for at least 30 minutes.

Your doctor will give you a schedule for your cell collection and infusion appointments. It is very important that you arrive on time for your appointments. If you miss an appointment and cannot be infused, your PROVENGE dose will not be usable. Your doctor will work with you to schedule a new appointment at the cell collection center. You may also get a new infusion appointment.

What are the possible or reasonably likely side effects of PROVENGE?

The most common side effects of PROVENGE include:

- chills
- nausea
- fatigue
- joint ache
- fever
- headache
- back pain

PROVENGE infusion can cause serious reactions.

Tell your doctor right away if

- you have breathing problems, chest pains, racing heart or irregular heartbeats, high or low blood pressure, dizziness, fainting, nausea, or vomiting after getting PROVENGE. Any of these may be signs of heart or lung problems.
- you develop numbness or weakness on one side of the body, decreased vision in one eye or difficulty speaking. Any of these may be signs of a stroke.
- you develop symptoms of thrombosis which may include: pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain that worsens on deep breathing.
- you get a fever over 100°F, or redness or pain at the infusion or collection sites. Any of these may be signs of infection.

Tell your doctor about any side effect that concerns you or does not go away.

These are not all the possible side effects of PROVENGE treatment. For more information, talk with your doctor.

What are the ingredients in PROVENGE?

The active components of PROVENGE are your own immune cells mixed with the other active component, a protein designed to produce an immune response to prostate cancer. The product is suspended in an infusion solution called Lactated Ringer's Injection, USP, an inactive ingredient.

If you would like more information about PROVENGE, talk with your doctor. You can also call toll-free 1-877-336-3736 or visit www.PROVENGE.com.

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