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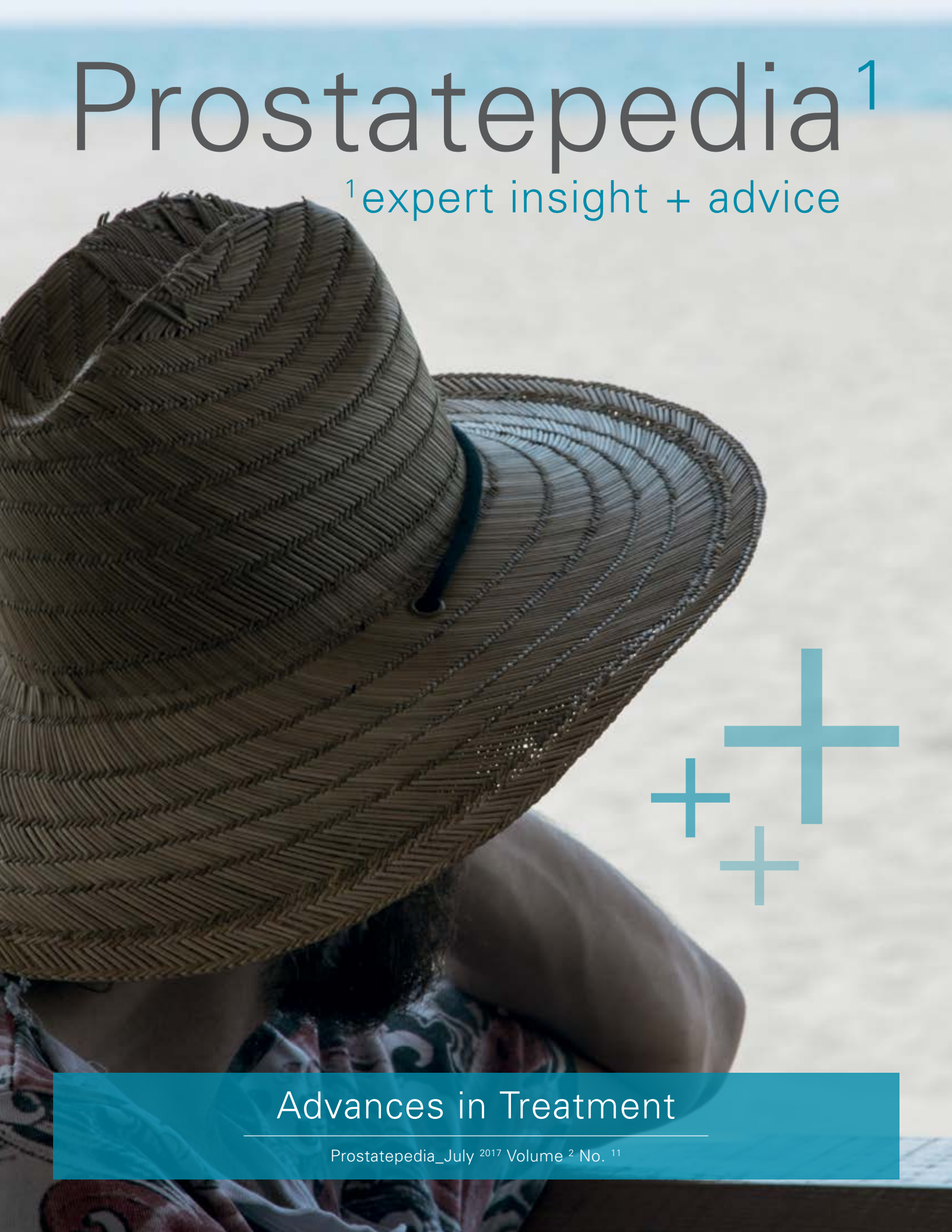

Advances in Treatment

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In this issue....

Treatment for prostate cancer is advancing rapidly. This month we talk about some of the developments that we think hold the most promise in the fields of urology, immunotherapy, medical oncology, and radiation therapy. You'll note the impact advances in imaging and precision medicine have had on almost every aspect of prostate cancer care.

But the field is moving even faster than this magazine's editorial calendar. While we were finalizing this issue, the results of two major clinical trials called STAMPEDE and LATITUDE presented their findings at the 2017 American Society of Clinical Oncology annual meeting in Chicago, Illinois. Both trials showed a dramatic benefit to adding Zytiga (abiraterone) to Lupron (leuprolide) when you start hormonal therapy.

To put this into perspective, several years ago a trial called CHAARTED showed that men with high-risk metastatic disease benefited greatly if we gave them Taxotere (docetaxel) at the same time as Lupron (leuprolide). Others confirmed these findings and as a result, we now have a new, more effective standard treatment for these men. (For some patients, a chemotherapy agent like Taxotere (docetaxel) poses a significant risk, though. We have other options for them.)

The results of the LATITUDE and STAMPEDE clinical trials show that Zytiga (abiraterone) is now a reasonable alternative to Taxotere (docetaxel). You can read both articles here https://tinyurl.com/yaqqcfpd and here https://tinyurl.com/yceljjwa.

These results mean we now have two very different drug options that we can add to Lupron (leuprolide) to dramatically improve your cancer control.

Charles E. Myers, Jr., MD

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Guest Commentary
Oliver Sartor, MD

Dr. Oliver Sartor, the Laborde Professor of Cancer Research in the Medicine and Urology Departments of the Tulane School of Medicine, is one of the leading researchers in advanced prostate cancer today. He is also the editor-in-chief of *Clinical Genitourinary Cancer* and the author of more than 300 scientific papers.

Dr. Sartor offers his perspective on this month's conversations.

Three of the biggest areas in prostate cancer right now are: 1) the use of the checkpoint inhibitor PD-1 to treat men with mismatch DNA repair defects, 2) the use of either PARP inhibitors or platinums to treat mismatch DNA repair defects, and 3) better imaging techniques.

Within the next year or two, we'll be able to define a subset of patients who will benefit from the PD-1 inhibitors that Dr. Charles Drake discusses in his conversation on immunology. I anticipate that PD-1 inhibitors may be meaningful for around 10% of men.

The FDA recently approved Keytruda (pembrolizumab) for those with mismatch DNA repair mutations, which applies to a subset of prostate cancer patients. This story will be meaningful to watch as testing for these mutations becomes more prevalent.

As Dr. Daniel Petrylak alludes to, there are now a variety of rapidly moving clinical trials looking at the combination of three DNA repair defects—BRCA1, BRCA2, and ATM. Data to support the use of PARP inhibitors in men with this combination of repair defects is rapidly evolving. This practice remains unproven in prostate cancer, though, despite promising preliminary data published by Dr. Joaquin de Mateo in the *New England Journal of Medicine* in 2016. [See *Prostatepedia* June 2016 for a conversation with Dr. Mateo about his work.]

But I do want to make sure that *Prostatepedia* readers are aware that if you have metastatic prostate cancer and a DNA repair defect—like BRCA1, BRCA2, and ATM—there is some reasonable preliminary data to support using carboplatin. We have a manuscript at press right now that shows that if you have an inherited BRCA2 mutation, there is better activity if a carboplatin plus a taxane are administered as opposed to just giving you a taxane alone. Thus carboplatin appears to be an option for men with certain DNA repair alterations.

Advances in imaging are also discussed in several of the conversations that follow. PSMA imaging is moving quickly. Axumin (fluciclovine F18) is the new imaging technique on the block with FDA approval. I think that in using these newer imaging techniques we will be able to define oligometastatic disease groups more and more efficiently. The consequences will be less therapy that just sets patients up to fail and, hopefully, more therapy that, if targeted to those lesions, will have a meaningful effect.

Stay tuned: the prostate cancer field is evolving really fast right now. I believe some men with advanced disease will potentially have molecularly targeted therapies available to them within the next several years. Pp!

Anthony D'Amico, MD
Radiation Therapy

Dr. Anthony D'Amico is Professor of Radiation Oncology at Harvard Medical School and Chief of the Division of Genitourinary Radiation Oncology at Brigham and Women's Hospital and Dana-Farber Cancer Institute in Boston, Massachusetts.

Prostatepedia spoke with him about advances in radiation oncology for prostate cancer.

Why did you become a doctor?

Dr. Anothony D'Amico: I was studying physics at Massachusetts Institute of Technology (MIT) when I was assigned jury duty. Believe it or not, one of the other jurors was a woman who later became my wife and whose mom happened to be the head of infectious disease nursing at a Boston hospital. I got exposed to medicine from her perspective.

Then, when I was in graduate school, I lost a woman who was a second mom to me during my childhood to breast cancer. After that, I decided to cross-register at Harvard Medical School, which I could do as an MIT student. I took introductory medical school classes—anatomy and physiology. I had an amazing experience and discovered that the medical students sitting next to me in the classroom were much more like me in terms of their desire and ability to want to help others than the graduate students sitting next to me at MIT in my physics courses.

I completed my PhD at MIT in radiological physics and decided to go to medical school. It was an eight-year commitment. At that point, it meant starting all over again, but it definitely was the right decision. I have never regretted that decision nor looked back. I'm extremely grateful.

The lesson I learned is that just because you're good at something doesn't necessarily mean it's what you should do. I was really amazing at physics and I'm great at medicine now, but I wasn't great at medicine when I started.

It's funny the path life takes you on.

Dr. D'Amico: There are no accidents. Everything happens for a reason.

What is the D'Amico Risk Stratification tool for prostate cancer?

Dr. D'Amico: The D'Amico Risk Stratification system is a pure exercise in mathematics. (This is the benefit of a physics background.) When it was published in 1998 in the *Journal of the American Medical Association*, a patient's decision to have surgery versus radiation therapy to treat their prostate cancer was based only on whether or not the man was healthy enough to have surgery. There was no consideration of how advanced his cancer was, whether the surgery was likely to completely remove the cancer, or whether a treatment like radiation might be just as effective, or possibly better, in terms of quality of life after treatment for that individual.

We came up with this risk stratification system. (I say we, because it wasn't just me. I worked in conjunction with a group of statisticians and other experts who gave a lot of thought to it.) We asked, "Why don't we look at the tumor itself as opposed to just the patient's age or health to decide whether surgery or radiation is best?"

We used the three basic indices—PSA, Gleason score, and clinical exam findings—to stratify men into three risk groups.

One group was composed of men who were likely to do well no matter what you did. That was the low-risk group. (Today, we sometimes just follow men with low-risk cancers with annual PSA and biopsy, especially if they're not in good health.)

At the other extreme were those with high-risk cancers—men unlikely to do well if you just offered them surgery

or radiation. These were people who needed something more, although in 1998 we didn't know what that *something more* meant. Today, we have a lot more to offer those men.

Anybody who didn't fit into those two groups was in the middle group: surgery or radiation may have been enough for most, but not for all. With those men, we waited to see what happened and eventually discovered other factors, like the number of positive biopsies divided by the number of biopsies obtained, to stratify these men into low or high risk.

That was the beginning. Eighteen years later, that system still exists as a starting point for further risk stratifying. People build upon it. It's a nice tool. I never expected it to be used in the way it is today because very few things in medicine actually last almost two decades. We were fortunate that the information was discovered at a time when people were ready to hear it.

What are the current points of controversy and/or trends in the field of radiation therapy for prostate cancer?

Dr. D'Amico: First of all, one of the most significant advances in our technical approach to radiation is image-guided radiation therapy (IGRT), which builds on intensity-modulated radiation therapy (IMRT).

Two decades ago, we had nothing to guide radiation treatment other than a regular x-ray, which only showed the bone. X-rays couldn't see anything else: not the organs, not organ motion, not respiratory motion, nor any other factor that might go into making radiation therapy more precise.

From x-ray, we went to CT-based planning that allowed us to see some structure, but still didn't fully account for motion.

Today, we have image-guided radiation therapy. We put markers in the organ—three gold seeds into the prostate or liver—and then take a picture each day, which shows us exactly where the target is. Using IMRT, we can create a radiation treatment that can treat a cancer the size of a dime with millimeter precision.

And we can account for motion. We can take pictures sequentially over seconds so that we can see how far the treatment area moves in one direction or the other when the patient is breathing. We can then sculpt the volume to account for respiratory and/or organ motion so we don't miss the target.

Right now, we're on the cusp of going from CT-based IMRT to MRI-based IMRT. MRI is a more sophisticated way of imaging structures that CT scans can't see. For example, the very bottom of the prostate, where the nerve bundles that control erectile function reside, is not very well visualized on CT scan, but it is very well visualized on MRI.

We're just now building machines that incorporate PET/CT that use functional imaging into radiation treatment planning and delivery. This means that we will be able to actually monitor the progress of a treatment *as it is being delivered* over the course of several weeks. We can see whether the cancer is now dead in a certain area or not, which means we can, in turn, modify treatment volume to make it smaller as we go along and only treat areas with still-viable cancer.

This is where we are right now in 2017. During the next five years, I expect that we'll be able to use functional imaging to guide and sculpt your treatment while it is actually happening in real time.

And all of that means fewer side effects after treatment?

Dr. D'Amico: Fewer side effects during and after treatment.

The next question is: can we make radiation treatments more efficient and shorter? This is called hypofractionation, or short-course radiation. In March 2017, the results of the third of three noninferiority studies looking at short-course radiation —meaning doing a treatment over the course of four weeks as opposed to eight or nine weeks—was published in the *Journal of Clinical Oncology*.

All three of these studies had a median follow-up of five to six years and all show that the shorter course appears, with respect to PSA recurrence, to be no worse and no better than a standard eight-week course.

However, we have to have a little patience with short-course radiation therapy. We're not quite ready to adopt it across the board because we've learned from prior experiences with other types of cancers, particularly gynecologic cancers, that it could take eight to 10 years before you see radiation's impact on the bladder and urethra when it's given very quickly like this.

But the results at the five- to six-year median follow-up are a very encouraging start. It says we have to stay tuned to see if these results hold up after another three to four years. If, after another three to four years, studies still show no or few urethral strictures or bladder neck contractures, we can think about using four weeks of radiation to treat prostate cancer instead of eight or nine weeks. This is very exciting.

There are people already adopting hypofractionation, but I caution against

that because the potential for toxicity to the urethra and bladder is real and requires more time to see.

The other thing I would say is that short-course radiation is making treatment more efficient for patients. Convenience is a good thing. But we don't expect the side effects to be less than what we see with full-course treatment. We offer fewer treatments simply for convenience. I am concerned when the decision is simply for convenience and not to create fewer side effects, a better quality of life, and/or improved cancer control for a patient. I think we really have to be sure that we're not causing any harm before we adjust our practices.

Are there any changes in how we approach men with just a few metastatic lesions?

Dr. D'Amico: If you give a man with two or three bone metastases—or oligometastatic disease—standard androgen deprivation therapy (ADT) and all of but one of those metastases go away, you do a study to figure out if that one remaining lesion might be sensitive to a different treatment. We now know that there are ways of using circulating tumor cells, as well as biopsies of metastatic lesions, to get a sense of whether or not men are sensitive to other advanced forms of treatment after initial standard hormonal therapy. The more sophisticated forms of treatment include hormonal therapy like Xtandi (enzalutamide), Zytiga (abiraterone), and chemotherapy like Taxotere (docetaxel). You can then try a different treatment on that one remaining metastasis. Or, you can sterilize that one bone metastasis with stereotactic body radiation therapy (SBRT) using very high doses.

There is a trial in the United Kingdom called STAMPEDE that is testing treating the metastatic lesions with high-dose radiation (e.g. SBRT), as well as treating the prostate. They are then giving standard hormonal therapy prospectively in a randomized fashion against the standard-of-care treatment, which is hormones and chemotherapy for metastatic disease. In that trial, they're treating the bone mets left after initial hormonal therapy as well as the prostate. In clinical trials, this is an interesting way to possibly afford someone with early metastatic disease a chance for prolonged survival. We should have the data from the trial in the near future.

You said that this is an approach we use if a man has one metastasis left after treatment, but what if he has three or four metastases remaining after treatment?

Dr. D'Amico: The more metastases that are left, the less likely this is to be of any benefit. You really do need to be cautious in how you think about it.

The other exciting thing on the horizon is the concept of systemic radiation. Xofigo (radium-223) is an alpha emitter used in castrate-resistant metastatic disease. Now Xofigo (radium-223) is being studied earlier in metastatic disease and also as a supplement to ADT in men with high-risk disease.

To that end, alpha therapy is extremely effective at killing anything within a millimeter of it. Some are also now tagging alpha emitters onto substances that are trophic, which means targeted for prostate cancer cells.

There are also ongoing studies that use nanoparticles tagged with an alpha emitter. These tagged nanoparticles can then be directed to the cancer cell based on a moiety (a substance directed right at the surface of the cancer cell) to try to kill it that way.

But all of this is research, not standard of care.

What about proton therapy?

Dr. D'Amico: We should really put to rest the idea that proton therapy for prostate cancer is better. It's not. We know from multiple studies that despite the fact that the dosimetry looks like it might be better, the actual cancer control and side effects look no better than what we see with IMRT or IGRT.

That makes complete sense from a physics standpoint. A proton's forte is in objects that do not move—parts of the body that you can completely immobilize like the brain or neck. Proton therapy basically allows you to dial the energy deposition with fraction-of-a-millimeter precision to a part of the body that does not move.

But the prostate moves. Even if you put a balloon into the rectum and blew it up and tried to immobilize it, it still would move because of respiratory motion. Because of that movement, you're not going to see an advantage to proton therapy since you have to widen the proton beam to cover the moving target.

Proton treatment is as good as IMRT or IGRT photon treatment, but I wouldn't want people to think that it's better. There is no proof that it is.

But this is not just a physics plan on a piece of paper outlining how we can treat an object that doesn't move. All of the studies comparing photons and protons that suggest the two are similar in terms of outcome and that one is not better than the other come from human clinical data.

Isn't proton therapy a lot more expensive than traditional radiation therapy?

Dr. D'Amico: Yes, proton therapy is 10 times the cost.

In my mind, we should be using proton therapy where we currently do use it here in Boston—in stationery brain tumors in children with diseases that will kill them if left uncontrolled. You can give higher doses using proton therapy in that situation because the brain tumor is circumscribed—identifiable—and doesn't move. Areas where you really have an advantage for protons are tumors behind the eye or tumors wrapping around the spinal cord or in the brain.

Are there any further thoughts on how radiation compares to surgery?

Dr. D'Amico: The ProtecT trial was published in the *New England Journal of Medicine* a couple of months ago. ProtecT is the first and only randomized study comparing surgery with radiation plus short-course hormones.

What I found very exciting about their results is that for 10 years we don't see a difference in metastatic prostate cancer between the two major modalities of either radiation or surgery. It's the first evidence that men with Gleason 6 or 7 prostate cancer truly have a choice between radiation therapy with short-course hormones or surgery. ProtecT is a randomized, 1,500-patient study. This is level-one evidence.

ProtecT also shows that the quality of life men experience following these two treatments is very different. Two recent papers also show that even with advances in robotic prostatectomy and in radiation, the side effect profiles of those treatments have not really changed relative to one another. The absolute rates of toxicity have decreased, but you still have more urinary incontinence and erectile dysfunction with surgery and more bowel issues with radiation.

How do we rank surgery versus radiation, knowing as we do that cancer control is truly equivalent? Patients can choose their treatment based on the side effect profile alone and not worry that they may die of prostate cancer if they make the wrong choice.

So the choice of surgery versus radiation comes down to personal preference?

Dr. D'Amico: Correct. Just like in breast cancer: lumpectomy and radiation versus mastectomy? Women have a choice. Men with a Gleason 6 or 7 prostate cancer have a choice.

Another exciting thing that came out of ProtecT is Comparison Arm for ProtecT (CaP). CaP is a PSA screening test in the United Kingdom tied to ProtecT. They have almost a half a million people randomized in the CaP study now. We should have the results next year.

The exciting thing about CaP is that it is a new way of screening. This isn't an annual PSA: it's a single PSA at about age 50. The study results will tell us whether or not we can be more cost effective with our PSA screening by getting a single value at 50. If that PSA result at age 50 is less than a certain number, we don't need to screen anymore. If it's more than a certain number, we do. I think that will represent a new way of thinking about screening. I think it will put PSA back on the map in a different way.

Do you think that the United States Preventive Services Task Force's stance on screening actually helped correct a trend toward overtreatment?

Dr. D'Amico: There are two sides. Their recommendations have definitely decreased overtreatment, but they have also caused some people who would have benefited from treatment to be underdiagnosed and therefore undertreated. The good side is less

overtreatment and less toxicity in elderly gentlemen with favorable risk disease who don't need treatment. Unfortunately, there are now some men who aren't being diagnosed until it is too late. I can tell you the number of people we see in their early 60s coming in with high-risk disease is increasing. That's a problem.

Are there any new thoughts about using ADT along with post-surgery radiation?

Dr. D'Amico: Two randomized trials have looked at combining hormonal therapy with radiation following surgery for PSA recurrence.

One trial called the RTOG study looked at 150 mg of Casodex (bicalutamide) for two years after surgery. The French GETUG-AFU 16 study also shows the same type of decreased recurrence with six months of Lupron (leuprolide) alone. Lupron (leuprolide), an LHRH agonist, is a more traditionally used treatment now. We have moved toward Lupron (leuprolide) and away from high-dose Casodex (bicalutamide) because high-dose Casodex (bicalutamide) has a huge impact on breast growth, but Lupron (leuprolide) does not.

Now, the RTOG study *did* show a survival benefit, while the French GETUG study did not. Then again, the RTOG is out 13 years while the GETUG trial is only out about six years. When the RTOG was only out six years, it also only showed a recurrence-free benefit. We expect that the GETUG study will also translate into a survival benefit, just like RTOG. That is our precedent for using Lupron (leuprolide) as opposed to using the high-dose Casodex (bicalutamide).

More effective and fewer side effects?

Dr. D'Amico: Fewer side effects in terms of gynecomastia, or breast growth, and probably just as effective.

Are there any changes in thoughts on brachytherapy?

Dr. D'Amico: The ASCENDE-RT trial looked at using external beam radiation and a brachytherapy boost as opposed to just high-dose radiation. They found that there was decreased recurrence with a brachytherapy boost, but there were also more side effects. The brachytherapy boost is a two-edged sword. Perhaps you can get better cancer control or fewer recurrences, but you're definitely going to have more side effects in terms of damage to the bladder and urethra.

Right now we're only using that approach in men who are unlikely to have those side effects—men who do not have a median lobe in their prostate. If you have a median lobe that pushes up into the bladder in the middle, you can have more side effects from brachytherapy.

We don't do brachytherapy in men who already have a very frequent stream or get up a lot at night to urinate because they're already subject to the more difficult urinary side effects. We don't do brachytherapy in people on anticoagulants like Coumadin (warfarin) because they're more likely to get rectal bleeding.

We consider brachytherapy for a man who is healthy, has a perfect stream, a small prostate, and is not on anticoagulants but has a large aggressive prostate cancer taking up both sides. Pp1

Charles G. Drake, PhD
Advances in Immunotherapy

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

Prostatepedia spoke with him about current trends in immunotherapy for prostate cancer.

Why did you become a doctor?

Dr. Drake: I was originally an engineer. In undergraduate school, I trained as an electrical engineer with a biomedical option. I thought that I would be able to design medical equipment—instrumentation and electronic equipment—that would help people. I wound up getting a masters degree in biomedical engineering. I did research; I was studying magnetic resonance imaging (MRI) and how to make better pulse sequences to measure blood flowing through vessels. But after some time, it became clear that technical innovation was less important to me than understanding the disease in terms of making a difference.

I then got my MD and PhD at the University of Colorado. This was a fantastic experience. In the lab, I studied basic immunological and genetic mechanisms in autoimmune disease. In some ways, autoimmune disease, in which the immune system is too strongly activated, is the opposite of cancer, in which the immune system is shut down by tumors. I don't think I would've been happy doing medicine without research or doing research without medicine.

What is your current position at Columbia University and how does the position differ from what you were doing at Johns Hopkins University?

Dr. Drake: This is a harder job. Some things are similar. I have a laboratory that studies the basic mechanisms of the way the immune system responds or doesn't respond to cancer, particularly focusing on prostate cancer and also other genitourinary cancers like kidney and bladder cancers. That part is fairly similar and is an area that I'm very passionate about.

What is different and exciting is that at Columbia, I've been tasked with building the genitourinary program. I'm going to hire somewhere between two and four additional physicians focused on genitourinary cancers. Since I'm in charge, I get to shape the program. That is the biggest difference: instead of being a part of a program, I'm lucky to be leading and building a program.

My research and laboratory career has been focused on using the immune system against cancer. So, we're going to build both the clinical trial infrastructure and hire clinicians who are of the same belief that the best way, or the most likely way, to lead to long-term remissions in cancers is with the immune system.

What type of immunotherapy can patients access today?

Dr. Drake: For prostate cancer, the only treatment that is currently available is the vaccine Provenge (sipuleucel-T). It has activity. With all the recent data on new drugs that block immune checkpoints, it's fallen off the radar a bit, but there are three randomized Phase III trials showing that Provenge (sipuleucel-T) increases survival in men with metastatic castrate-resistant prostate cancer. Another factor contributing to less recognition of Provenge (sipuleucel-T) is the widespread availability and efficacy of next-generation antiandrogens like Xtandi (enzalutamide) or Zytiga (abiraterone). When it's used, Provenge (sipuleucel-T) tends to be used earlier in the disease state, either right before or right after second-line antiandrogens.

That is what is available now.

What are some of the more promising approaches to immunotherapy being investigated now?

Dr. Drake: I'm not 100% sure that everybody in the prostate cancer community is aware of this, but investigators at Merck did what is called a basket trial. They looked at patients with cancers that have a defect in what is called mismatch repair. Cancers that have a defective mismatch repair accumulate many mutations. Those mutations serve as antigens, or targets, for the immune system. It was first shown by Drs. Luis Diaz and Dung Le at Johns Hopkins that in colorectal cancer, where mismatch repair is common, checkpoint blockade with anti-PD-1 is very effective. It turns out that there are mismatch repair patients with every kind of cancer, including prostate cancer.

Based on this large basket trial, the anti-PD-1 antibody Keytruda (pembrolizumab) was recently approved for patients' cancers that have mismatch repair defects. Across multiple tumor types, there have been really dramatic responses reported in the literature.

This means that prostate cancer patients who have mismatch repair defects now have a second immunotherapy option. What percentage of prostate cancer patients have mismatch repair? It's probably on the lower side, likely in the 3 to 5% range, but since prostate cancer is so common, that is actually a lot of patients.

I think that is fairly exciting and that perhaps the entire community is not completely aware that it is happening.

True mismatch repair is rare in prostate cancer, but a significant fraction of patients have other mutations that lead to DNA damage repair defects. Those defects are different and are called DNA damage repair mutations.

There have been some studies suggesting that this is actually pretty common in men with metastatic disease —as high as 10 to 20%. Those patients have been shown in a landmark paper by Dr. Johann de Bono published in the *New England Journal of Medicine* to respond to PARP inhibitors, which are reasonably well-tolerated oral drugs. There are now several ongoing trials testing this.

It is possible that these same patients might also respond to immunotherapy. I was part of a trial that Dr. Julie Graff published last summer that showed that out of the first 10 patients treated with Keytruda (pembrolizumab) who are progressing on Xtandi (enzalutamide), about three had a really beautiful response. Only one had true mismatch repair, but it could be that the other patients have mutations in DNA damage repair. That is important because that would extend the number of patients with prostate cancer who might be eligible for, or likely to respond to, anti-PD-1 or anti-PD-L1 agents.

Are there any other vaccines being investigated?

Dr. Drake: Hopefully before the end of the year, a trial called PROSPECT will read out. (Though it's hard to tell nowadays when trials are going to read out because we already have a reasonable number of options: six FDA-approved drugs for men with metastatic castration-resistant disease.) PROSPECT is an international randomized Phase III trial of about 1,200 men that looks at Prostvac, an off-the-shelf PSA-targeted vaccine. The trial's primary endpoint is overall survival.

Unlike the Provenge (sipuleucel-T) trials, which were sometimes a little complicated to interpret because we had crossover, patients on PROSPECT didn't crossover. That means that patients on the placebo arm who progressed were not eligible for Prostvac, instead, they went on to standard treatments. The lack of crossover means we expect a fairly clean set of survival data to come out from this large PROSPECT trial. There are a lot of folks in the prostate cancer community looking forward to seeing whether or not PROSPECT will have a survival benefit.

So then we'd have two vaccines for prostate cancer?

Dr. Drake: Provenge (sipuleucel-T) is an active drug with clear utility. The challenge with Provenge (sipuleucel-T) is that patients need to undergo leukapheresis to prepare this personalized vaccine. Prostvac is more like the vaccinia vaccine that was used for smallpox. It will be a bit easier to distribute widely.

Is inconvenience the only factor limiting Provenge (sipuleucel-T) use?

Dr. Drake: The prostate cancer field is like all other fields in that we tend to be trendy at times. When Provenge (sipuleucel-T) was first approved, there was a ton of enthusiasm about it and lots of people were using it. In fact, there was a bit of controversy over whether or not we could make enough of it.

With all the new drugs coming out, Provenge (sipuleucel-T) is probably used less than it once was. But this is something that has been FDA approved and has a clear survival benefit.

Are there any promising combinations of immunotherapy with other agents?

Dr. Drake: There are a number of trials looking at combining immunotherapy with other

agents. I was involved in a trial at Johns Hopkins University—Dr. Emmanuel Antonarakis is the principal investigator. In this trial, we combined an anti-PD-1 with an anti-CTLA4. In other cancers, this combination doubles response rates and induces more durable responses. The anti-PD-1 and anti-CTLA4 combination is already FDA approved for melanoma. There are Phase III trials that have completed enrollment in lung cancer and kidney cancer; we're awaiting those results.

Emmanuel and I started the first trial in prostate cancer in which we gave that combination to men with high-risk disease—that is men who had a mutation to an androgen receptor.

There is now another, larger trial led by my friend Dr. Sumit Subudhi at MD Anderson. They're going to look at the anti-PD-1 and anti-CTLA4 combination in about 90 prostate cancer patients across various disease states. This will make a really a nice complement to our smaller trial which will finish first. Sumit's trial will help define which disease state is most appropriate for the anti-PD-1 and anti-CTLA4 combination.

What are the side effects like with this anti-PD-1 and anti-CTLA4 combination?

Dr. Drake: It is a challenging side effect profile. The side effects of the combination of the anti-CTLA4 Yervoy (ipilimumab) plus anti-PD-1 Opdivo (nivolumab) are usually in the range of 50 to 60% of patients who have Grade 3/4 adverse events.

A lot of patients on these trials wind up needing steroids to turn off an autoimmune side effect. The beautiful thing is that the majority of side effects can be controlled with steroids alone. If we can't control the side effects with steroids, we can use anti-TNF

agents like Remicade (infliximab). Early on, there were some treatment-related deaths, but now the side effects are being much better managed.

But it's amazing: when a patient has a response to this combination and you turn off the immune system by treating a side effect with steroids, nearly all of the time, the antitumor immune response remains intact. It's really fascinating to me you could have an antitumor response that is not sensitive to steroids while the autoimmune side effects go away when you treat the patient with steroids.

The point that you raised, though, is that there is a high incidence of side effects with this type of combination. That is absolutely true, but we need to view it in context: these side effects are often quite manageable.

Also, clinicians are getting more experienced at managing side effects through the combination's use in melanoma. If the anti-PD-1 and anti-CTLA4 combination is approved in lung cancer and then in kidney cancer, it will become second nature for oncologists to manage these kinds of side effects.

In other words, it's a problem, but it's manageable and we're working on it?

Dr. Drake: Exactly. I think that we were lucky at Johns Hopkins and even here at Columbia to be able to participate in some of the early trials. We have a bit of a head start managing these side effects, but the average medical oncologist deals with patients without lymphocytes all the time. They also manage patients with severe nausea and vomiting. They could certainly manage autoimmune side effects; they just need to become a little bit more familiar with them.

Is there anything else you'd like patients to know about current trends in immunotherapy?

Dr. Drake: A group of patients generally left out of these immunotherapy trials is men who are earlier in their disease process. That is, men who have a rapidly rising PSA after primary therapy like surgery or radiation. The data suggests very strongly that if a man's PSA is doubling faster than every 12 months, they're very likely to have metastases within a year or two if they are not treated. Right now the common treatment is hormonal therapy, but we have some very good data suggesting that we should combine hormonal therapy with immunotherapy.

We're really lucky to have been able to start a series of trials for men with high-risk biochemically recurrent prostate cancer in which we give a short course of hormonal therapy along with immunotherapy.

I think that is really an unmet medical need for prostate cancer. We might have a better chance of getting long-term remissions in this disease stage. I know a lot of men in that situation feel bad because there is not that much clinical trial activity for them and not many standard treatments they can have other than hormonal therapy by itself.

But we're cognizant of the problem and are working on it.

What kinds of immunotherapies would you combine with hormonal therapy for these men?

Dr. Drake: We have some unpublished data from a new trial in which immunotherapy and hormonal therapy were given prior to surgery for high-risk patients. Hormonal therapy causes an influx of immune cells into the prostate gland. This is very clear. When the immune cells influx, they have PD-1 on them. The obvious combination is then hormonal therapy with a short course of anti-PD-1.

Quite frankly, I would like to do a trial in which we give a burst of immunotherapy with hormonal therapy, then stop and see if the men can recover their testosterone levels, normal life, and function while not having their PSA and cancer recur.

Hopefully, we can get such a trial open. We've got some fantastic junior faculty here at Columbia working very hard on it. We have some good corporate collaborators. I hope it will happen within the next year.

What are the obstacles?

Dr. Drake: It's always a challenge starting a new trial. This is not an industry-sponsored trial. This is an investigator-sponsored trial, and investigator-sponsored trials are always an order of magnitude harder than industry-sponsored trials. You have to write the trial; you have to raise the funding; you have to get corporate sponsorship, at least for the drugs. Of course, you have to go through the regular things like IRB (Institutional Review Board) approval. It's just a lot harder to do an investigator-initiated trial than one that comes from industry.

There are a lot of different parts to coordinate?

Dr. Drake: Exactly, but in the end hopefully it will be worth it, and will make a difference. Pp

Daniel P. Petrylak, MD
Advances in Medical Oncology

Dr. Daniel P. Petrylak, Professor of Medicine and Urology at Yale School of Medicine, has been a pioneer in the research and development of new drugs and treatments to fight prostate, bladder, kidney, and testicular cancers.

Prostatepedia spoke with him about advances in medical oncology for prostate cancer.

Why did you become a doctor?

Dr. Daniel Petrylak: I've always been interested in science. Growing up in the 1960s, I idolized the Mercury, Gemini, and Apollo astronauts. Through their achievements, they generated a sense of can-do problem-solving and the idea that we can use science to better the world and do better things. One of the great fortunes of my life is that I've actually been able to meet many of them.

When I was 16, I started working in a laboratory in New York doing work on protozoology. The person who trained me in the lab, Seymour Hutner, was a big believer in using protozoa to model a lot of different physiological processes that could potentially be used as a drug screen to look at anticancer drugs. I first became interested in cancer during that experience.

To me, oncology has the best balance between laboratory findings and applying those findings to patients.

What are the current points of controversy and/or trends in the field of medical oncology for prostate cancer?

Dr. Petrylak: The first controversy is over localized disease. There are really two forms of prostate cancer. There is the nonaggressive form that is not going to be lethal and that you'll die *with* and not *from*. Then, unfortunately, there is the lethal form of the disease that kills about 30,000 men a year in the United States. The controversy is how do you treat these patients? How do you decide who to treat and who not to treat?

For advanced metastatic disease, there are controversies over the right treatments, the right sequences of treatments, when to use other hormones, and when to use other chemotherapies. There are a lot of questions that need to be answered.

Unfortunately, prostate cancer has always been behind other tumors. If you look back to the 1990s, there was about five times less funding for prostate cancer than breast cancer. We were behind in funding compared to other tumors, but have made significant strides in increasing money available for research.

We're catching up in the area of personalized medicine. We didn't really have markers a couple of years ago. But now we're beginning to see markers—whether that be with BRCA mutations, BRCA-like mutations, or AR-V7—employed in the treatment of advanced metastatic disease to help select therapies. These approaches are in the advanced stages of development and have yet to be approved by the FDA. Those are the major controversies important today.

How have advances in imaging impacted how quickly we detect recurrences and how quickly a medical oncologist enters the picture?

Dr. Petrylak: The problem is that a lot of treatments are based on older generation imaging—standard bone scans and CT scans. But right now, when we are faced with a man who is asymptomatic with a rising PSA, we can potentially detect disease earlier using these newer imaging techniques like sodium fluoride PET.

The question is, do these patients still need to be treated in the same way we have been treating them? Will they get the same benefits if we treat them with the same techniques? I think that the potential for catching metastatic disease may be greater if you look earlier in negative conventional imaging areas.

The real question is how aggressively do you treat these men? We don't have randomized trials looking at men with a positive PET scan but no evidence of metastatic disease on imaging. When do you treat such a man? How do you treat him? This is a really important dilemma.

And approaches to treating metastatic disease can include surgery, radiation, and more systemic therapy?

Dr. Petrylak: Exactly.

Couldn't one assume if there are three or four metastases that there might also be other metastases that are still too small to detect through imaging?

Dr. Petrylak: It certainly could be that way. The trouble is that we need more data to help us understand that. Remember how heterogeneous this disease is. I've seen patients who have been alive for 15 years with metastatic disease. I've seen metastatic disease go away completely with hormone therapy. It's not common. It's rare. But how do you then select that patient out? How do you avoid overtreating a patient like that?

Can you talk a bit about both the AR-V7 and circulating tumor DNA tests?

Dr. Petrylak: Neither circulating tumor DNA tests nor tests looking at AR-V7 in circulating tumor cells are FDA approved for stratifying treatment.

What I think is crucial is that with these tests we may be able to select which patients are more likely or less likely to respond to individual treatment. If a patient is AR-V7 positive, he is less likely to respond to a next-generation antiandrogen like Zytiga (abiraterone) or Xtandi (enzalutamide). He may have a chance of responding to taxane-based therapy.

The problem with circulating tumor cell assays is that only about half of patients make circulating tumor cells. People are now beginning to look at other ways of assaying—circulating DNA and exosomes to pick up the AR-V7 splice mutations. There are also new methods being developed to increase the yield of circulating tumor cells in a patient.

"Only about half of patients make circulating tumor cells."

The AR-V7 test isn't available yet, is it?

Dr. Petrylak: Previously, the only way to get the AR-V7 assay was to ship a blood specimen to Johns Hopkins University. Epic Sciences has now developed a test.

How likely is it that your doctor will even know what to do with the information?

Dr. Petrylak: That is a good question. We still need prospective validation of these markers. That will come very soon.

What about some of the other molecular profiling tests available?

Dr. Petrylak: We generally don't use the chemotherapy assays where you get extreme drug resistance. But we're now starting to look at specific mutations by next-generation sequencing for targeting things like BRCA or BRCA-like genes. Lynparza (olaparib) and other PARP inhibitors are active for men with those DNA repair genes. The question is, of course, does platinum have activity in those patients as well? There may be some studies that will show that is true. Those studies are going to be coming in the future.

There are now drugs being developed to target AKT, the PTEN pathway. That may be one pathway to resistance to hormone therapy. All of these are now coming into play. The question is going to be how do we match a drug to it? How do you select a patient out?

I think that one of the advantages of circulating tumor cell DNA is if you take a biopsy, you only take a sliver of one metastasis. But we know there is a tremendous amount of heterogeneity in prostate cancer. These other techniques have an advantage as a greater way of detecting these signals.

Is it difficult to get biopsies of bone metastases?

Dr. Petrylak: You can do a biopsy of a bone metastasis. People have different drills that they use to take a bone biopsy. The problem with biopsy of a bone metastasis is the preparation. The standard decalcification preparation, which is used for normal pathology, can destroy a lot of the DNA that is needed for doing next-generation sequencing.

You have to handle the specimen very carefully. The yield after the preparation for bone is not as good as it is for a soft tissue lesion.

Are there any new developments in how we use Xofigo (radium-223)? I know there are some clinical trials investigating combining it with other agents like Provenge (sipuleucel-T).

Dr. Petrylak: Xofigo (radium-223) can be very useful in patients. The prevailing wisdom in the past has been to only give isotopes late in the course of the disease because

drugs like strontium and samarium had only palliative effects. There was also concern that strontium and samarium could cause prolonged myelosuppression (bone marrow suppression) in patients. Patients who are treated early in the course of their disease with strontium and samarium may have difficulty receiving subsequent chemotherapy.

Xofigo (radium-223) has an advantage over both strontium and samarium in that it is an alpha particle rather than a beta particle. The alpha particle will induce double-stranded DNA breaks as opposed to the beta particle's single-stranded breaks. Double-stranded DNA breaks cause much more DNA damage in the tumor cells; it is much more difficult for the body to repair that damage.

The alpha particle's other advantage is that it has a short nucleus, or radius of activity. It spares normal marrow and will hopefully cause less myelosuppression.

Xofigo (radium-223) has a survival benefit. It is approved for either pre- or post-chemotherapy.

There are a couple of interesting observations being made that will hopefully be confirmed in randomized trials. If you look at Xofigo's (radium-223) expanded access protocol, there does appear to be better survival when you combine Xofigo (radium-223) with Zytiga (abiraterone). There is also better survival when you combine Xofigo (radium-223) with Xgeva (denosumab).

Combinations give you more bang for your buck. Randomized trials are now evaluating these combinations. I think there is great promise in these combinations. We all know that there is an interaction between hormones and radiation therapy. Giving the two together is very interesting.

The immune question is an important one. We have some data that we're submitting for publication that shows that there is upregulation of PD-L1 on immune cells after patients receive Xofigo (radium-223).

The question is: does that make the patients more sensitive to subsequent immune therapy?

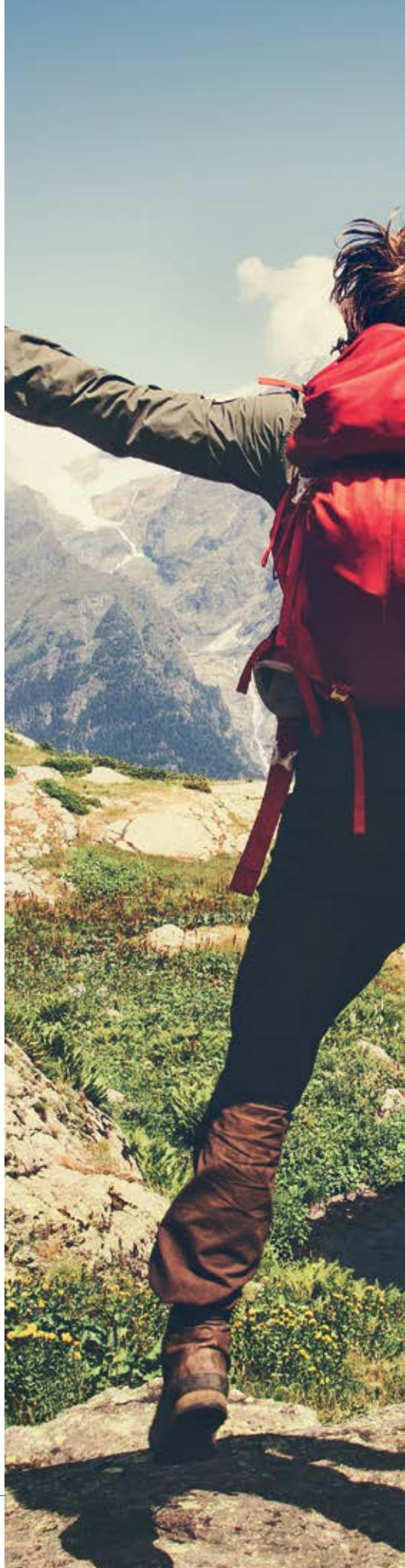
There are clinical trials looking at combinations of Keytruda (pembrolizumab) plus Xofigo (radium-223), vaccine therapy plus Xofigo (radium-223), atezoluzimab plus Xofigo (radium-223) and Provenge (sipuleucel-T) plus Xofigo (radium-223) This is an important venue for trying to synergize between different treatments.

Let's talk a bit about different forms of androgen deprivation therapy. A lot of men on Lupron (leuprolide) struggle with side effects and then switch to Firmagon (degarelix). What are the pros and cons of each?

Dr. Petrylak: The advantage to Firmagon (degarelix) over an LHRH agonist like Lupron (leuprolide) is that you eliminate the flare reaction that can occur when you give hormonal therapy. Initially, there is a surge in testosterone with an LHRH agonist. The testosterone levels then drop and you get castrate testosterone levels. This flare happens because of feedback inhibition.

But Firmagon (degarelix) will directly shut down LHRH. It's an antagonist, not an agonist, so there is no flare effect. If the flare effect does have any sort of effect on testosterone or on cancer cells, Firmagon (degarelix) will prevent it.

With androgen-related flare, we have seen patients with increased pain. They can have worsening of spinal



metastases causing cord compression. The question becomes: is there a long-term difference between these agents? Some laboratory data suggests there might be, but we're still looking for prospective confirmation.

For example, there are LHRH receptors on immune inflammatory cells. One thought is that you have activation with the LHRH agonists and, therefore, there may be more cardiovascular effects with agonists as opposed to antagonists due to inflammatory responses.

But does this truly translate on a prospective basis? That is being looked at.

There is a similar question about weight gain. Some animal data suggests that weight gain may be less in patients who receive antagonists versus those who receive agonists. There are ongoing trials to evaluate this. These are clearly important problems. One of the big problems with androgen blocking is that patients can get severe weight gain.

Especially since so many have preexisting cardiovascular disease.

Dr. Petrylak: Weight gain will not help with cardiovascular disease. Androgen block will not help the lipid profile. All of these are important factors.

Can you talk a bit about apalutamide (ARN-509)? I know it's still in Phase III trials, but if it does cross the FDA hurdle, how will it change the picture? How is it different from Xtandi (enzalutamide) and Zytiga (abiraterone)?

Dr. Petrylak: Theoretically, apalutamide (ARN-509) has an advantage over Xtandi (enzalutamide) from the standpoint that it does not cross the blood-brain barrier to the same degree that Xtandi (enzalutamide) does. Xtandi (enzalutamide) can be difficult for certain patients: they can sometimes have not-so-subtle mental status changes, including memory loss. Some patients complain that they can't function as well when they're on Xtandi (enzalutamide). They can't add a column of figures. They can't function at their work. But, fortunately, Xtandi (enzalutamide) is a very effective drug for their cancer. That necessitates either a dose reduction or a holiday from Xtandi (enzalutamide) if they experience these side effects.

We also see an increased rate of falls with Xtandi (enzalutamide). Whether that is due to an effect on the central nervous system or whether it's due to a sarcopenic effect is not really clear at this point.

The question is whether apalutamide (ARN-509) will have fewer of these effects. Theoretically, it would if it doesn't cross the blood-brain barrier. Apalutamide (ARN-509) affects the androgen receptor, while Zytiga (abiraterone) will cause abrogation of testosterone synthesis. There are randomized trials completed which compare apalutamide (ARN-509) combined with Zytiga (abiraterone) to Zytiga (abiraterone) alone.

Is there anything else you think patients should know about the current state of medical oncology for prostate cancer?

Dr. Petrylak: We're on the cusp of converting prostate cancer into a chronic disease, especially with the identification of markers. I think the next five to 10 years will be a very exciting time. Patients will start to see the benefit of the science we're using to understand more about prostate cancer. Pp1

Edward Schaeffer, MD
Advances In Urology

Dr. Edward Schaeffer is the Chair of the departments of Urology at Northwestern University Feinberg School of Medicine and Northwestern Memorial Hospital.

Prostatepedia spoke with him about the advances in urology.

Why did you become a doctor?

Dr. Edward Schaeffer: My whole life, I've been fascinated by how things work. Since the earliest age, I was really into mechanical things: how a watch or engine worked.

That interest eventually transitioned into the biologic sciences. How do cells work? How does the body work? This was always a fascinating thing to me. As an extension of that, I wanted to understand why people get sick. Why does a body's normal program fall apart? How do we restore it? Those things always fascinated me.

I continued to evolve my interest in medicine in a more and more sophisticated way. When I was in medical school, I had the opportunity to go to the National Institutes of Health (NIH) on a Howard Hughes Medical Institute Scholarship. I left medical school to study basic science and spent two and a half years studying how the immune system works. (I obtained a PhD based on my work at NIH.) But I wanted to take what science had to offer and use it for patient care.

When I came back to medical school from NIH, it was clear in my mind what I wanted to do: I wanted to become a physician-scientist. I wanted to take key clinical questions that my patients brought to me and understand them in the lab. Conversely, I wanted to take observations I made in the lab and see if they were also true in individuals.

> *"There has been a great hope that imaging would help in surgical planning."*

My decision to go into urology was based on a personal life experience. When I was a young child, my grandfather died of prostate cancer. I didn't know what was going on at the time, but I have vivid memories of my grandfather getting sicker and sicker. It had a high impact on me.

I only came to realize later in life as I was deciding to become a surgeon-scientist that he had died of prostate cancer. I knew then that I wanted to understand the disease that had killed my grandfather.

I've been in love with my profession ever since that day in 2000 when I made my decision.

I did all of my undergraduate and MD/PhD work at the University of Chicago. Then I figured that the best place in the world to study prostate cancer was Johns Hopkins University in Baltimore, Maryland, with Dr. Patrick Walsh—the field's contemporary leader. I packed my bags and moved to Baltimore. Johns Hopkins was an intense place, full of incredible minds. It was an amazing experience. Many people who went there thought it was just too intense, but I loved it.

After I trained there, I was invited to stay on as faculty. I progressed through to become a full professor, an endowed chair, and to run the prostate cancer program. I felt like I had reached the pinnacle of success and only had aspirations to further my clinic and my scientific mission.

Then the dean of Northwestern Medical School asked me if I would consider coming to Chicago to lead their Department of Urology.

Northwestern's Department of Urology had boasted some of the godfathers in the prostate cancer field, including Dr. Jack Grayhack and Dr. William Catalona who pioneered the development of the PSA blood test. I've now been here for 18 months.

What are the current points of controversy in the world of prostate cancer surgery—both for men who have been newly diagnosed and for those facing recurrence?

Dr. Schaeffer: Surgery for prostate cancer remains the gold standard, the best way to cure the disease. It is also the oldest treatment. Prostate cancer surgery was first performed in 1904; it's withstood the test of time.

The big hurdle for prostate cancer surgery has always been maintaining its outstanding cure rates while continuing to minimize postsurgical toxicity and side effects.

The operation has certainly evolved over the last 30 years. Dr. Patrick Walsh at Johns Hopkins University was my mentor. He perfected the open radical prostatectomy. Many Johns Hopkins alumni have now brought minimally invasive laparoscopic robotic prostatectomy online.

Today, for almost all cases, the laparoscopic robotic prostatectomy offers a state-of-the-art approach. Still, it is important for a man considering surgery for prostate cancer to find the most experienced surgeon he can. Ultimately, experience trumps approach.

You need to find a surgeon you like, because you're going to have your surgeon for the rest of your life. You need someone who has enough experience to give you a good outcome. Patients ask, "Should I come to you?" I say, "I'm confident I can help you, but we need to have a great relationship as I'm going to take care of you for the next 30 years…"

Is there a learning curve for robotic prostate cancer surgery?

Dr. Schaeffer: There is a learning curve to prostate surgery, period. Prostate surgery is incredibly complex. In an average surgeon's hands, it is a four-hour operation. The surgery requires an intense knowledge base. It's difficult whether you choose an open approach or a laparoscopic robotic approach.

"Ultimately, experience trumps approach."

I believe there are some subtle things about a robotic approach that an experienced surgeon can translate into better outcomes for patients. Ultimately, an open operation is not that different from a laparoscopic approach. But, yes, there is a very steep learning curve to robotic prostatectomy.

My other general philosophy is that I don't consider myself to be a technician —a r*obotic surgeon*. Rather, I proudly consider myself to be a physician who takes care of men with prostate cancer. One of my skillsets is that I'm able to perform prostate cancer surgery well. I do both open and laparoscopic approaches in my practice, though I favor the robotic approach. Ultimately, though, I consider myself to be an expert in prostate cancer who offers patients a good understanding of which treatment approach may be right for them. That may be surgery or radiation or surveillance.

What impact have recent advances in imaging had on prostate cancer surgery?

Dr. Schaeffer: I think that the most established imaging advancement is the multiparametric MRI of the prostate. Prostate MRI has been around for one to two decades, but only more recently have radiologists really worked out the best way to image the prostate. They've done a very good job. Now we're able to get excellent information about the anatomy of the prostate and, in many cases, the anatomy of an individual's prostate cancer.

MRI has had the greatest impact in the diagnosis of prostate cancer. Dr. Peter Pinto at the NIH has helped develop technology that takes that MRI image of the prostate and uses it during a biopsy in real time to sample suspicious areas. (See *Prostatepedia* October 2016 for a conversation with Dr. Peter Pinto about his work.) In my mind, that is a significant advance because it allows us to identify tumors that may have otherwise been missed by conventional approaches.

This is important in the initial diagnosis of prostate cancer. But it's also really important when we're thinking about suggesting active surveillance for a man with low-risk prostate cancer. If one can identify or confirm with an MRI that there is nothing suspicious in the prostate, then surveillance may make sense for some men. Imaging is a very powerful tool to help us risk stratify individuals considering surveillance.

There has also been a great hope that imaging would help in surgical planning. I believe in my heart of hearts that it can help, but the data suggests that the imaging is not quite ready to tell us precisely where the cancer is and where we should go a little wider to remove additional cancer during an actual operation.

an actual operation. I'm optimistic that we'll be there soon, but we're not quite there yet. We're making good strides.

MRI is also good for staging. It is very helpful for looking to see if there is any lymph node involvement. It's better, in my mind, than CT scan.

The next thing on the horizon is PET imaging. There are now several PET agents specific to prostate cancer. One of them is an agent targeted against prostate-specific membrane antigens, or PSMA. There is also an FDA-approved agent called Axumin (fluciclovine F18) that is also taken up by prostate cancer cells. These two PET-based agents and techniques—PSMA and Axumin—are going to change how we manage men with recurrent prostate cancer.

"Many surgeons and patients are enthusiastic about aggressively treating oligometastatic prostate cancer."

They are going to allow us to see current prostate cancers much better than we have been able to before. There is some emerging data on both that is very encouraging. Most of that work has been done in Germany, Europe, and Australia. America is a little bit behind in this particular aspect.

What are the current thoughts on the role of surgery for recurrent oligometastatic disease? [Oligometastatic disease means you only have three to five metastatic lesions outside of the prostate gland.]

Dr. Schaeffer: Many surgeons and patients are enthusiastic about aggressively treating oligometastatic prostate cancer. I'm also enthusiastic about the possibility that this approach could help patients. But I think it is very important for patients reading this interview to understand that these kinds of studies are totally experimental; we do not know yet

"PSMA and Axumin are going to change how we manage men with recurrent prostate cancer."

if these approaches will benefit men. Although I'm personally enthusiastic about these kinds of approaches—and am the principal investigator on a study exploring this called the TED trial. (TED stands for Trimodal Elimination of Disease and uses surgery, radiation, and systemic [chemo-hormonal] therapy to eliminate all visible evidence of prostate cancer.) However, I really only recommend that the average patient seek treatment for their oligometastatic or recurrent prostate cancer in the setting of a clinical trial. This is really experimental. We don't know if it helps and it may actually hurt people—this is why it needs to be done as a trial.

Is there any controversy over surgically treating the primary tumor when a man's cancer has already spread outside the prostate gland?

Dr. Schaeffer: No, I don't think there is any controversy in that. If you mean is there controversy in overtreating the prostate if a man has ogliometastatic disease, then yes, that is controversial. But in my mind, surgery benefits most men with large bulky high-grade cancers. Radiation is less effective in those cases.

In the last three to four years in my practice, I've seen more and more men with more advanced high-grade bulky cancers. I believe, although this hasn't been shown in a randomized clinical trial, that the best way to manage these cancers is the way we manage many other cancers: a multimodal approach of surgery followed by radiation and potentially chemotherapy.

Why do you think more and more people are being diagnosed with bulky high-grade disease?

Dr. Schaeffer: Several reasons. One, the United States Preventive Services Task Force (USPSTF) changed their recommendations in 2008 for men over 75 and in 2012 for men under 75 for PSA screening. It's well documented that there have been relaxations in PSA screening and that relaxations in PSA screening have resulted in fewer biopsies.

Think about the natural history of prostate cancer: if you had an aggressive localized cancer and left it alone for five to seven years, it would come back as a bulky aggressive cancer most probably involving the lymph nodes or beyond. And that is exactly what we've seen. Dr. Jim Hu published that exact observation in *JAMA Oncology* in December 2016. Unfortunately, we've now proved that what we thought would happen did in fact happen. The screening recommendations are not to the benefit of the patient. Fortunately, the USPSTF recently revised their recommendations and now suggest that PSA screening is something that physicians should bring up and discuss with their patients. This is a big step in the right direction. Pp[1]

Clinical Trial: Alicia Morgans, MD Cognitive Function

Dr. Alicia Morgans is a medical oncologist at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago. She specializes in treating advanced prostate cancer and is particularly interested in addressing treatment side effects.

Prostatepedia spoke with her about her clinical trial that looks at the cognitive effects that Xtandi (enzalutamide) and Zytiga (abiraterone) can have.

Why did you become a doctor?

Dr. Morgans: I've known since junior high school that I wanted to not only become a doctor but an oncologist. I knew I wanted to do something in science that engaged people and that I truly admired physicians.

When I would spend time with my grandmother over the summers, I would attend doctors' visits with her. I was fascinated by the way doctors could help people. Even when they didn't have a fix to a problem, they could at least serve as a witness to validate the patient's experience and lend support in any way they were able. I always thought that physicians were not only masters of curiosity and scientific investigation, but also masters of caring for other people. And oncology specifically has always been a really challenging puzzle to understand, and the best opportunity to form long-term relationships with patients.

Medicine is an amazing way for individuals to engage at a very deep level, not only with intricate and exciting science but also with really rewarding human interaction. I'm glad I made the decision.

What is your thinking behind your trial on the cognitive effects of Xtandi (enzalutamide) and Zytiga (abiraterone)?

Dr. Morgans: My research focuses on understanding the complications of cancer survivors and, specifically, understanding the complications of hormonal manipulation in men with prostate cancer. I've done work investigating osteoporosis and bone complications, cardiovascular complications, and metabolic complications like diabetes. The one area that I had not really explored, and that has been underexplored in the field, is the possibility that there may be cognitive changes associated with the hormonal therapies we use.

A patient who served as an inspiration for the study was a preacher who I met a few years ago, just a few weeks after his urologist started him on Xtandi (enzalutamide). His family was concerned because he developed a profound change in his motivation and planning skills, and he was unable to give sermons since starting the medication.

We were able to stop the medication, and a few weeks later, everyone said that he was back to normal. I just needed to understand why this might be the case. This led to the development of our study.

We are comparing the cognitive function of men starting Zytiga (abiraterone) or Xtandi (enzalutamide) over time to see if there is any difference between drugs that block the androgen receptor like Xtandi (enzalutamide) and drugs that just lower testosterone levels more completely like Zytiga (abiraterone).

Both of these drugs are used in the same patient population and are tremendously effective at controlling the cancer, so this comparison could be done safely.

I was fortunate to have some incredible collaborators with experience in traditional neurocognitive testing help develop the study protocol. In addition to comparing cognitive function between groups, the study validates a computer-based cognitive testing system (Cogstate) against traditional neurocognitive pen-and paper tests in the prostate cancer

population. If the measures appear to provide similar assessments, I hope to integrate computer-based cognitive testing into many prospective therapeutic studies just as patient reported outcome measures of pain, fatigue, and depression have been.

Finally, I have to mention that we were very fortunate to pique the interest of the Prostate Cancer Foundation in this work, and they were incredibly generous in conferring an award to fund the study.

Their award allowed us to integrate an assessment of possible genetic predisposition to developing cognitive dysfunction. The award also provides funds to integrate advanced neuroimaging with a noninvasive MRI series into the protocol. This will enable us to look at structural and functional changes that may happen in the brain during treatment.

We are doing this trial now because it is definitely an area of clinical concern in my practice. I don't think that previous work has been able to nail down which populations are at highest risk for cognitive dysfunction or develop a methodology that is both reliable and reproducible in larger scale settings. Our trial design may validate a computer-based methodology that can be expanded to other sites without requiring that trials include psychologists with neurocognitive expertise to administer cognitive tests. The computer-based method is less resource-intensive and more easily scalable.

Walk us through the details of the trial: what can patients expect? Do they need to come to you in Tennessee?

Dr. Morgans: We have a site open here at Vanderbilt University in Tennessee currently, and we will be opening at Northwestern University

How To Get Involved…

For more information, contact Dr. Alicia Morgans directly at alicia.morgans@vanderbilt.edu or call 615 875 2259.

in Chicago soon. We're also in the process of opening at the University of Southern California and the University of California, San Francisco.

We do have to see men in person to include them in the study, so they would need to come to one of those sites. If they are interested in the study, men who are about to start on either Xtandi (enzalutamide) or Zytiga (abiraterone) can sign an informed consent document to enroll in the trial at one of our study locations. They get baseline testing of their cognitive function, both with computer-based testing and pen-and paper testing, and then start their Xtandi (enzalutamide) or Zytiga (abiraterone) treatment as they normally would.

At three months, we'll collect blood samples for genetic analysis to see if there are specific genetic polymorphisms that may make an individual more or less likely to develop cognitive changes during treatment while on these medications. They continue on their treatment after that, and undergo additional neurocognitive testing at three months, six months, and 12 months. A portion of the patients will also get a brain MRI at baseline and 3 months to look for structural and functional changes that may occur during treatment.

Why are you only doing the MRI at baseline and three months in that smaller subset of patients? Why not at 12 months as well?

Dr. Morgans: We see the clinical change much sooner than 12 months, so we are hoping to see something, at least in functional testing, by three months. A particular series in the MRI sequence assesses things that change pretty quickly—like blood flow, connectivity, and metabolic activity. Blood flow can change within minutes, so conceivably, it could change over three months with continued exposure to treatment. Additionally, we planned to do the MRI when a majority of patients were still on their initial treatment. By the 12-month time period, we expect 25-35% of men to have stopped using Zytiga (abiraterone) or Xtandi (enzalutamide) for one reason or another. By testing at 3 months, we are more likely to be assessing patients who are still on the therapy assigned at the beginning, making our analysis much cleaner than if patients switch to another treatment before the follow-up MRI. If the treatment has been changed and we see changes in the MRI, we won't know if the changes are related to the treatment the patients had initially—Zytiga (abiraterone) or Xtandi (enzalutamide) —or due to the subsequent treatment that was started before the second MRI.

Are you also looking at what happens to people after they go off these medications?

Dr. Morgans: We are assessing everyone through the 12 month time point, so if patients stop the medications before that and remain enrolled in the study, they will be assessed on the next treatment. Assessments will be made based on intention to treat, meaning that patients will be analyzed in the treatment group in which they were at baseline at each time point.

Do you exclude people who are already suffering some form of cognitive impairment?

Dr. Morgans: If someone already has a diagnosis of dementia, they are excluded because it's going to be harder for us to measure a change in somebody who has already got more pronounced cognitive impairment.

If somebody has slight memory problems and has never been diagnosed with dementia, they are definitely allowed to participate, as long as they meet other inclusion and exclusion criteria. Men with untreated severe medical conditions or psychiatric conditions that are not controlled and stable, like uncontrolled delirium, uncontrolled severe depression, and uncontrolled severe anxiety disorders, will not be eligible to enroll because these can affect an individual's cognitive function.

Anybody who is actively abusing substances or medications like opioids, alcohol or other drugs, would also be excluded. Anybody who has used chemotherapy within the prior 12 months is excluded as well, because we do not want the analysis to be confounded.

Why is that?

Dr. Morgans: I'm sure most of your readers have heard of something called chemobrain. We don't want to measure chemo brain, or the effects of chemotherapy on the brain, because our interest is in understanding how manipulating hormone levels or blocking testosterone (androgen) receptors in the brain affects cognitive function. To do this accurately, we need to exclude people who may have other reasons for cognitive decline, so that we know that what we're measuring is what we're trying to measure. Chemobrain could really complicate our analysis. That is not to say that people who have had chemotherapy may not experience cognitive changes associated specifically with hormonal therapies, but for this trial, we need to exclude chemotherapy-treated patients so that we are not unable to separate out the changes due to chemotherapy versus those due to hormonal therapy. Pp[1]

Yigal Reouveni
Traveling for Cancer Care

Mr. Yigal Reouveni, of South Africa, talks to *Prostatepedia* about his prostate cancer journey.

How did you find out that you had prostate cancer?

Mr. Yigal Reouveni: I'd been having some problematic symptoms with passing water. I'd been suffering from a weak bladder.

My girlfriend kept telling me to go to a consult. In 2010, she forced me to go to a doctor. He checked me and everything was fine, but my PSA was 2.8. Unfortunately, he did not draw my attention to the potential danger. He just asked the receptionist to call me and tell me that I should have periodic checks, which I neglected to do for a year and a half.

After 18 months, it deteriorated to such an extent that it was beyond remedies, as we say. My PSA went up to 18.6, but the doctors could not really find any symptoms. My rectal examinations didn't show any indications of cancer. Only the biopsy showed that there was some sort of extensive disease in my prostate.

"I was really devastated."

What was your Gleason score?

Mr. Reouveni: My Gleason score was 9. After the biopsy, the doctor called me and said, "Mr. Reouveni, you have a major problem. You will not be able to have an operation. The only way to have some relief will be radiation and hormonal treatment." I didn't know anything about prostate cancer at that stage.

As soon as I discovered I had the disease, I started to read on the computer and familiarize myself with it. I was really devastated.

I was treated with hormone therapy. My PSA went down considerably to about 1.9 or 2. I had six months to decide what to do.

I went to Israel to consult with friends of the family. They also talked to other experts in the field.

I had a very good family friend who was a professor of radiology.

He heads a cancer research group in Beijing. I sent him all my medical reports and he analyzed my situation. He said, "An operation is out of the question. The cancer has gone out of the capsule and they suspect lymph node involvement. The only way to treat it is with radiation."

I decided to go to America for radiation. I stayed with my brother for three-and-a-half months.

"Cancer, as you know, is an individual disease."

What kinds of side effects did you experience?

Mr. Reouveni: They examined me using image-guided radiation therapy (IGRT) and made sure my internal organs were static while they were doing the radiation so that my bladder and rectum would not be affected. There was some collateral damage, but not much. There were some side effects during the radiation and, to a certain extent, after the radiation. But my side effects at the moment are minimal.

It's manageable?

Mr. Reouveni: I live a proper life. The effects have diminished over time.

Is it common in South Africa for people to travel so far for medical care?

Mr. Reouveni: It's not a complaint against the doctors here. I had two very good doctors. One of them is a professor. He said we would do the three-dimensional radiation. I asked, "Do you know about IMRT (intensity-modulated radiation therapy)?"

He said, "Yes, but we don't have it here."

Not many people can afford to go overseas, but I could.

I read day and night, researched techniques, statistics, and so on. I was stunned when I read that my chances were so bad because I had a Gleason 9. All the indications were gloomy; it was devastating. The fact that I'm here, functioning and feeling 100%, is a miracle.

Do you have any advice for men in a similar situation to yours?

Mr. Reouveni: Cancer, as you know, is an individual disease. Every person reacts differently. It's a mental struggle in my opinion.

"Don't lose vision. Just look forward."

Mentally, you must not succumb to the disease. I was 61 when I was diagnosed. I wanted to live. I had hope. When you've got hope and stamina and energy, you don't give up. You have to be strong. I know it's difficult and that every patient reacts differently, but keep hoping for good. Don't lose vision. Just look forward. Life is beautiful. I love every minute, every second. I work really hard. I'm a property developer and I wake up at six o'clock in the morning. I go to work. I come back home. I've got a girlfriend. I'm happy. Pp1

Angela Gaffney
Nutrients + Wellness

When it comes to health and healing, there is one simple rule we must follow: choose QUALITY over quantity. We've been trained to do just the opposite by focusing on calories versus the quality of the food we're putting in our body. It's time to shift perspective and start choosing foods that support cellular health, negate disease in the body, and provide the energy and focus necessary to heal.

There are three groups of nutrients that are important to consider when achieving health: macronutrients, micronutrients, and phytonutrients. We most commonly hear about macronutrients, the three food groups that provide energy to the body. These food groups include protein, carbohydrates, and fat. Most diet plans focus on increasing, decreasing, or balancing the macronutrients, but rarely take into consideration the quality of the foods we eat. Micronutrients are the vitamins and minerals the body needs. These micronutrients are needed in small amounts and are essential to healthy living.

While we don't hear about the third group of nutrients as often as we do the first two, it's arguably the most important nutrient to consume when trying to heal the body and achieve long-term health. Phytonutrients are chemical compounds that are only found in plant-based foods such as leafy greens, vegetables, fruit, beans, nuts, seeds, and whole grains. Phytonutrients are responsible for the color, taste, and smell of plant-based foods and provide robust, disease-fighting properties for the body. It's important to fuel up on these foods on a daily basis and be sure you're consuming a variety of colors; your health depends on it. The deeper the color, the more phytonutrient-rich the food.

Boost your health right away with this quick-and-easy exercise:

1. Add a minimum of two brightly colored plant foods to your breakfast, lunch, and dinner.

2. Increase your intake of leafy greens, vegetables, and fruit until you reach the optimal daily servings for each: 2 cups of leafy greens, 4 cups of vegetables, and 1.5 cups of fruit. You can also add a half cup of beans, an ounce of nuts/seeds, and a cup of whole grains to your daily intake for a healthy boost. No need to feel overwhelmed by these daily servings, just start wherever you are today and increase your daily serving of each category by 0.5-1 cup for one week. Increase again the next week, continuing until you reach the optimal daily servings.

Phytonutrient-rich foods provide a great foundation for healing and will care for the body through your cancer treatments. Adding these plant-based foods into your diet will help you eliminate cravings naturally and boost your energy for highly productive days.

Always choose quality over quantity for every meal and snack you consume. Start small by adding color to every meal and over time you'll reach the daily optimal servings of phytonutrient-rich foods. By doing so, you'll support your body in healing and health today and always. Pp[1]

Want to know more?

Wellness speaker Angela Gaffney teaches people simple and effective strategies to achieve health, increase productivity, and live stress-free while reaching their personal and professional goals.

To hire Angela to speak at your next event, discuss a wellness program for your corporation, or take advantage of complimentary health tools and recipes please visit www.AngelaGaffney.com

Jan Manarite Discussions About Survival

Jan Manarite joined the prostate cancer community in 2000 when her husband Dominic was diagnosed with advanced prostate cancer. She has gone on to become one of the most recognized advocates in the prostate cancer community today.

Prostatepedia spoke with her about patient advocacy and how survival statistics are being communicated to men with advanced (metastatic) prostate cancer.

How did you become involved in prostate cancer patient advocacy?

Ms. Jan Manarite: Many people, women and men, become passionate about something that caused them pain. For me, my husband was diagnosed with extremely advanced prostate cancer.

His PSA was over 7,000 and he had bone metastases throughout his entire skeleton except for his arms and legs. In fact, he had to be sedated so that he could lie down to do any type of imaging. They gave him general anesthesia because his spine was that bad. He woke up paralyzed. He recovered from that paralysis, but that is when I began to advocate for him.

After that terrible emergency experience, he lived for another 13 years. At about a year and a half into our journey, I began to really get involved in his treatments and, most of the time, choose them.

We had a great doctor who knew that we had to think outside of the box. I looked at my husband's medical records a lot. I talk now about how medical records speak. It's a really important message because you've got a lot of voices in your head: your doctor's voice, your wife's voice, your kid's voice, and the internet's voice. You don't know what your medical records are saying half the time. Not really. You think you do, but if you haven't read them and if you haven't googled a few of the big words, you don't know what your medical records are saying.

After reading his medical records, I found that I was often equipped to ask really good questions and to even make suggestions. I also knew my husband better than the doctor did. We had to switch doctors four times to find a doctor that we both liked.

How did that experience segue into involvement in the patient advocacy community?

Ms. Manarite: PCRI (Prostate Cancer Research Institute) helped me out a lot during that time. I spoke with Dr. Stephen Strum who opened my eyes to a few things and got me thinking in the right way—he called it "listening to the biology of the cancer." There is this great poster from the 2017 March for Science that says, "Science doesn't tell you what to think; it teaches you *how* to think." Dr. Strum was able to do that for me.

Dr. Strum liked what I was doing for my husband and offered me a job. I worked for PCRI, which is now under Dr. Mark Scholz's leadership, for 13 years.

What organization are you with now?

Ms. Manarite: I work with Mr. Mike Scott at Prostate Cancer International (https://pcainternational.org/) and Prostate Cancer InfoLink (https://prostatecancerinfolink.net/).

If you could give one bit of advice to patients and their caregivers what would it be?

Ms. Manarite: I recommend that people get a basic understanding of what their medical records are saying before they start to research online. When patients do that, they're not as prone to being overloaded with information. They'll target their searches based on what they're learning about their own prostate cancer.

Also, google the big words. You're going to be surprised at how much you can understand and how that can develop into better questions. Here's an example: on a CT scan report, lymphadenopathy simply means an enlarged lymph node, which is considered cancerous. That short explanation is important to patients: it's their cancer and their body.

"Talk to the doctor about the treatment's benefit and the nurse about the side effects."

Being overwhelmed is a problem, so I continue to drive home that message about reading your medical records.

A lot of men begin googling the minute they get that high PSA result—sometimes before they have even had a biopsy.

Ms. Manarite: Or they shut down. One or the other.

But you say men should go back to their medical records and start there?

Ms. Manarite: One hundred percent. The medical system has changed and now patients have to get involved. We have several terms for it, but the most accurate is *shared decision-making*, which is the first section of the new prostate cancer guidelines released by the American Urological Association/American Society for Radiation Oncology/ Society of Urologic Oncology in 2017. If you're sharing the decision, you don't need a doctor or medical professional's understanding of your medical records, you need a layman's understanding of your medical records. That is possible. It takes a little work, but most people are really surprised at how empowering it is.

Five new drugs for metastatic castration-resistant prostate cancer have been approved since 2010. Those new drugs have really changed the outlook for those men. Are doctors accurately conveying that change?

Ms. Manarite: I think it's probably all over the map. Every doctor is a little bit different. The message regarding survival is also all over the map. [Visit https://tinyurl.com/y7y2t57c to view a poster Ms. Manarite presented on this subject at the 2017 meeting of the American Association for Cancer Research.]

Too many times when I worked the PCRI Helpline, I would hear that men were being quoted outdated survival statistics. I definitely had an emotional reaction. I couldn't believe that they were told that. I thought it was unfair.

It was unfair for two reasons. Number one is that survival is the most important statistic they want to know. Number two: if you underquote survival statistics in any way, you begin to steal hope. And hope is the key to men staying involved in shared decision-making. Shared decision-making makes their care better. The poster I presented at the American Association for Cancer Research's annual meeting this year came from a 2013 article I wrote while at PCRI called "Understanding Survival Statistics." (https://tinyurl.com/lglz5b3)

Do you think the message needs to veer more toward optimism?

Ms. Manarite: I think the conversation needs to veer more toward honesty. The truth is that no one really knows how long someone will live because by the time survival statistics are published, they are already years old and therefore outdated. Things have already changed. New treatments could be developed during the next year or two. In addition, we know that staying involved in your cancer treatment decisions has a very positive effect on survival. It's hard to measure, but it's there and I lived it for 13 years.

Do you have any other advice for patients and their caregivers?

Ms. Manarite: Stay involved in your healthcare. If you're not the researcher but you have a wife or a daughter or a son who loves to research, let them do it. It really can add years to your life. You need someone digging and researching. I felt like a little bit of a detective when my husband was going through this. I would read the medical records, think about it, sleep on it, and wake up with an idea.

I've heard other advocates recommend taking someone with you to an appointment. Do you also make that recommendation?

Ms. Manarite: Absolutely.

What you'll find is that doctors have a tendency to talk about a treatment benefit, but every treatment decision has both a risk and a benefit.

Talk to the doctor about the treatment's benefit and the nurse about the side effects and the treatment's risks. That is a good way to work your appointment. You get two medical professionals. That's twice the time.

There is so much information. You're trying to sort things out. Sometimes you're exhausted just trying to work the medical system. Pp[1]

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

Talk to your doctor and visit XTANDI.com/info

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

ONCE-DAILY
Xtandi®
(enzalutamide)
40 mg capsules

ONCE-DAILY
Xtandi®
(enzalutamide)
40 mg capsules

Talk to your doctor and visit XTANDI.com/info

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

Important Safety Information

Who should not take XTANDI?

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

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

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

How should I take XTANDI?

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

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

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

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

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

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

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

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

astellas MEDIVATION

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.

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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.

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

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

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

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

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

How should I store XTANDI?

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

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

General information about XTANDI.

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

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

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

What are the ingredients in XTANDI?

Active ingredient: enzalutamide

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

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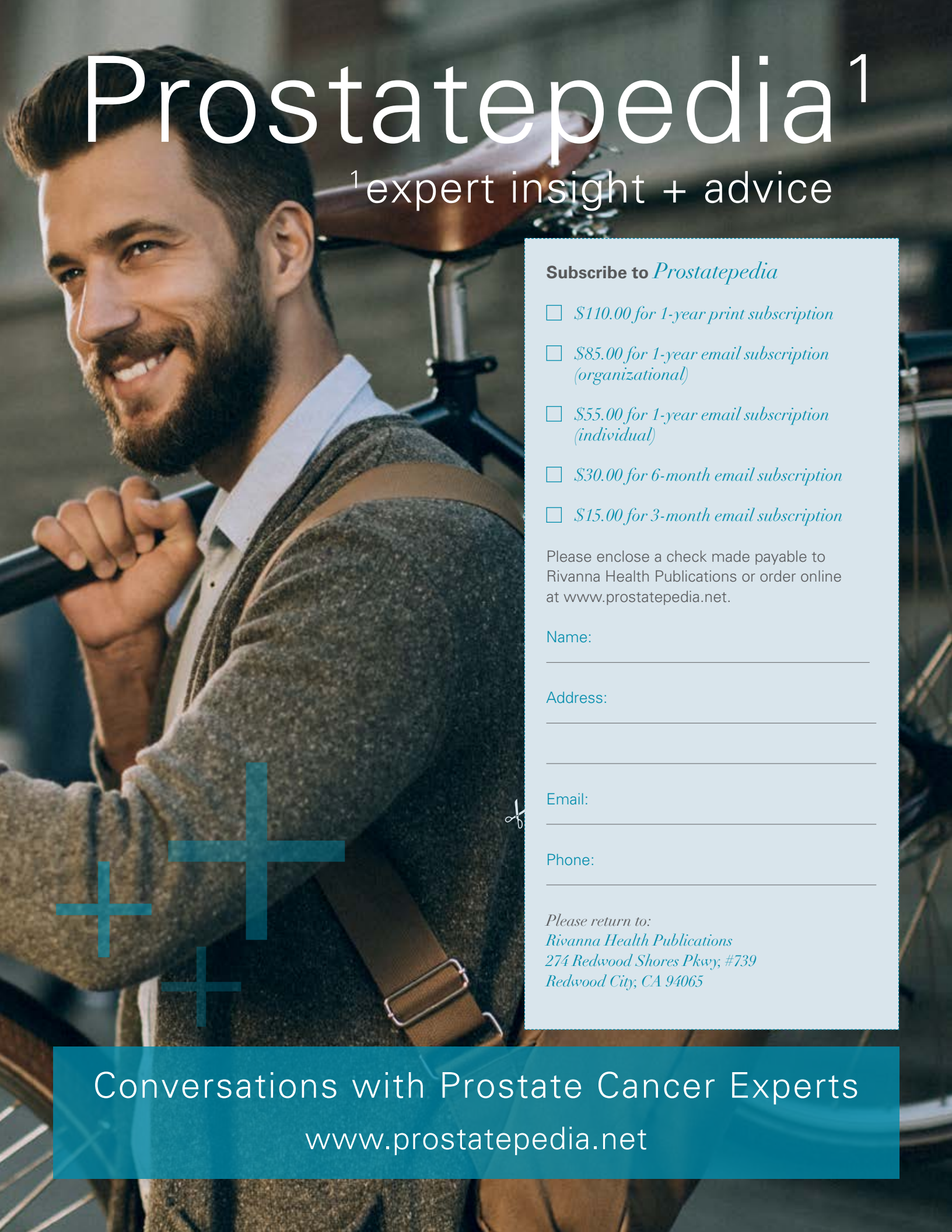
Revised: October 2016



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