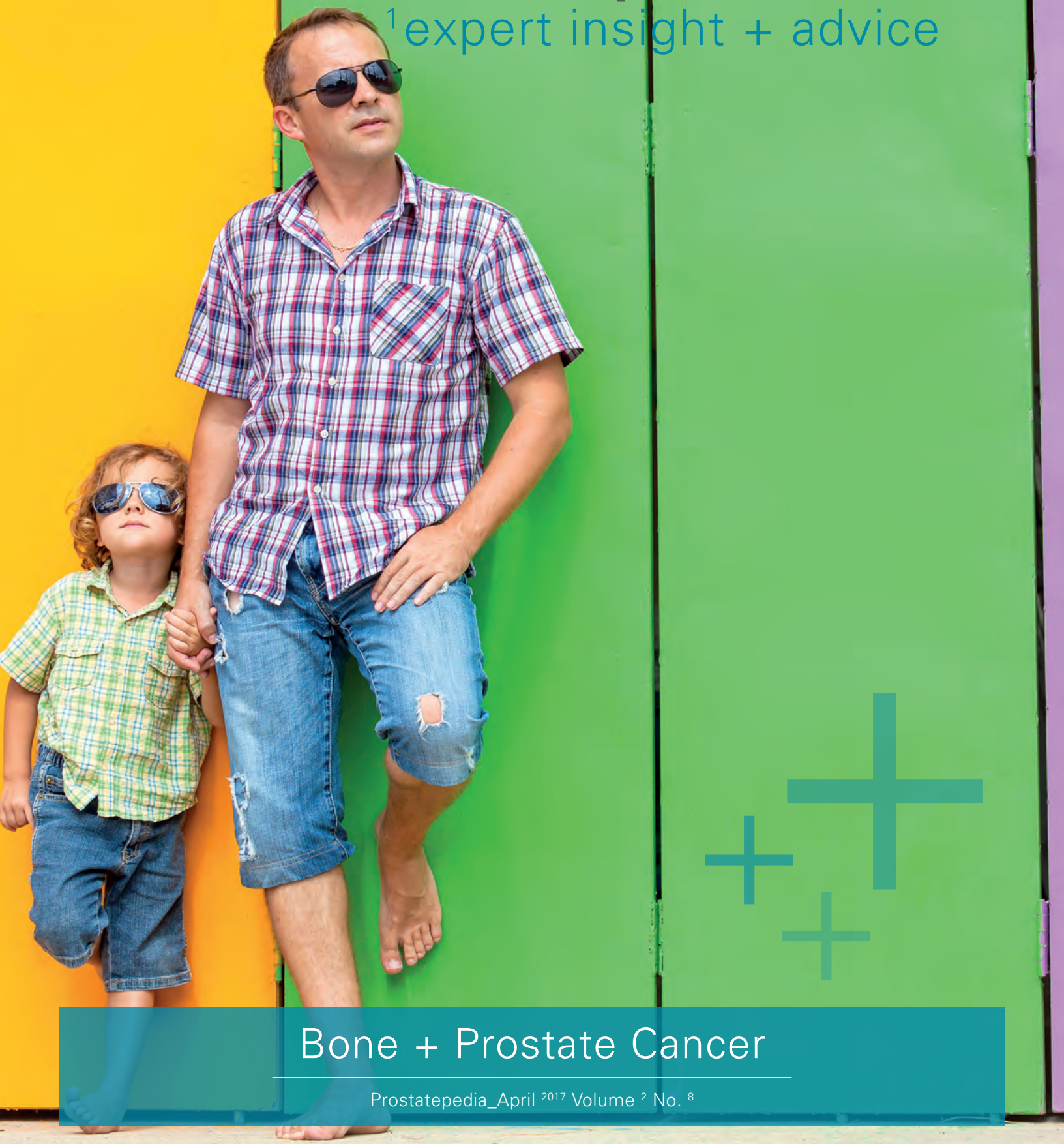
Prostatepedia[1]

[1]expert insight + advice



Bone + Prostate Cancer

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In this issue....

This month, we're talking about two major issues in the relationship between prostate cancer and bone.

First, bone is a primary site to which metastatic prostate cancer spreads. We discuss treatment options for men in this situation. Second, men on hormonal therapy develop osteoporosis. We discuss treatment options struggling with that complication.

Like reinforced concrete, bone owes its strength to the fact that it is a composite material. Concrete has excellent resistance to compressive loads, but is weak when confronted with bending forces. Steel is superior to concrete in its resistance to bending forces, but less effective in dealing with compression. Reinforced concrete deals with bending forces better than concrete and is better at compression than steel. In bone, the role of concrete is replaced by a calcium phosphate compound called hydroxyapatite. The role of the steel rebar is replaced by Type 1 collagen.

Bone is a dynamic tissue that is constantly broken down and then rebuilt in response to stress and injury. Osteoclasts cells break bone down; osteoblast cells build new bone.

When prostate cancer spreads to bone, it binds to exposed Type 1 collagen, which stimulates its growth. Prostate cancer cells and osteoblasts also stimulate each other's growth. The metastases that form are made up of prostate cancer and osteoblasts, as well as new bone put down by these cells. That is why these metastases are called osteoblastic.

The rate of new bone formation in these osteoblastic metastases is usually much higher than anywhere else in the adult skeleton, except for after a fracture.

We use this fact when detecting and treating prostate cancer. Radioactive isotopes taken up at sites of new bone formation are key to detecting metastases during a bone scan.

Radioactive isotopes that mimic calcium are used to treat prostate cancer. Xofigo (radium-223) is the most recent example. Because Xofigo (radium-223) is concentrated in bone metastases, there is limited damage to surrounding normal tissue.

Prostate cancer spread into bone involves reciprocal stimulation of cancer and normal bone cells. There is now an intense research focus on blocking the molecules involved in that process.

Xgvea (denosumab), an antibody that targets a protein called RANKL that normally stimulates osteoclasts to break down bone, is an example. It is is FDA-approved to treat osteoporosis. RANKL is also involved in the prostate cancer/bone interaction. A randomized trial showed that Xgeva (denosumab) also slows prostate bone metastasis progression.

A promising area of prostate cancer research involves identifying and targeting other molecules involved in the prostate cancer/bone interaction.

Charles E. Myers, Jr., MD

Contents:

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Oliver Sartor, MD
Xofigo + Bone Metastases

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 was also the Principal Investigator for the prospective randomized trial that led to the FDA-approval of Xofigo (radium-223) in May 2013

Prostatepedia spoke with him recently about how and why prostate cancer spreads to bone, how Xofigo (radium-223) works, and promising Xofigo (radium-223) combinations.

How does prostate cancer spread throughout the body? Does it always spread in the same way? Why does it spread so readily to bone?

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Dr. Sartor: Prostate cancer does have relatively predictable patterns of progression. We know that in the advanced stages, about 90% of patients will have bone involvement and a little over 40% will have lymph node involvement. As high as 20% of men have liver involvement in the later stages.

The exact reason for that pattern of spread is not well understood, but there does seem to be a special interaction between prostate cancer cells and bone.

There is some intriguing data that seems to indicate that prostate cancer cells bind to and grow in the same niche that bone marrow stem cells occupy. For some reason, that particular niche is very supportive of prostate cancer growth. That is the leading hypothesis for why prostate cancer patients end up with a preferential growth in bone.

The cells circulate widely. There is an old but good theory that talks about a seed-and-soil hypothesis. The seed is the cancer cell and the soil is where the cancer cells land and grow. The seed-and-soil hypothesis says you need a fertile seed and fertile soil. Unless you have both, it won't work. The soil of the bone marrow turns out to be particularly fertile for prostate cancer growth. We're still debating exactly why.

Is bone just fertile soil or do some prostate cancer treatments like hormonal therapy make it more fertile?

Dr. Sartor: There has been a bit of speculation over that. In truth, to me the data is quite speculative regarding treatment induced *soil changes*.

Even if you don't treat the cancer at all, there is still a propensity for bony spread. Does treatment promote that pattern of spread? Overall, I would say that is speculative.

What is a radiopharmaceutical?

Dr. Sartor: Radiopharmaceuticals are simply pharmaceuticals that are radioactive. There is a long history of using radioactivity in cancer treatment that goes back well over a century. Initial treatments were implantable radiation. Today, we call this brachytherapy or seed therapy: we actually put radioactive seeds into the tumor. We still do this today with localized prostate cancer.

There is a different class of radioactivity we've termed radiopharmaceuticals. We inject or ingest the radiopharmaceutical drug; the activity of the drug is dependent in part on its radioactivity. The concept of bone-targeted therapy with radiopharmaceuticals goes back to the 1950s.

Early data demonstrated that you could have bone pain relief with phosphorus-32. Phosphorus-32 is taken up into the bone. You could then radiate the areas where the phosphorus accumulates, which turns out to be osteoblastic lesions

of the bone. Those studies go back to the 1950s.

Fast-forward to the 1990s: an agent called Metastron (strontium-89) was FDA-approved. It was based on the same principal. Strontium is a calcium mimetic, or imitator. Metastron (strontium-89) goes to areas of rapid bone turnover, acting as a calcium mimetic, and then radiates the surrounding area.

The next agent to emerge was Quadramet (samarium-153-EDTMP), another bone radiopharmaceutical approved for the palliation of bone pain. It worked in the same way as Metastron (strontium-89) but the bone-binding agent is EDTMP.

Xofigo (radium-223) is also a calcium mimetic. The calcium mimetic binds the radiopharmaceutical to this bony area of turnover. (In these osteoblastic metastases—or bone metastases—you have higher areas of bone turnover.)

Xofigo (radium-223) is different from the prior therapies. It is an alpha particle, which may not mean very much to most people.

The preceding radiopharmaceuticals phosphorus-32, Metastron (strontium-89), and Quadramet (samarium-153-EDTMP) are all beta emitters.

A beta particle is really like an electron. An alpha particle has two protons and two neutrons. It's a huge particle relative to the beta and carries much more energy.

These huge particles can do a couple things. Number 1: they're more destructive. Number 2: they actually don't go very far into bone, which is surprising. An alpha particle is like a big Mack truck hitting a bunch of debris. You may not be able to hit

very far with your Mac truck, but you are going to cause a lot of destruction to what you actually do hit.

A beta particle is more like a speeding bullet. It will go further, but it won't do as much damage.

After some early studies indicating that Xofigo (radium-223) would have a positive effect on bone, they launched a large, over 700-patient comparative Phase III study. It was an interesting trial design, because men could get any type of treatment they wanted except for chemotherapy or experimental treatments (plus or minus radium-223)

Everybody was getting some form of hormone during the trial. This was in an older era, so they weren't getting Xtandi (enzalutamide) or Zytiga (abiraterone). They were getting agents like Nizoral (ketoconazole), Diethylstilbestrol (DES), (Ozurdex) dexamethasone, prednisone, Nilandron (nilutamide), etc.

The question was: could Xofigo (radium-223) add to the standard of care treatment? The randomization was standard of care treatments plus Xofigo (radium-223). Lo and behold, that did turn out to be a positive study. Xofigo (radium-223) was shown to prolong survival and to reduce the risk of death by about 30%.

It was FDA-approved and now Xofigo (radium-223) is in our broad armamentarium. We consider Xofigo (radium-223) for people with bone metastatic prostate cancer. If you don't have bone metastases, then it is not considered.

What should patients expect when they take Xofigo (radium-223)?

Dr. Sartor: There was a lot of initial fear about giving an alpha particle.

This is the first alpha particle ever approved for the treatment of human beings and the first alpha particle radiopharmaceutical.

There was a bit of trepidation and concern over what might happen. But what actually happened was not much. It was kind of interesting.

Xofigo (radium-223) is excreted in the bowel, so there is a little excess diarrhea. There is a little excess fatigue. About 3% of patients (over the placebo group) have vomiting. But 3% percent with vomiting and a little bit of diarrhea was not too much. If you compare that to chemotherapy, the side effects are much less.

There was a little bit of thrombocytopenia, which is the fancy word for low platelets. That is serious in some; I think it was about 7% of patients. About 1 or 2% of patients might have some white cell suppression.

Overall, Xofigo (radium-223) was extremely well tolerated. Most patients were surprised. They thought they would have some sort of ill effect, but it just didn't happen.

Why does Xofigo (radium-223) have a survival benefit?Can it just better target bone mets? Or is there something else going on?

Dr. Sartor: That is the obvious answer. There is more speculation.

The obvious part is you're taking people with bone metastatic disease and you kick the cancer where it hurts.

Bone is where the cancer is residing and where the disease burden is located. If you manage to alter that disease burden in a meaningful way, then it is not a surprise to me that you would end up with better survival. That is what we thought.

On a more speculative front, there is a hypothesis that if you decrease the burden in the bone, perhaps you decrease the burden elsewhere. But that is a hypothesis, not a fact.

What kind of combinations with Xofigo (radium-223) do you think look the most promising?

Dr. Sartor: From the very beginning, Xofigo (radium-223) was co-administered with other agents.

I mentioned the Phase III trial called ALSYMPCA. ALSYMPCA utilized that standard-of-care I talked about earlier. The older hormones people used [Nizoral (ketoconazole), Diethylstilbestrol (DES), (Ozurdex) dexamethasone, prednisone, Nilandron (nilutamide)], have been largely replaced by newer hormonal therapies like Zytiga (abiraterone) and Xtandi (enzalutamide).

We've now shown combinations with those newer hormonal therapies are safe. There have not been a lot of formal trials, but we have an expanded access program in which people co-administered Xofigo (radium-223) along with the newer hormonal therapies. It didn't seem to have any adverse events.

There is the possibility, which will require proper trials to determine, that it may be a good idea to combine these agents with Xofigo (radium-223). It wouldn't surprise me if that turned out to be the case.

If you go back to some of the initial radiation studies on treating the prostate, they found unequivocally that adding hormonal therapy to radiation led to better survival. This is conceptually similar in that you're using a new hormone and a new form of radiation.

There are a couple of hypotheses that seem to have more credibility than others. One of these is that a combination of Zytiga (abiraterone) and Xtandi (enzalutamide) plus Xofigo (radium-223) is better than Zytiga (abiraterone) or Xtandi (enzalutamide) alone. That is being evaluated in a Phase III trial that has fully accrued, so we'll have some answers on that.

That is one set of combinations that look promising.

Another area that is a bit provocative, but for which we don't yet have a proper study to ascertain if it's true or not, is the combination of Xofigo (radium-223) and Xgeva (denosumab). There does appear to be some data indicating that patients on both Xofigo (radium-223) and Xgeva (denosumab) do a little bit better than those on Xofigo (radium-223) alone. That is speculative at this time. It's not a properly controlled study. That is a hypothesis, not a fact.

Another approach that has some rationale is the combination of radiopharmaceuticals and immunotherapy. That combination may yield improvements in therapy. It would be very speculative to say that combination improves survival because those studies are not yet in place.

This is being explored in a trial combining Provenge (sipuleucel-T) with Xofigo (radium-223). The study is too small to give a plus or minus on the favorable clinical outcome and is designed to look at some of the immunologic effects. Dr. Emmanuel S. Antonarakis and colleagues at the Johns Hopkins University head the trial. Tulane University is also working on the project. (See page 18 for a conversation with Dr. Antonarakis about this trial.). Pp[1]

Raoul Concepcion, MD
A Urologist's View of Bone Metastases

Dr. Raoul Concepcion is the Director of The Comprehensive Prostate Center in Nashville, Tennessee and the past President of the Large Urology Group Practice Association (LUGPA.)

Prostatepedia spoke with him recently about approaches to bone metastases within urology groups.

How did you come to focus on prostate cancer?

Dr. Concepcion: I went through my training at Vanderbilt University Department of Urology in Nashville from 1984 to1990. At that point, our program was heavily weighted towards the surgical management of prostate cancer with nerve-sparing radical prostatectomy, as developed by Dr. Patrick Walsh at the Johns Hopkins School of Medicine. I also became interested in bladder cancer and bladder reconstruction because techniques for continent urinary diversion were being developed.

I went into independent practice in 1990 and maintained my focus on urologic oncology, specifically prostate and bladder cancer, and continued work in clinical research trials. By the mid-2000s, it became abundantly clear that many of the prostate cancer agents being developed in clinical trials,

"Bony metastases can be detected in a couple different phases of prostate cancer."

and ultimately gaining FDA-approval, would allow urologists to remain intimately involved in patient care as men progressed to castration resistance, as opposed to automatically sending them to medical oncology.

How does a urologist know when a man has developed metastases?

Dr. Concepcion: Fortunately, the majority of prostate cancer diagnosed today tends to be low-risk and associated with lower Gleason grades. For those men, active surveillance may be an appropriate treatment option. The challenge now is not to just identify prostate cancer, but to identify *significant* prostate cancer: those at risk for dying of their disease if left untreated. If you have Gleason -3 + 3, what we are now calling Group Pattern 1, or Gleason 3 + 4 (Group Pattern 2), the recommendation is not to do a staging work up. The likelihood of finding metastatic disease is very low. But if you *do* pick up a higher-grade clone on biopsy in a Gleason 4 or 5 prostate cancer, that man should definitely undergo a staging workup—usually a CT scan and bone scan—to look for metastatic disease.

Bony metastases can be detected in a couple different phases of prostate cancer. Sometimes, bone metastases are found at initial diagnosis during staging work-up. This usually happens with higher-grade tumors. The second phase is when men progress past definitive therapy and adjuvant treatment to we now call metastatic castration resistant prostate cancer (mCRPC).

After diagnosis, both low-grade and high-grade patients decide on prostate cancer management. Lower-grade patients can choose active surveillance, radiation therapy, radical prostatectomy, or even focal therapies like cryotherapy.

Options for higher-grade patients could include multi-modality therapy of surgery, radiation therapy, and hormones. These patients are really the people at risk.

After an individual has been treated definitively for prostate cancer, we measure his PSA after therapy. If his PSA starts to go up again, he is said to have a biochemeical recurrence.

For the most part, these patients do not have symptoms. They're not in pain. They don't have significant fatigue. Again, these are patients who have been definitively treated and are currently not on therapy.

Once his PSA starts to go up, we start to look at the rapidity with which it goes up. We call this PSA kinetics, or doubling time. If there is a rapid doubling time in a man who had a higher grade Gleason Pattern at diagnosis, we know he has a higher risk of developing metastatic disease.

We usually go ahead and get a scan when his PSA goes above 10. If that scan is still negative in a high-grade patient with a rapid doubling time, most urologists initiate androgen deprivation therapy. Androgen deprivation therapy, or hormonal therapy, tries to drive down testosterone levels into castration range.

If his PSA then starts to go up *again*, he now has, by definition, mCRPC. Again, these are patients with prostate cancer that has been definitively treated. They have then gone on androgen deprivation therapy until their testosterone levels got to less than 50, and then their PSAs started to go up again.

What is the trigger for the urologist to start looking again for bone metastases? That has never been really well defined.

I participated in a consortium of academic and community urologists, medical oncologists, and radiation oncologists called the RADAR (Radiographic Assessments for the Diagnosis of Advanced Recurrence) working group chaired by Dr. E. David Crawford to answer just that question.

We recommended that in such patients we should go ahead and look for metastases with a bone scan, a CT scan, or some of the new advanced imaging techniques when the PSA gets to 2.

"That has never been really well defined."

Why would you hesitate to look for bony metastases earlier?

Dr. Concepcion: I think most urologists, unfortunately, extrapolate what they know about PSA in the early stages when patients *aren't* on hormones to the castration resistant prostate cancer space.

If a patient had never been on hormones and his PSA is low, usually it means they don't have a lot of disease. It's become a real hurdle, an educational challenge, to get urologists to start thinking about that and not to wait until patients are symptomatic.

Do you think it would make sense for such a patient reading this to ask his urologist to scan him earlier?

Dr. Concepcion: Yes, I think that would be very appropriate. Unless you're being treated by a urologist with a lot of expertise… A lot of general urologists aren't going to know about the RADAR recommendations.

Are these scans usually done at the urologist's office or does the urologist refer the patient to someone else?

Dr. Concepcion: It depends. Most urologists in community practices, especially in bigger groups, have their own CT scans. That part of the work-up can be done in the urology office.

Technetium-based bone scans usually require a nuclear medicine department and are done in a hospital. A lot of times, we'll get a CT scan in our office and then coordinate with a free-standing imaging center or a hospital-based imaging center to get a nuclear medicine scan.

Does androgen deprivation therapy weaken the bone?

Dr. Concepcion: Androgen deprivation therapy has a profound effect. The initiation of androgen deprivation therapy—usually a shot of an LHRH analog, whether it be an agonist or an antagonist—automatically sets into play a cascade of events that will result in bone mineral density loss.

The goal of androgen deprivation therapy is to reduce testosterone levels so that we're not driving the tumor itself as we know that prostate cancer is a hormonally driven disease.

The problem is that testosterone in its native state within the male gets converted to estrogen. Estrogens are bone protective.

Most of your readers will understand that postmenopausal women are at an increased risk of developing osteopenia or osteoporosis. That is why postmenopausal women take a lot of calcium, vitamin D, and what we call oral bisphosphonate therapy.

The osteoclast, or the cells within the bones that break down bone, take up oral bisphosphonate therapy. This type of therapy actually reduces the amount of bone breakdown.

We know now that because of the lack of peripheral conversion to estrogen, prostate cancer patients on hormonal therapy can start to suffer significant bone mineral density loss.

Let me define significant. A female going through menopause usually has a loss of bone mineral density of about 1.5 to 1.8% per year. Men age 45 to 50 without prostate cancer usually have a bone mineral density loss of about 0.5 to 0.7%.

After a prostate cancer patient's first shot of androgen deprivation therapy, his bone marrow density loss will shoot up to somewhere between 3.5 to 4.5% per year.

That bone marrow density loss doesn't go on forever. It increases the risk of fractures and complications, but it doesn't set up an environment for prostate cancer cells to grow.

Can you use oral bisphosphonate therapy to protect the bones during this time?

Dr. Concepcion: It depends. We put all these men on calcium and vitamin D. We tell them to exercise. We encourage them to lose weight. We encourage them to stop smoking.

Many large urology groups across the United States have set up their own bone clinics specifically addressing these issues. (Urologists are the primary prescribers of androgen deprivation therapy.)

And some men do take bisphosphonates. There is a drug called denosumab, which is a fully human monoclonal antibody given subcutaneously to men with prostate cancer who are non-metastatic on androgen deprivation therapy.

If you're on androgen deprivation therapy and do not have evidence of spread into your bones, this drug is approved to help increase bone mineral density. Prolia given in a 60 milligrams dose subcutaneously every 6 months. It will increase bone density significantly.

Any side effects?

Dr. Concepcion: There tends to be some joint pain, but the side effect everybody worries about is osteonecrosis of the jaw. The incidence is less than 2 to 3%. The risk factors for developing osteonecrosis of the jaw usually occur in men with poor dental health. A gentleman with poor dental hygiene—gum disease, cavities, teeth that need to be pulled—should address those issues before starting denosumab.

I should note that the same molecule is approved for the prevention of skeletal-related events in men with documented metastatic disease. The Xgeva dose is 120 mg, monthly.

Is Xofigo (radium-223) a medication that urologists prescribe?

Dr. Concepcion: Xofigo (radium-223) is an alpha emitter radiopharmaceutical. The urology world has extensive history in the use of radiopharmaceuticals over the past 15 to 20 years.

The original radiopharmaceuticals were beta and gamma emitters. These drugs had been approved for prostate cancer patients with painful bony metastases.

If you had a patient with significant bone pain due to prostate cancer spread into the bone, you could send him to a radiation oncologist for external beam radiation. If the man had multiple areas, you could send him to get these radiopharmaceuticals.

The problem with the older radiopharmaceuticals—the beta and gamma emitters—is that they are smaller molecules. The bony metastases are in the cortex of the bone. When these older radiopharmaceuticals are given via an intravenous injection, they go

to where the bone is remodeling. The molecules then get into the bone marrow, which can cause myelosuppression. You become anemic.

The original radiopharmaceuticals were really only prescribed for palliation. They were given for pain relief. There was no survival benefit. Xofigo (radium-223) was approved in the United States in 2013, is an alpha emitting agent. This is a bigger molecule. The depth of penetration into the bone marrow is not significant. We see less myelosuppression.

Either a nuclear medicine specialist or a radiation oncologist gives Xofigo (radium-223), which was a one-minute intravenous injection once every four weeks for six consecutive months. It goes wherever calcium goes. Calcium goes to go wherever bone is remodeling, where the cancer cells break down the bone. Xofigo (radium-22) then follows calcium. It's what we call a calcium mimetic agent.

The registry trial for Xofigo (radium-223) showed a 3.6-month survival benefit. Xofigo (radium-223) is then a therapeutic agent. It is not just for palliation or pain relief. It also will help build new bone. It's very well tolerated.

It is FDA-approved for patients with metastatic castration resistant prostate cancer who have bony metastases. You cannot have cancer that has spread into your liver, lung, etc. You can have limited lymph nodal disease.

Why no visceral metastases?

Dr. Concepcion: Patients with visceral metastases are rapidly progressing. They're not going to see the beneficial effect of Xofigo (radium-223). They will need to move on quickly to a chemotherapeutic agent.

Most of us believe that you shouldn't wait until patients are symptomatic or having a lot of pain. We do know Xofigo (radium-223) reduces the amount of pain medicines a patient needs.

Many of us believe that you should start the drug earlier, when men are minimally symptomatic. That doesn't necessarily mean pain. Symptoms could include worsening fatigue. You're just not as active as you used to be. You may not be taking an opiate, but maybe you're taking a couple more Tylenol or Advil than you normally do. Instead of playing 18 holes of golf every week, now you're a little bit achy and tired and you're only playing nine holes.

It seems like those might be symptoms easily missed by patients.

Dr. Concepcion: Right. Sometimes the patient himself is very stoic about it. He may not report it, but the caregiver does.

Isn't that a common phenomenon in the prostate cancer world?

Dr. Concepcion: Patients are very stoic. Many are very proud and very robust. They don't want to admit that they're slowing down a little bit.

Is there anything else you think patients should know about Xofigo (radium-223)?

There are two agents, Xofigo (radium-223) and Provenge (sipuleucel-T), that don't necessarily result in a rapid drop in your PSA, but have a documented survival benefit in clinical trials.

How do you know it works? Urologists have to be better about monitoring, getting more scans, and scanning more frequently. Pp'

Fabio Almeida, MD
Imaging For Metastases

Dr. Fabio Almeida, Medical Director of Phoenix Molecular Imaging and a member of Prostate Cancer Research Institute's Board of Directors, has extensive experience in PET/CT imaging for prostate cancer.

Prostatepedia spoke with him recently about imaging to detect bone metastases.

How did you become involved in prostate cancer imaging?

Dr. Fabio Almeida: I'm a nuclear medicine specialist and an oncologic radiologist. I was the Director of Nuclear Medicine for the University of Arizona until about 2010. I then transitioned into concentrating on PET/CT imaging for oncology and had the opportunity to open our own research facility in Phoenix, Arizona. Our concentration has been the Carbon-11 Acetate PET/CT scan specifically for prostate cancer.

I am now the Medical Director at Phoenix Molecular Imaging (http://www.phxmi.com/) where we have open protocols. I see all sorts of cancers on a daily basis.

We recently expanded with three additional facilities offering MRI, CT, ultrasound, plain film, and other general nuclear medicine. We provide ultrasound and multi-parametric MRI services for our prostate cancer patients. We're really happy about the expansion.

In the years since we opened Phoenix Molecular Imaging, I've become a part of the prostate cancer imaging community.

I am very hands-on. I am very interactive. I do see most of the patients who come in for imaging. We discuss results right afterwards. We try to really make this a different experience for our prostate cancer patients: to get their questions answered and to help them navigate as much as possible.

It's exciting to be in a position to really try to do something different and to make the patient experience as exceptional as possible.

What kinds of imaging techniques might a prostate cancer patient encounter?

Dr. Almeida: Imaging is important across the spectrum of prostate cancer.

In the initial diagnosis or staging phase, ultrasound is still one of our very primary tools. Color Doppler adds a significant enhancement to ultrasound for evaluating the gland for size and obvious lesions.

We've begun to adopt multi-parametric MRI in that same scenario, because unlike any other imaging technique, MRI provides the ability to look at the prostate gland architecture and the different zones within the prostate gland. MRI does a very good job of helping us understand if we dealing with prostate cancer or not.

We now have a lot of guidelines, in particular PI-RADs, which provide standardization for radiologists on interpreting and providing results in way that is meaningful to clinicians. (The idea is to follow what we've been doing with breast mammography for a long time.)

PI-RAD is a five-point scale. When we say something is a PI-RAD 4 or PI-RAD 5, that means that we think there is some imaging characteristic highly suspicious for prostate cancer. A lower PI-RAD number tells us we need to keep watching the man's cancer or that we think his cancer is not suspicious.

It's challenging in that you do need to have high-end MRI equipment. You also need trained radiologists who are very familiar with interpreting the scans for it to be useful. We're still working on getting that information disseminated so that everybody in the imaging community is up to

speed. Every day that goes by I see another facility stepping up their skills. It's exciting.

So it's not about a facility being able to perform the scan, but also about them being able to interpret the results?

Dr. Almeida: Certainly. It's a steep learning curve.

Whenever we're using scaning to help us improve our detection rate of cancer, we need to be careful about things like *over-* and *under-calling*. Both have fairly detrimental effects. We really want to be as close to 90 to 100% accurate. That can be somewhat challenging to achieve with any diagnostic imaging test.

"Imaging is important across the spectrum of prostate cancer."

If you call everything you see, you're always going to catch the cancer, but you're also going to over-call a fair amount and subject people to additional testing or even potentially therapies they didn't need. If you're more conservative and only call the things that are obvious or big, you're going to miss subtle cancers. People with cancers that should be treated might not get the therapy they need.

That is the balance on any diagnostic test. We have to be careful.

MRI is a very sophisticated test. There are a lot of parameters and sequences that need to be reviewed. It takes some education to do that.

Are there other imaging techniques used to detect bone mets?

Dr. Almeida: We also talk about CT scanning and technetium bone scans as part of the initial workup.

Most urologists don't utilize those two techniques unless the patient is very high risk: a high-grade Gleason 7 or higher or bulky disease on digital rectal exam.

The urologist may then use a CT scan and a technetium bone scan to look for obvious metastases in the pelvic or abdominal lymph nodes or the bone.

The technetium bone scan has not been very useful for the urology community, because we only find bone metastases when there is a fair amount of disease. The man's PSA usually has to be pretty high—above10 or 20.

With the CT scan, we generally use a size-criteria. Cancer in small lymph nodes still goes undetected.

There are significant limitations to both CT and technetium bone scans.

What about PET/CT?

Dr. Almeida: I have significant experience with the PET/CT Carbon-11 Acetate scan. The Mayo Clinic in Rochester, MN works very heavily with the PET/CT Carbon-11 Choline scan.

There are a few other agents: 18F-Fluciclovine PET/CT was recently FDA-approved and a myriad of PSMA PET/CT agents are in development. All of these agents are useful in the recurrent setting—when a man's cancer has come back after treatment—rather then after initial diagnosis.

If we're trying to figure out if a gentleman with a rising PSA has cancer, these imaging techniques may still be problematic in that we cannot differentiate between cancer and common benign entities like benign prostatic hypertrophy and prostatitis.

"Patients can gain access to these agents by joining a clinical trial."

How do you use the tests then?

Dr. Almeida: We look to these imaging studies to help us improve on staging once we have established the patient has prostate cancer through a TRUS or standard random sextant biopsy.

Perhaps he has a moderate to high-grade or high-risk prostate cancer? PET/CT imaging help us evaluate the whole body: the lymph nodes in the pelvis and the abdomen and the bone.

Exactly how that imaging will impact initial staging or even change therapy from surgery to radiation to a multi-disciplinary approach is still to be determined.

This is an exciting area of research. I think we still need to do a fair amount of work to understand the impact this kind of imaging will have.

Are these highly specialized imaging techniques are only available in a clinical trial?

Dr. Almeida: As part of the initial workup and diagnosis for prostate cancer, all of these imaging agents are only available in an off-label or research setting. There is no FDA-approved PET/CT imaging agent for initial diagnosis and staging.

That translates into the scans not being covered by insurance? A patient would have to pay out-of-pocket…

Dr. Almeida: Correct, in the initial staging setting.

What about scans in the recurrent setting—when someone's cancer comes back after treatment?

Dr. Almeida: After radical prostatectomy or radiation (or both), a rise in PSA happens in about 40% of men. (That number varies according to whom you ask.)

Fairly low rising PSAs are really non-detectable on standard imaging. In this situation, PET/CT imaging agents are demonstrating themselves to be very useful.

With PET/CT Carbon-11 Acetate and Choline, we can find small amounts of residual recurrent disease and metastases difficult to find on MRI and impossible to find on any other imaging modality.

In the post-prostatectomy setting, this is particularly useful.

Our research with PET/CT Carbon-11 Acetate, which I think has been mirrored by research with Carbon-11 Choline and several PSMA agents, shows that we do have a threshold effect with PSA.

If we scan men with PSAs anywhere from 1.0 to 2.0, the test is almost always going to be positive. Our research indicates that a good guideline is to image when the PSA is over 1.1, with a detection rate of over 90%.

We also find that PSA doubling time has a significant impact. If the PSA is moving quickly—doubling in 3 or 4 months—these tests are very useful even if the PSA is only 0.2 to 0.5. Detection rate are about 60 to 80% when there is momentum behind that PSA.

We're usually able to find where these lesions are—and that can have a huge impact on patient care. Each scenario has a different treatment path. But if we don't know whether a man has a local recurrence or distant metastases, we have to assume he has widespread metastases. That has a huge impact on potential therapeutic choices.

Then you can choose between a local or systemic therapy?

Dr. Almeida: Yes—or whether a combination of approaches is best.

Let me give you an example. We image someone with a rising PSA after a radical prostatectomy. Small areas in his prostate bed and in his lymph node on the upper left of the pelvis light up on the Carbon-11 Acetate PET/CT scan.

That tells us that we should extend his salvage radiation therapy to the prostate bed and to lymph nodes in the pelvis. Depending on other risk factors, he will probably also benefit from at least a short course of systemic therapy. These kinds of scans can also have a significant impact on how we deliver that radiation.

Whereas, if the scan shows that he only had some disease in his prostate bed and not in any lymph nodes, he would probably do very well with radiation therapy to the prostate bed alone and no other therapy.

With this imaging, we may also see early, subtle bone metastasis, which will significantly change therapeutic approaches. Radiation still may be an option in that scenario, but we will need to deal with bone metastases. If there are only a few lesions—what we call oligometastatic—more and more of my radiation colleagues are adding additional radiation to those local areas. We might also add a few cycles of chemotherapy.

The imaging provides information so that we know when we need to be aggressive earlier.

It's worth knowing if a man has bone metastases where those lesions actually are?

Dr. Almeida: There are two schools of thought on that. Some urologists would say that if there is one bone metastasis, there have got to be multiple bone metastases. They then treat it as if the lesions are micro-metastatic and widespread.

That stance is appropriate when we're dealing with the technetium bone scan, because it pretty universally underestimates bone metastases.

But more advanced techniques like the 18F-Sodium Fluoride (NaF) PET/CT bone scan sees very small lesions of one or two millimeters in size in men with very low PSAs. It does a much better job of evaluating bone metastases and we do truly find patients with singular or oligometastatic bone metastases.

There is a lot of work being done on how patients respond to treating those few lesions more aggressively with a combination of radiation and systemic therapies.

But theoretically, if you see one bone lesion couldn't there be others you just can't see yet? Those micro-metastatic lesions you were just talking about?

Dr. Almeida: What we know with prostate cancer is that it does favor the bone environment as an area of metastasis. Bone has a rich blood supply; those cells do multiply in

that area. It is a fair assumption that if there is one bone metastasis, there are probably others.

That makes a case for if we treat one lesion with some sort of ablative technology (radiation, ultrasound, or radiofrequency) alone and do not address the rest of the bones, we will likely see that patient develop another bone metastasis pretty quickly.

Our studies show that in that scenario, about 50% of men treated with radiation alone will develop another bone metastasis in about 6 to twelve months.

That demonstrates that there are other metastases and that we really need a multi-disciplinary approach. Hormone therapy may need to be part of the mix. Some men are also likely to benefit from very early chemotherapy. It seems logical to hit those bone metastases from multiple different mechanisms.

Someone with widespread skeletal lesions will need even more aggressive therapy. Other options emerge, such as Xofigo (radium-223), as part of a whole bone directed therapy.

How valuable is this information? If patients have the resources, should they travel or pay out-of-pocket to be scanned?

Dr. Almeida: There are a couple of nuances to it. The PET/CT Carbon-11 Choline is covered by most Medicare plans at the Mayo Clinic in Minnesota.

PET/CT Carbon-11 Acetate remains part of a large-scale open access clinical trial. There is an out-of-pocket fee.

All of the PSMA agents are out-of-pocket if they aren't part of a clinical trial. But there are opportunities to get these scans at a relatively low cost or for free through a clinical trial.

The downside to a clinical trial is that some of the larger universities usually have a very specific protocol in mind. Additional care subsequent to the imaging study may need to be managed at that particular facility, so additional travel over time to that center would be required.

It's more difficult to take the results from the imaging studies back to your primary care provider and have them use that information to direct your therapy. It's not impossible, but it can be more challenging.

What can you tell us about Axumin?

Dr. Almeida: Axumin (fluciclovine) was FDA-approved last year. We are seeing Medicare beginning to reimburse. It is only approved in the case of recurrence, not for initial diagnosis or staging.

It shows some promise, but more information is necessary. Published research from Europe is not placing that agent's sensitivity or detection rates anywhere near what we've seen PET/CT Carbon-11 Choline and Carbon-11 Acetate.

We're still trying to understand exactly why that might be. It may be because of how the studies were performed, the equipment, or the reading criteria. Several factors that have nothing to do with the actual performance of that agent may explain the differences in sensitivity and detection rates.

A number of places are assessing its utility. The scan is available, but experience is still limited enough that we don't know exactly how to interpret some of the results we're getting.

Over the next year, more and more of these various agents—whether it be PET/CT Carbon-11 Acetate or Axumin (fluciclovine) or PSMA—will be available in clinical trials. Patients can gain access to these agents by joining a clinical trial.

Currently, the major downside to PSMA agents is that they all have a urinary tract excretion route, which means we'll see a fair amount of radioactivity in the bladder and along the ureter. This will interfere with the assessment of the prostate bed/area and pelvic lymph nodes. We may miss some local recurrences because of that, or we'll have to adjust our protocols to help us read around it. We don't see this issue with PET/CT Carbon-11 Acetate. But, because of the higher potential specificity of PSMA agents, it is likely that we'll see research heading down that path for the next couple of years.

Is there anything else you think patients should know about imaging?

Dr. Almeida: PET/CT scanning is a whole body technique. If it's done with a very high-end camera, it can be done pretty quickly. In our facility a PET scan takes between 15 and 20 minutes. We image from the pelvis all the way to the top of the head. It is a painless procedure.

By contrast, a multi-parametric MRI of the pelvis is a 45-minute to hour-long procedure. That is still tolerable. But an MRI from the pelvis to the top of the head would be an uncomfortably long procedure. It's not often done.

In general, we do not see side effects or allergies with Carbon-11 Acetate. So, it is a very safe test. Other imaging agents have potential serious allergic reactions.

It is simple for patients. That ease-of-use is propelling PET/CT imaging forward. Pp[1]

Clinical Trial: Emmanuel Antonarakis, MD Combining Xofigo + Provenge

Dr. Emmanuel Antonarakis is an Associate Professor of Oncology and Urology at the Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center.

Prostatepedia spoke with him recently about his clinical trial combining Provenge (sipuleucel-T) with Xofigo (radium-223).

How did you come to focus on prostate cancer?

Dr. Emmanuel Antonarakis: I have been a faculty member at the John Hopkins Sidney Kimmel Comprehensive Cancer Center for about seven years. During my fellowship, I met many patients who had advanced prostate cancer. At that time, there were very few FDA-approved therapies for Stage 4 prostate cancer. We had Taxotere (docetaxel) and nothing else.

I realized that there was an unmet medical need to develop new drugs and therapies for men with advanced prostate cancer.

I also had several members of my family, immediate and distant, diagnosed with prostate cancer. I decided to really research this disease and develop new clinical trials for those patients.

What is the thinking behind your clinical trial?

Dr. Antonarakis: There is a lot of interest in combining immune therapies with other drugs to make immunotherapy work better.

"We think radiation therapy can boost immunotherapy."

The FDA approved Provenge (sipuleucel-T) in 2010. We've been using that drug for the last seven years. We've seen that patient survival improves by approximately three to four months on Provenge (sipuleucel-T) compared to a placebo. However, we don't typically see PSA levels dropping, tumors shrinking, or symptoms improving.

While we recognize that Provenge (sipuleucel-T) is an immunotherapy that does have some activity in prostate cancer, the effects are fairly marginal. We, and others, have been trying to increase its effectiveness by combining it with other medications.

In this particular trial, we're combining Provenge (sipuleucel-T) with a radiopharmaceutical drug called Xofigo (radium-223).

Why? We think radiation therapy can boost immunotherapy for several reasons. One reason is that in patients who receive external beam radiotherapy, or conventional radiotherapy, healing tumor cells can release proteins called antigens from inside the cancer. Those antigens released into the circulation by radiotherapy can stimulate the immune cells that recognize and fight prostate cancer.

The second reason is that there is some preliminary evidence that these liquid radiotherapies—or radiopharmaceutical drugs that are injected into the veins, bind to the bone and then give off radiation particles at the bone—might also increase the number of antigens. An antigen is a substance foreign to the body that elicits an immune response. These antigens are released as part of the cancer cell into the circulation and are then recognized by a stimulated immune system.

The hypothesis is that if you combine Xofigo (radium-223) with Provenge (sipuleucel-T), you would see higher

immune responses against the tumor than if you used Provenge (sipuleucel-T) by itself.

What should patients expect?

Dr. Antonarakis: We're selecting hormone-resistant prostate cancer patients with one or more bone metastases. In other words, their cancer has progressed after standard hormone therapy, but they don't have any bone pain. Bone metastases have to be present, you have to have hormone-resistant disease, but you can't have bone pain.

Patients will be randomized to one of two groups. Group 1 will receive Provenge (sipuleucel-T) by itself, according to the FDA dose schedule of three doses two weeks apart.

"Liquid radiotherapies might also increase the number of antigens."

Group 2 will receive a combination of Xofigo (radium-223) plus Provenge (sipuleucel-T). The Xofigo (radium-223) will be given first according to the FDA dose schedule of intravenous injection every four weeks for six doses.

After the second out of six doses of Xofigo (radium-223), they will then receive the Provenge (sipuleucel-T). After Provenge (sipuleucel-T), they will receive the third through sixth doses of Xofigo (radium-223). In other words, we give Provenge (sipuleucel-T) in between the second and third Xofigo (radium-223) doses.

"We are guessing when the immune system will be most stimulated by the Xofigo (radium-223)."

Why in the middle?

Dr. Antonarakis: We are guessing when the immune system will be most stimulated by the Xofigo (radium-223). We hypothesize—and this is only a guess—that it will take at least two doses of Xofigo (radium-223) to release enough tumor antigens into the circulation to simulate the antitumor immune cells. We wanted to continue to give at least four additional doses of Xofigo (radium-223) after the immune system has been stimulated to see if we can maintain a prolonged immune stimulation period.

In a perfect world, we would have multiple different sequences, but that would require a much larger trial with at least four different study arms. We thought that was too complicated.

You said you were looking for patients with one or two bone metastases. Are you excluding those with more?

Dr. Antonarakis: Patients have to have a minimum of one bone metastasis, but there is no maximum. If a patient has a hundred bone metastases, he is eligible.

Patients cannot have liver or lung metastases larger than one centimeter in diameter. Why? Xofigo (radium-223) does not get into the liver or the lung. It only targets the bone. And we have never seen liver or lung metastases shrink with Provenge (sipuleucel-T) by itself. We wanted to exclude patients who wouldn't benefit from Xofigo (radium-223), so we decided to exclude liver or lung metastases more than one centimeter.

We also exclude patients with lymph node metastases more than three centimeters.

We allow small liver or lung metastases less than one centimeter and modest lymph node metastases less than three centimeters.

"...you can't have bone pain."

Is the trial being conducted only in Baltimore, Maryland?

Dr. Antonarakis: The trial is being conducted at four sites across the United States: John Hopkins University in Baltimore, Maryland is the lead site. The other sites are Tulane University in Louisiana; Duke University in North Carolina; and Cedars-Sinai Cancer Center in Los Angeles, California. Pp

How To Get Involved...

For more information, contact Dr. Emmanuel Antonarakis by emailing eantona1@jhmi.edu 8 or calling 410-955-8964.

Clinical Trial:
Rob Newton, MD
Exercise + Metastatic Prostate Cancer

Professor Rob Newton is the Associate Dean of Medical and Exercise Sciences and the Co-Director of the Exercise Medicine Research Institute, School of Medical and Health Sciences at Edith Cowan University in Perth, Australia.

Prostatepedia spoke to Dr. Newton about his role in Movember's Global Action Plan for Prostate Cancer and Metabolic Health.

How did you come to focus on exercise for prostate cancer patients?

Dr. Newton: Twenty-two years ago, my dad was diagnosed with prostate cancer. He had a prostatectomy and then went through six weeks of radiation therapy. He was about 75 at the time.

He was retired. After the surgery and radiation therapy he had overwhelming fatigue. Each day he'd wake up and sit on a chair in the backyard in the sun. He became weaker and weaker. His fatigue got worse.

He asked his urologist about it. He said. "I'm not recovering from the surgery. I can't do anything. " The urologist said, "Well, you're cured of cancer. That is the main thing."

But he had no quality of life. He had bowel and urinary incontinence. His muscles got smaller. He got weaker. He became totally sedentary. That is a recipe for developing cardiovascular complications, particularly, blood clots or stroke.

"The thinking used to be that people with cancer should rest."

Two years after that, he had a stroke. He was in the hospital for months on end. He was so weak that he couldn't get out of bed. Shortly after that, he passed away.

As an exercise scientist, I looked at that trajectory and thought there had to be a better way. My Dad received no post-operative support whatsoever.

All of the changes he went through were physiological outcomes that could be addressed through exercise. Exercise could have stopped or slowed the rate of his muscle decline and atrophy. We certainly could have delayed the stroke. If we had started him exercising—walking and resistance training to maintain his muscles and keep him functional—he probably would have lived longer. He would have had a better quality of life.

I had an Uncle who went through a similar thing. Back then, men didn't go to the doctor. He had this ongoing back pain that was so bad he couldn't play golf. Golf was his great love, but he couldn't play anymore because of the pain.

He went to the doctor and they did some tests. They said, "You've got metastatic prostate cancer. It's all through your lumbar spine. There is nothing we can do."

If he had gone to the doctor earlier, he probably would have lived five or 10 years longer. He passed away very rapidly, after a few months.

Both of those experiences motivated me to ask if exercise can improve quality of life. Can we keep prostate cancer patients more functional? Reduce their fatigue?

The thinking used to be that people with cancer should rest. But as an exercise scientist, I know that rest only results in a worst outcome. If patients

rest, they'll only decondition. Metabolic disorders like diabetes and cardiovascular disease will rapidly onset. Men will lose muscle, bone mass, and function. Of course, as soon as someone is bedridden or stuck in a chair, we know he will decline very rapidly and die.

Are there higher rates of depression in cancer patients who don't exercise?

Dr. Newton: Naturally. There is a very good body of literature showing that appropriate exercise, particularly resistance training, is as effective as the current antidepressant drugs on the market. There is an excellent study out of the University of Sydney in Australia demonstrating that resistance training is twice as effective at reducing depression as antidepressant drugs.

Exercise is critical for maintaining mental health. The human body was meant to move. When you're bedridden or stuck in a chair, your quality of life is poor. Your social interaction is reduced dramatically. The inevitable outcome is depression and a downward spiral. We also know that depression compromises our immune system. It's a vicious cycle. The depression also reduces your ability to fight cancer or other diseases.

For all of those reasons, I launched a series of research studies looking specifically at exercise as a potential medicine in the overall management of people with cancer. At that time, similar studies used aerobic exercise, which is certainly beneficial. But given many of the issues people with cancer face, resistance training is an equally important medicine.

For the personal reasons I spoke about earlier, our initial studies were predominantly in prostate cancer. We launched a fairly modest study to start.

We looked at men receiving testosterone suppression, or androgen deprivation therapy (ADT), for prostate cancer. We observed quite catastrophic changes while the men were on ADT. While ADT is very effective at slowing prostate cancer progression, quite often the side effects will actually kill a man before his cancer ever would.

The side effects were predominately metabolic syndrome, diabetes, and cardiovascular disease, but we also saw loss of muscle mass, loss of function, and rapid onset of osteoporosis. This resulted in a considerable change in patient perception. Many patients and clinicians began to question the use of ADT because of the side effects.

We tracked and reported on these considerable toxicities. This led to a randomized-controlled trial investigating resistance exercise in combination with aerobic exercise in people on ADT for prostate cancer. We reported that we could totally block most of the side effects of ADT. That study in turn led to a series of further studies.

We were originally predominately working in prostate cancer, but we have now initiated trials in breast and lung cancer and mesothelioma. We're about to start trials in bladder and brain cancers.

Still, the majority of our work is in prostate cancer because that is the most common cancer in men.

Can you talk a bit about your Movember-funded trial on exercise for men with metastatic prostate cancer?

Dr. Newton: Dr. Stacey Kenfield and her team at the University of California, San Francisco, published a key study in prostate cancer. Dr. Kenfield evaluated the physical activity of a large number of patients through questionnaires. They found that there was a 61% reduction in prostate cancer-specific mortality in men who exceeded a modest amount of physical activity each week. That is quite astounding: that you can more than halve your risk of all-cause mortality and get a 61% reduction in your prostate cancer-specific mortality risk through exercise. Their results were backed up by other studies in prostate, breast, and colorectal cancers.

Earlier studies in breast cancer also showed a similar relative risk if you did a certain amount of physical activity each week. Again, the amount of physical activity was quite modest and aligns nicely with the current recommendations of 70 to 150 minutes of vigorous to moderate aerobic exercise each week.

When those papers on breast cancer came out, the Editor of the *Journal of Clinical Oncology* said that this survival benefit parallels that of the leading chemotherapy agent. You get the same benefit from physical activity. (This is not to say you stop taking your chemotherapy and just exercise. Exercise will not cure you of cancer.)

These studies looked at general physical activity, not targeted exercise medicine. General physical activity could include walking the dog, doing a bit of swimming, or a bit of golf. This wasn't targeted exercise medicine. But they did change clinical practice quite markedly.

Oncologists and urologists are no longer advising against exercise, which they did 10 years ago. They were concerned exercise might exacerbate the cancer. That has been totally refuted. There is no evidence whatsoever that exercise

exacerbates cancer progression or is risky if it is done in a controlled environment.

Of course, the Holy Grail is to understand how exercise impacts cancer progression. How does it increase survival?

We need to do a randomized-controlled trial to see if we can increase survival in patients. What are the mechanisms? How does the body generate this internal medicine to help it fight cancer?

Movember has now pledged roughly $9 million for us to run the largest exercise trial in prostate cancer and the first exercise trial in prostate cancer to look at survival as the primary outcome.

What kinds of patients are you looking for?

Dr. Newton: We are looking for men with metastatic, castrate-resistant prostate cancer. All of the other therapies have failed and now, most likely, they'll be on the new super antiandrogens Xtandi (enzalutamide) or Zytiga (abiraterone). Their cancer has metastasized, most likely to their skeleton. They'll have bone lesions.

The most recent studies on Xtandi (enzalutamide) and Zytiga (abiraterone) show a four-month survival advantage, so we're also aiming for a survival advantage of four months. For this to be convincing evidence, we need to see if exercise can produce the same survival advantage as the leading antiandrogen therapy. That is why we chose to look at men with metastatic prostate cancer.

Is the trial only open to Australians?

Dr. Newton: The main regions involved are Australia, the United States, Canada, the United Kingdom, and Europe. Currently, we have 23 investigative sites.

That is a massive study.

Dr. Newton: It's the largest exercise intervention study in prostate cancer ever attempted.

Can you speak a bit more about the exercise program?

Dr. Newton: The exercise intervention we're implementing is highly advanced. It borrows on the enormous amount of sports performance research that has been conducted. Humans have been researching sports performance—and soldier performance—for millennia. An incredible amount of research has been done to improve the health and performance of soldiers and athletes.

We've drawn on all of that research to develop a sophisticated exercise prescription to increase the survival of cancer patients and to help us understand the roughly 10 to 12 potential mechanisms by which exercise suppresses tumor progression. We also hope to understand the mechanisms by which exercise supercharges our immune system.

Once we understand those mechanisms, we'll be able to design precision exercise medicine prescriptions to target various tumor types and stages for the greatest benefit of the patient. We need the right exercise medicine at the right dosage. Pp1

How To Get Involved…

For more information, contact Professor Rob Newton by emailing r.newton@ecu.edu.au or calling 011-61-419-907-774.

Patrick Fisher
Starting An Us TOO Support Group

Mr. Patrick Fisher is the co-founder and Chapter Leader of the Us TOO Rochester, New York support group.

Prostatepedia spoke with him recently about starting local prostate cancer support groups.

How did you come to lead a prostate cancer support group?

Mr. Patrick Fisher: I happened upon Us TOO International ((http://www.ustoo.org/) through my own experience as a prostate cancer survivor.

When I was diagnosed in 2010 I did not want to take part in a support group of any kind. I thought it would just be a room full of men not happy with their outcomes and did not want to be influenced by negativity about their choices. At that time, I guess I just wasn't ready to hear other people's opinions. I wanted to do my own research, make up my own mind, and move forward.

As naive as that might have been, it got me through. I decided on surgery. I had already lost five brothers and my father to different types of cancer. Then two of my surviving three sisters developed breast cancer. I felt that if surgery was an option towards a cure of my cancer, then I should pursue it. So I did.

However, in the weeks and months following surgery I developed severe urinary incontinence. In 2012 I started to look for help. That was when I realized the error of being close-minded about support groups. In my search, I learned there weren't any groups here in Rochester that specifically focused on patient education about prostate cancer, let alone side effects from treatment.

Not even through the local hospital?

Patrick: The concern I realized is this: there are so many treatment options men need to know about in order to make an informed decision that providers simply do not have the time to do a thorough job of educating their patients. Too often, a surgeon may inform men about surgery and a radiation therapist may inform them about radiation, but few are fully informed about other options such as cryotherapy, high intensity focal ultrasound, 3T-multiparametric MRI, proton beam radiation, Cyberknife, etc.

Some providers refer men to Gilda's Club, which has a national presence. The Rochester Gilda's Club makes an ongoing effort to reach out to men with prostate cancer. However, they're not funded specifically for those impacted by prostate cancer and subject matter experts do not typically facilitate the meetings they host. Without a facilitator present, there is no one available to correct any misinformation. This could result in some attendees leaving with wrong ideas about a particular diagnostic procedure or treatment option. In any case, at least Gilda's Club encourages men to gather for sharing their experiences and being a support to one another.

> *"That was when I realized the error of being close-minded about support groups."*

There was another group at the time called Man-to-Man, sponsored by the American Cancer Society. In 2012, the American Cancer Society decided to no longer fund men's support groups.

I had severe urinary incontinence after my surgery in 2010. While my surgeon was an exception to the rule and provided me with extensive information about the risks versus benefits of other treatment options

and provided urinary incontinence treatment, traveling the path to full recuperation was still a long road for me.

By 2012, I had had multiple therapies for incontinence, but grew increasingly frustrated with the idea of having to use pads.

So, I started to seek additional support systems and did some research on the Internet. That was when I happened upon an Us TOO chapter located in Batavia, NY, not far from Rochester, only to discover it was no longer functioning. Then I discovered there were Us TOO chapters in Buffalo and New York City, but those were a hundred or more miles away. There was no Us TOO chapter in Rochester.

I then contacted the Us TOO headquarters and talked with Terri Likowski. Terri shared that Us TOO also hoped to form a Rochester chapter.

Did Us TOO provide training or guidance on setting up a group?

Patrick: Us TOO is a global nonprofit with more than two hundred chapters in the United States and other countries. They provide access to support and education for those affected by prostate cancer. They have done a great job helping survivors and seeking sponsors (typically pharmaceutical companies) to fund publications about prostate cancer screening, imaging, diagnosis, treatment options and emerging research.

Initially, I just followed my instincts. When I was diagnosed with severe urinary incontinence, I retired from the University of Rochester Medical Center where I was a community educator for HIV vaccine trials sponsored by the National Institutes of Health.

"I became a witness to the benefit of consumer education for patients."

The position developed my skill for establishing community engagement. It also gave me first hand experience networking with local nonprofit organizations about other health issues. In my career as a community advocate, I became a witness to the benefit of consumer education for patients.

How did the group start?

Patrick: There was another Rochester survivor brought to my attention by Terri Likowski of Us TOO. I contacted him. The two of us seemed to have identical feelings about the need in the community. We concluded that all we could do was make an effort to see how the community responds to the idea.

I developed an ad and wrote a short article about the need for a local prostate cancer patient education effort. The ad identified a date and a location for our first meeting and invited like-minded people to attend. Terri Likowski provided me with a contact person at a well-known pharmaceutical company that manufactures one of the medications used by prostate cancer survivors. With two short phone calls, the drug company and a local urology office agreed to help pay expenses for the first call-to-action meeting. We ran the ad in a local Penny Saver. I believe the cost was $35.

One of our goals was to attract local urologists, oncologists and other survivors to attend. So, we decided not to have the meeting at a local church basement, but rather to find an appealing venue. I contacted a local golf course and country club to reserve a space. I arranged with their caterer for an evening meeting with a coffee bar, wine, and a vegetable and fruit tray. The total cost was under $700. The pharmaceutical company covered all expenses, including the 35 invitations to urologists and oncologists.

My expectations were low. I thought we might get eight to ten people. But much to our surprise, the room was packed. That first meeting made it clear: peer support for survivors and prostate cancer patient education were efforts that our community would indeed support.

More astonishingly, there were a few urologists in the room from different hospitals and urology centers that also wanted to support us and saw the need for such a group. That immediately gave us contacts within these various medical organizations.

We decided early-on those chapter meetings had to be more than a bitch session where men could complain. The focus had to be on patient education that increased awareness about treatment options and side effects. We also decided that our meetings had to be facilitated by urologists or subject matter experts.

And, so, Us TOO Rochester was formed at that first meeting in November 2012. We continue to conduct monthly meetings. In four years, the chapter grew from just an idea shared by two survivors to more than 350 members.

Meetings gave rise to more outreach, and more outreach resulted in more members. More members then gave rise to more local events. Members now help staff information tables at shopping malls and organize annual

fundraisers. Fundraisers include car-shows, motorcycle rides, and the annual SEA Blue Ribbon Walk for Prostate Cancer similar to the walk conducted annually by Us TOO in Chicago.

Unfortunately, the other co-founder for Us TOO Rochester had to leave the chapter due to work demands. He served for only three meetings and I have been the chapter leader ever since.

How many times a month does your group meet?

Patrick: We have been meeting on the second Thursday evening of each month since 2012.

Most of our meetings have been at the Jewish Community Center for Greater Rochester. Their Senior Resource Program allows our Chapter to meet in their conference room for free. I schedule a subject matter expert to facilitate each meeting. The topic changes from month to month. Everyone leaves feeling more informed about that month's topic than they did when they walked in.

How do you select the topic?

Patrick: At first, I suggested topics and found local providers willing to conduct presentations. In recent months I formed a Working Group of survivors who help select topics. The Working Group now also helps organize local events.

What is your group's current relationship with Us TOO?

Patrick: The Us TOO home office provides support to chapter leaders with monthly leader calls and a leader resource page on their website. They also provide forms and personnel

"Us TOO makes it easy."

to help ensure that chapter leaders have the guidance they need and that local printed materials correctly represent the Us TOO logo and brand. When we conduct a fundraising event, checks are made payable and sent to Us TOO so donors can benefit from the 501(C) (3) charitable deduction. A percentage of funds raised from our events support the Us TOO home office to help defray the cost of the free materials and resources provided to chapters. This agreement also makes it possible for our chapter to raise funds without the hassle of maintaining a private checking account..

For example, every year, Us TOO hosts the SEA Blue Prostate Cancer Walk & Run in Chicago. I followed their model and created a SEA Blue Ribbon Walk for Prostate Cancer in Rochester. We're hosting our third walk this summer. At the first one, we had approximately 80 participants, a handful of sponsors, and raised about $10,000. Last year we had more than 400 participants, many more sponsors, and raised about $25,000. From the proceeds, we made a donation to the prostate cancer patient survivorship fund at the University of Rochester Wilmot Cancer Institute, a local cancer treatment facility and prostate cancer research center.

Now we're looking for benevolent sponsors for next year and hope to grow even more.

Do you have any advice for men starting a local support group?

Patrick: Don't be afraid. Don't be timid. Talk it up with peers. I bet if you pick six of your male friends, you'd find that at least one of them is also dealing with prostate cancer and may be willing to help.

When I started this chapter, I went to the breast cancer coalition here in Rochester, got an appointment with the Executive Director and asked how they got started. She was very eager to share ideas. I executed some of her suggestions. I also invited her to speak at our first meeting about the benefit of patient support groups for people with cancer.

My suggestion for those interested in starting a local chapter is to first contact the folks at Us TOO. Then, identify a venue, which could simply be a church basement or a local restaurant. It doesn't have to be anything fancy. Try contacting a local urologist to see if he or she will facilitate a discussion group at the first meeting. Consider placing a short, well-phrased line ad into your local Penny Saver.

Us TOO Rochester has accumulated over 45 urologists, oncologists and pelvic floor therapists who have facilitated our meetings, all at no cost. At each meeting, I provide a sign-up sheet requesting phone numbers and email addresses for the purpose of future communications related to prostate cancer. I create a simple flyer for each month's meeting and then distribute it to all of the providers and people who have attended meetings.

Over time, our chapter has obtained the trust of these medical providers who now promote our meetings within their urology and oncology offices and often refer their patients to our chapter for additional support and information about treatment options.

But, reaching out to Us TOO is the way to get started. Have a conversation with Terri Likowski. Us TOO makes it easy. It doesn't make any sense to reinvent the wheel. You might be starting a new group in your area, but this has been done time and time again in locations across the country and around the world. All you have to do is follow their model.

Have you started any other programs with Us TOO?

Patrick: Yes. Us TOO has a program called Community Conversations. They select four cities with Us TOO chapters to conduct a lengthy community conversation about topics concerning prostate cancer. Us TOO Rochester was selected as a location for a Community Conversation on Saturday, June 17, 2017. The University of Rochester Medical Center Urology Group and Wilmot Cancer Institute will host the event. Our venue is a local country club in Rochester. We're looking forward to this event: June is National Men's Health Month.

Is there anything else you'd like to add?

Patrick: While I was diagnosed with severe urinary incontinence following my surgery, by being faithful to pelvic floor therapies and adhering to self-help recommendations, today I am no longer wearing any pads and have regained bladder control. The process of retraining my bladder (and my brain!) required 18 months and a lot of patience.

One day I stayed *dry* all day and have been pad-free ever since. I am proof that it is possible, and that over time even challenging recuperations can lead to success.

I have no regrets about choosing surgery. I have learned there are many men who agree and that many others have no regret about choosing radiation, proton beam radiation, or other treatments like hormone therapies. Pp[1]

Patients Speak
Mr. Brian Bancroft: Men Speak Out

Mr. Brian Bancroft spoke with *Prostatepedia* about his struggle with prostate cancer that had metastasized to his bones.

How did you find out you had developed bone metastases?

Mr. Brian Bancroft: I went to my family doctor in 2010 when I was 64. My statin prescription had expired and I went to get it renewed. He did a physical that included a blood test with a PSA check.

My PSA had been 1.3 every year for many, many years. All of a sudden it was 9.2. He said it was probably a mistake and that we'd just do a retest.

Right then, I started reading as much as I could. I knew nothing about the prostate or prostate cancer.

I came back a couple of weeks later for the retest. My PSA was now 10.2. He again said, "Don't worry about it."

I went on a course of antibiotics in case I had an infection and then had another PSA test. But now my PSA had risen to 15.2. It was increasing rapidly. He said, "You need to see a urologist."

I went to go see the urologist. We scheduled a biopsy. Meanwhile, time is passing. No one is in a hurry. It is now 2011 and I've turned 65. In the biopsy cores, the pathologist noted Gleason 6 cancer on one side of the prostate only.

I decided I wanted to have my prostate removed to get rid of the cancer. I scheduled with Dr. Alan Partin at Johns Hopkins University. Johns Hopkins looked at my pathology slides, but had an entirely different assessment: Gleason 8 in both sides of the prostate.

I then had a conventional technetium bone scan. The urologist really didn't want to do it. He said, "I do these bone scans all the time on patients and they always come back negative." But I insisted on having one as I had started feeling a dull pain in my pelvic area. In the scan, my skeleton lit up like a Christmas tree. There were too many bone lesions to even count.

He said, "You need to see an oncologist." This was on a Wednesday. He made me an appointment with an oncologist that coming Friday. But he wouldn't let me out of his office without a shot of Lupron (leuprolide) hormone therapy.

The oncologist said Lupron (leuprolide) was the right thing to do, but that I also needed to take one daily Casodex tablet (bicalutamide) along with it. The Lupron (leuprolide) shot lasts for three months and must be renewed as long as it remains effective.

During that initial three-month waiting time I had the urge to do something proactive. I was already reading everything I could find about prostate cancer.

I had bone lesions all over the place—primarily up and down my spine and in the pelvic area, but in other places too.

I read about a genius prostate cancer doctor in California named Dr. Bob Leibowitz at Compassionate Oncology. I went to his website, read the case histories and papers he had written, and ordered a DVD of a talk he had given. I didn't have much information to go on, but his patients were having such amazing successes. I wanted a success like the others, so decided to hitch my wagon to his treatment and went out there to see him. I saw his brilliant colleague, Dr. Jeffrey Turner, who was in charge of my treatment. Somewhat later, another brilliant *Dr. Bob* colleague, Dr. Sharooz Eshaghian, became my main oncologist.

If there is one thing I could tell people in my situation, it would be this: although there are a only a small handful of oncologists who focus in prostate cancer in the United States, go to one of them if you can. For me, it was as if I had been playing Little League baseball and all of a sudden was promoted to the Major Leagues! The difference was that great.

Compassionate Oncology's treatment protocol was a three-pronged approach. For hormone therapy, they used 13 months of triple hormone blockade. They switched me from Lupron (leuprolide) to Firmagon (degarelix), a newer agent that acts differently, but accomplishes the same thing. They increased my Casodex (bicalutamide) dose to three tablets daily and a daily Proscar (finasteride) tablet.

At the same time, I started 15 treatments of low-dose chemotherapy. I tolerated the chemotherapy reasonably well. I never got sick. Never became nauseated. I kept my hair, although it did get thinner. I lost my sense of taste for a while, but when it finally came back it was far better than before.

"My skeleton lit up like a Christmas tree."

At the same time, I began taking an antiangiogenic cocktail—various medications that thwart the formation of tiny capillaries that feed the cancer. Cancer needs a good blood supply to grow, so this starves the cancer of its lifeblood.

A side note: while I was on Lupron (leuprolide), I had the ever-present hot flashes. After switching to Firmagon (degarelix), for some reason the hot flashes ended.

The evening before my initial appointment at Compassionate Oncology in California, my wife's brother and his wife came to my hotel room to visit me. He is a pastor. They both asked if they could pray over me. I'd never had that experience before. From that moment on, I've never had any anxiety about the cancer. I seem to be at peace with everything. Oh, I still want to fight it with everything there is, but I do not worry about a bad outcome.

How were your doctors monitoring whether or not the treatments were working?

Brian: In the beginning, with regular PSA checks. Plus, I had a Color Doppler Ultrasound performed by Dr. Duke Bahn in Ventura, California. The Color Doppler Ultrasound images the prostate gland; you can see exactly where the cancer is. In my case, I had cancer in three locations, one near the edge of the prostate. That is the one that apparently leaked the cancer cells out into the bloodstream so they could spread to the rest of my body.

I had the Color Doppler Ultrasound test yearly, which showed the cancer sites to be shrinking and less active with less blood flow to them. I continue to have a complete blood profile every month with PSA test.

At first, I lived outside Pittsburgh and would go out to California every month. A little bit expensive, but I learned how to travel very economically. I got really good airplane rates. I had a relative I stayed with out there. I found a really cheap rental car company. It really wasn't that expensive.

I did have to find a cooperative oncologist in Pittsburgh who authorized my chemotherapy infusions the weeks I wasn't in California. I found a wonderful doctor: Dr. David Friedman.

Fairly quickly, my PSA went to an undetectable level. I should remind everyone that Casodex (bicalutamide) has the potential to flip-flop and start contributing to cancer growth rather than fighting it. This happened to me after only four months. With close monitoring, it was discovered and I switched to another medication.

Amazingly, today—six years later—my PSA is still undetectable.

Every November, I have an F-18 Sodium Flouride PET/CT scan. It's a full body scan from head to toe. I have MRIs as well. These are compared with the previous year's scans to see what is going on with the cancer. I still have the cancer, but it seems to be in a deep sleep. It's somehow in dormancy. It's not progressing. And now that I am quite stable, I only visit the oncologist every fourth month.

Did you have any side effects from the treatments you were on?

Brian: I didn't have major side effects. I didn't get sick from the chemotherapy. I never got nauseated, never threw up. I did feel light-headed, however, and my memory was horrible. I lost muscle strength and stamina. I lost taste.

Were you exercising?

Brian: No. I've been an exerciser my whole life, but I just lost my desire to exercise. I still did a lot of work around the house and everyday chores, but I didn't go running or do any intensive exercise.

My whole life I was never sick. I don't think I'd missed a day of work for 25 years. My only doctor's visits were for sports injuries; that is, until this situation cropped up.

Are you a member of a support group?

Brian: When I lived in Pittsburgh, I was a member of two different prostate cancer support groups. They were very good for me. I highly recommend anyone with prostate cancer join one. You learn so much. Plus, there is a great comfort in being with other guys

who have gone through or are going through similar treatments.

One of the groups I joined was originally called Gilda's Club. (The Pittsburgh Chapter has since changed their name to Our Clubhouse.) The other was an Us TOO group.

Three years ago, I moved to Nashville, Tennessee. Sadly, there are no support groups here. I've been trying to get something started, but it just never happens.

The groups in Pittsburgh were really wonderful. I still communicate with some of the guys.

Do you talk to other men outside of the support group about your experiences?

Brian: I talk to everybody. I have had such a good result and I want others to have this result. Prostate cancer is so common that there is no shortage of guys dealing with one aspect of it or another.

I've talked to guys with advanced cancer, some in dire situations. However, it seems to be very, very difficult to convince a person to see an oncologist specializing only in prostate cancer. Yes, I know there may be an expense to it. But it seems most men are so comfortable with their current doctor that they don't want to think about making a change. Had I not made the treatment change I did, there is no doubt I wouldn't be here today.

Do you have any other advice for men facing metastatic prostate cancer?

Brian: So many guys I talk with just go along with what their doctor says. It's so beneficial to read, read, and read everything about prostate cancer so you can discuss your treatments with some knowledge. If possible, go see an oncologist who specializes in prostate cancer.

> *"I still have the cancer, but it seems to be in a deep sleep."*

Compassionate Oncology is purely medical. They don't espouse any particular dietary or supplement regimen. Eventually, I discovered Dr. Snuffy Myers, who does recommend patients eat or avoid certain foods. I purchased his book the *New Prostate Cancer Nutrition Book* and have followed his dietary advice ever since. I follow a Mediterranean diet, avoid foods with arachidonic acid (red meats, egg yolks, dairy) and use his recommended supplements.

I'd be more then happy to talk to any of your readers about my experiences.

Do you think prostate cancer changed you in any way?

Brian: I became a happier person. I've never been down in the dumps, but now I try to be extra happy all the time. When I go into a store and someone asks me how I'm doing, I always have the same answer: I'm fantastic!

I talk to people more than I ever used to. If I'm standing in line, I'll chat with the person next to me. Every time I see somebody walking a dog, I stop and ask if I can pet the dog. I kneel down and ask, "What kind of a dog is this? What is the dog's name?" People love their dogs. They're so happy to tell you about their dog. It makes the owner feel happy and it makes me feel happy.

I never did that before. I was always friendly, but not outwardly friendly. It makes me feel better and gives me a good feeling about myself. Who knows whether that has any health benefit?

Why do I think I am having such a wonderful response? Early on, I stopped working at a very stressful job. I found medical treatments that quickly arrested a cancer that was advancing rapidly. I've never had any direct treatment to my prostate itself. Although I didn't exercise while under treatment, I do exercise now. I haven't had any of the newest prostate cancer treatments like Provenge (sipuleucel-T), Xofigo (radium-223), Xtandi (enzalutamide), or Zytiga (abiraterone), because I haven't needed them.

> *"I have made myself into a happier, more outgoing person."*

I've become a much more spiritual person. I follow healthier eating habits and continue to take certain beneficial medications and supplements.

I have made myself into a happier, more outgoing person. And my wonderful wife has been unbelievably supportive on this journey and is an incredible help!

I don't know why I'm doing this well and have to assume that maybe all of the above are somehow working together, each making its own contribution. Pp

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.

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

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

What should I tell my healthcare provider before taking XTANDI?

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

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

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

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

How should I take XTANDI?

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- 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.
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- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

The most common side effects of XTANDI include:

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

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

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

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

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

How should I store XTANDI?

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

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

General information about XTANDI.

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

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

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

What are the ingredients in XTANDI?

Active ingredient: enzalutamide

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

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

Revised: October 2016

Prostatepedia[1]

[1]expert insight + advice

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WHAT IS ZYTIGA® (abiraterone acetate)?

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

IMPORTANT SAFETY INFORMATION

Who should not take ZYTIGA® (abiraterone acetate)?

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

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

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

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

If you are taking ZYTIGA®:

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

ZYTIGA® may cause serious side effects including:

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

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

- Dizziness
- Fast heartbeats
- Feel faint or lightheaded
- Headache
- Confusion
- Muscle weakness
- Pain in your legs
- Swelling in your legs or feet

- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems.** You may develop changes in liver function blood tests. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA® and during treatment with ZYTIGA®. Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - Yellowing of the skin or eyes
  - Darkening of the urine
  - Severe nausea or vomiting

The most common side effects of ZYTIGA® include:

- Weakness
- Joint swelling or pain
- Swelling in your legs or feet
- Hot flushes
- Diarrhea
- Vomiting
- Cough
- High blood pressure
- Shortness of breath
- Urinary tract infection
- Bruising
- Low red blood cells (anemia) and low blood potassium levels
- High blood sugar levels, high blood cholesterol and triglycerides
- Certain other abnormal blood tests

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

THESE ARE NOT ALL THE POSSIBLE SIDE EFFECTS OF ZYTIGA®.

FOR MORE INFORMATION, ASK YOUR HEALTHCARE PROVIDER OR PHARMACIST.

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

ZYTIGA® can interact with other medicines.

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

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

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

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

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PATIENT INFORMATION
ZYTIGA® (**Zye**-tee-**ga**)
(abiraterone acetate)
Tablets

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

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

ZYTIGA is not for use in women.

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

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

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

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

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

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

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

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

What are the possible side effects of ZYTIGA?

ZYTIGA may cause serious side effects including:

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

  Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - yellowing of the skin or eyes
  - darkening of the urine
  - severe nausea or vomiting

The most common side effects of ZYTIGA include:

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

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

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

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

How should I store ZYTIGA?

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

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

General information about ZYTIGA.

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

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

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

What are the ingredients of ZYTIGA?

Active ingredient: abiraterone acetate

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

Manufactured by: Patheon Inc. Mississauga, Canada
Manufactured for: Janssen Biotech, Inc. Horsham, PA 19044

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