

# Prostatepedia<sup>1</sup>

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



## Aggressive Cancers

Prostatepedia\_August <sup>2017</sup> Volume <sup>2</sup> No. <sup>12</sup>

# *In this issue....*

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**In August, we're talking about what used to be thought of as a rare form of metastatic prostate cancer but now appears to be quite common. In this month's guest commentary, Dr. Neeraj Agarwal summarizes the problem of neuroendocrine cancer and frames the conversations that follow.**

You will notice a broad consensus among our experts that metastatic prostate cancer is a heterogeneous disease. Unfortunately, the large randomized Phase III trials that established our current treatment guidelines behave as if all metastatic prostate cancers are alike. As this is clearly not the case, treatment guidelines need to be interpreted with prostate cancer's heterogeneity in mind. This is especially true if your PSA is low for the amount of cancer that you have; if you have lytic bone metastases; or if your cancer is predominately in your liver, lung, or other organs rather than in your bone. If your cancer fits this picture, the conversations that follow may help you better understand your treatment options.

These atypical prostate cancer presentations are poorly served by standard treatments and yet we haven't really defined yet what the proper treatment might be.

Drs. Ana Aparicio, Himisha Beltran, and Daniel George have thought creatively about how we might better treat men with these atypical prostate cancer presentations.

It is already clear that patients with this aggressive presentation vary in their response to existing drugs as well as to agents currently in development. A key step will be to find molecular markers that predict which treatments are likely to be most effective for each patient. This type of research, while still early in the process, is progressing rapidly.

We now have laboratory models for neuroendocrine and anaplastic prostate cancers. It is possible to rapidly test agents in these models; that process has identified promising agents.

I think estradiol is one of these promising agents. One of my patients illustrates this nicely. A young man had at initial diagnosis a Gleason 10 prostate cancer with a 14-day doubling time. His cancer became PSA-negative while he was on Lupron (leuprolide) and Casodex (bicalutamide). He developed a large lytic metastasis in his pelvis. I asked a radiation oncologist to radiate his pelvic lytic lesion and then started him on estradiol. He entered a complete remission that lasted eight years. After eight years,

he developed an oligometastatic recurrence that I again asked a radiation oncologist to treat with radiation. He entered a remission. He finally developed metastatic cancer of the pancreas and is now receiving chemotherapy.

Over the years, I have seen estradiol result in multi-year cancer control in other patients with a similar presentation. I never understood how hormonal therapy like estradiol could work in a group of patients notorious for being unresponsive to hormonal treatment. But we now know that estradiol can act through the estrogen receptor beta to block the action of a protein called snail (SNAIL) that is important in neuroendocrine transformation and metastatic spread.

My point is that a diagnosis of aggressive prostate cancer doesn't mean you've only got a few months left. Years-long disease control can happen. It is in your best interest to seek out an expert in this form of prostate cancer—even if you have to travel great distances to see him or her.

*Charles E. Myers, Jr., MD*





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ISSN: 2381-4020

*Prostatepedia is published in Charlottesville,  
Virginia by Rivanna Health Publications, Inc*

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# Guest Commentary

## Neeraj Agarwal, MD



**Dr. Neeraj Agarwal is the Director of the Genitourinary Oncology Program in the Oncology Division, the Co-Leader of the Urologic Oncology Multidisciplinary Program, and the Associate Director of Clinical Trials at the Huntsman Cancer Institute at the University of Utah.**

**He offers his insights into this month's discussion on rare forms of prostate cancer.**

Until 2010, the only drug treatment we had for advanced prostate cancer was chemotherapy with Taxotere (docetaxel). Since then, we have seen the advent of many new drugs, including the drugs to target androgen signaling. Androgen signaling is a critical player in prostate cancer progression. Testosterone is needed for prostate cancer as a fuel; testosterone interacts with the androgen receptor, which is necessary for transcription within the prostate cancer cells.

These drugs induce a deeper blockage of androgen signaling. They include Zytiga (abiraterone) with prednisone, which diminishes the production of testosterone within the prostate cancer cells and adrenal glands, and Xtandi (enzalutamide), which is a next-generation androgen receptor blocker. We also have several new drugs that target

androgen signaling in similar fashions such as apalutamide (ARN-509), and darolutamide (ODM-201).

However, over the past five years, we have observed that literally every patient experiences disease progression on these newer androgen signaling-targeting drugs. When they progress, some unique features are seen.

In approximately 25% of these patients, their PSA values do not necessarily go up in proportion to their disease burden, while their scans show disease progression. This phenomenon is what we now call androgen-indifferent prostate cancer, or neuroendocrine prostate cancer.

Neuroendocrine or androgen-indifferent prostate cancer existed in the past. A small number of patients—maybe 5%—have neuroendocrine disease from the day they come in for their first biopsy. But now, as these patients are living longer, courtesy of the new androgen signaling inhibitors, the prevalence of neuroendocrine prostate cancer has been increasing steadily. These patients do not really respond well to further manipulation of androgen signaling.

We don't have standard guidelines in place to diagnose neuroendocrine or androgen-indifferent prostate cancer,

so physicians are not always sure what to do when they see this unusual presentation of prostate cancer.

Many renowned experts, such as Dr. Ana Aparicio or Dr. Himisha Beltran who are featured this month in *Prostatepedia*, are working on diagnosis, treatment, and establishing biomarkers for these patients.

From a clinician's perspective, I can tell a patient has neuroendocrine or androgen-indifferent prostate cancer when I notice disease progression on the scans with disproportionately low PSA levels, and an increase in other tumor markers, such as LDH (lactate dehydrogenase) and alkaline phosphatase.

If you notice these features, I recommend consulting with an expert who specializes in neuroendocrine-type prostate cancer. Seek out an NCI-designated comprehensive cancer center where oncologists are specializing in prostate cancer, and are likely going to be more familiar with this form of prostate cancer.

I think it's worth spending extra time, money, and effort up front for the correct diagnosis and a more appropriate treatment plan. PP





# Himisha Beltran, MD

## Neuroendocrine Prostate Cancer



**Dr. Himisha Beltran, an Assistant Professor of Medicine at Weill Cornell Medical College in New York City, is keenly interested in developing research programs to study neuroendocrine prostate cancer.**

*Prostatepedia* spoke with her about this aggressive form of prostate cancer.

*What is it about medicine and patient care that attracts you?*

**Dr. Beltran:** I'm a medical oncologist specializing in the treatment of patients with prostate cancer, but I also do cancer research focused on understanding treatment resistance, cancer genomics, and the development of molecularly based treatment strategies. It's hard to go back to what motivated me in the beginning. What I know now, in retrospect, is that what I like about being a doctor is being able to be a part of patients' lives, to really partner with them during the course of their disease, and to help them and their families navigate the next steps.

I do research to bring what we've learned to the patients. I think that both aspects of medicine—research and patient care—are congruent. Being a doctor can mean many things. For me, it's really about being able to offer cutting-edge technologies

and treatments to my patients and to be proactive on the research side by contributing toward the field's growing understanding of the biology



*“What I like about being a doctor is being able to be a part of patients' lives.”*



of the disease by integrating emerging science, technology, and medicine. Cancer treatment has progressed so much since I first started.

*Your research deals with a small subset of patients and is considered a specialized area of research. How did you become interested in neuroendocrine prostate cancer as opposed to another aspect of the disease?*

**Dr. Beltran:** I take care of prostate cancer patients at all different stages of their disease. We know that not all patients with prostate cancer are the same and they may respond variably to the therapies that we use. My research has focused on understanding mechanisms of treatment resistance and identifying subsets of patients that may benefit from nonstandard approaches.

Neuroendocrine prostate cancer is one subtype within the spectrum of advanced prostate cancer that tends to look and act differently compared to your typical prostate cancer. They tend to be less responsive to standard therapies and often do not make PSA.

That is really what led me to neuroendocrine prostate cancers. I was struck by how some patients had tumors that looked very different under a microscope and acted very different clinically than others looked and acted. By understanding a small subgroup of patients, we can also better understand the entire group. That is really what precision medicine is about: identifying subgroups of patients that either have clinical, molecular, or other features that will help guide treatment. While my research is focused on a small subgroup of men, I think the impact potentially affects many more.

*Let's back up a bit and define neuroendocrine prostate cancer.*

**Dr. Beltran:** Most prostate cancers consist of adenocarcinoma cells, which are derived from normal prostate tissue. They have more glandular prostate features. They express many prostate markers. When we say a cancer is neuroendocrine, we mean that the tumor looks less like a typical





adenocarcinoma and has features that look more like neuroendocrine cells, which have a distinctive morphology under a microscope. Neuroendocrine cells tend to be smaller and may not express classical prostate markers such as the androgen receptor, which is the target of many of our drugs like Zytiga (abiraterone) and Xtandi (enzalutamide). These cancers also acquire other distinct molecular features.

What we've learned in recent years is that neuroendocrine prostate cancer rarely arises de novo; they most commonly develop in later stages of prostate cancer progression from a preexisting prostate adenocarcinoma as a way for the cancer cells to evade therapy. The tumors try to change their identity to develop new ways to grow. There is a spectrum as tumors progress from androgen-driven prostate adenocarcinoma toward an androgen-independent neuroendocrine prostate cancer. Within this spectrum, the cancers may develop mixed or overlapping features, expressing some prostate markers but also acquiring new resistance markers.

### *Is there any way to predict who is going to develop treatment resistance?*

**Dr. Beltran:** By studying the clinical and molecular features of patients, how cancers evolve with time, and how these features affect the biology of the cancer, we now have better insights into mechanisms of response and resistance to specific therapies. This growing knowledge sets the stage for biomarker development. We are interested in identifying patients before they develop neuroendocrine prostate cancer. We are investigating the genomics and other molecular features of tumor biopsies and applying this to noninvasive approaches such as liquid biopsies—looking at cancer cells or DNA from cancers that may be detected in the

blood. If we can identify patients, we can also select patients most likely to benefit from a neuroendocrine type of regimen.

### *Are some treatments more likely than others to convert a patient's cancer from an adenocarcinoma to a neuroendocrine prostate cancer?*

**Dr. Beltran:** The backbone of therapy for advanced prostate cancer is hormonal therapy that targets the androgen receptor either through depletion of androgen production by the body or blocking the androgen receptor directly. While highly effective in most men with metastatic prostate cancer, eventually patients may stop responding to these drugs and develop treatment resistance. Most commonly, the cells resist therapy by reactivating androgen signaling through various mechanisms such as acquiring an activating mutation in the receptor itself to keep the receptor *on*.

Another alternative approach to resisting therapy is to turn on other pathways so that the cancer cells can grow even with the androgen receptor *off*. This is what neuroendocrine prostate cancers do. In this smaller proportion of patients, the tumors decide that the best way to evade therapy is to just get rid of the androgen receptor or to get rid of the dependence on the androgen receptor and acquire features that make them less like prostate cancers. We use the term *epithelial* or *lineage plasticity*. They start to acquire different molecular and histologic features to try to change their identity.

We see similar mechanisms of resistance in other cancers where there is effective targeted therapy: EGFR-mutated lung cancer, BRAF-mutated melanoma, and estrogen receptor-positive breast cancer for example.

### *What kinds of treatment options are available for men with this type of prostate cancer?*

**Dr. Beltran:** Neuroendocrine prostate cancer shares clinical and molecular features with other aggressive or high-grade neuroendocrine cancers, such as small-cell lung cancer. Therefore, we often use chemotherapy treatments similar to those used for small-cell lung cancers.

On the research side, there have been a number of therapeutic targets at various stages of preclinical development—either in clinical trials or in clinical development. There is an open clinical trial looking at a drug called Rova-T (rovalpituzumab tesirine) that has been previously tested in small-cell lung cancer. We're now enrolling other neuroendocrine cancers, including prostate. The drug is an antibody-drug conjugate that targets the protein DLL3, which is expressed on the cell surface of small-cell lung cancer, neuroendocrine prostate cancer, and other neuroendocrine tumors.

We have also been working to develop different ways to target the oncogene N-myc that is overactive in neuroendocrine prostate cancer and important for the biology of these tumors. One method is to target a protein that stabilizes N-myc called Aurora A Kinase; I am leading a clinical trial using the Aurora A kinase inhibitor alisertib.

We also know that these tumors can acquire significant epigenetic changes. There are a number of epigenetic drugs that have been developed, including drugs that target DNA or histone methylation. One epigenetic regulator that is overactive in neuroendocrine prostate cancer is EZH2. EZH2 inhibitors have shown promise in preclinical studies. There are currently early phase clinical trials testing EZH2 inhibitors







*“By understanding a small subgroup of patients, we can also better understand the entire group.”*



for all cancer types, not specifically for neuroendocrine prostate cancer.

There are also other targets in earlier stages of preclinical development including studies investigating the use of immunotherapy for this type of cancer. We are also thinking ahead toward rational combination or co-targeting strategies for patients.

Overall, we’re making progress. A few years ago, I would have said there was not much to think about. But now I think we have a lot of clues as to the overactive pathways in neuroendocrine prostate cancer, as well as the biologic markers that might help identify the right patients.

*How is small-cell or neuroendocrine prostate cancer diagnosed? Biopsy? Imaging?*

**Dr. Beltran:** Small-cell or neuroendocrine prostate cancer is diagnosed by tumor biopsy. The pathologist typically makes the diagnosis by looking at the morphologic features of the cancer under a microscope and may perform additional testing to look at expression of neuroendocrine markers or classical prostate markers to support the diagnosis.

One of the reasons why neuroendocrine prostate cancer was thought to be so rare was that doing metastatic biopsies on patients already diagnosed with prostate cancer was just not done in the clinic. It is only recently that we

are recommending biopsies to look for neuroendocrine prostate cancer in select patients with aggressive clinical features and low PSA levels.

Biopsies are also being considered to look for other emerging molecular targets. There are now several prostate cancer clinical trials targeting different mutations and alterations.

An obvious next step is to try to diagnose neuroendocrine prostate cancer noninvasively. Imaging is a noninvasive way to detect different cancers, but there hasn’t been any sort of imaging tool yet that can really identify these patients. We’re starting to see clues that there may be some molecular markers that are expressed that might help future research in this area. Another noninvasive approach we have been investigating is the use of liquid biopsies that include circulating tumor cells as well as circulating tumor DNA to see if there are clues that can help us identify these patients without a biopsy. This is still in research development.

*How close are we to having liquid biopsies available? Ten years down the line? Or is this something that you think will happen relatively quickly?*

**Dr. Beltran:** As a first step, we have been comparing tumor biopsies and liquid biopsies including circulating tumor DNA from patients in different disease states. We found that the liquid biopsy is able to capture the genomics of the cancer and is allowing us to evaluate dynamic changes. We are refining what we see in patients and then incorporating this into a prostate cancer circulating tumor DNA panel that we’re developing in an international collaboration. I’m working with multiple investigators as part of a Prostate Cancer Foundation consortium.

We hope to have an assay available for clinical testing within the year. We hope to get readouts over the next few years. You need to show that the test might be useful, which obviously takes a lot of time and many different cohorts.

*Is there anything that you think patients should know about these rare forms of prostate cancer?*

**Dr. Beltran:** It can be challenging when a patient gets a diagnosis of neuroendocrine prostate cancer and then reads on the Internet that this is a very aggressive form of prostate cancer without any treatments and poor survival. What I tell my patients is that this is really a spectrum and not everybody falls into that extreme part of the spectrum. What we’re learning is that there is a lot of overlap; not everybody with neuroendocrine prostate cancer has as aggressive disease as one might read about online.



*“Not everybody falls into that extreme part of the spectrum.”*



One thing I’ve learned in studying prostate cancer is that there can be clinical and molecular heterogeneity even within neuroendocrine and advanced prostate cancers. We’re just starting to be able to subset patients in a more useful way.

As a field, we have a much better understanding of the molecular landscape of advanced prostate cancer. This work has translated into new and more precise treatment strategies, but there is still a lot more to learn. [Pp1](#)

# Ana Aparicio, MD

## Rare But Lethal Forms of Prostate Cancer



**Dr. Ana Aparicio is an Associate Professor in the Department of Genitourinary Medical Oncology at the University of Texas MD Anderson Cancer Center in Houston, Texas.**

*Prostatepedia* spoke with her about rare but highly aggressive forms of prostate cancer.

*How did you become involved in such a specialized subset of prostate cancer research?*

**Dr. Aparicio:** I was very frustrated by the fact that we treat homogeneously a disease that we perceive in the clinic to be heterogeneous. It drives me crazy that different people walk into the clinic with different diseases and yet we do the same thing to each and every one of them.



*“If we peel back in that way, we will start to understand the disease.”*



This ends up meaning that many large Phase III trials are an enormous resource expense. It's difficult to advance the field. I had remarkable

responses for patients with Yervoy (ipilimumab) and yet the Phase III trial was negative. I felt like that was wrong. We should be smarter about what we're doing. We need to understand the heterogeneity of prostate cancer and incorporate that understanding into clinical trials. Otherwise, it's going to take us 200 years to make a difference in this disease.

I think of it in the following way. I take all of the prostate cancers and peel away the most aggressive ones. I then look to see how that relates to the rest of the disease. If we peel back in that way, we will start to understand the disease.

*So then the work you're doing can potentially change not only how we treat patients, but also how we design clinical trials?*

**Dr. Aparicio:** Yes.

*What is neuroendocrine prostate cancer?*

**Dr. Aparicio:** Neuroendocrine prostate cancer is a histological definition of a prostate cancer variant. The prostate is composed of glandular tissue. When a pathologist looks at your garden-variety prostate cancer under the microscope, she sees it is composed of groups of glands. That is why it's called *adenocarcinoma*: *adeno* meaning of or relating to the glands, *carcinoma*

referring to the cancer arising from epithelial tissue. It's cancer and not normal prostate tissue, but you can still recognize the glandular structures. Prostate adenocarcinomas respond very well to hormonal therapies.

On the other hand, small-cell prostate cancers basically look like sheets of cancer cells under the microscope. There is no glandular formation of any sort. These are small, round cells that have small amounts of cytoplasm (the gel-like material surrounding the nucleus) so their nuclei look very prominent. Small-cell cancers often express neuroendocrine markers, which are a type of protein expressed by a number of different tissue types and in a number of different cancers. Neuroendocrine markers are in no way specific to small-cell prostate cancers, but because the small-cell prostate cancers express them frequently, the other name that is given for small-cell prostate cancers is 'poorly differentiated neuroendocrine prostate carcinoma.' Many garden-variety prostate adenocarcinomas (those composed of groups of glands) also express these neuroendocrine markers. Again, the word *neuroendocrine* is not specific to small-cell cancers. *Small cell* refers to sheets of cells that are small with little amounts of cytoplasm.





The presence of small-cell cancer morphology on a surgical specimen or a biopsy is often associated with atypical clinical features for prostate cancer and a poor response to hormone therapies.

Garden-variety prostate adenocarcinomas most often spread to the bone and make round sclerotic (hardening) or osteoblastic bone metastases that show on a CT scan like a white patch.



*“If you are diagnosed with a primary small-cell prostate cancer you should be treated with chemotherapy.”*



In contrast, small-cell prostate carcinomas are often associated with what we call *lytic* (relating to disintegration) bone metastases, which show on a CT scan like a dark, punched-out hole. And that’s when the carcinomas go to the bone because they often don’t even show up in the bone. Men with small-cell cancer morphology can have exclusive visceral metastases, meaning their cancer has only gone to the liver, lymph nodes, or lung. They might also have bulky tumor masses, including bulky and symptomatic primary prostate tumors or bulky liver or lymph node masses. While they don’t respond well to hormonal therapies, small-cell prostate cancers often respond to chemotherapy.

A problem we ran into was that we would often find these atypical clinical features that I just described, but under the microscope where we expected to find small-cell prostate carcinoma morphology to justify chemotherapy, we didn’t. What happens

when we see those atypical clinical features, but the biopsy doesn’t show small-cell morphology? Our experience shows that those people don’t do well with hormone therapies. In other words, when we do a biopsy and we find small-cell carcinoma morphology, we know that those cancers need to have chemotherapy sooner rather than later, as opposed to treatment with hormonal therapy. They need early chemotherapy as well; so we coined the term *aggressive variant prostate cancers*, which are tumors that share clinical features with small-cell cancers but may have different morphologies under the microscope. When we do a biopsy, they might look like adenocarcinoma, but they behave like small-cell cancer.

*And you choose a different treatment path based on those findings?*

**Dr. Aparicio:** Right.

*Are small-cell and aggressive variant prostate cancers discovered in men who are newly diagnosed or in those whose cancers recur after treatment?*

**Dr. Aparicio:** There is a lot of discussion about that in the field. For the most part, small-cell carcinoma morphology emerges during the progression of the disease on hormone therapy. It is more common for us to find them after men have started therapy. Whether the underlying program that results in small-cell cancer was *already there* or if it’s *induced* by the hormone therapy is not clear.

*So then it is unclear whether small-cell and aggressive variant prostate cancers are there from the beginning or whether there is something about hormonal therapy treatment that induces this more aggressive form of prostate cancer?*

**Dr. Aparicio:** Right. I can tell you that from our data and our various clinical

trials it is looking more and more like the program was already there. The small-cell cancers, as I mentioned earlier, do not respond well to hormonal therapies so they are categorized as androgen-indifferent tumors. Androgen-indifferent small-cell cancers may show some minor response to a hormonal therapy, but the response is short-lived and unsatisfying, if you will.

The aggressive variants that we define clinically are also considered androgen-indifferent. Whether that program of androgen indifference is present at diagnosis is the question. Our data from clinical trials and from people with metastatic disease at initial diagnosis suggest that a large proportion of those are androgen indifferent from the get-go. That androgen indifference—that primary resistance—to the androgen receptor inhibitors and the AR-targeted therapies like Zytiga (abiraterone) and Xtandi (enzalutamide) is present from the beginning. But we know that people who are treated with Zytiga (abiraterone), Xtandi (enzalutamide), or any of the other AR-inhibitory drugs that we have, eventually develop resistance in those tumors. They might not be primarily resistant to those drugs, but they become secondarily resistant to those drugs.

This group of secondarily resistant prostate cancers is heterogeneous. Not all secondary resistances to the AR-targeted therapies are the same, but a subset of those secondarily resistant tumors are probably very similar to the primarily resistant ones.

*Is anyone able to predict which of these people will be resistant?*

**Dr. Aparicio:** Through various analyses, we arrived at a molecular signature for the androgen-indifferent tumors that consist of combined tumor suppressor defects. You have to have



at least two of three alterations in p53, RB1, or PTEN. If you have two out of those three altered tumor suppressor defects, you have a tumor that has the molecular signature we have identified as aggressive variance. Some recent papers look at genetically engineered mouse models and have confirmed the signature—confirmed that alterations in p53 and RB plus or minus PTEN are linked to androgen indifference.

*Are they now developing tests to see if people have two of these three alterations?*

Dr. Aparicio: Yes.

*And if a man does have two of these three alterations, would you then choose a different treatment for him based on that result?*

Dr. Aparicio: That's the goal: it allows us to pick the right treatment. Although, like I said, we're already pretty good at telling who has aggressive disease. But this test is important because one of the problems in prostate cancer has been that we've treated the disease like it's all one disease.

Look at leukemia as an example. If we treated chronic myelogenous leukemia, which is currently treated with a pill, the same way that we treat acute myelogenous leukemia, which requires multiple chemotherapies, that would be a problem.

And yet when we do Phase III clinical trials for prostate cancer, we lump together the chronic and the acute, which have different biologies. Because of this, we may have overlooked drugs or treatments that might have been beneficial for the acute diseases or vice versa. We just weren't able to show the benefit because we've mixed acute and chronic diseases.

A case in point: Yervoy (ipilimumab), a checkpoint inhibitor, missed the Phase III trial's primary endpoint in prostate cancer by a hair. That may have been due in part to the fact that a number of tumors included in those clinical trials were of the aggressive variant flavor and those don't benefit, but it is still possible that men with garden-variety prostate cancer might have benefitted from Yervoy (ipilimumab). That's the hypothesis.



*“You have to have at least two of three alterations in p53, RB1, or PTEN.”*

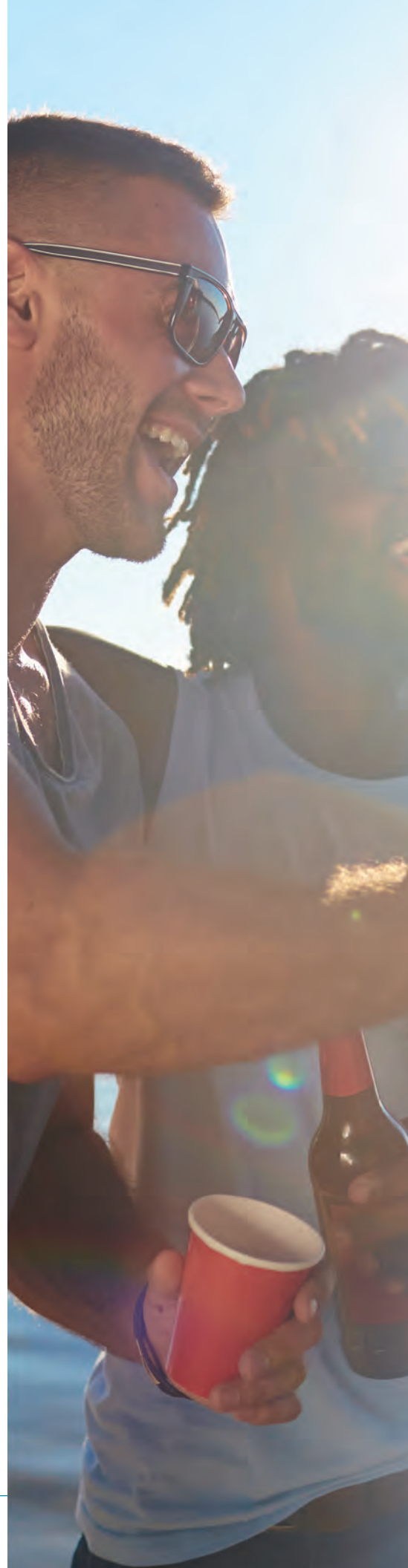


*So you're saying we can then better stratify patients going into clinical trials?*

Dr. Aparicio: Exactly.

*Will patients be able to benefit from all of this research right now or is the research you're discussing just increasing our understanding of small-cell and neuroendocrine prostate cancers?*

Dr. Aparicio: I think it is something that they're going to be able to benefit from very soon. These aggressive variant prostate cancers, aside from having these combined tumor suppressor defects, may also be enriched in DNA damage repair pathway alterations. BRCA1, BRCA2, and ATM mutations seem to be enriched in these aggressive variant prostate cancers. We know that tumors with these alterations are more sensitive to platinum. They're also more sensitive to a class of drugs called PARP inhibitors.







*What percentage of men has small-cell or aggressive variant prostate cancers?*

**Dr. Aparicio:** If you define it morphologically, meaning you require a biopsy that shows small-cell cancer, probably less than 10%. If you define it clinically and/or molecularly from reports, it is more on the order of 20-30%.

*That is actually a lot of men, considering how many have prostate cancer overall, isn't it?*

**Dr. Aparicio:** That's of the lethal prostate cancers, not out of the 200,000 men diagnosed each year. Rather, 20-30% of the 30,000 who unfortunately die from the disease each year.

*Is there anything else that you think patients should know about these rare lethal forms of prostate cancer?*

**Dr. Aparicio:** People who are diagnosed with primary small-cell cancer, which is not a common occurrence, tend to have very bulky and symptomatic primary tumors. It is key that if you are diagnosed with a primary small-cell prostate cancer you should be treated with chemotherapy. After chemo, an effort should be made to consolidate the treatment to the primary tumor with radiation, and in some cases, surgery, to avoid progression of the disease in the primary tumor. This is recommended because that primary tumor can become a source of a lot of symptoms and complications down the line. Because primary small-cell prostate cancer is rare, we don't have clinical trials to prove this, but I think that anybody who has encountered primary small-cell cancers in the clinic is aware of this problem of symptomatic local progression. It is something that needs to be addressed. It is important. PP



# *Clinical Trial: Daniel George, MD Antabuse + Neuroendocrine Cancer*

**Dr. Daniel James George is a Professor of Medicine and Professor in Surgery at Duke University.**

*Prostatepedia* spoke with him recently about a clinical trial he is running for men with neuroendocrine prostate cancer.

*What is it about practicing medicine that you find the most meaningful?  
What is it about the job that draws you?*

Dr. George: I think that in order to be really successful in anything you do for a living, you have to have a passion for it. I'm really passionate about patient interaction—the people that I meet. This is an intimate part of medicine.

As we get more into electronic documentation, telemedicine, and high-volume clinics, oncology is really special because of the intimacy and the bond between the physician, patient, and caregiver team.

We really join our patients in the fight against cancer, especially when we treat patients at a terminal stage when the disease is not curable. It really makes me appreciate the quality of life that we're able to offer these people, though it may not be the quantity of life we would like. In these cases, we develop treatments that change

the course of the disease, treatments that stay or reverse the disease for a period of time that allows patients to hit important milestones in their lives that they wouldn't otherwise achieve. This is incredibly rewarding.

*Is there more opportunity for interaction in prostate cancer oncology? You tend to see prostate cancer patients for much longer than you might another type of patient.*

Dr. George: Yes. There's chronicity to the care of prostate cancer patients that allows us to really get to know people over time and for them to get to know us. They want to know their doctors, and they want to know them personally—their families, what they care about, their positions, etc. It really gives you a chance to open up with patients over the years.

When we have patients that are on active treatments or clinical trials, we get to see them more often, and that creates more opportunity to open up to patients. Ultimately, as the disease progresses there is a tremendous amount of trust established. This allows us to help patients make the right decisions toward the end of life, which is a struggle no matter how good the relationships are.



*What is neuroendocrine prostate cancer?*

Dr. George: For a long time, people have known about neuroendocrine prostate cancer, which is a different biology of prostate cancer. The testosterone pathway drives most prostate cancers, as well as the androgen receptor or the testosterone receptor. That biology accounts for probably over 90% of initially presenting prostate cancers. A downstream protein that's coded for and turned on from the androgen receptor is prostate-specific antigen (PSA). We have a blood test for PSA that measures this biology to some extent.



*“We really join our patients in the fight against cancer.”*



Also, for a long time, we've known about the activity of the androgen receptor in prostate cancer through the PSA and its kinetics—its ups, downs, and whatnot. We have thought of neuroendocrine prostate cancer as a rare form of prostate cancer that—instead of growing out of the basal cell of the prostate and into a luminal cell, which secretes PSA—grows out



of a cell in the prostate environment called a neuroendocrine cell. It's called that because it's derived embryologically from the same types of cells derived from our endocrine system into neurons.

The neuroendocrine cell has characteristics very different from other prostate cancers. It doesn't have the androgen receptor, it can secrete different types of proteins like CEA or chromogranin, and it grows irrespective of our effects on testosterone. It can spread to soft tissues like the liver, lung, and other areas in a pattern that differs from the spread in more common prostate cancers. It's got an aggressive clinical course. It spreads quickly and can kill people in a matter of months.

More recently, we have come to understand that prostate cancer evolves in patients over time to have more and more neuroendocrine features. Some of our more novel ways of blocking the testosterone pathway with drugs like Zytiga (abiraterone) and Xtandi (enzalutamide) have stressed this system so much that we're seeing a greater percentage of patients evolve into or select for a neuroendocrine phenotype. This is becoming a more prevalent problem as patients live longer and as we use more of these hormone therapies.

### *How is the trial designed? What will you do and what should patients expect?*

**Dr. George:** This project started when we were looking at how to block the testosterone receptor downstream. Drugs like Zytiga (abiraterone) and Xtandi (enzalutamide) are fantastic at blocking the androgen receptor by binding to a certain part of the receptor called the ligand-binding domain. Over time, this can get overexpressed to such a level that these drugs can inhibit

it or result in a splice variant. A splice variant means that the DNA gets expressed only partially so that a shortened or truncated form of the receptor is made that doesn't have the ligand binding domain and is therefore completely resistant to those drug therapies. That's becoming more and more prevalent.

We looked to see if we could block some biology downstream. We found that when the androgen receptor is activated in these hormone resistant models, the copper transporter and other genes involved in copper metabolism were highly expressed. So, we tested drugs that would bind up copper, but it didn't work well. It only worked at very toxic levels.

Then we decided to turn this around. Instead of blocking copper, we fed the cancer copper. We allowed the cancer cells to accumulate a bunch of copper, and then we screened for drugs that would kill the copper-laden cells particularly in this setting. We found several drugs in the dicarbamate family. First and foremost is a drug called disulfiram, also commonly known as Antabuse. This is a drug that is used to block alcohol dehydrogenase, making alcohol toxic in alcoholics. However, in tumors, we found that when disulfiram binds copper, it becomes lethal to cancers.

We've taken this to clinic, and under an investigational new drug authorization from the FDA, we're going to load tumors with intravenous copper, image with a copper PET scan, and then treat patients with oral CX-02 (disulfiram) and additional oral copper.

This strategy gets interesting for neuroendocrine tumors is because the copper transporter is also essential for platinum transport. Copper and platinum are both cations (positively charged ions), and platinum

chemotherapies like carboplatin and cisplatin are very effective in neuroendocrine tumors for a period of time. For those cells to be sensitive to platinum, the platinum must get inside the cells, so we know they must also express the copper transporter. We think targeting this copper transport mechanism may represent a second and novel way to target neuroendocrine prostate cancer.

### *What kind of patients are you looking for?*

**Dr. George:** We are looking at three populations. We're looking at patients with neuroendocrine prostate tumors. We are also looking at patients who have progressed on Zytiga (abiraterone) or Xtandi (enzalutamide) because we think that those are the patients who have AR-V7, this truncated androgen receptor that has the biology. In mouse models, we've shown that this strategy is highly effective against those types of tumors as well.

In the third tumor type, we're looking at anaplastic prostate cancer. These are sort of low PSA-producing visceral metastases, or in other words, tumors that spread to the liver or the peritoneum (abdominal lining) and don't make a lot of PSA. We want to try this strategy in patients with these tumors for two reasons. First, these tumors are frequently sensitive to platinum-based chemotherapy, so, like the neuroendocrine tumors, they will likely also absorb copper. Second, because disulfiram is taken by mouth, we expect it to be absorbed into the bloodstream from the gut and travel to the liver. Antabuse (another form of disulfiram) is known to block alcohol dehydrogenase in the liver of alcoholics, so we are confident that CX-02 will also get into the liver effectively. It is also possible that we need less drug to treat patients with prostate cancer in their livers than in their bones.

If we see clinical effects in any of these populations, we're going to expand the studies out in that population.

*Is there anything else you'd like patients to know about the trial?*

**Dr. George:** There are not a lot of other exclusion criteria. You can have prior chemotherapy, you can have prior radiation therapy, and any prior hormonal therapies are allowed. It's a great protocol for patients who have exhausted other options, but who are still functional and want to try one more strategy. This is a great one to try.

All the therapy after the first two weeks of IV copper loading is oral. It's also a pretty good strategy for people to travel on. We think we can treat patients from many different areas and hope to see some therapeutic benefit.

The neuroendocrine prostate cancer population is difficult to characterize. Many patients don't view themselves as neuroendocrine because maybe they haven't had a biopsy recently. Many patients don't understand anaplastic prostate cancer. It's going to require some education, but potentially the more we can develop strategies specific to these populations, the more effective they could be.

*You said that people could travel for this trial. Does that mean they do not need to live near Duke University; or do you need to have them close by?*

**Dr. George:** The first month is a little busy because there are weekly infusions and drug levels that we'll look at with two PET scans. After the first month—really after the first two weeks—we'll only need to see patients once a month. They'll take the pills with them. That makes it easier for patients to come back and forth.







### *Are there any potential side effects?*


**Dr. George:** We have a lot of information regarding IV copper and CX-02 (disulfiram). Both are pretty well tolerated. We are not using a high dose of CX-02 (disulfiram), and we're not going to escalate it.

We will increase the amount of IV copper given to patients over the different dose levels, but even our highest dose level should be well within the safety range. We expect mild side effects, mostly associated with CX-02 (disulfiram). These include mild nausea or diarrhea and some neuropathy, numbness, tingling of the fingers or the toes, and peripheral neuropathy.

### *What else should patients know about this trial?*

**Dr. George:** The trial is funded through a mix of support that we are really grateful to have received. The V Foundation has given us a scholar award to fund one of the junior faculty on our project. The Peter Michael Foundation also funds us.

Sam Poley, the grateful son of a deceased patient of ours, has run a grassroots crowdsourcing campaign called Give 1 for Dad. They have continued to support this trial beyond its initial phase.

We have collaborated with a company called Cantex Pharmaceuticals that makes a novel formulation of disulfiram and oral gluconate, and they support the trial as well. 

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

For more information, contact Julia Rasmussen at [61919-681-9822](tel:61919-681-9822).



# Vedang Murthy, MD

## Prostate Cancer

### in India



**Dr. Vedang Murthy is a Professor in the Department of Radiation Oncology at Tata Memorial Centre in Mumbai, India.**

*Prostatepedia spoke with him about prostate cancer in India.*

*Why did you become a doctor?*

**Dr. Murthy:** When I was growing up in India, kids either became doctors or engineers. Because I did not enjoy mathematics and physics, I made the obvious choice and became a doctor!



*“They ask for that kind of a personal relationship.”*



I think practicing in India has been most rewarding. There is a certain respect that doctors get here that is quite unique. Patients, even the educated ones and those who are aware of the options available, put everything in your hands, almost without question. To justify that faith imposed on doctors, I think we need to make correct and balanced decisions. That's a very responsible position to be in.



*“About 60-70% of all patients present with metastatic disease.”*



*Do you feel a lot of personal responsibility because of that trust?*

**Dr. Murthy:** Certainly. Often that's the difference in choosing reasonably difficult—or even obvious—treatment options for patients. They say: “Doc, you should make decisions as if I'm your father,” or they ask for that kind of a personal relationship. I have not experienced this often in the West.

*How did you come to focus on prostate cancer specifically, as opposed to another type of cancer?*

**Dr. Murthy:** Once I finished my training—my MD in radiation oncology—I worked at the Royal Marsden Hospital in Sutton, United Kingdom, for about four and a half years. I worked with experts like Professors Alan Horwich and David Dearnaley, who really helped to hone my skills and knowledge. That is where I learned the tricks of the trade and developed some understanding

of urological cancers. When I returned to India in 2008, I continued treating urological cancer, along with head and neck cancers, for the next 10 years.

*How are men screened for prostate cancer in India?*

**Dr. Murthy:** Screening is absolutely not there for prostate cancer in any form currently. In fact, screening is not even there in a formal way for common cancers like cervical, colon, or breast cancer, which are very common in the West. Prostate cancer really comes down the line in terms of prevalence in India, so screening is not there. Because of this, most of the patients present to us in advanced stages. In fact, I would say about 60-70% of all patients present with metastatic disease, which is quite high. Of the remaining 30-40%, a majority have advanced cancer.

*So treating side effects really isn't an issue, right?*

**Dr. Murthy:** It is not the biggest or the primary issue. The main issue is the advanced nature of the disease. There is actually a difference in geography. In larger metropolitan cities, the incidence has increased in the last couple of decades. For example, in cities like Delhi, Bangalore, and Chennai, prostate cancer is the



second or third most common cancer in men, whereas overall, it is about seventh or eighth.

Because of changing lifestyles, food habits, and migration from rural to urban populations, incidence is on the rise in urban areas. When we look at the data for incidence, we talk in terms of cases per 100,000 people. On average, if you look at the total population of 1.3 billion people in India, that means about 60,000 new cancers every year, which is the same or higher than any large European country like Germany, France, or the United Kingdom, which average around 50,000 new cases per year.

*Are there also regional differences between northern and southern parts of India, or are the differences mainly between urban and rural?*

**Dr. Murthy:** We don't know. I think that the data is not robust enough to give us that information by region. Clearly, the larger, metropolitan cities have an increased incidence of disease due to lifestyle-related issues.

*What are the obstacles to getting screening programs in place?*

**Dr. Murthy:** A screening program must be initiated at the national level, not at the hospital or city level. At the national level, prostate cancer is just not ranked with the big killers like cervical, breast, lung, or oral cancers. These are the big healthcare issues that the policymakers have to contend with first. This is the main reason screening is not discussed right now.

There is talk among the urologists—among us treating prostate cancer—that we need some kind of targeted, symptom-based screening. But there are no defined, high-risk populations as you see in the West, such as





African-Americans or genetic-based risks. I think the urologists and general physicians have to be more aware of doing a PSA than they are currently in older men with urinary symptoms.

*Once a man is diagnosed, are there any kinds of support systems in place for him? I know in the United States there is a whole system of support groups and nonprofits that offer services. Is there anything similar in India?*

**Dr. Murthy:** There are no such support groups that I'm aware of. However, patients have a lot of family and societal support. Of course, there are nongovernmental organizations doing a lot of work but not specific to prostate cancer.

*Do men talk openly about their disease, or is it something that is private?*

**Dr. Murthy:** I don't think prostate cancer is spoken about generally in the community. Though there exists social stigma attached to breast cancer, or any male or female cancers of the genitalia, I suspect most of the population might be unaware that the prostate even exists! Because of this, I don't think there is any such stigma associated with it, just a pure lack of awareness.

*How do patients pay for medications in India? Do they have access to care?*

**Dr. Murthy:** In general, I would say 80% of the population pays out-of-pocket expenses. Even if they go to a state-funded institution where a lot of the treatment is subsidized, the cost of the drug is often not. Radiotherapy and surgery might be completely subsidized, but the cost of drugs is often just reduced and the patient pays the rest.

A number of state governments have begun to fund cancer patients. Many

receive government help in the form of a fixed purse like a state-funded insurance. There is very little medical insurance as such in the community. In cities, some people are covered by their employer's corporate insurance, but that's a minority.

*What are the biggest problems facing treatment of prostate cancer in India?*

**Dr. Murthy:** Late presentation is the biggest problem we currently face. We need symptom-based screening, particularly in the cities where incidence is higher. As anywhere else in the world, patients see urologists or general physicians in the first instance. But the urologists here tend to perform orchiectomy without other treatments, which can do a lot of harm, especially if the patient has nonmetastatic prostate cancer. Orchiectomy is a very good treatment for metastatic disease, but people tend to underestimate the side effects of androgen deprivation therapy. This must change.

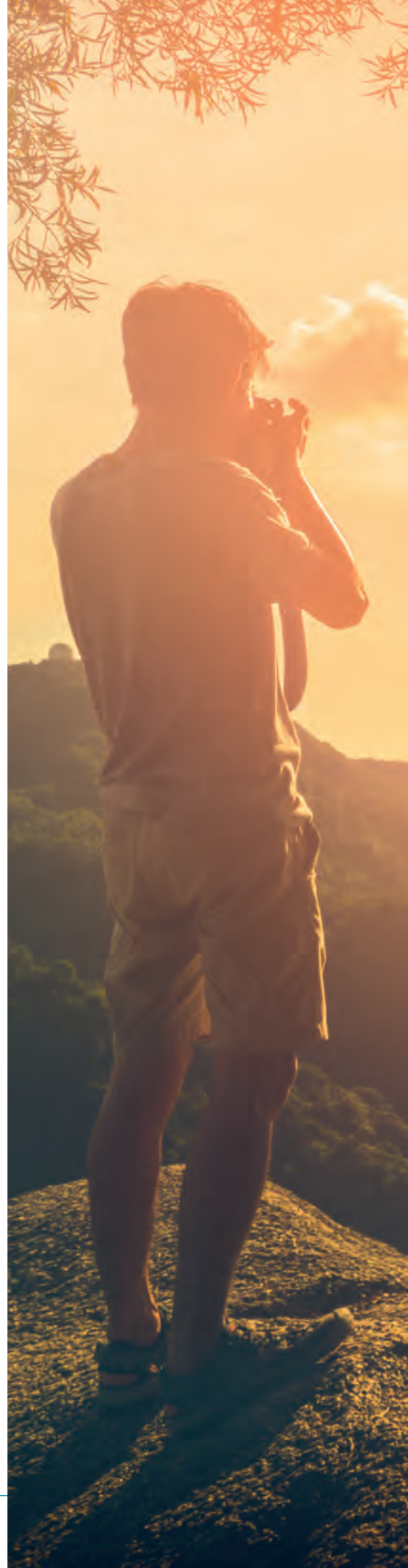


*“There are no defined, high-risk populations as you see in the West.”*




Similarly, transurethral resection of the prostate (TURP) is a very common procedure. Urologists often perform a TURP, remove the obstructing tissues, and then the patient feels better. It can have a lot of negative impact on future treatment like radiotherapy or even prostatectomy.

In the next 15-20 years, we face a looming epidemic due to lifestyle changes. I think what happened in the West is going to happen here, especially in the larger cities.







Indians face the burden of traveling long distances for treatment. If they want state-of-the-art treatment, they seek larger centers. For example, they come to Mumbai from far-flung areas. If they have, for example, radiotherapy for six to eight weeks, that is a large expense. And while receiving treatment, they often spend several times more on lodging than on the treatment itself.

We have begun to address this by introducing or developing hypofractionation schedules, which are much shorter. They have a much shorter treatment course: five to seven days rather than five to seven weeks. This reduces the burden of travel and out-of-pocket expenses as well as the burden on the hospital. Seven days versus seven weeks of treatment on the machine means a rapid turnover.

*Do you have any advice for men in India who have been diagnosed with prostate cancer?*


**Dr. Murthy:** The first advice would be not to panic—there is absolutely no need. Men who are diagnosed with prostate cancer need to seek treatment at a reasonably good center, either at a private organization or a state-funded hospital. There are a number of cancer centers—even the state-funded ones—that have pretty good state-of-the-art equipment and expertise with world-class care. There is no doubt about that. But patients have to show up, and in time, to benefit.

Lots of effective treatments are available, so it's unlike other types of cancers such as lung, pancreatic, or certain brain tumors where survival is limited and treatment lasts for a few difficult months. Even if it has spread and prostate cancer is diagnosed as metastatic, with the number

of effective treatment options, these men live a long and reasonably good quality of life. That's important to remember.

One of the accepted treatments for metastatic prostate cancer, which many men choose, is removal of the testes or an orchiectomy, which is effective and quite inexpensive as compared to lifelong hormonal injections. People should not be afraid or think of removal of testes as feminization—that is a common misconception. Of course, orchiectomy has side effects due to a lack of testosterone, but it is effective.

Depending on the stage and type, nonmetastatic prostate cancer—if it has not spread outside the prostate—is pretty much curable with radiotherapy, surgery, or a combination of these. Even metastatic cancer can be controlled for several years. A number of life-prolonging agents have recently become available, when just five years back, they were prohibitively expensive. They are still expensive, but the price is rapidly coming down, so we have gained access to some of these drugs at a reasonable cost now.

Many patients have bone pain, which is how prostate cancer spreads. Bone pain can be controlled effectively. Palliative radiotherapy is a very effective option. I have seen a lot of patients worry about taking painkillers because they've been told painkillers are addictive, but they miss the point. If you have cancer pain, you need to take the painkillers. That's what they're for. This is the kind of misconception we must clear up. 



# *Dispatches from the Hill: The Prostate Cancer Research Program's \$90M at Work*

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**Mr. Jamie Bearse is the CEO of ZERO — The End of Prostate Cancer ([www.zerocancer.org](http://www.zerocancer.org)). ZERO is a United States-based nonprofit with a mission to end prostate cancer.**

*In his second quarterly column, he updates us on American policies impacting prostate cancer patients.*

In my last column, I shared news about our annual fly-in day, the ZERO Prostate Cancer Summit, and the major research funding victory on Capitol Hill for prostate cancer advocates. Congress had just earmarked \$90 million for the Prostate Cancer Research Program (PCRP) in the FY17 budget as part of the Defense Appropriations Bill - a \$10M increase over last year. This is the program's first funding increase in more than a decade.

So, what does this funding upgrade mean for prostate cancer patients? More research and innovation directed at a cure? Yes. The additional \$10M will fund several additional projects; new research that could lead to more treatments and save lives.


The Department of Defense's (DoD) medical research programs are an epicenter for groundbreaking research. In the last six years,

the Prostate Cancer Research Program has awarded grants that have led to three new, life-extending treatments: ZYTIGA (abiraterone acetate), Xtandi (enzalutamide), and XGEVA (denosumab), as well as a genetic diagnosis profile to determine aggressive disease. The program has awarded more than 50 prostate cancer research grants in the last year alone.

In addition to funding critical research, the DoD program created a peer-review model, which brings patients into the R&D process, helping choose which ideas to fund. The program also created the Prostate Cancer Clinical Trials Consortium (PCCTC), collaboration between several top cancer centers in the U.S. The Consortium creates a knowledge center and makes conducting clinical trials more efficient and cost-effective, speeding up the pipeline for potential therapies. As a result of these programs, treatments for prostate cancer are no longer isolated to a laboratory, but instead are created with feedback from the prostate cancer community.

The outlook for continued funding of the DoD's PCRP is positive. Just prior to the July 4th recess, the House Appropriations Committee approved the FY18 Defense Appropriations Bill, which preserves

the \$90M annually for prostate cancer research. This is a step in the right direction thanks to the dedication of prostate cancer advocates and champions in Congress.

ZERO will fight every year to ensure that this critical research funding remains in the DoD's budget. The PCRP has a clear impact on prostate cancer, and thanks to the increased funding, we're one step closer to a much-needed cure. I hope that you'll join us to advocate for the PCRP and similar programs to help end prostate cancer. 







# *Patients Speak: Stan P.*

## *Dealing With Neuroendocrine Prostate Cancer*

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Stan P. has neuroendocrine prostate cancer. He spoke at length with *Prostatepedia* about his experiences with this rare, often aggressive form of prostate cancer.

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

Stan P: It was a PSA taken by my primary physician. It was taken



*“The real issue is there aren’t many doctors around who spend a lot of time with this type of cancer.”*



kind of late. It came out to be 6.2, which is fairly high. After that, I started consulting around trying to find a doctor to treat me. That was back in 2006.

*How did you find out that you had neuroendocrine prostate cancer? Was that when you were first diagnosed or was that after you’d been on some kind of treatment?*

Stan P: I was taking Zytiga (abiraterone) for almost two years. The physician was also running blood tests. One of the substances in the blood test that stood out was this bone-specific alkaline phosphatase. It started to go up while at the same time my PSA was undetectable. It had reached undetectable status about a year after taking Zytiga (abiraterone).

The physician saw this one level going up, so he prescribed an F18 sodium bone scan along with a couple of other specialized blood tests. One of the blood tests was LDH, which I think detects cellular injury. Another was chromogranin A that detects neuroendocrine tumors. The third one was CEA, carcinoembryonic antigen, a marker for colon and thyroid cancer.

The one that stood out was the chromogranin A. It was high. At the same time, the F18 scan showed two neuroendocrine tumors. One was in the ileum (the end of the small intestine) and the other one was in the C5 vertebrae. With the undetectable PSA, these results from the scan, and some of the blood results, the physician suggested that it was probably neuroendocrine, which I didn’t even understand at the time.



He said something about adenocarcinoma being differentiated into this neuroendocrine tumor. From that point, his recommendation was to try some platinum-based chemo. I was not feeling any symptoms. I was not in any pain, and I was still doing my normal thing. He recommended that I undergo Xofigo (radium-223).

*Were you still on the Zytiga (abiraterone) at this point or did he take you off the Zytiga?*

**Stan P:** I was still on Zytiga (abiraterone) when all this happened. He took me off later because my kidneys started to show side effects from it—high creatinine. He took me off of that to see if it would lower the creatinine levels, and it did, so he kept me off it. I continued to take an androgen agonist (degarelix), which I'm still taking.

*What was your initial reaction when you heard all this? Did you immediately start researching about neuroendocrine prostate cancer? How did you respond?*

**Stan P:** I had no idea what a neuroendocrine tumor was. I didn't even know what a PSA was. I got this medical explanation, and then when I started delving into it on the Internet, I found out that only 1% of the prostate cancer patients get this or have this condition. Then I knew it was serious.

There really are no cures. I consulted with two other prostate specialists. One was the chief of hematology and the other was the chief of prostate cancer research at a teaching hospital. One doctor said that he treats this through standard-of-care treatment, which means platinum-based chemo. The other doctor told me to go back on the Zytiga (abiraterone), which really didn't make any sense. My understanding is that this neuroendocrine tumor does not have any androgen receptors.

But the real issue is there aren't many doctors around who spend a lot of time with this type of cancer.

*What is your current doctor's plan going forward?*

**Stan P:** I just went through six months of Xofigo (radium-223) and completed that at the end of March. The recommendation has been to wait for three months and get a scan then. In the meantime, I take Firmagon (degarelix). During the six months on Xofigo (radium-223), I had a couple of scans. One was a technetium-99 bone scan, which was performed after two treatments with Xofigo (radium-223).



*"Then I knew it was serious."*



The strange thing was they only found one neuroendocrine cancer in the ileum. They did not find the one at the C5 vertebrae. Maybe the F18 was oversensitive to the scan. I don't know.

At the same time, I entered a clinical trial for C11 Acetate PET/CT scan. They were giving me these C11 Acetate PET/CT scans every month, and I decided I should stop doing that because it was affecting my blood counts too much. I had two C11 Acetate PET/CT scans, and both were uneventful. They didn't find anything, which I kind of expected because my PSA is undetectable. They did not detect any of the neuroendocrine tumors either.

Since ending the Xofigo (radium-223), I have not had any scans. I'm waiting

another month, and then I'll get another scan to see the effect of that.


During the time I was undergoing Xofigo (radium-223), the blood tests were becoming much more positive. The bone-specific alkaline phosphatase went down to normal levels. That indicated that maybe the tumor was not growing anymore. The plan right now is to just stay on Firmagon (degarelix) and get another scan in another month. Treatment will be scheduled then.

*Do you have any advice for other men who have been told that they have neuroendocrine prostate cancer?*

**Stan P:** First, make sure you actually have a neuroendocrine tumor. Then consult with a doctor who specializes in neuroendocrine prostate cancer. I found a nationwide list on the site [carcinoid.org](http://carcinoid.org).

And just keep the faith. I have a positive outlook that something's going to come to help me either put off the growth of this tumor or to cure it. I keep looking, and that's about all I can do. Just keep the faith.

*What about any advice for doctors treating patients like you?*

**Stan P:** I would recommend that the doctors educate themselves on the ongoing clinical trials for this disease. Even if they don't know about any while the patient is visiting them, they should at least tell the patient that they will do research themselves. I'm sure doctors have a better way of finding these things out than the layman. 





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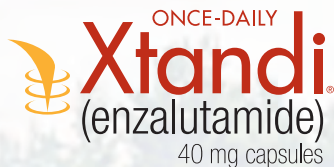
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- Have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form 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?”
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#### **How should I take XTANDI?**

- XTANDI is four 40 mg capsules taken once daily.
- Take XTANDI exactly as your healthcare provider tells you.
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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, 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.

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**Please see the Brief Summary on the following page and the Full Prescribing Information on [XTANDI.com](http://XTANDI.com).**



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

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

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

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

**How should I take XTANDI?**

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

**What are the possible side effects of XTANDI?**

**XTANDI may cause serious side effects including:**

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

decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

**The most common side effects of XTANDI include:**

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

XTANDI may cause infections, falls and injuries from falls.

Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

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

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

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

**How should I store XTANDI?**

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

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

**General information about XTANDI.**

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

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

For more information go to [www.Xtandi.com](http://www.Xtandi.com) or call 1-800-727-7003.

**What are the ingredients in XTANDI?**

**Active ingredient:** enzalutamide

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

**Marketed by:**

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

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**076-1977-PM**

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

Revised: October 2016





# Diagnosed with Prostate Cancer?

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### CHOOSING YOUR ROAD

Explore your treatment options so you can partner with your doctor to decide what is best for you.



### FINDING YOUR WAY

Learn how to adapt to changing relationships and begin to navigate other changes in your life.



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