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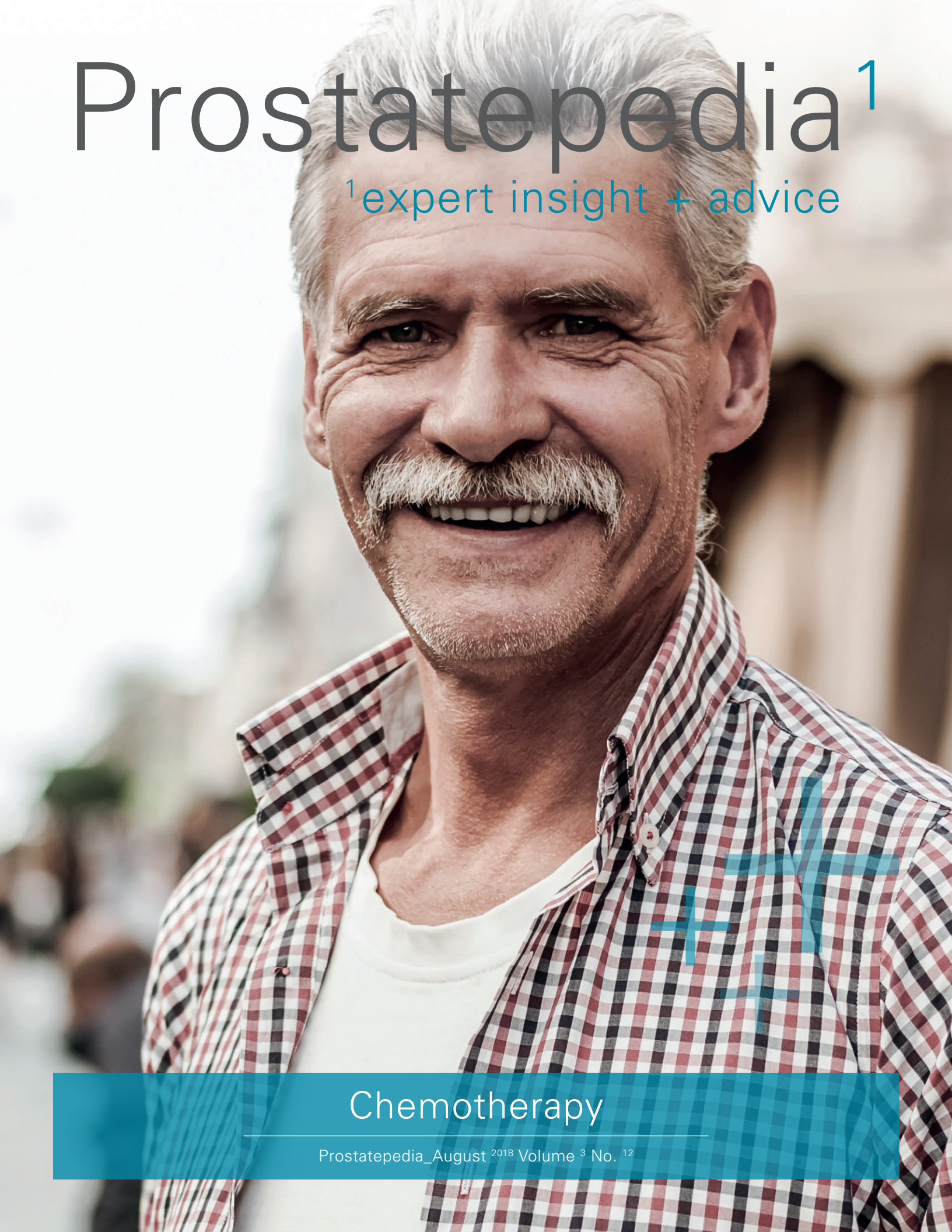

Chemotherapy

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In this issue....

Patients are often under the impression that chemotherapy drugs like Taxotere (docetaxel) and Jevtana (carbazitaxel) won't significantly improve survival and will only dramatically impair quality of life. A patient once said to me, "That sounds like a bad deal." I hope this issue of *Prostapedia* changes your view of chemotherapy.

The potential benefit of chemotherapy depends on where you are in the natural history of metastatic prostate cancer. If you have just been diagnosed with widespread metastatic prostate cancer, Lupron (leuprolide) plus Taxotere (docetaxel) can have a major benefit in terms of your survival. At this point, you are likely to tolerate chemotherapy better than you would if you had already been through multiple other treatments. However, even in patients who have been extensively treated before chemotherapy, this treatment can often provide significant relief of bone pain that outweighs the drug side effects.

The major alternatives to Taxotere (docetaxel) in this setting are the new androgen blocking agents, such as Zytiga (abiraterone), Xtandi (enzalutamide) or Erleada (apalutimide). Each of these drugs can cause side effects more severe than Taxotere (docetaxel) in some patients. Also, Taxotere (docetaxel) treatment extends for just six treatments done every 3 weeks. In contrast, the androgen blocking agents are typically given continuously until they fail to control your cancer.

In many other cancers, patients benefit greatly when we combine drugs. While the search for effective Taxotere (docetaxel)-based combinations has been going on for decades, no combination has survived rigorous Phase III testing. I, and many others in the field, think that this may be because prostate cancer is a very heterogeneous disease. The path to success requires that we understand at a molecular level the various forms of this disease and the key vulnerabilities of each variation. One example is the sensitivity of prostate cancers with a BRCA2 mutation to Paraplatin (carboplatin). Another example is the activity of Jevtana (carbazitaxel) + Paraplatin (carboplatin) in anaplastic prostate cancer.

There are several reasons to be optimistic about progress. First, research into the molecular heterogeneity of prostate cancer and the clinical implications thereof is proceeding rapidly. Second, leads that emerge from this research are being tested more rapidly and with greater sophistication than at any time in the past.

Charles E. Myers, Jr., MD Pp1

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Chemotherapy Today

There are very few people who don't immediately panic when they hear that they've been diagnosed with cancer. *Am I going to die,* most wonder, even if they don't voice that fear to their friends and family. Many patients have a similar reaction when their doctor suggests chemotherapy. But just as cancer itself is not always a death sentence, chemotherapy is not as bad as most think.

Chemotherapy for prostate cancer today is not your grandfather's chemo. Most side effects are manageable and don't stop men from going about their daily lives. And studies suggest that using chemotherapy earlier and not waiting until your disease has progressed has tangible benefits.

This month we take a deep dive into chemotherapy today. Dr. Ken Pienta frames this month's discussions and points out that the cultural view of chemotherapy as catastrophic to the patient is largely unfounded.

Dr. Nicholas Vogelzang outlines the history of chemotherapy for prostate cancer and muses about future directions.

Dr. William Oh explains the role chemotherapy plays in a prostate cancer treatment today.

Dr. Cy Stein talks about side effects associated with Taxotere (docetaxel) and Jevtana (cabazitaxel) and how to manage them.

Dr. Oliver Sartor explains the development of Jevtana (cabazitaxel) for prostate cancer.

Dr. Emmanuel Antonarakis talks about the potential impact of switching from Taxotere (docetaxel) to Jevtana (cabazitaxel) midway through treatment and vice versa.

Dr. Channing Paller introduces her clinical trial looking at combining Taxotere (Docetaxel) with intravenous Vitamin C. She's recruiting patients, so if you think you might be a fit for the trial, be sure to contact her.

Finally, both Mark Slaughter from Us Too! and Bill R. tell us about their experiences with chemotherapy for prostate cancer and their advice for men in similar situations.

The bottom line is that, if you've been prescribed either Taxotere (docetaxel) or Jevtana (cabazitaxel) for prostate cancer, there is no need to panic. Both drugs can have a dramatic impact on your survival, and their side effects can be managed with a little forethought and careful monitoring. Talk to your doctor about any concerns you have. Reach out to other men with prostate cancer who've had either of these medications. As with anything in life, the more you know going into the experience, the easier of a time you'll have. Many times we fear the unfamiliar..

And, as always, be sure to share this issue of Prostatepedia with your doctor. Use these conversations as a jumping off point for an honest discussion. She may agree or disagree with some of the points made in the interviews that follow. Talking about why she is taking a certain approach with your disease will help you feel more comfortable with any decision that the two of you agree upon.

There has never been a better time to be a prostate cancer patient, friends. Your doctor has many tools in her wheelhouse to fight your cancer. Pp!

Ken Pienta, MD
Guest Commentary

Dr. Kenneth J. Pienta, of the Johns Hopkins University School of Medicine, is an international expert in the development of novel chemotherapeutic agents for prostate cancer. He was the recipient of the first annual American Association for Cancer Research Team Science Award and is the author of more than 300 peer-reviewed articles.

He frames this month's conversations about chemotherapy for us.

In 2018, chemotherapy for prostate cancer continues to be one of the many options we have to lengthen the lives of patients suffering from metastatic prostate cancer. There are still multiple other therapies that we don't consider *chemotherapy*. Second-generation anti-androgen therapies like Zytiga (abiraterone), Erleada (apalutamide), and Xtandi (enzalutamide) are all now standards of care in castrate-resistant prostate cancer. We also have Xofigo (radium-223) as an option for patients with bony metastases.

There are two chemotherapies that have been approved for prostate cancer: Taxotere (docetaxel) and Jevtana (cabazitaxel). Now, the real challenge for patients and providers is when to use those chemotherapies.

"The real challenge is when to use those chemotherapies."

Multiple studies have demonstrated that, when you're newly diagnosed with metastatic prostate cancer, it may be beneficial to receive a limited number of doses of Taxotere (docetaxel) at the start of hormone therapy. That's especially true if you have multiple places where the cancer has spread. That's not correct for all people, but for some patients, it is a good option. More and more physicians are prescribing Taxotere (docetaxel) with a luteinizing hormone-releasing hormone (LHRH) antagonist at the start of therapy. However, that doesn't mean you cannot use Taxotere (docetaxel) after other things have failed. If you failed second-line hormone therapy or have failed radium therapy, Taxotere (docetaxel) is still a good option that helps people live longer.

Jevtana (cabazitaxel) continues to be a good chemotherapy option if patients have failed Taxotere (docetaxel).

Thank goodness we've seen over the last several years an increase in the number of drugs available to treat metastatic prostate cancer in addition to chemotherapy. Chemotherapy has been around for quite a while now, but there is still a role for it. Again, the challenge for all of us is: when do we slot them in for you?

The chemotherapy we use for prostate cancer is really a single agent chemotherapy, either Taxotere (docetaxel) or Jevtana (cabazitaxel). This is not the multi-agent therapy we use for other cancers, so the idea of major side effects is a bit overblown. For example, nobody vomits from chemotherapy for prostate cancer. The drugs we use to prevent that are too good.

We also have gotten much smarter about limiting the number of doses we use. We don't necessarily give chemotherapy until it doesn't work anymore. Often, we just give several doses and then take a break. If you get more than a couple doses of chemotherapy, you will still lose your hair temporarily.

Chemotherapy can make you feel more tired when it lowers your blood count, and it can make you more susceptible to infections, but people are very rarely hospitalized now for an infection from chemotherapy. It's virtually unheard of that somebody would die as a side effect of chemotherapy.

The major side effect of Jevtana (cabazitaxel) tends to be diarrhea, but again, as we've learned about the dosing of that drug, that has become more manageable. Another side effect of both drugs can be peripheral neuropathy, which is tingling in the fingers and toes. But we watch for that too. If you start to develop that, we tend to stop the drug. These are very tolerable medicines.

The word *chemotherapy* always evokes images of horror, but chemotherapy in 2018 is a lot different than it was even five years ago. We just know how to give chemotherapy much better.

"The idea of major side effects is a bit overblown."

When I started in the field 30 years ago, if you had metastatic castrate-resistant prostate cancer, survival was 6 months. Now, with the advent of all these newer therapies, we've gotten much better. The landscape of how to treat prostate cancer has changed completely in the last five years. It will change completely again in the next five years. The challenge is in what order are we going to use all these powerfully good drugs rather than having only one drug to give or none at all.

For us as physicians, it's an exciting time to take care of men with prostate cancer. Pp

Nicholas Vogelzang, MD, The History of Chemotherapy for Prostate Cancer

Dr. Nicholas Vogelzang is a medical oncologist at Comprehensive Cancer Centers of Nevada. He is a member of the 2018 Class of Giants of Cancer Care, a designation awarded to healthcare professionals advancing the field of oncology by their contributions in research and clinical practice.

He also serves as Associate Chair for the Genitourinary Committee of US Oncology, the Vice Chair SWOG GU committee, and the Associate Editor of *Kidney Cancer Journal and Clinical Genitourinary Cancer.*

Prostatepedia spoke to him recently about the development of chemotherapy for prostate cancer. He also offers advice for men prescribed chemotherapy and thoughts on a new class of drugs called PARP inhibitors.

What was it about medicine that drew you in?

Dr. Nicholas Vogelzang: I was raised in a very religious family. My dad was a pastor. We were seven kids. We'd go to church three times every Sunday and probably three times a week. Like a lot of Protestant families, the idea was that your chief aim in life was to glorify God and praise Him forever. The way you do that is by serving others. Out of the seven of us, there are three doctors, two nurses, and two CEOs. We did okay.

It was really all about service to others. Thus, medicine was a logical career. Fortunately, I had a decent brain, I could get along pretty well with people, and I was very much drawn to science. During my undergraduate and medical school years, I spent a fair bit of time in biology laboratories such as Argonne National Lab near Chicago. When I was in medical school, I was what the University of Illinois called a James Scholar, which allowed me to be fairly independent and again spend time conducting research. Researchers discover new knowledge by comparing the control (the old or standard approach) to the experimental (the new or potentially better approach). That training has served as a paradigm throughout my academic life.

When I started in my internal medicine career at Rush Presbyterian in Chicago, cancer was still in great need of better treatments. There had been some major advances that included the development of curative chemotherapy for childhood leukemia, Hodgkin's Disease/Non-Hodgkin's lymphoma, and testicular cancer, as well as development of chemotherapy that worked for some solid tumors of breast, lung, and colon cancer.

Yet, when I started to see prostate cancer patients in the late 1970s at the University of Minnesota, the assumption was that nothing really worked. Chemotherapy was declared as not worth doing for prostate cancer. That always struck me as odd because there was virtually no cancer for which you could not find some chemotherapy drugs that would work. But that thinking was probably the result of the high effectiveness of hormone therapy for prostate cancer. It lulled everyone into complacency. These were older men. The hormone therapy worked. The cancer pain went away. The theory was that we shouldn't give them a toxic medicine. That was the dominant paradigm.

There were a few voices in that wilderness of the 1970s. They were mostly urologists, interestingly. Gerald Murphy and Claude Merrin at Roswell Park used chemotherapy probably under the inspiration of James Holland, who was then at Roswell Park, and who developed chemotherapy along with Emil Frei and others at the National Cancer Institute (NCI) in the 1950-60s.

Dr. Murphy developed a whole series of early studies showing that chemotherapies had a clear but modest effect on metastatic hormone refractory or androgen independent prostate cancer in terms of decreasing pain and improving survival. Medical oncologists such as Chris Logothetis at MD Anderson, Alan Yagoda, Howard Scher, and Cora Sternberg at Memorial Sloan Kettering reported modest success as well.

Then there was a series of articles from my friends Derek Raghavan, Mario Eisenberger, and Ian Tannock in 1987-88 arguing that chemotherapy had no role in the treatment of prostate cancer.

It was yin and yang.One study would show that maybe there's some benefit. And then another showed that you're just harming the patients.

As I became a faculty member at University of Chicago in 1982, I was responsible for developing drugs for these patients, and it became clear that chemotherapy did, in fact, work. It wasn't common, but you could have dramatic effects in patients for whom hormone therapy had stopped working.

I remember five or six of my patients in the mid 1980s who were in terrible pain and had dramatic responses. One patient's response was so dramatic that I wrote up a case report. Thus, I became a member of the camp that encouraged chemotherapy use.

Then, along came Novantrone (mitoxantrone), a drug that was well tolerated and improved pain in a good number of patients. We ran two large studies. The group that I was leading at the time, called the Cancer and Leukemia Group B (CALGB), did one study. The Canadians, led by Ian Tannock, did the other one. Both showed a reduction in pain and a modest reduction in cancer activity—not much, but some. Those studies led the FDA to approve Novantrone (mitoxantrone) in 1996.

We had a lead from a laboratory run by Willie Kreis of Long Island Jewish Medical Center. Dr. Kreis told the CALGB members that this drug called Taxotere (docetaxel) was very effective against prostate cancer cells growing in the lab. CALGB members, with the concurrence of the NCI, voted to do a Phase II trial led by Diane Savarese. Taxotere (docetaxel) had been approved for breast cancer. It made sense that it would work for prostate cancer. In that trial, we saw a lot of patients for whom the drug worked.

We looked back at our CALGB Novantrone (mitoxantrone) data and compared it to the Taxotere (docetaxel). Docetaxel appeared better able to reduce PSA and to reduce pain. Moreover, patients were living three to four months longer than we would have expected.

After a series of meetings with the NCI and Sanofi, the drug's manufacturer, the decision was made to do two major studies. Sanofi did one study led by Dr Tannock and the Southwest Oncology Group (SWOG), led by Dr. David Crawford and Dr. Daniel Petrylak. CALGB did the other. In both cases, we compared Taxotere (docetaxel) to Novantrone (mitoxantrone). We wanted to make certain that everyone got Novantrone (mitoxantrone) so patients were allowed to cross over, which means that if you were randomized to Novantrone (mitoxantrone), you could get Taxotere (docetaxel) second or vice versa. It was an easy study to do.

Both of those studies were reported at the American Society of Clinical Oncology (ASCO) Plenary Session in 2003. That was the biggest, most prestigious site to present cancer research in the world. Both studies showed longer life, better pain control, higher rates of PSA decline, and shrinkage of the lymph nodes with Taxotere (docetaxel) compared to Novantrone (mitoxantrone).

The FDA approved Taxotere (docetaxel) based on those studies. Finally, after so many years, we had two drugs for prostate cancer. Recall that breast cancer had about 10 drugs approved at that time.

The next step came with a drug called Platinol (cisplatin). Platinol (cisplatin) had been developed in the 1970s, and it was very active for testicular, ovarian, lung, bladder, and other cancers. Everybody wanted Platinol (cisplatin) to be useful for prostate cancer, but it was pretty toxic, particularly for older men.

A less toxic carboplatin had some activity and is commonly used today but never gained FDA approval. A company came up with a non-toxic oral formulation of Platinol and conducted a 900-patient trial that went all the way to the FDA. Unfortunately, the FDA said the drug was not good enough to approve. It was very disappointing.

At the same time, Sanofi was developing a drug similar to Taxotere (docetaxel) that overcame some of its side effects: no hair loss and less nerve damage. They compared it to Novantrone (mitoxantrone), but this time, after Taxotere (docetaxel) had stopped working. As reported by Drs. Oliver Sartor and Johann de Bono, that drug improved survival, and that drug was Jevtana (cabazitaxel). Recently, it was compared directly to docetaxel but did not improve survival as compared to docetaxel.

In 2018, now we have three FDA approved drugs for castrate-resistant prostate cancer: Novantrone (mitoxantrone), Taxotere (docetaxel),

and Jevtana (cabazitaxel). It only took us 25 years to get them! That's really where we are today. We still don't have approval of Platinol, although everybody uses it because it works great for some patients.

There are certain other drugs that might be effective. We still use drugs like Toposar (etoposide) and Gemzar (gemcitabine). They're old now. No company will get behind their development anymore. They're no longer under patent. You can't really get much traction to get them through clinical studies. A drug called suramin had activity, but was abandoned without going to the FDA.

The platinum class of drugs has now been identified as being active in the small percentage of prostate cancer patients with DNA repair mutations, about 15-20 percent.

When we were studying the platinum drugs, we knew that some of the patients did really well, but we didn't know how to find them. Now, we think we know that those patients who do well on platinum have mutations in DNA deficient repair (DDR) enzymes. Some of the DDR mutations include genes such as BRCA-1, BRCA-2, ATM, FANC, and CHEK-2, which cause prostate cancer in men and breast and ovarian cancer in women. We now want to go back and do studies of platinum in these DDR mutation patients.

I use platinum routinely for patients and find a lot of success after patients fail on Taxotere (docetaxel) or Jevtana (cabazitaxel). So, though platinums are not FDA approved, we have four drugs.

Do you have any advice for men who have been prescribed chemotherapy? For many patients, it's a frightening thing. There's a cultural concept that chemotherapy is terrible.

Dr. Vogelzang: I understand how seriously patients take this issue, although it's an unfounded fear.

I have a patient who is dying. He's a retired pilot. He refused to take chemotherapy. Yet, he went to the Philippines and spent $30,000 on some herbal potion rather than go on chemotherapy. He came back far worse than when he left. At this point, he's trying chemotherapy, but he's just taken too long to get it.

There are a couple of things I'd say. Number one: don't wait too long. Take chemotherapy when you're strong.

Number two: all the side effects are reversible. You don't suffer the whole time, although fatigue is real. You'll have nausea for a day and some folks get bad diarrhea. We have developed dramatically effective drugs to prevent diarrhea, nausea, and vomiting. You don't vomit anymore. You may not even get nauseated. About the only thing you get is fatigue. Taxotere (docetaxel) can cause hair loss, but Jevtana (cabazitaxel) does not.

If you use an ice cap, like women do with breast cancer, you don't lose your hair. You can get some numbness in the fingers, but you can prevent that by using ice on your hands. There's even a product on the market now, called the cold cap, that you can buy for $300 or so that you wear on your head. It looks like a World War I flying cap from the Red Baron. You put it on your head during the one hour of chemotherapy. It virtually prevents the hair loss.

There are also mittens and stockings that protect against fingernail and nerve damage in the hands and feet. You can do it the inexpensive way and put your hands and feet in ice. People come into my clinic and ask what all those guys are doing with their feet in ice? It's to prevent nerve damage from the chemotherapy.

Like I said, Jevtana (cabazitaxel) avoids those side effects. I try to give Jevtana (cabazitaxel) whenever I can first for that reason. Usually, the insurance requires Taxotere (docetaxel) first because Jevtana (cabazitaxel) is a lot more expensive.

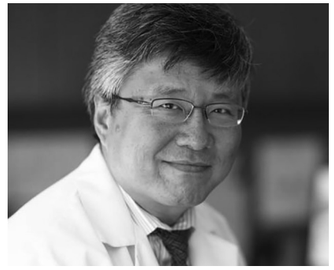
Jevtana (cabazitaxel) can be really well tolerated for a long time. I have one patient who is a rancher originally from Minnesota. He is on dose number 27 of Jevtana (cabazitaxel). His PSA started in the high hundreds and now it's 11. In some patients, chemotherapy is highly effective, long lasting, and is clearly not to be feared.

It's just urban legend that somehow chemotherapy is bad. We figured out many years ago that chemotherapy is not to be feared.

Is there anything else you'd like patients to know?

Dr. Vogelzang: New drugs called PARP inhibitors are coming. These are oral drugs with effects like chemotherapy. They're being developed for patients with DDR mutations. We're beginning to use those drugs more and more. They will cause low blood counts and mild anemia. Some of the side effects are similar to what we see with chemotherapy, but because they're oral medications, most men don't have as much fear of them. Five are in development. I think we're going to see one or two of them hit the market in the next year or two. Pp1

William Oh, MD
Chemotherapy for Prostate Cancer



Dr. William Oh, of the Mount Sinai Medical Center and the Icahn School of Medicine at Mount Sinai in New York City, is a medical oncologist and expert in the management of prostate, renal, bladder, and testicular cancers.

Prostatepedia spoke with him about the role chemotherapy plays in prostate cancer treatment strategies.

Why did you become a doctor?

Dr. William Oh: I have always enjoyed interacting with people. Before I became a doctor, I didn't really understand how important the personal relationship with patients could be for my own wellbeing, but it has turned out very much to be that way. From the time I was a child, many of my role models were doctors, such as my own pediatrician.

The healing aspect is what drew me to medicine. But after becoming a doctor, I've enjoyed the science of it, especially in oncology. Tying knowledge, research, new developments, and treatments together and delivering that back to my patients makes medicine such a satisfying field. That is really why I became a doctor, and why I continue to enjoy and feel privileged to be a physician and oncologist.

Have there been any patients who changed how you see your role?

Dr. Oh: I have many patients, of course, but certain patients always stand out in your mind.

When I was a medical student at Bellevue Hospital, a big city hospital, I was just learning how to draw blood at a time when medical students still drew blood. I remember I was sent into an IV drug user's room to draw his blood. He was particularly difficult to draw blood from, but he couldn't have been nicer and more patient with me. He was a relatively young guy, and he was trying to help me. "Doc," he said, "try this vein." This was a person who I would have never interacted with in my life, and yet, there he was. We had a shared mission: to help him, I needed to draw his blood.

It really opened my eyes to the physician-patient relationship. Many, many times since then, with patients from all different walks of life, I find the common threads of humanity. It sounds cliché, but that is really what medicine is about. A person who is sick—it doesn't matter how much money they have, what their race is, or their education—they all want to be taken care of.

What types of chemotherapy are available to prostate cancer patients today?

Dr. Oh: In many ways and for many patients, chemotherapy has a negative reputation. People tend to lump all chemotherapy drugs together, but it's very important to remember that there are hundreds of kinds of chemotherapy. The word chemotherapy really just means chemical therapy for cancer, but that's not the same thing for everyone.

There are two major chemotherapy agents approved and commonly used in prostate cancer: Taxotere (docetaxel) and Jevtana (cabazitaxel).

When Taxotere (docetaxel) was first approved in 2004, it was really an important milestone because up until that point, there were no drugs of any kind that were proven to improve survival in metastatic prostate cancer.

Taxotere (docetaxel) showed that it could be done. Then it took many years of research and clinical trials to get to the next set of drugs that improved survival, especially in castrate-resistant prostate cancer. These include drugs like Zytiga (abiraterone), Xtandi (enzalutamide), Provenge (sipuleucel-T), and Xofigo (radium 223).

Since 2004 with the approval of Taxotere (docetaxel), we still think improving survival is the most important goal for patients with advanced prostate cancer. As an oncologist, I felt the survival improvement is—for most patients–worth the side effects patients may have. This is a critical point, because many people think that chemotherapy has terrible side effects and doesn't do anything of value. That is not a fair stereotype. While it does have side effects, and it doesn't always work, in many ways, chemotherapy has great value for our patients in terms of improving both their survival and their quality of life.

The perception is definitely that the side effects of chemotherapy can be terrible, so how might chemotherapy improve quality of life?

Dr. Oh: When we first started giving chemotherapy for metastatic disease (and still today), patients were often very symptomatic. They had a very short expected lifespan, and they were in pain. They were weak. They couldn't walk. They would have a lot of side effects from cancer. The way that drugs like chemotherapy can boost quality of life is that, by shrinking the cancer—by directly killing cancer cells, we can make patients feel better. If they have fatigue or some hair loss from chemotherapy, that wasn't something they wanted, but they could be in a much worse state from the cancer itself. They were really suffering from it.

In balance, the chemotherapy was able to make them feel better by reducing their pain medication requirements and by improving their functionality and their appetite. We often see that.

When chemotherapy works—and it's not always—it can really shift a person's quality of life, and it also improves their duration of life. These are the two critical factors for any cancer drug.

When is a patient likely to encounter Taxotere (docetaxel) and Jevtana (cabazitaxel)? Why would your doctor choose one over the other?

Dr. Oh: When docetaxel was first approved, it was approved for metastatic castrate-resistant prostate cancer (CRPC). In that state, it had a relatively modest survival benefit on average. But for individual patients, it could have a dramatic benefit. We always thought, why wait till the patients develop CRPC? If we use it earlier, would it have a greater impact?

In 2015, the CHAARTED and STAMPEDE studies (see https://www.nejm.org/doi/full/10.1056/NEJMoa1503747) showed that early use of Taxotere (docetaxel) chemotherapy in men with newly diagnosed metastatic disease could have a very profound improvement on survival. In other words, rather than waiting for the cancers to become resistant to hormone treatments, if you used hormones with chemotherapy right up front—six cycles of Taxotere (docetaxel)—you could have a more dramatic improvement in overall survival. That changed the standard of care for how we use Taxotere (docetaxel) chemotherapy. Now it's an option for patients when they're newly diagnosed with metastatic disease.

Jevtana (cabazitaxel) was approved in 2010 based on the TROPIC study in patients who had already received first-line Taxotere (docetaxel). Jevtana (cabazitaxel) is currently a second-line chemotherapy agent. It does have a different set of side effects compared to Taxotere (docetaxel). For example, patients are less likely to lose their hair. It is in the same drug class as Taxotere (docetaxel); in other words, it's a taxane chemotherapy and works by inhibiting the microtubules that allow cancer cells to grow rapidly. Jevtana (cabazitaxel) was approved because, even in patients who had already received Taxotere (docetaxel), Jevtana (cabazitaxel) improves survival and may be an important second chemotherapy for patients to receive after they've already received Taxotere (docetaxel).

> *"There are hundreds of kinds of chemotherapy."*

Are these drugs ever used in combination with something else?

Dr. Oh: Generally, chemotherapy is not used in combination with other drugs because usually these drugs are given in sequence. Whether this is the correct way to do it or not is not 100 percent clear.

There are ongoing research studies to see if they can be combined safely rather than given in sequence because they may have an additive or synergistic benefit if you combine, for example, a chemotherapy drug with an androgen-receptor targeted therapy or with a bone-targeted therapy.

As in Erleada (apalutamide) or Xtandi (enzalutamide)?

Dr. Oh: Exactly.

What should men know if they've been prescribed one of these drugs?

Dr. Oh: Try not to have an uninformed 'gut reaction' to chemotherapy,

"This is absolutely the beginning of the story."

especially if you think automatically it's not the right treatment.

We know that chemotherapy may be less targeted than other drugs, but cancer cells are tricky and they often learn how to mutate and change. Chemotherapy can knock out many different kinds of cancer cells. That may be one of its advantages. It works differently than androgen-receptor therapy, immunotherapy, and bone therapy. Men should understand that chemotherapy is a very important option, especially when the cancer has become more aggressive.

For the most part, the side effects are manageable, right? It's not like some of the side effects of immunotherapy, which can be really devastating.

Dr. Oh: I think side effects from all of these drugs can be manageable for most men, and that includes chemotherapy, immunotherapy, and androgen-targeted therapy.

Readers may not know this, but some of my patients tolerate chemotherapy better than they tolerate some of the androgen-targeted therapies. Androgen-receptor blockade with drugs like enzalutamide or abiraterone can be really life-altering for some patients.

For some patients, chemotherapy is easier. It sounds paradoxical, and it's not always true, but each person responds differently. On average, the chemotherapy side effects are manageable. There are drugs to manage them, but you can adjust the dose and you can still get the benefit of the treatment if you have an experienced oncologist helping to manage the use of chemo.

Is there anything else men should know?

Dr. Oh: There are some exciting data regarding the use of an old chemotherapy that may have a new application, namely Paraplatin (carboplatin). It has been around for 30 to 40 years, but it may work specifically in tumors that have DNA repair abnormalities like BRCA2 mutations.

Even in the era of precision medicine, patients with BRCA-mutated cancers may benefit more from a drug like Paraplatin (carboplatin) chemotherapy. We know that Paraplatin (carboplatin) can be given, for example, with a drug like Taxotere (docetaxel) quite safely. Those kinds of combinations may be right for some patients if they have a DNA repair abnormality such as BRCA2.

That's really interesting. Do you think it's likely that there are other genetic mutations for which certain agents will be particularly useful? That this is just the beginning of that story?

Dr. Oh: This is absolutely the beginning of the story. We have failed to understand what drives each individual tumor. It feels overwhelming to think that each cancer is a little different from the others. But we're going to start to develop individualized treatment plans for patients based on the kind of tumors they have. We have used a one-size-fits-all approach so far, which is the wrong approach for many cancers.

Chemo will remain part of the solution; it just may not be given to everyone the way it has been in the past. PpI

Cy Stein, MD
Chemotherapy Side Effects

Dr. Cy Stein is a medical oncologist at California's City of Hope hospital. He routinely advises his fellow doctors to, "Never think about yourself. It's only about the patient."

Prostatepedia spoke with him about dealing with the side effects of chemotherapy for prostate cancer.

Why did you become a doctor? What was it about medicine that drew you in? What keeps you there?

Dr. Cy Stein: Why did I become a doctor? That's a very complicated question. It all started a long time ago. It caught my interest when I was a very young fellow, and it was my ideal throughout high school. Then I got hooked on chemistry when I went to college. I wound up with a PhD in Chemistry. I decided, very early on in the course of that study, that I really shouldn't try to pursue chemistry as a career. I should stick with medicine, which was more my inclination. Medicine was more broadly humanistic than chemistry ever could be, although chemistry is a wonderful science, and I enjoyed it very much.

What kept my interest in medicine was chemotherapy. Chemotherapy seemed to be a very good way of continuing my interest in chemistry. In those days, chemotherapy was what was used to treat cancer. Things are more sophisticated now, but it was virtually all chemotherapy.

Cancer was a great unmet challenge, and people were suffering terribly from it. I felt that if you had the ability to do something about it, you should put yourself out there and try.

"Cancer was a great unmet challenge."

What are the most common chemotherapy drugs that men with prostate cancer are likely to encounter today?

Dr. Stein: It all depends on what your definition of chemo is, but I take a very narrow definition that I think most of the community would take.

There are two chemotherapy drugs that exist for prostate cancer. One of them is called Taxotere (docetaxel). The other is Jevtana (cabazitaxel).

I don't consider drugs like Lupron (leuprolide) to be chemotherapeutic agents. We consider them to be hormonal agents because they act directly on testosterone. Testosterone, as I'm sure everybody knows, is the male sex hormone. In order to get responses in prostate cancer, physicians have to lower the patient's level of testosterone in their blood. That's not a chemotherapeutic way of doing it; that's a hormonal way of doing it. Similarly, the newer drugs that have come out recently are not chemotherapeutic agents either. I'm referring to Zytiga (abiraterone) and Xtandi (enzalutamide). We call them oral hormonals. Provenge (sipuleucel-T) is a kind of tumor vaccine, so it's really immunologic oncology. Xofigo (radium 223) is also not a chemotherapeutic agent, so we're down to two.

What are the differences between the two. When would Taxotere (docetaxel) be used over Jevtana (cabazitaxel)?

Dr. Stein: Taxotere (docetaxel) was first developed in 1995-1996 and has been on the market for a long time. It was originally used in breast cancer and lung cancer as well. Then it was introduced for use in prostate cancer.

There is significant amount of toxicity with Taxotere (docetaxel), although it is a very good drug. It is different

from Jevtana (cabazitaxel), even though both of the drugs are formed to the same general class of molecule, which we call taxanes. They both come from, ultimately, the needles of the Pacific Yew tree.

Even though the names sound similar, these are different drugs with different toxicity profiles. The important thing for a patient to remember is that, even though these drugs have side effects, at times we see spectacular responses from both of them. The side effects are manageable and definitely worth the effort for the patient because of the potential for the response that you can get.

Taxotere (docetaxel) has more side effects than Jevtana (cabazitaxel). Taxotere (docetaxel) seems to have more toxicity, and most important, the toxicity seems to get worse as patients age. Therefore, I find it extremely difficult, if not impossible, to give Taxotere (docetaxel) to men who are over 80.

What toxicities are we talking about?

Dr. Stein: For Taxotere (docetaxel), the major dose-liming toxicity is fatigue. People are not going to feel anything on the day that they get the Taxotere (docetaxel). The day after, they're going to feel pretty tired, and most men will want to just stay in bed. Their partners don't particularly like that, but it's probably best to leave them in bed because they're not going to be very functional for a day or more on Taxotere (docetaxel).

It's not uncommon for a man to say, "For three days after I get this drug, I'm very wiped out." I've even heard them say, "Five to seven days after I get this drug, I feel very wiped out." Then the men will get better, and eventually they will come back for their next cycle, and we'll do it all over again. It doesn't happen quite so much with Jevtana (cabazitaxel) because it is a little easier on the fatigue.

In terms of other side effects, one of the side effects that Taxotere (docetaxel) has, only in about 10% of cases, is febrile neutropenia. That is the white blood cell count goes down seven to nine days after getting the chemotherapeutic drugs and leads to an infection. The patient will have a fever of 100.4 or greater, and the febrile neutropenia requires antibiotics. With Jevtana (cabazitaxel), the incidence of febrile neutropenia is much, much higher. What I do is I make sure that all of my patients have Neulasta (pegfilgrastim) applied before they get the chemotherapy, to prevent their white count from going down.

"The side effects are manageable and definitely worth the effort."

There are some patients who may not need Neulasta (pegfilgrastim), but I prefer to sleep calmly at night. I don't want to worry about a patient getting febrile neutropenia on Jevtana (cabazitaxel), so I treat every one of my patients with Neulasta (pegfilgrastim).

In terms of other toxicities, many men say that Taxotere (docetaxel) also causes food to taste like cardboard. Their hair will certainly thin, but it probably won't all fall out. They may get tearing of the eyes. They may get changes in their nails such as brown bands that horizontally cross the nails. These disappear after discontinuation of treatment. They can also, potentially, get a little bit of fluid in their lungs, although in my experience that hasn't been a clinical problem. They can also, potentially, develop neuropathy.

It sounds rough, and for some men it is, but a lot of men go through it very well. They can have a tremendous response. I've seen any number of individuals have responses of 75% and even 90% in their PSA. These are the kind of individuals who live a great deal longer than if they didn't respond.

Jevtana (cabazitaxel) is a very similar story, except the fatigue is much less. The neuropathy is significantly less, although I have seen patients with neuropathy on Jevtana (cabazitaxel). The nail banding does not happen. The poor taste doesn't happen. The hair loss is greatly reduced. Fatigue is also significantly reduced, but there is still fatigue in some patients.

Because the toxicity profile is better with Jevtana (cabazitaxel), I don't hesitate giving this drug to patients who are over 80 years old. In my opinion, they seem to tolerate it better. I had a patient who was 90 years old and of sound mind and body. He didn't have much of a choice; he had two sons who were doctors. We talked it over and he said, "I want the drug." He got the drug, and I started him with a much lower dose than the full recommended dose. I titrated him up to tolerability, and he received 13 consecutive cycles of Jevtana (cabazitaxel). All his pain went away, and he lived an extra year.

Jevtana (cabazitaxel) has a lower dosage option that has just been approved. What has been the impact for your prostate cancer patients?

Dr. Stein: I use two doses of Jevtana (cabazitaxel): 25 mg/m² and 20 mg/m². The overall survival with both doses is identical, but at 25 mg/m², the PSA is more affected as opposed to the 20 mg/m². In other words, you have more PSA decline on the 25 mg/m² than you have on the 20 mg/m². Of course, you have less toxicity on the 20 mg/m². For those men who really follow their PSAs very closely, I *might*, all other things considered, recommend the 25 mg/m². For most men, I think the 20 mg/m² is just fine.

For Taxotere (docetaxel), the full dose is 75 mg/m². There's little evidence that you lose much in the way of efficacy if you go to 50 mg/m² to avoid toxicity, and I'll do that frequently.

Is there anything men can do to prepare themselves for these side effects?

Dr. Stein: Aside from communicating with their doctors and taking Claritin if you're receiving Neulasta (pegfilgrastim), I'm not sure there is anything you can do.

Is there anything else you'd like patients to know about chemotherapy for prostate cancer?

Dr. Stein: These are very realistic options for patients. Men can tolerate Taxotere (docetaxel) for maybe six to eight cycles. It's hard for men to get more. With Jevtana (cabazitaxel) it's unbelievable how much people can get because the toxicity is less. I know of a man who received 55 continuous cycles of Jevtana (cabazitaxel) and did extremely well. My own personal record is 33 cycles. In one of those cases, the patient had a 99% response in his PSA; he lived three extra years. He did extremely well.

I had another man who also got 33 cycles. His PSA was roughly 50 to 70 and it stayed that way for 33 cycles before he started to progress. I have seen quite a few remarkable responses. Pp

Oliver Sartor, MD
The Development of Jevtana (Cabazitaxel)

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.

Prostatepedia spoke with him about Jevtana (cabazitaxel) for prostate cancer.

Have you had a particular patient whose case changed how you see your role as a doctor or how you approach the art of medicine?

Dr. Oliver Sartor: Gosh, there are a lot of patients who stand out in my mind. One nearly miraculous case helped me to better understand that what's rare can be incredibly meaningful and that there's a lack of predictability about what we do every day.

Despite the fact that I've been working on this disease for about 28 years, there's still much more to learn. Being open to new possibilities and new thoughts and approaches are, in part, fueled by what I've seen in individual patients. Predictability is not always what we achieve.

It's a strange world we doctors live in. We make decisions that affect men's lives in very real ways. A lot of patients are convinced that we're better than we actually are. We all struggle to make decisions that are best for our patients, but the context of our knowledge is constantly changing and that brings both opportunity and disappointment.

What is Jevtana (cabazitaxel)?

Dr. Sartor: Jevtana (cabazitaxel) is chemotherapy. It's part of the taxane family. It has similarities and distinctions from the taxanes that people may be more familiar with, such as Taxotere (docetaxel) or paclitaxel.

Jevtana (cabazitaxel) was FDA approved in 2010. I was the co-Principal Investigator on the pivotal study and senior author on the *Lancet* manuscript for the TROPIC trial that led to FDA approval. The trial was designed to look at men who progressed after prior Taxotere (docetaxel) therapy.

At the time that trial was run, Taxotere (docetaxel) was the only known agent effective in prostate cancer. The trial showed that Jevtana (cabazitaxel) prolonged survival modestly, which gave men who had progressed after the known therapies available at that point additional hope.

When, along the patient journey, are men likely to encounter Jevtana (cabazitaxel)?

Dr. Sartor: Today, as in 2010, Jevtana (cabazitaxel) is FDA-approved in the post-Taxotere (docetaxel) space. Most people utilize it in that space. Men have to be fit enough to take chemotherapy —not all men are—and they have to have adequate bone marrow function. Jevtana (cabazitaxel) is one of the treatments that we consider for a wide variety of men in the post-Taxotere (docetaxel) space.

Is Jevtana (cabazitaxel) usually used alone or with other agents or treatments?

Dr. Sartor: In 2010, the TROPIC trial indicated effectiveness with Jevtana (cabazitaxel) as a monotherapy, although it was given in combination with prednisone.

The use of additional agents has been something that many others have explored, and in particular, in combination with Paraplatin (carboplatin). Before the approval of Jevtana (cabazitaxel), we were exploring Paraplatin (carboplatin) combinations. We published articles on this back in 2009 or so, using combinations of taxanes, predominantly Taxotere (docetaxel) and Paraplatin (carboplatin).

We found that a subset of men could really have outstanding responses to the combination. We laid a foundational observation that taxanes and Paraplatin (carboplatin) could be combined to yield better results than the taxane alone, particularly for patients who had progressed after Taxoter (docetaxel).

Today, we understand that better, mechanistically, and it may be due to the underlying presence of DNA repair defects. We, and others, have published on the responsiveness of patients who have mutations within DNA repair genes, especially BRCA-2. In that context, patients can have very rewarding responses with a combination of a taxane and Paraplatin (carboplatin). That accounts for probably somewhere around 25 percent of all patients. There may be additional patients who can benefit outside of those with DNA repair defects.

Today, we commonly use a Jevtana (cabazitaxel) and Paraplatin (carboplatin) combination. Occasionally we get really rewarding responses.

What are the side effects like for Jevtana (cabazitaxel) when alone and when used in conjunction with other agents?

Dr. Sartor: We have a really good handle on the side effects now. We ran a head-to-head comparison of Jevtana (cabazitaxel) and Taxotere (docetaxel) as part of a large trial called FIRSTANA. I was the senior author of that manuscript, published in the *Journal of Clinical Oncology* (JCO) last year. With two doses of Jevtana (cabazitaxel) and one dose of Taxotere (docetaxel), we found that there was more myelosuppression—more bone marrow suppression—than in those who received Jevtana (cabazitaxel)—and less neuropathy.

In my experience, people tolerate Jevtana (cabazitaxel) better than Taxotere (docetaxel. There seems to be less edema, less neuropathy, and probably fewer nailbed changes and alopecia (a fancy word for hair loss). We've found it to be well-tolerated.

Another important trial run by Drs. Mario Eisenberger and Johann de Bono called PROSELICA compared two doses of Jevtana (cabazitaxel): 20 mg/m² versus 25mg/m². They found that 20mg/m² worked just as well as 25mg/m² and with fewer side effects.

In my practice today, I start people at 20 mg/m² instead of the previous FDA approval of 25 mg/m². In that context, the drug is even better tolerated. We understand the dosing of the drug better because of these large trials.

That's important for men.

Dr. Sartor: Absolutely. It's critically important. And for doctors too. If we can manage the patient with similar outcomes and less toxicity, then we're achieving the goals that doctors and patients share: therapy with fewer side effects.

What else should men know about Jevtana (cabazitaxel)?

Dr. Sartor: Men are inevitably attracted to non-chemotherapeutic approaches because they are generally less toxic. At times, the very best choice for a patient involves a chemotherapy approach, so Jevtana (cabazitaxel) could be an effective option, even when hormones have failed. It's good to keep that option open.

When people refuse chemotherapy, they've closed off an option that could potentially be critical for their health. Men need to be open to all the possible lines of treatment.

There's a cultural prejudice against chemo. It seems wrapped up in the belief that cancer is always a death sentence; if you have chemo, you're just going to lose your hair and feel sick. But that's not necessarily true, right?

Dr. Sartor: I understand where that comes from. For many years, we got into a mode of giving more chemotherapy, believing it would be better. But it's just not. There are limitations to chemotherapy and its effectiveness. Sometimes, a gentler dose can have the same degree of positive effects with less of the adverse ones.

I'm a better doctor today than I was 20 years ago. One of the reasons is that I understand how to give all my agents in a manner that is both safe and more cost-effective while preserving the positive effects on any cancer progression.

We've worked hard to try to get better. We've learned how to manage chemotherapy and its side effects.

By the way, the same concept of lower dosage is true for Taxotere (docetaxel). I give docetaxel today differently than how I gave it ten years ago. Today, I use a 50mg/m² every two weeks and have found it to be much more tolerable than the older 75 mg/m² every three weeks. It's interesting to me how I can give the same drug in a slightly different manner to make it much more tolerable, which actually translates into potential increased effectiveness because we're not fighting the toxicities like we used to.

Life is all about balance. And it's good for men to know that physicians—at least the good ones—are doing their best to balance the toxicities and achieve the maximum benefits. That is a high priority for every good physician. Pp1

Emmanuel Antonarakis, MD
Switching from One Chemo Drug to Another

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 work on the benefit of switching men from Taxotere (docetaxel) to Jevtana (cabazitaxel)—or vice versa—if his PSA doesn't go down by 30% in the first twelve weeks of treatment.

Have you had any particular patients whose cases have changed the way you approach medicine or changed the way you think about your role as a doctor?

Dr. Emmanuel Antonarakis: There are many patients who have caused me to reconsider or change the way that I think about medicine. One particular example was a patient who was found to have a BRCA-2 mutation. I know that Prostatepedia has written about the BRCA-2 gene before.

Yes, we have.

Dr. Antonarakis: His perception and my perception of the excitement behind that genetic mutation were very different. My perception was: we found this BRCA-2 mutation! We've got this great clinical trial you can join. You can enroll in this trial and take a drug that you have a 90% chance of responding to.

The patient turned around and said, "Well you know what? I know that you guys are all very excited about this gene mutation and it sounds so futuristic and cool and exciting, but right now I don't think I want to have any therapy at all."

> *"There are many patients who have caused me to reconsider or change the way that I think about medicine."*

He was from a different country.

He said, "I think what I want to do is take some time now that I'm still feeling well to visit my homeland and see my family members. I will maybe spend three to six months there. Yes, I understand that this therapy is not available in that country and that I might be missing my window of opportunity. I'm very grateful that you did the genetic testing and that you found this mutation, but I think I'll just sit on this for now." And then he said something like, "Thanks, but no thanks."

He is still in his home country and will come back in about three months to see me again. At that time, he will decide whether he wants to do the trial, which might still be available.

It made me realize that sometimes the goals that we as academic physicians have and the goals that our patients have might be different. We all want our patients to live as long as possible and have the highest quality of life for as long as possible. For me as an academic investigator, I was excited by the prospect that I could offer this guy genetically targeted therapy but he didn't really want treatment at that particular point in time. His main purpose was visiting his family in his country of origin.

That was a lesson for me. Our goals might not always overlap, but we should always respect our patients' goals and be willing to view things in a different light.

Different people have different attitudes about treatment and cancer and life.

Dr. Antonarakis: Exactly.

You've published a paper on switching patients from Taxotere (docetaxel) to Jevtana (cabazitaxel) and vice versa. What is the thinking behind switching chemotherapeutic agents? Why would you want to switch agents earlier as opposed to when the first chemotherapy drug stops working?

Dr. Antonarakis: The motivation behind this paper was that the FDA-approved recommended dosing schedule for both Taxotere (docetaxel) and Jevtana (cabazitaxel) is a course of ten doses, given three weeks apart. When patients begin FDA-approved Taxotere (docetaxel) or FDA-approved Jevtana (cabazitaxel), they're often told by their oncologists that they should expect to receive this chemotherapy once every three weeks for up to ten doses. A patient may not receive ten doses or might stop the therapy before he reaches ten doses because he cannot tolerate the therapy and has unmanageable side effects, or his cancer begins to progress before he ever get to dose number ten. If his PSA begins to increase again at dose six or seven or the tumors begin to grow again, his oncologist might ask him to stop chemotherapy.

> *"Some patients might potentially benefit from a switch strategy."*

We then wondered whether the ten doses was a reasonable time to wait or whether there could be an early indicator, or an early sign, of therapy resistance or therapy futility without having to go through six, seven, eight, nine or ten doses.

The idea that we had was to test an early intermediate marker of sensitivity or resistance to the chemotherapy. The best marker of early sensitivity or resistance that we could think of was whether or not a patient had a 30% PSA drop within the first four cycles of therapy. As you recall, if the therapy is given once every three weeks, four cycles basically means 12 weeks, which roughly equates to about three months.

The decision to use this intermediate endpoint was not arbitrary; it was based on some large retrospective meta-analyses that have shown that the strongest predictor of overall survival in patients receiving both Taxotere (docetaxel) and also separately Jevtana (cabazitaxel) was whether or not patients had a 30% PSA reduction after 12 weeks.

Patients who do achieve at least a 30% or greater reduction in the first 12 weeks have a survival that's longer than patients who don't achieve that endpoint. We thought, well if this endpoint is strongly correlated to survival, perhaps we can use it as a decision point. If after four doses of therapy or 12 weeks of therapy a patient don't achieve a 30% reduction in PSA perhaps we should switch him to the other chemotherapy, rather than sticking with it and just waiting for either the toxicity to develop or the PSA or the radiographic disease to progress. That was the hypothesis.

We designed a relatively small study of about 63 patients. We used a 2:1 randomization so they were twice as likely to get Taxotere (docetaxel) compared to Jevtana (cabazitaxel). Approximately 41 patients got Taxotere (docetaxel) first. The other 22 patients, got Jevtana (cabazitaxel) first. Irrespective of which arm they were randomized to, they received the first four doses of chemotherapy in 12 weeks. We checked their PSA every three weeks.

At the end of the fourth dose, if the PSA level had dropped by 30% or more, the patients would continue on the same therapy on which they started. However, if patients did not achieve a 30% reduction or more, they would be switched to the other chemotherapeutic agent.

If a patient had a 25% reduction, we would switch him to the other agent because we thought that was not good enough. If someone received Taxotere (docetaxel), and their PSA dropped by 25%, even though it dropped by 25%, it did not meet that 30% threshold so they would then switch for the fifth dose to receive Jevtana (cabazitaxel) for the remainder of their chemotherapy. The inverse was also true. If the patient received Jevtana (cabazitaxel) first and also did not get a 30% reduction by week 12, in other words four doses, they would also switch to receive Taxotere (docetaxel).

The interesting thing that we found in both treatment arms was that the chance that a patient had a favorable PSA response, which was defined as a 50% or more decrease, was higher than we had seen in historical trials using each drug by itself without switching. To put some numbers on that, we found that there was about a 54% chance that patients would have a 50% reduction in PSA if they had to the opportunity to switch from one chemotherapy to the other, compared to about a 45% chance of PSA reduction in the historical data where patients did not switch.

Did it matter if they got Jevtana (cabazitaxel) first or Taxotere (docetaxel) first?

Dr. Antonarakis: What we found out is a bit of a paradox: people could benefit from the switch in both

directions. That was fascinating to us because, as we all know Jevtana (cabazitaxel) was specifically approved by the FDA as a second-line curative therapy only indicated in men who have failed Taxotere (docetaxel) first. Based on that reasoning, one might expect Jevtana (cabazitaxel) to work better after Taxotere (docetaxel) but not Taxotere (docetaxel) after Jevtana (cabazitaxel).

"Patients who are beginning their first chemotherapy should discuss this trial with their oncologist."

This is not what we found.

We found that in both directions, both from the Taxotere (docetaxel) to Jevtana (cabazitaxel) switch, but also in the Jevtana (cabazitaxel) to Taxotere (docetaxel) switch, there was a significant amount of patients, approximately half, who were salvaged by the crossover therapy. By salvaged, I mean those who did not achieve a 30% PSA reduction with the first drug but did achieve a PSA reduction of 50% or more after crossing over to the second drug. As I mentioned before, this occurred in both directions, both in patients receiving Jevtana (cabazitaxel) after Taxotere (docetaxel) and Taxotere (docetaxel) after Jevtana (cabazitaxel).

Are the side effects of Jevtana (cabazitaxel) a little bit easier to take than the side effects of Taxotere (docetaxel)?

Dr. Antonarakis: Interestingly, the side effects of Jevtana (cabazitaxel) in the published literature indeed appear to be slightly better. In this particular trial, which was very small obviously, they seemed comparable. In other words, we did not see any appreciable difference between the Taxotere (docetaxel) and the Jevtana (cabazitaxel) overall in terms of side effects. Taxotere (docetaxel) had a little bit more neuropathy nerve damage, which Jevtana (cabazitaxel) did not do. On the other hand, Jevtana (cabazitaxel) had a little bit more neutropenia, while the Taxotere (docetaxel) did not.

I would say that when patients receive these agents in a first-line setting, in other words, when they had not received another chemotherapy previously, their side effects were fairly comparable. I don't think there was a clear signal in terms of one drug being clearly safer than the other.

Does it matter which you get first?"

Dr. Antonarakis: From a side effect perspective, they're both fairly equivalent in terms of tolerability, with slight differences in neutropenia, which is worse with Jevtana (cabazitaxel) and neuropathy, which is worse with Taxotere (docetaxel).

What is the next step? Are you going to run a similar trial with more patients?

Dr. Antonarakis: One question that arises is if this small randomized trial is enough to change practice. Should a community oncologist or urologist give Taxotere (docetaxel) for four doses and wait to see if the patient's PSA drops by 30% or more? If it doesn't drop to 30% or more, should he to switch to Jevtana (cabazitaxel)?

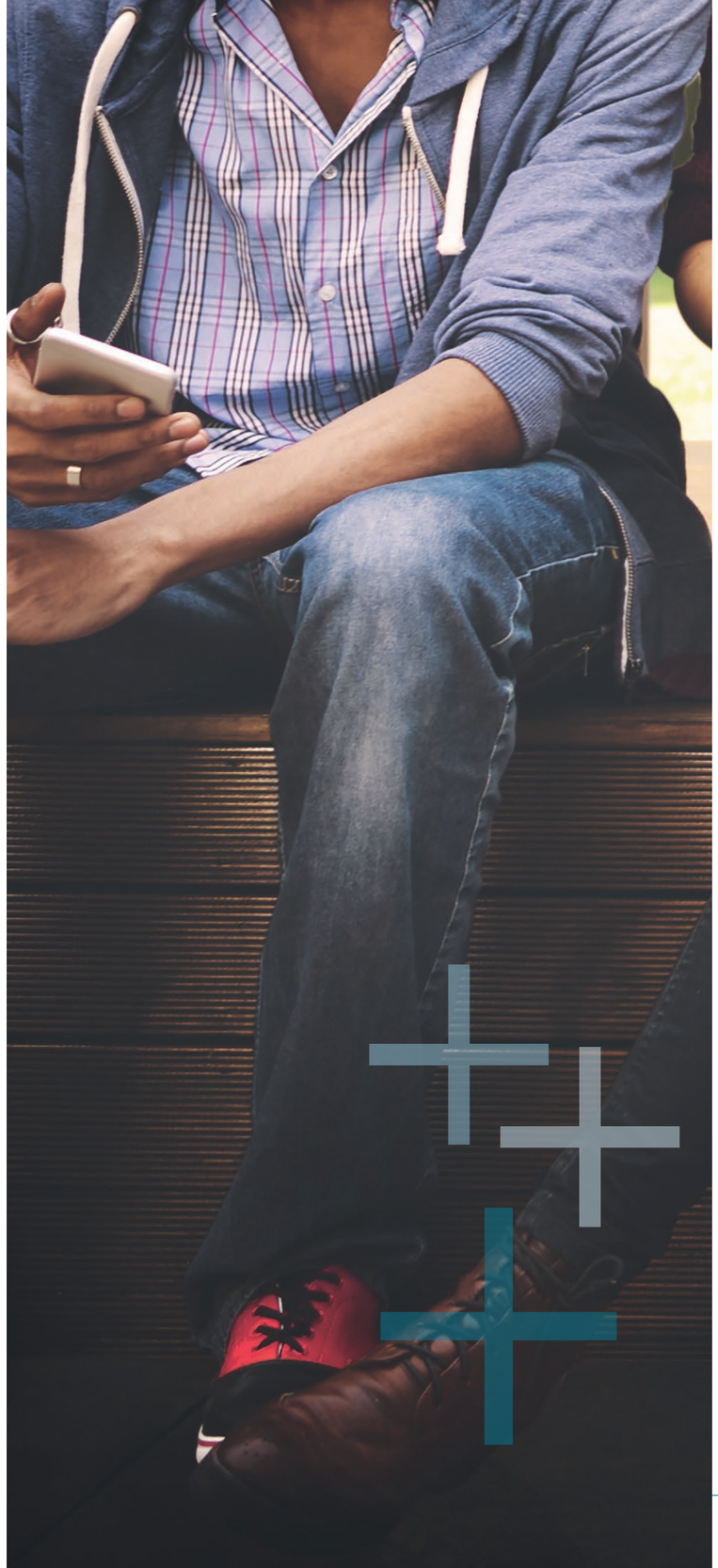
I have to admit that this is something that I have done in my practice a few times, but I really don't believe that this is ready for clinical practice yet. Yes, in this trial, we showed that the PSA response rates could potentially be improved by this switch strategy. What we did not demonstrate was whether this improves overall survival.

The ultimate question is does switching chemotherapy agents after four doses improve survival, compared to just waiting until we see radiographic or clinical progression to switch agents. That would, as you mentioned, require a larger Phase III randomized study. The idea of study design would be to randomize patients to the switch strategy versus no-switch. We would randomize one group of patients to receive chemotherapy and switch if their PSA did not drop by 30%. The second group of patients would start chemotherapy but would not be given the opportunity to switch, even if their PSA did not drop by 30% or more. The randomization would not necessarily be the randomization to the chemotherapy, but would be randomization to a switch strategy versus a stick-with-the-first-chemotherapy strategy.

Sanofi, which makes both Jevtana (cabazitaxel) and Taxotere (docetaxel), have not been eager eager to respond to such a study because of financial considerations and also because the patent life of Taxotere (docetaxel) is over and the patent life of Jevtana (cabazitaxel) will be expiring soon.

Unfortunately, we might be left with a Phase II study that may, potentially, not translate into a Phase III study. I think individual patients and individual oncologists may look at these data and might be convinced that some patients might potentially benefit from a switch strategy, especially those who did not have any degree of PSA reduction after four cycles.

An added complexity is that the popularity of chemotherapy is going down over time and the availability of non-chemotherapy agents is going up. A lot of these patients who may not have a 30% PSA reduction with one chemotherapy, might choose to do another hormone therapy, a radiopharmaceutical drug like Xofigo (radium-223), immunotherapy like Provenge (sipuleucel-T), or even a PD-1 inhibitor, or potentially a PARP inhibitor.



It might be difficult to convince a patient who has just failed one chemotherapy after four doses to go immediately to a second chemotherapy. I'm not 100% sure what the future will hold. I also don't think this is a trial that we could have conducted today.

What would you say to a man reading it? That this is worth talking to his oncologist about or is this just something interesting for him to know about?

Dr. Antonarakis: Patients who are beginning their first chemotherapy should discuss this trial with their oncologist, and together with the oncologist decide in a joint fashion whether switching from one chemotherapy agent to another after four doses might be right for him, especially if he's tolerating the chemotherapy well. If he tolerates the drug and his PSA has not dropped by 30% or is continuing to increase, then in my opinion rather than continue with the potentially futile therapy, a patient and his oncologist may wish to consider using this trial to guide or justify their choice of switching drugs earlier rather than later. Pp[1]

Clinical Trial: Combining Taxotere (Docetaxel) and Vitamin C

Dr. Channing Paller, an Assistant Professor of Oncology at Johns Hopkins University School of Medicine, focuses on translational research and clinical trials of developmental therapeutics in prostate and other solid tumors.

She is keenly interested in the rigorous evaluation of natural products in cancer treatment.

Prostatepedia spoke to her about her Prostate Cancer Foundation instigated and Marcus Foundation-funded clinical trial on combining intravenous Vitamin C with Taxotere (docetaxel).

Why did you become a doctor? What is it about medicine that keeps you interested?

Dr. Channing Paller: In high school, I had a wonderful biology teacher named Melanie Fields who saw something in me and recommended me for a part-time research position at the National Institutes of Health. I did my senior project in an NIH lab where I saw how Vitamin D could be an anticancer agent by causing differentiation of breast cancer cells.

Between that and other projects, in which I got to work with very advanced confocal microscopes, I began to think that we might cure cancer one day. I know now that curing cancer in the lab is 100 times easier than curing it in humans, but the NIH experiences excited me and persuaded me that hope was on the horizon.

What an exciting project for a high school student. That's unusual.

Dr. Paller: Julia Barsony, the lab director at NIH, was a great mentor. She believed that young people could be better in the lab than other people because they would "tell it like it is." Under one of the confocal microscopes once, I found that two genes had mutated in one of her cell lines, but others in the lab weren't aware of it. Instead of seeing what they thought I should see, I saw what I saw, and I told it like I saw it.

Beginner's mind.

Dr. Paller: Exactly.

Have you had any particular patients whose cases have changed how you see your role as a doctor?

Dr. Paller: Early in my career, I had a 60-year-old patient who had Stage IV lung cancer. It had taken over her entire left lung. She was given chemotherapy by another physician and had experienced every side

effect you could imagine, from hair loss to extreme nausea and vomiting. She came to me for a second opinion. She was a non-smoker, which gave me a clue that her cancer might respond to some new therapies. She refused standard-of-care chemotherapy because of the terrible side effects.

I remembered that one of my professors in medical school had begun exploring a newly discovered mutation in non-smokers with lung cancer called epidermal growth factor receptor mutation (EGFR). We tested the patient and found that she had the EGFR mutation. We started her on a drug called Tarceva (erlotinib), which targeted the EGFR mutation. That was ten years ago. Her cancer shrunk, and to this day, her scans show no evidence of cancer. She is still on the same pill; I just saw her on Monday.

The journey wasn't without bumps in the road. We started her on a full dose of 150 milligrams, and she broke out in a full body rash and severe diarrhea. She wanted to stop that therapy. But I found a publication describing a small experimental study that showed that 150 mg might not be needed to control her type of cancer, and that doses as low as 25 or 50 mg might work. We took the risk and cut her down to 50 mg; she's been on that dose ever since. The only thing that we've had to add is a little thyroid replacement therapy because the drug attacked her thyroid, but she lives a great life. She recently turned 70 and sees her two grandchildren all the time.

Experiences like this one energize my search for new genetic biomarkers that identify sub-populations, and then, with the whole translational research team, development and testing of treatments that help those subpopulations.

In a sense, we're curing cancer one percent at a time, as each new validated biomarker that identifies a treatable cancer allows us to extend and improve the quality of the lives of another small segment of the patient population. Finding those biomarkers is a large part of my research focus at Johns Hopkins.

Can you explain the thinking behind your trial on combining Taxotere (docetaxel) with ascorbic acid? Why ascorbic acid and Taxotere (docetaxel)?

Dr. Paller: One of my interests is studying natural products that people take as dietary supplements. We don't know whether they work or whether they cause harm, so I test them. Several of my clinical trials study these compounds rigorously in a placebo-controlled fashion, as we would with any cancer treatment.

I knew about a recent randomized study of high dose intravenous ascorbic acid (vitamin C) in ovarian cancer patients, which showed that ascorbic acid treatment combined with standard chemotherapy reduced toxicities from the chemotherapy and also trended towards improved overall survival. Vitamin C enabled the patients to receive more cycles of chemotherapy, and that was associated with longer overall survival.

In response to the findings in ovarian cancer, the Prostate Cancer Foundation sent out a request for proposals for early stage research on vitamin C's role in treating prostate cancer. We decided to initiate a large (60 patient) placebo-controlled trial with co-primary endpoints of quality of life and cancer response to the combination of intravenous (IV) vitamin C and chemotherapy. We are extremely grateful to the Marcus Foundation for supporting the trial.

We chose Taxotere (docetaxel) because it was first line and an easy place to start to answer the question. Jevtana (cabazitaxel) would have worked just as well.

What can you expect to happen during the trial?

Dr. Paller: We are conducting a randomized placebo-controlled Phase II trial of standard-of-care Taxotere (docetaxel) for metastatic castrate-resistant prostate cancer with either ascorbic acid or placebo, which is electrolytes and hydration, given twice a week in between the cycles of chemotherapy every three weeks.

Some people say that this is too big a commitment, so they get to take breaks if needed. They can miss a session or two here or there. They can even take two weeks' break, if needed. We're trying to help people live better, not chain them to the clinic.

These are people who would be prescribed Taxotere (docetaxel) anyway, right?

Dr. Paller: Right.

Does the Taxotere (docetaxel) need to be administered by you in Baltimore?

Dr. Paller: It needs to be administered at a site where we have the trial open, so that includes Sibley Memorial Hospital in Washington DC, Johns Hopkins in Baltimore, Thomas Jefferson in Philadelphia, University Hospital Centers in Cleveland, Karmanos Cancer Center in Detroit, and Anne Arundel Medical Center in Annapolis. We are open to adding other sites, as well.

We administer standard-of-care chemotherapy and then high doses of vitamin C of 1 gram per kilogram of body weight, twice a week. For every two patients randomized to vitamin C, one patient is randomized to the placebo intravenous fluid. It takes about 90 minutes, twice a week, allowing them to still have a life, which is terrific.

Our primary outcomes are quality of life measures as well as a 50% drop in PSA. Our secondary outcome measures are radiographic progression-free survival, safety, quality of life, and any decrease in the need for dose reductions of Taxotere (docetaxel).

How many patients are you looking to enroll?

Dr. Paller: Sixty-three.

Are there any specific eligibility criteria that men should be aware of?

Dr. Paller: We're looking for metastatic castrate-resistant prostate cancer patients who are eligible for Taxotere (docetaxel). They should have normal kidney function because the kidneys are required to process the high doses of intravenous Vitamin C.

What about costs?

Dr. Paller: It should be free to patients. Insurance companies pay for the chemotherapy. The clinical

trial pays for anything that is beyond standard of care.

If someone is interested in participating, should they contact you directly?

Dr. Paller: We'd be delighted to see them. Patients can contact me directly or they can go to www.clinicaltrials.gov and search for the clinical trial number: NCT02516670, or link to https://clinicaltrials.gov/ct2/show/NCT02516670. There, they will find emails and phone numbers for every site.

If you reach your endpoint with Taxotere (docetaxel), would you want to repeat this trial with Jevtana (cabazitaxel)?

Dr. Paller: If we see a difference, vitamin C could be added to other chemotherapies, absolutely.

Is there anything else you want patients to know, either about this trial or about the thinking that led to this trial?

Dr. Paller: This study matters. We know that each year complementary medicine practitioners administer more than 350,000 doses of intravenous ascorbic acid to treat more than 10,000 patients with cancer infections and other conditions. We have data on industry sales showing even more.

This trial is essential to let us know whether vitamin C in these high doses is safe, and whether it works. If it does work, we can ask insurance companies to consider paying for it as opposed to patients paying for it out-of-pocket. If it works, this shouldn't be a therapy exclusively for the rich. Pp

How To Get Involved…

For more information, email Dr. Channing Paller at cpaller1@jhmi.edu.

Patients Speak
Bill R.:
Getting Chemotherapy

Bill R. found out he had prostate cancer about a year and a half ago. He's been on Taxotere (docetaxel) and has just started Jevtana (cabazitaxel).

He spoke with *Prostatepedia* at length about his experiences with chemotherapy for prostate cancer.

How did you find out that you had prostate cancer?

Bill R.: We had just moved from California to Arizona for my retirement when I was diagnosed. I got to the point where I couldn't pee, so I ended up at the urologist.

After a bunch of tests, the urologist said, "You've got an enlarged prostate. You can either run around with a bag of pee tied to your leg for the rest of your life, or we can do a transurethral resection of the prostate (TURP) to cut part of it out." They did the TURP, and they biopsied it.

That's when they called me with the bad news. I had Stage IV prostate cancer that had metastasized. It was well along. It's not been a year and a half.

What was your reaction?

Bill R: It was a surprise, certainly not expected. It takes a while to internalize it, and the first question you ask is: how long have I got? That's like asking how to push a piece of string uphill. Nobody really knows the answer. They said that it's very aggressive and, without treatment, probably two years or less.

What kinds of treatment did you have?

Bill R: Everything happened almost immediately because they said it was aggressive, and I couldn't screw around. I was on androgen deprivation therapy (ADT): Lupron (leuprolide), which suppresses the testosterone, and Xgeva (denosumab). At the same time, I started chemo because the protocols at that time said the two of these together seemed to extend life.

Which chemo drug did you go on?

Bill R: Taxotere (docetaxel).

What was that like?

Bill R: Initially, I was in pretty good shape, and once I got diagnosed, I worked out even harder. I was swimming half a mile per day and more. I figured I had the strength in my body to get through this. Through the first three or four treatments of chemo, I had some of the usual effects, like constipation, occasional nausea, and stuff like that. I took a probiotic during treatment. That seemed to help. Other than that, I really didn't have much of a problem, although, each chemo session beats you further down into the dirt. It's once every three weeks, so you get weaker as you go through it.

Right, of course.

Bill R: They were going to do six chemo sessions, but my PSA just would not come down. They had expected it to drop close to zero, and we got down in the 20s, but that's about where it ended up.

They wanted to do two more chemo sessions, and I agreed to that. At that time, I had six chemo sessions, and the last two were pretty hard. It really did wipe me out in terms of energy and everything else. I didn't have a lot of reaction to it, though.

I had a moustache that got so thin, I just shaved it off. The hair on my head thinned, but I didn't lose all of it. It got very sparse, and I had little bald spots, but it was short and fuzzy. It all grew back differently. I now have a bunch of cowlicks, where before, I had nice straight hair. Chemo usually causes the fingernails to look awful for a while, and I lost my two big toenails, but they have now grown back, more or less.

The chemo started in September 2016 and ended February 2017. After the last chemo session, my PSA was still up at around 23 or 24. They worked on getting me approved for Provenge (sipuleucel-T), which is an early immune therapy. They extract your white blood cells and send them to a lab, where they do something, and then put them back in. I did that in the summer of 2017. Over the next several months, my PSA came down. It got to a low of about 11, but that's as low as it ever got.

There were times when the chemo was bad. In the beginning, I didn't realize how much you had to stay hydrated.

I didn't know that.

Bill R: Yes. They offered for me to come in a day later, and they pump you full of a liter of saline.

Were you able to keep going about your daily activities or were you incapacitated?

Bill R: It slowed me down. First of all, you don't know what you don't know, so you're not really prepared for this.

Chemo causes constipation, and if you're prepared for that, it's not a problem; you take laxatives ahead of time. But if you don't know that, it's a pretty miserable couple of days. From that standpoint, it slowed me down, but it didn't stop me from going about our daily routine.

For the first month or two, I continued to swim, though not as much as I had been. I assumed that if I stayed active it would help me through the chemo. I was never incapacitated in that sense.

There were a few days where either I didn't feel well or was really tired, so I didn't go out and pound the pavement or anything. In retrospect, it was hard to tell in the first month or so whether the chemo or the Lupron (leuprolide) was causing more issues.

Because you were taking them simultaneously?

Bill R: Yes. You're doing everything at the same time. I guess, in retrospect, I slowed down and had a few days of down time. But it didn't stop me from doing what I wanted to do.

I went out and bought a custom chopper motorcycle, and after my Provenge (sipuleucel-T) treatment in the summer, I took a 3,500-mile ride up to Sturgis, out through Yellowstone, and home. Two weeks later, we spent a month in Europe.

It was hard for me, but maybe it wasn't as hard on me as it might have been on others, simply because I was in pretty good shape when I started. If you're not in good shape, it could be tougher.

They give you some steroids to help you through this, and in the beginning, it took a while to get the steroids adjusted. They gave me too much, and I got mouth sores for a while. Once the steroids got adjusted, that was fine.

The worst part of the whole thing was after it was over. Inside of a week, I started to retain water. I put on 20 pounds, and it was all water. I'm not a big guy at about 150 pounds and 5'8", but I looked like the Pillsbury Doughboy. Living in Arizona, you run around in shorts all the time, and even the cargo shorts that I wore were so tight that they'd leave marks on my legs.

Were you able to start exercising again after everything was done?

Bill R: Yes. I started swimming again and working out. When I did the Provenge (sipuleucel-T) in the summer, that wasn't so bad, I guess. It's something that most people don't want to go through—let me put it that way. There were days I was extremely tired and didn't feel well.

I was able to get back on my feet, exercise, and lead a normal life. Doing that again, with what I know now, it probably would have been less of an impact on me. That's the challenge for a lot of people. You go into this, and you don't know what you don't know. The doctors don't really know how you're going to react to some of this either.

Right, because everybody is different.

Bill R: Exactly. They had to adjust things like the steroids, and then things were better. They expected my water retention.

I had some neuropathy damage in my feet, which is permanent. When I walk around, I feel like I'm walking on water bubbles all the time, so I'm not really stable. That took a while to get used to.

What advice do you have for men who are about to go on chemo?

Bill R: You're going into something unknown. Don't panic if something is not quite right. You're just going to have to work with your doctors to make sure that things work the way they should.

Your white blood cell counts drop; pay attention to that. You get really dehydrated; you've got to pay attention to that. You can have constipation, nausea, and in some cases diarrhea; you'll pay attention to that, and as long as you take some of the over-the-counter stuff, you're fine.

You lose your appetite. If you're married, you've got to tell your wife that it doesn't matter what she cooks because it's going to taste like crap. A candy bar, eggs, salad: they all taste like crap. And that lasts for the duration of the chemo.

As soon as you stopped the chemo, did your taste come back?

Bill R: It took about two months before my tastes and appetite returned. You tend to lose weight simply because everything tastes bad, so you don't want to eat it. But the best advice: try to catch this thing earlier, so you don't have to get to the chemo stage.

Beyond that, try and get yourself as strong as you can before you go into chemo. Don't panic if something isn't quite right. Listen to your body. Staying as active a possible seems to have helped me. I couldn't work out and do as much during the chemo as I did before. I was even jogging in the noonday sun here in Arizona at 65 years old. I'm not an athlete, but I just did what I could do. I bought a mountain bike and started riding through the desert.

Staying active will make you feel better, even if it's just going out for a walk every day, so you're not sitting there thinking, "I'm going to die, and this is awful."

Right. It's not good for anyone to dwell on that.

Bill R: Right. As soon as you head down that path, you're toast. You've got to find a way to live your life. It forces you to get all your affairs in order because you realize that you're going to pass away before you expect to.

I'm starting Jevtana (cabazitaxel) in a few months because the cancer has progressed.

I've heard people can tolerate Jevtana (cabazitaxel) a little better. The side effects are not as severe as Taxotere (docetaxel).

Bill R: That's what they're telling me, that I shouldn't expect things like water retention and so on. I am going through that now, so the doses are once every three weeks for six rounds. We'll see how that goes.

But it is what it is. I tell everybody if you live long enough, you're going to get prostate cancer.

That's actually true.

Bill R: It's only a question of when. If you get it like I did, earlier in life, it shortens your life. But if you get it when you're 90, nobody knows and nobody cares. Hopefully I've helped people a little bit.

A lot of it is mental. If you swear that this is going to be miserable, everything you look at will contribute to that feeling. Whereas, if you're determined to get through it with a positive attitude, it's not as bad. There's a lot in the mental side that really helps you get through it. Pp

Us TOO: Mark Slaughter's Prostate Cancer Story

Mark and Denise Slaughter talk about their experience with chemotherapy for prostate cancer.

The C word. No one can imagine beforehand the horror of being told you have cancer.

My problems began with urinary troubles: middle of the night urges, frequency, and the inability to go, start, or finish a urine stream. My primary care physician recommended a urologist.

My urologist was awesome and earned my confidence and trust with his approach. He explained he was trying to see a picture rather like a jigsaw puzzle, but in order to see the picture clearly, he needed more pieces of the puzzle. He convinced me to let him do a digital rectal exam (DRE).

The result was not good. On a 0-10 scale, 0-5 would indicate no problems and 5-10 would range from concern to panic. He said mine was about a 7 or 8. Very smooth everywhere, no evil nodules or lumps, but way too hard. Unlike the softer part of your thumb near the palm of your hand (like it should be), it felt like the harder area of your thumb where the bone is located. It was definitely a reason for concern.

Next, he talked me into a PSA test. I was one of the men who, about seven or eight years ago, read the controversial studies about PSA tests and unreliable results, and I took them to heart. Many organizations were saying PSA was overrated and shouldn't even be used. So, I had stopped letting doctors test mine. My PSA was tested and came back very bad. It was 259.

To see more of the picture, my doctor needed to do a biopsy. He respectfully listened to all of my logical arguments. No number of needle probes will show you enough of the prostate. Too many and you can damage a fragile little organ. Besides, you would access a sterile body part by going in through a sewer. He held his ground and said he really needed this important piece of the puzzle. My wife and I thought about it overnight and agreed to let him do the biopsy.

My biopsy procedure was a piece of cake. I was given an antibiotic before the procedure. An ultrasound device accurately guided the doctor, and he was able to get 12 samples: 6 from each side of the prostate. Of the 12, I was really only hurt by one of them. Each felt like someone quickly poked me with a pencil. I heard the device click. I required no pain medication and passed a little blood during urination for a few days afterwards.

Then the results came. Of the 12 needle biopsy locations, nine were found to contain high-grade cancer. Of those nine, eight had a Gleason score of 8, and the last one was scored at 7. The range for cancer is 6 to 10, so we knew this was a bad score. It meant the cancer had spread beyond the prostate gland.

My doctor said that the next step was to get CT and bone scans that, together, would show us where the cancer had spread in my body.

My next stop was the hospital for the scans. The procedures were simple and easy enough. The results were another story.

February 8, 2018 is a day emblazoned in my memory, a day I will never forget, the day time stopped. That was the day I was told I have the big C word: I have cancer.

My doctor was tactful but did not mince words. The CT scan showed cancer in my lymph nodes, in my groin, and up my back on both sides of my spine. The bone scan showed lesions in four places on my pelvis and six places on my ribs. The tests all showed that I have advanced Stage IV metastatic prostate cancer. There is no cure. But we can manage it with hormone treatments and chemotherapy. With no treatment, I might only have a couple of years to live. With treatments, perhaps three to five years.

Upon hearing this news, my first thought was: I am dead. I had been standing next to my wife Denise, who was seated at her desk as we listened on the speakerphone. I collapsed into a seated position on the floor and reached out to catch Denise as she fell out of her chair. We crumbled to the floor together, sobbing and wailing with wrenching heaves of our chests. Squeezing each other as though life had ended that very moment. We embraced. We cried. We cried. We cried.

Time stopped.

We laid together in a heap on the floor for a long time. By the time we climbed to our feet, we could hardly breathe. My face hurt from all the tears. Our eyes were swollen, our faces red below our eyes and otherwise colorless as though life itself had drained from our faces. It was like our lives were over.

My doctor referred us to an oncologist. We couldn't stand him. He was rude and dismissive as he explained the chemo treatment plan and the poor prognosis for the remainder of my life. It is an understatement to say that he lacked a good bedside manner. Several friends immediately recommended we get a second opinion.

A friend of mine, and my former primary care physician when we lived in Atlanta, told me to forget that guy and get myself to another center. I did just that. I did just that and found an incredible doctor who was instrumental in the CHAARTED study that showed excellent results of early chemotherapy treatment combined with hormone therapy for the treatment of advanced metastatic prostate cancer.

My first appointment with this doctor was an education in prostate cancer. He explained the course of the disease, different methods of treatments, and answered each and every question I had. He described the treatment options as the tools in his toolbox. Whenever one might fail to produce results, he would reach for another one. He explained new drugs, such as hormone therapy, and he explained chemotherapy. Some people prefer chemo because it is six treatments and you are done. Other people would rather take pills for the rest of their lives. No study showed any real difference in the outcome of chemo versus hormone therapy.

At first, I was going to go the hormone therapy route. I was terrified of chemo because of my preconceived notions and the horror stories from people I had known who went on chemo and suffered horrendous side effects before dying painful deaths.

But there was a major snag in my getting approval for hormone therapy. Because I am on Medicare and have the Part D drug coverage, I was not eligible for any financial aid from the pharmaceutical companies or from any other charitable organizations for hormone therapy. Consequently, it was going to cost me in the neighborhood of $5,000 per month for the rest of my life. This was a huge blow to overcome mentally and financially. There was no way I could afford that.

My doctor reassured me again that the results of chemo are as positive as those from hormone therapy. Medicare would pay for the chemo. Because of these two considerations, I chose to take the chemo. Believe me, nothing about taking chemo comes close to the fear and angst of anticipating it.

I am currently undergoing chemo. I am through the fourth of six cycles of Taxotere (docetaxel). The biggest side effect for me has been the infamous cancer fatigue, especially during the first week after chemo. It takes about all the energy I have to walk from my chair to my bed to take a nap.

My doctors gave me Compazine (prochlorperazine), which prevents nausea and has worked extremely well for me. I also take Lupron (leuprolide), which has caused some hot flashes, mostly in the late afternoon and evening. Sometimes I have night sweats. Cramps of my ankles are a bothersome little issue several times a week.

One thing I have not had at all is neuropathy. My wife read about studies done in Canada, the United Kingdom, and France that indicate icing of the fingers and toes during chemo infusions prevents any changes to fingernails and toenails as well as neuropathy. I asked my oncologist and he said although there are no definitive studies in the United States that show results, he didn't object to my doing it. My wife has faithfully kept my hands and feet iced during treatments. It's not pleasant, but it's certainly tolerable and offers a big pay-off. To me, it's like a kid playing in the snow with no mittens.

Each of my sessions lasts about 1.5-2 hours. Once in a while, when it feels too cold, I take my hands or feet out of the ice for a short break. Overall, my treatments have been far less of an ordeal that the initial fear of treatment.

Another side effect: hair loss. I have had heavy, patchy hair loss on my head that started about 13 days after my first chemo treatment. The afternoon when large patches of hair began falling out into my hands in the shower, I decided to take action. The next morning, slowly, deliberately, I dressed, collected my wallet and keys, walked to the garage, got in the car, drove to the nearest barber and got a buzz cut. I didn't think about it. I just did it. And it was one of the best decisions I have made. It is far easier to manage quarter inch long hair than patches of messy hair. I would say to any guy, wait and see if your hair begins to fall out, then just accept the fact and manage it.

As for sexual function, I am 66 years old and have suffered from erectile dysfunction for six or seven years. Hormone therapy is medical castration. The result is loss of sexual function. I rarely have any kind of erection, and even the size of my genitals has shrunken somewhat. But, with a loving partner, these things have not been so hard to accept. I still have the good feelings two people share in intimacy. I would rather be alive than fully-functional, sexually. I do admit my history has made this easier to accept than it might be for some younger men. The key here is perspective. Some choices in life are just hard. You have to decide what matters the most.

The biggest positive about chemo is that you do it and it's over forever. For me, six cycles of three weeks, then never again. This compared to a lifetime of multiple pills on a daily basis, worrying all the while about how long they might be effective.

On the down side, you have to get your head around walking into a room feeling good and letting them inject you with strong chemicals that will make you feel bad. It's rather bizarre. I live about 200 miles from my cancer treatment center, so the car trip and hotel stay give me way too much time to let bad thoughts get in the way before each treatment. Again, it's all about controlling your thoughts and attitude. I know it sounds trite, but holding onto a positive attitude really matters.

The routine at each treatment is: a lab test for blood markers, doctor appointment, and chemo infusion. If my blood looks good, the doctor approves the chemo, then the chemo is prepared and infused. I know it's working because the blood tests show positive results. My PSA has dropped from 259 to 20, 5, 2, and 1.7 over the first 4 treatments. Similarly, my testosterone has dropped from around 500 to less than 20, which the doctors consider insignificant. They tell me my testosterone level is that of a prepubescent boy, which is good because loss of testosterone starves the cancer.

My oncologist has not even discussed AR-V7 biomarkers with me because, so far, my cancer has been responsive to chemo. We have had some general discussions about castrate-resistant prostate cancer and that there are other options for continued hormone treatments after the Lupron (leuprolide), should it become ineffective.

I have a wonderful support group. First, my loving wife of 46 years is a registered nurse and the best advocate anyone could ever ask for. Second, I live in an active adult community of residents over 55. So many of my neighbors have been supportive and shared their own experiences with cancer. Third, I have a strong faith. My church friends have been amazing with calls, cards, food, gifts, and time for visits. It has been humbling to see how many dear friends I have and how supportive they are in my time of need. I think this is one of the biggest keys in getting through cancer.

I have to mention some of the person-to-person connections I have been provided with through Us TOO have helped greatly in terms of information and support.

My advice to anyone facing chemotherapy is to first go to the nearest national cancer center, get a top-rated oncologist who specializes in your particular cancer, ask questions, listen to suggestions, and make a shared decision with your oncologist and caregiver. Ask your team of doctors and pharmacologists for all information about drugs and their most common side effects. Each person's cancer is unique and your responses to drugs will also be unique.

The Grim Reaper follows us all. Most of our lives we ignore the inevitable fact that everyone will die. With a chronic, terminal diagnosis, the Grim Reaper comes up closer behind us. The key to survival is to never look back. Focus forward. Look to the light of day. Focus on the here and now. Enjoy life.

In a strange way, having advanced Stage IV metastatic prostate cancer is a gift. It has changed the focus of my life in positive ways. Because now, more than ever before, I live in the present. And life is more intense, fuller, and more complete than I could have imagined. Pp[1]

JEVTANA® (cabazitaxel) injection

Combat advanced prostate cancer after treatment with docetaxel.

An option today for TOMORROW'S OPPORTUNITIES

***In the clinical study, among 378 men who received JEVTANA, median overall survival[1] was 15.1 months, versus 12.7 months among 377 men who received mitoxantrone.**

[1]The median overall survival is the time, when 50% of the patients who receive a certain treatment are still alive.

Talk to your doctor and visit JEVTANA.com/info

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 Important Safety Information on next page.**

Talk to your doctor and visit JEVTANA.com/info

Who is JEVTANA for?

JEVTANA is a prescription anti-cancer medicine used with the steroid medicine prednisone. JEVTANA 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 worsened (progressed) after treatment with other medicines, including docetaxel.

Important Safety Information

JEVTANA may cause serious side effects, including:

Low white blood cells, which can cause you to get serious infections, and may lead to death. Men who are 65 years or older may be more likely to have these problems. Your healthcare provider (HCP):

- will do blood tests regularly to check your white blood cell counts during your treatment with JEVTANA.
- may lower your dose of JEVTANA, change how often you receive it, or stop JEVTANA until your HCP decides that you have enough white blood cells.
- may prescribe a medicine for you called G-CSF, to help prevent complications if your white blood cell count is too low.

What is most important to know about JEVTANA?

Tell your HCP right away if you have any of these symptoms of infection during treatment with JEVTANA: fever (take your temperature often during treatment with JEVTANA), cough, burning during urination, or muscle aches.

Also, tell your HCP if you have any diarrhea during the time that your white blood cell count is low. Your HCP may prescribe treatment for you as needed.

Severe allergic reactions can happen within a few minutes after your infusion of JEVTANA starts, especially during the first and second infusions. Your HCP should prescribe medicines before each infusion to help prevent severe allergic reactions.

Tell your HCP right away if you have any of these symptoms of a severe allergic reaction during or soon after an infusion of JEVTANA: rash or itching, skin redness, feeling dizzy or faint, breathing problems, chest or throat tightness, or swelling of face.

JEVTANA can cause severe stomach and intestine problems, which may lead to death. You may need to go to the hospital for treatment.

Vomiting and diarrhea can happen when you receive JEVTANA. Severe vomiting and diarrhea with JEVTANA can lead to loss of too much body fluid (dehydration), or too much of your body salts (electrolytes). Death has happened from having severe diarrhea and losing too much body fluid or body salts with JEVTANA. Your HCP will prescribe medicines to prevent or treat vomiting and diarrhea, as needed with JEVTANA.

Tell your HCP if: you have vomiting or diarrhea, or if your symptoms get worse or do not get better. JEVTANA can cause a leak in the stomach or intestine, intestinal blockage, infection, and bleeding in the stomach or intestine. This can lead to death. **Tell your HCP if you get any of these symptoms:** severe stomach-area (abdomen) pain, constipation, fever, blood in your stool, or changes in the color of your stool.

Kidney failure may happen with JEVTANA, because of severe infection, loss of too much body fluid (dehydration), and other reasons, which may lead to death. Your HCP will check you for this problem and treat you if needed.

Tell your HCP if you develop these signs or symptoms: swelling of your face or body, or decrease in the amount of urine that your body makes each day or blood in your urine.

Lung or breathing problems may happen with JEVTANA and may lead to death. Men who have lung disease before receiving JEVTANA may have a higher risk for developing lung or breathing problems with JEVTANA treatment. Your HCP will check you for this problem and treat you if needed.

Tell your HCP right away if you develop any new or worsening symptoms, including: trouble breathing, shortness of breath, chest pain, cough or fever.

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

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JEVTANA® (cabazitaxel) injection

Important Safety Information– *continued*

Who should not receive JEVTANA?

Do not receive JEVTANA if: your white blood cell (neutrophil count) is too low, you have had a severe allergic reaction to cabazitaxel or other medicines that contain polysorbate 80 (ask your HCP if you are not sure), you have severe liver problems or you are pregnant. JEVTANA can harm your unborn baby or possibly cause loss of pregnancy.

What should I tell my HCP before receiving JEVTANA?

Before receiving JEVTANA, tell your HCP if you:

- had allergic reactions in the past
- are age 65 or older
- have kidney or liver problems
- have lung problems
- are a male with a female partner who is able to become pregnant. Males should use effective birth control (contraception) during treatment with JEVTANA and for 3 months after your final dose of JEVTANA.

JEVTANA may cause fertility problems in males. This may affect your ability to father a child. Talk to your HCP if you have concerns about fertility.

Tell your HCP about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. JEVTANA can interact with many other medicines. Do not take any new medicines without asking your HCP first. Your HCP will tell you if it is safe to take the new medicine with JEVTANA.

What are the possible side effects of JEVTANA?

Common side effects of JEVTANA include:

- low red blood cell count (anemia) is common with JEVTANA, but can sometimes also be serious. Your HCP will regularly check your red blood cell count. Symptoms of anemia include shortness of breath and tiredness.
- low blood platelet count is common with JEVTANA, but can sometimes also be serious. Tell your HCP if you have any unusual bruising or bleeding.
- numbness, tingling, burning or decreased sensation in your hands or feet
- blood in your urine. Tell your HCP if you see blood in your urine
- fever
- diarrhea
- tiredness
- nausea
- vomiting
- constipation
- weakness
- stomach pain
- back pain
- change in your sense of taste
- shortness of breath
- cough
- joint pain
- hair loss
- decreased appetite

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

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

Please see the Brief Summary on the next two pages.

Summary of Information about JEVTANA® (cabazitaxel) Injection (JEV-ta-na)

Rx Only

What is the most important information I should know about JEVTANA?

JEVTANA may cause serious side effects including:

Low white blood cells. Low white blood cells can cause you to get serious infections, and may lead to death. Men who are 65 years or older may be more likely to have these problems. Your healthcare provider:

- will do blood tests regularly to check your white blood cell counts during your treatment with JEVTANA.
- may lower your dose of JEVTANA, change how often you receive it, or stop JEVTANA until your healthcare provider decides that you have enough white blood cells.
- may prescribe a medicine for you called G-CSF, to help prevent complications if your white blood cell count is too low.

Tell your healthcare provider right away if you have any of these symptoms of infection during treatment with JEVTANA:

- fever. Take your temperature often during treatment with JEVTANA.
- cough
- burning on urination
- muscle aches

Also, tell your healthcare provider if you have any diarrhea during the time that your white blood cell count is low. Your healthcare provider may prescribe treatment for you as needed.

Severe allergic reactions. Severe allergic reactions can happen within a few minutes after your infusion of JEVTANA starts, especially during the first and second infusions. Your healthcare provider should prescribe medicines before each infusion to help prevent severe allergic reactions.

Tell your healthcare provider or nurse right away if you have any of these symptoms of a severe allergic reaction during or soon after an infusion of JEVTANA:

- rash or itching
- skin redness
- feeling dizzy or faint
- breathing problems
- chest or throat tightness
- swelling of your face

Severe stomach and intestine (gastrointestinal) problems. JEVTANA can cause severe stomach and intestine problems, which may lead to death. You may need to go to a hospital for treatment.

- Vomiting and diarrhea can happen when you receive JEVTANA. Severe vomiting and diarrhea with JEVTANA can lead to loss of too much body fluid (dehydration), or too much of your body salts (electrolytes). Death has happened from having severe diarrhea and losing too much body fluid or body salts with JEVTANA. Your healthcare provider will prescribe medicines to prevent or treat vomiting and diarrhea, as needed with JEVTANA.

Tell your healthcare provider if:

- you have vomiting or diarrhea
- your symptoms get worse or do not get better

JEVTANA can cause a leak in the stomach or intestine, intestinal blockage, infection, and bleeding in the stomach or intestine. This can lead to death. **Tell your healthcare provider if you get any of these symptoms:**

- severe stomach-area (abdomen) pain
- constipation
- fever
- blood in your stool, or changes in the color of your stool

Kidney failure. Kidney failure may happen with JEVTANA, because of severe infection, loss of too much body fluid (dehydration), and other reasons, which may lead to death. Your healthcare provider will check you for this problem and treat you if needed.

Tell your healthcare provider if you develop these signs or symptoms:

- swelling of your face or body
- decrease in the amount of urine that your body makes each day
- blood in your urine

Lung or breathing problems. Lung or breathing problems may happen with JEVTANA and may lead to death. Men who have lung disease before receiving JEVTANA may have a higher risk for developing lung or breathing problems with JEVTANA treatment. Your healthcare provider will check you for this problem and treat you if needed.

Tell your healthcare provider right away if you develop any new or worsening symptoms, including: trouble breathing, shortness of breath, chest pain, cough or fever.

What is JEVTANA?

JEVTANA is a prescription anti-cancer medicine used with the steroid medicine prednisone. JEVTANA 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 worsened (progressed) after treatment with other medicines that included docetaxel.

JEVTANA is not for use in females.

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

Who should not receive JEVTANA?

Do not receive JEVTANA if:

- your white blood cell (neutrophil count) is too low
- you have had a severe allergic reaction to cabazitaxel or other medicines that contain polysorbate 80. Ask your healthcare provider if you are not sure.
- you have severe liver problems
- you are pregnant. JEVTANA can harm your unborn baby or possibly cause loss of pregnancy.

Before receiving JEVTANA, tell your healthcare provider about all your medical conditions, including if you:

- had allergic reactions in the past
- are over the age of 65
- have kidney or liver problems
- have lung problems
- are a male with a female partner who is able to become pregnant. Males should use effective birth control (contraception) during treatment with JEVTANA and for 3 months after your final dose of JEVTANA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. JEVTANA can interact with many other medicines. Do not take any new medicines without asking your healthcare provider first. Your healthcare provider will tell you if it is safe to take the new medicine with JEVTANA.

How will I receive JEVTANA?

- JEVTANA will be given to you by an intravenous (IV) infusion into your vein.
- Your treatment will take about 1 hour.
- JEVTANA is usually given every 3 weeks. Your healthcare provider will decide how often you will receive JEVTANA.
- Your healthcare provider will also prescribe another medicine called prednisone for you to take by mouth every day during treatment with JEVTANA. Your healthcare provider will tell you how and when to take your prednisone.

It is important that you take prednisone exactly as prescribed by your healthcare provider. If you forget to take your prednisone, or do not take it on schedule, make sure to tell your healthcare provider or nurse. Before each infusion of JEVTANA, you may receive other medicines to prevent or treat side effects.

What are the possible side effects of JEVTANA?

JEVTANA may cause serious side effects including:

- **See "What is the most important information I should know about JEVTANA?"**

Common side effects of JEVTANA include:

- Low red blood cell count (anemia). Low red blood cell count is common with JEVTANA, but can sometimes also be serious. Your healthcare provider will regularly check your red blood cell count. Symptoms of anemia include shortness of breath and tiredness.
- Low blood platelet count. Low platelet count is common with JEVTANA, but can sometimes also be serious. Tell your healthcare provider if you have any unusual bruising or bleeding.
- diarrhea
- tiredness
- nausea
- vomiting
- constipation
- inflammation of the bladder has happened in men who have previously received pelvic radiation therapy. Tell your healthcare provider if you have blood in your urine, burning sensation during urination, or frequent or urgent need to urinate.
- weakness
- stomach (abdominal) pain
- blood in your urine. Tell your healthcare provider or nurse if you see blood in your urine.
- back pain
- decreased appetite
- shortness of breath
- hair loss
- cough

JEVTANA may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if you have concerns about fertility.

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 JEVTANA. 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.

General information about the safe and effective use of JEVTANA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about JEVTANA that is written for health professionals.

What are the ingredients in JEVTANA?

Active ingredient: cabazitaxel

Inactive ingredient: polysorbate 80

Manufactured by: sanofi-aventis U.S. LLC,
Bridgewater, NJ 08807 A SANOFI COMPANY

For more information, go to www.sanofi-aventis.us or call 1-800-633-1610.

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