Prostatepedia[1]

[1]expert insight + advice

Chemotherapy

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In this issue....

This issue marks a new era for this publication as it is the first to be published under the NASPCC umbrella. We anticipate that this will allow us to reach a much larger audience.

As an old hand in the field, it is very gratifying to see the steady stream of high-quality clinical trials define the best treatment options for those with advanced disease. The good news is that, for most patients with advanced disease, you and your physician have a range of options so that treatment can be tailored to your situation.

For patients with newly diagnosed metastatic prostate cancer, a vast majority of patients should no longer be treated solely with testosterone suppressing agents, such as LHRH agonists like Lupron (leuprolide). Instead, they should receive these agents combined with either Taxotere (docetaxel) or one of the newer androgen antagonists, such as Xtandi (enzalutamide). Indeed, the literature on cytotoxic chemotherapies, like Taxotere (docetaxel), is so intertwined with anti-androgens that these hormonal agents occupy a considerable portion of this issue. This serves patient interests well, as many will need to discuss anti-androgens as an alternative to chemotherapy.

This issue is information-dense and it is not practical to highlight all of the key points in this introduction. Instead, I would like to highlight two relatively new drugs that look as if they might have a major impact. The first is Nubeqa (darolutamide), which is FDA-approved and in the same drug family as Xtandi (enzalutamide) and Erleada (apalutamide). The latter two cross the blood-brain barrier (BBB) and can impair brain function and can be associated with seizures. Nubeqa (darolutamide) does not cross the BBB and is much less likely to cause central nervous system toxicity (CNST). The second drug is Relumina (relugolix), an oral drug that blocks the production of testosterone much more effectively than Lupron (leuprolide). In comparison, Relumina (relugolix) has a lower risk of cardiovascular events, but it is not yet approved for the treatment of prostate cancer.

Each of our interviewees discusses the impact of the Novel Coronavirus on the management of prostate cancer patients. The good news is that, with proper precautions, it is possible to give chemotherapy safely despite the pandemic.

Charles E. Myers, Jr., MD

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Contributors:

Editor-in-Chief
Jessica Myers-Schecter

Editor-in-Chief Emeritus
Dr. Charles "Snuffy" Myers

Publisher
National Alliance of State Prostate Cancer Coalitions

Copyeditors
Lito Velazquez
Anne Arasin

Proofreader
Robert M. Protz, MS

Designer
Verity Burgess

Administrative Offices
NASPCC
1999 Avenue of the Stars
Suite 1100
Los Angeles
California 90067

Report from ASCO 2020
Merel Grey Nissenberg
President, NASPCC

National Alliance of State Prostate Cancer Coalitions

In the last few years, advanced prostate cancer has been examined in new ways and trials designed for various subtypes of advanced disease. There is **non-metastatic but castrate-resistant prostate cancer (no longer responsive to hormonal therapy) called nmCRPC; there is metastatic but castrate-sensitive prostate cancer (still responsive to hormonal treatment) called mCSPC; and of course metastatic castrate-resistant prostate cancer, called mCRPC (cancer that has spread beyond the prostate and which is no longer responsive to hormonal therapy)**. New drug approvals have included treatments for the non-metastatic space in order to postpone or prevent metastases (nmCRPC); and some of those drugs have now been approved or await approval in the metastatic hormone-sensitive prostate cancer space. It can be confusing. Added to that are emerging treatment possibilities based on genetic alterations (such as BRCA 1/2) and on other gene repair defects, so some of the prostate cancer treatments are in a new class of drugs including, for example, PARP inhibitors. Imaging in prostate cancer is also growing as a field in which some agents are being used for diagnosis and for treatment. Even immunotherapy in prostate cancer (Sipuleucel-T or Provenge) is being examined in combination with other agents to increase efficacy. This Report can only cover a fraction of the 200+ Abstracts presented last month.

Although ASCO 2020 was held as a virtual, instead of an in-person event, there were important presentations in prostate cancer, available to online registrants, that provided data likely to affect clinical practice going forward. Some of the most significant presentations provided the updated data from the 3 major trials in **non-metastatic, castrate-resistant prostate cancer (nmCRPC).** These are the trials that examined apalutamide, darolutamide, and enzalutamide, all of which showed OS (overall survival) benefit for the study patients. In the first clinical trial, **SPARTAN**, presented by Dr. Eric Small of the Helen Diller Family Comprehensive Cancer Center at UCSF, apalutamide (Erleada) was found to offer a survival benefit versus placebo, even after crossovers to the active agent took place. [Abstract 5516] The trial tested apalutamide versus placebo for 1207 patients with non-metastatic castrate-resistant prostate cancer who had a PSA doubling time of 10 months or less. Previous reports had shown an improvement in metastasis-free survival with apalutamide. The median follow-up now was 52 months. The median OS for the apalutamide patients was 73.9 months versus 59.9 months with placebo. Time to chemotherapy was also improved with apalutamide. There was a clear survival benefit with apalutamide, and this is true even though 80% of the patients receiving placebo eventually received therapy either at progression or with crossover to apalutamide when the study was unblinded. This means the study looked at an active agent early, versus later. The clinically relevant results reported at ASCO 2020 added to the hopeful findings reported earlier in the trial.

Second, the final survival analysis of the **ARAMIS Trial** was also reported out at ASCO 2020 by Dr. Karim Fizazi of the Institut Gustave Roussy in Villejuif, France. [Abstract 5514]. Darolutamide (Nubeqa) showed significant overall survival (OS) over placebo along with delayed onset of cancer-related symptoms and later chemotherapy. [Abstract 5514] In this trial, 1509 patients were randomized almost 2:1 to either darolutamide twice a day or placebo, while continuing ADT. Crossover was allowed at the unblinding, and 170 patients crossed over to begin taking darolutamide. Although the median OS wasn't reached in either arm, darolutamide did reduce the risk of

death by 31%. Key adverse events were similar in both arms, and the trial concluded that it was efficacious in both metastasis-free survival and OS.

The third Trial in the non-metastatic CRPC space with final data to report was the **PROSPER Trial**, the results of which were presented by Dr. Cora Sternberg of Weill Cornell Medicine and New York-Presbyterian Hospital in New York. The earlier results of improved metastasis-free survival had now translated into an overall survival (OS) benefit of almost 1 year in patients receiving enzalutamide (Xtandi). [Abstract 5515] The enrolled patients had non-metastatic disease, a PSA doubling time of 10 months or less, and a PSA of at least 2 ng/mL at screening, who were randomized 2:1 to enzalutamide or placebo. The median OS was 67 months with enzalutamide and 56.3 months with placebo, a 27% reduced risk of death. Grade 3 or higher adverse events were seen in 48% of the enzalutamide patients versus 27% of patients in the placebo group. Finally, it was postulated that **PROSPER** offers prospective validation of metastasis-free survival as a potential surrogate endpoint for OS in non-metastatic castrate-resistant prostate cancer.

Finally, Abstract 5561 analyzed all three trials together, and confirmed the points about safety made by Dr. Fizazi, showing that darolutamide has a favorable safety profile compared with apalutamide and enzalutamide. Darolutamide showed a much lower incidence of fall, dizziness, mental impairment, hypertension, fatigue and severe fatigue. Most importantly, darolutamide has significantly lower blood-brain penetration - resulting, among other things, in a reduced amount of neurocognitive side effects.

Other interesting reports from ASCO 2020 included the Phase III **TITAN**

Trial [Abstract 5006] which showed that for men with metastatic castrate-sensitive prostate cancer (mCSPC) (still responding to testosterone therapy), adding apalutamide to androgen deprivation therapy (ADT) improved radiographic progression-free survival (PFS) as well as overall survival (OS). This finding was the same, regardless of having had prior docetaxel. The earlier analysis had shown that TITAN had met both primary endpoints of OS and radiographic PFS. Now the final data presented here showed a 33% reduction in risk of death and a 52% decrease in the risk of disease progression, with 82% OS at 2 years in the apalutamide arm. TITAN included patients with both high- and low-volume disease. Of note, apalutamide has not yet been approved for these patients in the metastatic space who are still castrate-sensitive. **And** in the **ENZAMET Trial** [Abstract LBA2], results showed that 80% of men with metastatic castrate-sensitive prostate cancer (mCSPC) who received enzalutamide (a nonsteroidal antiandrogen) along with testosterone suppression therapy (standard of care) were alive after 3 years, compared to 72% of men who received testosterone-suppression therapy along with other nonsteroidal antiandrogens (bicalutamide, nilutamide, or flutamide). Dr. Neeraj Agarwal of the Huntsman Cancer Institute at the University of Utah reported on this data and said that the quality of life in the TITAN Trial was preserved in ENZAMET.

The Phase III **PROfound Trial** demonstrated that in metastatic castrate-resistant prostate cancer (mCRPC) , men with certain genetic defects, eg. DNA damage repair mutations such as HRR (homologous recombination repair) gene alterations, and whose disease progressed while receiving enzalutamide or abiraterone, had longer progression-free survival (PFS) and better measures of response when treated with olaparib (a PARP inhibitor) than with physician's choice of new hormonal therapy (enzalutamide or abiraterone). Notably, the olaparib patients had better health-related quality of life than the other treatment arm. This is important because these metrics come directly from patients giving us their perspective. And with regard to health-related quality of life, in the **ARCHES Study** men with metastatic hormone-sensitive prostate cancer who received enzalutamide in addition to androgen deprivation therapy (ADT) were able to maintain high-functioning health-related quality of life (HRQoL). ARCHES was a Phase III trial of 1150 men; in earlier reporting it had shown that men who received enzalutamide with their ADT (as opposed to placebo) showed improved radiographic progression-free survival compared to those who only received ADT.

The **CARD Study** looked at the efficacy and safety in older patients with metastatic castrate-resistant prostate cancer (mCRPC) who received cabazitaxel versus abiraterone or enzalutamide. Significant improvement was seen in radiographic progression-free survival (PFS), progression-free survival, and overall survival (OS). The patients had all received docetaxel and progressed within 12 months on an alternative androgen-receptor-targeted-agent (ARTA): abiraterone or enzalutamide. CARD analyzed the impact of age (below 70 and 70 and older). Analysis showed that radiographic progression-free survival in the cabazitaxel arm was improved for both age groups. A higher rate of adverse events was reported in the older group for both arms. The overall survival benefit was seen even when patients had low hemoglobin, high baseline neutrophils to lymphocyte ratio, and high PSA values at baseline. Multivariate analysis of the results confirmed this was a true benefit.

A stunning result was seen in the Phase III **HERO Trial**, leading to relugolix soon becoming the first orally administered androgen deprivation therapy (ADT) for advanced prostate cancer. 96.7% of patients in the study who received relugolix, an LHRH receptor antagonist, had sustained testosterone suppression to castrate levels through week 48, compared to 88% of patients in the control arm who received leuprolide acetate (lupron), an LHRH agonist and the current standard of care. Patients were randomized 2:1 to either take relugolix orally once a day or lupron through an injection every 3 months over the course of 48 weeks. Additionally, relugolix proved superior to lupron on all of the study's secondary endpoints. This included a confirmed PSA response at day 15; the probability of castration and profound castration at day 15, and follicle-stimulating hormone suppression at week 24. Not to mention, the testosterone reductions with relugolix happened very quickly; 56% of patients had testosterone suppression below 50 ng/dL after just 4 days of treatment. This compared to 0% of the lupron patients. The other major benefit occurred with respect to MACE (major adverse cardiovascular events), which occurred in only 2.9% in the relugolix group versus 6.2% in the lupron group. This is a crucial finding because death from cardiovascular events is the most common cause of death in men with prostate cancer. A testosterone

recovery sub-study also yielded much better results for the relugolix group (54% of men versus 3% on lupron).

Other trial results of interest include a biomarker analysis of **KEYNOTE-199**, a trial of pembrolizumab in men with metastatic castrate-resistant prostate cancer (mCRPC) for whom docetaxel had failed. The Phase II KEYNOTE-199 demonstrated that pembrolizumab monotherapy had shown antitumor activity in those patients for whom docetaxel had failed (docetaxel-refractory). This presentation at ASCO was a look at the association between pre-selected molecular biomarkers and clinical outcomes. It was noted that tumor mutational burden and PD-L1 CPS (combined positive score for PD-L1 positive disease) were associated with a better PSA response. Unfortunately the study had too few patients to draw any conclusions on overall survival (OS), disease control rate (DCR), and ORR. Further study was said to be warranted.

In the accruing Phase III **TALAPRO-2** study of talazoparib (TALA) plus enzalutamide for patients with first-line metastatic castrate-resistant prostate cancer (mCRPC), the investigators will be looking at this parp-inhibitor for prostate cancer treatment. TALAPRO-2 will be a follow-up to **Phase II TALAPRO-1** which found that monotherapy with talazoparib appeared to have excellent antitumor activity in men with metastatic castrate-resistant prostate cancer (mCRPC) and BRCA 1/ 2 genetic alterations who had been pretreated with docetaxel.
There are so many combinations of therapies now being tested in prostate cancer – especially in the spaces of (1) metastatic, castrate-sensitive prostate cancer (mCSPC) and (2) non-metastatic, castrate-resistant prostate cancer (nmCRPC), along with the tentative use of drugs targeting genetic mutations and DNA alterations. Better outcomes are hopefully on the horizon.

Another topic receiving attention at ASCO 2020 was advances in Prostate-Specific Membrane-Antigen (PSMA) Imaging. Because cancers of the prostate express high levels of PSMA, it has become a logical target for developing techniques in diagnosing and treating prostate cancer. "The Evolving Role of PSMA-Based Diagnostics and Therapeutics in Prostate Cancer" was in fact a presentation in an ASCO 2020 Education Session. Worldwide there have been almost 850 studies regarding PSMA PET imaging published in the last 4 years. PSMA-PET has been incorporated into European prostate cancer guidelines in the treatment of patients with persistent PSA after radical prostatectomy, and in the imaging of patients with biochemical recurrence. However, there is little data on overall survival. Theranostics is based upon a combination of a diagnostic biomarker and a therapeutic agent, and involves treatment of a target with a specific isotope. Various studies are underway. Additionally, there are several possible uses of PET imaging in advanced prostate cancer, and sometimes opportunities to combine more than one type of PET scan. In some reports, in as many as 76% of cases management of patients changed based on PSMA imaging. In just one example of a study using PSMA, the Phase III **CONDOR Trial** utilized 18-F-DCFPyL-PET CT for patients with biochemical recurrence (BCR). Results of the study found that PSMA-targeted PyL-PET/CT detected and localized occult disease in most of the patients with BCR who had had equivocal or negative imaging using conventional imaging, changing physician management in a majority of those patients.

There were also presentations on PSA and its involvement in various stages of prostate cancer and treatment, and on Circulating Tumor Cells (CTC's) and their potential in this disease.

In immunotherapy, the only agent approved in prostate cancer by the FDA to date is Sipuleucel-T (Sip-T) (Provenge). In a randomized trial presented in an abstract at ASCO 2020, 32 patients with asymptomatic, bone-predominant metastatic CRPC without any visceral metastases larger than 1.0 cm, had been randomized 1:1 to Sip-T alone or with 6 doses of Radium-223. Men in the combination arm began Sip-T between the 2nd and 3rd doses of Radium-223. The primary immunological endpoint was PA2024-specific T-cell proliferation 6 weeks after the first Sip-T infusion. Clinical endpoints were radiographic PFS, PSA response equal to or greater than a 50% decline, AlkPhos response equal to or greater than a 30% decline, and safety. Findings were that the combination of Sip-T and Radium-223 was associated with improved clinical outcomes and a higher rate of PSA responses than Sip-T alone. The data was said to suggest a synergistic effect with the combination since neither Sip-T nor Radium-223 alone was associated with reliable PSA responses, but larger randomized trials are planned.

This year's virtual ASCO 2020 offered a wealth of information and exciting and hopeful data. Work in all of these areas and others continues. Pp[1]

Daniel James George, MD
Chemo for PCA Today

Dr. Daniel James George is Professor of Medicine and Professor in Surgery and Director of Genitourinary Oncology in the Duke Cancer Institute at Duke University.

Prostatepedia spoke with him recently about chemotherapy for prostate cancer.

Can you give us an overview of chemotherapy for men with prostate cancer in 2020?

Dr. Daniel George: Chemotherapy for prostate cancer has been around for 20 years. We have chemotherapy that dates back further than that, but it was ineffective therapy. The first life-prolonging, effective chemotherapy was Taxotere (docetaxel) chemotherapy. That came around the beginning of 2000 with some Phase II studies and established itself in 2004 with two large Phase III studies that demonstrated a survival benefit, albeit modest, in men with metastatic castrate-resistant prostate cancer.

The big breakthrough in the last five years with chemotherapy has been the recognition of the benefit associated with chemotherapy when given upfront with hormonal therapy for men with metastatic hormone-sensitive prostate cancer. This was based on the CHAARTED study first, and then on a study called Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE), which is a large, multi-armed study based in the United Kingdom of various regiments in this patient population of metastatic but hormone-naive or hormone-sensitive prostate cancer.

What the studies have both shown is that there is a 30-40% improvement in survival for men who are diagnosed with this metastatic hormone-sensitive prostate cancer, and started on hormonal therapy and Taxotere (docetaxel) chemotherapy at the same time, rather than waiting until men become resistant to the hormonal therapy and into what we call castration-resistant disease. By giving the two therapies together upfront, we improve the benefit for chemotherapy. We see a higher survival rate, and because these patients live longer, on average for four years or more, that 30-40% improvement in survival is translated to anywhere from a year to a year and a half improvement in survival on average.

It's a tremendous increase in the benefit associated with chemotherapy, and it's a shorter course of chemotherapy. We only treat for six cycles of therapy. There are competing therapies, besides chemotherapy, for that space, and a number of novel hormone agents, like Xtandi (enzalutamide) or Erleada (apalutamide), have also demonstrated a survival benefit in that space. Chemotherapy seems to work best when we give it up front, but it is not frequently given there, since there are alternative approaches for patients. Chemotherapy today is still mostly given to patients that have castration resistant prostate cancer.

Is it because these other agents are more effective or because the side effect profiles are more acceptable?

Dr. Daniel George: From a clinical benefit perspective, chemotherapy and novel hormonal therapies are mostly equivalent, but most physicians believe chemotherapy is more toxic on patients than these novel hormonal agents. We're just beginning to do some patient preference studies to try to understand if patients would prefer a shorter course of chemotherapy and then be treated with just standard androgen deprivation therapy (ADT) versus taking a second hormone pill in

addition to their ADT for three or four years of therapy. It's not entirely clear. Physicians feel like the patients would prefer the hormonal therapy. It's less risky than the chemotherapy, but for your body, there are cumulative consequences to taking added hormonal therapy for that many years that may be less recognized.

For instance, patients may be losing more muscle mass or getting weaker bones or increasing their risks of falls and fractures from those years of additional hormonal therapy than they would from the shorter, but perhaps a more intense course of chemotherapy. Nonetheless, it seems like the most common practice patterns are to treat patients primarily with the hormonal therapies in that initial setting and then with chemotherapy later.

The other study that has reinforced the value of chemotherapy is called The CARD study, which came out in the fall of 2019. The CARD study looked at the role of a second chemotherapy course with a drug called Jevtana (cabazitaxel). It specifically targeted patients that were treated with hormonal therapy (ADT), became castration resistant, and subsequently received a secondary hormonal therapy like Xtandi (enzalutamide) or Zytiga (abiraterone), and then also received chemotherapy with Taxotere (docetaxel). Patients were randomized to either receive another hormonal strategy, either Xtandi (enzalutamide) or Zytiga (abiraterone), whichever one they hadn't received, or Jevtana (cabazitaxel) chemotherapy.

Jevtana (cabazitaxel) chemotherapy, in that setting, improved the progression-free survival compared to the alternative hormonal therapy. What was surprising however, was that the secondary end point of overall survival was also improved in the Jevtana (cabazitaxel) arm. Patients who progressed on the Xtandi (enzalutamide) or Zytiga (abiraterone) could have crossed over to Jevtana (cabazitaxel), and many did, but that delay in chemotherapy by using a second hormone pill that was largely ineffective partially compromised the effectiveness of chemotherapy, suggesting that using chemotherapy earlier rather than later is key.

These studies suggest that there's still an ongoing role for chemotherapy. We cannot deny that this is important, life-prolonging therapy in prostate cancer, both Taxotere (docetaxel) and subsequent Jevtana (cabazitaxel) chemotherapy. These data also suggest that the timing matters. Giving these drugs early, whether it be upfront with the primary hormonal therapy or when patients progress on one oral novel hormonal therapy in the castration-resistant setting, maximizes the benefits associated with chemotherapy.

Are there any current clinical trials for chemotherapy that you have your eye on?

Dr. Daniel George: We've been trying to develop other chemotherapy agents in prostate cancer for a while. In this time of COVID-19, we're beginning to recognize the need to minimize patient visits. Oral chemotherapies do not require patients to come into the health system and be exposed to other patients. The less they need to get IV therapies, the safer our clinics will be.

There was an oral chemotherapy called Spera (satraplatin), a platinum-based chemotherapy like Platinol (cisplatin). It was a pill therapy. Unfortunately, it failed to improve the median survival for patients in its Phase III study. Interestingly, we did see a 30% subset of patients who responded to this agent but we did not understand why. More recently, with the recognition that that a subset of prostate cancer patients, maybe 20-30%, have genetic alterations in DNA-damaged repair genes like BRCA2, and based on these alterations, their tumors are susceptible to treatment with poly ADP ribose polymerase (PARP) inhibitors that are now approved for prostate cancer.

PARP inhibitors are an oral chemotherapy that have relatively low rates of side effects. This new treatment class will lend itself to new combinations of treatment as well as opportunities to revisit platinum-based chemotherapy like Spera (satraplatin) in patients with DNA damage repair defects. There's also an oral form of taxane (ModraDoc006) that's being combined with ritonavir, an agent that boosts the intratumoral exposure of ModraDoc006. It's an interesting strategy to target and concentrate the oral taxane in the tumor. Those strategies are exciting.

We're also beginning the era of prostate-specific membrane antigen (PSMA) targeted therapies. Those are with radiopharmaceuticals. But it's possible that antibody or other small molecule-targeted chemotherapy around PSMA could also be beneficial in this field.

What are the implications of the pandemic for men who are getting chemotherapy?

Dr. Daniel George: Chemotherapy, on the surface, lowers the immune system and puts people at risk for infections. We naturally think of chemotherapy as being immune suppressive, but the immune system is complicated. There's not just one type of immune protection.

When we think about the infections that chemotherapy, particularly Taxotere (docetaxel) or taxane-based chemotherapies, put people at risk for, they're primary bacterial infections. It lowers the neutrophils, which are the first line of defense for bacteria and other pathogens. When it comes to viral infections, they're a little bit different. They're managed more through our lymphatic system, through our lymphocytes, and through other sorts of inflammatory reactions. People are more afraid to take chemotherapy during this time of COVID-19 but it is not entirely clear that taxane-based chemotherapy would put people at the same degree of risk for complications with COVID-19 as it would for bacterial infection.

Any immune suppression is dangerous, and if you get a viral infection, you could get additional infections with bacteria as well. I don't want to minimize this, but I don't want to overblow it either. I think that the concerns around chemotherapy and COVID-19 are still somewhat theoretical. My concern is that the patients we give chemotherapy to for prostate cancer have lethal disease. And most of these patients have lethal disease within the next two to three years. We're dealing with a known risk of a near term mortality versus a theoretical infection that has a relatively low mortality risk in the general population.

For the individual patient, it still makes sense in most circumstances to continue with chemotherapy. At Duke, we try to minimize that risk. We try to minimize the additional patients that are coming into the clinic and do video visits for patients on oral therapies and other therapies that we can minimize so that these patients that have to come in for IV therapies get the least amount of exposures.

We screen everybody before they come to our clinics with questionnaires around symptoms and exposures, and we temperature check everybody. We minimize the number of additional people that can accompany any patient in for clinic visits. Those measures have largely kept COVID-19 out of our clinics. We've been able to keep those clinics relatively safe. I would encourage patients to continue to treat their cancers aggressively when indicated. As concerned as we are about COVID-19, trust that medical centers are doing everything in their power to minimize that risk.

So you're saying for the men who were being prescribed chemotherapy, the risk of prostate cancer far outweighs the risk of any potential COVID-19, right?

Dr. Daniel George: I think so. There is some theory that the hormonal therapy that these men are continued on can be protective. There is some retrospective preliminary data out of Italy that suggests that they may be at far lower risk of developing COVID-19 or dying of COVID-19 if they're on hormonal therapy. But I would treat these patients as an increased-risk population regardless of that.

What has the response been among your patients for telemedicine, and are there some aspects that you'll retain long term?

Dr. Daniel George: My patients appreciate telemedicine since I have patients that come in from quite a distance. The time they spend traveling to Duke, the time they spend getting their tests done and waiting for the results, waiting to see me, it builds up a lot of stress, anticipation, and anxiety. A lot of that is minimized when they stay at home and when they have a scheduled time I'm going to call or they're going to get onto the computer and we're going to video visit together. By having a relaxed and private atmosphere and removing the necessity to travel, levels of stress and anxiety go down.

It does take away from our interactions, and it does limit my assessments since there are no vital signs. There's no physical exam. We can get labs and we can get scans done, but there are other aspects to our assessment that we're not able to do. On the whole, it's a big advantage. When we use it on the appropriate patients, it's an incredibly efficient and resource-saving approach. I don't see it going away. I see it continuing to be broadly accepted into our practice. In fact, I'm setting up a half-day clinic once a week, long-term now for just telephone and video visits. I think that will persist past COVID-19.

Even the patients that come in for tests like a CT scan and labs, they don't have to wait around. They can get those scans, go home, and by the time they get home, I've got the results and then we talk about it. A lot of my patients are in survivorship mode. They're in remission, and we're checking to see if they're staying in remission. If they do have disease progression, I'm going to get them right back in to follow up and talk about what the next steps are in any follow-up studies that we want to do. It's a good mechanism for a significant percentage of our patients. Pp1

Mark Fleming, MD
Chemotherapy for Prostate Cancer

Dr. Mark Fleming is a medical oncologist with Virginia Oncology Associates. Dr. Fleming is keenly interested in cancers of the bladder, kidney, prostate, and testicle, as well as Phase 1 novel drug development. He serves as the Medical Director of US Oncology's Genitourinary Research Committee.

He spoke with *Prostatepedia* about chemotherapy for prostate cancer.

Can you give us an overview of chemotherapy for prostate cancer as it stands in 2020?

Dr. Fleming: For localized prostate cancer, there is evidence that with men with high-risk disease who choose radiation (as defined by their Gleason Score, prostate-specific antigen [PSA], and risk of recurrence), adding chemotherapy, Taxotere (docetaxel), is beneficial. Chemotherapy doesn't change anything that we're doing since men still get hormonal therapy or androgen deprivation therapy (ADT). Subtypes for radiation therapy include brachytherapy, stereotactic radiation therapy, or traditional external beam radiation therapy (EBRT). The one area where we don't see a clear benefit of chemotherapy is in men who have what we call the rising PSA clinical state.

If we do not see any evidence of disease, there's no definitive evidence of a benefit of adding chemotherapy. There are two chemotherapies that are traditionally used: Taxotere (docetaxel) and Jevtana (cabazitaxel), which are both taxanes. There are also two classes of metastatic disease: castrate-sensitive or hormone-sensitive disease, or castration-resistant metastatic disease. Men have a variety of treatment options that are available. Immunotherapy is FDA approved. Targeted therapy, which targets the androgen receptor, is approved. Recently, we added targets for genomic-based men with DNA repair mutations like BRCA, BRCA1, or BRCA2.

There is a class of drugs called poly ADP ribose polymerase (PARP) inhibitors that is beneficial, and chemotherapy is part of that armamentarium. We don't know the "right" sequence of how to use the multitude of agents that we have. But men do better when they are willing to accept all of the treatment options, those who add more to their salad of options than just, "I don't want chemotherapy." The way that I look at it is, "Okay, I can make you a salad that tastes good, but the more things that you allow me to do, the more likely that I can expose your cancer, challenge it, and try to fight it in as many ways possible, and chemotherapy is just one of those ways."

Today's chemotherapy is not your grandfather's chemotherapy. Men who accept all their options tend to do better. In the initial trial, what's called TAX 327, we asked men, "Is your quality of life better before chemotherapy or is your quality of life better after chemotherapy?" And it was overwhelmingly better after chemotherapy since we helped get their disease under control.

There's lots of myths when it comes to chemotherapy, and I encourage men to have a multidisciplinary view. Have a urologist on board who typically does a diagnosis, a medical oncologist who, in addition to chemotherapy, can provide the range of treatment options, and a radiation oncologist since some therapies involve them as well.

What is behind the reluctance of some men to go on chemotherapy?

Dr. Fleming: It's an unfortunate reluctance, but men with prostate

cancer tend to have preconceived notions. And those preconceived notions are not necessarily founded or up to date in terms of what is going on. I have a chart, and when someone tells me they don't want chemotherapy, I start crossing therapies off and tell them, "Okay, well, it's two less treatments that we can use." Probably more than that. Men do better when they use all those options as opposed to just selectively take à la carte options off the menu.

It takes time. It takes a physician who's willing to listen to the patient's concerns. The quality of life issue was embedded right into the initial trial with TAX 327 or Taxotere (docetaxel).

What about this notion of using chemotherapy early versus late? Can you talk a little bit more about that?

Dr. Fleming: All prostate cancer is not the same. Their burden of disease impacts our treatment recommendations such as number of sites of disease and visceral involvement (lung, or liver). Do they have high-burden disease with greater than five bone lesions? There's not just one playbook for the treatment of prostate cancer. There are times when I use upfront chemotherapy followed by the agent Xtandi (enzalutamide) or Erleada (apalutamide), which are shown to be beneficial in trials. If you talk to a radiation oncologist, they tend to do more radiation oncologist treatments. If you talk to a urologist, they provide treatments within the urologist armamentarium. And if you talk to a medical oncologist, there is a range of options that we can do since medical oncologists traditionally give chemotherapy. There are some advanced urology

clinics with chemotherapy embedded within urology practices that do a good job of having that conversation. But you have to talk to the people that administer the medicine. It's beneficial to get a conglomerate of opinions and then decide which way to go. To get the disease under control, we should give the best treatments up front since there are long-term implications on the bone marrow when you radiate things from that perspective.

Pain, to me, equals chemotherapy. That's one of my simple rules. If someone has pain related to prostate cancer, they're symptomatic, and more likely than not, I'm going to offer systemic chemotherapy. The initial trial clearly showed that it helped men live longer. It helped improve their pain, and it improved the quality of life. It's the trifecta. Those are the types of things that help me decide when it's appropriate for someone to have chemotherapy.

What impact has COVID-19 had on administering chemotherapy?

Dr. Fleming: The biggest impact that the pandemic has had is that it has delayed men getting treatment. I encourage men to continue with their health-related issues. You can still be monitored. You can still get lab work. We're all doing tele-health. But when someone needs systemic treatment, most medical offices have not stopped administering treatments. We use social distancing and plexi- glass between patients. We limit the number of patients and staff within the office. We have people wear masks. Patients who are on active treatment need to continue their treatment, so they've had a minimal impact on the administration.

We're cautious. There is data that suggests that patients who have a cancer diagnosis are more susceptible to the complications related to COVID-19. We take that seriously. You should decide with the patient whether it's the right thing for them to do.

Do you have any tips or advice for men who are about to go on chemotherapy, especially if they're nervous?

Dr. Fleming: Their nervousness, their fear is probably bigger than the reality. I typically can't give chemotherapy if a patient sees me too late. Patients run into complications. It's always good to have multidisciplinary input early on. There's not just one sequencing for prostate cancer. What I mean by that is, one should not necessarily always go from an oral agent like Zytiga (abiraterone), Xtandi (enzalutamide), to Provenge (sipuleucel-T), or radium. All of them need chemotherapy. It has to include mutual multidisciplinary environments from the point of diagnosis, and then the right treatment should be determined for the right time. There's clear evidence that men tolerate chemotherapy well. In my practice, the oldest patient I've given chemotherapy to is 93 years old. People think a 93-year-old can't do chemotherapy, and he did. He tolerated it well, and he responded to treatment. Talk to your physicians, not just a medical oncologist, but also your urologist. It's just getting over the myths.

Take advantage of all the options that you have. The treatment for prostate cancer continues to evolve. There are a lot of exciting things coming down the pike. Pp1

Professor Rosalind Eeles, FMedSci, PhD, FRCP, FRCR: Genomics + Chemo

Professor Eeles, who has both a private and a National Health System practice at the Royal Marsden in London, leads a program of research in genetic predisposition to prostate cancer and management of individuals with BRCA and other repair gene mutations. She is an author on over 400 papers and has edited a major textbook on genetic predisposition to cancer.

She talks with *Prostatepedia* about her clinical trial, which is looking at DNA repair defects and carboplatin chemotherapy.

What is the thinking behind the trial?

Professor Eeles: Increasingly, cancer treatments are becoming more precisely targeted at patients who are known to have a specific genetic makeup.

We know that carboplatin chemotherapy is effective in women being treated for ovarian cancer and who have inherited a mutation in a DNA repair gene such as BRCA1 or BRCA2. This trial has been designed to evaluate whether using carboplatin chemotherapy in men with advanced prostate cancer (who have completed all standard treatments) and who are known to have inherited a mutation in a DNA repair gene may also benefit from being treated with carboplatin.

What can patients expect to happen step by step?

Professor Eeles: Men who are eligible to take part are offered a genetic test (via a blood test) to see whether they have inherited a mutation in a DNA repair gene.

"All men who have advanced prostate cancer and who have completed most standard lines of treatment are eligible to take part."

For those who have a gene mutation identified, they can be offered up to 10 three-weekly cycles of carboplatin chemotherapy after all standard treatments have been completed. They are offered a bone scan and detailed CT scan before the treatment starts. We conduct regular scans and blood tests to assess whether their cancer is responding to the treatment.

Is there any specific eligibility criteria you would like to highlight?

Professor Eeles: All men who have advanced prostate cancer and who have completed most standard lines of treatment are eligible to take part.

Do you have any last comments or thoughts for patients about the trial?

Professor Eeles: Some of the genes we are testing may have implications for the wider family if a mutation is found. We ensure that all participants are referred to colleagues in a cancer genetics unit to enable the family to have genetic counselling and further genetic testing, where appropriate. This may mean that close relatives are identified as being at a higher risk of certain cancers, and screening or preventative measures can be offered. We fully support you and your family in finding out more information about any gene mutations that we find in this research. Pp[1]

Ana Aparicio, MD
Taxane Chemo + Carboplatin

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

Prostatepedia spoke with her about her clinical trial looking at Jevtana (cabazitaxel), Paraplatin (carboplatin), and Lynparza (olaparib) in men with aggressive variant prostate cancer.

What was the thinking behind the trial that you're running, and what is the context in which it's occurring?

Dr. Aparicio: We have defined a group of prostate cancers that's different from the rest in that they are more aggressive than typical prostate cancer and do not respond well to hormonal therapies. We have called them *aggressive variant prostate cancers* or AVPC. Normally, if not using hormonal therapies, we would give chemotherapy, usually a single-agent taxane, such as Taxotere (docetaxel) or Jevtana (cabazitaxel). However, we showed in a clinical trial that patients with AVPC did better if, instead of using a taxane chemotherapy alone, we added Paraplatin (carboplatin) to the taxane.

However, they didn't do well enough. They responded more than if they had just had a taxane alone. But the response, although often dramatic, was short lived. We wanted to prolong that response. We know that these aggressive cancers are characterized by functional deficits in DNA repair pathways. There's been a lot of talk about mutations in genes that are involved in DNA repair being good markers for cancers that are more sensitive to a type of drug called the poly ADP ribose polymerase (PARP) inhibitors and platinum chemotherapies. What we proposed was that even if the cancer doesn't have those genomic mutations, the aggressive clinical features and the molecular profile that we defined, also makes those more sensitive to these agents.

In the current trial, we treat patients with six cycles of chemotherapy up front. Once there is a response from the chemotherapy, under normal circumstances, we would observe, and wait for that cancer to grow again before doing anything else. In the trial, instead of just observing, we give patients a PARP inhibitor, Lynparza (olaparib), as maintenance therapy because we expect that that will make the cancer stay under control for longer. The goal is to have 96 people participate. We've had a little bit of a delay with COVID-19, but we're almost there. We're at 92 participants and, from what we have seen so far, it does seem to be a strategy that works well for some people. We asked patients to allow us to take biopsies before and after the chemotherapy to get at the molecular determinants of response to these therapies so that we can add other therapies that can make these combinations even more effective.

While the addition of the PARP inhibitor may delay the growth of these aggressive tumors further, we still have a way to go. Patients eventually still progress, and we want to do better. We know that both chemotherapy and PARP inhibitors have an immunomodulatory effect. We think of them as drugs that simply kill the cancer cells, but they also do something to the immune system. They may be working by activating the immune system. For example, as cancer cells die, they might release more signals that activate the immune system to make it attack the cancer. So, we took a page from some of the other tumor types, like small cell lung cancer and triple negative breast cancer, which are similar to aggressive variant prostate cancers and decided to combine our chemotherapy-PARP inhibitor combo with an immunotherapy in a follow up to

this trial, which should be opening in September. In this upcoming clinical trial, patients with AVPC will receive one cycle of Jevtana (cabazitaxel) and Paraplatin (carboplatin), undergo a tumor biopsy, and then receive another five cycles of both chemotherapies together with an anti-programmed cell death protein 1 (PD-1) immune checkpoint inhibitor. After two cycles of all three drugs given together, we will ask for another tumor biopsy, to see whether the anti-PD-1 helps the chemotherapy be more effective in stimulating the immune system. Once the patient has completed 6 cycles of chemotherapy (5 of them with the anti-PD-1, they are randomized to maintenance with a PARP inhibitor alone versus a PARP inhibitor with the anti-PD-1 to find out how the PARP inhibitor modulates the immune tumor microenvironment in the maintenance setting and whether adding the anti-PD-1 to the PARP inhibitor in the maintenance setting helps it work better. This is somewhat different from other trials that are looking at the combination of an anti-PD-1 with a PARP inhibitor from the start, not in the maintenance setting, after chemotherapy induction. It may be that in maintenance, you no longer need the anti-PD-1 or that you do, because it helps to maintain that response for a longer period of time. In any case, our biospies will help us determine the contribution of the anti-PD-1 and will allow us to find new targets that guide further combinations, which we hope, will eventually lead to cures.

What's the side effect profile like since you keep adding agents?

Dr. Aparicio: Since we're sequencing them instead of putting them all together, it's tolerable. In the clinical trials with chemotherapy plus immunotherapies (anti-PD-1 or anti-programmed death-ligand 1 [PD-L1] antibodies), they didn't see excess or unexpected toxicity. Patients had the side effects from chemotherapy that you would expect and the side effects from the anti-PD-1 or PDL-1 that you would expect, but there wasn't more toxicity from either when they were given together. This is not surprising since they have such different mechanisms of action. It's not like you're putting five chemotherapy agents together which might cause the nausea to go through the roof for example.

"We give patients a PARP inhibitor as maintenance therapy."

What is the eligibility criteria for both trials?

Dr. Aparicio: Patients must have AVPC, and let me explain a bit better what that means. If you're in clinic, people walk in and there are clinical features that are associated with poor outcomes and poor responses to hormone therapies, and these clinical features are often associated with histological variants of the disease. A histological variant is a type of cancer that grows in the prostate, for example, but does not look under the microscope like a prostate cancer. Small cell or poorly differentiated neuroendocrine prostate carcinomas and sarcomatoid prostate carcinomas are rare histological variants of prostate cancer. It so happens that they often present with a clinical behavior that is unusual for garden variety prostate cancer (for example, large bulky tumor masses are unusual in typical prostate cancer but are frequently present in men with these rare histological variants). These rare histological variants don't respond well to hormonal therapies and they have poor outcomes since we don't have good therapies specific to them.

What we realized is that 9 out of 10 times, these atypical and aggressive clinical features are present but when we do a biopsy, we don't find the expected histological variant under the microscope. And we realized that if you had the atypical and aggressive clinical features, your disease was highly likely to behave as though you did have a histological variant. So, we put together a list of seven of these clinicopathological features that are atypical and associated with the aggressive histological variants and selected patients based on these criteria for a clinical trial to show that the presence of at least one of these aggressive clinicopathological features indicated that you were highly likely to benefit from the combination of a taxane and a platinum as I described earlier. We then took tumor samples donated by our patients, and arrived at a molecular profile that characterizes these aggressive variant prostate cancers. This molecular profile consists of having combined defects in at least two of three tumor suppressors: p53, retinoblastoma (rb), and PTEN. You can have alterations in those tumor suppressors by a variety of mechanisms, and not all of the alterations have the same functional output. We're working to refine and be more specific about what can be considered a "defect" in these tumor suppressors.

So, to be eligible for these trials, a patient must have at least one of the atypical clinicopathological

features and/or the presence of the molecular profile of the AVPC. These clinical pathological features include things like, a response of less than six months to hormone deprivation therapies or the presence of a large, bulky, primary tumor, which are unusual for prostate cancer. Prostate cancer generally goes to the bones, and results in round, sclerotic bone metastases. But it does not typically give large lymph nodes or very large prostate metastasis. Another example is if there is disease growing in the liver or in a lymph node but the PSA is not going up proportionally. That's also unusual for prostate cancer. Or mostly lytic bone disease, meaning more of a destructive kind of bone metastasis, in contrast to the typical sclerotic bone metastases of prostate cancer.

What impact has COVID-19 had on this trial and any other trials that you're running?

Dr. Aparicio: This clinical trial required biopsies at baseline and biopsies after six cycles of chemotherapy. We weren't able to do those. However, we kept the clinical trial open since, when someone has AVPC, this is a chemotherapy that we would be recommending regardless. It's all about weighing the risks vs the benefits. If you have AVPC, the benefit of starting you on chemotherapy outweighs the risk of the COVID-19 situation. If you have aggressive variant features, most of the time we're going to give you this chemotherapy (a combination of platinum and taxane) whether on trial or not, so we kept the study open. There were some patients who we would have started right away on the chemotherapy had there not been COVID-19, but we felt that in their particular case it was too risky and it was better to wait a bit before starting chemotherapy. So, we have had some delays, but we did keep it open and did have a few people get started on it since we would have treated them anyway with this chemotherapy regimen.

People didn't pull out of the study, but less people were willing to travel to get started on it. Since the chemotherapy portion of it is just standard chemotherapy, it's not new drugs, people who were already on it were able to get it at home. We were able to do a lot of it at a distance. That helped significantly.

Were some of your support staff diverted to other areas for COVID-19?

Dr. Aparicio: I'm impressed by how our leadership has handled this whole thing. They've made a big effort to ramp up all the telehealth, particularly for clinical research. All of our research staff is off site, and they communicate with patients on trial remotely. They're doing a lot of remote consenting through video conference and electronic consenting. They've done a great job of making it work for everybody safely.

If a man reading this is interested in participating in either trial, who can he contact?

Dr. Aparicio: They can contact me anytime. All my contact information is publicly available, or they can go through myMDAnderson. They can request a visit or ask to contact the research team, and we'll be happy to communicate with them.

For the current trial, they can have most of their treatments at home, and there are four slots left for that one.

For the upcoming trial, the anti-PD-1 that will be used is not yet FDA-approved which means that patients will have to come down to get their treatment every 3-4 weeks throughout the trial.

"Patients must have what we have called aggressive variant prostate cancers."

This is part of a broader effort to get a classification of prostate cancer that is meaningful and that helps guide our therapy and our clinical research. We haven't made as many advances in prostate cancer since we keep lumping all of it in the same bucket, and it's just not the same disease so the effect of any new therapy that might work in one subset but not another, gets diluted. There are some prostate cancers that behave like a chronic disease, even metastatic prostate cancers that are truly like a chronic disease and respond beautifully to hormone therapy for a prolonged period of time. The question for those is, how do we limit the time on hormone therapy? Hormone therapy has its toxicity. Can we arrive at a combination that will get rid of it completely? In contrast, for the "AVPC, we need to find more effective therapies. That's why separating them is so critical. Pp1

Patients Speak
My Experience with Chemo

Gabriel Rosko spoke with *Prostatepedia* about his prostate cancer journey and experiences with chemoterhapy.

What was your life like before you had prostate cancer?

Gabriel Rosko: At the time, we were living in Califon, New Jersey. We had a nice, comfortable home at the top of a hill. We could overlook a lot of the scenery in the little, rural town of Califon.

I've been in business for myself for a long time. I'm a financial advisor, and we do other financial products. We are still in business. We're still doing things today, working. I'm 78, so sometimes I wonder why, but it is what it is. I just do what I do, and I enjoy it. There's no pressure anymore to make money, get more clients or recognition or anything like that. I take care of the people I already have. My wife is Sheila and it's a great marriage, a lot of fun.

"I shook, literally, like the adrenaline was pumping through my body uncontrollably."

I was kind of oblivious to prostate cancer, never knew what it was. It took me a long time to figure out what prostate-specific antigen (PSA) meant. This was 23 years ago. In those days, there was a deal in New Jersey that if you had medical insurance, you could get a physical for no cost. Now, that's common, but that wasn't as common back then.

This was in December, and I said, "You know what? I'm going to go get a physical." I had a full physical and went to visit my parents down in Florida. I came back and the doctor told me, "Boy, your PSA is 25." I didn't know what it was. He said, "There's a possibility

of cancer there." So I had to go and find a urologist, and my friends referred me to a guy down in Somerville, New Jersey. Dr. Anthony Catanese.

They did a biopsy. On the 16th of January, my son's birthday party, the doctor called and said, "Well, your biopsy was positive. You have prostate cancer." I remember I shook, literally, like the adrenaline was pumping through my body uncontrollably. Like if you just missed an accident, you know. For the split second after you missed the accident everything's fine. You feel fine. But the second after that, all of a sudden you start shaking. I literally shook for about 30 days.

I did a lot of investigating, went to New York, called up all my friends, shared it with them. I wasn't ashamed about the cancer that I had. I wanted their input. It was different than it is today. There was not a lot of support out there, not a lot of information. I went to three or four different places, and then I finally decided to have a radical prostatectomy by the urologist that I went to see first. And I did.

We had a great life. We still have a great life with this "cancer" hanging over our heads.

So you had surgery, and then when did you end up getting chemotherapy?

Gabriel Rosko: My PSA was low after the surgery for about five years. Then it started to rise again, and it was recommended that I have radiation therapy. So I had radiation therapy at Chilton Hospital in Wayne, New Jersey.

I felt nothing. And my PSA went down for about another four years. Then it started rising again.

Then, I went down to see Dr. Myers. I likened him to an artist. Rather than just the pure science, he would try different things. So I did. I tried different things. It was working. My PSA would go up a little bit, down a little bit, up a little bit, down a little bit. We managed that way for a few years. Then, I was put on Lupron (leuprolide). That would reduce the PSA, and then it would go up again. I would take more Lupron (leuprolide). We did that for 10 years, which brings us up to 2018.

"We have a great support group; not only our family, but our friends that are there for us and support us."

Then I had a full PET scan, and they discovered that I had a couple of hot spots, one in my hip and one on my spine. They weren't sure about the one on my spine. They were pretty sure about the one on my hip. And then they also had another one in my lymph node. So I had metastatic prostate cancer, but now what to do?

I started to research immunology on my own since I figured immunology would be best. I discovered this guy, Charles Drake, at New York Presbyterian Hospital.

He told me, "Immunology really isn't working in prostate cancer at this time, but what we should do is give you chemo." So I started chemotherapy in 2018.

The most difficult part of the chemotherapy was getting into the city and parking. I didn't feel a thing. I got nauseated several times, but never threw up, just felt nauseated.

I was on Taxotere (docetaxel) for six cycles, and it wasn't bad at all. I would go in on a Tuesday. I had a golf match the next day, Wednesday, and I played one of the best golf games I've ever played. After that, my PSA was low. They put me on Zytiga (abiraterone) for all of 2019.

Then I talked to Dr. Drake and I said, "I don't want to be on Zytiga. I don't want to be on this. I want to try something different." I had been researching another program, Bipolar Androgen Therapy (BAT). It's where they give you no treatment. They try to rid your body of any hormones and allow your cancer, essentially, to grow, and then bombard your cancer with testosterone. The theory is that it'd be like you've starved the cancer. The cancer grows on testosterone, and you've been starving it for all this time, and then when you bombard it with testosterone it doesn't know what to do with it and it could kill itself.

So that's where I am right now. I've been off of Zytiga and any other cancer drugs since October, and my PSA is steady at around two. I'm waiting for my PSA to go up so that they can start giving me the testosterone.

How often are you getting your PSA checked?

Gabriel Rosko: I have to go in every six weeks.

Have you had any nervousness about going in to get your PSA checked because of COVID-19?

"I was on Taxotere (docetaxel) for six cycles, and it wasn't bad at all."

Gabriel Rosko: Well, no. Not at all. I have another problem. I have Lyme Disease. We live on a farm. We have 36 acres. We live in the woods here and fields. I've taken antibiotics every year for the last 25 years, whether I needed it or not. If I had a tick on my body around here, they just give you the antibiotic. But this past March, I had a tick bite, so they put me on doxycycline. I was on that for 60 days. Everything was fine, but as soon as I got off of it, my arms and legs started aching. My fingers are stiff. I'm on amoxicillin right now. We'll have to see what happens.

Do any of those medications impact PSA?

Gabriel Rosko: I don't know. I couldn't tell you. I told Dr. Drake what was going on. He said, "You want to get rid of the pain? Take the prednisone." So I took prednisone for eight days, felt great, but prednisone reduces your immune system so that your immune system is no longer attacking the bacteria. So you don't feel the pain but you have a reduced immune system, which is not good. You can do it temporarily, and that's what I did, just temporarily.

Do you have any thoughts or advice for men who are about to go into chemotherapy?

Gabriel Rosko: Sheila was diagnosed with lymphoma last year, so she

finished her chemotherapy back in November. We've managed both my situation and Sheila's situation by doing a lot of work on being human. We're not afraid to share ourselves. We lead a reasonably healthy lifestyle as far as food and exercise are concerned. We have a great love for ourselves and our family. We've been together 40 years. We have five children and 11 grandchildren. We have a loving family. That has helped us a lot as far as coping. Sometimes, we do have our fears. We're going to die. We want to live into our 90s. I'm 78, Sheila's 76. We have a great support group; not only our family, but our friends that are there for us and support us. Looking back, I think they've helped a lot, a great deal.

We've contributed to prostate cancer. I'm the president of the Prostate Cancer Coalition of New Jersey. We support other men and their families with prostate cancer. We get phone calls all the time. I didn't have a support group when I was diagnosed, and I wanted to provide that for other men.

How do you feel the telemedicine is working right now?

Gabriel Rosko: I think it's fine. I think it's terrific. If I want to go and see Dr. Drake, I have to drive 60 miles into New York City. It's a pain in the neck getting there. It's a pain in the neck parking. It's expensive. What happens? He looks at your test results, talks to you a little bit, takes your blood pressure, and chats. You can do that right here and now. It's not a big deal. I've just seen him twice in the last six months. It saves me a lot of time, some money, and aggravation going into New York. Pp1

JEVTANA®
(cabazitaxel)
injection

Combat advanced prostate cancer after treatment with docetaxel.

Not an actual patient

JEVTANA helped men **live longer***

Living for today
LOOKING FORWARD to tomorrow

***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.

INDICATION

JEVTANA (cabazitaxel) is a prescription medicine used with the steroid medicine prednisone to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body, and that has worsened (progressed) after treatment with other medicines that included docetaxel.

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

IMPORTANT SAFETY INFORMATION

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

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.

  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 on 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.
- **Severe stomach and intestine (gastrointestinal) problems.**
  - **JEVTANA can cause severe vomiting and diarrhea, which may lead to death.** 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. **You may need to go to the hospital for treatment.** 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, which may 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, decrease in the amount of urine that your body makes each day or blood in your urine.
- **Inflammation of the bladder and blood in the urine**. Blood in the urine is common with JEVTANA, but it can also sometimes be severe. Some people who have had pelvic radiation in the past may develop inflammation of the bladder and blood in the urine that is severe enough that they need to be hospitalized for medical treatment or surgery. Your healthcare provider will check you for these problems during treatment with JEVTANA. Your healthcare provider may stop your treatment with JEVTANA for a short time, or permanently, if you develop inflammation of the bladder and bleeding that is severe.
- **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 of full Prescribing Information on the following pages.

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), or you have severe liver problems.

What should I tell my HCP before receiving JEVTANA?

Before receiving JEVTANA, tell your HCP if you:

- are age 65 or older
- had allergic reactions in the past
- have kidney or liver problems
- have lung problems
- are pregnant or plan to become pregnant. JEVTANA can cause harm to your unborn baby and loss of pregnancy (miscarriage).
- 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 the last 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 most common side effects of JEVTANA?

The most common side effects of JEVTANA include:

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

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 the FDA at 1-800- FDA-1088.

Please see Brief Summary of full Prescribing Information on the following 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
  - feeling dizzy or faint
  - chest or throat tightness
  - skin redness
  - breathing problems
  - swelling of your face
- **Severe stomach and intestine (gastrointestinal) problems.**
  - **JEVTANA can cause severe vomiting and diarrhea, which may lead to death.** 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. **You may need to go to a hospital for treatment.** Your healthcare provider will prescribe medicines to prevent or treat vomiting and diarrhea, as needed, with JEVTANA.

    Tell your healthcare provider right away if you develop 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, which may lead to death.**

    Tell your healthcare provider if you develop 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 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 spread to other parts of the body, and that has worsened (progressed) after treatment with other medicines that included docetaxel.

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

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

- are over the age of 65
- had allergic reactions in the past
- have kidney or liver problems
- have lung problems
- are pregnant or plan to become pregnant. JEVTANA can cause harm to your unborn baby and loss of pregnancy (miscarriage).
- 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 the last 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?"**
- **Inflammation of the bladder and blood in the urine.** Blood in the urine is common with JEVTANA, but it can also sometimes be severe. Some people who have had pelvic radiation in the past may develop inflammation of the bladder and blood in the urine that is severe enough that they need to be hospitalized for medical treatment or surgery. Your healthcare provider will check you for these problems during treatment with JEVTANA. Your healthcare provider may stop your treatment with JEVTANA for a short time, or permanently, if you develop inflammation of the bladder and bleeding that is severe.

The most 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
  - weakness
  - stomach (abdominal) pain
  - 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

JEVTANA is a registered trademark of sanofi-aventis

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: March 2020

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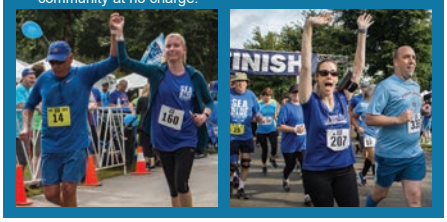

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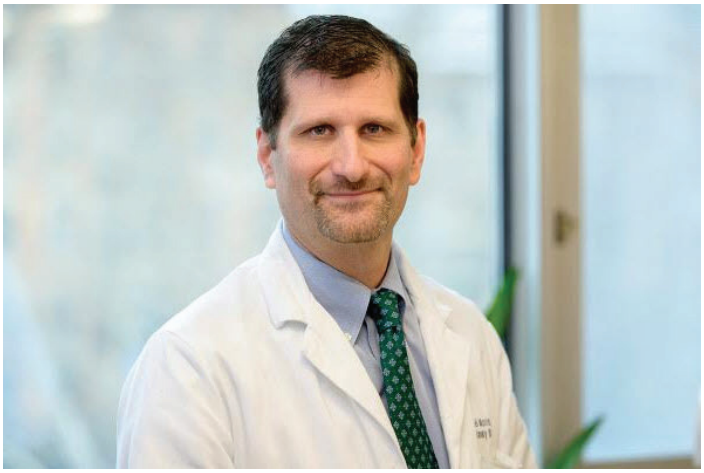

Dr. Morris is prostate cancer specialist, clinical investigator, and the Section Head of Prostate Cancer of the Genitourinary Oncology Service at Memorial Sloan-Kettering Cancer Center. He earned his medical degree from the Mount Sinai School of Medicine in New York, and performed his internship and residency in Internal Medicine at Columbia Presbyterian Medical Center. He then completed his medical oncology fellowship at Memorial Sloan-Kettering Cancer Center, where he was the Chief Fellow as well.

Dr. Morris has led numerous clinical trials, but he has a particular research focus on targeted therapy for prostate cancer, especially those that bridge the fields of Medical Oncology and Nuclear Medicine. In the field of therapeutics, he has focused on radio immunotherapy and other radio-conjugates, bone directed therapy, and other targeted therapies. In the field of diagnostics, he has a keen research interest in developing novel imaging technologies for metastatic prostate cancer and in developing novel imaging biomarkers. He has been a co-developer of the Prostate Cancer Working Group 2 and 3 Consensus Criteria, and novel prostate-specific imaging technologies such as FDHT PET and PSMA-directed PET imaging.

In addition, he is the Medical Director of the Department of Prostate Cancer Clinical Consortium, and chairs the GU Committee of the Alliance for Oncology Trials in Oncology (formerly CALGB).

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MODERATOR
William Goeren, LCSW-R, ACSW, OSW-C, SEP
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TO JOIN THIS SUPPORT GROUP, PLEASE VISIT
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NASPCC
1999 Avenue of the Stars
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California 90067
info@prostatepedia.net
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