

## Advanced Prostate Cancer and its Treatment – A Patient Guide

*UCSF Genitourinary Medical Oncology Program*

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This handout was developed to provide you with general information about the different treatments available for advanced prostate cancer at UCSF. In general, we define prostate cancer as advanced when it requires additional treatment beyond surgery and radiation. Most of the following treatment options are for patients with metastatic advanced prostate cancer. The term *metastatic* refers to prostate cancer that has spread from the prostate to distant sites, such as bones and lymph nodes. Men who have no visible evidence of cancer at distant sites, but whose PSA is rising may be offered some of these treatments; this condition is known as *rising-PSA* or *PSA-only* prostate cancer. Also, many of the terms below refer to whether or not hormone therapy has been administered, and if it remains effective in controlling the cancer. A person whose disease is responding to hormone therapy is considered to have *hormone-sensitive* prostate cancer, whereas a person whose disease is growing despite hormone therapy is considered to have *castration resistant* prostate cancer or CRPC. This term refers to cancer that is progressing despite a testosterone level that is  $\leq 50$  ng/dL, which is also called the 'castrate range'.

The UCSF Genitourinary Medical Oncology Program has a strong commitment to delivering state of the art care, improving existing treatments, and developing entirely new therapies for men with all stages of prostate cancer. We have an extensive clinical trials program that applies to virtually all patients, but not all patients treated at UCSF participate in these trials. Participation in clinical trials is not necessary to receive care at UCSF. This handout briefly describes both standard and investigational treatments for prostate cancer. We will provide more information about specific treatment options during your visit. The specific treatment options available to you will depend on the treatments you have already received and on your current medical condition.

### Hormone Therapy

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*Hormone therapy* is frequently the first treatment offered for patients with metastatic prostate cancer; it is also an option for some patients who choose not to have surgery or radiation for cancer that is confined to the prostate, and for some patients with a rising PSA after surgery and/or radiation. The male hormone testosterone causes the growth of prostate cancer, and reducing testosterone levels in the body with hormone therapy can kill prostate cancer cells. Testosterone is primarily produced by the testicles, with a small supply made by the adrenal glands. Hormone therapy, otherwise known as *androgen deprivation therapy* or *ADT*, refers to treatments that reduce testosterone levels.

There are two treatment options that reduce the supply of testosterone from the testicles. One method is to remove the testicles surgically, known as orchiectomy. This is rarely done but is an option. The other option is to start medications that stop the production of testosterone from the testicles. These include leuprolide (injection: Lupron®; implantable: Viadur®; subcutaneous: Eligard®), goserelin (Zoladex®), or degarelix (Firmagon®). These medications are as effective as orchiectomy in reducing testosterone levels and treating prostate cancer. Side effects of both surgery and the medications can include hot flashes, low sexual desire and impotence, fatigue, mood changes, muscle loss, weight gain, anemia, and in some patients on long term therapy, *osteoporosis* (thinning of the bone). To maintain bone health, we recommend that all patients on hormone therapy take calcium (500-1000mg/day) and vitamin D3 (400IU/day). In many cases blood levels are evaluated, as low vitamin D levels are common and some individuals require a higher dose of the supplement. Patients should also participate in weight-bearing exercise regularly (which also helps to maintain muscle tone and reduce fatigue). The effects of ADT on metabolism may be responsible for the increased risk of diabetes and heart disease. Given this, we strongly recommend aerobic and resistance exercise to maintain cardiovascular health, bone strength and quality of life. The impact that hormone therapies have on an individual's sex life is equally as important as the other side effects, and we hope to provide an open, supportive environment for you to discuss this if you wish; we can also refer you to our urology program for the treatment of erectile dysfunction.

In order to effectively address all of these issues we have established a program called STAND: Supportive Therapy during Androgen Deprivation. This program involves monthly visits to the center for nutrition and exercise training and evaluation sessions. We are testing whether this intense approach is feasible and whether it can help reduce some of these side effects.

You may also be started on an oral medication called an *antiandrogen*. The most common is bicalutamide (Casodex®) but may also include flutamide (Eulexin®), or nilutamide (Nilandron®). Enzalutamide (Xtandi®) and ARN-509 are also antiandrogens but are typically only used in CRPC. Currently, ARN-509 is only available on experimental protocols. These medicines block the effects of testosterone, regardless of where the testosterone is produced (testicles or adrenal glands), which can further treat prostate cancer. Most physicians who treat prostate cancer feel that these medications are equivalent to one another. Antiandrogens can make blood tests that measure liver function abnormally high, and on rare occasions may need to be stopped because of this; the liver function tests return to normal in the vast majority of patients once the drug is stopped. Therefore, we recommend checking liver tests regularly after starting any of the antiandrogen pills. Flutamide may cause mild stomach distress and diarrhea. Nilutamide can very rarely result in shortness of breath (stop the drug immediately and call us) or decreased ability of the eyes to adjust to changes in light (e.g. going from daylight into a tunnel).

There are alternative ways of administering ADT. While many patients stay on ADT continuously, some patients are treated with *intermittent* therapy. This involves an injection every 3 months with or without an antiandrogen pill, until the PSA falls to its lowest point and then for a total of 9 to 12 months. The drugs are then stopped, followed by careful PSA monitoring (usually every 1 to 3 months). When the PSA rises to a level predetermined by you and your oncologist, the medications are started again for 9-12 months at which point they are stopped and the PSA allowed to rise again, and so on. The benefit to this approach is that you will be off hormone therapy for a period of time during which you may experience less side effects. We typically do intermittent ADT in patients without metastasis. In patients with metastasis intermittent ADT is inferior therapy to continuous. Your provider will discuss with you whether you are an appropriate candidate for intermittent hormone therapy.

## The Next Step After Hormone Therapy: Antiandrogen Discontinuation

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As stated above, CRPC is diagnosed if PSA rises or new tumors develop despite the combined use of testosterone-lowering injections and antiandrogen pills, the next step is to stop the antiandrogen pills. While these medications may be effective initially in slowing the growth of prostate cancer, after a period of time antiandrogens may add fuel to the fire and feed the cancer. For this reason, approximately 10-15% of patients will have an improvement in their disease when the antiandrogen pill is stopped. HOWEVER, EVEN WHEN CRPC DEVELOPS, LUPRON, ZOLADEX, or ELIGARD SHOULD NOT BE STOPPED. In order to determine if you are having a response to antiandrogen discontinuation, PSA will be checked when you stop taking the antiandrogen and every 4 weeks thereafter. If your PSA declines or remains stable, no further treatment is undertaken until the PSA rises again. Responses to antiandrogen discontinuation last an average of 5 months, but it can last for several years in some patients.

## Castrate Resistant Prostate Cancer: After Antiandrogen Discontinuation

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If PSA continues to rise and/or tumors continue to grow after stopping flutamide, bicalutamide, or nilutamide, subsequent treatment options depend on the characteristics of the disease. There are six general categories of treatment that can be considered, which will be described briefly below; your provider will discuss with you the relative benefits and side effects of the treatments that are best medically suited for you, and provide you with additional written information. Some of our therapies are investigational in nature; hence, there may be restrictions placed by the National Cancer Institute, the FDA, or the trial sponsor, on situations in which a particular treatment can and cannot be used.

### *1. Second Generation AR Hormonal Therapy:*

**Abiraterone acetate (Zytiga®)** shuts down hormone production in the adrenal gland like ketoconazole; however, it is more effective and often better tolerated. It is taken orally once daily in conjunction with prednisone taken twice daily. In men who had previously received docetaxel chemotherapy (see below), those who were treated with abiraterone had improved survival, better PSA responses, and more shrinkage of tumors than those men who were treated with prednisone alone. Therefore, abiraterone was FDA-approved in 2011 for patients whose castrate resistant prostate cancer worsened despite chemotherapy. In 2012, abiraterone was FDA-approved for men who have not yet received chemotherapy, as a study in this group of men showed improved survival and delayed growth of tumors as well as development of new tumors in men treated with abiraterone. Side effects include increased blood pressure and fluid retention.

**Enzalutamide (Xtandi®)** is a newer and stronger antiandrogen pill, and it blocks the effects of testosterone on prostate cancer cells even in patients who have developed resistance to the other antiandrogen pills. In patients who had previously received chemotherapy, enzalutamide improved survival, PSA response, and tumor response when compared to placebo. Enzalutamide was FDA-approved in 2012 for men who have previously been treated with chemotherapy. Studies in patients who have not previously received chemotherapy are ongoing. The drug is taken daily by mouth (with or without prednisone) and is well tolerated. There were rare reports of seizures in men treated with enzalutamide, so please discuss any prior history of seizures with your healthcare provider.

Less commonly, other medications are utilized.

**Sequential use of antiandrogens:** approximately 20-40% of patients whose cancer has worsened on one of the antiandrogens may benefit from trying another one of these drugs. This approach is most suitable for patients who are not having any symptoms due to prostate cancer and in whom the PSA is rising slowly. While changing from one antiandrogen to another may provide benefit, an antiandrogen that has stopped working should not be reused.

**Ketoconazole (Nizoral®)** is another form of hormone therapy best suited for patients who have minimal symptoms due to prostate cancer, wish to be treated first with less aggressive treatment, or may be unable to tolerate more aggressive treatment. Ketoconazole works by shutting down testosterone production by the adrenal glands. Approximately 50-60% of patients will experience benefit from this therapy. Side effects include nausea, liver function test abnormalities, and mild fatigue; these will resolve if the drug is discontinued. Rarely, patients develop rashes. In addition to making testosterone, the adrenal glands balance minerals and fluids in the body by producing the hormone hydrocortisone. For this reason, all patients on ketoconazole will also receive hydrocortisone pills to replace what the body normally produces. Certain statin medications can cause serious drug interactions when taken with ketoconazole. If you are on a statin, please speak to your healthcare provider about alternative cholesterol medications that can be used safely.

## *2. Chemotherapy:*

Chemotherapy refers to drugs that directly kill prostate cancer cells. Usually, these medicines are given intravenously in our infusion clinic.

**Docetaxel (Taxotere®)** is a chemotherapy given intravenously every 3 weeks in conjunction with prednisone taken twice daily. The combination of docetaxel and prednisone has been shown to prolong survival in men with metastatic CRPC as well as in those who have newly diagnosed metastatic prostate cancer and are initiating ADT. In patients with CRPC Approximately 50-60% of men treated with docetaxel will have a significant decrease in PSA, and 20-40% will have shrinkage of measurable tumors. Side effects may include neuropathy (nerve damage that usually occurs after many doses, typically described by patients as numbness or tingling in the fingers and toes), fatigue, fluid retention, and nausea.

**Cabazitaxel (Jevtana®)** is a chemotherapy option for men who have already received docetaxel. Like docetaxel, cabazitaxel is given every 3 weeks in conjunction with prednisone taken twice daily. The combination of cabazitaxel and prednisone received FDA-approval for the treatment of metastatic hormone-refractory prostate cancer in men who have already received docetaxel, having shown improved survival in these patients. Major side effects are diarrhea, low blood counts, and impairment of the immune system that may put you at risk for serious infections. Due to the risk of infection during the time when you are neutropenic (when your white blood cell count is low, usually 7-10 days after receiving cabazitaxel), cabazitaxel is often given with a medication called Neulasta® that can boost the immune system.

There are other chemotherapeutic options than can be used after (sometimes in combination with) docetaxel and cabazitaxel. While these drugs have not been shown to improve survival, they can be effective in select patients, helping to control symptoms and eliciting objective responses in some men. Your care provider will discuss these options if they are medically suited for you.

### *3. Immunotherapy:*

These agents have the potential of stimulating your immune system to fight prostate cancer. These treatments are usually well tolerated, but may not work for everyone.

**Sipuleucel-T (Provenge®)** is a cell-based therapy that stimulates your immune system to fight against prostate cancer. Provenge must be custom-made for each patient: first, patients have their blood run through a machine in an outpatient infusion center for 2-3 hours in order to extract certain immune system cells; second, these cells are mixed with a protein that is commonly found on prostate cancer cells; finally, the mixture is returned to the patient in a 1-hour infusion, given 2 days after the immune cells are extracted. The whole process is repeated 2 more times over the course of a month. This process alerts your immune system that prostate cancer cells should be attacked as if they were foreign invaders. In clinical trials in men with hormone refractory prostate cancer, those who received Provenge live an average of 4 months longer than those who did not; some men were alive 3 years later. Interestingly, men who lived longer with Provenge did not have reductions in PSA or shrinkage of their tumors. Provenge was the first anticancer vaccine therapy to be FDA-approved in 2010. Side effects are mild, including flu-like symptoms that resolve within a few days, and rarely, allergic reactions at the time of infusion.

### *4. Radio-Isotope Therapy:*

Radio-isotopes such as Samarium and Strontium have been available in the clinic for many years but have been used only in limited settings. They had been largely replaced by the use of chemotherapy and avoided because of potential damage that they do to the bone marrow, and the fact that no isotope had ever been proven to prolong survival. Recently, however, a study with Radium-223 demonstrated that administering 6 treatments with this isotope can decrease bone related complications of the cancer as well as improve survival. These treatments are now FDA approved and are typically used in patients who have already received chemotherapy or who are not deemed healthy enough for chemotherapy. Radium-223 (known as Xofigo) is injected intravenously and hone in on areas of bone that are being damaged by the cancer. A number of studies also show that patients can concurrently receive Xofigo and other treatments such as Xtandi, Zytiga and even chemotherapy. Side effects are generally mild – the bone marrow needs to be monitored with regular blood tests and some patients have reported mild diarrhea.

### *5. DNA repair targeting:*

About 25% of patients have mutations in their tumors that make the tumor unable to repair damaged DNA. These mutations are called BRCA2, ATM and FANCC and can only be determined through a tumor biopsy. Patients with these mutations can be treated with a chemotherapy called carboplatin or with a class of drugs called the PARP inhibitors. Studies of the sequence and combination of these therapies are being tested now. The PARP inhibitor Olaparib is approved for use in breast cancer and has been shown to be very useful in the majority of prostate cancer patients who have these mutations.

### *6. Investigational Therapies:*

There are many opportunities to participate in clinical trials at UCSF. Some of the clinical trials include investigational agents, and others include the FDA-approved therapies described above, using them in novel ways or in combination with investigational agents. For example, at UCSF, enzalutamide and abiraterone are being combined and compared to enzalutamide alone.

## **Other investigational trials include:**

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- ARN-509: a new antiandrogen (like enzalutamide) that may work in men who have hormone-refractory prostate cancer; at UCSF, a study using ARN-509 instead of, or in combination with standard hormone therapy in patients with PSA-only prostate cancer is ongoing.
- Cabazitaxel: The CaMP study (Cabazitaxel plus Mitoxantrone and Prednisone) will test whether the combination of cabazitaxel and mitoxantrone with prednisone is effective and safe for patients with hormone refractory prostate cancer who have never previously received chemotherapy. There is another study that tests the combination of cabazitaxel and abiraterone in patients with hormone-refractory prostate cancer who have never previously received chemotherapy.
- LEE-011 plus Docetaxel. LEE-011 is an oral therapy that blocks CDK4/6, a protein in cancer cells that promotes the survival and proliferation of cancer cells.
- Selinexor is an oral therapy that blocks XPO-1, a pore in the nucleus of cancer cells that exports tumor suppressing proteins. The theory is that by ‘trapping’ these suppressor proteins in the nucleus of the cancer cell, it may slow the growth of the cancer.
- Ipilimumab- this is an immune therapy that works by unleashing your body’s “T” lymphocytes against cancer cells. It is FDA approved for melanoma skin cancer but not for prostate cancer. It is administered by vein and is currently being tested in combination with Sipuleucel –T.
- IL-7 – CITN Study. This is a novel immune therapy also designed to enhance the body’s natural immunity against prostate cancer. It is being tested in an experimental protocol at UCSF and several other sites nationwide.
- Listeria Vaccine- a modified form of the bacterium that causes listeriosis is being tested in advanced prostate cancer. It generates a powerful immune response that may lead to regressions of tumors.
- Bromodomain (BET) inhibitors are being tested, these may target some of the mechanisms that make the cancer resistant to hormonal therapy.
- Molecular imaging with techniques such as C-11 acetate/choline or PSMA PET scans are being researched and in some cases may alter treatment decisions, in particular in patients with a rising PSA after surgery or initial radiation.

## **Accessing and Analyzing Metastasis: Research Biopsies**

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UCSF has a large program designed to obtain biopsies from sites of metastatic disease such as the bone and liver, when available, from patients with CRPC. A large part of our research is aimed at being able to more accurately describe the types and subtypes of prostate cancer that evolve during months and years of treatment. Obtaining these biopsy tissues may eventually enable us to tailor therapies for patients. Your doctor may discuss your participation in one of these biopsy programs.

In addition to this we have a number of experimental programs designed to analyze tumor tissue that is circulating in the blood. Many of these techniques (circulating tumor cells, cell free DNA and others) are done as part of other experimental protocols.

In general, most clinical trials require that your prostate cancer is worsening to be eligible. If you are responding to a particular treatment, participation in a clinical trial might not be possible at the present time, but may be appropriate in the future. We have an extensive clinical trials program, and your care provider will discuss any trials for which you may be eligible.

Additionally, UCSF has an active and growing **Phase I/Developmental Therapeutics** program led by an experienced multidisciplinary team. In general, phase I trials evaluate the safety of new pharmaceutical compounds in a small number of patients. If you participate in a phase I trial, you will see an oncologist that specializes in phase I trials in conjunction with your current oncologist. At any given time, we have 3-7 phase I trials available, and we will discuss them with you on a case-by-case basis.

## Other Therapies

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Zoledronic acid (Zometa®) and denosumab (XGEVA®) are medications that are used to prevent thinning of the bones. They have also been shown to reduce the rate of bone-related events (e.g. fractures, bone pain, new bone lesions) in patients with hormone refractory prostate cancer who have bone metastases. Zometa is given by vein every 3-4 weeks by a 15-30 minute infusion. Side effects of Zometa include kidney damage (we check your kidney function with a blood test before every dose) and flu-like symptoms. XGEVA is given by injection monthly. XGEVA can lower calcium and phosphorus levels in your blood, so these must be checked before each dose. Both Zometa and XGEVA should be taken in combination with a calcium and vitamin D3 supplement.

Both Zometa and XGEVA can rarely cause a condition called *osteonecrosis*, or bone damage, of the jaw. If you are currently undergoing or planning dental work (routine cleaning is ok), please discuss this with your care provider.

Please note that this is a very general information document. We will be providing you with considerably more information as we discuss the treatment options that are best medically suited for you. Our primary commitment is your well-being. Please let us know if there is more information that you need. Should you have any additional questions, please feel free to contact us at 415-353-7171. Our webpage has updated listings of clinical trials and other materials of interest, and can be accessed at <http://cc.ucsf.edu/trials> (type in keywords: *prostate cancer*).

