UCSF Urologic Oncology Program
Advanced Prostate Cancer and its Treatment

An Information Handout Written for our Patients with Advanced Prostate Cancer
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This sheet has been developed to provide you with general information on the different treatments available for advanced prostate cancer at UCSF. Many of the terms describe the disease in relation to whether or not hormonal therapy (see below) has been administered. For example, a person who is responding to hormonal therapy is considered to have *hormone sensitive* prostate cancer, whereas a person who has prostate cancer that is growing despite hormone therapy is considered to have *hormone refractory* prostate cancer. We define *advanced* prostate cancer as prostate cancer that requires additional therapy beyond surgery and/or radiation. The treatment options available to you will depend on what kind of treatment you have already had and what your current condition is.

Many (but not all) of the following treatments are options for patients with metastatic prostate cancer. The term *metastatic* means that the prostate cancer has spread (or *metastasized*) outside of the prostate to a distant site, such as bone or lymph nodes. Patients who have no evidence of disease at distant sites but whose PSA (prostate specific antigen: a blood test which is usually increased with active prostate cancer) is climbing may also be candidates for some of the treatments described. The term most commonly used for this condition is *rising PSA*, or "PSA-only" Prostate Cancer.

Throughout this handout we discuss both standard and experimental treatments for prostate cancer. At the UCSF Urologic Oncology Program, we have a strong commitment to delivering state of the art standard care for patients with all stages of prostate cancer, improving the effectiveness of existing therapies and developing entirely new therapies for this disease. We have an extensive and very active research clinical trials program that applies to virtually all patients. While we may discuss participation in clinical trials with you, not all patients treated at UCSF participate in these trials and participation in a clinical trial is not necessary to receive care at UCSF. Please note that this is only a very general information sheet, and that new treatments are continuously added to our list. We will be providing you with considerably more information as we discuss your treatment options.

I. Hormonal Therapy for Prostate Cancer

Hormone therapy is frequently the first treatment offered for patients with metastatic disease, for some patients who choose not to have radiation or surgery, and for some patients with a rising PSA after radiation or surgery. The male hormone testosterone causes the growth of prostate cancer, and elimination of testosterone with hormonal treatments can kill prostate cancer cells. Testosterone is mostly produced by the testicles, and a smaller supply comes from the adrenal glands (glands that sit on top of the kidneys). "Hormonal therapy" refers to

treatments designed to reduce the amount of testosterone that enters the prostate cancer. Another term for "hormonal therapy" is "androgen deprivation therapy" (ADT).

There are two treatments that reduce the supply of testosterone from the testicles to the prostate tumor. One method is an orchiectomy, or the surgical removal of the testicles. The other is an injection of leuprolide (Lupron®), goserelin (Zoladex®), implantable leuprolide (Viadur®), or subcutaneous leuprolide (Eligard®) medications that stop the production of testosterone. These injections are available in 1, 3, 4, 6-month and 1 year preparations. The efficacy in controlling prostate cancer is the same for all of the injections as it is for orchiectomy. Side effects of both orchiectomy and the injections can include hot flashes, and, in virtually all patients, low sexual desire and impotence (inability to have an erection). There can be fatigue, muscle loss, weight gain, anemia (a lowering of the red blood cells which can contribute to fatigue), diabetes, and in some patients on long-term therapy, osteoporosis or thinning of the bone. There are some medications that may help decrease hot flashes. Medications also exist to treat anemia and osteoporosis. We generally recommend that all patients on hormonal therapy take calcium (500–1000 mg/day) and vitamin D (400 IU/day) in order to prevent bone loss. In addition, weight-bearing exercise is helpful in maintaining muscle tone, reducing fatigue and possibly slowing bone loss. The impact that hormone treatments have on an individual's sex life is equally as important as other side effects, and we hope to provide an open, supportive environment for you to discuss this if you wish. If desired, we can refer you to our urology program for treatment of erectile dysfunction.

In addition to the injections or surgery, you may also be started on an oral medication called an antiandrogen, which includes flutamide (Eulexin®), bicalutamide (Casodex®), or nilutamide (Nilandron®). These medicines block the effects of the male hormone testosterone on making prostate cancer cells grow, regardless of where the testosterone is produced (testicles or adrenal glands). Most physicians who treat prostate cancer feel that Eulexin, Casodex, and Nilandron are equivalent. These drugs may also be used sequentially (e.g., nilutamide after bicalutamide) if one drug becomes ineffective.

The side effects from Eulexin may include mild stomach distress, such as diarrhea. Eulexin, Casodex, and Nilandron can make blood tests that measure liver function (liver enzymes) abnormally high, and, on rare occasion, the drug may need to be stopped because of this. The liver enzymes return to normal (in the vast majority of patients) once the drug is discontinued. Because of this, we recommend checking blood tests that measure the liver enzymes one month after starting Eulexin, Casodex or Nilandron, and then at least once every 3 months. Diarrhea and abnormalities in liver enzymes occur in less than 5–10% of patients. Nilandron will very rarely result in shortness of breath (stop the drug at once and call us) or decreased ability of the eyes to adjust to changes in light (i.e., going from daylight into a tunnel).

Although many patients stay on androgen deprivation therapy continuously, some patients are treated with *intermittent* therapy. This involves taking a shot (Lupron, Zoladex or Eligard) plus a pill (Eulexin, Nilandron or

Casodex) until the PSA falls to its lowest point and for a total of 9 to 12 months. The drugs are then stopped, followed by careful PSA monitoring (usually once every 1 or 2 months). When the PSA starts to climb and reaches about half of the previous highest PSA level, the drugs are started again until the PSA falls again, and so on. The benefits to this approach include being off hormone therapy for a period of time, and possibly prolonging the time to when the cancer becomes resistant to hormones. While we have considerable experience with this approach, it remains unproven.

Alternative ways of administering hormonal therapy are also utilized. When Casodex is given at a high dose (3 pills a day instead of 1), some studies have shown that it may be equivalent to the use of a Lupron shot plus low-dose Casodex. These studies suggest that there may be fewer side-effects with this approach, although confirmatory studies are needed. The combination of Eulexin or Casodex plus finasteride (Proscar) has also been shown to be very effective in lowering PSA in patients without the use of Lupron, Zoladex, or Eligard. These approaches are generally not used in patients with metastatic prostate cancer.

II. The Next Step After Hormonal Therapy: Eulexin/Casodex/Nilandron Discontinuation

If the PSA rises despite the combined use of a shot plus an antiandrogen pill, the next approach will be to stop the pill (Eulexin, Casodex or Nilandron). Although Eulexin, Casodex or Nilandron may be effective initially in slowing tumor growth by blocking the action of testosterone on the tumor, after a period of time (usually more than 6–8 months) the Eulexin, Casodex or Nilandron 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 Eulexin, Casodex, or Nilandron is stopped. However, Lupron, Zoladex, or Eligard injections should never be stopped. Improvement in the disease is usually manifested as a decrease in PSA, usually within 4 to 8 weeks of discontinuation of Eulexin, Nilandron or Casodex. In order to determine if you are having a response, a PSA will be drawn around the time you stop taking Eulexin, Nilandron or Casodex, and then every 3–4 weeks. If your PSA declines or remains stable, no further treatment is undertaken until the PSA starts to climb. PSA levels are usually checked monthly. Responses to Eulexin, Nilandron or Casodex discontinuation last an average of 5 months, but in some patients responses have lasted for several years.

III. Options After Stopping Eulexin/Casodex/Nilandron

If the PSA continues to rise and/or tumors continue to grow after stopping Casodex, Eulexin, or Nilandron, treatment options again depend on certain characteristics of your disease. Three general categories of treatment can be considered: 1) additional hormonal therapies, 2) investigational therapy, and 3) chemotherapy. Some of the therapies available are described in this handout. We will discuss with you the relative benefits and side effects of each therapy, and provide you with additional written information about the therapies you are interested in pursuing. Which therapy is best for you will depend on your wishes and the therapies medically best suited for you. In addition, since some of our therapies are investigational in nature, there may be restrictions placed by the

National Cancer Institute, the FDA, or the sponsor of the trial, on situations in which a given treatment can and cannot be used.

1. ***Additional Hormone Therapy***

A) Sequential Use of Eulexin, Casodex or Nilandron. Around 20–40% of patients whose disease has worsened on one of these medications may benefit from trying another one of these drugs. These approaches are best used when the PSA is rising slowly. Results, if any, are generally seen within 1–2 months. While changing from one type of antiandrogen pill to another may be of benefit, once one antiandrogen pill is stopped, it should not be re-initiated.

B) Ketoconazole (Nizoral®) is another form of hormonal therapy, which is ideal for patients who may be unable to tolerate more aggressive treatment, who have minimal symptoms, or who wish to be treated first with less aggressive treatment. Ketoconazole works by shutting down testosterone production by the adrenal glands. About 50–60% of patients will benefit from this therapy. This therapy is relatively easy to take (pills) and has modest side effects. About 15% of patients have nausea, and 5% will have abnormalities of blood tests that measure the liver's function (liver enzymes), although both resolve if the drug is discontinued. Rarely, patients will develop rashes. Many patients on ketoconazole notice a sensation of sticky skin, and a mild increase in fatigue is common. In addition to making testosterone, the adrenal glands serve to balance minerals and fluids in the body by producing the hormone hydrocortisone. For this reason, all patients on ketoconazole also receive hydrocortisone (two pills in the morning and 1 pill at night) to replace what the body normally produces. There are usually no side effects from the hydrocortisone. While taking ketoconazole, patients must not take certain "statin" cholesterol drugs (e.g., Lipitor, Pravachol, or Zocor) since there can be serious adverse drug interactions of these medications with ketoconazole. If you are on a cholesterol medication, please talk with your healthcare provider prior to starting ketoconazole because there are alternative cholesterol medications such as fluvastatin (Lescol), rosuvastatin (Crestor), or ezetemibe (Zetia) which do not interact with ketoconazole.

C) Diethylstilbesterol (DES). DES is an estrogen pill that has been found to be effective in treating prostate cancer after conventional hormones have stopped working. While it is generally well tolerated, breast enlargement and nipple tenderness are common. Because a small percentage of patients (5–10%) develop blood clots while receiving DES, a low dose of Coumadin (a blood thinner) is usually administered as a pill along with DES in order to prevent this. DES is not available at pharmacies and requires a special mail order. It is not recommended for patients with prior blood clots, strokes, or heart attacks.

D) Steroids. Steroids such as prednisone and dexamethasone are active against prostate cancer for some individuals. They are especially useful when used alone in patients with bone pain or weight loss, and are also used as part of chemotherapy combinations.

2. ***Investigational Therapies***

There are many options for participation in clinical trials at UCSF. In general, most clinical trials require that there be progression of your cancer to be eligible. If you are responding to a given treatment (e.g. hormonal therapy) participation in a trial may not be possible at the present time, but may be more appropriate at a later time.

A) *Immune Therapy*. There are several agents that have the potential of stimulating your immune system to fight cancer. These treatments are usually well tolerated but it is not known how effective they are.

1. GM-CSF. Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF, or Leukine) has been shown to stimulate an anti-cancer immune response in patients with prostate cancer. GM-CSF is a growth factor for immune cells and white blood cells, and is identical to a protein your body naturally makes in smaller quantities. GM-CSF is injected under the skin using a small insulin syringe daily for 14 days, followed by a 2-week break. Side effects can include back pain and reactions like welts at the site of injection, both of which last only a few days. In a current study, we are adding anti-CTLA-4 antibody (see below) to GM-CSF therapy to see if the combination is more potent. We are also looking at the effects of GM-CSF in patients who are about to have a radical prostatectomy. The purpose of this study is to determine if the GM-CSF stimulates an immune reaction against the cancer within the prostate gland itself. Finally, as described in the chemotherapy section below, we are testing GM-CSF in patients who have already received chemotherapy, as a way of prolonging the time before chemotherapy needs to be re-started.

2. Anti-CTLA-4 Antibody (Ipilimumab). T cells are powerful immune cells that can attack prostate cancer. Normally, prostate cancer cells are not strongly identified by T cells as targets for attack. This is due to the presence of certain inhibitors on T cells, which act as a brake on their ability to kill cancer cells. One of these brakes is the CTLA-4 protein. By blocking the function of this protein with an antibody (anti-CTLA-4) the brakes on the immune system are released, and T cells may target the prostate cancer more effectively. Anti-CTLA-4 therapy is usually injected by vein every 4 weeks. Patients with any pre-existing autoimmune disorder (such as rheumatoid arthritis, lupus, psoriasis, or vasculitis) cannot receive anti-CTLA-4, as it is possible that treatment with anti-CTLA-4 will make those conditions worse. Anti – CTLA-4 therapy is being combined GM-CSF (described above) in patients with metastatic hormone refractory prostate cancer in patients who have not yet been treated with chemotherapy. In patients who have already been treated with chemotherapy, we also have a study combining anti-CTLA-4 therapy with radiation to an area of the bone involved with prostate cancer.

B) *Growth Factor Inhibitors*

While prostate cancer is very sensitive to stimulation by the male hormone testosterone, a variety of other growth factors are able to cause prostate cancer growth. The insulin-like growth factor (IGF-1) is a hormone

that is normally produced in everyone but which has also been shown to stimulate prostate cancer growth. NDGA (short for meso-Nordihydroguareacetic acid) is an IGF-1 inhibitor pill that we are evaluating in patients with a rising PSA. We are also conducting a study with a drug called Sandostatin administered as an intramuscular injection every month. Sandostatin has been shown to reduce levels of IGF-1 in the blood. In addition, an antibody called IMC-A12 that blocks the action of the IGF-1 receptor is also available as part of a clinical trial. Another drug, AMG102, blocks the action of a growth factor called human hepatocyte growth factor (HGF), which is thought to have multiple important roles in cancer growth. This drug is given by vein once every three weeks in combination with chemotherapy (Mitoxantrone) to patients who have already had chemotherapy.

C) *Hormonal Therapy*

We are developing an investigational drug called Abiraterone acetate, which has many features similar to ketoconazole and also appears to shut down testosterone production by the adrenal glands, but may be slightly easier to take. It appears to be at least as effective as ketoconazole. Abiraterone appears to have side effects that are different from ketoconazole (e.g. it does not cause nausea but may increase the blood pressure), and may also work in situations in which ketoconazole has stopped working. Abiraterone acetate is being tested in patients with prior ketoconazole treatment who have not had chemotherapy and in patients with no prior ketoconazole who have already received chemotherapy. We are also evaluating a new investigational drug called HE3235, which also appears to shut down testosterone production by the adrenal glands. Like Abiraterone, HE3235 may also increase the blood pressure. This drug will be tested in patients who have already had chemotherapy.

D) *Anti-Angiogenesis Therapy*

This refers to treatment targeted at stopping new blood vessel formation (angiogenesis), which is necessary for cancer growth. We are evaluating several of these agents. One is called bevacizumab. It is FDA-approved for use in multiple other types of cancer but not for prostate cancer. It is administered by vein once every two weeks in combination with hormonal therapy for men whose prostate cancer is sensitive to hormones in an upcoming study to see if it makes the hormonal therapy work for a longer period of time.

3. *Chemotherapy*

Chemotherapy refers to drugs that directly kill prostate cancer cells. Chemotherapy can consist of *conventional* FDA approved drugs, as well as new investigational drugs.

A) *Docetaxel* (Taxotere) is a standard chemotherapy drug given by vein in the outpatient setting once every 3 weeks. Prednisone is an oral steroid which is taken twice daily. The combination of Docetaxel and Prednisone has received FDA approval for the treatment of metastatic hormone refractory prostate cancer, as it has been shown to prolong survival in these patients. Approximately 50–60% of patients will have a

significant lowering of PSA with this therapy, and 20–40% of patients will have shrinkage of measurable tumors (e.g., enlarged lymph nodes).

Patients treated with Docetaxel are at risk of developing nerve damage (neuropathy). This neuropathy is generally described by patients as numbness and/or tingling in the fingers and toes. Neuropathy usually occurs only after many doses of the medication. Some patients need to stop treatment with Docetaxel due to neuropathy. There are also medications to treat neuropathy. Docetaxel can also cause fluid retention leading to swelling of the legs, but this is usually prevented by a steroid (dexamethasone) given before and after the administration of Docetaxel. In addition, some patients treated with Docetaxel develop other side effects, such as fatigue and changes in their fingernails.

B) Intermittent Chemotherapy

The current standard method of treating patients with Docetaxel is to treat continuously (usually with every three week infusions) until the drug stops working or until side effects require that we stop. We are studying whether it is more beneficial to stop the chemotherapy when a response has been achieved (and re-starting the therapy later, when needed) or whether continuous therapy is best. In addition, we will be looking to see whether the addition of GM-CSF (an immune stimulant described above) during periods *off* chemotherapy can delay the time until the chemotherapy needs to be restarted.

C) Abraxane

Abraxane is another drug similar to Docetaxel that is administered by vein once a week. It is approved for use in breast cancer and is being evaluated on a clinical trial for use in prostate cancer. It may have less side effects than Docetaxel and is being evaluated as an alternative to Docetaxel for metastatic hormone refractory prostate cancer.

D) Chemotherapy for anaplastic prostate cancer

Anaplastic prostate cancer is a general term used to refer to a form of prostate cancer that does not respond well to hormonal therapy, spreads to organs such as the liver, as well as the form of prostate cancer known as small cell prostate cancer (neuroendocrine prostate cancer). These are rare but aggressive types of prostate cancer. We are currently studying the use of sequential intravenous chemotherapy with carboplatin plus taxotere followed by cisplatin plus etoposide in these patients.

E) Chemotherapy after Docetaxel

1. Mitoxantrone (Novantrone)

   Mitoxantrone is given by IV injection over 30 minutes in the outpatient infusion center every 3 weeks. This drug has received FDA approval for the treatment of prostate cancer. Its primary role is in

controlling pain. It is often combined with Prednisone, similar to the manner in which Prednisone is added to Docetaxel. We will occasionally combine it with Navelbine, discussed below.

2. Ixabepilone

Ixabepilone is an investigational chemotherapy similar to Docetaxel. It is given by vein in the outpatient setting every 21 days, and may work in situations where Docetaxel has stopped working. Ixabepilone can result in fatigue, and like Docetaxel, nerve damage (neuropathy). We are currently studying the combination of Mitoxantrone with Ixabepilone in which both drugs are administered by vein every 3 weeks.

3. Vinorelbine (Navelbine)

Vinorelbine is given by IV injection in the outpatient infusion center, and is usually given weekly. It is often combined with mitoxantrone. Major side effects of vinorelbine include hair loss, fatigue, neuropathy, and decreased blood counts.

4. Oral Cyclophosphamide (Cytoxan)

Cytoxan is given as an oral tablet daily. Major side effects of cytoxan include hair loss, nausea and vomiting, blood in urine, and decreased blood counts.

5. Adriamycin/Cytoxan

Adriamycin (Doxorubicin) and Cyclophosphamide (Cytoxan) are given by IV injection every 3 weeks. Major side effects of Adriamycin include fatigue, nausea and vomiting, and decrease in the ability of the heart to pump. Major side effects of Cytoxan are described above.

4. Other Therapies

Zoledronic Acid (Zometa®) is a type of medication called a bisphosphonate that is used to prevent thinning of the bones. Zometa has also been shown to reduce the rate of bone-related events (fractures, worsening bony pain, and new lesions on bone scan) in patients with hormone resistant prostate cancer who have bone metastases. We are currently investigating the role of Zometa in patients with earlier stages of prostate cancer, most notably in patients who are about to start or have just started hormone therapy for metastatic prostate cancer to bone. Zometa is given by vein every 3 to 4 weeks by a 15-20 minute infusion. There is a small risk of kidney damage, although this is minimized by checking kidney function before giving each Zometa dose. Also, 10–20% of patients develop a flu-like syndrome (muscle aches, fever, bone pain, extreme fatigue) beginning 24 to 48 hours after a Zometa infusion, which usually last 24 to 48 hours. This syndrome usually gets milder with each subsequent treatment and can be effectively treated with ibuprofen (Motrin, Advil) or acetaminophen (Tylenol®). This therapy should be taken in combination with a calcium and vitamin D supplement. Rarely, Zometa has caused bone damage in the jaw when patients undergo

dental extractions. If you are currently undergoing dental work (routine cleaning is fine) or have such work planned, please discuss this with your physician prior to starting Zometa.

Samarium (Quadramet) and *Strontium*: These are forms of radiation therapy that can be administered by a one-time intravenous injection. They can be used very effectively to reduce pain in the bones in patients who have cancer that has spread to the bones. The procedure is very similar to undergoing a bone scan. While usually an outpatient procedure, rarely it may require an overnight hospital stay.

Please note that this is only a very general information sheet, and that new treatments are continuously added to our list. We will be providing you with considerably more information as we discuss your treatment options. Our primary commitment is to your well being. Please let us know if there is more information that you need. Should you have additional questions, please feel free to contact us at 415-353-7171. Our web page has updated listings of protocols and other material of interest, and can be accessed at http://cc.ucsf.edu/trials (type in keyword *prostate cancer*).

Other useful phone numbers:
Genitourinary oncology practice front desk: (415) 353-7171
Mt. Zion infusion center: (415) 353-7108
Jay Trovato, RN: (415) 353-9268
Julie Russell, RN: (415) 353-7085