

A Pathway to Hope

ADVANCED STAGE



Arizona
UROLOGY
SPECIALISTS™



UNDERSTANDING ADVANCED PROSTATE CANCER AND TREATMENT OPTIONS

Advanced-stage prostate cancer is cancer that has spread (metastasized) beyond the prostate or has returned after treatment. While these types of cancers are often not curable, many treatment advances offer hope. Your provider may recommend several treatment options as you go through your advanced-stage prostate cancer journey that can help enhance and extend your quality of life.

New treatments for advanced prostate cancer offer many quality of life benefits. For men with advanced prostate cancer, our treatment goals are twofold:

1. To put the cancer into remission or slow its progression and symptoms
2. To allow for a continued, high quality of life with prostate cancer

REMISSION VS. PROGRESSION

While treatments for advanced prostate cancer do not “cure” you, they can be effective in putting the prostate cancer into remission. Cancer that is not in remission will progress or grow. This is measured by three factors:

1. A PSA blood test
2. New or increased size of prostate lesions on imaging
3. Symptoms that interfere with quality of life:
 - Decreased appetite
 - Unintentional weight loss
 - Bone pain
 - Nausea
 - Excessive/overwhelming fatigue

When advanced prostate cancer progresses, your care provider will typically recommend a change in your treatment plan.

GENETIC COUNSELING

It has been found that 12 to 20% of metastatic prostate cancer patients have inheritable DNA repair gene mutations that predispose them and/or their family to prostate cancer disease progression and higher risk of failure of androgen-receptor inhibitor medications (Xtandi, Zytiga, etc.). Examples of these gene mutations include BRCA1, BRCA2 (most known for breast cancer risk), ATM, and CHEK2. Our providers typically recommend that metastatic prostate cancer patients undergo genetic testing. A

typical blood draw in the office or mobile blood draws can be arranged.

If results are positive/abnormal, we will recommend a referral to a genetic counselor to discuss the implications and impact such testing has on your treatment and family members. Genetic testing can provide valuable information about how you may respond to certain treatments as well as help determine appropriate clinical research studies.

Your provider can refer you to a genetic counselor near you.

TREATMENTS FOR ADVANCED PROSTATE CANCER

HORMONE THERAPY OR ANDROGEN DEPRIVATION THERAPY (ADT)

The goal of hormone therapy or Androgen Deprivation Therapy (ADT) is to eliminate testosterone and other androgens (male sex hormones) because these molecules are the fuel that prostate cancer uses to grow.

Though not curative, hormone therapy can be effective for several years. Some men can be on it for many years, while others may only be on it for a short time before the prostate cancer grows or progresses.

When hormone therapy/ADT may be recommended:

- In combination with radiation for a better chance of cure
- For metastatic disease as initial treatment
- For a recurrence of prostate cancer following radical prostatectomy, radiation therapy, or other therapies
- For men who are not candidates for surgery or radiation therapy and are not interested in observation

There are two categories of hormone treatments:

- Medical therapy is used to stop the production of testosterone by the testicles and other androgens from the adrenal glands. There are multiple options including short and long-term injections as well as daily oral medication.

- Surgical therapy, known as bilateral orchiectomy, is performed to remove both testicles. The testicles are the main source of testosterone production.

Medications include:

- Firmagon® (degarelix) or Orgovyx® (relugolix)
- Camcevi®, Lupron Depot®, and Eligard® (leuprolide)
- Trelstar® (triptorelin)
- Casodex® (bicalutamide)

Potential Side Effects

- Hot flashes
- Loss of sex drive
- Weakened muscles
- Fatigue
- Irritability
- Bone density loss (long-term)

Prostate cancers that stop responding to hormone therapy and continue to grow despite the extremely low levels of androgen in the body are called castration (or castrate) resistant. Even though it may appear that the ADT is no longer working, your provider may continue this treatment as it may be working for some areas of the cancer even though it is not working in other areas. Stopping ADT altogether may cause all areas of the cancer to grow unchecked.



Xtandi® (enzalutamide)

When your cancer is recurrent after surgery or radiation, becomes metastatic, or is castrate-resistant (PSA rises despite testosterone being low), you may be a candidate to start Xtandi which blocks androgen receptors inside the cancer cells. Xtandi is an androgen receptor inhibitor that, in preclinical studies, has been shown to work within prostate cancer cells to:

- Induce cell death
- Decrease proliferation
- Decrease tumor volume

The drug is two pills taken once daily. In clinical studies, Xtandi reduced the risk of death by 34%, reduced the risk of starting chemotherapy by 72%, and reduced the risk of imaging progression or death by 62% more than the placebo.

Potential Side Effects

- Fatigue
- Upset stomach or other gastrointestinal side effects
- Increased blood pressure

Nubeqa® (darolutamide)

Nubeqa has shown benefit in combination with chemotherapy for metastatic hormone-sensitive patients or when the prostate cancer becomes castrate-resistant (PSA rises despite testosterone

being low) but has not spread to other areas of the body such as lymph nodes or bone. When the cancer produces its own androgens, those androgens need to bind to a receptor to have an effect. Nubeqa can block the receptors inside the cells.

In clinical studies, Nubeqa improved metastasis-free survival for 22 more months than the placebo. The drug is taken orally (by mouth) twice daily with food.

Potential Side Effects

- Fatigue
- Extremity pain
- Liver enzyme increase
- Bilirubin increase
- Neutrophil decrease
- Rash

Erleada® (apalutamide)

When your cancer becomes metastatic or castrate-resistant (PSA rises despite testosterone being low), you may be a candidate to start Erleada. Erleada works by inhibiting the androgen receptor and was shown to improve metastases-free survival by over two years compared to placebo. In clinical studies, there was a 52% reduction in the risk of distant metastasis or death and a 33% reduced risk of death. The drug is taken orally once daily.

Potential Side Effects

- Rash
- Fatigue
- Upset stomach or other gastrointestinal side effects
- Falls/fractures
- Seizure (extremely rare)

Zytiga® (abiraterone acetate)

Zytiga is an FDA-approved, once-daily oral prescription medicine that is used along with prednisone to treat men with metastatic castrate-resistant prostate cancer who previously had docetaxel chemotherapy.

While ADT decreases the blood level of testosterone to very low levels, over time the cancer cells can mutate and produce testosterone to help stimulate the growth of new cancer cells. Zytiga works to stop the production of androgens in the cancer cells so that PSA levels can decrease. Zytiga stops androgen production in the cancer cells, it also stops certain steroids from being produced in the adrenal glands. For this reason, your provider will typically use Zytiga in combination with low-dose prednisone.

Zytiga is two pills taken once daily on an empty stomach.

Potential Side Effects

- High blood pressure
- Fluid retention/leg swelling
- Low potassium levels
- Abnormal liver enzymes

Taking low-dose prednisone can prevent many of these side effects but may cause other side effects including bruising, puffiness, and a slightly higher risk of infection.

Frequent blood work and check-ups are necessary every two weeks for the first 2-3 months after first starting this medication to monitor for the above side effects.

IMMUNOTHERAPY

Immunotherapy may be used for men with advanced prostate cancer who have worsening disease on hormone therapy. Immunotherapy, including therapeutic vaccines and other biologic approaches, utilizes your immune system to selectively target cancer cells.

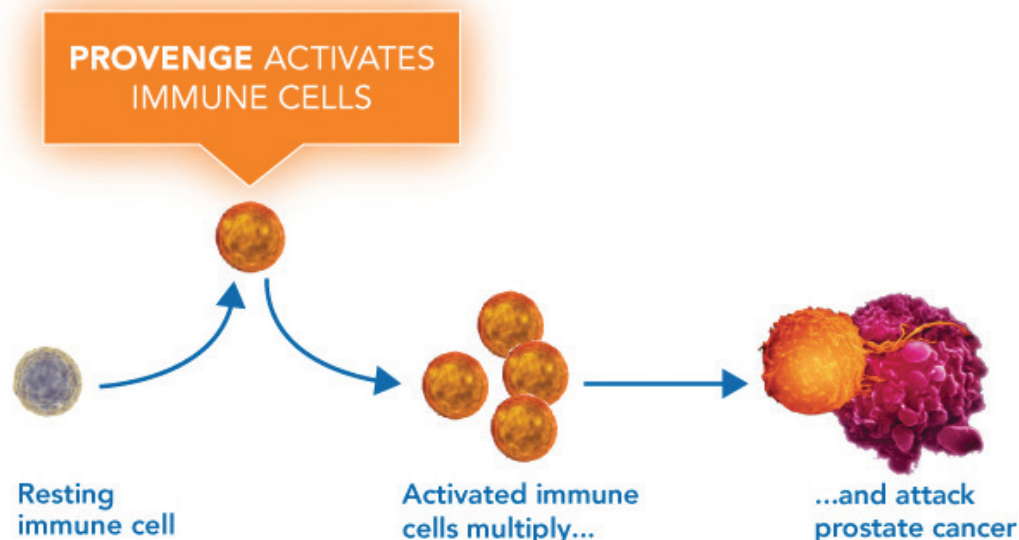
Provenge® (sipuleucel-T)

Provenge is an option for certain men with advanced prostate cancer that uses the body's immune system to fight advanced prostate cancer.

Provenge stimulates the immune system to fight cancer and is designed specifically for each individual cancer patient. Each dose consists of your immune cells that have been trained to seek and attack prostate cancer cells. Because Provenge is immunotherapy and not a chemotherapy drug you will not experience the common, sometimes difficult, side effects often experienced with chemotherapy.

How Provenge is Administered

- To make each dose, your blood is drawn through a tube to a machine that collects a small portion of immune cells from the blood sample. This process is called leukapheresis (pronounced loo-kuh-fuh-REE-sis).



- Each dose of Provenge is made just for you, using your cells. These blood cells are then mixed with prostate cancer proteins that help the white blood cells multiply and target the prostate cancer cells.
- The cells are then delivered back into your body via an IV infusion two days after they are withdrawn. This process is repeated for a total of three infusions scheduled over a four-to-five-week period.

Because Provenge uses your blood cells, there are virtually no allergic reactions or risk of damage to your organs. Once you have completed the treatment, you never need it again. It can take up to six months for the treatment to activate your immune response, so the cancer can progress in that period, which is why it is preferred to begin Provenge early in the disease process.

Potential Side Effects

- Chills
- Fatigue
- Mild fever
- Nausea
- Headache
- Joint ache

Benefits of Provenge

- In a clinical study, Provenge reduced the risk of death in men by 22.5%
- Treatment is complete after three infusions, given approximately two weeks apart
- Fewer side effects

Keytruda® (pembrolizumab)

Keytruda is for patients with specific genetic mutations. Keytruda works by blocking the PD-1 pathway to help prevent cancer cells from hiding from the immune system. Keytruda helps the immune system detect and fight cancer cells.

TARGETED THERAPY

PARP Inhibitors are a type of targeted therapy that blocks an enzyme that the prostate cancer cells need to repair themselves before they die. This type of targeted therapy kills cancer cells while sparing surrounding healthy cells. PARP inhibitors may improve survival in men with prostate cancer that does not respond to hormone therapy.

Lynparza® (olaparib), Talzenna® (Talzoparib) or Akeega™ (Niraparib/abiraterone)

For metastatic castrate-resistant prostate cancer with positive BRCA1/2, ATM, or about 15 other DNA Damage Response and Repair (DDR) positive genetic abnormalities, Talzenna reduced the risk of imaging progression or death by 55%. In patients who have progressed on Xtandi, Zytiga, or chemotherapy, Lynparza may reduce the risk of disease progression or death by 66% compared to retreatment with Xtandi/Zytiga. Lynparza reduced the risk of death by 31% in studies. Among all mutations, it showed a 51% reduction in disease progression or death.

Lynparza is a pill taken twice daily, Talzenna is taken once daily, and Akeega is taken once daily on an empty stomach with a low-dose steroid pill.

Potential Side Effects

- Anemia
- Nausea
- Diarrhea
- Fatigue
- Decreased appetite
- Cough and/or shortness of breath
- Deep vein thrombosis, severe anemia, and low white blood cell count

MEDICATIONS USED TO IMPROVE BONE HEALTH

Metastatic prostate cancer commonly spreads to the bones, where it can cause bone pain and brittle bone disease (osteoporosis). These symptoms can also arise during hormone therapy when levels of testosterone are very low. Your physician may prescribe medications that can reduce or reverse bone loss that may result from hormone therapy and minimize other complications of bone metastases.

Xgeva® and Prolia® (denosumab)

Xgeva is used for prostate cancer patients with metastatic bone disease to prevent fractures and spinal cord compression. For prostate cancer that has invaded the bones, Xgeva is given monthly to strengthen the bones. Xgeva and Prolia contain denosumab, a protein (monoclonal antibody) that works to slow down bone destruction caused by cancer spreading to the bone (bone metastasis).

Xgeva is administered once every four weeks as a single injection under the skin. Xgeva has few side effects and does not affect the kidneys, liver, or heart. However, it increases your risk of low calcium levels and falls, which is why calcium supplements are often recommended.

Prolia is used to increase bone mass in men with non-metastatic prostate cancer who are receiving androgen deprivation therapy and are at high risk for fracture. Prolia is administered once every six months, as a single injection.

Zometa® (zoledronic acid)

If you are at risk of bone density loss due to long-term androgen deprivation therapy (lowering testosterone) Zometa is a medication given by IV infusion in the arm monthly and has been shown to reduce bone fractures, radiation therapy to bone, surgery to bone, or spinal cord compression. Kidney function and calcium levels need to be monitored monthly.

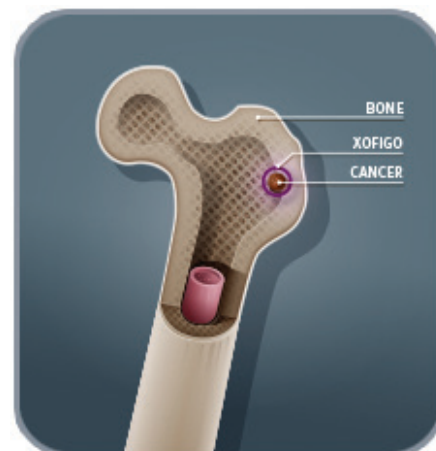
Potential Side Effects (all bone-sparing medications)

- Low calcium
- Nonhealing jaw lesions (ONJ)
- Bone pain
- Atypical fractures
- Nausea and/or vomiting
- Fatigue
- Anemia
- Constipation
- Fever
- Difficulty breathing

RADIOTHERAPY

Radiotherapy is a treatment that involves the use of CT or MRI-guided high-energy radiation to treat cancer. Radiopharmaceuticals are treatments injected to deliver targeted radiation doses where the cancer is located. The high-energy radiation used during radiotherapy permanently damages the DNA of cancer cells, causing them to die. Nearby healthy tissues may also suffer temporary cell damage from radiation but these cells are usually able to repair the DNA damage and continue growing normally. For people with incurable cancers, radiotherapy is a very effective method of controlling symptoms.

To reduce the potential damage to the rectum during radiation, a SpaceOAR hydrogel may be placed during marker placement to separate the rectum from the prostate and reduce the risk of rectal complications.



Xofigo® (radium RA 223 dichloride)

Xofigo is a therapy that is used to treat prostate cancer that has spread to the bones, is castrate resistant, and causes metastatic symptoms such as bone pain, progressive excessive fatigue, unintentional weight loss, nausea/decreased appetite, or decreased functional performance.

Xofigo contains radium 223, which is a radioactive material that targets rapidly growing cells in the bones. The radiation targets and kills the cancer cells in your bones but does limited damage to surrounding healthy cells. Xofigo is administered through a series of six injections – once a month for six months with blood work prior. The injection only takes a few minutes, and you can resume normal daily activities. Your provider will monitor your health throughout treatment, and follow-up appointments will be scheduled.

Potential Side Effects

- Mild Nausea, vomiting, diarrhea
- Anemia
- Bone marrow suppression
- Decreased kidney function

Pluvicto™ (lutetium-177 PSMA)

Pluvicto is indicated for men who have progressing disease after androgen receptor pathway inhibitors and chemotherapy seen on PSMA PET scan. It is a radiation therapy delivered by the PSMA tracer that is specific to prostate cancer. It is given by IV injection every six weeks for six doses.

Potential Side Effects

- Fatigue
- Dry mouth
- Nausea
- Anemia
- Decreased appetite
- Constipation



CHEMOTHERAPY

When prostate cancer is widespread or has progressed on previous anti-androgen medication therapies, chemotherapy has been shown to slow the progression of the disease and increase overall survival. Chemotherapy targets cells that grow and divide quickly, limiting their ability to grow and causing the cells to die. These drugs include:

- Docetaxel® (plus prednisone)
- Jevtana® (cabazitaxel)

Potential Side Effects

- Fatigue
- Extremity swelling
- Numbness and tingling in extremities (neuropathy)
- Bone marrow suppression and lowered immunity

If chemotherapy is recommended, our providers will coordinate a referral to a medical oncologist.

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