IMMUNOTHERAPY for the Treatment of Genitourinary Cancers

Sections include
- Bladder Cancer
- Kidney Cancer
- Prostate Cancer

Published in partnership with Society for Immunotherapy of Cancer
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Cancer can develop in almost any part of the body, including the genitourinary (GU) system. The GU system is made up of the parts of the body that involve the male and female urinary tract and the male reproductive organs (see Figure 1). Cells typically divide in an orderly fashion. When they are worn out or damaged, they die, and new cells replace them. Cancer develops when genes begin to change, or mutate, within the structure of normal cells. These cells — now called cancer cells — grow and push against normal cells. Sometimes they form tumors; other times, as in the case of blood cancers, they don’t. Tumors can be benign (noncancerous) or malignant (cancerous).

Cancer can metastasize (spread) to other organs, tissues, bones or blood, but it is diagnosed according to where in the body it begins. If cancer starts in the kidney, it is known as kidney cancer. If it spreads to the brain, however, it is still considered kidney cancer and treated as such. It does not become brain cancer.

Depending on a person’s type, stage of diagnosis and unique characteristics, such as previous treatments, age and general health, various options may be used to treat cancer that affects the organs in the GU system.

- **Surgery** is the removal of the tumor and surrounding normal tissue.
- **Chemotherapy** involves drugs to stop the growth of cancer cells. How it is given depends on the type and stage of the cancer.
- **Radiation therapy** is the use of high-energy X-rays or other types of radiation to kill cancer cells or stop them from growing.
- **Targeted therapy** includes drugs or other substances to attack cancer cells directly, usually by targeting a specific abnormal gene or protein.
- **Immunotherapy** activates the body’s immune system to enable immune cells to attack and destroy cancer cells.

This guide offers an easy-to-understand explanation of immunotherapy and explores several types that are approved to treat bladder, kidney and prostate cancers. Other novel treatments that are not yet FDA-approved for these and other GU cancers may be available through clinical trials as researchers continue to improve existing therapies and explore new ones. Additional strategies, such as using pembrolizumab (Keytruda) for the treatment of some solid tumors that are microsatellite instability-high cancer (MSI-H), may also be considered.

To be a candidate for immunotherapy, you must meet certain criteria, such as having a functioning immune system, not having an autoimmune disorder and not being taking immunosuppressive medications. Biomarker testing may also be a requirement because some immunotherapies are approved to treat cancers in people with specific biomarkers present.

**THE ROLE OF THE IMMUNE SYSTEM**

To better understand how immunotherapy is effective against these types of cancer, it helps to have basic knowledge about the immune system. Your body faces harmful organisms every day that could negatively affect your health. To keep you healthy, you have an immune system that works steadily behind the scenes to identify and eliminate these organisms. You are typically aware of your immune system only when an infection or irritation occurs. When a bug bites your skin, for example, you may develop an itchy, red bump. The bump is a physical sign that your immune system is working. Over a period of days, your immune system causes the reaction to the bite and heals it.

Another example is when you develop a cold. Germs can sometimes get past the natural defenses of the immune system — your nostrils, skin, saliva and mucus coating the inner linings of organs, eyes and mouth — and you may experience a cold. Your healthy immune system works to destroy the virus or bacteria that caused your illness and helps you recover.

**KEY PARTS OF THE IMMUNE SYSTEM**

The immune system is a complex network of cells, molecules, organs and lymph tissues working together to defend the body against germs, cancer cells and other microscopic invaders. The first job of the immune system is to distinguish between what is part of the body (“self”) and what is not part of the body (“non-self”). Once the immune system determines that a cell is non-self, or foreign, to the body, it begins a series of reactions to identify, target and eliminate the non-self cells.

The key driver of the immune system is the lymphatic system. The lymphatic system circulates clear fluid called lymph through the body to do several things:

- Defend the body against harmful substances, such as germs
- Fight infections
- Drain fluids in the body’s tissues from the bloodstream to help the body maintain proper fluid levels
- Filter lymph through the lymph nodes
- Filter blood through the spleen
- Identify and eliminate cancer cells

**HOW THE IMMUNE SYSTEM REMEMBERS**

Although cancer cells can be clever, the immune system has a long memory when it comes to battling dangerous cells. When your immune system encounters a virus, such as chicken pox, the memory T-cells check to see if that virus has any characteristics of cells they have attacked in the past. If they do, your memory T-cells offer you immunity from that virus, and you don’t come down with another case of chicken pox. If they don’t, the memory T-cells alert the rest of the immune system about the virus and tell it to make more immune cells to attack and keep you from getting the disease again. Memory T-cells stay alive and store this information for a long time, offering the ability to be effective long after treatment ends. Investigators believe that effective immunotherapy can result in cancer-specific memory cells providing long-term protection against cancer.
Lymph nodes, located throughout the body (with larger concentrations near the chest, abdomen, groin, pelvis, underarms and neck), circulate lymph. Although lymph and lymph nodes make up a large part of the lymphatic system, it also includes other organs, such as the skin, thymus, spleen, appendix, tonsils and adenoids. These organs collect, filter and circulate lymph. The lymph moves to the lymph node, where the foreign objects, such as bacteria, viruses, toxins and chemicals, also known as antigens, are eliminated. You may notice swollen lymph nodes in your neck, for example, when you have a cold or sore throat. Those lymph nodes swell as they work to rid your body of the infection.

Lymphocytes (white blood cells) are a major part of the immune system. They begin in the bone marrow and develop from lymphoblasts (immature cells found in bone marrow). Lymphoblasts mature into infection-fighting cells. The two main types of lymphocytes are B-lymphocytes (B-cells) and T-lymphocytes (T-cells).

Another major component is your skin, the immune system’s first barrier of protection. When you skin your elbow, for example, the barrier is broken and harmful substances can easily enter the body. Immediately after the injury occurs, immune cells in the injured tissue begin to respond. They call other immune cells that have been circulating in your body to gather at the site and release messenger proteins, called cytokines, to call other immune cells to help defend the body. This is called an immune response. The immune cells can recognize any bacteria or foreign substances as dangerous and begin to destroy them with a general attack.

HOW THE IMMUNE SYSTEM ATTACKS CANCER
Cancer develops when one or several abnormal cells divide and multiply to become a mass of abnormal cells (tumor). Mutations in DNA may cause normal cells to become abnormal or different enough from the body that the immune system may recognize the cancer cells as non-self, which may stimulate an immune response. But, because the cells started as normal cells, the immune system may still see the cancer cells as part of the body and not coordinate an attack. In this way, the tumor cells are able to “hide” from the immune system.

As you think about how cells in the body interact, it is important to know that the surface of a cell is not completely round and smooth. Instead, it contains various proteins, sugars, fats and other molecules that stick out from the cell's surface. These components contain information that is shared between cells through chemical signals and their receptors.

One of the key cells needed to stimulate an immune response is the antigen-presenting cell (APC). APCs are able to find and pick up dangerous antigens, "eat" them and prepare them to be presented to other cells by sharing the antigens on their surface to be recognized by T-cells. In this manner, the APC sounds an alarm that there is an intruder in the body, and T-cells respond to this alarm. When a T-cell encounters an APC, it changes into either a killer T-cell to fight the intruder or a helper T-cell to begin assisting or "helping" the immune response.

HOW CANCER EVADES THE IMMUNE SYSTEM
Cancer cells are smart. Over time, not only can they change, they can use multiple methods to escape or confuse the immune system. They can produce proteins on their surface that they use to hide from the immune system, like camouflage. In addition, they can create their own messengers (cytokines), which means that the cancer cells can communicate and confuse other immune cells, allowing the cancer to take control of certain parts of the process that the body uses to regulate the immune response. This means that even if the immune system recognizes the cancer, it may not be able to successfully start or maintain an attack long enough to kill the cancer cells.

The longer the cancer cells face a weakened immune response, the more they are able to adapt, and the easier it is for them to manipulate immune cells inside the tumor’s location (sometimes called the microenvironment). The microenvironment typically contains cancer cells, normal connective tissues that form the structure of the tumor and provide access to blood vessels that drive tumor growth, and several cell types that contribute to tumor development. Immune cells found in this area are often referred to as tumor-infiltrating lymphocytes (TILs). Because the tumor can control the cells in the area, the tumor can trick TILs into becoming useless or even helping the tumor grow.

For example, APCs in the tumor area may be confused by signals from tumor cells, preventing them from functioning properly and making them incapable of sounding the alarm about a threat. In some cases, tumors can increase the activity of regulatory T-cells inside the area. These regulatory T-cells are designed to end immune responses. Thus, they naturally slow down the immune system after an immune attack is completed. By increasing the activity of regulatory T-cells, the tumor is recruiting the body’s own immune cells to fight off the attack, using the very processes that normally protect the body to help the cancer cells multiply undetected.

Tumors often contain more than one type of cell, and, when a tumor changes the composition of its cells, this can confuse the immune system. The longer the immune system is exposed to the tumor, the weaker the immune response becomes. Although your immune system can kill some of the dangerous cells, it may not be able to destroy all of them or prevent them from multiplying. Certain immunotherapy agents, however, are designed to help your immune system do just that. Immunotherapy treatments offer different ways to address how tumors manipulate the immune system and how immunotherapy drugs are designed to reverse those processes.
Curtis Garbett was only 39 years old when he was diagnosed with Stage IV bladder cancer. With no family cancer history, the diagnosis was shocking. Throughout many successes and some disappointments during treatment, Curtis took a collaborative approach with his oncologist. A strong and passionate advocate for others with bladder cancer, he created the Crush It for Curtis Foundation to raise awareness and educate others about bladder cancer.

In 2015, I started urinating more frequently and was feeling more tired than usual. I didn’t think it was very serious, so I delayed going to the doctor. After the symptoms persisted for two months, I asked my primary care physician about it at my yearly checkup. The doctor ordered bloodwork, and the results showed my kidney function was really high. My doctor set up an appointment with a nephrologist for the next day.

The nephrologist said I was in acute renal failure and needed to go to the hospital right away. Not realizing the seriousness of my condition, I asked him if it could wait until Monday because I had a lot of plans scheduled for the weekend. He said absolutely not. I went to the hospital where they did an ultrasound and discovered that I had a tumor in my bladder the size of a softball.

I broke down and cried. All of the unknowns scared me. I wasn’t sure how I got this because I had no history of cancer in my family. I called my mom immediately after they found the tumor. I knew my family would be a huge support for me, but I had no idea what I was about to face.

On the following Monday, I had a transurethral bladder tumor resection (TURBT) to remove most of the tumor. On Tuesday, I had a second TURBT to try to remove any remaining tumor cells left in my bladder. The doctor was pretty confident he got all of it but cautioned me that there was a one percent chance that microscopic tumor cells could have escaped during the surgeries.

My health was great for almost a year. I had checkups to make sure nothing returned. In December 2015, my urologist reviewed the results of a routine CT and saw a spot in my lung area and in the retroperitoneal area. That’s when I was diagnosed with Stage IV bladder cancer.

I went into a daze. How could I go from having no tumor to Stage IV? I must have fallen into that one percent. I was sent to a university hospital with a strong genetics program because it was considered rare to develop bladder cancer at 39 years old. I had a biopsy to remove the spot found on my lung. The medical oncologist sent me for genetic testing, and I learned I have the FGFR mutation.

I did the standard of care 12 weeks of chemotherapy, I tolerated chemotherapy well and had some fatigue, but I didn’t have the nausea and vomiting most people think of with this treatment, and I didn’t lose my appetite. Most likely because I was also on a steroid.

My medical oncologist recommended I see bladder cancer specialists at a nearby well-known hospital. When I finished chemotherapy, they determined my tumors had melted away, and they saw no evidence of cancer. At the time, I felt like it was a miracle.

I went another year without a sign of cancer. Then in April 2017, a CT revealed another spot in my mediastinal area. Apparently, only one out of ten people has a complete response to chemotherapy for bladder cancer. So, although I thought I had beaten the odds, it turned out that I had not.

My oncologist and I discussed the available treatment options. The doctor recommended a clinical trial that was testing an immunotherapy drug in combination with a targeted therapy agent that was an FGFR inhibitor. I was accepted into the trial and started receiving this treatment. I had some unusual side effects. My eyebrows fell out, and my upper eyelashes grew very long. I had a better response rate than most, and by the end of the trial, I had a 100 percent response rate. However, the cancer returned three to four months later as tumors smaller than a pinky finger nail in my mediastinal area.

I felt very discouraged. I asked my doctor, “Now what?” And, “Are we going to run out of options?” The doctor reassured me that we had lots of options to explore. I couldn’t return to the trial, but I did go back on the immunotherapy drug that had been in the trial. At the same time, my doctor worked behind the scenes to get me approved for a drug that was only approved for kidney cancer. He was successful and added that new targeted therapy to my medication plan, which still included the immunotherapy. The biggest side effect of this treatment is fatigue.

As of May 2018, my tumors were shrinking with good results. The plan is to keep me on this combination and continue getting CTs every three months to check my progress.

Bladder cancer has a stigma and more awareness is needed. It’s the fourth most commonly diagnosed cancer today, yet people don’t talk about it. To help raise awareness, I created the Crush It for Curtis Foundation.

Don’t wait to get checked out if you notice more frequent urination or blood in the urine. Find a support group, whether it’s close family and friends or online. It’s good to talk to other cancer survivors. Because you are not alone, and always ask questions about everything, especially genetic testing and next generation molecular testing. It’s important to have a good relationship with your doctor. Researchers are discovering more about bladder cancer every day, and more new treatment options are available than ever before. Remain hopeful.
The bladder is a hollow organ in the pelvis, and its primary function is to hold urine before it exits the body. The urine travels to the bladder from the kidneys — where it’s made — through tubes called ureters. The bladder wall is flexible, enabling the bladder to hold approximately two cups (500 cc) of urine. When it’s full, the muscles in the bladder wall contract and force the urine out of the body through a tube called the urethra.

WHAT IS BLADDER CANCER?
Bladder cancer begins when healthy cells in the bladder lining, most commonly urothelial cells, change and grow uncontrollably, forming a mass called a tumor. A tumor can be cancerous or benign. A cancerous tumor is malignant, meaning it can grow and spread to other parts of the body. A benign tumor means the tumor can grow but will not spread.

The most common type of bladder cancer is urothelial carcinoma, also called transitional cell carcinoma, and it has two subtypes: papillary and flat. Papillary tumors grow from the bladder’s inner lining toward the center of the bladder, and flat tumors grow along the surface of the lining.

Other types of bladder cancer include squamous cell carcinoma, adenocarcinoma and small cell carcinoma. All three are almost always invasive.

In addition, bladder cancer tumors can be further classified as one of three types.

1. **Noninvasive bladder cancer** hasn’t yet penetrated any layers of the bladder.
2. **Nonmuscle-invasive bladder cancer** has grown into the lamina propria layer but not into muscle.
3. **Muscle-invasive bladder cancer** has grown deep into the bladder wall and possibly to tissue outside of the bladder.

**FDA-APPROVED BLADDER CANCER IMMUNOTHERAPIES**

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**IMMUNOTHERAPY FOR BLADDER CANCER**

Immunotherapy uses the body’s own immune system to treat many different types of cancer, including bladder cancer. Immunotherapy helps the immune system recognize and attack cancer cells that have been hiding and targets them for destruction, which is very different from other types of cancer treatments. Several types of immunotherapy have been approved for bladder cancer.

**Intravesical Therapy**
Bladder cancer was the first cancer type to receive an approved immunotherapy agent, which was a breakthrough for modern immunotherapy. This agent, bacillus Calmette-Guérin (BCG), was approved by the FDA in 1990 and continues to be one of the main treatments for nonmuscle-invasive bladder cancer.

BCG contains a weakened version similar to the bacterium that causes tuberculosis. It is delivered directly into the bladder through a catheter. This is called intravesical therapy (see Figure 1). BCG attaches to the inside lining of the bladder and stimulates the immune system to destroy the tumor. BCG is used for early-stage bladder cancer and as treatment to reduce the risk of recurrence in noninvasive bladder cancers, commonly after surgery to remove the tumors.

BCG is no longer the only immunotherapy approved to treat bladder cancer. More recently, other classes of immunotherapy have become available, including checkpoint inhibitors and a cytokine.

**Immune Checkpoint Inhibitors**
Several immune checkpoint inhibitors are approved to treat locally advanced or metastatic urothelial carcinoma, the most common form of bladder cancer, in people with whom disease progressed during or following chemotherapy containing a platinum drug or in whom disease progressed within 12 months after neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

To understand how immune checkpoint inhibitors work, it helps to learn about parts of the immune system. Lymphocytes (white blood cells) are a major part of the immune system. They begin in the bone marrow and develop from lymphoblasts (immature cells found in bone marrow). Lymphoblasts mature into infection-fighting cells. The two main types of lymphocytes are B-lymphocytes (B-cells) and T-lymphocytes (T-cells).

**B-cells** develop in the bone marrow and mature into either plasma cells or memory cells. Plasma cells make antibodies to fight germs and infection. Memory cells help the body remember which antigens attacked the body so it can recognize them if they return.

**T-cells** also develop in the bone marrow but travel to the thymus to mature into helper T-cells, killer T-cells, regulatory T-cells or memory T-cells. Each type of T-cell plays a part in the immune system.

- **Helper T-cells** identify foreign, or nonself, antigens and communicate with other immune system cells to coordinate with the B-cells or other T-cells for an attack.
- **Killer T-cells** directly attack and destroy cancer cells, or normal body cells infected with a virus, by inserting a protein that causes them to enlarge and burst. One type of killer T-cell specifically targets cancer cells.
- **Regulatory T-cells** slow down the immune system after an immune response is finished.
- **Memory T-cells** can stay alive for years, continuing to fight off the same invading cells. Memory is the basis of immune protection against disease in general and explains why we usually don’t become infected with some diseases, such as chicken pox, more than once.

Checkpoints keep the immune system “in check,” preventing an attack on normal cells by slowing down or eliminating activated immune cells, or through the use of regulatory T-cells that can block activated immune cells. A series of signals between the correct proteins and receptors on cell surfaces turn off activated T-cells or tell the regulatory T-cells to slow down the immune system after an immune response is finished.

To better understand how this happens, think of the proteins and receptors on a cell’s surface as puzzle pieces. Proteins have “tabs” that protrude (stick out), and receptors have...
"spaces" that curve inward. When the puzzle pieces fit together, chemicals and information are exchanged between the cells, triggering signals to slow the immune system.

- **CTLA-4** (cytotoxic T-lymphocyte-associated protein 4) is a receptor that binds with certain molecules to tell the immune system to slow down.

- **PD-1** (programmed cell death protein 1) is a receptor involved with telling T-cells to die and to reduce the death of regulatory T-cells (suppressor T-cells). Both have an effect to slow down an immune response. PD-1 can only tell the immune system to slow down if it connects with PD-L1.

- **PD-L1** (programmed death-ligand 1) is a protein that, when combined with PD-1, sends a signal to reduce the production of T-cells and enable more T-cells to die.

When PD-1 (the receptor) and PD-L1 (the protein) combine, the reaction signals the immune system that it is time to slow down. One of the ways cancer can outsmart the immune system is by producing PD-L1 (the protein) on the surface of its cells and using it to camouflage its appearance so that T-cells will think they are normal cells. When a T-cell encounters PD-L1 on a cancer cell, it sends a signal for the immune system to slow down. This is a normal way to prevent the immune system from attacking normal cells in the body.

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**Advocate for yourself, and always ask questions about everything, especially genetic testing and next generation molecular testing.**

~ Curtis Garbett, Stage IV bladder cancer survivor

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Immune checkpoint inhibitors are drugs that prevent the proteins and receptors (puzzle pieces) from fitting together and triggering the slowdown of the immune system.

When an immune checkpoint inhibitor is given, the immune system is not so easily fooled by the cancer. By not slowing down, it’s like the immune system develops X-ray vision and can see through the disguise. This keeps the immune response on and also helps the immune system recognize cancer cells as foreign cells.

The following types of immune checkpoint inhibitors are currently approved for bladder cancer:

- **Anti-PD-1 drugs**, which allow for the continued or increased activation of T-cells and enable them to continue fighting cancer.

- **Anti-PD-L1 molecules**, which allow the T-cells to see through the disguises of some tumor cells, recognize them as the enemy and attack them.

**Cytokines**

Cytokine immunotherapy is a type of non-specific immune stimulation that aids in communication among immune cells and plays a big role in the full activation of an immune response. This type of immunotherapy works by introducing large amounts of laboratory-made cytokines to the immune system to promote specific immune responses.

The cytokines approved for bladder cancer are interferons, which boost the ability of certain immune cells to attack cancer cells as well as stimulate the immune system.

Other types of treatment are also available. Be sure to talk with your doctor about which treatment options are best for you, especially since not all immunotherapies are approved for all types and stages of bladder cancer.

**COMMON SIDE EFFECTS**

Like other cancer treatments, immunotherapy may have side effects (see *Side Effects*, page 13). Because these drugs work by stimulating the immune system, it’s important to pay attention to your side effects. Your doctor will monitor you closely for complications during treatment, and your medical team will rely on you to communicate your side effects frequently because they may develop rapidly and may range from mild to life-threatening. Seek treatment immediately, regardless of time of day, for symptoms including high fever, inflammation, swelling, severe abdominal pain or shortness of breath.

Immune-related adverse events are the most serious side effects of immune checkpoint inhibitors. They are not common but can occur when the immune system is over-stimulated by the treatment, which may cause inflammation, swelling or redness. Symptoms may come on suddenly and require immediate medical attention, which is why monitoring them is critical to helping you recover. Following are some of the systems that may be affected by immune-related adverse events when being treated for bladder cancer:

- Cardiovascular (cardiomyositis)
- Endocrine (endocrinopathies)
- Gastrointestinal (colitis)
- Liver (hepatitis)
- Neurologic (encephalitis)
- Pulmonary (pneumonitis)
- Skin (dermatitis)
The kidneys are a pair of bean-shaped organs located in the back of the abdomen. There is one on each side of the spine, and they are protected by the lower ribcage. Each kidney is approximately four to five inches (about 10 to 12 cm) long, which is about the size of a fist (see Figure 1).

The kidneys are a part of the urinary tract, and their main function is to filter all of the blood in the body. As the blood in the body passes through the kidneys multiple times each day, the kidneys filter out excess water, salt and waste products. This creates urine, which then travels to the bladder for storage until urination. The kidneys also play a role in controlling blood pressure and making red blood cells.

WHAT IS KIDNEY CANCER?
Kidney cancer begins when abnormal cells in the kidneys start to grow out of control and form one or more masses – or tumors – within the kidneys. Kidney cancer can range from one tumor in one kidney to several tumors in both kidneys. Tumors are often found on ultrasounds or CTs done for other purposes. Such accidentally discovered cancers may be found before the cancer cells have spread to other organs. As the use of imaging tests has increased, the frequency of detecting kidney cancer at an early stage has also increased.

If the tumor is not detected until after the cancer cells have spread, the cancer has metastasized to one or more distant sites in the body. When this happens, treatment involves the primary site in the kidneys as well as the metastatic site or sites.

Renal cell carcinoma (RCC) is the most common type of kidney cancer. RCC has several subtypes, classified mainly by the appearance of the tumor cells under a microscope. The subtypes include clear cell, papillary, chromophobe, translocation, collecting duct, renal medullary carcinoma and unclassified. The subtype can both influence treatment choices and help doctors determine if the cause of the cancer is an inherited genetic syndrome.

IMMUNOTHERAPY FOR KIDNEY CANCER
Immunotherapy is used to treat many different types of cancer using the body’s own immune system. Immunotherapy helps the immune system recognize and attack cancer cells that have been hiding and target them for destruction, which is very different from other types of cancer treatments. Several types of immunotherapy are approved for kidney cancer, including cytokines and immune checkpoint inhibitors.

Cytokines
Cytokines are proteins that enable cells to send messages to each other. Cytokine immunotherapy is a type of nonspecific immune stimulation that aids in communication among immune cells and plays a big role in the full activation of an immune response. This type of immunotherapy works by introducing large amounts of laboratory-made cytokines to the immune system to promote specific immune responses. The cytokines approved for kidney cancer boost the ability of certain immune cells to attack cancer cells. Interleukin and interferon are types of cytokine immunotherapies.

The first immunotherapy approved for kidney cancer by the U.S. Food and Drug Administration (FDA) was a type of cytokine called interleukin-2 (IL-2) for metastatic kidney cancer. IL-2 boosts lymphocyte production to increase the immune system’s attack on the cancer cells. Later, a type of interferon was approved for kidney cancer. It is sometimes paired with other medications. Interferon slows tumor growth and the division of cancer cells as well as stimulating the body’s immune system.

Other types of treatment are available. Be sure to talk with your doctor about the options that are best for you. Keep in mind that not all immunotherapies are approved for all types and stages of kidney cancer.

Immune Checkpoint Inhibitors
Several checkpoint inhibitors are approved to treat advanced RCC, the most common form of kidney cancer, in people who have received prior antiangiogenic therapy or who are previously untreated.

To understand how checkpoint inhibitors work, it helps to learn about parts of the immune system. Lymphocytes (white blood cells) are a major part of the immune system. They begin in the bone marrow and develop from lymphoblasts (immature cells found in bone marrow). Lymphoblasts mature into infection-fighting cells. The two main types of lymphocytes are B-lymphocytes (B-cells) and T-lymphocytes (T-cells). B-cells develop in the bone marrow and mature into either plasma cells or memory cells. Plasma cells make antibodies to fight germs and infection. Memory cells help the body remember which antigens attacked the body so it can recognize them if they return.

T-cells also develop in the bone marrow but travel to the thymus to mature into helper T-cells, killer T-cells, regulatory T-cells or memory T-cells. Each type of T-cell plays a part in the immune system.

- **Helper T-cells** identify foreign, or non-self, antigens and communicate with other immune system cells to coordinate with the B-cells for an attack.
- **Killer T-cells** directly attack and destroy cancer cells, or normal body cells infected with a virus, by inserting a protein that causes them to enlarge and burst. One type of killer T-cell specifically targets cancer cells.
- **Regulatory T-cells** slow down the immune system after an immune response is finished.
- **Memory T-cells** can stay alive for years, continuing to fight off the same invading cells. Memory is the basis of immune protection against disease, in general, and explains why we usually don’t become infected with some diseases, such as chicken pox, more than once.

Checkpoints keep the immune system “in check,” preventing an attack on normal cells by slowing down or eliminating activated immune cells, or through the use of regulatory T-cells that can block activated immune cells. A series of signals between the correct pro-
patients and receptors on cell surfaces turn off activated killer T-cells or tell the regulatory T-cells to slow down the immune system after an immune response is finished.

To better understand how this happens, think of the proteins and receptors on a cell’s surface as puzzle pieces. Proteins have “tabs” that protrude (stick out), and receptors have “spaces” that curve inward. When the puzzle pieces fit together, chemicals and information are exchanged between the cells, triggering signals to slow the immune system.

- **CTLA-4** (cytotoxic T-lymphocyte-associated protein 4) is a receptor that binds with certain molecules to tell the immune system to slow down.
- **PD-1** (programmed cell death protein 1) is a receptor involved with telling T-cells to die and to reduce the death of regulatory T-cells (suppressor T-cells). Both have an effect to slow down an immune response. PD-1 can only tell the immune system to slow down if it connects with PD-L1.
- **PD-L1** (programmed death-ligand 1) is a protein that, when combined with PD-1, sends a signal to reduce the production of T-cells and enable more T-cells to die.

When PD-1 (the receptor) and PD-L1 (the protein) combine, the reaction signals the immune system that it is time to slow down. CTLA-4, however, can connect with more than one protein, which is a more complex reaction than the PD-1 and PD-L1 interaction. When CTLA-4 combines with any of the various proteins, it also tells the immune system to slow down.

One of the ways cancer can outsmart the immune system is by producing PD-L1 (the protein) on the surface of its cells and using it to camouflage its appearance so that T-cells will think they are normal cells. T-cells only expect normal cells to produce PD-L1, so when a T-cell encounters PD-L1 on a cancer cell, it is tricked into sending the signal for the immune system to slow down. This is a normal way to prevent the immune system from attacking normal cells in the body.

Immune checkpoint inhibitors are drugs that prevent the proteins and receptors (puzzle pieces) from fitting together and triggering the slowdown of the immune system.

When an immune checkpoint inhibitor is given, the immune system is not so easily fooled by the cancer. By not slowing down, it’s like the immune system develops X-ray vision and can see through the disguise. This keeps the immune response on and also helps the immune system recognize cancer cells as foreign cells.

The following types of immune checkpoint inhibitors are currently approved to treat RCC:

- **Anti-CTLA-4** antibodies allow the T-cells to continue fighting cancer cells instead of shutting down.
- **Anti-PD-1** drugs allow for the continued or increased activation of T-cells and enable them to continue fighting cancer.

Some, if not all, currently approved immune checkpoint inhibitors are also known as monoclonal antibodies (mAbs). Antibodies (a type of protein) are the body’s way of tagging an antigen (foreign substance). They are produced from plasma cells, which are mature forms of B-cells. Antibodies are produced for specific antigens. They bind to the antigen and allow the rest of the immune system to recognize the antigen as foreign and target it for destruction.

Made in a laboratory and designed to target specific tumor antigens, mAbs work in different ways, such as flagging targeted cancer cells for destruction, blocking growth signals and receptors and delivering other therapeutic agents directly to targeted cancer cells. They can also be created to carry cancer drugs, radiation particles or laboratory-made cytokines (proteins that enable cells to send messages to each other) directly to cancer cells. When a mAb is combined with a toxin, such as a chemotherapy drug, it travels through the system until it reaches the targeted cancer cell, where it attaches to the surface, gets swallowed by the tumor cell and breaks down inside the cell, releasing the toxin and causing cell death.

**COMMON SIDE EFFECTS**

Each type of immunotherapy typically results in some side effects (see Side Effects, page 13). You will be monitored closely throughout treatment for complications, and your medical team will count on you to alert them as soon as you experience a side effect to ensure it can be addressed immediately. Timing is especially important because side effects from immunotherapy can progress rapidly and may become life-threatening very quickly. It is crucial to seek treatment immediately, regardless of time of day, for symptoms including high fever, inflammation, swelling, severe abdominal pain, diarrhea, chest pain, unexplained coughing or shortness of breath.

The most serious side effects of immune checkpoint inhibitors are known as immune-related adverse events. Although they are not common, they can occur when the immune system is overstimulated by the treatment, which may cause inflammation, swelling or redness. These may come on suddenly and require immediate medical attention, which makes understanding what to watch for so important. Following are some of the systems that may be affected by immune-related adverse events when being treated for kidney cancer:

- Cardiovascular (cardiomyositis)
- Endocrine (endocrinopathies)
- Gastrointestinal (colitis)
- Liver (hepatitis)
- Neurologic (encephalitis)
- Pulmonary (pneumonitis)
- Renal (kidneys) (nephritis)
- Skin (dermatitis)

**ADDITIONAL RESOURCES**

- **Society for Immunotherapy of Cancer**: www.sitcancer.org
- **American Cancer Society**: www.cancer.org Cancer Immunotherapy
- **American Society of Clinical Oncology**: www.cancer.org Kidney Cancer: Treatment Options
- **Kidney Cancer Association**: www.kidneycancer.org Treatment Options
- **National Cancer Institute**: www.cancer.gov Immunotherapy to Treat Cancer
The prostate gland, which is found only in men, develops before birth and grows rapidly during puberty. In young men, it is generally the size of a walnut and continues to grow with age, as long as male hormones are present in the body.

The prostate is located below the bladder, in front of the rectum and behind the penis (see Figure 1). It surrounds the urethra (the tube that carries urine and semen out of the body through the penis), and its primary function is to produce seminal fluid, which adds liquid to semen as well as nourishes and protects sperm cells.

WHAT IS PROSTATE CANCER?
Prostate cancer occurs when normal cells within the prostate gland mutate and grow out of control, usually forming a tumor of abnormal cells. Most prostate cancers grow slowly and stay in the prostate. Many of these cancers can be watched carefully (active surveillance) or effectively removed or destroyed with treatment. However, some prostate cancers are aggressive. Malignant (cancerous) tumors can spread to other body parts if they are not found and treated early enough. When cancer spreads, it is likely to travel to nearby lymph nodes and then to bones and other organs. Prostate cancer that spreads is referred to as advanced prostate cancer.

Nearly all prostate cancers are adenocarcinomas, which develop in the gland cells in the prostate. A very small percentage of prostate cancers are sarcomas, small cell carcinomas, transitional cell carcinomas or neuroendocrine tumors.

More than 90 percent of prostate cancers are detected while still confined to the prostate and nearby organs, primarily due to the prostate-specific antigen (PSA) test. Early diagnosis is generally made using transrectal ultrasound (TRUS) guided biopsy.

The incidence of prostate cancer increases with age more quickly than any other cancer. It’s more common in African-American men and Caribbean men of African descent. Other factors that raise the risk of developing prostate cancer include a family history of the disease and possessing certain inherited gene mutations.

IMMUNOTHERAPY FOR PROSTATE CANCER
Immunotherapy uses the body’s own immune system to recognize and attack cancer cells that have been hiding and targets them for destruction. This approach is quite different from that of other types of cancer treatments. Currently, one type of immunotherapy is approved to treat advanced prostate cancer, and it comes in the form of a vaccine.

Vaccine
Two types of vaccines are used against cancer: preventive vaccines and therapeutic (or treatment) vaccines. Preventive vaccines are given before a person develops cancer with the goal of stopping it from forming. Treatment vaccines may be given to treat existing cancers. Anti-cancer vaccines are created from either viruses or tumor cells that have been changed in a laboratory. Their goal is to direct immune cells to the cancer cells. Some of these vaccines are custom-made for the patient's specific tumor type while others are "off-the-shelf" vaccines that contain one to more than 100 antigens that are common to the patient's type of cancer. The first FDA-approved immunotherapy for prostate cancer is an antigen-presenting cell-based treatment vaccine specifically for metastatic castration-resistant (hormone refractory) prostate cancer (see Figure 2).

You may be a candidate for this treatment if you are on hormone therapy and have a rising PSA level, if your cancer has spread from the prostate to other places in your body, and if you are not taking narcotics for cancer-related pain.

This vaccine is unique in that it is personalized for each patient. As a result, getting it involves more than simply getting an injection at the doctor's office. It is a multi-step process that requires a commitment from the patient, especially in terms of timing. If you are considering this option to treat your advanced prostate cancer, it's helpful to be aware of what to expect.

Treatment begins with the collection of your blood cells in a process known as leukapheresis. Your blood is passed through a machine that collects some of your immune (white blood) cells, while the rest of the blood (platelets and red blood cells) is returned to your body. This is an outpatient procedure that typically takes about three to four hours.

The blood that was collected is sent to a special facility where the white blood cells are modified to be able to recognize and destroy prostate cancer cells. A dose of the vaccine is then created especially for you.

Three or four days later, you are given the dose of the vaccine by infusion (an intravenous fluid). This is generally given on an outpatient basis in your doctor's office or treatment center and will likely take a little more than an hour.

This entire process is repeated two more times, approximately one to two weeks apart. You will have a total of six appointments — three cell collections and three infusions. The full treatment generally takes about a month.

Once these modified white blood cells are injected back into your body, they activate cancer-killing T-cells that travel through the bloodstream looking for cancer cells to destroy. A distinct characteristic of immunotherapy is its potential to remain effective long after treatment ends, a feature called...
“memory.” This means the immune system can continue to seek out and attack cancer cells until they are eliminated. When your immune system encounters a virus, such as chicken pox, it automatically remembers if it is exposed to it again and offers you immunity, meaning you usually don’t get another case of chicken pox. With immunotherapy, your immune system may be able to recognize a specific type of cancer cell easier, which can lead to long-term, cancer-free remission of that type and increased overall survival. This is the same characteristic that allows a traditional vaccine, such as the tetanus vaccine, to remain effective for many years.

It is crucial to stay on schedule with the cell collection and infusion appointments. The doses are made for you only, and they have an expiration date. If you miss an appointment and don’t receive the dose when you are supposed to, you must have your cells collected again so another dose can be made especially for you. Because a missed appointment will delay treatment, you are encouraged to be diligent about keeping your appointments. Consider asking a loved one or caregiver to help you remember, or explore the many online schedules and calendar apps that are available. Many have reminder features that are very helpful.

If you need additional treatment after receiving this vaccine, other options, such as chemotherapy, hormone therapy and radiotherapy, may be available to you. More immunotherapy agents, including other types of vaccines, are currently being studied in clinical trials (see Exploring Clinical Trials, page 12).

COMMON SIDE EFFECTS

One of the potential benefits of immunotherapy is that it tends to affect only cancer cells. Other forms of treatment are more likely to affect healthy cells in addition to cancer cells. For example, surgery, chemotherapy, androgen deprivation therapy and radiation therapy kill rapidly multiplying cells, which include cancer cells as well as healthy cells that also multiply quickly, such as blood cells and cells in the gastrointestinal tract. The accompanying destruction of healthy cells and tissues contributes to common side effects, such as fatigue, nausea and vomiting, hair loss and low blood counts. Immunotherapy is different because it primarily targets cancer cells. Although there may be fewer side effects from immunotherapy than with other cancer treatments, it is realistic to expect that you will experience some (see Side Effects, page 13).

Since these drugs work by stimulating the immune system, it’s important to pay attention to every side effect you experience. Your doctor will monitor you closely for complications during treatment, and your medical team will rely on you to communicate your side effects frequently because they may develop rapidly and may range from mild to life-threatening. Seek treatment immediately, regardless of time of day, for symptoms including high fever, inflammation, swelling, severe abdominal pain or shortness of breath.

Ask your doctor which side effects to expect with vaccine therapy and when they may happen. Some may occur right away, while others may not show up for months or years after treatment. Once you know what to watch for, ask your doctor about the best ways to prevent or treat them if they occur. When in doubt about any side effects, contact your doctor.

The only side effect that I experienced with immunotherapy was that I slept for 24 hours after my first infusion. It was much needed sleep, so I thought it was phenomenal.

~ Todd Seals, Stage IV prostate cancer survivor

ADDITIONAL RESOURCES

- Society for Immunotherapy of Cancer: www.sitcancer.org
- American Cancer Society: www.cancer.org
- American Society of Clinical Oncology: www.cancer.net
- National Cancer Institute: www.cancer.gov
- Us TOO: www.ustoo.org
- ZERO - The End of Prostate Cancer: www.zerocancer.org

PROSTATE CANCER TREATMENT POTENTIAL SIDE EFFECTS

Treatment vaccine therapy

- Back pain
- Chills
- Fatigue (feeling tired)
- Fever
- Headache
- Joint ache
- Nausea

FIGURE 2

<table>
<thead>
<tr>
<th>PROCESS OF PERSONALIZED VACCINE THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. You receive the vaccine, and the modified cells activate other immune cells so they can recognize and destroy the cancer cells.</td>
</tr>
<tr>
<td>2. A dose of the vaccine is created just for you.</td>
</tr>
<tr>
<td>3. These cells are sent to a lab, where they are modified to recognize and destroy cancer cells.</td>
</tr>
<tr>
<td>4. The patient’s own immune cells are extracted from the body.</td>
</tr>
</tbody>
</table>

Antigen-presenting cells

Immune cells

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I’d never tolerated my body telling me what to do until suddenly, in 2010, at 59 years old, it called an executive board meeting without consulting me first. I had back pain I tried to ignore, and a loss of appetite that couldn’t be rationalized away. Although I wouldn’t admit it, my gradual loss of energy defeated the iron will I’d maintained for more than 40 years as a sheet metal technician and HVAC business owner. For the first time in my life, I felt like I’d lost control.

In 2011, a series of tests, including an MRI, CT and biopsy, confirmed that my prostate specific antigen (PSA) had tested at 398. I was diagnosed with metastatic prostate cancer that had spread to my lymph nodes and bones. I felt like I’d been given a death sentence. My wife, Janet, and I were shocked and devastated, and I sought the care of a world-renowned prostate cancer oncologist. My cancer was advanced enough that I did not qualify for chemotherapy or radiation. My doctor prescribed a tri-monthly shot to keep my bones from breaking down due to the spread in my bone marrow, daily hormone pills to inhibit the production of prostate cancer-feeding testosterone, and tri-monthly painful hormone shots of another testosterone blocker.

Janet, meanwhile, began a concerted attack against the cancer on the home front. She removed toxic conventional and processed foods and replaced them with those that are natural and organic, including cancer-fighting berries, pomegranates, kale, cruciferous vegetables, yams and, occasionally, organic, grass-fed meats and wild Pacific seafood. She bought new cleaning and personal hygiene products, including soaps, toothpaste and cleaning agents, dramatically changing our lifestyle and improving my quality of life.

After a year of hormone therapy, my PSA level that had dropped to 0.1 climbed again to 19; the hormones had become ineffective. My oncologist enrolled me in a clinical trial for immunotherapy. Over a six-week period, a leukapheresis process would intravenously separate some of my white blood cells from the red and extract them from my body. The white cells would be transported to a lab and strengthened with nutrients. Three days later, they would be returned to the hospital and infused back inside me to fight the cancer cells. The entire process would happen three times beginning in early 2013.

Unfortunately, my first session was plagued by at least 15 failed, painful attempts to insert a huge needle in my veins until both of my arms were black and blue. My veins were too small. The nurse felt awful. I was so angry, and all I could do was hug her and assure her that I would survive the ordeal. My wife and I left with a resolve that I couldn’t participate in the clinical trial. My oncologist, however, scheduled a surgical procedure of inserting temporary ports through my jugular vein and out of my chest where the white blood cells would be extracted. It was scary, but I pushed forward.

Each session took four hours to complete and caused me to experience chills, dizziness and some weakness. When it was done, my doctor surgically removed the ports, and I was prescribed another hormone blocker.

My PSA level gradually and blessedly
Janet Jones took on the role of caregiver for her husband after he was diagnosed with Stage IV prostate cancer. She encouraged him to share his feelings with her throughout treatment instead of closing up. She chronicled her experience in a book, “The Trial of Stage IV Prostate Cancer,” so other women can help the men in their lives.

Euvon and I met in 1976 in an R&B band. He was the smooth bassist, and I was one of three vocalists. What began as a tepid friendship evolved into romance and was sealed in marriage in 1979.

I gave up my career as an executive assistant to support Euvon the day after we married. That role took a critical turn when, in 2011, my rock-solid, healthy husband’s 59 year-old body broke down during a swim challenge with a nine-year-old boy. After weeks of bone pain and weight loss, several in-depth tests revealed the horrible diagnosis of Stage IV prostate cancer with a prognosis that his life would be significantly cut short.

Heartbroken, I prayed for wisdom and understanding about what this rerouted purpose meant for us. I needed great faith and strength to fight this formidable foe that had invaded our lives and his body. Euvon and I searched for a reputable hospital and an oncology team that specialized in prostate cancer care. His oncologist determined that because it had metastasized to his lymph nodes and bones, he was not a candidate for surgery, chemotherapy or radiation therapy.

Euvon pushed past his pain and fear of uncertainty and continued his rigorous work schedule, while undergoing hormone therapy and immunotherapy. I, on the other hand, took on the personal task of becoming a student of his diagnosis, gleaning a plethora of information about the causes, symptoms and stages of prostate cancer.

I researched the natural and alternative medicines, vitamins and other resources that could sustain him through his treatment protocol; what foods needed to be organic, grass-fed or cage-free; and the organic and chemical-free household and personal hygienic products that I felt were safer for our environment and bodies.

I took an independent approach in caring for Euvon. My most important goal was to encourage him to talk about everything he was feeling, physically, emotionally and spiritually, so he wouldn’t drift to a place where I couldn’t reach him.

Euvon’s willingness to communicate with me allowed me to be more proactive in his daily life and better assist with long-term decisions. I attended his initial appointments, tests and procedures. Once his treatment plan was established, he often went to the hospital from work.

Eventually, my caregiving role intensified in the food department. Our new diet was so nutritious, yet he refused to eat it. Its earthiness, he claimed, was like eating dirt and made him nauseated. I told him he needed to respect this nutritious diet if we were to continue upon this road of “in sickness and in health.” Gradually, the meals became more innovative and creative once he became involved in their preparation.

Convincing him to adhere to our new dietary regimen tested his patience and mine. Yet, we understood that our strength lay in battling together against this deadly disease with discipline. Our extended family and friends were also very supportive.

One of our more difficult days was when Euvon had sudden stabs of breakthrough pain he experienced while dining out. I could barely get him out of the restaurant and drive him home. However, his worst side effect was post-biopsy once the numbing medicine wore off. He was in so much pain. God has answered our prayers along the way, and Euvon has improved tremendously.

My advice to women who are caring for husbands with prostate cancer is to realize our job is to give them the best quality of life possible. We also need to dedicate time for ourselves in order to maintain our physical and emotional health.

The hardest part of caregiving for me was the constant weakness in my soul from all the unknowns. My peace came from knowing that, whatever the outcome, we would win.

Whenever I felt overwhelmed, composing and recording songs calmed me. I also chronicled our journey, in the form of a memoir, which, according to Euvon’s oncologist, was written “to encourage every man, for the sake of everyone who loves that man, to take an alternative road when it comes to their health.” Our book is available at www.jones4life.com.

This experience has taught me that it’s not been about us, but about encouraging families to be proactive in their loved one’s care and encouraging men to do whatever it takes to prevent being one of the more than 200,000 men diagnosed with prostate cancer each year.

The best advice I’ve received is, “Let us not be weary in doing good, for at the proper time, we will reap a harvest if we do not give up,” which was written in the Holy Bible, my Book of Life.
Many advances in cancer treatment today are a result of medical research performed in clinical trials. Recently, many immunotherapy agents have been approved to treat several cancer types, including some genitourinary (GU) cancers. Researchers are using this knowledge to continue to make progress in the treatment of other cancer types.

Many clinical trials are currently taking place to evaluate different components of GU cancer treatment, including patient responses to existing therapies, the effectiveness of combining immunotherapy with other therapies, the result of modifying the order of the agents given, how to avoid toxicities, managing immune-related adverse events and more. Doctors and scientists also continue to explore why immunotherapy is effective for some people but not for others, even when they have the same cancer.

Clinical trials present many potential benefits, such as the opportunity to access leading-edge treatments that aren’t yet widely available. They may be an alternative if your current treatment isn’t working as well as it once was, or if you have a rare type of cancer that hasn’t been studied as much as others. At the same time, trials can present potential risks or inconveniences. Almost every type of cancer treatment has side effects. Those in clinical trials are no different and may not be fully known.

Before volunteering, you will receive detailed information about the trial in a document known as the Informed Consent. This form details the purpose of the research, including your role in the trial, how the trial will work, risks, benefits and other pertinent information. To ensure that you fully understand, you are required to review the form during the Informed Consent process. Before signing it, check with your insurance providers to determine the procedures that are covered and those you will be expected or required to pay out of pocket. Although many trials may cover the costs of certain treatments, other expenses may be your responsibility. It is important for you to have this information before you begin participating in the trial.

**SEARCHING FOR A CLINICAL TRIAL**

Along with asking your doctor about available clinical trials, you’re encouraged to research them on your own (see Assistance & Support Resources, page 16). Sometimes navigating the online search tools can be overwhelming. To help you know what to expect, screenshots from a mock clinical trial search site are shown below.

Before you begin, have your exact diagnosis, pathology report and details of previous treatments handy. If you find a clinical trial that appears to be a good fit but is no longer accepting patients, your doctor may appeal to the U.S. Food and Drug Administration (FDA) for expanded access, also referred to as compassionate use. If you don’t find a clinical trial, know that new clinical trials are being added all the time. You may choose to continue searching while you move forward with your current treatment plan.

**[STEP 1] FILL IN YOUR INFORMATION**

**Enter Your Diagnosis**

You may conduct multiple searches to create more options. For example, first enter the diagnosis, such as “bladder cancer” and do the search. Next, try “advanced bladder cancer” then “genitourinary cancer” to compare the different results.

**Desired Location**

If you prefer to find a clinical trial that is close to home, enter your home address. If you are willing and able to travel for treatment, enter other locations.

**[STEP 2] READ YOUR SEARCH RESULTS**

The name of the clinical trial will appear at the top of the results page.

**Recruitment Status**

This indicates whether the trial is actively recruiting, not yet recruiting or otherwise inactive. This will change, so continue to check for status updates.

**Summary of Study**

This contains detailed information about the clinical trial’s purpose and the treatment being tested. This section is usually written for health care providers and may be difficult to understand. That’s OK. If you find a clinical trial that interests you, print out the information so your doctor can explain it to you.

**Eligibility Criteria**

This outlines the criteria you must meet to be eligible for the trial, such as the stage of disease or previous treatments you’ve had.

**Contacts and Locations**

This may contain the contact information for the clinical trial investigators, staff and sponsors. They may be able to provide additional information about the study.

**Sponsor**

This is the organization that is responsible for the clinical trial. It may be a pharmaceutical company or biotechnology company, university or the National Cancer Institute (www.clinicaltrials.gov).
**Side effects can occur** with any type of cancer treatment, including immunotherapy. Although the side effects associated with immunotherapy are typically fewer and may be less severe than other cancer treatments, there is a risk of serious side effects. This risk exists because immunotherapy drugs work by altering the way that the immune system works, and it is possible they may cause the immune system to attack normal, healthy parts of the body, such as the intestines, liver, lungs, kidneys, hormone-making glands or others. Your doctor will monitor you closely to treat these complications before they become serious or even life-threatening. Before beginning treatment, your doctor will determine what is normal for you by performing a baseline assessment for monitoring throughout treatment.

Preventing and managing side effects is extremely important for the success of your treatment. Your health care team members will do all they can to help prevent and minimize side effects, and they will rely on frequent communication from you. These side effects may develop rapidly, and it is important to report them to your medical team as soon as symptoms begin, even if you think they are trivial. Seek treatment immediately, regardless of time of day, for any medical emergencies, including high fever, inflammation, swelling, severe abdominal pain or shortness of breath.

They can occur as soon as treatment begins or after treatment stops. The side effects may also develop later – even weeks or months after stopping treatment. Therefore, it is important to remember that they may occur, and you should report any symptoms to your doctor or nurse for at least three months after completing treatment.

Discuss with your doctor the possible short-term and long-term side effects that may be possible with your type of treatment. Keep in mind that immunotherapy is still relatively new, and doctors and researchers continue to learn about the side effects that accompany different treatments.

It’s also important to realize that having a side effect does not mean that the immunotherapy is or isn’t working. Some people may experience little to no side effects with successful treatment.

The goal is to treat the cancer successfully with as little discomfort and disruption as possible. Noticing and treating side effects from immunotherapy early often results in a better outcome because you may be able to avoid an interruption in treatment.

The following are some of the side effects that may be associated with immunotherapy.

**Immunorelated adverse events (IRAEs), the most serious of the possible side effects, are not common but can occur when the immune system is overstimulated by the treatment. This may cause inflammation, swelling or redness, which may be painful. Some people may not be able to physically feel these symptoms, so making and keeping regular check-ups with your doctor is extra important.**

The systems affected by immune-related adverse events and common symptoms are as follows. Ask your doctor for a complete list of symptoms and side effects that may apply to you.

- **Cardiovascular** (cardiomyositis): Chest pain, shortness of breath, swelling in the legs, palpitations (rapid heartbeat), changes in EKG reading
- **Endocrine** (endocrinopathies): hyperthyroidism, hypothyroidism, extreme fatigue, persistent or unusual headaches
- **Gastrointestinal** (colitis): diarrhea with or without bleeding, abdominal pain, bowel perforation
- **Liver** (hepatitis): yellow skin or eyes (jaundice), nausea, abdominal pain, fatigue, fever
- **Nervous system** (neuropathies): numbness or tingling, pain, burning, loss of feeling in the hands or feet, sensory overload, sensory deprivation
- **Neurologic** (encephalitis): confusion, hallucinations, seizures, changes in mood or behavior, neck stiffness, extreme sensitivity to light
- **Pulmonary** (pneumonitis): chest pain, shortness of breath
- **Renal (kidneys)** (nephritis): Decrease in urine output, blood in urine, swelling in ankles, loss of appetite
- **Skin** (dermatitis): Rash, skin changes

**Fatigue** is the most common side effect reported in multiple immunotherapy agents, including checkpoint inhibitors and cytokines. Fatigue associated with cancer is different than simply feeling tired and may cause you to feel physically, emotionally or mentally exhausted. Fatigue can be caused or worsened by several factors.

- The extra energy your body uses to repair healthy tissues damaged during treatment
- Other side effects, such as pain, nausea and vomiting
- Medications to relieve side effects
- The interaction of two or more medications

**Flu-like symptoms**, such as fever, chills, aches, headache, drowsiness, nausea, vomiting, runny nose, loss of appetite and low or high blood pressure, may occur with cytokines. The exact process of how flu-like syndrome develops is not fully known. However, it’s generally believed that certain medications affect the body in a similar way as the flu virus. Both cause an inflammatory reaction in the immune system, which spurs a variety of symptoms.

**Diarrhea** is common with checkpoint inhibitors and cytokines, and can vary in severity and duration. It can lead to severe dehydration and electrolyte imbalance but also could be a signal that your immune system is going into overdrive. Call your health care team if you experience symptoms that interfere with your daily activities, such as severe abdominal cramping or episodes that make you fearful of leaving your home.

**Mild skin reactions**, such as bumpy or itchy red rashes, may occur. These reactions can be common with checkpoint inhibitors. Other skin problems include yellowing or changes in skin color, inflammation, blistering, hives, pale patches, dryness, cracking of the fingers, sun sensitivity and flushing or redness. Although rarely severe, these symptoms can be uncomfortable. Your doctor may recommend a corticosteroid, numbing medicine, antihistamine, medicated creams or antibiotics.

**Nausea and vomiting** may be caused by immunotherapy and other drug therapies, such as chemotherapy and targeted therapy. It is much easier to prevent nausea and vomiting than to control them once they’ve started. Recent advances have led to the development of antiemetics, which can help prevent and control them.

**Constipation** is a symptom many people experience. It is characterized by difficulty passing stools or a decrease in bowel movement frequency as compared to your normal bowel schedule. People often refer to constipation issues as “feeling backed up,” and it sometimes is accompanied by pain, cramming or swelling of the abdomen.

Although it is a very common symptom, constipation can be extremely uncomfortable and can affect your quality of life. If left untreated, it can even cause serious medical is-
sues, such as a bowel obstruction. It is important to talk to your doctor about constipation and to manage your symptoms as they occur. **Muscle and joint pain** may occur. Myalgia is the medical term for any type of muscle pain and may include consistent, deep and throbbing or random, piercing pain. It can affect small or large areas or your entire body. Your muscles may feel weak or tired, and pain may range from mild to severe. Often, symptoms of myalgia also include pain in your joints, which is known as arthralgia.

Myalgia and arthralgia caused by treatments or medications typically resolve once treatment ends. There are options for pain management during treatment, however, so talk to your doctor if your muscle or joint pain persists or worsens. Keep a record of the pain you’re experiencing. Write down information about the type of pain you have, where you feel it, the severity and how long it lasts, how it affects you and any possible triggers. Your doctor will ask you questions about your pain to determine the best way to treat or manage it. **Infusion-related reactions** refer to any unexpected reactions after receiving a drug and are generally due to an immune response against the drug. The reaction usually, but not always, occurs rapidly after exposure to the drug. The symptoms may be mild, consisting of minor itching, skin rash, fever and chills or more serious, such as shaking chills, low blood pressure, dizziness, difficulty breathing and irregular heart beating. The likelihood of such a reaction may differ based on the drug. Treatment may include stopping the drug, giving it more slowly, use of analgesics and antihistamine medication, or sometimes corticosteroids. **Injection site reactions** can be painful and distressing. Although most are not serious, check with your doctor because your health care team may choose to modify your treatment to prevent further reactions.

**Coughing** can be a symptom of some immunotherapies. A cough may be an indication of pneumonitis, which is inflammation of the lungs. Any coughing or difficulty breathing should be reported to your doctor.

**EMOTIONAL SIDE EFFECTS**

► **Anxiety** is often described as feeling nervous, stressed, worried and/or tense. Symptoms of anxiety may include faster heartbeat, feeling sick to your stomach, having difficulty concentrating, feeling tightness in your chest area, or feeling shaky or dizzy. Being anxious may make it difficult to cope with treatment, deal with daily life or prevent your body from healing properly after treatment.

**What to try:**
- Explore relaxation techniques, such as deep breathing, meditation, muscle relaxation, hypnosis, biofeedback and yoga.
- See a mental health specialist.

► **Depression** is more complex than just feeling sad or hopeless, but these emotions can accompany it, along with feelings of panic, hopelessness and discouragement. Depression can result from low hormones, a chemical imbalance in the brain, uncontrolled pain and other unrelieved symptoms. It can range from mild to severe. Many antidepressants are available, and each has its own side effects.

**What to try:**
- Perform regular physical activity, breathing exercises or meditation.
- Contact your doctor immediately if you have thoughts of hurting yourself or others.

► **Emotional paralysis** is a feeling of being overloaded and out of control. This is a common feeling after being diagnosed with cancer, and it can occur while going through treatment. Learning new medical terms, undergoing treatment and coordinating multiple medical appointments may feel overwhelming.

**What to try:**
- Take charge of the things you can control.
- Ask your doctor to explain your diagnosis and treatment plan.

► **Fear** is a common reaction to finding out you have cancer. It is also a normal side effect of going through treatment. Fears associated with treatment include not knowing what to expect, pain during or after treatment, inability to do daily activities while in treatment, a change in appearance (hair loss or scars), fertility issues or sexuality challenges.

**What to try:**
- Become informed. Learn as much as you can about your cancer and your treatment.
- Talk to others going through similar treatment.
- Grief is the feeling of distress or sorrow due to the loss of something.

► **Grief** is the feeling of distress or sorrow due to the loss of something. People often expect physical side effects from cancer and its treatment, but emotional side effects are also likely to occur before, during or after treatment. Common emotional side effects include the following:

- **Fear** is a common reaction to finding out you have cancer. It is also a normal side effect of going through treatment. Fears associated with treatment include not knowing what to expect, pain during or after treatment, inability to do daily activities while in treatment, a change in appearance (hair loss or scars), fertility issues or sexuality challenges.

**What to try:**
- Educate yourself about the type of cancer you have.
- Consider joining a support group.

► **Guilt** is the sense that you’ve done something wrong. You may feel responsible or blame yourself for developing cancer due to actions you did or didn’t take regarding your health or lifestyle. You may also feel you are upsetting loved ones or that you are a burden to them. Some people may feel guilty about not having a positive attitude all the time. In some cases, patients may be envious of other people’s good health.

**What to try:**
- Talk with a counselor.
- Be kind to yourself when you don’t have a positive attitude during treatment.

► **Loneliness** is a feeling of being alone and isolated from others. Cancer patients often feel alone or alienated from others for several reasons. You may feel your diagnosis prevents you from living the life you once had. If friends avoid visiting or calling, you might feel no one understands.

**What to try:**
- Talk to others who have the same type of cancer as you.
- Contact a member of your faith or spiritual community.

► **Uncertainty** is the feeling of hesitation, indecision or doubt. You may be uncertain of how the treatment will go and about your future. That can lead to feelings of fear, anxiety or anger.

**What to try:**
- Educate yourself about the type of cancer you have.
- Consider joining a support group.

Although many emotional side effects are negative, some survivors report having positive emotions, such as gratitude, hope, peace, appreciation and clarity about life and goals. Many survivors find strength they never dreamed they had, and they develop lasting relationships with people they’ve met as a result of their diagnosis. However, don’t expect to have positive feelings right away or ever. Everyone is different.

If you experience any of the negative emotional side effects, talk to a member of your health care team. They are trained to help you and to find the resources you need to be better prepared to complete your treatment. Some experts they may recommend include chaplains, social workers, psychologists and psychiatrists.
**Antibody** – A protein produced by the immune system in response to a foreign substance, such as a virus or bacterium.

**Antigen** – Any substance that causes the body to make an immune response against that substance. Antigens include toxins, chemicals, bacteria, viruses, abnormal proteins in cancer cells, or other substances that come from outside the body.

**Antigen-presenting cells (APCs)** – Special cells that digest invading cells or soluble (can be dissolved in water) protein antigens and present them to the T-cells and B-cells so they know what to attack.

**B-cells** – Immune cells that produce antibodies for specific antigens that will bind to the antigens and mark them for destruction by other immune cells.

**Biologic product** – Medications made from living organisms, such as vaccines, oncolytic viruses, human cells and tissues, and gene therapies.

**Biosimilar** – A biological drug that is very much like another biological drug (called the reference drug) that has already been approved by the U.S. Food and Drug Administration (FDA). Biosimilar drugs and reference drugs are made from living organisms, but they may be made in different ways and of slightly different substances.

**Cancer cells** – Cells with damaged DNA (mutations) that causes abnormalities in normal cell growth and division. In some cases, new cancer cells grow uncontrollably, and old cancer cells don’t die when they should, resulting in a malignant tumor or cancer.

**Checkpoint inhibitors** – Drugs that block specific immune checkpoint pathways and prevent T-cells from shutting down.

**Clinical trial** – A research study in which people are assigned in a specified manner to one or more interventions to determine the effects on a health or behavioral problem. Your doctor and the study team are responsible for processing participants in a clinical trial, what procedures are involved, how the experimental drug is thought to work, possible side effects that are known, how many patients will be treated on the trial, how long you will need to stay on the trial, reasons to stop the treatment, any costs associated with your participation and alternative options. You must sign a consent form prior to participating in a clinical trial, and you have the right to stop participating usually at any time, although it is important to let your doctor know if you want to stop.

**Cytokines** – Proteins released by immune cells to communicate with other immune cells. Certain cytokines, such as interferon and interleukin, help regulate specific immune system functions.

**Dendritic cell (DC)** – A type of antigen-presenting cell (APC) responsible for processing antigen material and presenting it to the T-cells and B-cells for activation, along with regulating other immune cells.

**Downregulation** – Reducing either the overall immune system response or the specific responses of certain immune cells.

**Granulocyte-macrophage colony stimulating factor (GM-CSF)** – A cytokine protein responsible for stimulating bone marrow and promoting the growth of immune cells, especially dendritic cells.

GM-CSF is currently used to restore white blood cells that have been depleted in people receiving chemotherapy and is being used and studied as a treatment boost when combined with other immunotherapies.

**Immune cells** – The cells of the immune system involved in defending the body against infectious disease, foreign invaders and cancer cells.

**Immune checkpoint inhibitors** – Drugs that block specific immune checkpoint pathways. These drugs allow the immune system to recognize and attack cancer cells.

**Immune checkpoint pathways** – The system of checks and balances in place to prevent overactivation of the immune system. Different pathways function at different stages of the immune response to help regulate the length and intensity of T-cell activity. Turning on an immune checkpoint typically results in shutting down the immune system response. This shutdown can be prevented by treatment with immune checkpoint inhibitors.

**Immunosuppression** – A condition in which the immune system is prevented from launching successful attacks to protect the body against infection and disease.

**Immunotherapy** – A type of cancer treatment that focuses on using the body’s own immune system to fight cancer.

**Immune-related adverse events (IRAEs)** – Autoimmune reactions that occur as a result of immunotherapy treatment. This is thought to be due to an overactive immune response against normal tissues.

**Interferon** – A substance that can improve the body’s natural response to infections and other diseases. Interferons interfere with the division of cancer cells and can slow tumor growth. Interferon also helps activate the immune response. The body normally produces these substances. They are also made in the laboratory to treat cancer and other diseases.

**Interleukin** – A protein produced by cells of the immune system that helps regulate the production of other immune cells, how they function during an immune response and their production of cytokines. Versions of this protein may also be made in the laboratory.

**Major histocompatibility complex (MHC)** – A set of proteins on the surface of normal cells and some immune cells that influence the interaction of normal cells with immune cells. MHC molecules also help identify cells that belong to a single individual (“self”) and can mediate transplant rejection when they are different between a person and a transplanted organ.

**Memory cells** – T-cells and B-cells from a specific immune reaction that continue to circulate in the body even after the infection is resolved. They “remember” specific antigens and can multiply rapidly upon subsequent exposure, creating an immediate immune response already trained to eliminate the threat. This response protects people from getting the same infection twice and may help defend against cancer recurrence.

**Monoclonal antibodies (mAbs)** – Antibodies made in a laboratory that are designed to target specific parts of cancer cells, which may include certain proteins or molecules on the surface of the cancer cells. These can stimulate or block receptor targets. For cancer immunotherapy, they are meant to stimulate an immune response in the same way as naturally produced antibodies do.

**Natural killer (NK) cells** – White blood cells that contain enzymes that kill virally infected cells and tumor cells. They also communicate with T-cells to help regulate their development and response.

**Oncolytic virus** – A virus that can infect and multiply within cancer cells, causing them to die. These viruses may be manufactured or naturally occurring, and can be used to target and destroy specific tumor cells. They may also induce an immune response.

**PD-1 (programmed cell death-1)** – The receptor in the PD-1 checkpoint pathway that sends negative signals to the T-cell when it connects to a PD-ligand 1 or PD-ligand 2 (PD-L1 or PD-L2). These negative signals normally slow down or stop the immune response when it’s no longer necessary. Some cancer cells have PD-L1 on the surface and this likely shuts off the immune response, allowing a cancer to grow.

**Proliferation** – Cell division and growth. This is a process that T-cells and B-cells use to increase the numbers of infection- or cancer-fighting cells. This is also an abnormal process in some normal cells that leads to cancer.

**Receptors (immune receptors)** – Proteins on the surface of immune cells that bind to ligands on the surface of other immune cells. This connection typically results in immune cell signaling that regulates specific immune system functions.

**Regulatory T-cells** – T-cells that help maintain the necessity, strength and duration of an immune response by regulating T-cell activity. In general, these T-cells shut down the activated (or “effector”) T-cells, such as cancer-fighting T-cells, at the end of an immune response. Certain tumor cells have the ability to increase regulatory T-cell activity, which decreases the overall immune response against the cancer.

**Standard of care** – A treatment regimen that is accepted by medical experts and is widely used as a treatment for a specific type of cancer.

**T-cell receptors (TCRs)** – Molecules found only on the surface of T-cells. TCRs must bind to special molecules on the surface of antigen-presenting cells before they can receive information about a threat.

**T-cells** – Immune cells that recognize specific antigens during antigen presentation. T-cells are the major players in the immune system’s fight against cancer. Their activation and activity are two of the main focuses in immunotherapy research.

**Tumor-infiltrating lymphocytes (TILs)** – A type of immune cell that has moved from the blood into a tumor cell. This may be considered an indicator of the immune system is attempting to attack cancer. Although TILs are not found in all cancers, the goal of immunotherapy is to increase the number of TILs within the tumor microenvironment.

**Tumor microenvironment** – The area surrounding a tumor, inside which normal cells, molecules and blood vessels help sustain the tumor. The microenvironment contributes to the behavior, proliferation and spread of the tumor. The tumor is capable of affecting its own microenvironment.

**Upregulate** – Increase either the overall immune system response or the specific responses of certain immune cells.

*Some definitions courtesy of the website of the National Cancer Institute (www.cancer.gov).*
BLADDER CANCER
Action on Bladder Cancer ................................................................. actiononbladdercancer.org
American Bladder Cancer Society ...................................................... bladdercancer.org
Bladder Cancer Advocacy Network .................................................. www.bcan.org
United Ostomy Associations of America, Inc ..................................... www.ostomy.org

CANCER EDUCATION
American Cancer Society .................................................................. www.cancer.org
American Society of Clinical Oncology ........................................... www.cancer.net
CANCER101 .......................................................................................... www.cancer101.org
CancerCare ......................................................................................... www.cancercare.org
CancerQuest ....................................................................................... www.cancerquest.org
Centers for Disease Control and Prevention (CDC) .............................. www.cdc.gov
Get Palliative Care ............................................................................... www.getpalliativecare.org
Global Resource for Advancing Cancer Education (GRACE) ............... www.cancergrace.org
The Hope Light Foundation ................................................................. www.hopelightproject.org
LIVESTRONG Foundation ................................................................ www.livestrong.org
National Cancer Institute .................................................................. www.cancer.gov
National Comprehensive Cancer Network (NCCN) ......................... www.nccn.org
NCCN Contact Center (cancer information service) ......................... 800-422-6237
OncoLink ............................................................................................. www.oncolink.org
Patient Power ..................................................................................... www.patientpower.info
PearlPoint Nutrition Services ............................................................ www.pearlpoint.org
Pine Street Foundation ........................................................................ www.pinetreetfoundation.org
Scott Hamilton Care Foundation ....................................................... www.scottcares.org
Triage Cancer ...................................................................................... www.triagecancer.com

CAREGIVERS & SUPPORT
4th Angel Patient & Caregiver Mentoring Program .......................... www.4thangel.org
CanCare ............................................................................................... www.cancercare.org
CANCER101 ........................................................................................ www.cancer101.org
Cancer Action ...................................................................................... www.canceractionic.org
Cancer and Careers ............................................................................ www.cancerandcareers.org
CancerCare ........................................................................................ www.cancercare.org
Cancer Connection ............................................................................ www.cancerconnection.org
Cancer Hope Network ...................................................................... www.cancerhope.org
Cancer Information and Counseling Line ....................................... 800-525-3777
Cancer Really Sucks! .......................................................................... www.cancerreallysucks.org
Cancer Support Community .............................................................. www.cancersupportcommunity.org
Cancer Support Helpline ................................................................. 888-793-9355
Cancer Survivors Network ................................................................ www.csn.org
Cancer Wellness Center ..................................................................... www.cancerwellness.org
Caregiver Action Network ................................................................. www.caregiveraction.org
CaringBridge ....................................................................................... www.caringbridge.org
Center to Advance Palliative Care .................................................... www.capc.org
Cleaning For A Reason ....................................................................... www.cleaningforareason.org
Cooking with Cancer ......................................................................... www.cookingwithcancer.org
Cuddle My Kids .................................................................................. www.cuddlemylkids.org
Family Caregiver Alliance ................................................................. www.caregiver.org
Fighting Chance ................................................................................ www.fightingchance.org
Friend for Life Cancer Support Network ........................................... www.friend4life.org, 866-374-3634
The Gathering Place .......................................................................... www.touchedbycancer.org
Guide Posts of Strength, Inc. ............................................................... www.guidepostsofstrength.org
The Hope Light Foundation ................................................................. www.hopelightproject.com
Imeman Angels .................................................................................. www.imemanangels.org
Lacuna Loft .......................................................................................... www.lacunaloft.org
The LGBT Cancer Project – Out With Cancer .................................. www.lightcancer.org
LIVESTRONG Foundation ................................................................ www.livestrong.org
LivingWell Cancer Resource Center ............................................... www.livingwellirc.org
Lotus Helping Hands ........................................................................... www.lotoshelpinghands.com
The Lydia Project ............................................................................... www.lydiaproject.org
MyLifeLine.org Cancer Foundation .................................................. www.mylife-line.org
Patient Empowerment Network ....................................................... www.powerfulpatients.org
Patient Power .................................................................................... www.patientpower.info
SHARE Caregiver Circle .................................................................... www.sharecancersupport.org/caregivers-support

CLINICAL TRIALS
ACCESS: ............................................................................................... cantria.com/access
AccrualNet ......................................................................................... www.accrualnet.cancer.gov
ACT (About Clinical Trials) ............................................................... www.learnaboutclinicaltrials.org
Center for Information and Study on Clinical Research Participation ................................................................ www.searchclinicaltrials.org
CenterWatch ....................................................................................... www.centerwatch.com
ClinicalTrials.gov .............................................................................. www.clinicaltrials.gov
Lazarus Cancer Foundation .............................................................. www.lazarus.org
LIVESTRONG Foundation ................................................................. www.livestrong.org
MolecularMatch ................................................................................. www.molecularmatch.com
My Clinical Trial Locator ................................................................. myclinicaltriallocator.com
National Cancer Institute ................................................................. www.cancer.gov/cancerclinicaltrials
NCCN Contact Center (Cancer Information Service) ....................... 800-422-6237
Stand Up To Cancer ............................................................................ www.standup2cancer.com
TrialCheck .......................................................................................... www.trialcheck.org

FINANCIAL ASSISTANCE
BenefitsCheckUp ................................................................................. www.benefitscheckup.org
Bringing Hope Home ......................................................................... www.bringinghopehome.org
CancerCare ......................................................................................... www.cancercare.org
Cancer Financial Assistance Coalition ...........................................'www.cancerfa.org
HealthWell Foundation .................................................................... www.healthwellfoundation.org
Hope Lodge ........................................................................................ www.cancer.org/treatment/supportprograms/hopelodge
Medicare.gov ...................................................................................... www.medicare.gov
NeedyMeds ........................................................................................ www.needymeds.com
Partnership for Prescription Assistance ........................................... www.pparx.org
Patient Access Network Foundation ................................................ www.panfoundation.org
Patient Advocate Foundation ............................................................ www.patientadvocate.org
Patient Services, Inc .......................................................................... www.patientservicesinc.org
RxAssist ............................................................................................. www.rxassist.org
RakPse ................................................................................................ www.rakpse.com
Social Security Administration ........................................................ www.ssa.gov
Social Security Disability Resource Center ...................................... www.ssrc.org
State Health Insurance Assistance Programs ................................... www.shipatac.org

IMMUNOTHERAPY
The Answer to Cancer ....................................................................... www.theanswertoacancer.org
Cancer Research Institute ................................................................. www.cancerresearch.org
Immuno-Oncology ............................................................................ www.immuno-oncology.com
Society for Immunotherapy of Cancer ............................................. www.sitcancer.org

KIDNEY CANCER
Action to Cure Kidney Cancer ......................................................... www.ackc.org
Kidney Cancer Association .............................................................. www.kidney.org
National Kidney Foundation ............................................................ www.kidney.org

MENTAL HEALTH SERVICES
American Psychosocial Oncology Society Helpline ................................ 866-276-7443

NUTRITION
American Cancer Society ................................................................. www.cancer.org
CancerCare ......................................................................................... www.cancercare.org
LIVESTRONG Foundation ................................................................. www.livestrong.org
OncoLink ............................................................................................ www.oncolink.org
PearlPoint Nutrition Services .......................................................... www.pearlpoint.org
Physicians Committee for Responsible Medicine ................................ www.pcrm.org/health/cancer-resources

PAIN MANAGEMENT
American Chronic Pain Association .................................................. theacpa.org
Cancer Pain Research Consortium ................................................... www.cancerpainresearchconsortium.org
LIVESTRONG Foundation ................................................................. www.livestrong.org
This patient education guide was produced with support from:

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