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Second Edition

IMMUNOTHERAPY *for the treatment of* GENITOURINARY CANCERS

Content includes

- BLADDER CANCER
- KIDNEY CANCER
- PROSTATE CANCER

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Society for Immunotherapy of Cancer

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Immunotherapy for the Treatment of Genitourinary Cancers

Second Edition

IN THIS GUIDE

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Society for Immunotherapy of Cancer

→ **The Society for Immunotherapy of Cancer (SITC)** is the world's leading member-driven organization specifically dedicated to improving cancer patient outcomes by advancing the science and application of cancer immunotherapy. Established in 1984, SITC, a 501(c)(3) not-for-profit organization, serves scientists, clinicians, academicians, patients, patient advocates, government representatives and industry leaders from around the world. Through educational programs that foster scientific exchange and collaboration, SITC aims to one day make the word "cure" a reality for cancer patients everywhere.

FOR MORE INFORMATION SEE PAGE 13

For more information on cancer immunotherapy...

Visit **sitcancer.org/patientcourse** for patient resources from the Society for Immunotherapy of Cancer (SITC)

Discuss immunotherapy as a part of your new path forward

Receiving a cancer diagnosis can feel overwhelming, and it may be difficult to digest all the new information you've been given. The first step toward understanding it is to know the specific type and stage of your diagnosis and how immunotherapy may fit into your treatment plan.

This guide explains bladder, kidney and prostate cancers, the immune system, immunotherapy and the types of immunotherapy approved for genitourinary (GU) cancers, and ways to help manage your treatment experience and potential side effects. 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.

A good source of information about immunotherapy is the Society for Immunotherapy of Cancer (SITC), a member-driven organization specifically dedicated to improving cancer patient outcomes by advancing the science and application of cancer immunotherapy.

To learn more about immunotherapy, its research and how it is improving outcomes for many cancer types, go to the SITC website for patients at www.sitcancer.org/patient on your device or computer.

THE GENITOURINARY SYSTEM

Cancer can develop in almost any part of the body, including the GU system, which is made up of the parts of the body that involve the male and female urinary tracts and the male reproductive organs (see Figure 1).

Bladder

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 bladder is a hollow organ that stores urine before it exits the body during urination. It can hold approximately two cups (500 cc) of urine. The flexible, muscular bladder wall contracts to move urine out of the body through a tube called the urethra. The bladder wall is composed of four layers: urothelium, lamina propria, muscularis propria and serosa.

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.

Bladder cancer tumors can be classified as one of three types.

1. **Noninvasive bladder cancer** hasn't 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.

Kidneys

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.

The kidneys are part of the urinary tract, and their main function is to filter the blood. These two bean-shaped organs are 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 cm to 12 cm) long, which is about the size of a fist.

All of the blood in the body passes through the kidneys many times each day, and the kidneys filter out excess water, salt and waste products. The end result of this filtering process is urine, which then travels to the bladder, where it's stored until urination. The kidneys also play a role in controlling blood pressure and making red blood cells.

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, transitional cell, collecting duct, renal medullary carcinoma and unclassified. Knowing the subtype can both influence treatment choices and help doctors determine if the cause of the cancer may be related to an inherited genetic syndrome.

Prostate

Prostate cancer occurs when normal cells within the prostate gland mutate and grow out of control, usually forming a tumor of

FIGURE 1
GENITOURINARY ANATOMY

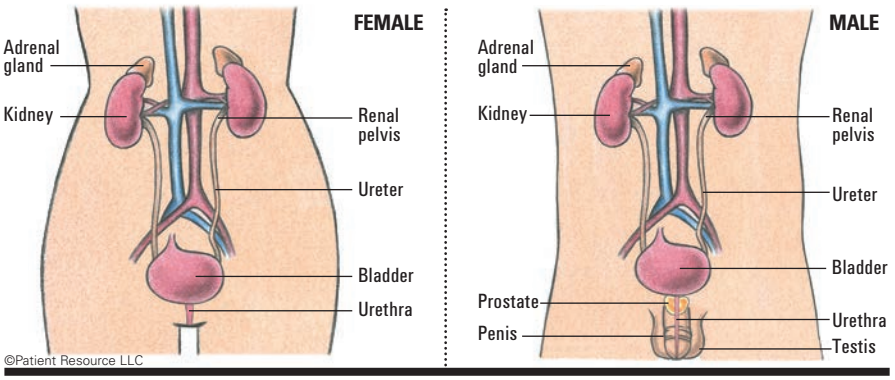
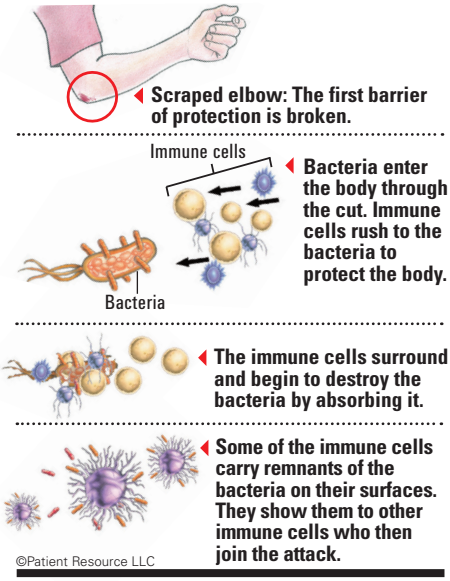


FIGURE 2
NORMAL IMMUNE RESPONSE



abnormal cells. Most prostate cancers grow slowly and stay in the prostate.

Part of the male reproductive system, the prostate gland is located below the bladder, in front of the rectum and at the base of the bladder (see Figure 1, page 1). The prostate makes seminal fluid that carries and protects sperm in semen. Just behind the prostate are the seminal vesicles, a pair of small glands that manufacture and store most of the seminal fluid. The urethra is a tube that goes through the prostate and carries urine and semen from the body through the penis.

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.

WHAT IS THE IMMUNE SYSTEM?

To understand how your immune system can be used to treat cancer, it's helpful to know it's a complex network of cells, molecules, organs and lymph tissues working together to defend the body against germs, microscopic invaders and even cancer cells.

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 or foreign). Viruses are one type of germ that can infect humans as they enter into the normal cells of the body. The immune system has developed sophisticated ways to determine if a cell is normal or may contain a virus, or is abnormal for other reasons, such as injury or cancer.

Once the immune system determines that a cell is abnormal (or foreign to the body), it begins a series of reactions to identify, target and eliminate the infected cell. This process represents a way to protect against injury and foreign substances. When you scrape your elbow, for example, the skin's protective barrier is broken, and harmful non-self substances, such as germs, can easily enter the body (see Figure 2, page 1).

HOW THE IMMUNE SYSTEM WORKS TO ELIMINATE CANCER

Each part of the immune system plays a role in defending the body. Like any good team, these parts must be able to alert each other and communicate messages so the system can respond quickly to threats. Most cells communicate by sending chemical signals.

The surface of a cell is not completely round and smooth. It is covered with receptors and proteins, which work like puzzle pieces. Proteins (sometimes called "ligands" when they stick out of the surface of cells) have "tabs" that stick out, and receptors have "spaces" that curve inward. When the puzzle pieces fit together (known as binding), chemical signals and information are exchanged in a biochemical reaction. Cells also contain various proteins, sugars, fats and other molecules that stick out of their surfaces. These components contain information that is shared between cells.

An immune response typically begins when B-cells and helper T-cells identify a threat (non-self antigen) and tell the rest of the immune system. The body then ramps up its production of T-cells to fight. Killer T-cells are sent to destroy cells that contain the non-self antigens. Regulatory T-cells are sent to slow the immune system down once the cells that contain non-self antigens have been eliminated. This prevents the killer T-cells from attacking healthy parts of the body. T-cells then return to normal levels.

The immune system uses this same process to recognize and eliminate cancer cells, but the process is more complicated. Cancer cells are created by the body, so the normal ways to find and fight invading germs from outside the body aren't always effective. The immune system may have difficulty identifying cancer cells as non-self. It may still see them as part of the body and not coordinate an attack. If the body can't tell the difference between tumor cells and normal cells, the tumor cells may be able to "hide" from the immune system.

Cancer cells are smart. Over time, they can change and use multiple methods to escape or confuse the immune system. One way is to produce proteins on their surface to hide from the immune system, like camouflage. Another is to create their own messengers (cytokines), which enable the cancer cells to communicate and confuse other immune cells. That allows the cancer to take control of certain parts of the process that the body uses to regulate the immune response. So, 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 referred to as the tumor microenvironment.

Immunotherapy offers a way to help the immune system outsmart the cancer cells. The various forms of immunotherapy are able to take the brakes off the immune system, boost the immune system with modified T-cells, or can be combined with certain types of chemotherapy, targeted therapy or radiation therapy.

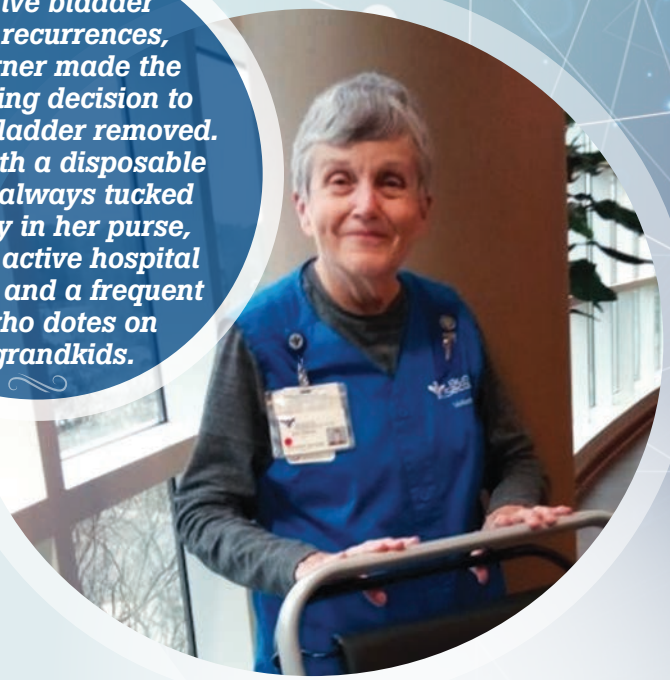
Read on to learn about these strategies and how they reinforce the immune system to find and destroy cancer cells. ■

Questions for your doctor

- **Am I a good candidate to receive immunotherapy?**
- **Will I have other treatments along with immunotherapy?**
- **How will we know immunotherapy is working?**
- **What side effects are associated with immunotherapy?**
- **How can the side effects be managed?**

A neobladder is the way to go for this survivor

After five bladder cancer recurrences, Ann Garner made the life-altering decision to have her bladder removed. Today, with a disposable catheter always tucked discreetly in her purse, she is an active hospital volunteer and a frequent flier who dotes on her grandkids.



I'd never heard of bladder cancer until my diagnosis in 2005. My grandpa died of colon cancer, my father and brother lived through prostate cancer and two aunts survived breast cancer. But cancer in the bladder was a new one for me and my husband, Clarence. As it turned out, this was just the beginning of how bladder cancer would change both our lives in the years to come.

In 47 years of marriage, I saw my husband cry only once. Just a week after we learned I had cancer, he had a stroke. He broke down in his hospital room. "Here I am in this (darned) hospital bed with this (darned) stroke," he said, "when I should be taking care of you." I squeezed his hand and told him to think of our wedding vows; we'd promised for better, for worse, in sickness and in health. "We'll take care of each other," I told him. "We'll get through this together." And that's exactly what we did for the next five years.

The cancer was diagnosed at Stage I. Both tumors were small and hadn't grown into the bladder wall. My urologist explained the standard of care for early-stage bladder cancer was bacillus Calmette-Guérin (BCG). It's injected straight into the bladder. Because it doesn't go through your whole system like many other treatments, my side effects were minimal. Heavy fatigue the next day was about it. I hadn't retired yet from 32 years as a secretary at our county high school, so I'd schedule late Thursday afternoon treatments, take Friday off to rest and be back to work Monday.

Noninvasive bladder cancer has a high recurrence rate, about 50 percent within the first five years. Mine came back within six months. Over the next four years, I had five recurrences and one borderline, always with multiple small tumors. We stayed with BCG treatments, adding another immunotherapy after two years. I believe those treatments and my follow-ups – every three months – kept the tumors from progressing past Stage I. But we lived with the fear that the next tumors could be later-stage.

My urologist felt strongly that my bladder should be removed before tumors became invasive and broke through the bladder wall. He referred me for a second opinion at a large teaching and research hospital. The bladder cancer specialist agreed with my urologist: my bladder had to come out.

He performed a radical cystectomy with lymph node dissection, removing my entire bladder. A partner in his practice then began reconstructive surgery to create a "neobladder" replacement using a small segment he removed from my small intestine. He stretched and shaped the piece of intestine to form a pouch, connecting the top to the ureters running from the kidneys and the bottom to the urethra, just like a real bladder. If all went well with the neobladder, I'd be able to urinate the normal way after an adjustment period.

It was a huge decision, but my urologist really put us at ease. He clearly described the risks and benefits, answering all our questions. He explained that it's a complex surgery with no guarantees. Also, a neobladder can stop working. After a lot of discussion and prayers, we said, "Let's go for it," and I've never had a single regret.

A year later, life was pretty much back to normal when the unthinkable happened. Clarence, my rock for nearly half a century, was also diagnosed with bladder cancer. His was Stage IV, and he was gone in less than six months. Until something like that happens, you don't realize how much "family" you really have. Besides two wonderful daughters, their husbands and my three adorable grandkids, I was supported by a loving church family and school family. I also had a close friend to confide in and my faith to comfort me.

The neobladder worked for four-and-a-half years. Since then, I've needed to "self-catheterize" three times a day. I insert a small disposable catheter into my urethra to drain the urine in my neobladder into the toilet.

Today, I volunteer two days a week transporting patients at a nearby hospital. Recently, a patient mentioned that she prays her cancer goes into remission. So I told her I am a cancer survivor myself. She said, "You had cancer, and you're pushing my wheelchair down these long halls?" I laughed and said I get in my steps without paying a club membership.

Many people think their life is over when they hear the word "cancer." I am living proof that it isn't. ■

Understanding the many ways to jumpstart an immune response

Through clinical trials, researchers have discovered multiple ways to harness the potential of the body's own immune system and enable it to recognize and eliminate cancer cells. Today, several types of immunotherapy are approved to treat bladder, kidney and prostate cancers.

IMMUNE CHECKPOINT INHIBITORS

Checkpoints keep the immune system "in check" by turning off immune cells or killing the immune cells. This may be normal after an infection has been cleared, but, in cancer, this may occur prematurely, allowing the cancer to continue to grow. Other cells called regulatory T-cells may also turn down activated immune cells. When the correct checkpoint proteins and cell receptors connect, a series of signals is sent to the immune system to slow down once an immune response is finished. Three checkpoint receptors have been used in cancer treatment. (Others have been identified as potential drugs, but these are the only ones useful so far.)

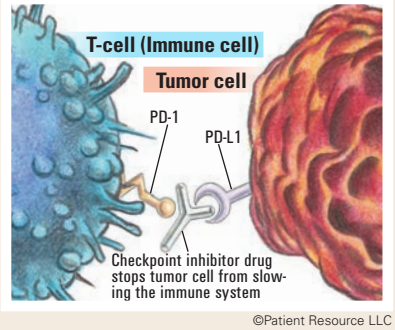
1. **CTLA-4 (cytotoxic T-lymphocyte-associated protein 4)** is a receptor that binds with certain molecules to tell the immune system to slow down.
2. **PD-1 (programmed cell death protein 1)** is a receptor involved with telling T-cells to stop and reducing the death of regulatory T-cells (suppressor T-cells). Both of these effects slow down an immune response. PD-1 can tell the immune system to slow down only if it connects with its natural ligands, PD-L1 or PD-L2.
3. **PD-L1 (programmed cell 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 stop. PD-L1 is commonly expressed by cancer cells, and this can communicate through PD-1 on T-cells to eliminate killer T-cells near the cancer cell.

When PD-1 (the receptor) and PD-L1 (the protein) combine, the reaction signals it's time for the T-cell to slow down. CTLA-4, however, can connect with more than one protein and also tells the immune system to slow down.

Checkpoint inhibiting drugs prevent connections between checkpoints. This keeps the immune response active, which allows the immune cells to continue fighting the cancer. Immune checkpoint inhibitors help the immune system to better recognize cancer cells as foreign cells.

IMMUNE CHECKPOINT INHIBITORS

An immune response is controlled with checkpoints, which are the "brakes" of the immune system. If the checkpoints PD-1 and PD-L1 connect, the immune system slows down and becomes less efficient at finding and attacking cancer cells. Immune checkpoint inhibitors prevent PD-1 and PD-L1 from connecting, enabling the immune system to continue working hard to eliminate cancer cells.



MONOCLONAL ANTIBODIES

Antibodies (a type of protein) are the body's way of tagging a specific antigen (foreign substance). They bind to the antigen, which allows the rest of the immune system to recognize the antigen as foreign and target it for destruction.

Monoclonal antibodies (mAbs) (pronounced "mab") are laboratory-made antibodies that are designed to target specific tumor antigens. They can 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. Then it attaches to the surface, gets swallowed by the tumor cell and breaks down inside the cell, releasing the toxin and causing cell death.

Different types of mAbs are used in cancer treatment, but they should not be confused with mAbs that directly attack certain components in or on cancer cells, a type of treatment known as targeted therapy.

- **Naked mAbs** work by themselves. No drugs or radioactive particles are attached.
- **Conjugated mAbs** have a chemotherapy drug or a radioactive particle attached to them. They are used to deliver treatment to the cancer cells.
- **Bispecific mAbs** are made up of two different mAbs and can attach to two different proteins at the same time. In some cases, the two proteins may both be on a cancer cell. In other cases, one protein may be on a cancer cell and one on a T-cell, thereby connecting the T-cell to a cancer cell.

NONSPECIFIC IMMUNE STIMULATION

This treatment strategy boosts the whole immune system instead of boosting it against one specific antigen. It can be used alone or in combination with other treatments to produce increased and longer-lasting immune responses. Different types of nonspecific immune stimulation used in GU cancers include cytokines and modified bacteria.

- **Cytokines** aid in immune cell communication and play a big role in the full activation of an immune response. This approach works by introducing large amounts of laboratory-made cytokines to the immune system to promote nonspecific immune responses as a systemic therapy. Two types of cytokines are used to treat GU cancers. Interleukins help regulate the activation of certain immune cells. Interferons boost the ability of certain immune cells to attack cancer cells.
- **Modified bacteria,** such as bacillus Calmette-Guérin (BCG), have been changed to ensure that they will not cause a harmful infection while stimulating an immune response in certain cancers. These may be given as an injection, infusion or as an intravesical (directly into the bladder) therapy.

VACCINES

Two types of vaccines are used against cancer. Preventive vaccines are given before a person develops cancer with the goal of stopping it from forming. Therapeutic vaccines treat existing cancers. These vaccines are created from viruses, tumor cells or white blood cells that have been changed in a laboratory. They activate T-cells against the cancer and direct these T-cells to the cancer cells. Some are custom-made for the patient's tumor type while others are "off-the-shelf" vaccines that contain one to more than 100 targets (also known as antigens) common to a specific type of cancer. ■

Research advances immunotherapy treatments for GU cancers

Most immunotherapies commonly used to treat or slow disease progression in GU cancers were once studied, fine-tuned and approved through medical research called clinical trials. With the help of volunteers diagnosed with GU cancers, clinical trials investigate new immunotherapy drugs or drug combinations to find out if they are safe, more effective than the current standard of care or provide a new patient benefit, such as milder side effects.

Within the past few years, immunotherapy for GU cancers has become an intensive area of clinical trials research. The advances that have resulted have led to rapid approvals for several new drugs and drug combinations, providing more treatment options – and more hope – to people diagnosed with bladder, kidney and prostate cancers.

Many studies focused on GU cancers are underway to research new cancer vaccines and reengineered cytokines with fewer serious side effects. Another very active area of research is focused on developing additional immune checkpoint inhibitors, which allow the immune system to continue its fight against cancer by blocking specific proteins on T-cells (see *Treatment Options*, page 4).

Immunotherapy has changed the treatment landscape for GU cancers, leading more people to consider clinical trials as a first treatment option, particularly with late-stage cancer. Ask your doctor about clinical trials or research online (see *Assistance*, page 12). In some cases, a clinical trial may offer the best chance for a positive outcome. ■

WHAT ARE CLINICAL TRIALS?

- Clinical trials are medical research studies that are frequently used to test new therapies.
- Enrollment in clinical trials is voluntary.
- The details of a trial are outlined in the *Informed Consent* form, which participants must sign before beginning a trial.
- Participants can withdraw from a clinical trial at any time for any reason.

MYTHS vs FACTS

A clinical trial is a last resort. In some situations, a clinical trial may offer the best option among treatments you're considering and may even be the first option to consider.

If my doctor doesn't bring it up, I can't participate. Many trials take place at the same time, making it very difficult for your doctor to know about every trial. That's why you're encouraged to search for a clinical trial on your own.

I'll have to travel to a major city to take part in a trial. Not necessarily. Although some people travel to take advantage of some trials, more are available all over the country in hospitals, treatment centers and doctor's offices.

Once I start the trial, I have to finish it. Participation is always voluntary. You may choose to leave the trial at any time, for any reason, and opt for standard-of-care treatment.

I'm too old to be in a clinical trial. Seniors may respond differently to treatment and may develop different side effects. Having them enrolled in a trial helps researchers develop the right treatments for older people.

BENEFITS OF PARTICIPATION

- Access to leading-edge treatments that aren't yet available for your type or stage of disease.
- Typically higher level of care because you will be closely monitored by your oncologist and the clinical trial medical team.
- Being an active partner in your own care.
- Knowing you are contributing to the future of cancer care.

HOW TO FIND A CLINICAL TRIAL

- Ask your doctor about available trials for which you may qualify.
- Search online. Start with this list of clinical trial sites. Depending on your diagnosis, there could be hundreds. Ask friends and family to help.
- Have your exact diagnosis, pathology report and treatment details available to see if you meet a trial's criteria.
- Discuss possible trials with your doctor to determine whether they are an option for you.

CLINICAL TRIAL SITES

ACT (About Clinical Trials)
learnaboutclinicaltrials.org

Center for Information & Study on Clinical Research Participation
www.searchclinicaltrials.org

CenterWatch
www.centerwatch.com

ClinicalTrials.gov
www.clinicaltrials.gov

National Cancer Institute
www.cancer.gov
Bladder Cancer Clinical Trials
Clinical Trials to Treat Kidney (Renal Cell) Cancer
Prostate Cancer Clinical Trials

See more links on page 12.

QUESTIONS TO ASK YOUR DOCTOR

Should I consider a clinical trial?

What tests and treatments are involved?

Is travel required to participate?

Will you continue to manage my care?

Will it affect my daily life, such as my ability to work?

How long will the trial last?

Unlocking the immune system's potential offers new hope

Immunotherapy is making it increasingly possible for many people with GU cancers to live longer, better-quality lives because training the immune system to respond to cancer has the potential for a more lasting response that can extend beyond the end of treatment. Multiple types of immunotherapy have been approved for GU cancers and are detailed in this section.

Treatment options for GU cancers may include surgery, chemotherapy, immunotherapy, radiation therapy or targeted therapy, and they may be used alone or in combination. Clinical trials may also be considered if any of the standard-of-care therapies are not effective.

Your doctor will create your treatment plan based on the location, stage, grade, size and extent of the cancer, whether it is primary or recurrent (has returned), your overall health, personal preferences and other factors. Discussing the goal of treatment and the potential side effects and long-term effects of each therapy will be key to helping you make informed decisions.

Immunotherapy for GU cancers may be used as first- or second-line therapy. First-line therapy is the first treatment given for a disease. When used by itself, first-line therapy is the one accepted as the best treatment. Second-line therapy is given when the first-line therapy doesn't work or stops working.

You will need to meet certain criteria to be a candidate for immunotherapy. If you have a pre-existing autoimmune disorder, be sure to discuss it with your doctor. Your doctor may test your blood or tumor for biomarkers that may qualify you for immunotherapy. Likewise, a history of certain infections, such as hepatitis B or C and tuberculosis, are important for your doctor to know before making a decision about your treatment.

Biomarkers are substances, such as genes, proteins or molecules, produced by cancer cells or other cells in the body. Biomarkers are also called tumor markers, molecular markers, biological markers or serum markers. Biomarkers that may be tested in GU cancers for immunotherapy are PD-L1 expression, and levels of microsatellite instability-high (MSI-H) and mismatch repair deficiency (dMMR).

MSI-H describes cancer cells that have a greater than normal number of genetic markers called microsatellites, which are short, repeated sequences of DNA. Every time a cell reproduces itself, it makes a copy of its genes and DNA. During the process, errors in duplication can be made, much like a misspelled word. The body normally corrects the error, but sometimes it isn't caught and fixed. It then becomes a mutation that is reproduced in later versions of the cell. Cancer cells that have large numbers of microsatellites may have defects in the ability to correct mistakes that occur when DNA is copied. Research has shown that cancers with MSI-H features respond better to immunotherapy. MSI-H is often tested in certain types of cancer, such as colorectal cancer, but may not always be tested in GU cancers. You can ask your health care team about testing your tumor for this biomarker.

Immunotherapy is not effective for every person, even if it is approved for that person's cancer type. Scientists are studying patient responses to immunotherapy to find out why. They are also investigating other methods for using the immune system to fight cancer to improve the effectiveness of this treatment (see *Clinical Trials*, page 5).

Immune checkpoint inhibitors may have serious side effects called immune-related adverse events (irAEs) because they can overstimulate the immune system, causing it to attack healthy tissue. It's important to be alert to any symptoms of these side effects and report them immediately to your health care team (see Table 1, page 10). Your doctor will monitor you closely during treatment.

BLADDER CANCER

The U.S. Food and Drug Administration (FDA) approved the first-ever immunotherapy in 1990, and it was bacillus Calmette-Guérin (BCG) for bladder cancer. It was considered a breakthrough for modern immunotherapy and is now a standard-of-care treatment. Today, more types of immunotherapy are approved to treat bladder cancer.

Immune Checkpoint Inhibitors

This class of immunotherapy blocks PD-1 and PD-L1 from connecting, which prevents the immune system from slowing down its attack on cancer. These medications are given intravenously (IV) through a needle inserted into a vein in your arm and are considered systemic, meaning they travel throughout your body (see Figure 2).

Immune checkpoint inhibitors are approved for urothelial carcinoma, a type of bladder cancer. These are approved for bladder cancer that is locally advanced (cancer that has spread to nearby tissue or lymph nodes) or metastatic, which has spread to other areas of the body. For some diagnoses, your doctor must perform PD-L1 testing to determine if your level is high enough for an immune checkpoint inhibitor. Some are approved for first-line therapy and others are approved for second-line therapy.

You may qualify for first-line treatment if your tumors express PD-L1 or you cannot receive chemotherapy. If you meet any of the following criteria, you may qualify for an immune checkpoint inhibitor as a second-line therapy:

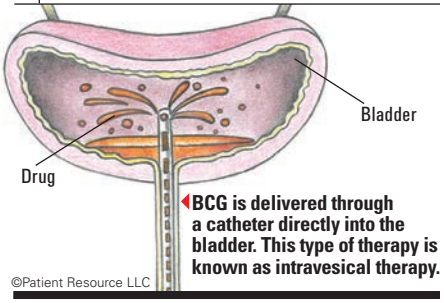
- You cannot receive any platinum-containing or cisplatin chemotherapy regardless of PD-L1 status.
- You previously had chemotherapy but the cancer returned.
- You have had disease progression following prior treatment, have no other treatment alternatives and test positive for microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR).

Monoclonal Antibodies

This type of immunotherapy was recently approved for bladder cancer. The monoclonal antibody (mAb) approved for urothelial carcinoma is a conjugated mAb, meaning it combines two types of drugs: an antibody and a chemotherapy.

The antibody allows the drug to target specific receptors on a cancer cell and then delivers the chemotherapy directly to it. This mAb is approved for locally advanced or metastatic urothelial cancer in patients who previously received an immune checkpoint inhibitor and a platinum-containing chemotherapy. It is considered a second-line therapy.

FIGURE 1
ANATOMY OF BLADDER AND BCG TREATMENT



Nonspecific Immune Stimulation

Two classes of this type of immunotherapy have been approved by the FDA for treating urothelial cancer: cytokines and modified bacteria (see *Treatment Options,* page 4).

Two types of cytokines are approved for use in urothelial cancer: interleukins and interferons, which were some of the first types of immunotherapy approved.

The other immunotherapy is a modified bacteria that has been changed to ensure it will not cause an infection while stimulating an immune response. This modified bacteria for bladder cancer was the first immunotherapy ever approved. It continues to be one of the main treatments for nonmuscle-invasive bladder cancer.

The modified bacteria is 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). The drug attaches to the inside lining of the bladder and stimulates the immune system to destroy the tumor. It is approved for early-stage bladder cancer and to reduce the risk of recurrence in noninvasive bladder cancers, commonly after surgery to remove the tumors.

Clinical Trials

Research to find other forms of immunotherapy for bladder cancer is currently underway, and new therapies may be approved in the future. One focus is on drugs that block CTLA-4, an immune checkpoint pathway (see *Treatment Options*, page 4).

Investigators continue to evaluate multiple types of immunotherapy for treating earlier stages of bladder cancer and recurrent cancer. Ask your doctor if you should consider a clinical trial (see *Clinical Trials*, page 5).

FDA-APPROVED BLADDER CANCER IMMUNOTHERAPIES

Cytokine
- interferon alfa-2b (Roferon-A, Intron A, Alferon)

Immune checkpoint inhibitors
- atezolizumab (Tecentriq)
- avelumab (Bavencio)
- durvalumab (Imfinzi)
- nivolumab (Opdivo)
- pembrolizumab (Keytruda)

Modified bacteria
- bacillus Calmette-Guérin (BCG)

Monoclonal antibody
- enfortumab vedotin-ejfv (Padcev)

As of 4/14/20

KIDNEY CANCER

Immunotherapy has expanded the landscape of treating advanced renal cell carcinoma (RCC), the most common form of kidney cancer. In certain situations, it has become standard of care as first-line therapy for advanced RCC. Recently, the U.S. Food and Drug Administration (FDA) has approved several combination immunotherapy treatments. These medications are given intravenously (IV) through a needle inserted into a vein in your arm and are considered systemic, meaning they travel throughout your body (see Figure 2).

Immune Checkpoint Inhibitors

More options for treating kidney cancer are now available due to the approval of immune checkpoint inhibitors. In many cases, this class of immunotherapy is standard of care for advanced RCC, and some immune checkpoint inhibitors are also considered first-line therapy. The inhibitors currently approved block PD-1, PD-L1 or CTLA-4 (see *Treatment Options*, page 4). The FDA has also approved multiple immune checkpoint inhibitor combinations for advanced and metastatic RCC. Combinations with some targeted therapies have also been approved.

You may qualify for first-line treatment with some of the immune checkpoint inhibitors if you have advanced RCC or are classified as intermediate or poor-risk and haven't had previous treatment.

This class may also be used as second-line therapy for advanced RCC if you previously received antiangiogenic targeted therapy or your tumors test positive for microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR), and your tumors progressed after previous treatment and you have few alternative options.

FDA-APPROVED KIDNEY CANCER IMMUNOTHERAPIES

Cytokines
- interferon alfa-2b
- interleukin-2 (IL-2) (Aldesleukin, Proleukin)

Immune checkpoint inhibitor
- nivolumab (Opdivo)

POSSIBLE COMBINATION THERAPIES
- avelumab (Bavencio) and axitinib (Inlyta)
- ipilimumab (Yervoy) and nivolumab (Opdivo)
- pembrolizumab (Keytruda) and axitinib (Inlyta)

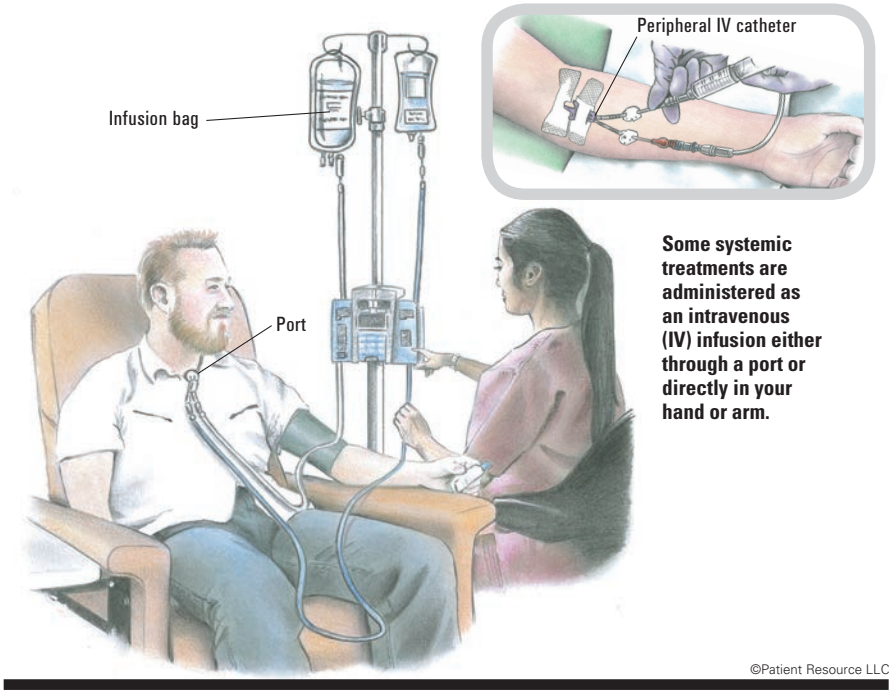
As of 4/14/20

Nonspecific Immune Stimulation

Two cytokines, a type of nonspecific immune stimulator, were the first type of immunotherapy approved for RCC: interleukins and interferons. They are not as widely used today as immune checkpoint inhibitors.

A type of interferon is still occasionally used in combination with a targeted therapy for metastatic RCC. Researchers in clinical trials are testing if cytokines make a good combination with immune checkpoint inhibitors. But immune checkpoint inhibitors and targeted therapy options have largely

FIGURE 2
SYSTEMIC THERAPY



Some systemic treatments are administered as an intravenous (IV) infusion either through a port or directly in your hand or arm.

replaced the use of interferon.

High-dose interleukin was one of the first immunotherapies approved to treat metastatic RCC. It offered a longer duration of complete remission, but patients are now carefully selected for this treatment because of the high level of side effects.

Clinical Trials

Immunotherapy for RCC is a large focus in clinical trials. Researchers are studying cancer vaccines to treat kidney cancer and prevent a recurrence with advanced RCC. Modified cytokines are also an area of research. The goal is to create an effective treatment with fewer serious side effects. With the increased use of immune checkpoint inhibitors, studies are ongoing to find more that are effective in kidney cancer. Ask your doctor if you are a candidate for a clinical trial.

PROSTATE CANCER

A treatment vaccine is the first and only immunotherapy for prostate cancer. The U.S. Food and Drug Administration (FDA) approved it for asymptomatic or minimally symptomatic metastatic castration-resistant (hormone refractory) prostate cancer. It is an antigen-presenting cell-based treatment vaccine, and it is a systemic therapy that is given intravenously (IV) through a needle inserted into a vein in your arm (see Figure 2, page 7).

Vaccine

This treatment vaccine stimulates the immune system to recognize and attack prostate cancer cells. Each dose is specially prepared for each patient and requires several visits to the physician. First, white blood cells are removed from the man's blood. They are enhanced to fight the prostate cancer and then infused back into the man through a vein. The aim of the treatment is to delay growth of the cancer and extend life. The treatment is used alone as a first-line therapy or with other treatments such as radiation or hormone therapy.

You may be a candidate for this treatment if you are on hormone therapy and have a rising prostate-specific antigen (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, receiving 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 is collected is sent to a special facility where a portion of the white blood cells are modified to be able to stimulate the immune system against the prostate cancer cells. The vaccine induces prostate-specific T-cells that can 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 intravenously (IV) through a vein in your arm. 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 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 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 online schedules and calendar apps that are available. Many have helpful reminder features.

If you need additional treatment after receiving this vaccine, other options, such as chemotherapy, hormone therapy and radiotherapy, may be available to you.

FDA-APPROVED PROSTATE CANCER IMMUNOTHERAPY

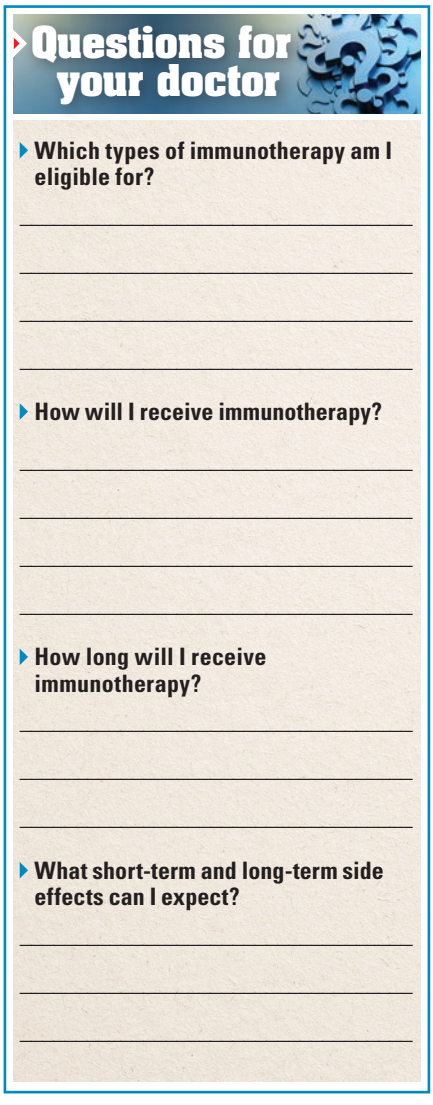
Vaccine

- sipuleucel-T (Provenge)

As of 4/14/20

Clinical Trials

Other types of immunotherapy are being evaluated in clinical trials. Ask your doctor if this may be a treatment option for you (see *Clinical Trials*, page 5). ■



Sound advice from a dedicated wife and caregiver

During the past two years, Roxana Phillips has felt scared, anxious, angry and lonely. She's also felt positive, passionate, grateful and loved. Why all the ups and downs? Because the love of her life was diagnosed with advanced prostate cancer, and she is his caregiver.

Cancer has affected many dear people close to me. We lost my mom to breast cancer when I was 17. My dad died of melanoma years later. My niece is a mucosal melanoma survivor, and I had skin cancer. My best friend and a beloved uncle succumbed to liver cancer, and my twin brother is a testicular cancer survivor. Therefore, I've always been very aware of my and my husband's health, which probably explains why I noticed symptoms even before Doug did.

After six months of doctor's appointments, tests and monitoring, Doug learned he had aggressive prostate cancer at 65 years old. This diagnosis, however, isn't just his. We're in this together. The love we have for each other is ridiculously strong. I can't imagine my life without him, and I am committed to doing everything I can to help him live a full life.

We are extremely grateful to our wonderful doctors, nurses and radiation oncologist. A referral to an outstanding oncologist led to hormone therapy, surgery and radiation therapy. I wanted them to surgically remove everything that was suspicious. Ultimately, it was Doug's body and his final call.

Doug had hormone shots to shrink the tumor followed by a minimally invasive robot-assisted radical prostatectomy. The surgeon discovered the cancer had spread to the seminal vesicles and one lymph node. After recuperating, Doug began about 38 days of radiation therapy to eliminate any remaining cancer cells. The treatment was successful.

About a year later, his PSA level began to rise again so the oncologist added a different hormone therapy to his treatment plan. I always keep an eye on him, often noticing major and minor side effects he doesn't seem to be aware of.

One morning, Doug admitted he'd been trying for a few hours to urinate with no success. He had a doctor's appointment for it later that day, but I suggested we get ready to make the 40-minute highway journey early. I offered to drive because I could tell he wasn't feeling well. He balked a little at leaving so early, but I'm glad I insisted. We weren't even halfway to the doctor's office before he was in extreme pain, agonizing like I'd never heard before. I drove straight to the emergency room.

A urethral stricture (likely from scar tissue) caused his urine to back up. His pain was excruciating. After a few hours and fervent prayer, he urinated, and the pain went away immediately. Surgery shortly afterward corrected the problem, and he had to self-catheterize for three months to keep his urethra from narrowing again.

That was by far the worst experience we'd had. I felt helpless and angry at not being able to relieve his pain. It was a lesson in trusting in God and my instincts to get to the doctor sooner, and remaining calm behind the wheel.

Doug's doctors monitor him closely. He isn't nervous before his follow-ups, but I am. It's overwhelming, and having a solid support system helps. My faith in God is the foundation of mine. I believe He is a healer and has a hand in everything that happens to us.

Family and friends are supportive, but my family is scattered around the world and I never want to overload my friends. So Doug and I attend an extremely helpful local support group twice a month called the Prostate Network. I checked them out and told Doug to come with me when he was ready. They have a meeting that focuses on educating survivors and their family members or caregivers about treatment advances. Another puts prostate cancer survivors and caregivers, which mostly means wives, in separate rooms. We listen to doctors and speakers and then talk about everything — new medicines, tests, medical breakthroughs, and ways to manage side effects, exercises, diet and more. We're always sharing and learning from each other.

I wish more wives would attend. It's possible they aren't sure how to show support. I hope hearing my story helps them realize how valuable their presence can be. It is at times like these when our husbands can really use our help. ■

Practical advice from Roxana

- *Make sure he goes to his preventive medical appointments.*
- *Be aware of his health and habits, and encourage him to see a doctor when you notice a change. (It's not nagging.)*
- *Keep a log of his test results, symptoms, doctors' visits and medications.*
- *Choose a medical team you trust and respect.*
- *Go to every appointment and treatment. I often pick up info he doesn't hear and vice versa.*
- *Be involved in treatment planning, but respect his choices. It's his body.*
- *Find a support group for you both. Never be afraid to share or ask for advice.*
- *Have a support system rooted in faith, church, family, friendship or whatever gives you comfort.*
- *Take care of yourself: keep your medical appointments, eat nutritiously, exercise, relax and ask for help. It's easier said than done, but keep trying!*

Manage side effects to improve quality of life

When you're facing cancer treatment, it's normal to have concerns about how side effects may alter your day-to-day routine and activities. Almost all cancer treatments come with side effects, which can vary from mild to severe, and immunotherapy is no different. Help is offered through supportive care, sometimes called palliative care. This valuable set of services is available at most cancer centers and hospitals to address the physical, emotional, practical, financial and spiritual challenges you and your loved ones may face following your cancer diagnosis.

A key focus of supportive care is to provide solutions to help prevent, minimize and manage your treatment-related side effects and cancer-related symptoms. The better you feel, the better you'll be able to complete your scheduled therapies. Research has shown that receiving these services as soon as possible after diagnosis improves overall quality of life and may make it easier to complete your treatment.

Side effects of immunotherapy may not appear until a few months into treatment — or even years afterward. They may affect one or more systems of your body not related to the cancer site. Each drug has different possible side effects. Before treatment begins, ask your doctor for a list of symptoms to watch for and strategies for managing them. Determine when you should contact your doctor's office about symptoms and when to seek emergency care. Alert your health care team as soon as symptoms arise, even those that seem trivial. Prompt treatment can help prevent more serious complications and can keep you more comfortable during treatment.

POTENTIALLY SEVERE SIDE EFFECTS

Although severe side effects are not common, they are possible. The chance of a side effect and the type varies with different immunotherapy drugs and combinations.

Cytokine release syndrome can occur if immune cells affected by treatment rapidly release a large amount of cytokines into the bloodstream. Symptoms may include fever, headache, nausea, rapid heartbeat, decreased blood pressure and difficulty breathing. Reactions are usually mild but can be life-threatening.

Immune-related adverse events (irAEs) can develop rapidly and become serious or even life-threatening without swift medical attention (see Table 1). They may occur if the treatment overstimulates the immune system.

You may not be able to physically feel these symptoms at first, so it's essential to schedule and keep all medical appointments. Routine laboratory tests and imaging may detect irAEs at an early stage. Be sure to contact your medical team if symptoms occur between appointments and remain alert to the possibility of irAEs for up to two years after treatment ends. An important point is that many of the side effects associated with immunotherapy can be easily corrected if they are treated quickly. Therefore, it is very important to contact your health care team as soon as possible if a side effect develops.

Infection can occur as a result of low white blood count (neutropenia). Contact your doctor immediately – do not wait until the next day – if you have any of these symptoms: oral temperature over 100.5°F, chills or sweating; body aches, chills and fatigue with or without fever; coughing, shortness of breath or painful breathing; abdominal pain; sore throat; mouth sores; painful, swollen or reddened skin; pus or drainage from an open cut or sore; pain or burning during urination; pain or sores around the anus; or vaginal discharge or itching.

Infusion-related reactions may occur with immunotherapy given intravenously (IV), usually soon after exposure to the drug. Common symptoms are itching, rash or fever; more serious symptoms include shaking, chills, low blood pressure, dizziness, breathing difficulties and irregular heartbeat. Reactions are generally mild but can become life-threatening if not promptly treated.

COMMON SIDE EFFECTS

These side effects may occur with the types of immunotherapy used to treat the genitourinary cancers discussed in this guide, so only some will apply to your treatment. Keep in mind that each individual reacts differently to cancer therapy. Symptoms may be more

TABLE 1
IMMUNE-RELATED ADVERSE EVENTS (irAEs)

Body System	irAE	Symptoms & Signs
Cardiovascular	Myocarditis	Chest pain, shortness of breath, leg swelling, rapid heartbeat, changes in EKG reading, impaired heart pumping function
Endocrine	Endocrinopathies	Hyperthyroidism, hypothyroidism, diabetes, extreme fatigue, persistent or unusual headaches, visual changes, alteration in mood, changes in menstrual cycle
Gastrointestinal	Colitis	Diarrhea with or without bleeding, abdominal pain and cramping, bowel perforation
Liver	Hepatitis	Yellow skin or eyes (jaundice), nausea, abdominal pain, fatigue, fever, poor appetite
Nervous system	Neuropathies	Numbness, tingling, pain, a burning sensation or 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
	Headache	Pain that persists for more than 24 hours and does not respond to pain medications
Pulmonary/lung	Pneumonitis	Chest pain, shortness of breath, unexplained cough or fever
Renal/kidneys	Nephritis	Decreased urine output, blood in urine, swollen ankles, loss of appetite
Skin	Dermatitis	Rash, skin changes, itching, blisters, painful sores

intense when these drugs are combined or given with another type of treatment.

Appetite loss or decreased appetite can potentially lead to serious complications. Your body needs good nutrition to help maintain your strength, to heal if you've had surgery and to keep you as healthy as possible during treatment. Poor nutrition can slow your recovery and can worsen other treatment-related side effects, such as fatigue and weakness. Your health care team may refer you to a dietitian.

Constipation is an uncomfortable condition that is more easily prevented than resolved. Before beginning treatment with this potential side effect, talk to your doctor about preventive medications or dietary and lifestyle changes you can make. If you are already constipated, do not use over-the-counter remedies without first checking with your health care team.

Coughing is a common symptom but may also signal pneumonitis (inflammation of the lungs) or a respiratory tract infection. Contact your doctor immediately so the cause of the cough can be determined and managed, particularly if the cough is new or changing.

Diarrhea, if left untreated, can lead to dehydration and loss of essential nutrients. It may also signal an immune system nearing overload. Ask your doctor about preventive medication before your treatment begins. If you have more than six episodes in 24 hours or diarrhea that routinely keeps you homebound, contact your health care team. Never use over-the-counter anti-diarrheals without checking with your health care team.

Fatigue related to cancer treatment is more severe and lasts longer than typical fatigue, and it may not be relieved by sleep. A proven remedy is regular exercise. Even a daily 10-minute walk can make a difference. Aim for eight hours of sleep each night, pace yourself each day and save your energy for people and activities that are most important to you.

Flu-like symptoms include fever, chills, aches, headaches, drowsiness, nausea, vomiting, runny nose, loss of appetite and changes in blood pressure. Report symptoms to your doctor immediately, as they may signal a more serious condition.

Cancer diagnosis can affect your emotional well-being

Being diagnosed with cancer and undergoing treatment can affect you emotionally as well as physically. It's common to experience anger, fear, sadness, guilt and anxiety. Supportive care services can connect you with resources to help you work through your feelings. Consider talking with a mental health professional who sees cancer patients. These suggestions may also help.

- Allow yourself to fully express your emotions when they occur to help you avoid releasing bottled-up feelings in unhealthy ways.
- Cancer survivors can be a great source of support, friendship and insight. Ask about cancer support groups available in your community, options for online support or phone-based peer support programs.
- Explore meditation, gentle yoga, massage therapy, deep breathing exercises or other relaxation techniques.
- Get outside, regardless of the season. Getting fresh air and being out in nature can be therapeutic.
- Express your feelings by writing in a journal.
- Take charge of things you can control. If decision-making feels overwhelming, ask loved ones to handle routine decisions for now.
- Give yourself permission to grieve the loss of the life you had before cancer. Share your feelings with someone you trust.
- Staying positive is important, but it's just as important to give yourself a break when you need it.
- Find something to laugh about every day.
- It's extremely important to talk with your doctor about feeling depressed, hopeless or desperate, particularly if these feelings last more than a few days. Seek medical attention immediately for thoughts of suicide.

Joint pain (arthralgia), **muscle pain** (myalgia) or **pain** in general may occur and typically resolves when treatment ends. People with rheumatologic or other autoimmune conditions may see these symptoms worsen or "flare," so ensure your doctor is aware of all your medical conditions.

Nausea may occur, although vomiting is less common. Both are easier to prevent than to control, so ask your doctor about antiemetics (anti-nausea drugs) before beginning a treatment with this potential side effect. Or you can ask about resources for non-drug approaches, such as progressive muscle relaxation, guided imagery, acupuncture, self-hypnosis or biofeedback.

Peripheral neuropathy is a nerve problem that can cause tingling, numbness, pain, muscle weakness or a burning sensation. It usually begins in the hands or feet and progresses over time. Normal activities such as maintaining your balance, writing legibly and buttoning clothes can become difficult. Talk to your doctor about how to get relief.

Shortness of breath (dyspnea) or trouble breathing after walking or exercise may be a sign of an infection or inflammation in the lungs. If this occurs, with or without an accompanying cough, you should inform your health care team.

Skin reactions may include sunburn-like redness and irritation; bumpy or itchy rashes; dry, flaky skin that may itch; blisters or hives; inflammation; or changes in skin color or cracking around the fingertips. Reactions can potentially become severe without prompt treatment, so report these symptoms to your health care team. ■

Questions for your doctor

- **How likely is it that I will have serious side effects?**
- **How can I prepare for potential side effects? What happens if side effects interrupt my daily routine?**
- **How soon after I receive treatment will side effects start?**
- **Whom should I call if I think I have a side effect?**

Support and financial resources available for you

BLADDER CANCER

Action on Bladder Cancer ..... actiononbladdercancer.org
American Bladder Cancer Society ..... bladdercancersupport.org
Bladder Cancer Advocacy Network ..... www.bcan.org
United Ostomy Associations of America, Inc. ..... www.ostomy.org
Your Cancer Game Plan ..... www.yourcancergameplan.com/bladder

CAREGIVERS & SUPPORT

4th Angel Patient & Caregiver Mentoring Program 4thangel.org
CanCare ..... cancare.org
CANCER101 ..... www.cancer101.org
Cancer and Careers ..... www.cancerandcareers.org
Cancer*Care* ..... www.cancercare.org
Cancer Connection ..... www.cancer-connection.org
Cancer Hope Network ..... www.cancerhopenetwork.org
Cancer Information and Counseling Line 800-525-3777
Cancer Really Sucks! ..... www.cancerreallysucks.org
Cancer Support Community ..... cancersupportcommunity.org
Cancer Support Helpline 888-793-9355
Cancer Survivors Network ..... csn.cancer.org
Caregiver Action Network ..... www.caregiveraction.org
CaringBridge ..... www.caringbridge.org
Center to Advance Palliative Care ..... www.capc.org
Chemo Angels ..... chemoangels.com
The Children's Treehouse Foundation ..... www.childrenstreehousefdn.org
Cleaning for a Reason ..... www.cleaningforareason.org
Connect Thru Cancer ..... www.connectthrucancer.org
Cooking with Cancer ..... www.cookingwithcancer.org
Family Caregiver Alliance ..... www.caregiver.org
Fighting Chance ..... www.fightingchance.org
Friend for Life Cancer Support Network friend4life.org, 866-374-3634
The Gathering Place ..... www.touchedbycancer.org
Guide Posts of Strength, Inc. ..... www.cancergps.org
The Hope Light Foundation ..... hopelightproject.com
Imerman Angels ..... www.imermanangels.org
Lacuna Loft ..... www.lacunaloft.org
The LGBT Cancer Project – Out With Cancer ..... www.lgbtcancer.org
Livestrong Foundation ..... www.livestrong.org
LivingWell Cancer Resource Center ..... www.livingwellcrc.org
Lotsa Helping Hands ..... www.lotsahelpinghands.com
LUNGevity Caregiver Resource Center ..... www.lungevity.org/caregiver
The Lydia Project ..... thelydiaproject.org
MyLifeLine.org ..... mylifeline.org
Patient Empowerment Network ..... www.powerfulpatients.org
Patient Power ..... www.patientpower.info
SHARE Caregiver Circle ..... www.sharecancersupport.org/caregivers-support
Stronghold Ministry ..... www.mystronghold.org
Support Groups ..... www.supportgroups.com
Triage Cancer ..... www.triagecancer.org
Vital Options International ..... www.vitaloptions.org
Walk With Sally ..... www.walkwithsally.org
Well Spouse Association ..... www.wellspouse.org
weSPARK Cancer Support Center ..... www.wespark.org

CLINICAL TRIALS

ACT (About Clinical Trials) ..... www.learnaboutclinicaltrials.org
Cancer Support Community ..... cancersupportcommunity.org
Center for Information & Study on Clinical Research Participation ..... www.searchclinicaltrials.org
CenterWatch ..... www.centerwatch.com
ClinicalTrials.gov ..... www.clinicaltrials.gov
Lazarex Cancer Foundation ..... www.lazarex.org
Livestrong Foundation ..... www.livestrong.org
National Cancer Institute ..... www.cancer.gov/clinicaltrials
NCI Contact Center (cancer information service) 800-422-6237

IMMUNOTHERAPY

Cancer Research Institute ..... www.cancerresearch.org/patients
Cancer Support Community ..... cancersupportcommunity.org
Immuno-Oncology ..... www.immunooncology.com
Society for Immunotherapy of Cancer ..... www.sitcancer.org

KIDNEY CANCER

Action to Cure Kidney Cancer ..... www.ackc.org
Kidney Cancer Association ..... www.kidneycancer.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
Cancer*Care* ..... www.cancercare.org
Cancer Support Community ..... cancersupportcommunity.org
Livestrong Foundation ..... www.livestrong.org
OncoLink ..... www.oncolink.org
PearlPoint Nutrition Services ..... www.pearlpoint.org

PROSTATE CANCER

Arkansas Prostate Cancer Foundation ..... www.arprostatecancer.org
Center for Prostate Disease Research ..... www.cpdr.org
da Vinci Surgery ..... www.davincisurgery.com
Ed Randall's Fans for the Cure fans4thecure.org
Malecare, Inc. ..... www.malecare.com
Prostate Advocates Aiding Choices in Treatment ..... paact.help
Prostate Cancer Foundation ..... www.pcf.org
Prostate Cancer International, Inc. ..... pcainternational.org
Prostate Cancer Journey ..... prostate-cancer-log.blogspot.com
Prostate Cancer Research Institute ..... www.pcri.org
Prostate Cancer Roundtable ..... www.prostatecancerroundtable.net
Prostate Conditions Education Council ..... www.prostateconditions.org
The Prostate Health Education Network ..... prostatehealthed.org
The Prostate Net ..... www.theprostatenet.org
Prostate Network ..... www.prostatenetwork.org
Urology Care Foundation ..... www.urologyhealth.org
Us TOO International Prostate Cancer Education & Support Network ..... www.ustoo.org
ZERO – The End of Prostate Cancer ..... www.zerocancer.org

REIMBURSEMENT & PATIENT ASSISTANCE PROGRAMS

Astellas Pharma Support Solutions ..... www.astellaspharmasupportsolutions.com/patient, 800-477-6472
AstraZeneca Access 360 ..... www.myaccess360.com, 844-275-2360
AstraZeneca Patient Savings Programs For Specialty Products ..... www.astrazenecaspecialtysavings.com, 844-275-2360
AstraZeneca Prescription Savings Program (AZ&ME) ..... www.azandmeapp.com, 800-292-6363
Bavencio CoverOne ..... coverone.com, 844-826-8371
Bristol-Myers Squibb Access Support ..... bmsaccesssupport.bmscustomerconnect.com/patient, 800-861-0048
Bristol-Myers Squibb Patient Assistance Foundation ..... bmspaf.org, 800-736-0003
Dendreon On Call ..... www.dendreononcall.com, 877-336-3736
Genentech Access Solutions ..... genentech-access.com/patient, 866-422-2377
Genentech BioOncology Co-pay Assistance Program ..... copayassistancenow.com, 855-692-6729
Genentech Patient Foundation ..... gene.com/patients/patient-foundation, 888-941-3331
Imfinzi Access 360 ..... www.myaccess360.com/patient/patient-branded-imfinzi/home.html, 844-275-2360
Intron A Patient Assistance Program merckhelps.com/intron%20%20a, 800-727-5400
Keytruda KEY+YOU ..... keyplusyou.com, 855-398-7832, press 2
Keytruda Patient Assistance ..... merckaccessprogram-keytruda.com/hcc/, 855-257-3932
Merck Access Program ..... merckaccessprogram.com/hcc/
Merck Helps ..... merckhelps.com, 800-727-5400
Opdivo with You ..... patientsupport.bmscustomerconnect.com/opdivo-with-you-registration, 855-673-4861
Padcev Support Solutions ..... astellaspharmasupportsolutions.com/products/padcev/index.aspx, 888-402-0627
Pfizer Oncology Together ..... pfizeroncologytogether.com/patient, 877-744-5675
Pfizer RxPathways ..... pfizerrxpathways.com, 844-989-7284
Prometheus IV Bolus Proleukin Inpatient Reimbursement 877-776-5385
Provenge Dendreon On Call ..... www.dendreononcall.com, 877-336-3736
Tecentriq Access Solutions ..... genentech-access.com/patient/brands/tecentriq, 866-422-2377
Yervoy Patient Access, Reimbursement and Co-Pay Support ..... yervoy.com/adjuvant/financial-resources, 800-861-0048

➥ *For more resources, go to* PatientResource.com

GLOSSARY

Words to know: These definitions may help as you discuss your diagnosis and treatment with your health care team.

Antibody: A protein produced by the immune system in response to a foreign substance (antigen), such as a virus or bacteria.

Antigen: Any foreign substance that triggers the body's immune response. Antigens include chemicals, bacteria, viruses, toxins, abnormal proteins on cancer cells and other substances from outside the body.

B-cells: Specialized immune cells that help defend the body by producing antibodies that bind to specific antigens (foreign substances), marking 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. Immunotherapy is typically a biologic product.

Cytokines: Proteins that help immune cells communicate with each other to regulate specific functions in the immune system. Laboratory-made versions, such as interferons and interleukins, are designed to help fight cancer.

Helper T-cells: This type of immune cell can identify antigens (substances foreign to the body) and communicate with killer T-cells, B-cells and others to coordinate an immune response against the antigens.

Immune-related adverse events (irAEs): Side effects that can occur if immunotherapy overstimulates the immune system, causing inflammation in one or more systems of the body. Most irAEs are mild to moderate, but they can be serious and even become life-threatening without swift medical attention.

Immune checkpoint inhibitors: Drugs that block specific immune checkpoint pathways, allowing the immune system to recognize and attack cancer cells.

Immune checkpoint pathways: A system that prevents over-activation of the immune system by regulating T-cell activity at different stages of the immune response. Turning on an immune checkpoint typically shuts down the immune response. Immune checkpoint inhibitors can prevent this shutdown.

Killer T-cells: A type of immune cell that can kill certain cells the immune system identifies as foreign to the body, such as cancer cells and virally-infected cells. Also called cytotoxic T-cells.

Lymphocytes: Specific immune cells (white blood cells) in lymph tissue and blood that help the body's immune system fight cancer and infection. The main types are B-lymphocytes (B-cells) and T-lymphocytes (T-cells).

Memory cells: Certain T-cells and B-cells involved in a specific immune response keep circulating through the body long afterward, "remembering" the antigen (foreign substance) if it reappears and coordinating an immediate immune response. The memory response protects people from getting certain diseases more than once and may help defend against cancer recurrence.

Microsatellite instability-high (MSI-H): Describes tumor cells with a high number of mutations (changes) in the microsatellites, which are short, repeated sequences of DNA. Knowing whether a tumor is MSI-H may help determine the best treatment.

Monoclonal antibodies (mAbs): Laboratory-made proteins created to target and bind with specific proteins or molecules on the surface of cancer cells. In cancer immunotherapy, mAbs may stimulate an immune response in the same way naturally produced antibodies do or may be used to block a specific interaction (for example, an interaction that shuts down the immune response).

Oncolytic virus: A virus that can infect and multiply within cancer cells, causing them to die. These naturally occurring viruses can also be manufactured to target and destroy specific tumor cells, or to create or improve an immune response.

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

Regulatory T-cells: Cells that generally shut down activated cancer-fighting T-cells at the end of an immune response. Certain tumor cells can increase this activity, reducing the overall immune response against cancer.

T-cells: A type of white blood cell (lymphocyte). T-cells develop into helper T-cells, killer T-cells, memory T-cells and regulatory T-cells that play essential roles in helping the immune system fight infection and disease. T-cell activation/activity is a key focus of immunotherapy research.

Some definitions courtesy of the website of the National Cancer Institute (www.cancer.gov)

SITC Guidelines: The Society for Immunotherapy of Cancer (SITC) offers guidelines for medical professionals regarding the recommended use of immunotherapy treatment and immune-related adverse event management. Guidelines for some genitourinary cancers and several other cancers are currently available at → **www.sitcancer.org/guidelines**

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