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Sixth Edition

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UNDERSTANDING CANCER IMMUNOTHERAPY

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Sixth Edition

UNDERSTANDING CANCER IMMUNOTHERAPY

IN THIS GUIDE

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FOR MORE INFORMATION SEE PAGE 16

For more information on cancer immunotherapy...

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

Harness and unleash the power of the immune system

Your immune system is a powerful protection mechanism that works around the clock to defend you from harmful germs and internal stresses to normal cells in the body. After years of research, doctors have found a way to unleash its cancer-fighting potential, too. Immunotherapy harnesses the power of the immune system by helping it recognize cancer cells that have been hiding and targeting them for destruction. This guide explains how the immune system works, the various types of immunotherapy available and ways to help manage your treatment and follow-up care.

To understand how your immune system can be used to treat cancer, it's helpful to know how it works. It's a complex network of cells, molecules, organs and lymph tissues working together to defend the body against germs and other microscopic invaders from the environment. It can protect against cell damage or stress, and even fight cancer cells.

A significant benefit of the immune system is its ability to create immunity, or protection, from infectious disease (see *How the Immune System Remembers,* below). A major advantage is that once the immune system has been engaged in fighting an infection, it can remember and provide long-term, in some cases life-long, protection against a specific infection. And this advantage is key to using immunotherapy against cancer.

Immunity can be natural (innate) or acquired (adaptive). People are born with natural immunity, which includes physical barriers to the internal body parts and offers several defenses against harmful microorganisms. Barriers include skin and mucous membranes, which prevent harmful substances from entering the body. This protection is non-specific, meaning it does not target any particular harmful organism.

The acquired immune system is built up over time through exposure to germs in the environment. This provides protection against multiple types of infections, and this occurs because infectious organisms (or germs) have proteins called antigens, which are substances that stimulate an immune response. Antigens include toxins, chemicals, bacteria, viruses or other substances that originate outside the body. The acquired immune system can adapt to new germs and remember them, providing longer-lasting protection. This long-lasting protection is called immune memory.

Germs sometimes get past these defenses. When you scrape the palm of your hand, for example, the barrier is broken and harmful substances can easily enter the body (see Figure 1). Immediately after the injury, 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 where antigens are entering the body. The immune cells identify the antigens as dangerous and begin to destroy them with a general attack. This is called an immune response.

HOW THE IMMUNE SYSTEM WORKS

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 non-self germ that can infect humans as they enter, and often hide inside, the normal cells of the body.

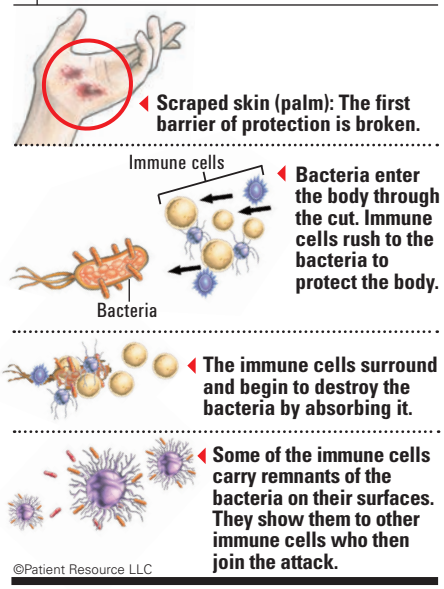
The immune system has developed sophisticated ways to determine if a cell is normal or if it may contain a virus or be abnormal for other reasons, such as injury or cancer. The immune system recognizes abnormal cells or germs by "seeing" antigens, which are the specific proteins or other molecules on the surface of an infected or abnormal cell. Once the immune system determines that a cell is not normal (or foreign to the body), the immune system begins a series of reactions to identify, target and eliminate the abnormal cell.

The driving force of the immune system is the lymphatic system, which is made up of the spleen, thymus, adenoids, tonsils and lymph nodes. Lymph, a clear fluid, circulates throughout the lymphatic system and through the lymph nodes. It collects and filters bacteria, viruses, toxins and chemicals, which are circulating in the lymphatic system and bloodstream. Lymph nodes are small bean-shaped structures located throughout the body, with large concentrations near the chest, abdomen, groin, pelvis, underarms and neck.

Lymph contains lymphocytes, a type of white blood cell that attacks infectious agents and abnormal 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. B-cells produce protein antibodies that attach to infectious organisms, such as bacteria and some viruses, marking them for destruction. However, they can only identify them, not destroy them. Plasma cells make antibodies to fight germs and infection. Memory cells help the body remember which antigens have been attacked previously so it can recognize them more quickly if they return (see *How the Immune System Remembers*, below).

FIGURE 1
NORMAL IMMUNE RESPONSE



HOW THE IMMUNE SYSTEM REMEMBERS

One of the biggest strengths of the immune system is that it can develop immunity to an infectious disease so that the body doesn't get sick a second time. This is known as immunological memory.

Both memory B-cells and T-cells are created when the body is fighting an antigen. Both remember the specific antigen and continue to circulate in the bloodstream, waiting for it if it ever returns. This provides long-lasting immunity to many different types of possible threats. Common examples include the measles and chickenpox. Once you have been infected with these diseases, you rarely get them again.

The immune system's ability to recognize cancer cells when they try to return is a main goal of immunotherapy, and investigators believe that effective immunotherapy can result in cancer-specific memory cells. If the body can remember cancer and prevent it from recurring, this can lead to long-term, cancer-free remission and increased overall survival in a way that no other cancer therapies can.

T-cells also develop in the bone marrow and mature in the thymus into four cell types: helper, killer, regulatory and memory T-cells. Each responds to non-self antigens in different ways.

- **Helper T-cells** identify non-self antigens and tell other immune system cells to coordinate with the B-cells for an attack.
- **Killer T-cells** directly attack and destroy infected or cancer cells by releasing a protein that causes infected or cancerous cells to enlarge and burst.
- **Regulatory T-cells** slow down the immune system after an immune response, and they inhibit T-cells that attack healthy cells that weren't eliminated before leaving the thymus.
- **Memory T-cells** recognize and respond to previously encountered non-self antigens, and do so very quickly. Memory T-cells stay alive in your blood for years, continuing to fight the same invading cells.

All of the white blood cells circulate throughout the lymphatic system carrying out each cell's specific function. B-cells monitor for non-self antigens and alert the T-cells if they are found. T-cells then signal each other to attack and destroy the antigen. These parts must be able to alert each other and communicate messages so they can respond quickly to threats.

Most cells communicate by sending chemical signals. It's important to know that the surface of a cell is not completely round and smooth. It is covered with receptors and proteins, which work like puzzle pieces. Proteins 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 also contain information that is shared between cells. Thus, communication may occur when cells connect with each other through proteins and receptors on the surface. Alternatively, cells may also communicate by releasing chemical signals, which are called cytokines, when they signal cells of the immune system.

HOW CANCER HIDES FROM THE IMMUNE SYSTEM

An immune response begins when the immune system identifies an antigen as non-self. B-cells communicate to the T-cells that a threat has been identified. The B-cells make antibodies to flag the non-self antigen for the T-cells to attack. After being alerted by the B-cells, the T-cells produce more T-cells, then look for and destroy the non-self antigen. Once the antigen is gone, the immune system slows down to prevent the T-cells from attacking healthy parts of the body, and T-cells return to normal levels (see *How the Immune System Responds to a Threat*, page 3). Your doctor can use this information to determine if you have an infection because early after an infection, the white blood cells may increase, and then they return to normal when the infection is cleared. This can be easily measured by a blood test.

The immune system uses this same immune response process to recognize and eliminate cancer, but it becomes more complicated. Cancer cells are created by the body, so the normal ways to find and fight invading cells from outside the body aren't always effective. Because cancer cells are created from our own cells, the immune system may have difficulty identifying cancer cells as non-self and may 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. In addition, even if there is an initial immune response, it may be turned off by regulatory cells before the cancer is completely destroyed.

Cancer cells have also developed multiple methods to escape detection by the immune system. One way includes disguising themselves by producing proteins on their surface that mimic the proteins found on healthy cells. This makes them look like normal, healthy cells. If the cancer cells are successful, the immune system will be fooled and the cancer cells can continue to attack the body.

Another way includes creating chemical messengers to confuse communication between the immune cells. In some cases, they can trick the immune system into slowing down. This allows the cancer to take control of the process 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.

Cancer cells aim to weaken the immune system. The longer they face a weakened immune response, the more they're able to adapt and grow, and the easier it is for them to manipulate immune cells inside the tumor's location, sometimes called the tumor microenvironment.

Immunotherapy offers the immune system reinforcements to keep up its fight against cancer in multiple ways by preventing the system from slowing down, boosting it with modified T-cells or combining it with chemotherapy or radiation therapy. ■

» IMMUNE SYSTEM BASICS

Following are definitions for some parts of the immune system. More terms about immunotherapy are located in the Glossary, page 16.

Antibodies are proteins produced by the immune system in response to a foreign substance (antigen). Each antibody can bind to only one specific antigen to tag it for destruction.

Antigens are foreign substances that trigger an immune response. They can be toxins, chemicals, bacteria, viruses or other substances that come from outside the body.

B-cells are 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. They also can become plasma cells and memory cells.

Cytokines are proteins produced by immune cells that help foster communication between cells, and hence, help to coordinate an immune response. Cytokines were among the first immunotherapy drugs used to treat cancer.

Immune cells make up part of the immune system. These cells are created from stem cells in the body's bone marrow and later become other types of white blood cells.

Lymphatic system includes the bone marrow, spleen, thymus, lymph nodes and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells).

Lymphocytes are 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 include certain T-cells and B-cells that are involved in a specific immune response. They circulate through the body long after an initial immune response, "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.

Receptors (immune receptors) are 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.

T-cells are a type of immune cell that helps kill tumor cells and control immune responses. T-cells help the immune system fight infection and disease. T-cell activation/activity is a key focus of immunotherapy research.

White blood cells are part of the body's immune system. They help the body fight infection and other diseases. Lymphocytes are a type of white blood cell.

Treatment options expand with more immunotherapies available

Immunotherapy uses the power and complexity of the immune system to find and attack cancer cells. It is uniquely positioned to defeat cancer compared with other treatment options, such as surgery, chemotherapy, radiation therapy and targeted therapy. It uses the body's natural immune system to target cancer cells exclusively, leaving healthy cells alone. The immune system is smart and adaptable just like cancer, so it can learn to recognize cancer cells and attack them. It also has the ability to remember specific cancer cells so they can be found and targeted in the future if the cancer returns, which may provide a long-lasting response to treatment.

Another advantage of using immunotherapy is its effectiveness at treating cancers that are resistant to chemotherapy and radiation therapy. And, it is approved for multiple cancer types (see *FDA-approved Cancer Immunotherapies,* page 13). It is also being researched in clinical trials for use in other cancers, especially rare and hard-to-treat cancers, so more cancer types may have immunotherapy options in the future. In addition, studies are evaluating combining immunotherapy drugs with other immunotherapy drugs and other cancer treatments, such as chemotherapy. These studies have found promising combinations for the treatment of certain types of cancer.

In some cases, immunotherapy may be considered the standard-of-care therapy, which is the best treatment known for a particular cancer. It may be used as first-line or second-line therapy. First-line therapy is the first treatment given for a particular stage of cancer. Second-line therapy is given when the first-line therapy doesn't work or is no longer effective. Immunotherapy may also be given as local or systemic treatments. Local treatments are injected into a lesion or applied topically to the skin close to a cancer, whereas systemic treatments travel throughout the body and are usually given by an intravenous (IV) infusion or orally (see Figures 9 and 10, page 12).

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. Following are some of the types of immunotherapy used to treat cancer.

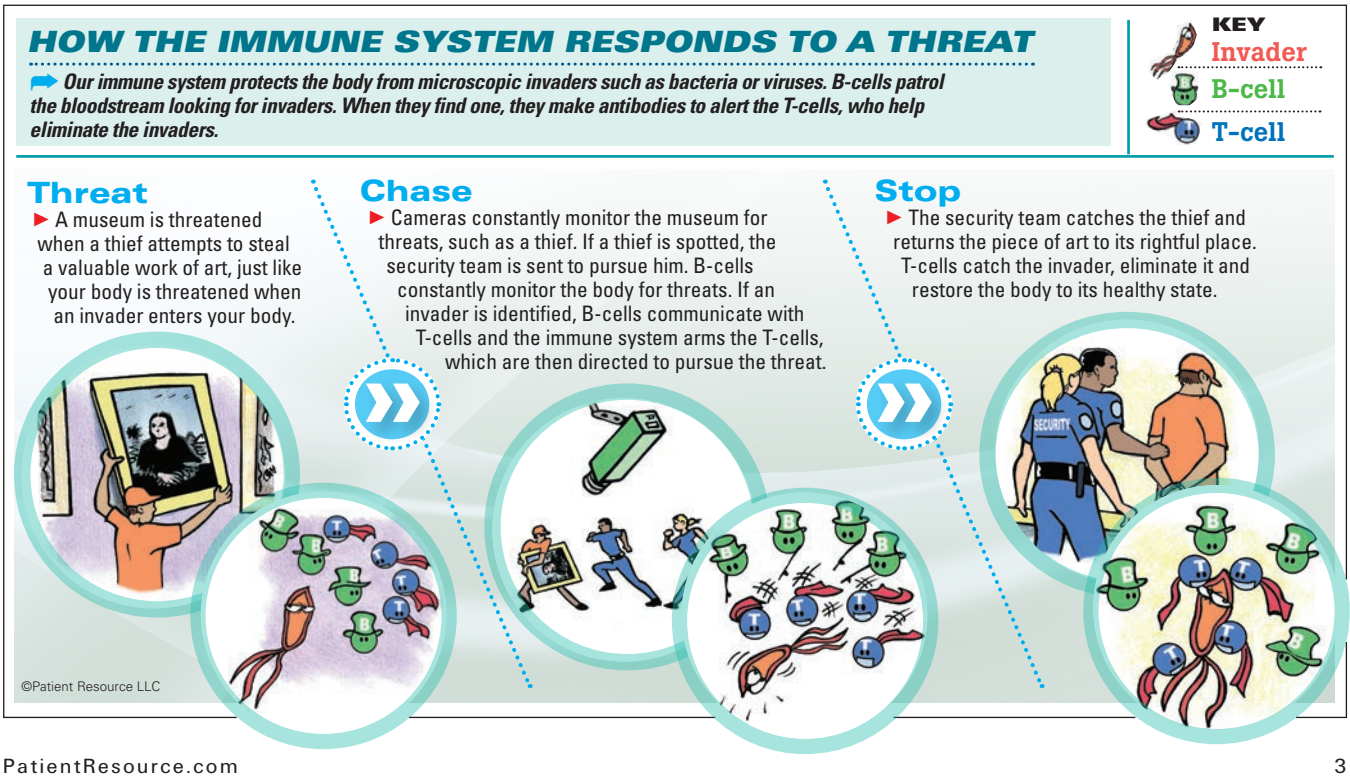
ADOPTIVE CELLULAR THERAPY

Also called adoptive cell therapy, cellular adoptive immunotherapy or T-cell transfer therapy, this treatment enhances or changes the body's immune cells to better fight cancer. It does this through different strategies.

In one strategy, a patient's T-cells are collected from a blood sample, and new receptors called chimeric antigen receptors (CARs) are added that enable the T-cells to recognize specific antigens (foreign substances) on cancer cells. These engineered T-cells are called CAR T-cells. They are multiplied in a laboratory and then infused back into the patient. The goal is for the T-cells to multiply, seek and destroy the cancer cells that carry those specific antigens.

Using tumor-infiltrating lymphocyte therapy, the doctor isolates T-cells that have attached to a patient's tumor (tumor-infiltrating lymphocytes, or TILs), helps them multiply outside of the body, and then administers them back to the patient.

Still being researched in clinical trials are T-cell receptor therapy and natural killer (NK) cell therapy. In some cases, a patient's T-cells are unable to recognize tumor cells or become activated. T-cells are removed and re-engineered in a laboratory with a new T-cell receptor that allows them to target specific cancer antigens. The modified T-cells are then injected back into the body. NK cell therapy focuses on natural killer cells, which



are a type of white blood cell. Adding CARs to NK cells to help them better target cancer cells is also under investigation.

IMMUNE CHECKPOINT INHIBITORS

The immune system generally makes enough white blood cells to fight non-self cells, such as bacteria and viruses, and is able to mobilize into larger numbers of infection-fighting cells when needed.

When the immune system is alerted to the threat of an antigen, such as by proteins found on bacteria or viruses, it ramps up production of T-cells, which attack and destroy the cells carrying the protein antigens. After an attack, the immune system must slow down so that the T-cells don't begin to attack healthy cells. The immune system is kept in check by turning off or killing the immune cells. It does this through the use of checkpoints, a natural set of biological checks and balances that regulates the immune system.

Checkpoints prevent the immune system from attacking itself and help to slow down a response to an antigen once it has been removed as a threat. This normally happens when the correct checkpoint proteins and cell receptors connect. A series of signals is then sent to the immune system to slow down once an immune response is finished. But the immune system sometimes allows cancer to grow unchecked because it may not recognize it as foreign, or the immune response may be shut down prematurely by checkpoints.

Three checkpoint receptors that slow down the immune system are used in cancer treatment: PD-1 (programmed cell death protein 1), PD-L1 (programmed death-ligand 1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4).

When PD-1 (the receptor) and PD-L1 (the protein) combine, the reaction slows down the immune system. PD-1 is found on T-cells and when it binds to PD-L1, the PD-1 causes the T-cell to stop functioning, and often the T-cell dies. Scientists discovered PD-L1 may be found on cancer cells and this can cause cancer-fighting T-cells to be destroyed. There are now diagnostic tests to determine how much PD-L1 is made by a cancer. CTLA-4 is another checkpoint like PD-1. CTLA-4, however, can connect with more than one protein, which is a more complex reaction than with PD-1 and PD-L1.

Checkpoint-inhibiting drugs prevent connections between checkpoints. They prevent the immune response from slowing down, which allows the immune cells to continue fighting cancer. Immune checkpoint inhibitors help the immune system to better recognize cancer cells as foreign cells.

Some immune checkpoint inhibitors are approved as tumor-agnostic treatment, which means they are approved to treat any kind of cancer that has the molecular alterations known as microsatellite instability-high (MSI-H), deficient mismatch repair (dMMR) or tumor mutational burden-high (TMB-H). 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 (dMMR). 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. When cancer cells have this feature, they are more sensitive to destruction by immune checkpoint inhibitors. Tumor mutational burden measures the number of mutations within a tumor. TMB-H describes cancer cells that have a high number of gene mutations. This may make it easier for the immune system to recognize these cells as foreign and attack them.

IMMUNOMODULATORS

Immunomodulatory drugs may stimulate or slow down the immune system in indirect ways. They may boost the immune system and the effects of other therapies on the tumor and the tumor microenvironment, slow or stop the growth of the tumor and its blood vessel formation, improve the bone marrow micro-

How Immunotherapy Is Given

Immunotherapy can be administered in different ways.

- **Intravenously (IV), which is injected into a vein in your arm.**
- **Orally, which is taken in pill form by mouth.**
- **Topically, which is applied to the surface of skin.**
- **Intratumorally, in which a drug is injected directly into the cancer.**
- **Intravesically, which is injected into the bladder.**

Identifying biomarkers to detect response to immunotherapy

Most cancer is caused by genetic changes in DNA. Detecting these changes at the microscopic level with biomarkers is becoming an increasingly valuable part of diagnosing and treating many cancers. As a result, the use of biomarkers is expanding rapidly.

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. Other biomarkers may be cells, especially immune cells.

Biomarkers may be prognostic, predictive or diagnostic. A prognostic biomarker provides information about a person's overall cancer outcome, regardless of therapy. Evidence suggests that certain T-cells, for example, when found at higher numbers in melanoma tumors, are associated with a better prognosis and response to immunotherapy. A predictive biomarker gives information about the effect of a specific treatment approach. Diagnostic biomarkers help determine the type of tumor.

The following biomarkers may be tested to determine eligibility for immunotherapy.

Microsatellite instability-high (MSI-H) or **deficient mismatch repair** (dMMR) may indicate if the cancer is caused by genes that have problems repairing themselves. Cancers with MSI-H features appear to respond better to immunotherapy.

High PD-L1 expression in the tumor cells or immune cells in the tumor's microenvironment may indicate that a patient may be a good candidate for immune checkpoint inhibitors. However, testing this biomarker alone is not sufficient to determine a therapeutic response to immunotherapy in all patients.

Tumor-infiltrating lymphocytes (TILs) are determined from a biopsy, and cancers with higher numbers of TILs and those with TILs inside the tumor have been shown to have a better prognosis and may respond better to immunotherapy. Some treatments result in higher TILs and may be a biomarker for response with these therapies.

Tumor mutational burden (TMB) is an assessment of the number of genetic mutations in a tumor. It can help doctors determine if a patient will respond to immunotherapy. It is believed that the higher the TMB level is, the more likely the patient will respond.

Not all people who receive immunotherapy respond. Researchers are not sure why this happens, and more research is needed so immunotherapy is only given to someone who may respond to it.

environment or have an anti-inflammatory effect, slowing the growth of the cancer. They are generally considered systemic treatments, but some may be given directly into the tumor.

MONOCLONAL ANTIBODIES

Antibodies (a type of protein) are the body's way of tagging a specific antigen (foreign substance) and are normally made by B-cells. Antibodies 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 "mabs") are laboratory-made antibodies designed to target specific tumor antigens. They can flag targeted cancer cells for destruction, block growth signals and receptors and deliver 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 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. For example, one side of the antibody can bind to an antigen on a cancer cell and the other side can bind to a receptor on a T-cell. This brings killer T-cells close to cancer cells and helps generate an immune response against cancer cells.

NONSPECIFIC IMMUNE STIMULATION

This treatment strategy boosts the whole immune system. It can be used alone or in combination with other treatments to produce increased and longer-lasting immune responses. Nonspecific immune stimulation includes 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 some 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 (see Figure 1, above right).

ONCOLYTIC VIRUS IMMUNOTHERAPY

This type of immunotherapy uses viruses that directly infect tumor cells to kill cancer cells and cause an immune response. It is typically given as a local treatment directly to the tumor. One oncolytic virus uses a weakened version of the herpes simplex virus. It has been changed from the original and contains granulocyte-macrophage colony stimulating factors (GM-CSFs), a type of cytokine that stimulates an immune response. The virus targets specific cancer cells, infects them and duplicates itself continuously within the cell until it ruptures. This rupture kills the cancer cell and releases the GM-CSF cytokine produced by the virus to promote an overall immune boost. This process increases the chance that the attack can also begin killing cancer cells that have not been infected with the virus.

Other viruses are also being evaluated as potential cancer treatments.

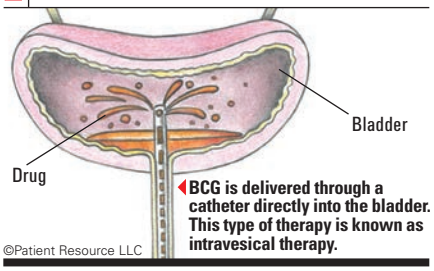
PHOTOPHERESIS

This type of immunotherapy is used to treat cutaneous T-cell lymphoma (CTCL), a rare type of NHL, and other blood disorders. It is a procedure in which blood is removed from the body and treated with ultraviolet light and drugs that become active when exposed to light. The blood is then returned to the body. It is being studied in the treatment of some blood and bone marrow diseases and graft-versus-host disease (GvHD).

RADIOIMMUNOTHERAPY

This is a type of radiation therapy in which a radioactive substance is linked to a monoclonal antibody (mAb) and injected into the body. The radioactive substance gives off radiation, which may help kill cancer cells. Radioimmunotherapy is being used to treat some types of cancer, such as lymphoma.

FIGURE 1
BCG TREATMENT



VACCINES

Two types of vaccines are used against cancer. Preventive vaccines are given before a person develops cancer. For example, the human papillomavirus (HPV) vaccine helps prevent infection from this virus but also protects against certain types of cancer associated with it. Therapeutic vaccines treat existing cancers and are created from viruses, tumor cells or white blood cells that have been changed in a laboratory. 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. ■

Questions for your doctor

- **What is the goal of my treatment plan?**
- **Am I a good candidate to receive immunotherapy?**
- **What is the process for receiving my immunotherapy treatment?**
- **How long will I receive treatment?**

Be your own advocate when searching online for a clinical trial

Within the past few years, immunotherapy has become an intensive area of clinical trials research. The resulting advances have led to approvals for several new drugs and drug combinations, providing more treatment options – and more hope – to people diagnosed with many types of cancer.

As you consider clinical trials, keep in mind that so many take place at the same time in a variety of locations that it is difficult for your doctor to know about them all. So while your health care team is exploring potential trials, you can, too. To help you get started, follow these step-by-step instructions.

1 Gather your exact diagnosis, pathology report, any imaging reports (such as from CTs or MRIs) and details of previous cancer treatments to help determine if you meet the basic eligibility criteria. Consider asking friends or family members to search as well.

2 Know where to look. Clinical trials search sites are hosted by a variety of organizations, and no single site contains every open clinical trial. New trials are continually being added, so check back often. You may also choose to keep searching while moving ahead with your treatment plan. Some internet sites that maintain up-to-date information on clinical trials are listed below.

3 Once you and your doctor find a clinical trial, it's important to know next steps. Although every clinical trial is different, most follow a general process. Your eligibility will be assessed when you and/or your doctor first contact the clinical trial coordinator to express interest and learn more details. If you are a likely candidate, you'll meet with the principal researchers to further determine your eligibility and answer your questions about the study. You may meet the clinical trial team, which may include doctors, nurses, specialists, the trial coordinator, social workers or other health care professionals. A physician trial investigator will enroll you in the trial and is responsible for the conduct of the trial.

4 Before entering the trial, you will be given an Informed Consent form that provides detailed information about it. Review the document carefully. Consider sharing it with loved ones. Discuss anything you don't understand with your doctor. Before you sign the Informed Consent form, contact your insurance provider to find out which procedures, tests, follow-ups, etc., are covered and which you may be required to pay out of pocket.

5 Continue to be your own advocate. After you begin a clinical trial, keep asking questions and alert your health care and trial teams about new symptoms and side effects. And remember, you may choose to leave the trial at any time, for any reason, and return to standard of care. ■

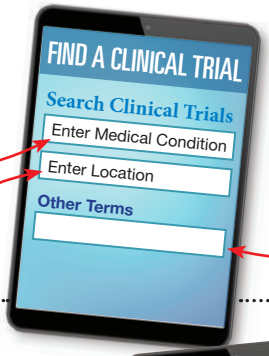
GETTING STARTED ON YOUR ONLINE SEARCH

Be an active participant in your own care by researching available trials online. These instructions will help guide you through the process.

[STEP 1] FILL IN YOUR INFORMATION

Enter Your Diagnosis
For example, enter "colon cancer." To create more options, you can also conduct a search for "advanced colon cancer," then compare results.

Desired Location
If you prefer a clinical trial close to home, enter your home address. Enter additional locations if you're willing and able to travel for treatment.



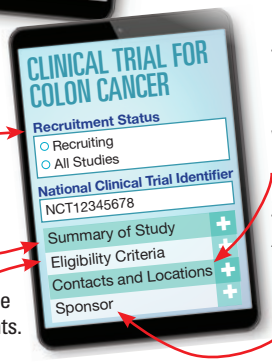
Other Terms
You can refine your search even more by adding a particular treatment type or genomic mutation. You can also add a National Clinical Trial identifier, which is a unique eight-digit code preceded by "NCT" that is assigned to each trial.

[STEP 2] READ YOUR SEARCH RESULTS

Recruitment Status
This indicates whether the trial is actively seeking patients, not yet recruiting or is otherwise inactive. The status will change, so check for updates.

Summary of Study
Here you'll find details about the purpose of the clinical trial and the treatment being studied. This section is usually written for health care providers, so it may be difficult to interpret. In that case, print out the information to discuss with your doctor.

Eligibility Criteria
This outlines the criteria you must meet to be eligible for the trial, such as the stage of disease, sites of metastasis, overall health requirements and previous treatments.



Contacts and Locations
This may contain contact information for the clinical trial investigators, staff or sponsors, who may be able to provide more details about the study.

Sponsor
This is the entity responsible for the clinical trial. It may be a pharmaceutical or biotechnology company, a university, the National Cancer Institute or others.

CLINICAL TRIAL SITES

- **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/clinicaltrials

IMMUNOTHERAPY HELPS SURVIVOR BECOME THE COMEBACK KING

Being diagnosed at 66 with Merkel cell carcinoma, a rare and aggressive type of skin cancer, was difficult for Gary King to accept. Given only six months to live, he tried conventional treatments. But when it continued spreading, his oncologist recommended an immunotherapy that was showing great promise treating this type of cancer. Within four treatments, the tumors were gone. Today, Gary is a huge proponent for immunotherapy and encourages others to try it. He is retired and living happily with his wife of more than 40 years.

One day while combing my hair, I felt a small bump on the back of my head on the right side. It felt like a pimple so I didn't think too much about it. About a week or two later, I noticed it had gotten bigger. I asked my youngest son, who is a nursing aide, and my wife to look at it. We thought it might be a pimple, cyst or a boil, but it wasn't red and didn't have any pus.

It continued to grow. About a month later, I called a dermatologist. She said it was not a cyst because it wasn't filled with liquid. She sent a sample to pathology, and six days later on December 27, 2016, she told me it was Merkel cell carcinoma, a rare and aggressive type of skin cancer. She explained it has a very poor outcome and that I was "in trouble." She connected me right away with a surgeon.

I'm a Vietnam veteran who flew medivac helicopters during the war, and I was never frightened then. But, hearing I had cancer scared me. I was afraid I was going to die.

I had the bump removed a week or so later. The surgery left a perfect circle, about the size of a mayonnaise jar lid, on the back of my head. The reconstructive surgeon created a scalp flap to cover the hole from the original surgery, then grafted a piece of skin from my thigh to my scalp. She secured everything in place with 50 staples.

Two weeks later, all the lymph nodes on the right side of my neck were removed. I followed that with 30 radiation treatments. I am not a claustrophobic person, but having that cage molded to your face and strapped down can definitely be scary. The music they piped into the room during my treatment helped. I had requested The Eagles. During the nine-minute treatment, I listened to "Hotel California," "Peaceful Easy Feeling" and "Witchy Woman." Knowing the songs helped me to know how much longer I had left in the treatment.

One month later, a PET revealed seven tumors, one in each femur, two in my liver and three in my lower vertebrae. I was officially diagnosed with Stage IV Merkel cell carcinoma and given only six months to live. I was devastated.

My oncologist suggested an immunotherapy that had just been approved. He explained the immunotherapy removes the mask from the cancer cells so your immune system can see them. Once the mask is gone, your immune system puts on its boxing gloves and beats up the cancer.

He advocated for me when my insurance declined to pay for it, and he was successful. I received my first dose on July 20, 2017, and continued treatment every three weeks.

A follow-up PET on October 5 overwhelmed the doctor. He said it wasn't good news. It was great news! He said my scan was dark as coal, meaning there was no sign of cancer. In technical terms, the tumors had been resolved.

I was in shock, but this time, it was the good kind. Within four treatments, I had gone from Stage IV cancer to remission. It was incredible!

Because this cancer often returns, I've continued the treatments with a growing number of weeks between doses. My doctor plans to keep me on it until I reach my five-year diagnosis anniversary.

The side effects are manageable. I am a bit short of breath when I first get up in the morning, but it goes away. My back and chest get itchy, but it's nothing a good stick can't take care of. I sneeze more, and always in threes. My sleep, appetite and energy are mostly unaffected. And, I get my infusion and drive myself home the same day.

Don't wait to get something checked out by a medical professional. And, always consider getting a second opinion. It may be helpful to find a research doctor who is more knowledgeable about immunotherapy. Go to reputable online resources to find more information. If you're not sure which ones, ask your doctor. There is an abundance of misinformation out there.

Immunotherapy is amazing. To me, it is the drug find of the century. If your doctor doesn't bring it up as a potential treatment or doesn't want to try it, ask why. It could be because it may not work for you, but you have nothing to lose by asking. Take charge, and don't give up. It helped me come back from Stage IV cancer. ■

Immunotherapy creates an optimistic outlook for many diagnoses

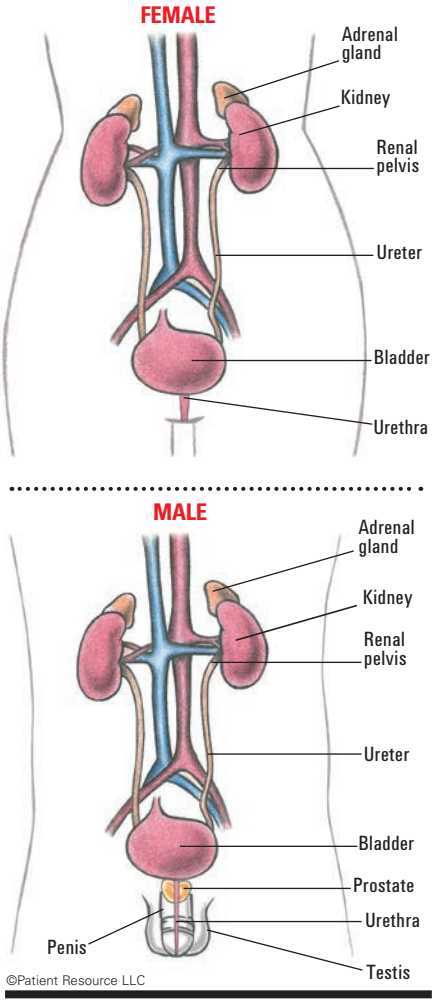
This section introduces the cancer types for which at least one type of immunotherapy is approved by the U.S. Food and Drug Administration (FDA) (see *FDA-approved Cancer Immunotherapies*, page 13). More cancer types and indications continue to be added as researchers work to improve existing therapies and explore new ones. Other novel treatments that are not yet approved for these and other cancer types may be available through active trials (see *Clinical Trials*, page 6).

BLADDER CANCER

The FDA approved the first-ever immunotherapy, bacillus Calmette-Guérin (BCG) for bladder cancer, in 1990. Today, more types of immunotherapy are approved to treat bladder cancer (see anatomy, Figure 1).

Immune checkpoint inhibitors are approved for urothelial carcinoma, a type of bladder cancer, which 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 (see *Identifying Biomarkers to Detect Response to Immunotherapy,* page 4). Some immunotherapy drugs are approved for first-line therapy and others are approved for second-line therapy.

FIGURE 1
GENITOURINARY ANATOMY
(Bladder, kidney and prostate cancers)



You may qualify for first-line therapy if your tumors express high levels of PD-L1 as determined by an FDA-approved test or if 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 for urothelial carcinoma:

- You cannot receive any platinum-containing or cisplatin chemotherapy regardless of PD-L1 status.
- You previously had chemotherapy but the cancer returned.
- You have disease progression after prior treatment, have no other treatment alternatives and your tumor tests positive for microsatellite instability-high, deficient mismatch repair or tumor mutational burden-high.

Also approved is a conjugated monoclonal antibody (mAb), meaning it combines two types of drugs: an antibody and a chemotherapy (see *Exploring Immunotherapy,* page 5). 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.

Cytokines and modified bacteria, two types of nonspecific immune stimulation, are also approved to treat urothelial cancer. The two types of cytokines are interleukins and interferons, which are some of the first types of immunotherapy approved.

A modified bacteria has been changed to ensure it will not cause an infection while stimulating an immune response. This modified bacteria for bladder cancer is the first immunotherapy ever approved and 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, page 5). 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.

BREAST CANCER

Immunotherapy may be an option for treating some advanced triple negative breast cancers, also called TNBC. TNBC is estrogen-receptor *(ER)*, progesterone-receptor *(PR)* and human epidermal growth factor receptor-2 (*HER2*) negative, and is a form of breast cancer that has not responded to drug treatment in the past.

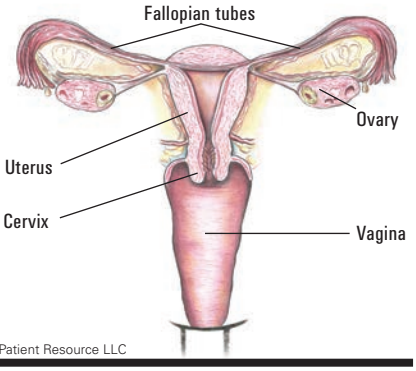
The first immunotherapy treatment approved targets PD-L1 positive, unresectable locally advanced or metastatic TNBC in combination with chemotherapy.

The other is a type of monoclonal antibody (mAb) known as a conjugated mAb. 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. It is approved for patients with metastatic TNBC who have received at least two prior therapies.

CERVICAL CANCER

Immunotherapy is an option for certain types of cervical cancer, which develops in the cervix, the lower, narrow end of the uterus that leads to the vagina (see anatomy, Figure 2). Approved as a second-line therapy, an immune checkpoint inhibitor treats recur-

FIGURE 2
FEMALE REPRODUCTIVE ANATOMY
(Cervical and endometrial cancers)



rent or metastatic disease for women whose tumors express PD-L1 as determined by an FDA-approved test and whose disease has progressed on or after chemotherapy.

COLORECTAL CANCER

Your doctor may use biomarker or genetic testing to determine the best treatment option for you (see anatomy, Figure 3). Testing for biomarkers in colorectal cancer is used to plan treatment. The most common biomarkers in colorectal cancer are *RAS*, *KRAS* and *NRAS* mutations. Your doctor may also test for the *BRAF* mutation, human epidermal growth factor receptor-2 (*HER2*) overexpression and Lynch syndrome, which is an inherited disorder that increases your risk of colorectal cancer. Your doctor will also look specifically for DNA errors and mutations caused by high microsatellite instability (MSI-H) and deficient mismatch repair (dMMR) to determine eligibility for immunotherapy.

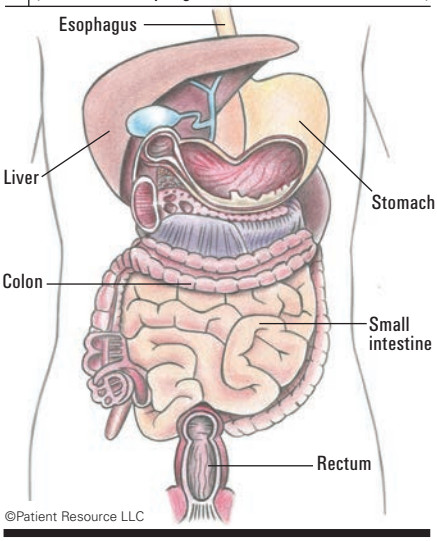
The immunotherapies approved for colorectal cancer are immune checkpoint inhibitors. These medications are indicated for people who have unresectable, metastatic MSI-H or dMMR colorectal cancer as first-line therapy or after it has progressed after treatment with chemotherapy. A combination of two immune checkpoint inhibitors is approved for children and adults who have MSI-H or dMMR metastatic colorectal cancer that has progressed after chemotherapy.

ENDOMETRIAL (UTERINE) CARCINOMA

An immune checkpoint inhibitor is approved in combination with a targeted therapy to treat women who have advanced endometrial cancer that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), whose cancer has not been controlled by systemic therapy and who are not candidates for curative surgery or radiation therapy.

The uterus is a pear-shaped, hollow organ in the pelvis (see anatomy, Figure 2). In some patients, endometrial cancer may have MSI-H or dMMR seen on review of the tissue. These patients would be eligible for immunotherapy with immune checkpoint inhibitors.

FIGURE 3
GASTROINTESTINAL ANATOMY
(Colorectal, esophageal, liver and stomach cancers)



ESOPHAGEAL CANCER

The two most common forms of esophageal cancer are named for the type of cells that become cancerous: squamous cell carcinoma develops from squamous cells in the esophagus and adenocarcinoma develops from epithelial cells in the esophagus (see anatomy, Figure 3).

Immune checkpoint inhibitors are approved for recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus, with tumors that express PD-L1 as determined by an FDA-approved test, and with disease progression after one or more prior lines of systemic therapy; and for patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after treatment with chemotherapy.

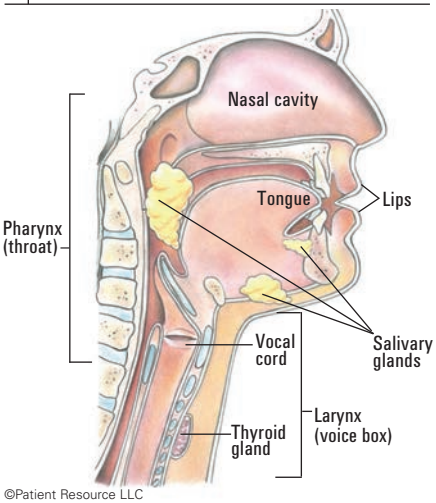
HEAD AND NECK CANCER

Immunotherapy is less invasive than some surgeries, bringing new hope to people diagnosed with head and neck cancers (see anatomy, Figure 4).

The type of immunotherapy that is FDA-approved for head and neck cancer is immune checkpoint inhibitors. They are approved for recurrent or metastatic head and neck squamous cell carcinoma that progressed during or after chemotherapy that contained a platinum drug.

To receive this form of immunotherapy, you may be required to meet certain criteria. One requirement may be biomarker testing because some types of immunotherapy are approved to treat cancer that expresses a protein called PD-L1. If there is a large amount of this protein in or on your tumor, immunotherapy alone may be used. If not, immunotherapy may be combined with chemotherapy.

FIGURE 4
ANATOMY OF THE HEAD AND NECK



KAPOSI SARCOMA

Two types of cytokines and an immunomodulator are currently approved to treat AIDS-related Kaposi sarcoma, one of the four types of soft tissue sarcoma. Kaposi sarcoma can form in the skin, lining of the mouth, nose and throat, lymph nodes and other tissues of the body. Because of its location, Kaposi sarcoma is often thought of as a skin cancer rather than a sarcoma.

KIDNEY CANCER

The approval of immune checkpoint inhibitors has added to the immunotherapy treatments approved for renal cell carcinoma (RCC), which is the most common type of adult kidney cancer (see anatomy, Figure 1). 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 (cytotoxic T-lymphocyte-associated protein 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 have not 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 deficient mismatch repair (dMMR), and your tumors progressed after previous treatment

and you have few alternative options.

Two cytokines, a type of nonspecific immune stimulator, were the first type of immunotherapy approved for RCC: interleukins and interferons. Although 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. High-dose interleukin 2 (IL-2) 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.

A monoclonal antibody (mAb) is approved to treat advanced RCC. This conjugated mAb combines an antibody and a chemotherapy, allowing the drug to target specific receptors on a cancer cell and then deliver the chemotherapy directly to it.

LEUKEMIA

Each type of leukemia responds differently to various therapies, so your medical team will recommend treatment options based on your type of leukemia and other factors, including your age, overall health and prognosis (predicted outcome from treatment) (see anatomy, Figure 7). It is important to learn as much as possible about your diagnosis and the available options so you can confidently partner with your medical team to make treatment decisions and manage your disease.

Following are the types of immunotherapy that are approved to treat various forms of leukemia. One or a combination of treatments may be used with immunotherapy, including chemotherapy, targeted therapy and stem cell transplantation. A variety of options continue to be researched for leukemia and other cancers in clinical trials.

A form of adoptive cellular therapy (T-cell therapy) called chimeric antigen receptor (CAR T-cell) therapy is approved to treat children and young adults who have B-cell precursor acute lymphocytic leukemia (ALL) (see Figure 5). Research in clinical trials continues to explore CAR T-cell therapies alone and in combination with other drugs for certain types of leukemia and other cancers.

A cytokine in the form of interferon is approved to treat chronic myeloid leukemia (CML) although it is not typically used as a first-line treatment.

Monoclonal antibodies are approved to treat certain types of leukemia, used alone or in combination with other therapies.

An immunomodulator may be used alone or in combination with other therapies to treat certain leukemia diagnoses.

LIVER CANCER

The most common type of primary liver cancer is hepatocellular carcinoma (HCC) (see anatomy, Figure 3, page 9). Immune checkpoint inhibitors are the type of immunotherapy currently approved to treat HCC in people who were previously treated with a specific type of targeted therapy. This type of immunotherapy may be used alone or in combination with other therapies. More recently, another immune checkpoint inhibitor in combination with an antiangiogenesis treatment was approved for the treatment of liver cancer as first-line therapy when the PD-L1 expression is high in cancer cells.

LUNG CANCER

It is important for your doctor to determine your specific type of lung cancer because each has unique characteristics and responds differently to treatment (see anatomy, Figure 6). Adenocarcinoma, squamous cell and large cell lung cancer are sometimes referred to collectively as non-small cell lung cancer (NSCLC). Small cell lung cancer (SCLC) is an aggressive form of lung cancer that is defined as limited-stage (confined to one part of the chest, in just one part of the lung and in nearby lymph nodes) or extensive-stage (spread to other parts of the body, such as the bone, brain or other lung).

For advanced lung cancer, your doctor may recommend PD-L1 testing, which may indicate whether you're a candidate for immune checkpoint inhibitor immunotherapy.

Immune checkpoint inhibitors are the type of immunotherapy currently approved to treat lung cancer. First approved to treat a specific type of lung cancer in 2015, immunotherapy options are now available for advanced and metastatic NSCLC, extensive-stage SCLC and metastatic SCLC that progressed after platinum-based chemotherapy after at least one other line of therapy. Used alone or in combination with other treatments, such as chemotherapy, targeted therapy and radiation therapy, immunotherapy may be used as first- or second-line therapy in lung cancer. Immune checkpoint inhibitors may also be used after chemo-radiation therapy in unresectable NSCLCs.

LYMPHOMA

Lymphoma can be classified into two main categories: Hodgkin lymphoma (HL) and non-

FIGURE 6
LUNG ANATOMY

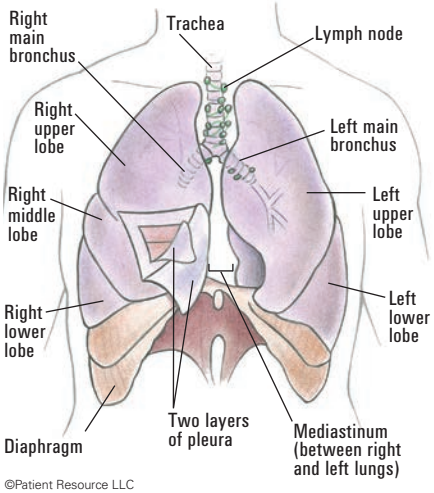


FIGURE 5
CAR T-CELL THERAPY

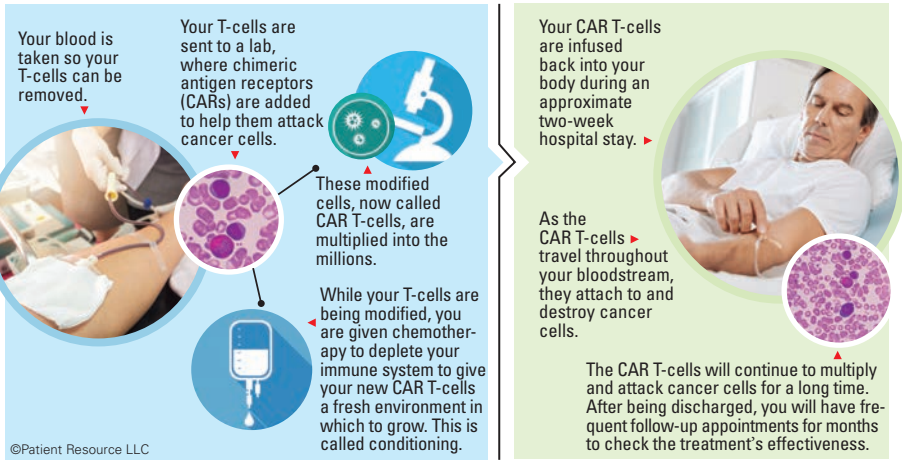
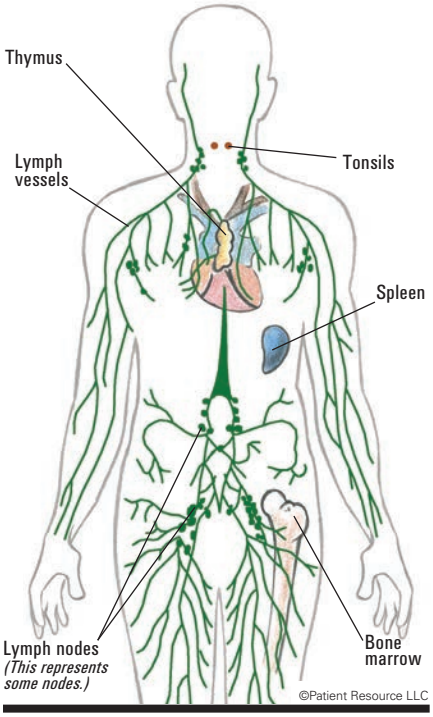


FIGURE 7

THE LYMPHATIC SYSTEM

(Leukemia, lymphoma, multiple myeloma and myelodysplastic syndromes)



Hodgkin lymphoma (NHL) (see anatomy, Figure 7). Because more than 60 different subtypes of NHL exist, determining the subtype is important because treatment will vary. Not all treatments will be effective for each subtype.

Various types of immunotherapy are approved to treat certain lymphoma diagnoses, bringing hope to many by offering the possibility of long-term remission.

Adoptive cellular therapy (T-cell therapy) in the form of chimeric antigen receptor (CAR T-cell) therapy is approved to treat several types of lymphoma, including patients up to age 25 years old in some instances (see Figure 5). Clinical trials continue to explore CAR T-cell therapies alone and in combination with other drugs for additional types of lymphoma and other cancers.

Cytokines are one of the first immunotherapy strategies approved for some lymphomas. Although they are not as widely used as they once were, they are still an option for treating certain types of lymphoma.

Immune checkpoint inhibitors may be used to treat classical HL that has relapsed or progressed after an autologous stem cell transplant or primary mediastinal B-cell lymphoma.

Monoclonal antibodies (mAbs), including naked mAbs, conjugated mAbs and bispecific mAbs, are widely used to treat many types of lymphoma. Some are combined with a radioactive substance in a type of immunotherapy called radioimmunotherapy.

Photopheresis, a type of immunotherapy first introduced in the 1980s, is used to treat cutaneous T-cell lymphoma (CTCL), a rare type of NHL, and other blood disorders.

MELANOMA

Some of the very first types of immunotherapy approved were for melanoma, a type of skin cancer, and it remains a cancer that generally responds well to this treatment. Using immunotherapy to treat melanoma has improved the prognosis for many people with Stage III or IV disease.

Once considered only for metastatic cancers, immunotherapy may now be used as a first-line or second-line therapy for melanoma. Local treatments are injected into a lesion or applied topically to the skin, and systemic treatments travel throughout the body (see Figure 9, page 12). It is also sometimes used, alone or combined with other treatments when melanoma has spread to other areas of the body.

Cytokines, immune checkpoint inhibitors, a monoclonal antibody and an oncolytic virus are other types of immunotherapy used to treat advanced melanoma. Immune checkpoint inhibitors are now also used to prevent melanoma recurrence in patients with Stage III melanoma after surgical removal of the melanoma.

MULTIPLE MYELOMA

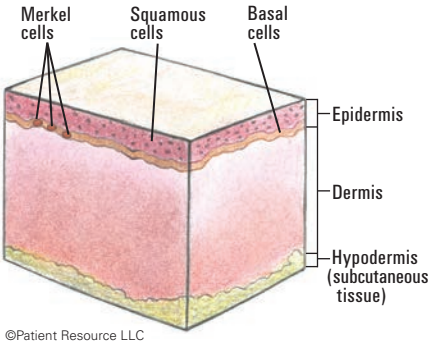
Using immunotherapy to treat multiple myeloma is making it possible for some people to manage their disease and live longer with a better quality of life (see anatomy, Figure 7). Types of immunotherapy approved to treat multiple myeloma include immunomodulatory drugs and monoclonal antibodies (mAbs).

To treat multiple myeloma, immunomodulators are often combined with chemotherapy that may prevent the growth of new blood vessels that tumors need to grow. They are also often combined with a corticosteroid. Immunomodulators are most often used along with other treatments to improve initial response, stimulate the immune system and/or stop disease progression. These drugs can be effective in treating newly diagnosed multiple myeloma and relapsed or refractory disease.

Additionally, mAbs are a treatment option that may be used alone or in combination with other systemic therapies, such as a corticosteroid or an immunomodulator.

FIGURE 8

ANATOMY OF THE SKIN



MYELODYSPLASTIC SYNDROMES

Immunotherapy in the form of an immunomodulator is approved in some instances to treat transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a 5q chromosomal abnormality with or without cytogenetic abnormalities (see anatomy, Figure 7). This immunomodulator is given orally.

PROSTATE CANCER

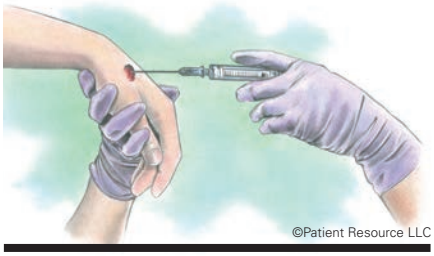
A treatment vaccine is the first and only immunotherapy for prostate cancer (see anatomy, Figure 1, page 8). Approved for asymptomatic or minimally symptomatic metastatic castration-resistant (hormone refractory) prostate cancer, it is an antigen-presenting cell-based treatment vaccine. The treatment is used alone as a first-line therapy or with other treatments such as radiation therapy or hormone therapy.

FROM THE PHYSICIAN'S DESK

Howard L. Kaufman, MD, FACS

"Immunotherapy is a quickly evolving field, and we use this newer treatment whenever appropriate. Along with currently approved therapies, many clinical trials are underway that may offer access to other types of immunotherapy. I encourage you to discuss this potential option with your doctor."

FIGURE 9
LOCAL 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.

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

SKIN CANCER

Immunotherapy may be used to treat certain types of skin cancer under certain conditions, such as when cancer is advanced and/or surgery isn't possible (see anatomy, Figure 8, page 11).

Skin cancer can develop anywhere on the body. Basal cell carcinoma (BCC) is the most common form of skin cancer in the United States, with more than 20 subtypes and variants. Squamous cell carcinoma (SCC) is less common than BCC. It is sometimes called squamous cell carcinoma of the skin, cutaneous squamous cell carcinoma (cSCC) or squamous cell skin cancer to differentiate it from SCC that develops in other parts of the body. Sometimes skin cancer may have features of both basal cell and cSCC, and these are usually treated like a SCC.

There are several SCC subtypes and related forms. Actinic keratosis is a common skin condition also referred to as sun spots or age spots. These slow-growing lesions are most likely to appear on the face, balding scalp, forearms and backs of hands. Actinic keratosis is considered a pre-cancer because it sometimes progresses to become SCC. Immunomodulators are topical treatments approved to treat actinic keratosis.

Squamous cell skin cancer in situ (in SY-too), also called Bowen disease, is SCC in its very earliest form and involves only the superficial layer of skin. It grows very slowly, and without treatment, it may become SCC. Marjolin's ulcer, which can be aggressive, is SCC that develops at the site of an old scar, burn or non-healing wound.

Merkel cell carcinoma (MCC) is among the many rare types, subtypes and variants of cancer that affect the skin. It forms in the top layer of skin near the nerve endings. Because MCC is highly aggressive, it grows rapidly and is likely to spread, first to nearby lymph nodes and then to distant areas. These may include skin and lymph nodes elsewhere in the body, the brain, lungs, bones and other organs. MCC may also be referred to as neuroendocrine carcinoma of the skin.

Four immune checkpoint inhibitors may be used in certain instances for people with nonmelanoma skin cancer. Two treat Merkel cell carcinoma, and the other two are for cSCC. Treatment is currently approved for locally advanced or cSCC that has metastasized (spread to other parts of the body).

Although basal cell carcinomas have not responded well to immune checkpoint inhibitors, small BCCs have been treated with topical immunotherapy with good responses. This may be considered when surgery is not possible or may be difficult.

STOMACH (GASTRIC) CANCER

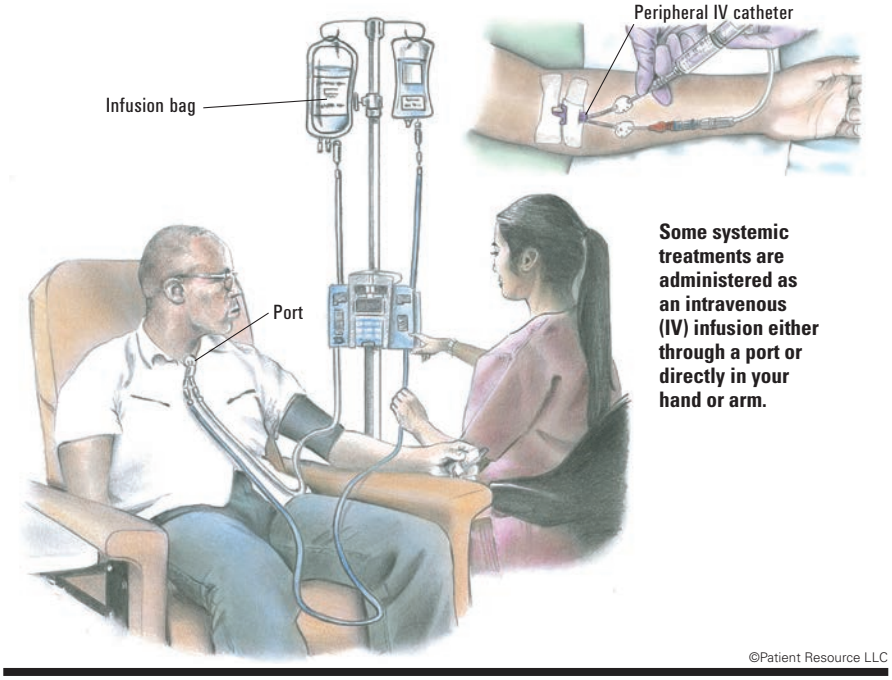
Stomach cancer forms in the tissues lining any part of the stomach (see anatomy, Figure 3, page 9). Your doctor will consider the stage of the cancer, including the size and location, along with other factors before recommending a treatment plan.

Currently, an immune checkpoint inhibitor is approved to treat certain stomach cancer diagnoses, including cancers that have metastasized (spread to other parts of the body) or recurred (returned), are positive for the biomarker PD-L1 as determined by an FDA-approved test, and have disease progression on or after two or more prior lines of specific therapy. ■

Questions for your doctor

- **Do I have to do another type of treatment before trying immunotherapy?**
- **With immunotherapy, will I be monitored more frequently?**
- **Should I tell my other health care providers that I'm on immunotherapy?**
- **If immunotherapy isn't a current option for my cancer type, can I get it through a clinical trial?**

FIGURE 10
SYSTEMIC THERAPY



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

FDA-APPROVED CANCER IMMUNOTHERAPIES

➡ ***Used alone or in combination with other therapies, these immunotherapy drugs are approved to treat certain cancer types and subtypes. Each therapy is prescribed based on specific criteria. Talk with your doctor about how immunotherapy may fit into your treatment plan. If you have a pre-existing autoimmune disorder, such as rheumatoid arthritis or lupus, be sure to discuss it with your doctor before receiving immunotherapy.***

BLADDER CANCER
- atezolizumab (Tecentriq)
- avelumab (Bavencio)
- bacillus Calmette-Guérin (BCG)
- durvalumab (Imfinzi)
- enfortumab vedotin-ejfv (Padcev)
- interferon alfa-2b (Roferon-A, Intron A, Alferon)
- nivolumab (Opdivo)
- pembrolizumab (Keytruda)

BREAST CANCER
Triple Negative Breast Cancer
- atezolizumab (Tecentriq)
- sacituzumab govitecan-hziy (Trodelvy)

CERVICAL CANCER
- pembrolizumab (Keytruda)

COLORECTAL CANCER
- ipilimumab (Yervoy)
- nivolumab (Opdivo)
- pembrolizumab (Keytruda)

ENDOMETRIAL CANCER
- pembrolizumab (Keytruda)

ESOPHAGEAL CANCER
- nivolumab (Opdivo)
- pembrolizumab (Keytruda)

HEAD AND NECK CANCER
- nivolumab (Opdivo)
- pembrolizumab (Keytruda)

KAPOSI SARCOMA
- interferon alfa 2-b (Roferon-A, Intron A, Alferon)
- interleukin-12
- pomalidomide (Pomalyst)

KIDNEY (RENAL) CANCER
- avelumab (Bavencio)
- interferon alfa-2b (Roferon-A, Intron A, Alferon)
- interleukin-2 (IL-2) (Aldesleukin, Proleukin)
- ipilimumab (Yervoy)
- nivolumab (Opdivo)
- pembrolizumab (Keytruda)

LEUKEMIA
Acute myeloid leukemia
- gemtuzumab ozogamicin (Mylotarg)
- venetoclax (Venclexta)

Acute T-cell (lymphoblastic) leukemia
- interferon alfa

B-cell chronic lymphocytic leukemia
- alemtuzumab (Campath)
- rituximab (Rituxan)

B-cell precursor acute lymphoblastic leukemia
- blinatumomab (Blincyto)
- tisagenlecleucel (Kymriah)

Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
- tagraxofusp-erzs (Elzonris)

Chronic lymphocytic leukemia
- obinutuzumab (Gazyva)
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)
- rituximab and hyaluronidase human (Rituxan Hycela)
- venetoclax (Venclexta)

Chronic myeloid leukemia
- interferon alfa

Hairy cell leukemia
- interferon alfa-2b (Roferon-A, Intron A, Alferon)
- moxetumomab pasudotox-tdfk (Lumoxiti)
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)

LIVER CANCER
- atezolizumab (Tecentriq)
- ipilimumab (Yervoy)
- nivolumab (Opdivo)
- pembrolizumab (Keytruda)

LUNG CANCER
- atezolizumab (Tecentriq)
- durvalumab (Imfinzi)
- ipilimumab (Yervoy)
- nivolumab (Opdivo)
- pembrolizumab (Keytruda)

LYMPHOMA
Hodgkin lymphoma
- brentuximab vedotin (Adcetris)
- nivolumab (Opdivo)
- pembrolizumab (Keytruda)
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)

Non-Hodgkin lymphoma
Adult T-cell lymphoma
- interferon alfa

Angioimmunoblastic T-cell lymphoma
- brentuximab vedotin (Adcetris)

B-cell NHL
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)

Diffuse large B-cell lymphoma
- axicabtagene ciloleucel (Yescarta)
- polatuzumab vedotin-piiq (Polivy)
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)
- rituximab and hyaluronidase human (Rituxan Hycela)
- tafasitamab-cxix (Monjuvi)
- tisagenlecleucel (Kymriah)

Follicular lymphoma
- ibritumomab tiuxetan (Zevalin)
- interferon alfa-2b (Roferon-A, Intron A, Alferon)
- lenalidomide (Revlimid)
- obinutuzumab (Gazyva)
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)
- rituximab and hyaluronidase human (Rituxan Hycela)

High-grade B-cell lymphoma
- axicabtagene ciloleucel (Yescarta)
- tisagenlecleucel (Kymriah)

Intravascular large B-cell lymphoma
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)

Large B-cell lymphoma
- axicabtagene ciloleucel (Yescarta)
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)
- tisagenlecleucel (Kymriah)

Mantle cell lymphoma
- brexucabtagene autoleucel (Tecartus)
- lenalidomide (Revlimid)
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)

Marginal zone B-cell lymphoma
- lenalidomide (Revlimid)
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)

Mycosis fungoides
- brentuximab vedotin (Adcetris)
- mogamulizumab-kpkc (Poteligeo)

Peripheral T-cell lymphoma
- brentuximab vedotin (Adcetris)

Primary central nervous system lymphoma
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)

Primary cutaneous anaplastic large cell lymphoma
- brentuximab vedotin (Adcetris)

Primary mediastinal large B-cell lymphoma
- axicabtagene ciloleucel (Yescarta)
- pembrolizumab (Keytruda)
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)

Sézary syndrome
- mogamulizumab-kpkc (Poteligeo)

Small lymphocytic lymphoma
- venetoclax (Venclexta)

Systemic anaplastic large cell lymphoma
- brentuximab vedotin (Adcetris)

Waldenström macroglobulinemia
- rituximab (Rituxan)
- rituximab-abbs (Truxima)
- rituximab-pvvr (Ruxience)

MELANOMA
- atezolizumab (Tecentriq)
- interferon alfa-2b (Roferon-A, Intron A, Alferon)
- interleukin-2 (IL-2) (Aldesleukin, Proleukin)
- ipilimumab (Yervoy)
- nivolumab (Opdivo)
- peginterferon alfa-2b (Sylatron)
- pembrolizumab (Keytruda)
- talimogene laherparepvec (Imlygic)

MICROSATELLITE INSTABILITY-HIGH CANCER
- pembrolizumab (Keytruda)

MULTIPLE MYELOMA
- belantamab mafodotin-blmf (Blenrep)
- daratumumab (Darzalex)
- daratumumab and hyaluronidase-fihj (Darzalex Faspro)
- elotuzumab (Empliciti)
- isatuximab-irfc (Sarclisa)
- lenalidomide (Revlimid)
- pomalidomide (Pomalyst)
- thalidomide (Thalomid)

MYELODYSPLASTIC SYNDROMES (MDS)
- lenalidomide (Revlimid)

PROSTATE CANCER
- sipuleucel-T (Provenge)

SKIN CANCER
Actinic keratosis
- imiquimod (Aldara, Zyclara)

Cutaneous squamous cell carcinoma
- cemiplimab-rwlc (Libtayo)
- pembrolizumab (Keytruda)

Merkel cell carcinoma
- avelumab (Bavencio)
- pembrolizumab (Keytruda)

Primary superficial basal cell carcinoma
- imiquimod (Aldara, Zyclara)

STOMACH (GASTRIC) CANCER
- pembrolizumab (Keytruda)

TUMOR MUTATIONAL BURDEN-HIGH CANCER
- pembrolizumab (Keytruda)

As of 8/7/20

Inform yourself about potential treatment-related side effects

Like all cancer treatments, immunotherapy may cause side effects. And when used in combination with other treatments, they can be more intense. Keep in mind, however, that not every person will have every side effect. Each type of immunotherapy is unique, so request a list of potential concerns specific to the therapy you'll receive.

Your health care team will draw on supportive care services to help manage any physical and emotional distress that stems from your illness and treatment. The goal is to help you maintain a good quality of life from the time you're diagnosed through treatment and survivorship.

Side effects of immunotherapy may not appear until a few months into treatment or even years afterward. Ask your nurse navigator about available supportive care services so you can make a plan for how to respond if a side effect occurs. Alert your team as soon as any symptoms appear that have been identified as needing immediate attention. Prompt treatment may help prevent more serious complications.

POTENTIALLY SEVERE SIDE EFFECTS

Severe side effects aren't common but can occur with certain types of treatment. Ask your doctor if you are at risk, how to identify the symptoms and when to seek emergency care. Report symptoms immediately if they occur. The side effects can be easily corrected if they are treated rapidly.

Cytokine release syndrome can occur if immune cells affected by treatment rapidly release large amounts of cytokines into the bloodstream. This is called a "cytokine storm." Cytokines are a type of protein made by certain immune and non-immune cells that can stimulate or slow down the immune system. Reactions are usually mild but can be severe and even life-threatening. Symptoms may include headache, fever, nausea, rash, low blood pressure, rapid heartbeat and difficulty breathing.

Immune-related adverse events (irAEs) may occur with certain immunotherapy drugs. They can occur if the immune system becomes overstimulated by treatment and causes inflammation in one or more organs or systems in the body (see Table 1). Some irAEs can develop rapidly, becoming severe and even life-threatening without swift medical attention. Before beginning immunotherapy, talk with your doctor about your risk for irAEs and learn the symptoms.

Making and keeping all medical appointments on schedule is very important because routine laboratory tests and imaging may detect an irAE in its early stages before you can feel symptoms. Contact your health care team if symptoms arise between appointments, and remain alert to the possibility of irAEs for up to two years after completing immunotherapy. Let your navigator know if transportation could be a problem if irAEs develop. Your navigator can arrange transportation services for you.

Infection can occur as a result of a low white blood cell count (neutropenia) or other factors. This side effect is possible but very rare with most forms of immunotherapy. This may be more commonly seen when immunotherapy is given with or soon after chemotherapy or radiation therapy. 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 most frequently occur with treatment given intravenously (IV) through a vein in your arm, usually soon after exposure to the drug. Reactions are generally mild, such as itching, rash or fever. More serious symptoms such as shaking, chills, low blood pressure, dizziness, breathing difficulties or irregular heartbeat can be serious or even fatal without medical intervention.

Tumor lysis syndrome (TLS) may occur after treatment of a fast-growing cancer, especially certain blood cancers. Symptoms may include vomiting, diarrhea, muscle cramps or twitches, neuropathy and decreased urination. TLS can potentially cause damage to the kidneys, heart, liver or other organs.

COMMON SIDE EFFECTS

Anemia results from an abnormally low red blood cell count. Red blood cells carry oxygen to the body's tissues. Symptoms may include fatigue, weakness, shortness of breath or dizziness. It can be temporary or long lasting.

Constipation is characterized by difficulty passing stools or by less frequent bowel movements compared to your usual bowel habits. The best way to manage constipation

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

is to prevent it. Talk to your doctor about preventive medications or beneficial changes you can make in your diet or lifestyle.

Coughing or difficulty breathing should be reported to your doctor immediately. Coughing may signal pneumonitis (inflammation of the lungs).

Decreased appetite may occur as a result of cancer treatment. Your body needs more nutrients to replenish the healthy cells that support you before, during or after treatment to prevent weight loss, maintain your strength and energy, tolerate the side effects of treatment better, reduce your risk of infections and recover faster. If you are not able to maintain a healthy weight, talk with your health care team or a registered dietitian about ways to supplement your diet with the nutrition support you need.

Diarrhea is common with immune checkpoint inhibitors and cytokines. It can lead to dehydration and electrolyte imbalance and may signal that the immune system is nearing overload. Contact your health care team immediately if you have four or more bowel movements than usual in a day, blood in the stools, episodes that keep you homebound or severe abdominal cramping. Make your treatment team aware of your normal bowel habits so these patterns can be factored in to managing your bowel regimen going forward.

Difficulty breathing (dyspnea), with or without coughing, can be a side effect but may also signal a serious condition, such as pneumonitis or a respiratory tract infection. Contact your doctor immediately if you are short of breath or have difficulty breathing.

Fatigue is the most common side effect for many types of immunotherapy. Cancer-related fatigue is more severe than general tiredness, lasts longer and may not be relieved by sleep. It can leave you physically, emotionally and/or mentally exhausted. Balance activity with rest each day, focusing only on activities that are most important to you. If fatigue regularly keeps you from your normal activities and things you enjoy, talk with your health care team about your options.

Flu-like symptoms may occur with some immunotherapies, such as cytokines and CAR T-cell therapy. Symptoms may include fever, chills, aches, headaches, drowsiness, nausea, vomiting, runny nose, loss of appetite and blood pressure changes.

Headache can be a common side effect. A headache that occurs and does not go away within 24 hours could be a sign of inflammation of the pituitary gland. This should be reported to your health care team.

Heart palpitations may occur. Contact your doctor immediately about abnormal heart rhythm, dizziness or lightheadedness.

Muscle and joint pain may occur with immune checkpoint inhibitors. Pain ranges from mild to severe, affecting the whole body or just certain areas. Pain typically resolves when treatment ends. If it persists or worsens, discuss pain management options with your doctor.

Nausea and vomiting may occur, particularly when immunotherapy is combined with other types of treatments. Both are much easier to prevent than control, so ask your doctor about taking antiemetics (anti-nausea drugs) before treatment begins to prevent nausea and vomiting from happening at all. Severe vomiting can lead to dehydration. Contact your doctor about any of these serious symptoms: more than three episodes of vomiting an hour for at least three hours, blood in vomit, vomit resembling coffee grounds; weakness or dizziness; or being unable to keep your medications down, eat solid food for more than two days or drink more than 8 cups of fluid or ice chips in 24 hours.

Neutropenia is a low number of neutrophils, a type of white blood cell. Neutrophils play an important role in preventing infection. Having an abnormally low number increases the risk of infection. Neutropenia also makes it more difficult for an infection to resolve if bacteria do enter the body. You can reduce your risk of getting an infection with frequent hand washing, avoiding crowds and using extra precaution to avoid injuries. Neutropenia is possible but not very common after immunotherapy. It is more likely to occur when immunotherapy is given with or soon after chemotherapy or radiation therapy.

Skin reactions are common with immune checkpoint inhibitors and cytokine therapy. Be alert for changes in skin color, inflammation, blistering, hives, dryness, cracking around fingertips, flushing or redness. A corticosteroid, numbing medicine, antihistamine, medicated cream or antibiotic may be recommended. Most reactions are mild to moderate, but some can become severe without early treatment.

Upper respiratory tract infections, including coughing, nasal congestion and fever, may occur. These can disrupt treatment, so it is important to practice good hygiene, such as proper hand washing, to help reduce the spread of infection. ■

Take care of your emotional well-being

It's natural to feel a range of emotions after receiving a cancer diagnosis. Your life circumstances are changing, and it can be unsettling. Ask your health care team about the supportive care resources available. Take advantage of proven coping strategies, such as journaling, physical activity and support groups, and consider these suggestions for managing the following emotions.

Anger: Express your anger in healthy ways. Exercise, or talk with a trusted friend about your feelings.

Anxiety: Explore relaxation techniques, such as deep breathing, meditation, yoga, muscle relaxation exercises or massage. Share your anxieties with a good listener.

Depression: Discuss ongoing feelings of sadness, hopelessness, despair or emotional numbness with your health care team immediately. Depression is a potential side effect of some immunotherapy treatments. It can also occur if your disease symptoms or treatment side effects aren't being relieved. Contact your doctor if depression continues for more than a week. Get immediate medical attention if you have thoughts of suicide.

Emotional overload: Deep breathing exercises, yoga, meditation or guided imagery may be useful in calming your mind. Make a concerted effort to focus on just one thing at a time. Delegate tasks and chores to friends and loved ones who can lend a hand.

Fear: Knowledge helps relieve feelings of fear. Learn as much as possible about your type of cancer and treatment plan so you'll know what to expect. Join a support group or find one online to talk with others who've had similar experiences and challenges.

Grief: It's normal to mourn the loss of your health and a future that didn't include cancer. Allow yourself permission to fully grieve. Turn to loved ones or a spiritual community for comfort.

GLOSSARY

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

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.

Cytokine: Protein that helps 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.

Cytokine storm: This occurs when the bloodstream receives too many cytokines too quickly. Cytokines are good for the immune system when released regularly, but too many can be life-threatening. Cytokine storm may occur after some forms of immunotherapy, such as CAR T-cell therapy.

Durable response: The disappearance of cancer in response to treatment that lasts for longer than a specified time, typically at least one year. This does not always mean the cancer has been cured.

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.

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. These are common after treatment with immune checkpoint inhibitors.

Immunomodulators: Substances that stimulate or suppress the immune system to prevent the spread of cancer.

Interferon: A type of protein (cytokine) produced in the immune system that can improve the body's response to fight infection and disease. Interferons can interfere with the division of cancer cells.

Interleukin: A type of protein (cytokine) made in the immune system that helps regulate the body's immune response. Laboratory-made interleukins are used in cancer therapy, alone or combined with other drugs, to boost the immune system.

Microsatellite instability-high (MSI-H): Describes tumor cells with a high number of mutations in the microsatellites, which are short, repeated DNA sequences.

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. mAbs may also be used to deliver chemotherapy or radiation to the tumor cell.

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.

PD-1 (programmed cell death-1): PD-1 is the protein that controls the body's immune responses. These proteins are located on T-cells (an immune cell). When the PD-1 protein is bound to a PD-L1 protein, it restricts the T-cells' ability to kill cells. Some immune checkpoint inhibitors block PD-1, which allows the T-cells to kill cancer cells.

PD-L1 (programmed cell death ligand-1): PD-L1 is the protein that binds to PD-1 on T-cells and causes them to die. Research has shown that PD-L1 is found on cancer cells and this may be one reason why T-cells are ineffective against cancer. Blocking PD-1 or PD-L1 may reverse T-cell death and allow immune cells to destroy cancer tissue.

Radioimmunotherapy: A radiation therapy that consists of a radioactive substance attached to a monoclonal antibody that is injected into the body. Once injected, the antibody can attach to cancer cells and allow the radioactive substance to give off radiation.

Tumor-infiltrating lymphocyte (TIL): A type of immune cell (T-cell) that has moved from the bloodstream into a tumor to attack cancer cells. In cancers where TILs are present, the goal of immunotherapy is to increase their number or killing function.

Tumor microenvironment: The area that surrounds and sustains a tumor. It is made up of normal cells, molecules and blood vessels.

Tumor mutational burden-high (TMB-H): Describes cancer with a high number of genetic mutations in the tumor. It is believed that the higher the TMB level is, the more likely the patient will respond to immunotherapy.

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 cancers are currently available at ➔ **www.sitcancer.org/guidelines**

Support and financial resources available for you

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
Connect Thru Cancer....www.connectthrucancer.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
The Hope Light Foundation....hopelightproject.com
Imerman Angels....www.imermanangels.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
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
Well Spouse Association....www.wellspouse.org
weSPARK Cancer Support Center....www.wespark.org

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

PRESCRIPTION EXPENSES

America's Pharmacy....americaspharmacy.com, 888-495-3181
Cancer*Care* Co-Payment Assistance Foundation....www.cancercarecopay.org, 866-552-6729
Cancer Financial Assistance Coalition....www.cancerfac.org
Good Days....www.mygooddays.org, 972-608-7141
HealthWell Foundation....www.healthwellfoundation.org, 800-675-8416
Medicine Assistance Tool....medicineassistancetool.org
National Organization for Rare Disorders....rarediseases.org, 203-744-0100
NeedyMeds....www.needymeds.org, 800-503-6897
Patient Access Network Foundation....www.panfoundation.org, 866-316-7263
Patient Advocate Foundation Co-Pay Relief....www.copays.org, 866-512-3861
RxAssist....www.rxassist.org
RxHope....www.rxhope.org
RxOutreach....rxoutreach.org, 888-796-1234
SingleCare....www.singlecare.com, 844-234-3057
Together Rx Access....www.togetherrxaccess.com, 800-444-4106

REIMBURSEMENT & PATIENT ASSISTANCE PROGRAMS

Amgen Assist 360....amgenassist360.com/patient, 888-427-7478
Amgen Safety Net Foundation....amgensafetynetfoundation.com
Astellas Pharma Support Solutions....astellaspharmasupportsolutions.com/patient, 800-477-6472
AstraZeneca Access 360....myaccess360.com, 844-275-2360
AstraZeneca Patient Savings Programs For Specialty Products....astrazenecaspecialtysavings.com, 844-275-2360
AstraZeneca Prescription Savings Program (AZ&ME)....azandmeapp.com, 800-292-6363
Bausch Health Patient Assistance Program....bauschhealthpap.com, 833-862-8727
Bavencio CoverOne....coverone.com, 844-826-8371
Blincyto Assist 360....amgenassist360.com/patient/blincyto-cost-assistance, 888-427-7478
Bristol-Myers Squibb....bms.com/patient-and-caregivers/get-help-paying-for-your-medicines.html, 800-721-8909
Bristol-Myers Squibb Access Support....bmsaccesssupport.bmscustomerconnect.com/patient, 800-861-0048
Bristol-Myers Squibb Patient Assistance Foundation....bmspaf.org, 800-736-0003
Celgene Patient Support....www.celgenepatientsupport.com, 800-931-8691, EXT 4082
Darzalex Janssen CarePath....www.janssencarepath.com/patient/darzalex/patient-support, 844-553-2792
Darzalex Patient Support....www.darzalex.com/patient-financial-support, 844-553-2792
Dendreon On Call....dendreononcall.com, 877-336-3736
Elzonris Stemline ARC....elzonris.com/stemline-arc, 833-478-3654
Empliciti Patient Support....www.empliciti.com/financial-resources, 844-367-5424
Gazyva Access Solutions....genentech-access.com/patient/brands/gazyva, 866-422-2377
Genentech....gene.com/patients/financial-support
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....myaccess360.com/patient/imfinzi-durvalumab, 844-275-2360
Imlygic Co-Pay and Reimbursement Resources....imlygic.com/savings-and-support, 888-657-8371
Intron A Patient Assistance Program....merckhelps.com/intron%20%20a, 800-727-5400
Janssen CarePath....www.janssencarepath.com, 877-227-3728
Janssen Prescription Assistance....www.janssenprescriptionassistance.com
Johnson & Johnson Patient Assistance Foundation, Inc.....www.jjpaf.org, 800-652-6227
Keytruda KEY+YOU....keytruda.com/key-you-sign-up, 855-398-7832, press 2
Keytruda Patient Assistance....merckaccessprogram-keytruda.com/hcc/, 855-257-3932
Kyowa Kirin Cares....kyowakirincares.com/poteligeo-patients, 833-552-2737
Libtayo Surround....libtayo.com/support, 877-542-8296, option 1
Lilly Cares Foundation Patient Assistance Program....lillycares.com, 800-545-6962
Lilly Oncology Support....lillyoncologysupport.com, 866-472-8663
Lumoxiti InnateCares Program....lumoxiti.com/patient/patient-resources/innate-cares, 844-694-6628
Merck Access Program....merckaccessprogram.com/hcc/
Merck Helps....merckhelps.com, 800-727-5400
Novartis Financial Assistance....patient.novartisoncology.com/financial-assistance, 800-282-7630
Novartis Patient Assistance Now....patientassistancenow.com, 800-245-5356
Opdivo with You....patientsupport.bmscustomerconnect.com/opdivo-with-you-registration, 855-673-4861
Padcev Support Solutions....astellaspharmasupportsolutions.com/products/padcev, 888-402-0627
Pfizer Oncology Together....pfizeroncologytogether.com/patient, 877-744-5675
Pfizer RxPathways....pfizerrxpathways.com, 844-989-7284
Polivy Access Solutions....genentech-access.com/patient/brands/polivy, 866-422-2377
Pomalyst Patient Support....celgenepatientsupport.com/pomalyst-patient/find-financial-help, 800-931-8691, EXT 4082
Poteligeo Resources and Support....poteligeo.com/resources-and-support.html, 833-552-2737
Prometheus IV Bolus Proleukin Inpatient Reimbursement....877-776-5385
Provenge Dendreon On Call....dendreononcall.com, 877-336-3736
Revlimid Patient Support....revlimid.com/mds/financial-assistance, 800-931-8691
Rituxan Hycela Access Solutions....genentech-access.com/patient/brands/rituxanhycela, 866-422-2377
Rituxan Patient Assistance Programs....www.rituxan.com/patient/resources/rituxan-patient-assistance, 888-249-4918
Sanofi Genzyme CareASSIST....www.sanoficareassist.com, 833-930-2273
Sanofi Genzyme Patient Support Services....sanofigenzyme.com/patient-support/patient-services
Sanofi Patient Connection....sanofipatientconnection.com, 888-847-4877
Sarclisa CareASSIST....www.sanoficareassist.com/sarclisa, 833-930-2273
Seattle Genetics SeaGen Secure....www.seagensecure.com, 855-473-2873
Tecentriq Access Solutions....genentech-access.com/patient/brands/tecentriq, 866-422-2377
Teva Cares Foundation Patient Assistance Programs....tevacares.org, 877-237-4881
Teva Oncology Core Reimbursement Assistance & Support....tevacore.com/patient-assistance, 888-587-3263
Thalomid Patient Support....celgenepatientsupport.com/thalomid-patient, 800-931-8691, EXT 4082
Trodelvy Access Services....www.trodelvy.com/patient/support, 844-876-3358
Venclexta Access Solutions....genentech-access.com/patient/brands/venclexta, 866-422-2377
Yervoy Patient Access....www.yervoy.com/adjuvant/financial-resources, 800-861-0048
Yescarta Patient Support....www.yescarta.com/support, 844-454-5483
Zevalin Reimbursement Support & Patient Assistance....zevalin.com/support-resources-and-downloads/reimbursement-support-and-patient-assistance, 888-537-8277

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

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