PATIENT RESOURCE

FOR HEALTH CARE PROFESSIONALS

Immunotherapy for the treatment of Melanoma

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Society for Immunotherapy of Cancer

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Immunotherapy for the Treatment of Melanoma

Edition for Health Care Professionals

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"If you have the opportunity to try immunotherapy, I recommend it. It took a little bit longer for the entire treatment, but it was easier on my body–and I feel great."

~ Janice Updike, Stage III melanoma survivor

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OVERVIEW

For decades, doctors and researchers have conducted clinical trials to further progress in the clinical implementation of tumor immunotherapy. Former President Jimmy Carter's success with immunotherapy for advanced melanoma and Vice President Joe Biden's Cancer Moonshot Initiative have brought this new treatment type, as well as cancer treatments in general, into the spotlight for the general public. As a result, health care professionals may experience a spike in inquiries about this new treatment.

Several immunotherapy agents are now available for melanoma. Although surgery often remains the first line of treatment, especially for early-stage melanomas, the U.S. Food and Drug Administration (FDA) is rapidly approving new immunotherapy medications for advanced melanoma.

WHAT IS IMMUNOTHERAPY?

Immunotherapy is a type of treatment that uses the body's own immune system to recognize and kill cancer cells. Cancer cells often can fool the body into not recognizing they are dangerous. If the body can't tell the difference between cancer cells and healthy cells, cancer cells may be able to "hide" from the immune system. To identify cancer cells as a threat and target them for destruction, immunotherapy uses substances either made by the body or in a laboratory to enhance recognition or effector function of the immune response against the cancer.

Different types of immunotherapy exist. Each works in a unique way to slow and stop the growth of cancer cells, stop cancer cells from spreading to other parts of the body and help the immune system work better overall at destroying cancer cells. Some immunotherapy treatments boost the body's immune system while others train the immune system to attack cancer cells:

- **Checkpoint inhibitors** are an important part of the immune system due to their ability to keep immune cells from attacking normal cells in the body. Checkpoints are proteins on immune cells that need to be turned on or off to start/stop an immune response. The immune system uses checkpoints to prevent itself from attacking normal cells in the body and deleted immune cells after their functions have been completed, for example following clearance of an infection. But melanoma cells sometimes hijack these checkpoints to avoid being attacked by the immune system. Checkpoint inhibitors target the checkpoint proteins, helping to restore the immune response against melanoma cells.
- **Cytokines** are soluble molecules that enable immune cells to communicate with each other. Cytokines work together to make sure that the immune response is of the right strength and length of time. Laboratory-made versions of cytokines are sometimes used to boost the immune system in people with melanoma.
- **Oncolytic viruses** are viruses altered in a laboratory so that they preferentially infect and kill mainly cancer cells. Along with killing the cells directly, the viruses can also alert the immune system to attack the cancer cells.
- **Cancer vaccines** are substances that stimulate the immune system to fight infection or disease. Cancer vaccines strengthen the immune system against cancer cells.
- **Nonspecific immune stimulators** boost the immune system in a general way to help the immune system attack cancer cells.

Certain immunotherapies work well when given alone. Others work better in combination with additional treatment strategies.

At present, the clinical use of immunotherapy is largely restricted to the adjuvant treatment of Stage III and systemic treatment of Stage IV melanomas, although there is intense interest in evaluating immunotherapy as neoadjuvant or adjuvant therapy for all stages.

WHY IS IMMUNOTHERAPY IN DEMAND?

Immunotherapy has the potential to achieve durable clinical responses in some patients. In addition, an improved quality of life may also make immunotherapy an attractive choice for people who have this treatment option. Immunotherapy may be an option for patients to consider because the side effects, although prevalent, may be easier on patients compared to typical chemotherapy-related toxicities, and with appropriate attention, can be simple to manage. The side effect profile differs from other types of cancer therapeutics. Some side effects occur as a result of an overactive immune system, not the destruction of healthy cells, as often occurs with cytototoxic chemotherapy. Because not as many healthy cells are damaged with immunotherapy, some patients have reported a different range of side effects (see page 11).

One limitation to immunotherapy is that it can be very effective in some patients but not in others. Researchers continue to explore why this happens to determine how to improve existing therapies and to develop new ones through clinical trials. Researchers are interested in identifying biomarkers that may be able to better predict which patients are likely to respond to which immunotherapy agents or combinations.

Several immunotherapy agents or regimens are currently approved by the FDA for the treatment of melanoma (see page 7). Other novel treatments that are not yet FDA-approved may be accessible through clinical trials (see page 14). Discuss the opportunity to participate in a clinical trial with your patients if they have not responded to other therapies or if you feel this may be the best treatment option for them. Provide them with multiple resources, and encourage them to become advocates for their own health by learning about and researching available clinical trials. A menu of active melanoma immunotherapy trials can be found at www.clinicaltrials.gov. ■

A LONG HISTORY

Cancer treatments are not discovered overnight. More than a century ago, Dr. William B. Coley worked with doctors and people with cancer to study how cancer tumors reacted to bacterial infections. His treatments for people with inoperable tumors consisted of injecting a combination of bacteria directly into the tumors. The treatment shrank the tumors and sometimes even led to a cure. Dr. Coley believed the body's increased response to the bacteria also helped fight off the cancer.

William B. Coley

More recently, in the 1960s, Dr. Donald Morton began experimenting with a vaccine that was intended not to prevent cancer but to stimulate the body's immune system to attack cancer cells once they had developed. An early proponent of immunotherapy, particularly cancer vaccines, Dr. Morton was at the forefront of global cancer research and treatment, with a focus on melanoma. His work with bacillus Calmette-Guerin (BCG) for melanoma led to the approval of BCG for bladder cancer, the first successful immunotherapy against a human tumor.

ADDITIONAL RESOURCES

- **American Society of Clinical Oncology:** www.cancer.net
  Understanding Immunotherapy
- **Society for Immunotherapy of Cancer:** www.sitcancer.org

An exclusive look at immunotherapy for melanoma

FROM THE EXPERTS

Two leaders in the field of immunotherapy for melanoma offer their insights about using this treatment and the potential it holds for people with melanoma.

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Immunotherapy is a different approach to fighting cancer, and melanoma is one cancer type that this treatment is now approved for. As immunotherapy for melanoma has gained publicity, more patients are aware of it and are asking for more information about it.

WHAT IS IMMUNOTHERAPY?

Immunotherapy boosts a patient's own immune system to attack cancer. This approach is different than traditional strategies, such as chemotherapy and radiation, which attack both healthy cells and cancer cells equally.

According to Dr. Balch, "Health care professionals should understand that immunotherapy on its own does not treat cancer. Immunotherapy treats a deficient or abnormal immune system to treat the cancer. We want the patient's immune system to recognize the cancer and attack it as a foreign invader."

Since immunotherapy is engaging a person's own immune system, it mostly leaves healthy cells alone, resulting in different side effects compared with chemotherapy. The side effects of immunotherapy are in a category of autoimmunity, because these checkpoint inhibitors may break tolerance to "self-antigens." Not losing their hair and not suffering from intense nausea can make a difference to patients in terms of quality of life. This, along with the fact that many people are living longer after receiving this treatment, are big draws for people to try this treatment.

"There are many reasons to use immunotherapy," says Dr. Kaufman. "In addition to the different side effect profile mentioned, we often see more durable responses with immunotherapy than with chemotherapy. Although chemotherapy often works quickly by directly killing tumor cells, immunotherapy responses may occur later because it takes time to activate the immune system and then target the cancer. What doctors and professionals need to realize is this may result in a more delayed response, but typically the patient may actually be looking better and feeling better."

Dr. Balch emphasizes that the health care industry is still learning about and evaluating this treatment as its application is being incorporated into standard care practices.

"We are still learning how immunotherapy works. More research needs to be done. We are not yet sure if it can be used alone or if it's best in combination with other therapies. We need more trials involving patients with earlier stage disease."

As more immunotherapy success stories are promoted in the media, patients are beginning to ask about it, and health care professionals should be prepared.

"Patients frequently request immunotherapy now," Dr. Kaufman says. "Many people seek me out for that. I even had a patient with breast cancer come to me seeking immunotherapy. I told her I specialize in melanoma. She said, 'I know, but you're the only one I can get immunotherapy from.'"

People need to understand that immunotherapy isn't a blanket strategy for every type and stage of cancer right now, but more clinical trials are being conducted to expand the reach.

MANAGING SIDE EFFECTS

Since immunotherapy works differently than other cancer treatments, health care professionals need to be aware of immunotherapy complications and monitor closely, because early intervention can reverse the symptoms after the immunotherapy is stopped and steroids begun.

"Monitoring is key with treating patients with immunotherapy," Dr. Balch says. "In fact, immunotherapy requires more monitoring, assistance and follow-up than any other cancer treatment option. It is important for health care professionals to understand that and to educate patients that professionals are available 24/7 to call and discuss their problems."

Both Dr. Kaufman and Dr. Balch agree that health care professionals need to monitor and assist patients more closely because of the side effects. Although the side effects with immunotherapy are typically less common than with chemotherapy or radiation therapy, some side effects, usually in the form of an autoimmunity, can be severe and may need immediate attention.

"Professionals must educate the patient on how to recognize the early warning signs of a potentially seri-

ous side effect," says Dr. Balch. "Patients need to not be afraid to call the doctor at the earliest signs of symptoms. With autoimmune responses, if caught early, 90 percent of the time, an autoimmunity [caused by the immunotherapy] can be reversed with steroids and by temporarily taking the patient off of the immunotherapy. If the patient waits too long [to report symptoms], it can cause irreversible autoimmunity and possibly death. Colitis can progress to death, and an attack on the endocrine system can be permanent. Patients need to be told whom to call after normal office hours if they have side effects. Stress to them that they should not be afraid to call. If they experience any symptoms that are beyond what is normal for them, they should call their doctor's office immediately."

It's also important to realize that side effects can be delayed with immunotherapy, sometimes occurring even months after going off the drugs.

"Professionals need to watch patients closely when they are on immunotherapy drugs," says Dr. Kaufman. "Patients on immunotherapy need to be monitored more, even as long as three to four months after treatment stops since both therapeutic responses and side effects may occur late."

DETERMINING CANDIDATES

In determining which patients are good candidates for this treatment, Dr. Kaufman offers several tips.

"We need to look at the tumor and cells as well as the patient and his or her condition and age. One thing we've found in a newly published study is that older patients who've used immunotherapy are showing better survival rates than expected. It was believed that elderly patients, or those over 65-70 years of age, were not good candidates for immunotherapy and it wasn't safe for them because their immune systems may not work as well. We are finding that thinking is wrong. Age is not a good reason for preventing a patient from trying immunotherapy.

"Candidates with autoimmune or suppressed immune systems or chronic steroid use typically have not been considered good candidates because they were excluded from clinical trial participation. But we are finding now that some people with these conditions can benefit from immunotherapy with minimal increase in potential adverse events. They may just need more monitoring than other patients."

Dr. Balch explains that in clinical trials, patients with later-stage melanoma are responding better to immunotherapy.

"It is amazing that even in patients with advanced disease who have failed other systemic treatments, we are getting a strong response," Dr. Balch says. "We must systematically evaluate the benefits and risks of immunotherapy, including combinations of therapies in a progression of clinical trials, starting with patients with advanced cancer to assess the risk versus benefits, and then progressing to a goal of increasing survival rates in surgical patients in the form of adjuvant or neoadjuvant therapy."

CLINICAL TRIALS

Patients may have multiple fears about participating in clinical trials for immunotherapy for melanoma. It is important for health care professionals to help calm their fears.

Cost is one of the biggest fears patients may have with joining a trial. Encourage your patients to read the fine print in their consent forms, and discuss costs with their insurance company before beginning a trial.

"Immunotherapy is a revolutionary treatment and has shown amazing results, but because it's so new, it's very expensive. Even if the insurance company will pay for part, having to pay 5 percent to 10 percent of the copay can still be very expensive for the patient," Dr. Balch says. "Also, patients need to know that many pharmaceutical companies will pay for the drugs if they are eligible for a clinical trial, which can be a significant incentive to consider."

Patients often think if they don't get the clinical trial drug they may risk not getting good treatment. Dr. Balch says he assures all of his patients they get the standard of care treatment, which has been built upon the results of clinical trials of the past.

Dr. Kaufman offers other reminders for professionals to share.

"Every drug used today was developed through a clinical trial," Dr. Kaufman says. "That's how we approve new drugs. Tell the patient they will get a lot of attention on a trial, and doctors can intervene more effectively. People often will say they don't want to be a guinea pig. It's important to remind them that these studies are reviewed by many groups and are very well-vetted. Trials are the best form of medicine today. They are the cutting edge of medicine now."

MORE RESEARCH NEEDED

Both Dr. Balch and Dr. Kaufman agree that much more research is needed on immunotherapy.

"I'm involved in a study with the oncolytic virus therapy, talimogene laherparepvec (Imlygic). We've tested it in Stage III and IV, now we are working backward and testing it in Stage II melanoma," Dr. Kaufman says. "We know that 50 percent of Stage II melanomas recur after surgery and often at a higher stage. So, in this study, we are looking at giving patients with Stage II melanoma oncolytic virus therapy six weeks before their planned surgery. We want to see if they will have an immune response to the cancer after the surgery. If successful, this could be one of the first neoadjuvant immunotherapy approaches for the treatment of melanoma."

Other areas of research include immunogenomics and the value of immunotherapy drugs.

"Immunogenomics is going to be one of the hottest topics discussed over the next decade," says Dr. Kaufman. "We don't have a good handle on it now, and it may be more established for targeted therapy and precision medicine right now. We need to learn more about immune-related genes. We'd like to get to a place where we can predict a patient's immune response to know if they are a good candidate for immunotherapy. [In the future,] we may be able to better predict a patient's response to immunotherapy, which in turn may help us determine which immunotherapies to use first.

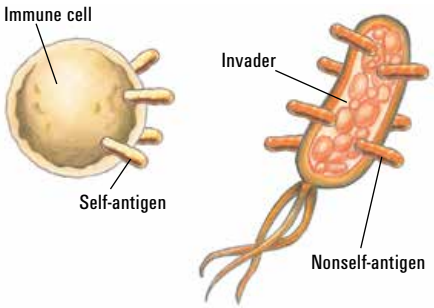
"Also, I want to mention the value proposition of immunotherapy drugs. Value incorporates clinical benefit, adverse event profile and economic costs. In addition, impact of patient quality of life should also be considered. Recently, there has been significant focus on the cost aspects of cancer treatment. While value is, of course, important, we have very little, if any, data on value for immunotherapy drugs. To date, most value analyses in oncology have focused on chemotherapy endpoints, which are completely different. Since patients on immunotherapy are living longer and have different side effects, the value proposition may be very different. These factors need to be weighed against the economic costs of the drugs. Furthermore, since immunotherapy works differently than chemotherapy, we need to consider if we can reduce the costs by reducing the amount of the drugs we are giving to patients. Some patients respond slowly, but the question of whether they need to stay on treatment waiting for the response is not clear. Maybe we can still get the response we want but at lower doses. Maybe patients don't need to stay on the drugs as long to reach the same desired effect. We can't approach immunotherapy with a chemotherapy mindset. We need to design end points and studies that are specific to immunotherapy and that are separate from chemotherapy. We are not there yet, but we need to get there." ■

Immunotherapy is a fundamentally different approach to treating melanoma and other cancers. It involves the use of the same natural defenses a body uses every day to fight infection. In some patients, the cancer is able to trick the body's immune system so that cancer cells can "hide" in plain sight. Immunotherapies help the immune system recognize cancer as a foreign invader and help build on the healing capabilities of the immune system with drugs and other techniques (see *The Role of Monoclonal Antibodies* on page 5).

HOW THE IMMUNE SYSTEM WORKS

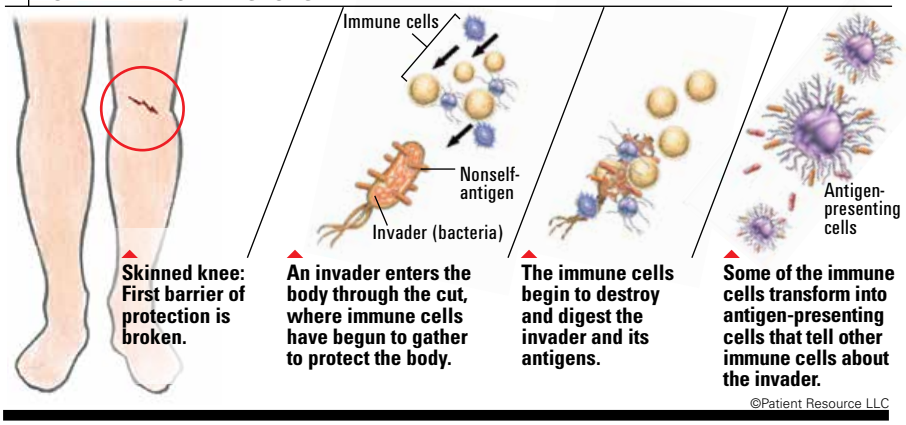
The immune system is the body's natural defense against infection and disease, including cancer, and protects the body from substances that can cause harm, such as bacteria and viruses (also called germs). The cells of the immune system continuously flow through the body, looking for germs that may be invading the body. The immune system recognizes invaders by their antigens, which are proteins on the surface of the invading bacteria or on virus-infected cells (see Figure 1). Every cell or substance has its own specific antigens, and a person's cells carry "self-antigens" that are unique to that individual. Cells with self-antigens are typically not a threat. Invading germs, however, do not originate in the body and so do not carry self-antigens; instead, they carry what are called "nonself-antigens." The immune system is designed to identify cells with nonself-antigens as harmful and respond appropriately. Most immune cells release cytokines (messengers) to help them communicate with other immune cells and control the response to any threats.

FIGURE 1
TYPES OF ANTIGENS



All cells, including normal body cells, have antigens, or proteins, on their surface. Self-antigens are proteins that are specific to an individual person, and cells with self-antigens are usually not a threat to the body. People carry self-antigens on normal cells, such as liver, colon and thyroid cells. However, invading cells are not part of the body and so do not have self-antigens. Instead, they have nonself-antigens. The immune system can identify cells with nonself-antigens as harmful and begin an attack on those cells.

FIGURE 2
NORMAL IMMUNE RESPONSE



FACING A NORMAL INVADER

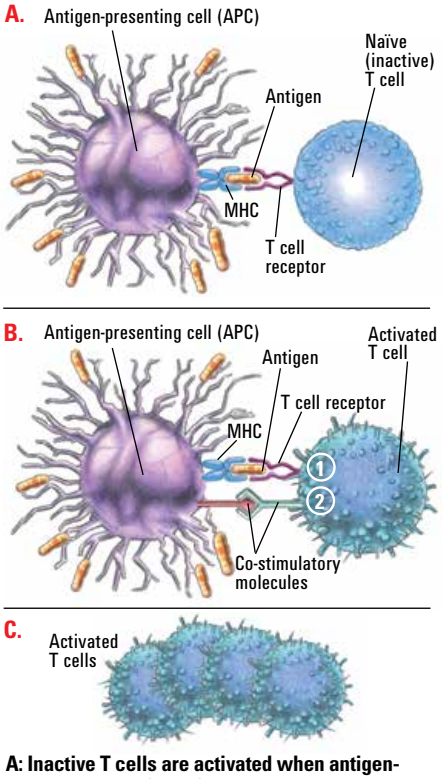
The immune system works constantly to keep the body free from infection. Understanding how the immune system responds in an ordinary situation will make it easier for your patients to see how it can be enhanced to face a more serious condition such as cancer. To help explain the immune system to your patients, use the following example:

When you skin your knee, for example, the immune system's first barrier, the skin, is broken, and harmful substances can easily enter the body (see Figure 2). As soon as the injury occurs, immune cells in the injured tissue begin to respond and also call other immune cells that have been circulating in your body to gather at the site and release cytokines to call other immune cells to help defend the body against invasion. The immune cells can recognize any bacteria or foreign substances as invaders. Immune cells, known as natural killer cells, begin to destroy the invaders with a general attack. Although this attack can kill some of the invaders, it may not be able to destroy all of them or prevent them from multiplying.

At the same time, other immune cells called dendritic cells start to engulf or "eat" the invaders and their nonself-antigens. This process causes the dendritic cells to mature into antigen-presenting cells (APCs). These APCs expose the invading cells to the primary immune cells of the immune system—the B and T cells—so that these cells can recognize the invading cells. B cells work rapidly to produce antibodies which help identify and stop the invading bacteria. Viruses, unlike bacteria, like to hide inside normal cells and may be more difficult for the immune system to recognize. T cells, however, are designed to find abnormal fragments of viruses inside normal cells. Before these T cells have been activated to fight viruses and other invaders, they're known as "naïve" T cells.

APCs communicate with and activate the naïve T cells by connecting to them through protein molecules on their surfaces. A specific set of proteins on the APC, called the major histocompatibility complex (MHC), must connect to the receptor on each T cell. This first important connection is sometimes re-

FIGURE 3
T CELL ACTIVATION



A: Inactive T cells are activated when antigen-presenting cells (APCs) connect with the T cell.

B: Two signals (see 1 & 2) are necessary for complete activation.

C: Activated T cells then multiply to defeat the threat.

ferred to as Signal 1. This connection allows the T cell to recognize antigens on invading cells as a threat (see Figure 3).

Before a T cell can be fully activated, however, additional molecules on the surfaces of both cells must also be connected to confirm that an attack against the invader is necessary. This second signal is known as the co-stimulatory signal, or Signal 2. If a T cell receives Signal 1 but not Signal 2, the T cell will die, and the attack is shut down before it even started.

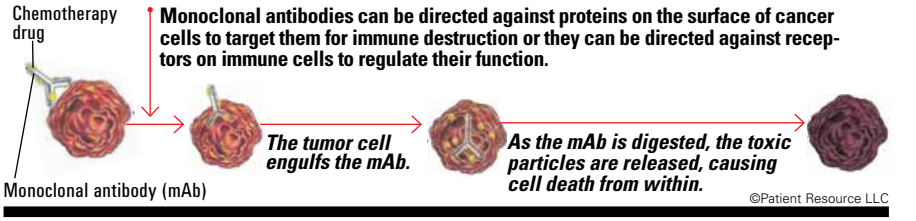
When a T cell receives both Signal 1 and Signal 2, it is able to recognize the invading cells and destroy them. This fully activated, or effector T cell, then multiplies to expand the number of T cells that are equipped to defeat the threat (see Figure 3). Multiple generations of immune cells are created by the same immune response, and then some T cells transform into regulatory T cells, which work to slow and shut down the immune response once the threat is gone.

Other T cells may become memory T cells. They can stay alive for months or years, continuing to fight off the same invading cells again. Memory is the basis of immune protection against disease in general and explains why we don't become infected with some diseases, such as measles or chicken pox, more than once.

THE ROLE OF MONOCLONAL ANTIBODIES

One of the body's natural immune responses to foreign substances is the creation of antibodies specific to the antigens (proteins) found on the surface of invading germ cells. Some antibodies can recognize portions of proteins on the surface of cancer cells. Monoclonal antibodies (mAbs) are antibodies made in a laboratory that are designed to target specific tumor antigens. They work in different ways:

- **Flagging targeted cancer cells for destruction.** The mAb acts as a flag that attaches to parts found only on the surface of specific cancer cells, marking them for destruction by other immune cells.
- **Blocking growth signals and receptors.** Some mAbs are designed to block the mechanisms that cancer cells use to grow, such as access to the blood vessels necessary for growth.
- **Delivering other therapeutic agents directly to targeted cancer cells.** The mAbs can be made to carry cancer drugs, radiation particles or laboratory-made cytokines directly to cancer cells. When a mAb is combined with a toxin, such as a chemotherapy drug, it travels through the system until it reaches the targeted cancer cell, where it attaches to the surface, gets swallowed by the tumor cell and breaks down inside the cell, releasing the toxin and causing cell death. Combining mAbs with radiation particles, a treatment known as radioimmunotherapy, allows for radiation to be delivered in lower doses over a longer period of time directly to specific cancer cells. This direct form of radiation delivery typically damages only the targeted cells (see figure below).



FACING CANCER

Everyone's immune system uses the same method to attack cancer, but the process is more complicated because cancer cells are created by the body. Because of this, the normal ways to find and fight invading cells from outside the body aren't always effective. If the body can't tell the difference between the tumor cells and normal cells, the tumor cells may be able to "hide" from the immune system. Use this example to illustrate this process for your patients:

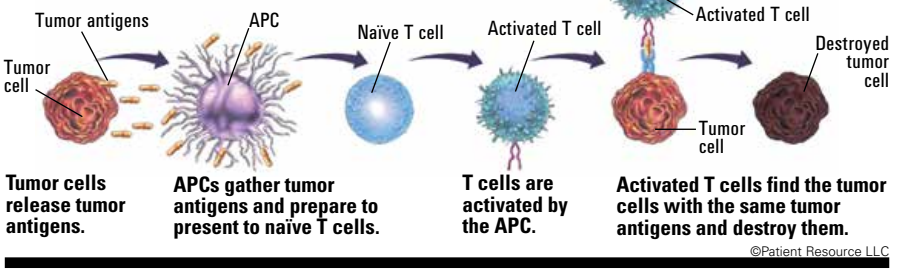
Think of allergy shots given to relieve the symptoms of an airborne allergen, such as pollen or pet dander. Increasing doses of a specific allergen are injected into a person over a series of visits to the doctor, which causes the body to develop a tolerance to pollen. This type of therapy can provide temporary or permanent relief of symptoms. However, the body no longer sees the pollen as an invader, so the immune system stops attacking it. The case with cancer cells is often similar. In early stages, cancer cells may shed proteins into the body. As these proteins circulate through the bloodstream, the body begins to develop a tolerance for the cancer cells. And once that tolerance exists, the immune system may not recognize these cancer cells as a threat. Then, just like the pollen, the cancer cells may be safe from an immune system attack.

In some cases, the DNA changes (mutations) that cause the cancer may be different enough to stimulate an immune response similar to the response described for invading virus cells. If the immune system detects the cancer, the APCs must share the information with the T cells, which are the primary players in the fight against cancer (see Figure 4). The MHC on APCs must connect to receptors on T cells, and the T cells must receive both Signal 1 and Signal 2 in order to become activated and multiply. If Signal 2 is not received, the response will shut down (see Figure 5, page 6). A T cell can function properly against the cancer only if it recognizes the cancer as harmful, receives the proper signals to become activated, and continues to get signals to continue the attack.

Tumor cells can create cytokines, which means that cancer cells can communicate with and confuse other immune cells, allowing the cancer to take control of certain parts of the process that the body uses to regulate the immune response. So, even if the immune system recognizes the cancer, it may not be able to successfully start or maintain an attack long enough to kill the cancer cells.

The ability of T cells to become activated and attack cancer is at the heart of immunotherapy research. One specific area of research focuses on how cancer cells can trick the immune system into turning on "checkpoint pathways" early. Checkpoint pathways are part of the system of checks and balances

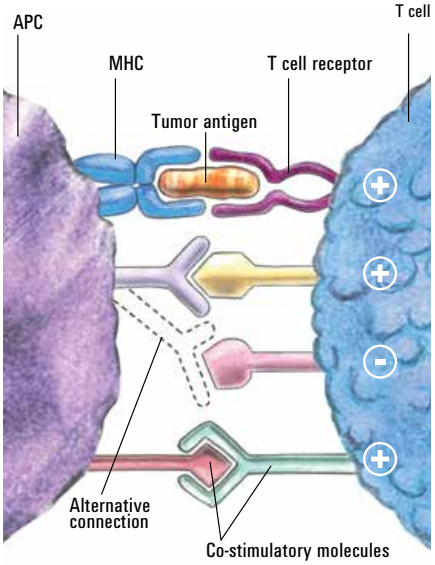
FIGURE 4
HOW THE IMMUNE SYSTEM ATTACKS CANCER



that allow the immune cells to evaluate the attack against the threat at multiple stages. The pathways essentially function as the "brakes" when the body determines the response is no longer needed. By using signals to confuse other immune cells into putting on the brakes, the cancer can shut down the attack before it has responded effectively and thus, the cancer cells continue to grow. Blocking the effect of these checkpoint pathways can restore the normal function of the immune cells. Recent breakthroughs in immunotherapy research have involved two main checkpoint pathways: the CTLA-4 immune checkpoint pathway and the PD-1/PD-L1 immune checkpoint pathway (see Figure 6).

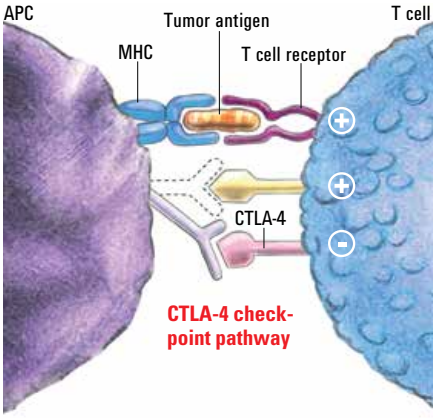
The longer the cancer cells face a weakened immune response, the more they're able to adapt, and the easier it is for them to manipulate immune cells inside the tumor's microenvironment, an area in which the tumor grows. This area, or microenvironment, typically contains cancer cells, normal connective tissues that form the structure of the tumor, access to blood vessels that drive tumor growth and several cell types that contribute to tumor development. Immune cells found in this area are often referred to as tumor-infiltrating lymphocytes (TILs). Because the tumor can control cells in this microenvironment, the tumor can trick TILs into becoming useless or even helping the tumor grow. For example, APCs may be confused by signals from tumor cells, preventing the APCs from functioning properly, and making them incapable of sounding the alarm about a threat. In some cases, tumors can upregulate (increase) the activity of regulatory T cells inside the microenvironment. With this increased activity, regulatory T cells are actually working to reduce the immune response around the tumor by turning off the other cancer-specific T cells. It's as if the tumor recruits the body's own immune cells to fight off the attack, using the very processes that normally protect the body. The longer the immune system is exposed to the tumor, the weaker the immune response becomes. Immunotherapy research focuses on identifying different ways tumors manipulate the immune system and how to reverse those processes. ■

FIGURE 5
CELL SIGNALS

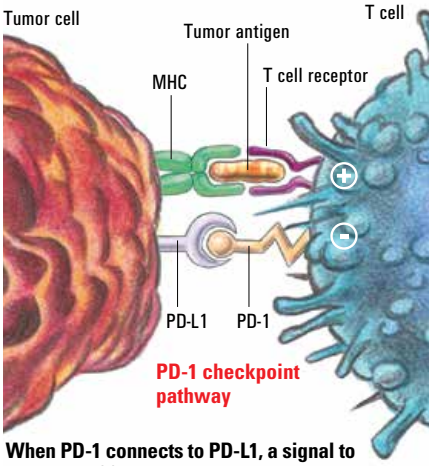


Signals are necessary to activate and shut down a T cell. A molecule on one cell may have the ability to connect with different receptors on another cell. When the connection creates an activation signal (+), the immune response continues. Alternatively, if the connection creates a signal to shut down, the immune response begins to shut down (-). The delicate balance of signals regulates the strength and duration of the immune response.

FIGURE 6
CHECKPOINT PATHWAYS



When the CTLA-4 molecule connects instead of other molecules, a signal to shut down (-) is sent to the T Cell.



When PD-1 connects to PD-L1, a signal to shut down (-) is sent to the T cell which then becomes inactive.

WORDS TO KNOW

Antibody – A protein created by B cells in direct response to specific antigens. An antibody attaches itself to its respective antigen, marking it for other immune cells to "see" and destroy.

Antigen – A protein produced by a cell, virus or bacteria. In the case of cancer antigens, the protein or part of a protein is on the surface of the cancer cell or substance that alerts the immune system. This causes the production of antibodies or creates T cells that can recognize and potentially destroy the cancer cell expressing that antigen.

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

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

Cytokines – Soluble molecules released by immune cells to communicate with other immune cells; certain cytokines, such as interferon and interleukin, help regulate specific immune system functions.

Major histocompatibility complex (MHC) – A set of proteins on the surface of certain immune cells that influence the interaction of normal cells with immune cells. Antigen-presenting cells show digested antigens to T cells through the MHC on their surface, which allows the T cell to "see" the antigen and recognize it as foreign. The connection between the MHC and the receptor on the T cell is the first signal necessary to activate the T cell to respond to a tumor and destroy it.

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

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

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

ADDITIONAL RESOURCES

- **American Cancer Society:**
  www.cancer.org
  Cancer Immunotherapy
- **American Society of Clinical Oncology:**
  www.cancer.net
  Understanding Immunotherapy
- **I'm the Answer to Cancer:**
  www.theanswertocancer.org
  Cancer Immunotherapy Treatments

TREATMENT OPTIONS

Immunotherapy is one of several types of treatment considered to be standard of care for melanoma. The common types of treatment are the following:

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

The use of the body's own immune system makes immunotherapy fundamentally different from other cancer treatments. Many immunotherapy strategies currently exist (see Table 1). Additional immunotherapies, used alone and in conjunction with other treatments, are being studied in clinical trials (see page 14).

Immunotherapy depends on a functioning immune system, so it will likely be important that your patients not have any autoimmune disorders and are not taking any chronic immunosuppressive medications. After taking into consideration these and other factors, such as their overall health, type and stage of their melanoma and treatment history, one or a combination of these treatments may be recommended.

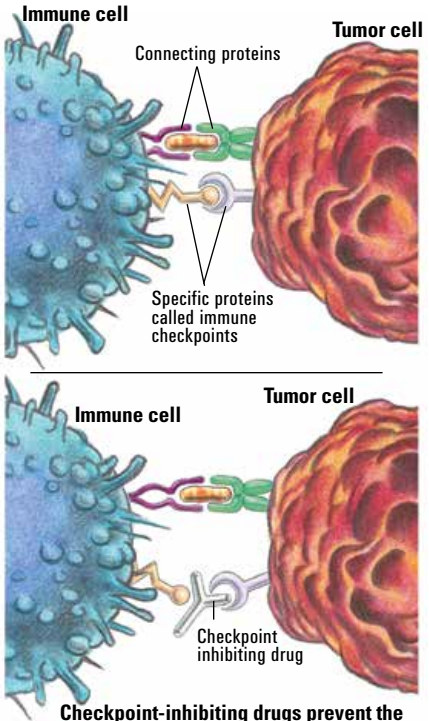
Once treatment begins, monitoring is key. More monitoring, assistance and follow-up occurs with immunotherapy than for most other treatment options. The patient will likely undergo radiographic imaging to allow the doctor to evaluate how well treatment is working by measuring the size of the tumor as treatment progresses. The side effects of immunotherapy can include what has been termed an "immune-mediated adverse event," which mimics an autoimmune response in almost any tissue. However, if caught early, these immune-mediated adverse events can be reversed with corticosteroids and, if severe, a temporary break from immunotherapy may be indicated. You should discuss the potential side effects with your patient, and remind them that they should alert their health care team immediately if they notice warning signs (see page 11).

If immunotherapy is not suggested for the patient, reassure them that multiple methods can be used to combat cancer, and other approaches may be effective. In addition, your patient may be a candidate for a clinical trial that offers access to a leading-edge treatment that is not yet available (see page 14). Discuss all of the options with your patient before treatment begins. ■

TABLE 1
FDA-APPROVED IMMUNOTHERAPY STRATEGIES FOR MELANOMA

Class of treatment	Purpose	Type of treatment	Drug
Checkpoint inhibitors	Prevent the immune system from shutting down in the body and restore the immune response against melanoma cells	CTLA-4 inhibitor	ipilimumab (Yervoy)
		PD-1 inhibitor	nivolumab (Opdivo) pembrolizumab (Keytruda) Combination therapy of ipilimumab with nivolumab
Cytokines	Boost the immune system overall		interferons, interleukins, hematopoietic growth factors aldesleukin (interleukin-2; Proleukin); peginterferon alfa-2b (Sylatron)
Oncolytic viruses	Kill tumors, primarily those that cannot be surgically removed	Oncolytic virus therapy	talimogene laherparepvec (Imlygic/T-VEC)
Vaccines	Activate the immune system	Vaccine	bacillus Calmette-Guerin (BCG) vaccine
Non-specific immune stimulators	Boost the immune system overall	Toll-like receptor agonists	imiquimod (Aldara)

CHECKPOINT INHIBITORS



Checkpoint-inhibiting drugs prevent the connections between the checkpoints. This prevents the immune response from stopping, which allows the immune cells to continue fighting the cancer.

WORDS TO KNOW

CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4) – A protein receptor found on the surface of T cells. This protein is part of the CTLA-4 checkpoint pathway, which can shut down an immune system response in its early stages. Certain cancer cells have the ability to turn on this checkpoint, which stops the immune response against the cancer cells.

Immune checkpoint pathways – The system of checks and balances in place to prevent overactivation of the immune system. Different pathways function at different stages of the immune response to help regulate the length and intensity of T cell activity; turning on an immune checkpoint typically results in shutting down the immune system response.

Interferon – A protein released by immune cells that helps regulate different immune cell activity; types of interferon include alfa, beta, gamma and lambda. Different types help regulate different functions, including prompting increased T cell activity, stimulating natural killer cells or affecting certain cell functions that influence tumor cell growth. Laboratory-made versions of the IFN-alfa protein are currently FDA-approved to treat certain types of cancer.

Interleukin – A protein produced by cells of the immune system that helps regulate the production of certain immune cells, how they function during an immune response and their production of cytokines. The laboratory-made version of this protein, aldesleukin (Proleukin), is currently FDA-approved to treat metastatic melanoma and metastatic renal cell carcinoma (kidney cancer).

STAGING MELANOMA

Once cancer is diagnosed, a physician determines the stage of the cancer. Melanoma is categorized into one of five main stages (0 through IV). The size, location and whether the melanoma has spread are used to determine the stage.

Melanoma is usually staged twice. First, a physician will consider the results of the patient's physical exam and any imaging tests that were done, and assign a clinical stage. Then, after a biopsy or surgical procedure, a pathologist will examine tissue taken from the tumor (and possibly nearby lymph nodes) and assign a pathologic stage. The second staging is more precise and is the key to deciding treatment options.

Both the clinical and pathologic stages of melanoma are classified according to the tumor, node, metastasis (TNM) system developed by the American Joint Committee on Cancer (AJCC) (see Table 2).

The first classification of the primary melanoma in the TNM system is for the thickness of the tumor (T). Each T classification is further divided into groups according to whether ulceration (a break in the outer layer of skin over the melanoma) is absent (subcategory a) or present (subcategory b). For example, a non-ulcerated melanoma 3 millimeters (mm) thick is classified as T3a, whereas an ulcerated melanoma 2 mm thick is classified as T2b. Another factor for thin melanomas (less than 1 mm thick) is the mitotic rate, which measures how fast the cancer cells are dividing and multiplying.

The node (N) classification is used to describe how many lymph nodes contain melanoma cells. The N category includes subcategories to describe the number of cancer cells in the lymph nodes. If the cancer cells in the nodes can be seen only with a microscope, the metastasis (spread) is considered to be microscopic (a). If enough cancer cells are in the lymph node that the doctor can feel the mass during a physical exam or can see the mass on an X-ray, it's said to be "macroscopic" lymph node involvement (b). Another subcategory (c) indicates whether melanoma has spread to the lymphatic vessels leading to a lymph node. This is known as "in-transit melanoma," which is metastatic melanoma found between the original tumor and the nearby cluster of lymph nodes.

The metastasis (M) category is used to classify the melanoma according to whether the cancer has spread beyond the region where the melanoma started to distant sites.

Once the melanoma is classified according to the TNM system, an overall stage of disease is assigned (see Table 1). Stage I and II melanomas are considered to be local (or localized) disease. Stage III melanoma is referred to as regional disease, and Stage IV is known as distant metastatic or advanced disease. ■

TABLE 1
STAGES OF MELANOMA

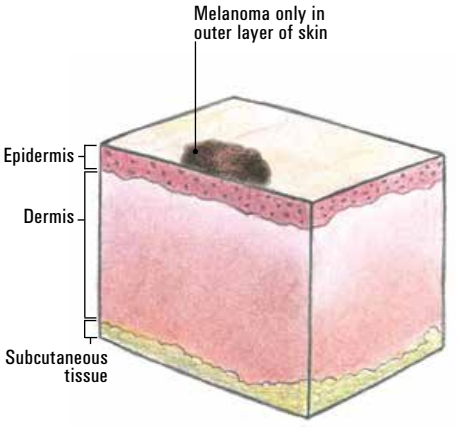
Stage	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b T2a	N0 N0	M0 M0
IIA	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0
IIIA	T1-T4a T1-T4a	N1a N2a	M0 M0
IIIB	T1-T4b T1-T4b T1-T4a T1-T4a T1-T4a	N1a N2a N1b N2b N2c	M0 M0 M0 M0 M0
IIIC	T1-T4b T1-T4b T1-T4b Any T	N1b N2b N2c N3	M0 M0 M0 M0
IV	Any T	Any N	M1

TABLE 2
TNM SYSTEM FOR CLASSIFYING MELANOMA

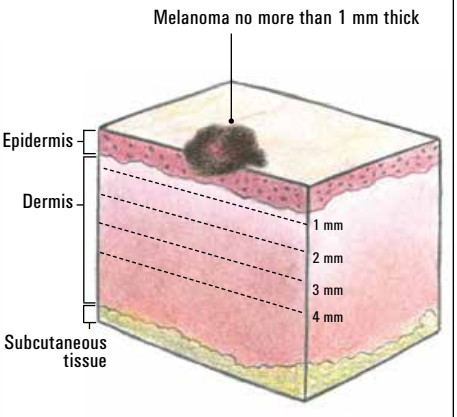
Stage	Description
Tumor (T)	
Tx	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis	Also known as "melanoma in situ," melanoma cells are found only between the outer layer (epidermis) and the inner layer (dermis) of skin and have not yet invaded these layers. This lesion is considered precancerous.
T1 **T1a** **T1b**	Melanoma is no more than 1 millimeter (mm) thick (about the thickness of a credit card). Melanoma is no more than 1 mm thick, without ulceration and a mitotic rate of less than 1/mm^2. Melanoma is no more than 1 mm thick, either with ulceration or a mitotic rate of 1/mm^2 or greater.
T2 **T2a** **T2b**	Melanoma is thicker than 1 mm but not more than 2 mm thick. Melanoma is thicker than 1 mm but not more than 2 mm thick, without ulceration. Melanoma is thicker than 1 mm but not more than 2 mm thick, with ulceration.
T3 **T3a** **T3b**	Melanoma is thicker than 2 mm but not more than 4 mm (about one-tenth of an inch) thick. Melanoma is thicker than 2 mm but not more than 4 mm, without ulceration. Melanoma is thicker than 2 mm but not more than 4 mm, with ulceration.
T4 **T4a** **T4b**	Melanoma is thicker than 4 mm. Melanoma is thicker than 4 mm, without ulceration. Melanoma is thicker than 4 mm, with ulceration.
Node (N)	
Nx	Regional lymph nodes cannot be assessed.
N0	No melanoma found in regional lymph nodes.
N1 **N1a** **N1b**	Melanoma found in one lymph node. Microscopic metastasis found in one lymph node. Macroscopic metastasis found in one lymph node.
N2 **N2a** **N2b** **N2c**	Melanoma found in two to three lymph nodes. Microscopic metastasis found in two to three lymph nodes. Macroscopic metastasis found in two to three lymph nodes. In-transit melanoma or satellite lesions are found, without metastasis to lymph nodes.
N3	Melanoma is found in four or more lymph nodes, or in two or more lymph nodes that appear to be joined together (known as matted lymph nodes). Or, melanoma is found as in-transit lesions or as satellite lesions that have spread to the lymph nodes.
Metastasis (M)	
Mx	Metastasis cannot be assessed.
M0	No metastasis.
M1a **M1b** **M1c**	Metastasis to skin, subcutaneous tissues or distant lymph nodes. Metastasis to lung. Metastasis to any other distant organs.

STAGES OF MELANOMA

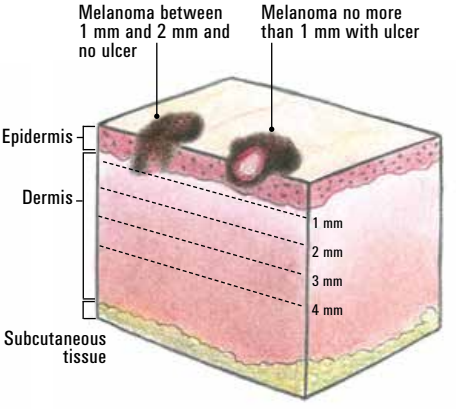
Stage 0



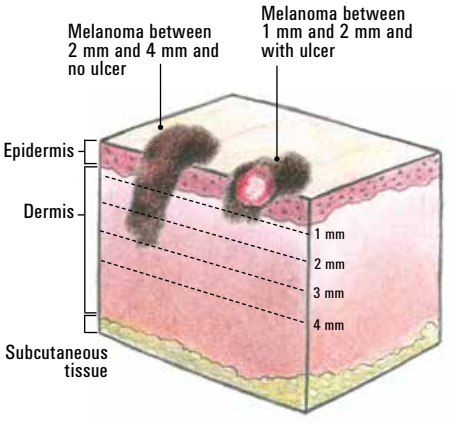
Stage IA



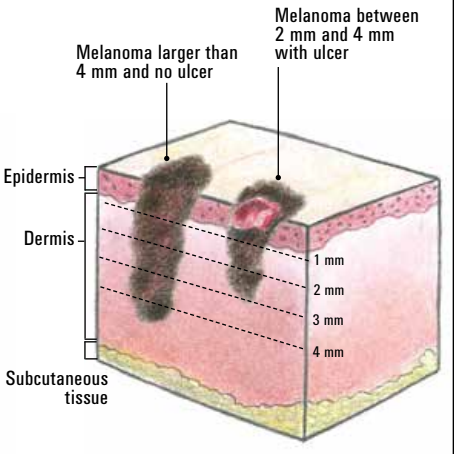
Stage IB



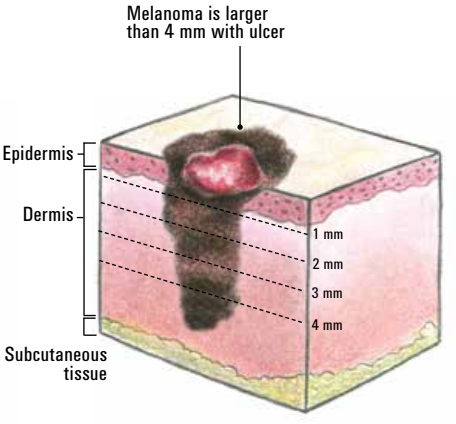
Stage IIA



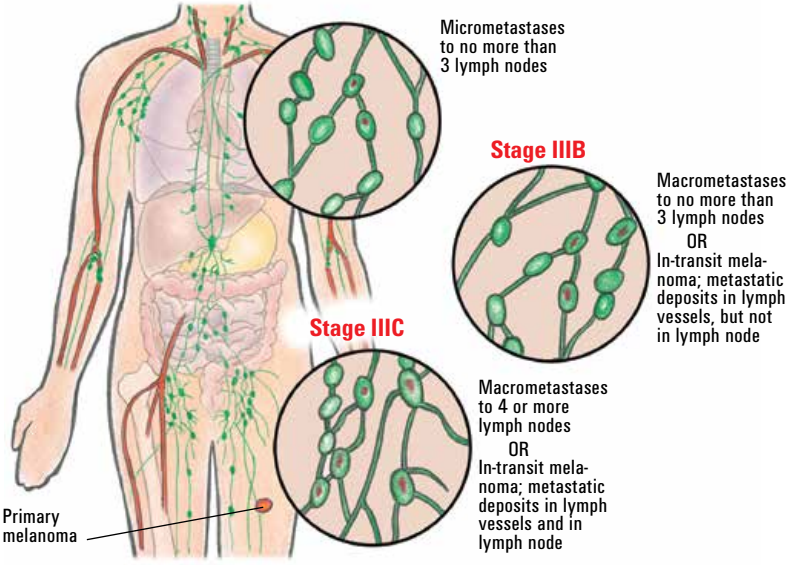
Stage IIB



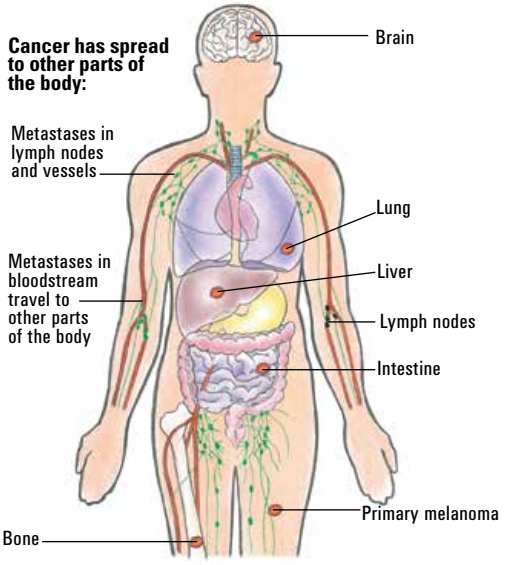
Stage IIC



Stage IIIA



Stage IV



TAKE LIFE A DAY AT A TIME

One month before my wedding in 1979, I had a mole removed from my left shoulder that I think I'd had all of my life. The dermatologist thought it looked fine but decided to send it to the lab. It came back as Stage III melanoma. We were all devastated.

Soon after, I had surgery to remove three lymph nodes. They also tested positive for melanoma. I was 21 years old, about to be married and newly diagnosed with cancer. I asked, "Why me?" I didn't know if I was going to make it through a year or even six months. I was pretty scared, but my husband never wavered.

For the first six months, I had a monthly follow-up scan. I considered participating in a national clinical trial, but it would have involved regular air travel to a distant city. They couldn't guarantee me I wouldn't be in the "surgery only" group, so I made the difficult decision not to enroll.

That period was a bit of a haze. I still wondered why this had happened to me, and I was depressed and discouraged. I knew, however, that I had to become a more positive person. I put my faith in my doctors and made it through with their help and the encouragement, support and prayers of my husband and family. I was cancer-free for the next three years.

In 1982, my life fell apart. I began having severe headaches, and my right hand kept falling asleep. I was working in a dental office and couldn't hold onto the tools. My primary care physician sent me for another CT scan, and the doctors discovered the melanoma had spread to my brain.

Looking back, I know that my neurosurgeon is the reason I'm alive today. His colleagues thought there was no hope in doing the surgery. He disagreed. His decision to do the brain surgeries and his encouragement and positive attitude kept me going.

The first brain surgery to remove the tumor was a craniotomy on the left side. After the tumor was removed from my brain, I had no feeling on the right half of my body. My doctor then found a second brain tumor, and I had surgery to remove the tumor from the lower section near the base of my brain. Six weeks after that, during a routine chest x-ray, he found a tumor in my lung. I wondered how much more my body could take, but I had a lobectomy to remove one of the lobes on my left lung.

Recovering from the surgeries made me very fatigued, but I knew I had to get started with physical therapy. The numbness on my right side slowly went away, with the exception of my right hand. I could grip things, but I had no feeling in it. I still have no feeling in it today. I taught myself to print with my left hand, and sometimes it was very frustrating.

In addition to everything else, half of my head was shaved because of the surgeries. Back then, wigs were not very pretty, so sometimes I wore bandanas. I continued to work at the dentist's office and tried to have a sense of humor about it all, but it saddened me when I realized I was losing my childhood dream of becoming a dental hygienist. I left the dental office and went to work in a very upbeat and busy job so I wouldn't have time to think and be discouraged.

I began an immunotherapy clinical trial at a local hospital. The treatment was an injection in my lymph node areas to build up my immune system with the goal of no recurrence. Every two weeks for about a year, the injections alternated between the lymph nodes under my arms and in my groin. My only side effect was tenderness for a day or two after the injections.

Toward the end of treatment, our marriage had grown much stronger. After much discussion and prayer, we decided to risk having children. I badly wanted to start a family and had been waiting for years. Fortunately, we had two healthy children.

My life changed a lot after my diagnosis. Using sunscreen turned into a daily habit, and I became more outspoken about preventing melanoma. I'm a big believer in prayer, and I started looking at life as a day-to-day miracle from God. I looked for a way to help others going through cancer treatment, so I began volunteering for the Bloch Cancer Foundation. I want everyone to see that I'm living proof of the results of hard work, a great support team and a positive attitude.

I am so thankful, especially for my physicians. Every time my surgeon sees me he says he can't believe I'm here because I did not have an easy road. I fought to come back from the surgeries and the depressing times. If you have the opportunity to try immunotherapy, I recommend it. It was scary not knowing exactly what was being injected, but I have not had a recurrence. In my experience, it took a little bit longer for the entire treatment, but it was easier on my body—and I feel great.■

PERSONAL JOURNEY | JANICE UPDIKE

Janice Updike is a long-time survivor of metastatic melanoma. After several surgeries, including two on her brain, and a lengthy immunotherapy clinical trial, she feels great. She is confident her cancer-free status stems from a talented and intuitive medical team, a great support system and her strong faith.

SIDE EFFECTS

Although using immunotherapy to treat melanoma typically results in fewer side effects that are less severe than those associated with other forms of cancer treatment, some side effects still can occur, and some can be severe. However, data on the long-term effects of immunotherapy are not yet available. Not everyone will experience the same side effects with immunotherapy, and some people may not experience any side effects at all. Symptoms can vary in severity and differ according to the type of immunotherapy (see Table 1).

Many side effects can be managed with over-the-counter medications. However, some symptoms can be severe. With immunotherapy, side effects can indicate that the immune system has become too active and could put patients at risk for an autoimmune disorder. If treated early, these symptoms can be corrected with corticosteroids, and immunotherapy can be resumed at a later date. Often, the dose of the immunotherapy medication can be adjusted to prevent future autoimmunity, if caught in time. It is important to educate the patient about what they should do if they have symptoms. Emphasize to them the importance of contacting a member of your health care team immediately and frequently so you can help monitor them and their symptoms. Remind them to seek treatment immediately for any medical emergencies, including high fever, severe abdominal pain or shortness of breath.

Common side effects associated with immunotherapy include the following.

■ **Immune-mediated adverse reactions** have not been a commonly reported side effect of immunotherapy, but they can occur with certain types of immunotherapy medications. Explain to your patient how to recognize an immune-mediated adverse reaction, as some of these side effects may not produce symptoms they can feel. These reactions occur when the immune system is overstimulated by the treatment and may cause inflammation, including swelling, redness or pain, that they may or may not be able to physically feel.

With immune-mediated adverse reactions, certain organs may become inflamed, which can cause hepatitis (liver), dermatitis (skin) and enterocolitis (small intestine, colon). It can also damage the nerves and endocrine glands. One of the more common side effects with checkpoint inhibitors and cytokines is a change in the function of the thyroid gland. This can sometimes be corrected with thyroid replacement medication and requires monitoring of thyroid function on a regular basis.

If not treated early, these symptoms can lead to life-threatening complications. Treatment will need to be sought early for immune-mediated adverse events.

TABLE 1
COMMON SIDE EFFECTS OF IMMUNOTHERAPIES FOR MELANOMA

Name or Type of Drug	Side Effects
bacillus Calmette-Guerin (BCG) vaccine	Injection-site pain; flu-like symptoms with a headache, aches and high temperature
imiquimod (Aldara)	Injection-site reactions or local skin reactions such as itching, burning, superficial reddening of the skin, flaking/scaling/dryness, scabbing/crusting, swelling, hardening of normally soft tissues or organs as a reaction to inflammation
interferons, interleukins, hematopoietic growth factors aldesleukin (Interleukin-2; Proleukin)	Flu-like symptoms such as fever, chills, aches and fatigue; severe allergic reaction; lowered blood counts; changes in blood chemistry; organ damage (usually to heart, lungs, kidneys, liver or brain)
ipilimumab (Yervoy)	Fatigue, diarrhea, itching, rash, and other immune-mediated adverse reactions such as enterocolitis, hepatitis, dermatitis, neuropathy and endocrinopathy
peginterferon alfa-2b (Sylatron)	Depression and other neuro-psychiatric disorders, fatigue, elevated liver enzymes, fever, headache, decreased appetite, muscle pain, nausea, chills, injection-site reaction
pembrolizumab (Keytruda)	Fatigue, itchy skin, rash, constipation, diarrhea, nausea, decreased appetite, change in thyroid function
nivolumab (Opdivo)	Rash, fatigue, muscle or joint pain, bone pain, diarrhea, itchy skin, nausea, change in thyroid function
talimogene laherparepvec (Imlygic, T-VEC)	Fatigue, chills, fever, nausea, flu-like symptoms, injection-site pain

■ **Fatigue** is the most common side effect reported in multiple immunotherapies. Fatigue and feeling tired are often found in the class of therapies known as checkpoint inhibitors, cytokines and oncolytic virus therapy.

The fatigue associated with cancer is different than simply feeling tired because they haven't had enough rest. Fatigue from cancer or its treatment may cause people to feel physically, emotionally or mentally tired and exhausted. Explain that symptoms of fatigue include missing work, spending less time with friends and family, sleeping more, and having difficulty remembering things or not thinking clearly. Encourage them to talk with you about any of these symptoms.

An evaluation of the patient's fatigue level throughout their treatment and recovery, including doing a distress screening, is recommended.

■ **Flu-like symptoms,** such as fever, chills, aches, headache, drowsiness, nausea, vomiting, loss of appetite and low blood cell counts, can occur if treatment includes cytokines or oncolytic virus therapy. These symptoms can range from mild to severe.

To manage flu-like symptoms, getting enough rest will be important. You might recommend taking acetaminophen. You also might suggest taking any oral treatments at bedtime to help minimize symptoms. If a cough develops, suggest they drink plenty of water and other fluids to keep their throat moist.

■ **Diarrhea** is a common side effect with the checkpoint inhibitor class of immunotherapies for melanoma, specifically the PD-1 and CTLA-4 inhibitors.

The symptoms can vary in severity and duration. It is important to discuss what to expect with this side effect, including how long it may last and when to consider emergency treatment. Diarrhea can lead to severe dehydration and electrolyte imbalance but also could be a symptom that the immune system is going into overdrive.

Tips to manage diarrhea include drinking clear liquids, avoiding milk products, eating low-fiber foods, eating frequent small meals, choosing foods that are high in potassium, avoiding foods that can irritate the digestive tract and trying probiotics. Anti diarrheals may be useful for minimal diarrhea but corticosteroids should be started if more than seven bowel movements per day occur, or if diarrhea is associated with crampy

→ **SIDE EFFECTS** *(continued on page 13)*

FINANCIAL CONSIDERATIONS

Once melanoma is diagnosed, peoples' first thoughts may not be financial. They want and need to focus on their treatments and getting back to a healthy life. But the financial aspect has an impact on their overall health, happiness and well-being.

The cancer-related expenses they experience will be unique to them, dependent on their diagnosis, recommended treatment plan, follow-up care and level of insurance coverage. Managing these expenses is crucial. Many patients need help understanding their insurance, planning their budget and seeking financial assistance.

TYPES OF CANCER-RELATED COSTS

Cancer-related costs can be grouped into two types of expenses: medical and lifestyle. The medical expenses include medical office visits, tests, treatments, drugs and caregiving.

Less obvious are the lifestyle costs, or the increases in routine living expenses related indirectly to treatment. For example, after a melanoma diagnosis, patients may spend more money on transportation and travel, legal help and financial services. They may also need to hire help for child or elder care, meal preparation or housecleaning. These additional expenses are a burden on their own but are even more substantial when combined with the possibility that income may be reduced if the patient and/or partner are unable to work the same number of hours during treatment.

Cancer-related costs can add up quickly, so it's important for the health care team to talk to the patient about the cost of cancer care as early as possible. Patients may be embarrassed to bring up costs with the health care team. One study found that although more than half of the patient participants wanted to talk to their doctors about costs, only 19 percent actually did—and it paid off. Fifty-seven percent of the patients who had conversations with their doctors about their financial concerns felt that it helped significantly decrease their costs, and even more felt it decreased their anxiety during the course of their treatment.

Many people are hesitant to ask about cutting costs because they fear their treatment will suffer. However, depending on a patient's specific insurance coverage, alternative treatment options that are less expensive but just as effective may be possible.

In one survey by the American Cancer Society, about 5 percent of insured people with cancer said they delayed or opted against treatment because of cost.

COVERAGE BASICS

Health insurance helps patients afford the care provided by their doctors. Health insurance ultimately helps patients pay the cost of their medical care by contributing financially toward a portion of the total bills.

As part of the Affordable Care Act, everyone is required to purchase a health insurance plan to cover their medical needs or they must pay a financial tax penalty. Under the Affordable Care Act, the government must maintain an exchange in each state, also known as a Health Insurance Marketplace, which allows people to compare and select an affordable health insurance plan to meet their needs. These marketplaces are a central point for those who do not have employer-sponsored insurance, those who have previously been denied coverage because of a pre-existing condition (such as cancer) or those who are interested in switching from their current plan.

Some patients may qualify for government-assisted health insurance, including Medicaid or Medicare. Medicaid programs are designed to help people with limited means gain high-quality care, and these programs are managed at the state level. Medicare is a federal health system designed for those age 65 or older or those who are disabled.

HELP FOR THOSE WHO CAN'T PAY

Despite the best planning and intentions, some patients may find some bills are too big to pay. Assure them that they are not alone in their struggle. In fact, one study showed that 68 percent of people with cancer and caregivers experience financial hardship during treatment.

Many organizations, such as the Patient Advocate Foundation, provide free counseling to patients burdened by medical debt. The Foundation can help patients apply for financial assistance and communicate with their doctors, insurers and creditors.

As part of your patients' health care team, you can provide them with an application for a charity care program, begin the process for requesting a discount or a reduced bill, or arrange an affordable payment plan for the remaining balance.

Many nonprofit groups have programs to help patients who can't pay their bills, including services like co-pay assistance, travel aid and child care.

Remind patients that no matter what their financial situation is, they should never

PATIENT MEDICATION REIMBURSEMENT ASSISTANCE & PROGRAMS

AbbVie Patient Assistance Foundation....www.abbviepaf.org, 800-222-6885
Amgen First Step....www.amgenfirststep.com, 888-657-8371
ARIAD Patient Access and Support....www.ariadpass.com, 855-447-7277
Astellas Pharma Support Solutions....www.astellaspharmasupportsolutions.com, 800-477-6472
AstraZeneca Prescription Savings Program (AZ&ME)....www.azandmeapp.com, 800-292-6363
Bayer Healthcare Pharmaceuticals....866-575-5002
Bayer Healthcare Pharmaceuticals REACH Co-Pay Assistance Program....www.reachpatientsupport.com, 866-639-2827
Boehringer Ingelheim Cares Foundation Patient Assistance Program....http://us.boehringer-ingelheim.com, 800-556-8317
Boehringer Ingelheim Solutions Plus....www.bisolutionsplus.com, 877-814-3915
Bristol-Myers Squibb Access Support....www.bmsaccesssupport.bmscustomerconnect.com, 800-861-0048
Bristol-Myers Squibb Patient Assistance Foundation....www.bmspaf.org, 800-736-0003
Eisai Reimbursement Resources....www.eisaireimbursement.com
Genentech Access Solutions....www.genentech-access.com/patients, 866-422-2377
Genzyme Patient Support Services....www.genzyme.com/patients/patient-support-services, 800-745-4447
Gilead Patient Access....www.gilead.com/responsibility/us-patient-access
GSK Access....www.gsk-access.com, 866-518-4357
IMLYGIC Cost Assistance....www.imlygic.com/patient, 888-427-7478
Janssen Prescription Assistance....www.janssenprescriptionassistance.com
Johnson & Johnson Patient Assistance Foundation, Inc....www.jjpaf.org, 800-652-6227
Keytruda Patient Assistance....www.merckaccessprogram-keytruda.com, 855-257-3932
Lyrica CoPay Savings Card....www.lyrica.com/Lyrica_Co-pay_Download, 800-578-7076
Merck Access Program....www.merckaccessprogram.com, 855-257-3932
Merck Helps....www.merckhelps.com, 800-727-5400
Novartis Patient Assistance Now....www.patientassistancenow.com, 800-245-5356
Onyx 360....https://enrollment.onyx360.com, 855-669-9360
Pfizer RxPathways....www.pfizerrxpathways.com, 866-706-2400
Prolia Co-Pay Program....www.proliasupport.com, 877-776-5421
R-PHARM US Access + Support....http://rpharm-us.com, 855-991-7277
Sandoz One Source....www.sandozonesource.com, 844-726-3691
Sanofi Patient Connection....www.sanofipatientconnection.com, 888-847-4877
Sylatron Patient Assistance....www.merckhelps.com/SYLATRON, 855-257-3932
Takeda Patient Assistance....www.takeda.us/responsibility/patient_assistance_program.aspx, 800-830-9159
Teva Cares Foundation Patient Assistance Programs....www.tevacares.org, 877-237-4881
Teva Oncology Core Reimbursement Assistance & Support....www.tevacore.com, 888-587-3263
Together with TESARO....www.togetherwithtesaro.com, 844-283-7276

alter or stop their treatment without talking to their health care team. Many people with cancer avoid filling prescriptions or receiving treatment when they're worried about paying the bills, but doing this can seriously damage their health. You can work with your patients to find a better solution for them.

PAYING FOR CLINICAL TRIALS

Although clinical trials are crucial for advancing cancer research and treatment, patient participation is low. Cost concerns may be one reason patients decline to volunteer. Research shows that many people with cancer believe their insurance company won't provide reimbursement and choose not to participate to avoid adding to their out-of-pocket expenses. Health care professionals can help educate patients about available resources, such as the Affordable Care Act.

Through the Affordable Care Act, all private insurance companies are required to cover routine patient-care costs from in-network providers associated with an approved clinical trial. An approved trial is defined as a trial in any phase that is aimed at preventing, detecting or treating cancer. Patient-care costs include those related to doctor visits, hospital stays and some testing procedures that are part of standard care, which would be incurred in a clinical trial and in standard treatment. Research costs, which are directly related to the clinical trial and include drugs and procedures, are typically covered by the trial sponsor.

For example, a patient's insurance company may not consider follow-up tests and imaging studies done solely for data collection and analysis as part of routine patient-care costs. Participation in an unapproved trial may result in the insurance company declining coverage. Even though clinical trial coverage has expanded, patients should still be encouraged to discuss costs with the clinical trial administrators and reach out to their insurance company for an explanation of coverage. Remind patients that before they sign the consent form, it is extremely important to address all of their cost and payment questions and concerns up front.

Some federal programs help pay the costs of care during clinical trials: Medicare, TRICARE and the Department of Veterans Affairs (VA).

Health care professionals should be familiar with resources that offer financial assistance for patients who incur costs not covered by their health insurance and for those who have no insurance coverage at all. These resources may include local or national advocacy groups, other cancer-related fundraising organizations and the trial sponsor. Talk with the insurance representative on your team to help field patient questions. Have the resources available so that your team can pass the information on to the patient. ■

HELP IS AS CLOSE AS A SMARTPHONE

→**Finding help paying for medications can be overwhelming,** but thanks to the National Comprehensive Cancer Network's new phone application – the NCCN Reimbursement Resource App – help is just a few taps away. Patients can download the application through the Apple iTunes Store or Google Play Store, and can search for reimbursement for their medications by cancer type or drug name, or just browse available reimbursement or assistance programs.

My Resource Search is a free, easy-to-use tool for on-the-go help for financial and insurance issues related to health care. Harnessing the power of the National Uninsured and Underinsured Resource Directories, the app allows both insured and uninsured patients the ability to quickly identify the community, national and charity programs that can assist in their health care needs. My Resource Search is perfect for patients currently experiencing a health crisis or providers who want to guide their patients to programs that may be able to reduce their barriers to care. My Resource Search is available free through the Apple iTunes Store or Google Play Store.

The Healthcare Bluebook on the Apple iTunes store helps consumers save money by equipping them with "Fair Price" information about thousands of health care services and procedures that enable them to become smart health care shoppers. Due to price variances among providers, smart shoppers can save thousands of dollars on common procedures like MRIs, orthopedic surgeries and preventive screenings. Whether they have high deductible health insurance or no insurance at all, Healthcare Bluebook's Fair Price will help the patient understand what they should pay for a procedure.

SIDE EFFECTS *(continued from page 11)*

abdominal pain or hemorrhage.

Remind patients to call your health care team if they experience symptoms that interfere with their daily activities, such as severe abdominal cramping, or that cause them to fear leaving their home.

■ **Mild skin reactions,** such as bumpy or itchy red rashes, can occur. Checkpoint inhibitors most often feature itching and/or rashes as common side effects.

Other skin problems include yellowing or other changes in skin color, blistering, hives, pale patches and flushing or redness.

Although these symptoms are rarely severe, they can be very uncomfortable. Depending on the type of itching, you might recommend a corticosteroid or a topical anesthetic. If the itching affects their sleep, the doctor may prescribe an antihistamine, such as cetirizine (Zyrtec) or diphenhydramine (Benadryl). Medicated creams may be prescribed to help manage itchy skin or rashes. In some cases of rash, antibiotics may be prescribed.

Early treatment may improve your patients' symptoms, so encourage them to contact the treatment team at the first sign of a reaction.

■ **Depression** is a common side effect of cancer and its treatment. It can affect mood, behavior, and ability to think and concentrate, as well as initiate physical symptoms including fatigue, loss of appetite, difficulty falling asleep or extreme tiredness. Some treatments are associated with mood changes, such as depression, suicidal thoughts or other psychiatric conditions. If your patients notice any mood changes that develop as part of their treatment, recommend that they call the physician's office.

It is very important to discuss any concerns the patient may have about potential side effects before their treatment starts. Communication between your health care team and the patient is crucial for managing side effects during immunotherapy. Provide patients with a list of whom to contact if they have urgent questions or if side effects develop, especially after normal office hours. ■

ADDITIONAL RESOURCES

- **Cancer Support Community:**
  www.cancersupportcommunity.org
  Is Immunotherapy Right for You?
- **National Cancer Institute:**
  www.cancer.gov
  Types of Cancer Treatment: Immunotherapy

ABOUT CLINICAL TRIALS

Hundreds of clinical trials throughout the United States are currently being held to evaluate immunotherapy drugs as new treatments for melanoma, in combination with other strategies or as new uses for existing treatments. New participants are needed for these studies to succeed, but many patients are fearful of participating in clinical trials. Health care professionals can be instrumental in influencing and encouraging patient participation.

ENCOURAGE PATIENTS TO TRY CLINICAL TRIALS

Offer these reasons for why a patient should consider participating in a clinical trial:

1 A clinical trial may offer a worthwhile alternative to a treatment that is not working as well as expected.

2 A clinical trial may significantly improve the patient's quality of life. Discuss the advantages and disadvantages of participating, especially addressing any concerns about side effects.

3 Tell patients they will not only help identify treatments that work, they'll help eliminate those that don't. Patients likely don't realize the integral role they play in helping refine and improve the way millions of people with all types and stages of melanoma are treated.

4 Educate them about how treatments become approved by the U.S. Food and Drug Administration by telling them every treatment available today went through clinical trials to get FDA approval.

5 Assure your patients that they will be treated with dignity and respect and will receive the highest quality of care for melanoma.

GETTING STARTED

To be eligible for an immunotherapy clinical trial, a patient must have a properly functioning immune system. In addition, the patient must meet certain eligibility criteria (cancer type, overall health, treatment history, etc.).

Current clinical trials using immunotherapy for melanoma with open recruitment as of September 16, 2016, are displayed in this section. Each trial listed is categorized as "cancer immunotherapy" on www.clinicaltrials.gov.

Encourage patients to keep researching available trials, especially if they locate a clinical trial that is not recruiting in their area. Remind them that new studies and new phases are happening all the time. ■

TIP | FROM OUR ADVISORY BOARD

Dr. Waun Ki Hong

"If your patient qualifies for a trial, they are going to make a meaningful contribution to cancer therapies, and potentially help the next person who receives the same diagnosis."

Share this information with your patient and explain how to learn about a specific trial with these instructions:
[1] Visit www.clinicaltrials.gov. [2] Enter the trial record number into the search box located at the top of the Web page. The trial record number is a unique identification code assigned to each clinical study. [3] The trial will be "Recruiting" or "Not yet recruiting," which means the studies are either actively looking for participants or getting ready to look for participants.

MELANOMA IMMUNOTHERAPY CLINICAL TRIALS

Includes all open and/or recruiting studies categorized as "cancer immunotherapy" (as of September 16, 2016) by the U.S. National Institutes of Health at www.clinicaltrials.gov

Title	Cancer Type	Treatment	Location	NCT Number
Evaluation for NCI Surgery Branch Clinical Studies	Synovial Cell Cancer; Melanoma; Colorectal Cancer; Lung Cancer; Bladder Cancer		MD	NCT00001823
Immunotherapy Using Tumor Infiltrating Lymphocytes for Patients With Metastatic Cancer	Metastatic Colorectal Cancer; Metastatic Gastric Cancer; Metastatic Pancreatic Cancer; Metastatic Hepatocellular Carcinoma; Metastatic Cholangiocarcinoma	Biological: Young TIL; Drug: Aldesleukin; Drug: Cyclophosphamide; Drug: Fludarabine; Drug: Pembrolizumab	MD	NCT01174121
Vaccine Immunotherapy for Recurrent Medulloblastoma and Primitive Neuroectodermal Tumor	Medulloblastoma; Neuroectodermal Tumor	Biological: TTRNA-xALT; Biological: TTRNA-DCs	CA; DC; FL; NC	NCT01326104
Comparison of High-dose IL-2 and High-dose IL-2 With Radiation Therapy in Patients With Metastatic Melanoma	Metastatic Melanoma	Other: Radiation therapy and high-dose IL-2; Drug: High-dose IL-2	OR	NCT01416831
Vemurafenib With Lymphodepletion Plus Adoptive Cell Transfer & High Dose IL-2 Metastatic Melanoma	Metastatic Melanoma	Drug: High Dose Interleukin-2 (IL-2); Procedure: ACT with TIL Infusion; Drug: Vemurafenib; Drug: Lymphodepletion	FL	NCT01659151
Ipilimumab and Imatinib Mesylate in Advanced Cancer	Advanced Cancers	Drug: Ipilimumab; Drug: Imatinib Mesylate	TX	NCT01738139
Dendritic Cell Activating Scaffold in Melanoma	Melanoma	Biological: WDVAX	MA	NCT01753089
Tumor-Infiltrating Lymphocytes After Combination Chemotherapy in Treating Patients With Metastatic Melanoma	Stage IIIA Skin Melanoma; Stage IIIB Skin Melanoma; Stage IIIC Skin Melanoma; Stage IV Skin Melanoma	Biological: Aldesleukin; Drug: Cyclophosphamide; Drug: Fludarabine Phosphate; Other: Laboratory Biomarker Analysis; Biological: Therapeutic Tumor Infiltrating Lymphocytes	WA	NCT01807182
The Effects of Vemurafenib + Cobimetinib on Immunity in Patients With Melanoma	Melanoma	Drug: Vemurafenib	DC; MA; TX; VA	NCT01813214
Immunotherapy Using Tumor Infiltrating Lymphocytes for Patients With Metastatic Ocular Melanoma	Metastatic Ocular Melanoma; Metastatic Uveal Melanoma	Drug: Aldesleukin; Drug: Cyclophosphamide; Drug: Fludarabine; Biological: Young TIL	MD	NCT01814046
Dendritic Cell Vaccines + Dasatinib for Metastatic Melanoma	Metastatic Melanoma	Biological: DC vaccine; Drug: Dasatinib	PA	NCT01876212

Title	Cancer Type	Treatment	Location	NCT Number
Epacadostat and Vaccine Therapy in Treating Patients With Stage III-IV Melanoma	Mucosal Melanoma; Recurrent Melanoma; Recurrent Uveal Melanoma; Stage IIIA Skin Melanoma; Stage IIIA Uveal Melanoma; Stage IIIB Skin Melanoma; Stage IIIB Uveal Melanoma; Stage IIIC Skin Melanoma; Stage IIIC Uveal Melanoma; Stage IV Skin Melanoma; Stage IV Uveal Melanoma	Drug: Epacadostat; Other: Laboratory Biomarker Analysis; Biological: MELITAC 12.1 Peptide Vaccine	GA; NC; NH; OH; VA	NCT01961115
Immunotherapy Using Tumor Infiltrating Lymphocytes for Patients With Metastatic Melanoma	Metastatic Melanoma	Drug: Aldesleukin; Drug: Fludarabine; Drug: Cyclophosphamide; Biological: Young Tumor Infiltrating Lymphocytes (Young TIL); Drug: Keytruda (pembrolizumab) - ONLY FOR RETREATMENT	MD	NCT01993719
A Phase 1 Study of AM0010 in Patients With Advanced Solid Tumors	Melanoma; Prostate Cancer; Ovarian Cancer; Renal Cell Carcinoma; Colorectal Carcinoma; Pancreatic Carcinoma; Non-small Cell Lung Carcinoma; Solid Tumors; Breast Cancer	Drug: AM0010; Drug: Paclitaxel or Docetaxel and Carboplatin or Cisplatin; Drug: FOLFOX (Oxaliplatin/Leucovorin/5-Fluorouracil); Drug: gemcitabine/ nab-paclitaxel; Drug: Capecitabine; Drug: Pazopanib; Drug: Pembrolizumab; Drug: Paclitaxel; Drug: nivolumab; Drug: Gemcitabine/carboplatin	CA; CO; FL; MA; NY; OK; TN; TX	NCT02009449
Cellular Adoptive Immunotherapy Using Autologous CD8+ Antigen-Specific T Cells and Anti-CTLA4	Melanoma	Drug: Cyclophosphamide; Procedure: CD8+ T Cells; Drug: Interleukin-2; Drug: Ipilimumab	TX	NCT02027935
Immunotherapy Study for Patients With Stage IV Melanoma	Stage IV Melanoma; Metastatic Melanoma	Drug: HyperAcute-Melanoma (HAM) Immunotherapy; Drug: Ipilimumab; Drug: Pembrolizumab; Drug: Nivolumab	IA; IL; NC; TN	NCT02054520
Study of IDO Inhibitor in Combination With Checkpoint Inhibitors for Adult Patients With Metastatic Melanoma	Metastatic Melanoma; Stage III Melanoma; Stage IV Melanoma	Drug: Indoximod; Drug: Ipilimumab; Drug: Nivolumab; Drug: Pembrolizumab	GA; IA; MN; NM; PA; UT	NCT02073123
Molecularly Targeted Therapy in Treating Patients With BRAF Wild-type Melanoma That is Metastatic	Recurrent Melanoma; Stage IIIA Melanoma; Stage IIIB Melanoma; Stage IIIC Melanoma; Stage IV Melanoma	Other: cytology specimen collection procedure; Drug: MEK 162 therapy or molecularly targeted therapy; Procedure: therapeutic procedure; Other: laboratory biomarker analysis; Other: quality-of-life assessment	AZ; CT; FL; IN; MD; MI; MN; TN; TX	NCT02094872
A Phase I Trial of T Cells Expressing an Anti-GD2 Chimeric Antigen Receptor in Children and Young Adults With GD2+ Solid Tumors	Sarcoma; Osteosarcoma; Neuroblastoma; Melanoma	Biological: Anti-GD2-CAR engineered T cells; Drug: AP1903; Drug: Cyclophosphamide	MD	NCT02107963
Galectin Inhibitor (GR-MD-02) and Ipilimumab in Patients With Metastatic Melanoma	Metastatic Melanoma	Biological: 1 mg/kg GR-MD-02; Biological: 2 mg/kg GR-MD-02; Biological: 4 mg/ kg GR-MD-02; Biological: 8 mg/kg GR-MD-02; Biological: Ipilimumab	OR	NCT02117362
Phase 1 Study of Intradermal LV305 in Patients With Locally Advanced, Relapsed or Metastatic Cancer Expressing NY-ESO-1	Melanoma - Currently Enrolling; Non-small Cell Lung Cancer - Enrollment Completed; Ovarian Cancer - Enrollment Completed; Sarcoma - Enrollment Completed	Biological: ID-LV305	CA; CT; MA; MN; NJ; SC; TX; WA	NCT02122861
Adoptive Therapy Using Antigen-Specific CD4 T-Cells	Melanoma; Sarcoma	Drug: Ipilimumab; Drug: Cyclophosphamide; Biological: CD4+ T cells	TX	NCT02210104
Dabrafenib and Trametinib Followed by Ipilimumab and Nivolumab or Ipilimumab and Nivolumab Followed by Dabrafenib and Trametinib in Treating Patients With Stage III-IV BRAFV600 Melanoma	Recurrent Melanoma; Stage IIIA Skin Melanoma; Stage IIIB Skin Melanoma; Stage IIIC Skin Melanoma; Stage IV Skin Melanoma	Drug: Dabrafenib; Biological: Ipilimumab; Other: Laboratory Biomarker Analysis; Biological: Nivolumab; Other: Quality-of-Life Assessment; Drug: Trametinib	AK; AL; AR; CA; CO; CT; DE; FL; GA; HI; IA; ID; IL; IN; KS; KY; MD; MI; MN; MO; MS; MT; NC; ND; NE; NJ; NM; NV; NY; OH; OK; OR; PA; RI; SC; SD; TN; TX; VA; WA; WI; WV	NCT02224781
RTA 408 Capsules in Patients With Melanoma - REVEAL	Melanoma; Unresectable (Stage III) Melanoma; Metastatic (Stage IV) Melanoma	Drug: Omaveloxolone Capsules (2.5 mg/ capsule); Drug: Ipilimumab (3 mg/kg); Drug: Nivolumab (3 mg/kg)	AL; AR; CA; DC; DE; FL; MA; NC; NJ; TX	NCT02259231
Neoadjuvant Pembrolizumab for Unresectable Stage III and Unresectable Stage IV Melanoma	Unresectable Malignant Neoplasm; Melanoma; Metastatic Melanoma; Stage IV Melanoma; Stage III Melanoma	Drug: Pembrolizumab	MO	NCT02306850
Study Of OX40 Agonist PF-04518600 Alone And In Combination With 4-1BB Agonist PF-05082566	Neoplasms	Drug: PF-04518600; Drug: PF-04518600; Drug: PF-04518600 plus PF-05082566; Drug: PF-04518600 plus PF-05082566	CA; TX; WA	NCT02315066
Ex Vivo-Activated Lymph Node Lymphocytes in Treating Patients With Stage IIIC-IV Melanoma	Stage IIIC Skin Melanoma; Stage IV Melanoma	Procedure: lymph node; Biological: X-ACT	OH	NCT02327390
A Comparison of Matured Dendritic Cells and Montanide in Study Subjects With High Risk of Melanoma Recurrence	Melanoma	Biological: DC Vaccine; Biological: Montanide Vaccine; Biological: Poly-ICLC	NY	NCT02334735
Study of Pembrolizumab (MK-3475) Versus Placebo After Complete Resection of High-Risk Stage III Melanoma (MK-3475-054/KEYNOTE-054)	Melanoma	Biological: pembrolizumab; Other: placebo	CA; FL; GA; IA; IL; MO	NCT02362594

Title	Cancer Type	Treatment	Location	NCT Number
In Situ, Autologous Therapeutic Vaccination Against Solid Cancers With Intratumoral Hiltonol	Melanoma; Head and Neck Cancer; Sarcoma; Non-Melanoma Skin Cancers	Biological: Hiltonol	GA; MD; NY; PA	NCT02423863
Trial of Vemurafenib and Cobimetinib in Patients With Advanced BRAFV600 Mutant Melanoma	Melanoma	Drug: Cobimetinib; Drug: Vemurafenib	MD	NCT02427893
A Pilot Study to Evaluate PBR PET in Brain Tumor Patients Treated With Chemoradiation or Immunotherapy	Intracranial Tumors; Glioblastoma; Melanoma	Other: PBR PET; Biological: Cancer Immunotherapy; Radiation: Radiation and chemotherapy	MA	NCT02431572
A Study Of Avelumab In Combination With Other Cancer Immunotherapies In Advanced Malignancies (JAVELIN Medley)	Advanced Cancer	Drug: Avelumab; Drug: PF-05082566; Drug: PF-04518600; Drug: PF-04518600	CA; DC; FL; GA; MA; MI; NC; PA; TN; TX; WA	NCT02554812
Pilot Study of Vigil + Pembrolizumab for Advanced Melanoma	Melanoma Recurrent; Malignant Melanoma; Melanoma	Biological: Vigil; Drug: Pembrolizumab	TX	NCT02574533
GR-MD-02 Plus Pembrolizumab in Melanoma Patients	Melanoma	Drug: GR-MD-02; Drug: Pembrolizumab	OR	NCT02575404
Pembrolizumab in Treating Patients With HIV and Relapsed, Refractory, or Disseminated Malignant Neoplasms	AIDS-Related Non-Hodgkin Lymphoma; Classical Hodgkin Lymphoma; HIV Infection; Locally Advanced Malignant Neoplasm; Metastatic Malignant Neoplasm; Recurrent Hepatocellular Carcinoma; Recurrent Hodgkin Lymphoma; Recurrent Kaposi Sarcoma; Recurrent Malignant Neoplasm; Recurrent Melanoma of the Skin; Recurrent Non-Hodgkin Lymphoma; Recurrent Non-Small Cell Lung Carcinoma; Refractory Hodgkin Lymphoma; Refractory Malignant Neoplasm; Solid Neoplasm; Stage IIIA Hepatocellular Carcinoma; Stage IIIA Non-Small Cell Lung Cancer; Stage IIIA Skin Melanoma; Stage IIIB Hepatocellular Carcinoma; Stage IIIB Non-Small Cell Lung Cancer; Stage IIIB Skin Melanoma; Stage IIIC Hepatocellular Carcinoma; Stage IIIC Skin Melanoma; Stage IV Non-Small Cell Lung Cancer; Stage IV Skin Melanoma; Stage IVA Hepatocellular Carcinoma; Stage IVB Hepatocellular Carcinoma	Other: Laboratory Biomarker Analysis; Biological: Pembrolizumab	MD; WA	NCT02595866
A Prospective Randomized and Phase 2 Trial for Metastatic Melanoma Using Adoptive Cell Therapy With Tumor Infiltrating Lymphocytes Plus IL-2 Either Alone or Following the Administration of Pembrolizumab	Melanoma	Drug: Cyclophosphamide; Drug: Fludarabine; Drug: Aldeslaukin; Drug: Pembrolizumab; Biological: young TIL	MD	NCT02621021
Combining PD-1 Blockade, CD137 Agonism and Adoptive Cell Therapy for Metastatic Melanoma	Melanoma (Skin); Skin Cancer	Drug: Nivolumab; Procedure: Surgery to Remove Tumor for Growth of TIL; Drug: CD137; Drug: Cyclophosphamide; Drug: Fludarabine; Biological: TIL Infusion; Drug: Interleukin-2	FL	NCT02652455
A Pilot Study to Evaluate the Safety and Efficacy of Combination Checkpoint Blockade Plus External Beam Radiotherapy in Subjects With Stage IV Melanoma	Melanoma	Drug: Ipilimumab; Drug: Nivolumab; Radiation: Radiotherapy	CA; NY; TN	NCT02659540
Phase I Study of Ipilimumab (Immunotherapy) and MGN1703 (TLR Agonist) in Patients With Advanced Solid Malignancies	Advanced Cancers; Melanoma	Drug: MGN1703; Drug: Ipilimumab	TX	NCT02668770
Phase 1 Study of GRN-1201 in HLA-A*02 Subjects With Resected Melanoma	Melanoma	Biological: GRN-1201	OH; OR; PA; UT	NCT02696356
Ipilimumab vs Ipilimumab Plus Nivolumab in Patients With Stage III-IV Melanoma Who Have Progressed or Relapsed on PD-1 Inhibitor Therapy	Melanoma	Drug: ipilimumab; Drug: nivolumab	NY	NCT02731729
GI Complications in Cancer Immunotherapy Patients	Malignant Melanoma		MA	NCT02784366
A Phase 1 Study of TSR-022, an Anti-TIM-3 Monoclonal Antibody, in Patients With Advanced Solid Tumors	Advanced or Metastatic Solid Tumors	Drug: TSR-022; Drug: anti PD-1 antibody	AZ; CA; CO; FL; IL; TN	NCT02817633
Adoptive T Cell Immunotherapy for Advanced Melanoma Using Engineered Lymphocytes	Melanoma	Biological: Escalating Doses	IL	NCT02870244
Trial of Intratumoral Injections of TTI-621 in Subjects With Relapsed and Refractory Solid Tumors and Mycosis Fungoides	Solid Tumors; Mycosis Fungoides; Melanoma; Merkel-cell Carcinoma; Squamous Cell Carcinoma; Breast Carcinoma; Human Papillomavirus-Related Malignant Neoplasm; Soft Tissue Sarcoma	Drug: TTI-621	CA; OR; PA; WA	NCT02890368
A Personalized Cancer Vaccine (NEO-PV-01) w/ Nivolumab for Patients With Melanoma, Lung Cancer or Bladder Cancer	Urinary Bladder Cancer; Bladder Tumors; Transitional Cell Carcinoma of the Bladder; Malignant Melanoma; Melanoma; Skin Cancer; Carcinoma; Non-Small-Cell Lung; Lung Cancer	Biological: NEO-PV-01; Biological: Nivolumab; Other: Adjuvant	CA; MA; TX	NCT02897765

PATIENT ASSISTANCE RESOURCES

CAREGIVERS & SUPPORT

4th Angel Patient & Caregiver Mentoring Program....www.4thangel.org
Bloch Cancer Hotline....800-433-0464
CanCare....www.cancare.org
CANCER101....www.cancer101.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 Support Community....www.cancersupportcommunity.org
Cancer Survivors Network....http://csn.cancer.org
Caregiver Action Network....www.caregiveraction.org
CaringBridge....www.caringbridge.org
Cuddle My Kids....www.cuddlemykids.org
Family Caregiver Alliance....www.caregiver.org
Friend for Life Cancer Support Network....www.friend4life.org
Guide Posts of Strength, Inc....www.cancergps.org
The Hope Light Foundation....www.hopelightproject.com
I Can Cope....www.cancer.org/icancope
Imerman Angels....www.imermanangels.org
The LGBT Cancer Project – Out With Cancer....www.lgbtcancer.org
LIVESTRONG Foundation....www.livestrong.org
Lotsa Helping Hands....www.lotsahelpinghands.com
MyLifeLine.org Cancer Foundation....www.mylifeline.org
Patient Empowerment Network....www.powerfulpatients.org
Patient Power....www.patientpower.info
PearlPoint Cancer Support....www.pearlpoint.org
SHARE Caregiver Circle....www.sharecancersupport.org/support
Strike Out Cancer....www.strikeoutcancer.com
Stronghold Ministry....www.mystronghold.org
Triage Cancer....www.triagecancer.org
Vital Options International....www.vitaloptions.org
Well Spouse Association....www.wellspouse.org
Wonders & Worries....www.wondersandworries.org

CLINICAL TRIALS

ACCESS....www.access.cantria.com
AccrualNet....http://accrualnet.cancer.gov
ACT (About Clinical Trials)....www.learnaboutclinicaltrials.org
Center for Information and Study on Clinical Research Participation....www.searchclinicaltrials.org
CenterWatch....www.centerwatch.com
Coalition of Cancer Cooperative Groups....www.cancertrialshelp.org
LIVESTRONG Foundation....www.livestrong.org
PearlPoint Cancer Support....www.pearlpoint.org
MolecularMatch....www.molecularmatch.com
My Clinical Trial Locator....http://myclinicaltriallocator.com
National Cancer Institute....www.cancer.gov/clinicaltrials
National Institutes of Health....www.clinicaltrials.gov
Stand Up To Cancer....www.standup2cancer.org
TNBC Foundation Clinical Trials Matching Service....www.tnbcfoundation.org/clinical-trials
TrialCheck....www.trialcheck.org

HEALTH CARE PROFESSIONAL RESOURCES

Academy of Oncology Nurse & Patient Navigators....www.aonnonline.org
American Institute for Cancer Research....www.aicr.org
American Joint Committee on Cancer....www.cancerstaging.org
American Society of Clinical Oncology....www.asco.org
American Society of Pediatric Hematology/Oncology....www.aspho.org
American Society for Radiation Oncology....www.astro.org
National Cancer Institute....www.cancer.gov
National Comprehensive Cancer Network....www.nccn.org
Oncology Nursing Society....www.ons.org
Society for Immunotherapy of Cancer....www.sitcancer.org

IMMUNOTHERAPY

The Answer to Cancer....www.theanswertocancer.org
Cancer Research Institute....www.cancerresearch.org
Immuno-Oncology....www.immunooncology.com
Society for Immunotherapy of Cancer....www.sitcancer.org

MELANOMA

A Cure in Sight (ocular melanoma)....http://acureinsight.net
AIM at Melanoma Foundation....www.aimatmelanoma.org
American Academy of Dermatology....www.aad.org
Basal Cell Carcinoma Nevus Syndrome Life Support Network....www.bccns.org
Melanoma Hope Network....www.melanomahopenetwork.org
Melanoma International Foundation....www.melanomainternational.org
Melanoma International Foundation Forum....www.melanomaforum.org
Melanoma Patients Information Page....www.melanoma.org/community/mpip-melanoma-patients-information-page
Melanoma Research Alliance....www.curemelanoma.org
Melanoma Research Foundation....www.melanoma.org
Mollie's Fund....http://molliesfund.org
Ocular Melanoma Foundation....www.ocularmelanoma.org
Outrun the Sun....www.outrunthesun.org
The Skin Cancer Foundation....www.skincancer.org
Skin of Steel....http://skinofsteel.org
SunWise....www.neefusa.org/sunwise

PRESCRIPTION EXPENSES

American Cancer Society....www.cancer.org, 800-227-2345
Brenda Mehling Cancer Fund (patients 18-40)....www.bmcf.net, 661-310-7940
Cancer*Care* Co-Payment Assistance Foundation....www.cancercarecopay.org, 866-552-6729
Cancer Financial Assistance Coalition....www.cancerfac.org
The CHAIN Fund Inc....www.thechainfund.com, 203-691-5955
Foundation for Health Coverage Education....www.coverageforall.org
GoodDays....www.gooddaysfromcdf.org, 972-608-7141
HealthWell Foundation....www.healthwellfoundation.org, 800-675-8416
NeedyMeds....www.needymeds.org, 800-503-6897
Partnership for Prescription Assistance....www.pparx.org, 888-4PPA-NOW
Patient Access Network Foundation....www.panfoundation.org, 866-316-PANF
Patient Advocate Foundation Co-Pay Relief....www.copays.org, 866-512-3861
Patient Services, Inc....www.patientservicesinc.org, 800-366-7741
Rise Above It (youth, young adults)....www.raibenefit.org
RxAssist....www.rxassist.org
RxHope....www.rxhope.com, 877-267-0517
RxOutreach....www.rxoutreach.com, 888-796-1234
Stupid Cancer....www.stupidcancer.org, 877-735-4673
Together Rx Access....www.togetherrxaccess.com, 800-444-4106

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