PATIENT RESOURCE

take one FREE

CONTENT REVIEWED BY A DISTINGUISHED MEDICAL ADVISORY BOARD

Immunotherapy for the treatment of Melanoma

A TREATMENT GUIDE FOR PATIENTS AND THEIR FAMILIES

WHERE INFORMATION EQUALS HOPE

Published in partnership with

sitc
Society for Immunotherapy of Cancer
www.sitcancer.org

PRP PATIENT RESOURCE PUBLISHING®

TABLE OF CONTENTS

Immunotherapy for the Treatment of Melanoma

IN THIS GUIDE

CO-EDITORS-IN-CHIEF

Charles M. Balch, MD, FACS
Professor of Surgery, The University of Texas MD Anderson Cancer Center
Editor-in-Chief, Patient Resource LLC
Editor-in-Chief, Annals of Surgical Oncology
Past President, Society of Surgical Oncology

Howard L. Kaufman, MD, FACS
Chief Surgical Officer, Associate Director for Clinical Science, Rutgers Cancer Institute of New Jersey
President, Society for Immunotherapy of Cancer

***SPECIAL THANKS TO**

Tara Withington, CAE – *Executive Director, SITC*
Lianne Wiggins – *Program Manager, SITC*
Mike Scorzo, Ed.D – *Director of Online Education, SITC*
Jody Felski – *Senior Development Manager, SITC*

The Society for Immunotherapy of Cancer (SITC) is the world's leading member-driven organization specifically dedicated to professionals working in the field of cancer immunology and immunotherapy. Established in 1984, SITC is a 501(c)(3) not-for-profit organization with a growing constituency of academic, government, industry, clinical and basic scientists and medical professionals from around the world. SITC's mission is to improve cancer patient outcomes by advancing the science, development and application of cancer immunology and immunotherapy through core values of interaction/integration, innovation, translation and leadership in the field.

Learn more at www.sitcancer.org

PATIENT RESOURCE

Chief Executive Officer	**Mark A. Uhlig**
Publisher	**Linette Atwood**
Co-Editor-in-Chief	**Charles M. Balch, MD, FACS**
Co-Editor-in-Chief	**Howard L. Kaufman, MD, FACS**
Patient Advisory Board	**Lisa Greaves**
Senior Vice President	**Debby Easum**
Vice President, Operations	**Leann Sandifar**
Managing Editor	**Lori Alexander, MTPW, ELS, MWC™**
Senior Editors	**Dana Campbell** **Colleen Scherer**
Graphic Designer	**Michael St. George**
Medical Illustrator	**Todd Smith**
Production Manager	**Jennifer Hiltunen**
Vice Presidents, Business Development	**Amy Galey** **Kathy Hungerford** **Stephanie Myers Kenney**
Account Executive	**Melissa Amaya**
Office Address	**8455 Lenexa Drive** **Overland Park, KS 66214**
For Additional Information	**prp@patientresource.com**
Advisory Board	**Visit our website at PatientResource.com to read bios of our Medical and Patient Advisory Board.**

For Additional Copies: To order additional copies of *Patient Resource Cancer Guide: Immunotherapy for the Treatment of Melanoma,* visit PatientResource.com, call 913-725-1600, or email orders@patientresource.com.

Editorial Submissions: Editorial submissions should be sent to editor@patientresource.com.

OVERVIEW

Immunotherapy is the newest type of treatment available for people with cancer. For decades, doctors and researchers have conducted clinical trials to further the progress in immunotherapy as cancer treatment. 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.

Cancer cells have a sneaky way of fooling the body into not recognizing they are dangerous. If the body can't tell the difference between cancer cells and healthy cells, the cancer cells may be able to hide. Immunotherapy uses the body's own immune system to slow the growth of and kill cancer cells by using substances made either by the body or in a laboratory. These substances allow the immune system to identify cancer cells as a threat and target them for destruction.

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 types of immunotherapy boost the body's immune system, and 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 or stop an immune response. The immune system uses checkpoints to turn on an immune response, when appropriate, and turn it off, when necessary, to prevent itself from attacking normal cells in the body. But melanoma cells sometimes use 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 proteins that enable cells to send messages to 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 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.

Although certain immunotherapies work well when given alone, others work better in combination with additional treatments.

The opportunity to have an improved quality of life is making immunotherapy an attractive choice for people who have this treatment option. Although traditional treatments, such as chemotherapy, for example, target cancer cells, healthy cells also are damaged, resulting in side effects such as alopecia (hair loss) and nausea. With immunotherapy, side effects may still occur, but they are primarily the result of an overactive immune system, not the destruction of healthy cells. Because not as many healthy cells are damaged, some patients have reported fewer and less severe side effects (see page 8). Additionally, immunotherapy has the potential to remain effective long after the treatment is over, a feature called "memory." This feature is the same one that allows a tetanus vaccine, for example, to remain effective for many years. For people with cancer, this effect can lead to long-term, cancer-free remission and better overall survival.

It is important to note that immunotherapy is effective for some patients but not for others, even when they seem to have the same cancer. Doctors and scientists continue to study this puzzling characteristic, along with how to improve existing therapies and develop new ones, through clinical trials. If immunotherapy is not an option for you, your doctor will recommend one or more of the treatments considered "standard of care" (approved and recommended) (see page 6).

Additionally, you may be able to take advantage of treatments that are not yet FDA-approved by participating in a clinical trial (see page 10). Before you make any treatment decisions, talk to your doctor about whether you are eligible for a clinical trial. ■

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

WORDS TO KNOW

Cancer cells – Cells with damaged DNA that causes mutations in normal cell growth and division. New cancer cells grow uncontrollably and old cancer cells don't die when they should, resulting in a malignant tumor or cancer.

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

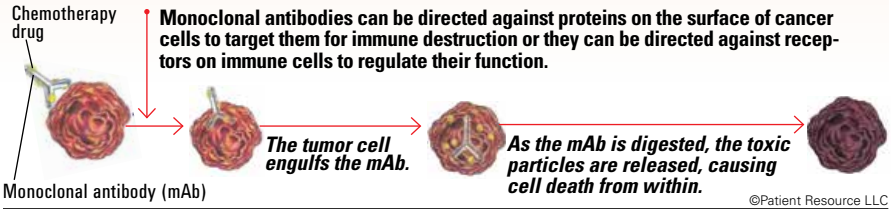
Standard of care – A treatment regimen that is accepted by medical experts as a proper treatment for a specific type of cancer and is used widely by healthcare professionals to treat patients. This can also be called best practice, standard medical care and standard therapy.

Immunotherapy may sound complicated, but when you think about how it uses the same natural defenses your body uses every day to fight infection, you may be able to better understand how it works. Sometimes your body's own defenses aren't enough to wipe out something as intense as cancer, so doctors use immunotherapy to build on the healing capabilities of your immune system with drugs and other techniques (see *The Role of Monoclonal Antibodies*).

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).



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 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. People carry self-antigens on normal cells, such as liver, colon, and thyroid cells. 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.

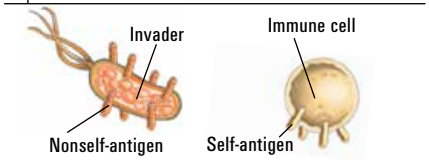
FACING A NORMAL INVADER

Your immune system works constantly to keep your body free from infection. Understanding how your immune system responds in an ordinary situation will make it easier to see how it can be enhanced to face a more serious condition such as cancer.

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.

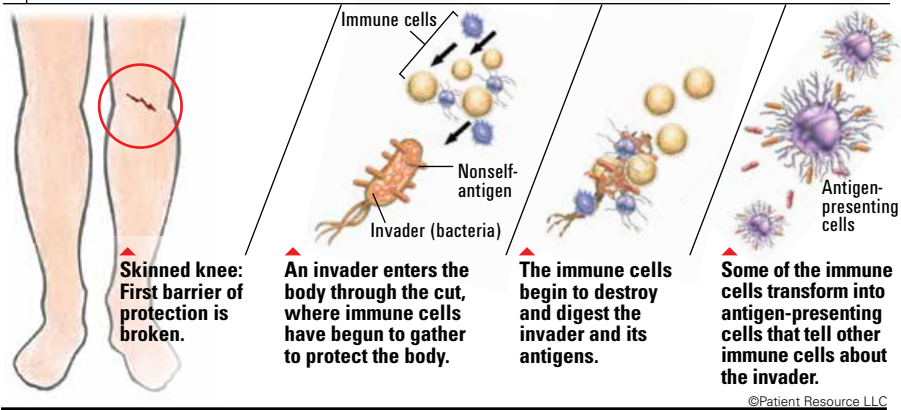
At the same time, other immune cells called dendritic cells start to "eat" the invaders and their nonself-antigens. This process causes the dendritic cells to transform into antigen-presenting cells (APCs). These APCs expose the invader cells to the primary immune cells of the immune system—the B and 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 cells. Viruses, unlike bacteria, like to hide inside normal cells and may

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



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 referred to as Signal 1. This connection allows the T cell to recognize antigens on invading cells as a threat.

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 T cell then multiplies to develop an army of T cells that is equipped with the necessary weapons 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.

FACING CANCER

Your 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 tumor cells and normal cells, the tumor cells may be able to "hide" from the immune system.

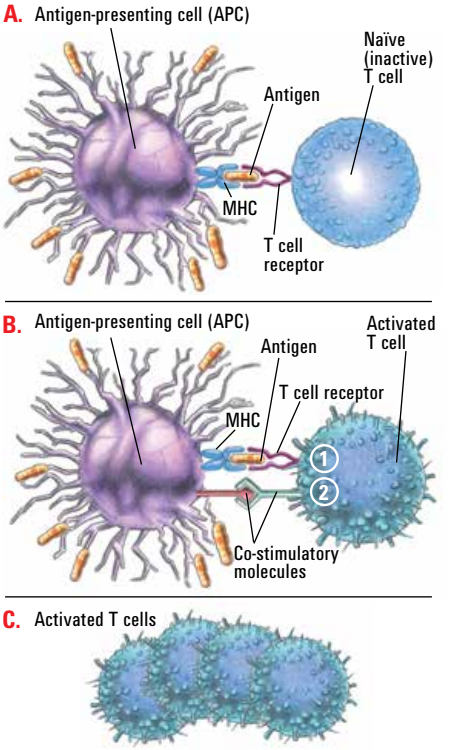
As an example, think of allergy shots given to relieve the symptoms of a pollen allergy. Increasing doses of a specific allergen are injected into a person over a series of visits to the doctor, which causes the body to develop a tolerance to pollen. This type of therapy can provide temporary or permanent 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 show cancer cell materials to T cells, 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. 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 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.

FIGURE 3
T CELL ACTIVATION

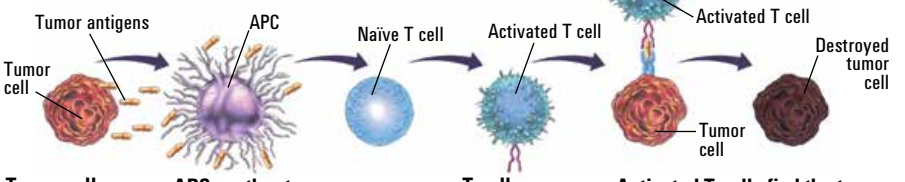


A: Inactive T cells are activated when antigen-presenting cells (APCs) connect with the T cell.

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

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

FIGURE 4
HOW THE IMMUNE SYSTEM ATTACKS CANCER



Tumor cells release tumor antigens.

APCs gather tumor antigens and prepare to present to naïve T cells.

T cells are activated by the APC.

Activated T cells find the tumor cells with the same tumor antigens and destroy them.

→ **UNDERSTANDING THE IMMUNE SYSTEM**
(continued on page 9)

STAGING MELANOMA

Once your cancer is diagnosed, your physician will determine 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. Following your diagnosis, your doctor will use the staging information to select the best treatment options for you.

Melanoma is usually staged twice. First, your physician will consider the results of your 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. Because the pathologic stage is based on more details about your specific melanoma, this second staging is more precise and is the key to deciding which treatment options may be best.

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 in the body.

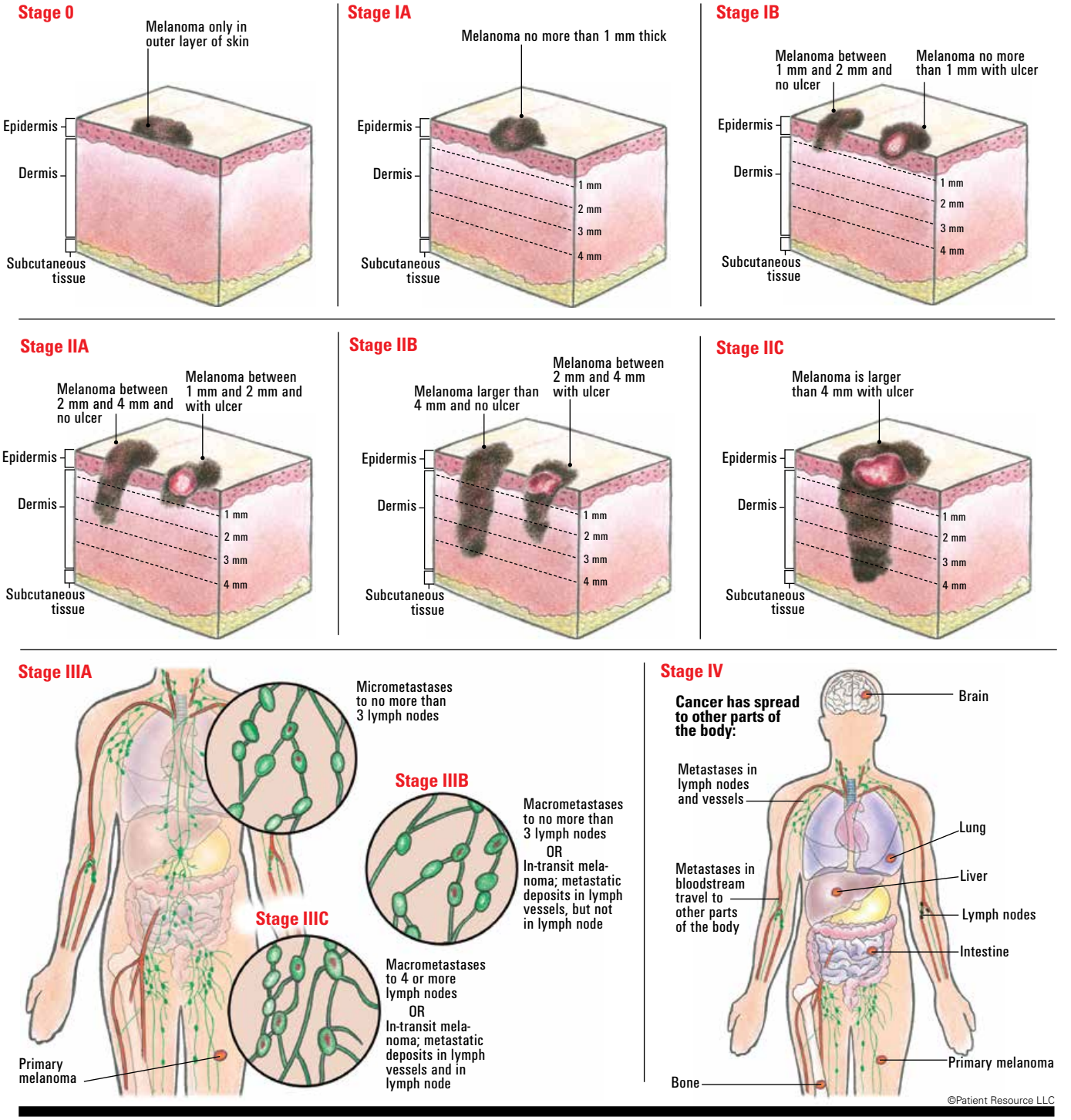
TABLE 1
STAGES OF MELANOMA

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



Once the melanoma is classified according to the TNM system, an overall stage of disease is assigned (see Table 1). Stage 0 is known as "melanoma in situ" and is considered to be precancerous. 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. ■

WORDS TO KNOW

Biopsy – A procedure to remove tissue for examination to determine if melanoma is present.

Dermis – The dense inner layer of skin below the epidermis.

Epidermis – The upper layer of skin.

Lymph node – Found throughout the body, lymph nodes are small organs in the lymphatic system that filter lymph fluid, trapping bacteria, viruses and other foreign substances which are then destroyed by special white blood cells called lymphocytes. Cancer can spread to nearby lymph nodes.

Macrometastases – The spread (metastasis) of cancer from its original location to other sites in the body with the tumor large enough to be seen by the naked eye.

Micrometastases – The spread (metastasis) of cancer from its original location to other sites in the body with the newly formed tumors being too small to be detected by the naked eye. A microscope must be used.

Subcutaneous tissue – A deep layer of loose, irregular connective tissue beneath the skin.

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 directly, usually by targeting a specific abnormal gene or protein.
- Immunotherapy activates the body's immune system to enable immune cells to attack and destroy cancer cells.

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 10).

Immunotherapy depends on a functioning immune system, so it will likely be important to make sure that you do not have an autoimmune disorder or are not taking any immunosuppressive medications. After taking into consideration these and other factors, such as your overall health, type and stage of your melanoma and your treatment history, your doctor will recommend one or a combination of treatments.

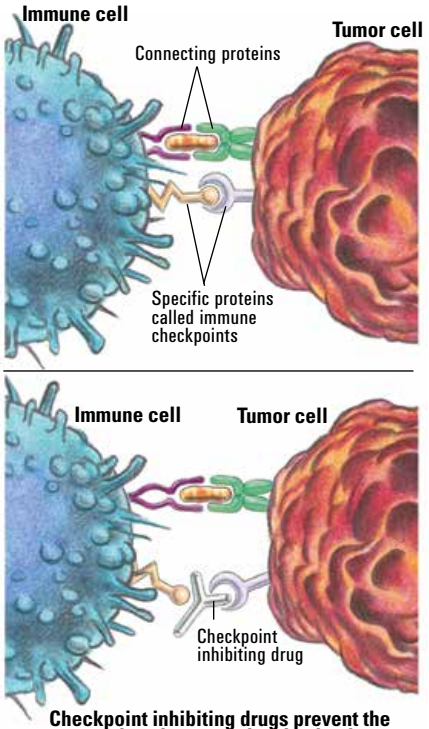
Once treatment begins, monitoring is key. More monitoring and follow-up occur with immunotherapy than with most other forms of treatment. You will likely undergo testing to allow your doctor to evaluate how well treatment is working by measuring the size of the tumor as treatment progresses.

If immunotherapy is not suggested for you, do not be disappointed. All of the approved treatments for melanoma are extremely effective strategies. In addition, you may be a candidate for a clinical trial that offers access to a leading-edge treatment that is not yet available (see page 10). Ask your doctor about all your options, taking into consideration possible side effects, before making any treatment decisions. ■

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.

Checkpoint inhibitors – Drugs that block the activation of specific immune checkpoint pathways and prevent T cells from shutting down.

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).

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

RIGHT TIME, RIGHT PLACE

In August 2014, I felt a lump under my arm while I was showering. I had an upcoming appointment with my endocrinologist, so I asked her about it. She wrote a prescription for an ultrasound. I work in the medical field, so I knew something was wrong when the ultrasound technician called in the radiologist instead of sending me home after the test. He performed a second ultrasound and told me he wanted to do a biopsy. The results showed a malignant neoplasm, but the report couldn't pinpoint what it was so he sent the samples to an oncologist. On my 33rd birthday, I was diagnosed with poorly differentiated melanoma.

The oncologist referred me to several cancer centers, one being a well-known center within driving distance of my home. Several doctors there reviewed my case and came back with several different treatment plans. I wasn't comfortable with any of the plans, so I reached out to another melanoma specialist also suggested by my oncologist. I clicked with him immediately and embarked on my treatment journey.

Because the melanoma was poorly differentiated, we decided to remove only the tumor for more study, leaving the lymph nodes intact. My oncologist also suggested a clinical trial, but that scared me. I didn't want to be a guinea pig. While I was considering it, I was shopping with my mom when we ran into her oncologist (my mom is a breast cancer survivor). She told me to absolutely do the clinical trial because it would give me access to the most leading-edge treatment available. That was all I needed to hear.

To complicate matters, I was set to be married on October 25. After discussions with my surgeons, we agreed to wait until after the wedding to remove the tumor, if we postponed the honeymoon. After the tumor was removed and tested, it was confirmed as Stage III melanoma. This led to a follow-up surgery in early February to remove the lymph nodes in the area, and all of the lymph nodes came back clear.

After the surgery in February, I let my body heal for three or four months before beginning the clinical trial. It was good timing because an immunotherapy clinical trial using two drugs was just opening up. It was a double-blind study, meaning no one would know which of the two immunotherapy drugs I would receive. One drug would take down the shields around the cancer cells, while the other one would boost my immune cells.

The clinical trial lasted a year. I didn't have many side effects at all. I was fatigued, but not enough to take any extra time off from work. I also was a little depressed. I'm not sure if that was due to the treatment or just the fact that I was going through this situation in general. It was minor, and I never had to see a doctor for it. I keep a close eye on lymphedema, a known complication resulting from the removal of lymph nodes. If I start to experience swelling, I will probably begin wearing a compression sleeve.

Based on my side effects and the ones that other people in my clinical trial had, I think I know which drug I received. If I'm right, I believe I am the first Stage III person in the country to receive Opdivo in a melanoma clinical trial. I asked my doctor if I would ever know, but he told me the only way I'd ever be unblinded is if the melanoma returns. In that case, they would have to give me the other drug. That answer was good enough for me—I won't ask again! I'm cancer-free, I feel great and I'm following up with frequent scans.

I had a tremendous support system. My family constantly checked on me and prayed for me. My friends were there for my surgeries, and my wife was incredible. She's a nurse, which was a big help. This situation put some big dents in the "princess view" she had of our wedding, but she was a trooper. I made it up to her by finally taking her on a honeymoon to a resort in Grenada. We went big—private hut, butler service and lots of sunblock.

I received exceptional care throughout my treatment, and my medical team did an excellent job of educating me about my condition and immunotherapy. I had some frustrations regarding my clinical trial. I encourage everyone to read the fine print on their consent forms. There are often hidden costs that you don't expect to have to pay for, so I would address everything with the hospital and clinical trial administrators before getting started. But don't let that discourage you. Health care is always complicated. It's just best to have a solid understanding of every facet of your treatment plan.

I feel very fortunate that everything worked out like it did. I think it was a combination of being in the right place at the right time and cashing in on some good karma I had out there. If you are considering a clinical trial, my advice is to go for it. You're not a guinea pig. You're helping expand the reach of what that drug offers. For me, I found value in helping others who may walk a similar path. Gather opinions, research credible resources and understand the studies.

Most important, stay positive but allow yourself to feel your emotions. You're wholly entitled to feel and express them however you see fit. It's not the time to put on a brave face for others. Your emotions guide you through a journey of feelings. Let that happen without guilt, resentment or embarrassment. ■

PERSONAL JOURNEY | ADAM CAPEZZUTO

Adam Capezzuto, 34, admits to feeling invincible in his younger days. His cavalier attitude about sunscreen and tanning could have contributed to a Stage III melanoma diagnosis. Thanks to a skilled medical team, a successful clinical trial and a little bit of "right time, right place," Adam is now cancer-free.

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. 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, if your symptoms are severe, it is important to contact your health care professional immediately. With immunotherapy, side effects can indicate that your immune system is too active and could put you at risk for an autoimmune disorder. If treated early, these symptoms can be corrected with corticosteroid medications and your treatment can be resumed at a later date. Your doctor may be able to adjust the immunotherapy medication to prevent future autoimmunity if the symptoms are noted early enough. So, it is important for you to communicate with your doctor's office frequently so they can help monitor you and your symptoms. 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.

This type of reaction, which occurs when the immune system is overstimulated by the treatment, may cause inflammation, swelling or redness, which may or may not be painful. Some organs may become inflamed, which can lead to 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 the checkpoint inhibitors and cytokines is a change in the function of the thyroid gland. This can sometimes be corrected with thyroid replacement medication. Your doctor will likely monitor your thyroid function through a blood test.

Talk to your doctor about how to recognize an immune-mediated adverse reaction, as some side effects may not produce obvious symptoms you can feel. These reactions will need to be confirmed through blood tests. It is important to tell your doctor if you think you may have this reaction so that you can receive treatment as soon as possible to avoid any life-threatening complications.

■ **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 you haven't had enough rest. Fatigue from cancer or its treatment may cause you to feel physically, emotionally or mentally tired and exhausted. If you begin to miss work, spend less time with friends and family, sleep more, have difficulty remembering things or can't think clearly, talk with your doctor or nurse.

An evaluation of your fatigue level throughout your 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 your treatment includes cytokines or oncolytic virus therapy. These symptoms can range from mild to severe.

To manage flu-like symptoms, get enough rest. Ask your doctor if you can take acetaminophen. Consider taking any oral treatments at bedtime to help minimize symptoms, if your doctor approves. If a cough develops, drink plenty of water and other fluids to keep your throat moist.

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

The symptoms can vary in severity and duration. It is important to talk with your health care team about what to expect with this side effect, 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

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

symptom that your 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 your digestive tract and trying probiotics.

Call your health care team if you experience symptoms that interfere with your daily activities, such as severe abdominal cramping, or that cause you to fear leaving your home.

■ **Mild skin reactions,** such as bumpy or itchy red rashes, can occur. These reactions are some of the most common side effects of checkpoint inhibitors.

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, a corticosteroid or numbing medicine may be recommended by your doctor. If the itching affects your sleep, your doctor may prescribe an antihistamine, such as cetirizine (Zyrtec) or diphenhydramine (Benadryl). Medicated creams may be prescribed to help you manage itchy skin or rashes. In some cases of rash, antibiotics may be prescribed.

Contact your doctor at the first sign of a reaction because early treatment may improve your symptoms.

■ **Depression** is a common side effect of cancer and its treatment. In addition to affecting your mood, depression can affect your behavior and ability to think and concentrate, as well as be associated with physical symptoms, including fatigue, loss of appetite, difficulty falling asleep or extreme tiredness. Depression can be serious and include suicidal thoughts or other psychiatric disorders. Call your doctor's office if you notice any mood changes that develop during your treatment.

Discuss any concerns you have about any potential side effects with your doctor before starting treatment. Communication with your health care team is crucial in managing all side effects during immunotherapy. Once you start treatment, ask your doctor about whom to contact if you have urgent questions about side effects, 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

UNDERSTANDING THE IMMUNE SYSTEM *(continued from page 3)*

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 location (sometimes called the microenvironment area). The area, 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 area, 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 area. With this increased activity, regulatory T cells are actually working to reduce the immune response around the tumor by turning off the other cancer-fighting 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. ■

ADDITIONAL RESOURCES

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

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 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 – Proteins 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.

ABOUT CLINICAL TRIALS

Hundreds of clinical trials throughout the United States are currently being held to evaluate immunotherapy drugs as new treatments for melanoma, either alone or in combination with other treatments.

Every cancer treatment being used today came from a clinical trial, like chemotherapy and radiation therapy, yet people are sometimes hesitant to volunteer because they do not know much about the clinical trial process. Don't let fear of the unknown keep you from having access to leading-edge treatments. Ask questions of your medical team to help you make an informed decision.

You may consider participating in a clinical trial for the following reasons:

1 Your current treatment may not be working as well as expected, and a clinical trial may offer a worthwhile alternative.

2 A clinical trial may significantly improve your quality of life. Discuss your personal situation with your medical team, so they are aware of your expectations regarding side effects.

3 You may have a rare type of melanoma that hasn't been studied as much as other types.

4 By simply participating, you play an integral role in helping refine and improve the way millions of people with all types and stages of melanoma are treated. Your participation will help researchers not only identify those treatments that are effective but also those that aren't.

GETTING STARTED

In addition to having a properly functioning immune system, you must meet certain eligibility criteria (cancer type, overall health, treatment history, etc.) to qualify for a clinical trial. 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.

To learn about a specific trial, 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. 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.

If you locate a clinical trial that is not recruiting, don't be discouraged. New studies are happening all the time, so be sure to keep checking to find available trials. ■

SURVIVOR VOICE | **» Janice** | *Stage III melanoma*

"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."

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
Cancer*Care*....www.cancercare.org
Cancer Support Community....www.cancersupportcommunity.org
The Hope Light Foundation....www.hopelightproject.com
Imerman Angels....www.imermanangels.org
LIVESTRONG Foundation....www.livestrong.org
MyLifeLine.org Cancer Foundation....www.mylifeline.org
PearlPoint Cancer Support....www.pearlpoint.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
My Clinical Trial Locator....http://myclinicaltriallocator.com
National Cancer Institute....www.cancer.gov/clinicaltrials
National Institutes of Health....www.clinicaltrials.gov
TrialCheck....www.trialcheck.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

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
RxAssist....www.rxassist.org
RxHope....www.rxhope.com, 877-267-0517
RxOutreach....www.rxoutreach.com, 888-796-1234
Together Rx Access....www.togetherrxaccess.com, 800-444-4106

REIMBURSEMENT & PATIENT 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

This patient education guide was produced with support from:

AMGEN®

MERCK

Bristol-Myers Squibb