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Immunotherapy for the Treatment of Melanoma

Second Edition

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Immunotherapy for the Treatment of Melanoma

Second Edition

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ABOUT MELANOMA AND THE IMMUNE SYSTEM

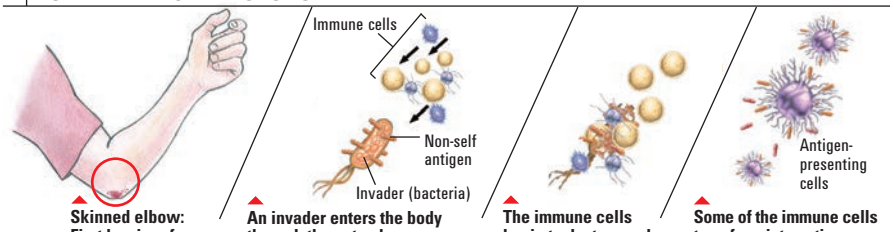
Cancer occurs when genes change or mutate within normal cells. These cells – now called cancer cells – grow and push against normal cells and form tumors. Melanoma is a cancer that starts in skin cells known as melanocytes, which produce melanin, the substance that colors the skin, hair and eyes. Melanomas can develop anywhere on the skin, as well as in the eyes, mouth, genitals and anal area, but they are more likely to start on the trunk (chest and back) in men and on the legs in women. The neck and face are other common sites. Melanocytes may also form moles that can turn into melanoma. Other names for this cancer include malignant melanoma and cutaneous melanoma.

Melanoma is considered the most serious of all of the skin cancers because it can spread into deep layers of skin as well as to lymph nodes and other organs. The skin's layers include the epidermis (outer layer), dermis (inner layer) and hypodermis (subcutaneous tissue). Melanoma typically develops in the epidermis, which contains melanocytes. There are four main types of melanoma of the skin: acral lentiginous melanoma, lentigo maligna melanoma, nodular melanoma and superficial spreading melanoma.

Depending on the type and stage of the melanoma and unique characteristics, such as previous treatments, your age and general health, it may be treated with one, or a combination, of the following.

- **Surgery** is the removal of the tumor and some surrounding normal tissue.
- **Chemotherapy** involves drugs to stop the growth of or directly kill cancer cells throughout the whole body. How it is given depends on the type and stage of the cancer.
- **Radiation therapy** uses high-energy X-rays or other types of radiation to kill cancer cells or stop them from growing.
- **Targeted therapy** involves drugs or other substances designed to attack cancer cells directly 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.

FIGURE 1
NORMAL IMMUNE RESPONSE



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Receiving a melanoma diagnosis can be overwhelming. By becoming an active partner in your care, you make your health care team immeasurably stronger and more effective. Knowledge leads to sound choices, which bring comfort and hope. This guide offers an easy-to-understand explanation of the types of immunotherapy used to treat melanoma.

IMMUNOTHERAPY FOR MELANOMA

Melanoma was one of the first cancer types to receive immunotherapy approvals. Cytokines were the first type of immunotherapy used, and now immune checkpoint inhibitors, immunomodulators and oncolytic virus therapy are also approved (see *Treatment Options,* page 6).

Immunotherapy is very different from other types of cancer treatment. It helps the immune system recognize and attack cancer cells that have been hiding and targets them for destruction. It typically involves destroying only specific cancer cells, which may result in fewer side effects.

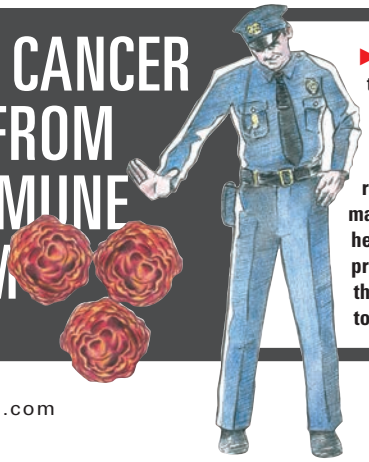
To be a candidate for immunotherapy, you must meet certain criteria. You must have a functioning immune system and not be taking immunosuppressive medications. If you have a pre-existing autoimmune disorder, you must discuss it with your doctor. Biomarker testing may be a requirement, particularly in clinical trials, because some types of immunotherapy are approved to treat cancers in people who have specific biomarkers (see *The Rising Importance of Biomarkers in Melanoma,* page 7). A few biomarker tests are now available for melanoma, and research is ongoing to find new tests that can help guide doctors to recommend immunotherapy only to the patients who are the most likely to respond to it.

It's important to note that immunotherapy is not effective for every person, even if it is approved for that person's cancer type. Doctors and scientists are involved in clinical trials usually to study patient response to immunotherapy, as well as to improve existing therapies and develop new ones (see *Exploring Clinical Trials,* page 9).

WHAT IS THE IMMUNE SYSTEM?

To better understand how immunotherapy is effective against melanoma, it helps to have basic knowledge about the immune system. You usually are only aware of your immune system when an infection or irritation occurs, but your immune system works steadily behind the scenes to identify and eliminate harmful organisms that could negatively affect your health. When you skin your elbow, for example, the barrier is broken and harm-

HOW CANCER HIDES FROM THE IMMUNE SYSTEM



The immune system faces many challenges as it attempts to protect the body from cancer. Imagine a police officer (a T-cell) who encounters an unexpected person (a cancer cell). The officer asks for identification to determine if the person should be let go or stopped. If the police officer thinks the person does not pose a threat (a healthy cell), he will let him go. But he may call for backup (activate the immune system) if there is reason to believe the person is dangerous (a cancer cell). However, the unexpected person may use fake identification or a disguise to appear friendly so the police officer will think he is a normal person and send him on his way. To disguise itself, the cancer cell produces proteins on its surface to alter its appearance, making it look like a normal, healthy cell. If the cancer cell is successful, the T-cell will be fooled and will let the cancer cell continue to attack the body.

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ful substances can easily enter the body (see Figure 1, page 1).

The immune system is a complex network of cells, molecules, organs and lymph tissues working together to defend the body against germs, cancer cells and other microscopic invaders. Germs can also sometimes get past the natural defenses of the immune system – your nostrils, skin, saliva and the mucus coating the inner linings of your organs, eyes and mouth – and you may get a cold, for example. A healthy immune system works to destroy any viruses or bacteria (non-self antigens) that cause your illness and helps you recover.

This network is driven by the lymphatic system, which is made up of lymph nodes, as well as the spleen, thymus, adenoids and tonsils. Lymph, a clear fluid, is circulated throughout the body through the lymph nodes. Lymph collects and filters out bacteria, viruses, toxins and chemicals known as antigens, which are circulating in the lymphatic system and bloodstream. Lymph nodes are located throughout the body, with large concentrations near the chest, abdomen, groin, pelvis, underarms and neck.

Lymph contains lymphocytes, a type of white blood cell that attacks infectious agents. Lymphocytes begin in the bone marrow and develop from lymphoblasts (immature cells found in bone marrow). Lymphoblasts mature into infection-fighting cells. The two main types of lymphocytes are B-lymphocytes (B-cells) and T-lymphocytes (T-cells).

B-cells develop in the bone marrow and mature into either plasma cells or memory cells. Plasma cells make antibodies to fight germs and infection. Memory B-cells help the immune system remember which antigens attacked the body so it can recognize them and respond if they return (see *Expanding the Immune System's Memory,* page 6).

T-cells also develop in the bone marrow but travel to the thymus to mature into one of four types of T-cells, each with its own role in the immune system.

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

THE IMMUNE SYSTEM VS. CANCER

The first job of the immune system is to distinguish between what is part of the body ("self") and what is not part of the body ("non-self"). Once the immune system determines that cells are non-self, or foreign, to the body, it begins a series of reactions to identify, target and eliminate them. The immune system can identify normal cells that are under stress from an infection or other disease process, such as cancer. Just like the immune system would fight bacteria or other infections, the system can detect and potentially eliminate cells that are stressed. Although this is a complex process, scientists have made great progress in understanding how this happens.

To understand how cells interact in the body, it is important to know that the surface of a cell is not completely round and smooth. Cells are covered with receptors and proteins, which work like puzzle pieces. Proteins have "tabs" that stick out, and receptors have "spaces" that curve inward. When the puzzle pieces fit together (known as binding), chemical signals and information are exchanged in a biochemical reaction. Cells contain various proteins, sugars, fats and other molecules that stick out of the cell's surface. These components contain information that is shared between cells.

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

The normal process for an immune response begins when B-cells and helper T-cells identify a threat (non-self antigen) and tell the rest of the immune system. The body then ramps up its production of T-cells to fight. Killer T-cells are sent to destroy the non-self cells. Regulatory T-cells are sent to slow the immune system down once the non-self cells have been eliminated to prevent the T-cells from attacking healthy parts of the body. As a result, T-cells return to normal levels.

The immune system uses the same process to recognize and eliminate cancer as it does to remove other non-self cells, but the process is more complicated. Cancer cells are created by the body, so the normal ways to find and fight invading cells from outside the body aren't always effective. The immune system may have difficulty identifying cancer cells as non-self. It may still see them as part of the body and not coordinate an attack. If the body can't tell the difference between tumor cells and normal cells, the tumor cells may be able to "hide" from the immune system (see *How Cancer Hides from the Immune System*, page 1).

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

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

ADDITIONAL RESOURCES

- **Society for Immunotherapy of Cancer:** www.sitcancer.org
- **American Academy of Dermatology Association:** www.aad.org
  Melanoma
- **American Cancer Society:** www.cancer.org
  What is Cancer Immunotherapy?
- **American Society of Clinical Oncology:** www.cancer.net
  Melanoma: Introduction
- **ClinicalTrials.gov:** www.clinicaltrials.gov
- **Melanoma Research Alliance:** www.curemelanoma.org
  Melanoma: What You Need to Know
- **Melanoma Research Foundation:** www.melanoma.org
  Melanoma Treatment - Immunotherapy
  What is Melanoma?
- **The Skin Cancer Foundation:** www.skincancer.org
  Types of Melanoma
  What is Melanoma?

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Immunotherapy offers new hope against melanoma

As a dermatologist, Dr. Vivian Bucay has seen a lot of skin abnormalities. So when her belly button became dry and flaky, she became concerned and did a biopsy. The results indicated she had a rare form of melanoma. After combining several therapies, she continues to practice dermatology in Texas and enjoy her life with her husband, Moises, and three adult daughters, Yemile, Daniela and Gabriela.

I noticed the skin inside my belly button was dry and flaking. It wasn't painful, tender or bleeding, but it would leave a residue on the inside of the fabric when I wore dark clothing. After a few weeks, I wanted to find out what was causing it. Being a dermatologist, I was able to do my own biopsy. I suspected psoriasis or eczema, but I wasn't concerned about cancer because I had never had a mole inside my belly button. When the pathologist called me on May 10, 2006, to tell me it was melanoma, I was shocked.

I called my husband, Moises, and then I called a local surgical oncologist to whom I refer my melanoma patients. He ordered blood tests, PET, CT, endoscopy, colonoscopy and an MRI.

After these test results came back, I was diagnosed with amelanotic melanoma that was ulcerated. Amelanotic melanoma is a type of melanoma that lacks melanin and is often clear or has a slightly reddish or pink color. The first step was to remove the melanoma and do a sentinel node biopsy to see if it had spread to my lymph nodes. I had the surgery and went home the next day. Three days later, I found out that the sentinel lymph node was positive for melanoma. My diagnosis was upgraded to Stage IIIB melanoma.

On May 30, I had a second surgery called a radical groin dissection to find and remove all of the lymph nodes in my groin. Twenty-eight lymph nodes were removed, and two more were positive for melanoma. I shifted into full "let's-fight-this-cancer" mode.

During my six-week recovery, I visited cancer centers in Texas and Pennsylvania to explore treatment options. Doctors at both centers recommended I consider clinical trials. In the meantime, I started a high-dose intravenous immunotherapy treatment in July for one month, and then followed that up with self-administered subcutaneous injections at home for the next two months. This treatment was done to reduce the chance that the melanoma would recur. I only had a bit of fatigue with this treatment.

I found a clinical trial I wanted to try and enrolled in October. The trial was testing a new type of immunotherapy to see if it could prevent progression from Stage III to Stage IV. Every two weeks, I commuted to Los Angeles for laboratory tests or medication. I received one dose every two months. The only side effect I developed was a rash. I was in the trial until February 2007. I had to drop out after I progressed to Stage IV with lung metastases, which was confirmed after a lung biopsy. The good news is that this drug was approved in 2011 to treat Stage IV patients.

In April, I started another immunotherapy treatment that was approved for Stage IV melanoma. I received the treatment in the intensive care unit at a hospital because of the serious side effects and toxicities. The treatment was given through a central line in my arm. A dose was given every eight hours for a total of 14 doses, which is called a cycle. Two cycles (referred to as a course) were given a week apart, and then a CT was performed one month later to monitor my response. This lasted through June. With this treatment, I had chills, flu-like symptoms, nausea and fluid retention (up to 15 pounds at a time). As of early August, my CT scan showed I had a complete response, meaning the cancer was no longer detectable after finishing treatment. Another CT scan in the fall confirmed the findings.

It's imperative to allow others to take care of you during this time. Friends and family often feel helpless, and letting them take you to a doctor's appointment or treatment or send a meal goes a long way for you and for them. The most important thing during this battle is to direct all your energy to getting better. I reserve my worrying for the usual things, like my daughters.

Remember to stay calm. Advanced melanoma is no longer a death sentence, and no one has the right to take hope away from you. Consider a clinical trial. Be your own strongest advocate by getting all the information you can, but, at the same time, allow the physicians and their teams to take care of you. ■

STAGING MELANOMA

Your oncologist will use a process called staging to determine the typical behavior and treatment options for managing your melanoma. Staging is based on knowledge of your melanoma's size, thickness, location and the extent of spread. Melanoma staging includes clinical information as well as pathology information based on close examination of biopsy or surgical melanoma specimens.

First, your oncologist will evaluate the results of your physical exams, skin biopsies and any imaging tests, and assign a clinical stage. Then your surgical team may remove all or some of the tumor/lesion and biopsy nearby lymph nodes. A pathologist will examine the tissue samples under a microscope and discuss the findings with your oncologist before assigning a pathologic stage, which is a more precise diagnosis that's key to making a treatment decision.

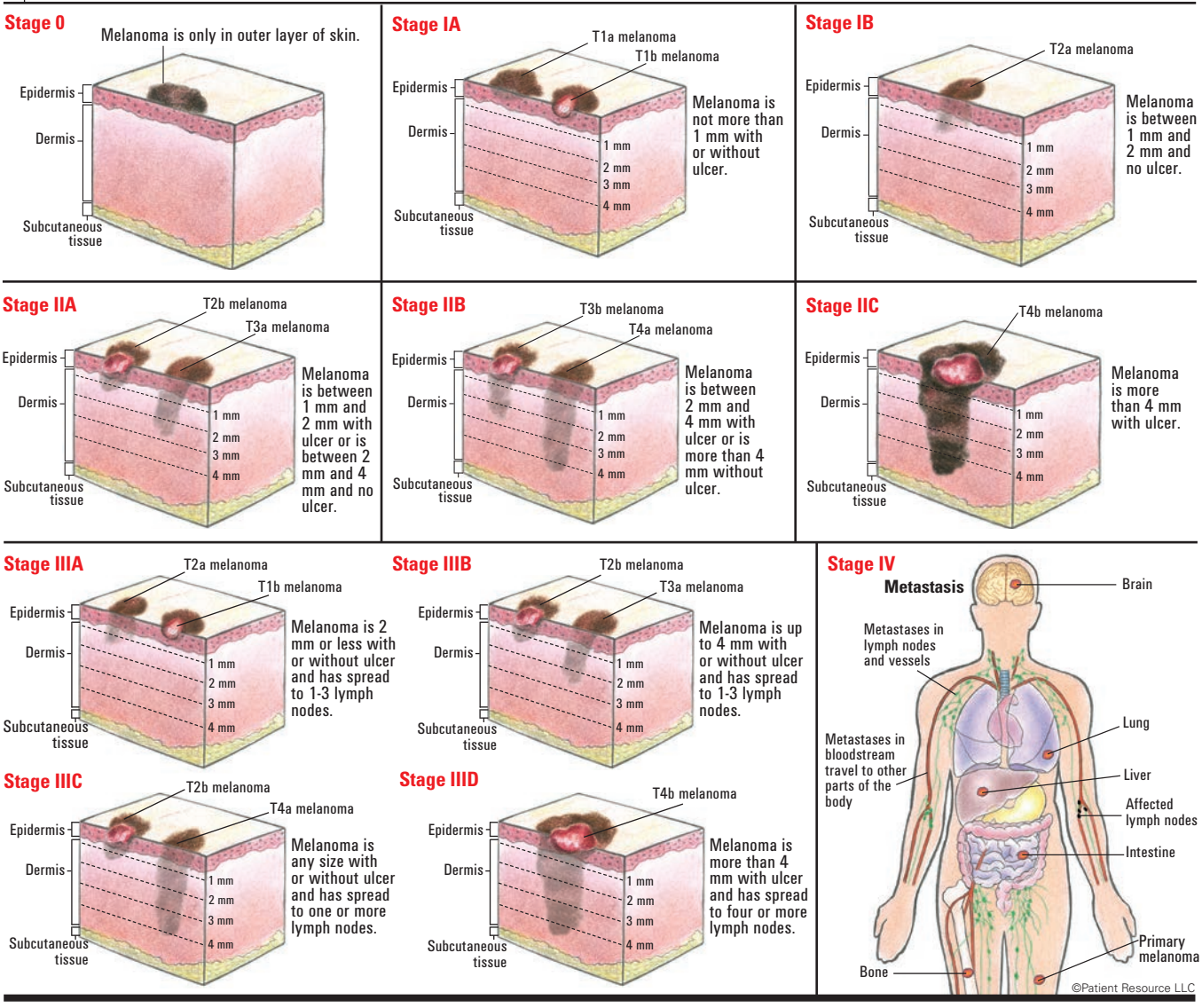
Clinical and pathologic stages of melanoma are both classified using the tumor, node, metastasis (TNM) system, with each letter describing an aspect of cancer growth. The staging system was developed by the American Joint Committee on Cancer (AJCC) (see Tables 1 and 2).

The tumor (T) is classified based on the thickness or depth of the tumor/lesion. It ranges from T0, meaning no evidence of a primary tumor, to T4, meaning the tumor is thicker than 4 millimeters (thicker than two stacked nickels). Subcategories indicate whether the tumor has ulcerated (broken through the skin). In general, the thicker the melanoma, the more aggressively the disease may behave and the more important further treatment may be.

The node (N) classification describes how extensively the melanoma has spread to regional (nearby) lymph nodes. Subcategories a, b and c indicate increasing amounts of cancer cells in the nodes. Similar to increasing thickness being associated with worse outcomes, the more lymph nodes involved with melanoma, the more concerning the disease will be.

The metastasis (M) category classifies the melanoma according to whether and where it has metastasized (spread) from the original site, such as the skin or soft tissue, lungs or central nervous system. Another factor is whether the blood level of lactate dehydrogenase (LDH) is elevated. LDH is a prognostic biomarker that helps doctors

STAGES OF MELANOMA OF THE SKIN



monitor melanoma progression and better predict survival rates.

Once your melanoma is classified with the TNM system, an overall stage can be determined. Stage 0 is called "melanoma in situ" and is considered to be precancerous. Stage I and II melanomas are referred to as local or localized disease, which means the cancer has not spread beyond the original site. Stage III is called regional disease, meaning the melanoma has spread to nearby tissues, lymph nodes or organs. Stage IV is called distant metastatic or advanced disease because the melanoma has metastasized (spread) to distant parts of the body. The treatment options selected for therapy are based on the stage of your tumor. ■

ADDITIONAL RESOURCES

- **Society for Immunotherapy of Cancer:** www.sitcancer.org
- **AIM at Melanoma Foundation:** www.aimatmelanoma.org
  Stages of Melanoma
- **American Academy of Dermatology Association:** www.aad.org
  Public and Patients
- **ClinicalTrials.gov:** www.clinicaltrials.gov
- **Melanoma Research Alliance:** www.curemelanoma.org
  Understanding Melanoma Staging
- **Melanoma Research Foundation:** www.melanoma.org
  Stages of Diagnosis
- **National Cancer Institute:** www.cancer.gov
  Melanoma Treatment – Patient Version

TABLE 1
STAGES OF MELANOMA OF THE SKIN

Stage	T	N	M
0	Tis	N0	M0
IA	T1a T1b	N0 N0	M0 M0
IB	T2a	N0	M0
IIA	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0
IIIA	T1a/b-T2a	N1a or N2a	M0
IIIB	T0 T1a/b-T2a T2b/T3a	N1b, N1c N1b/c or N2b N1a-N2b	M0 M0 M0
IIIC	T0 T1a-T3a T3b/T4a T4b	N2b, N2c, N3b or N3c N2c or N3a/b/c Any N ≥ N1 N1a-N2c	M0 M0 M0 M0
IIID	T4b	N3a/b/c	M0
IV	Any T, Tis	Any N	M1

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science+Business Media.

TABLE 2
AJCC TNM SYSTEM FOR CLASSIFYING MELANOMA OF THE SKIN

Classification	Definition	
Tumor (T)		
T Category	**Thickness**	**Ulceration status**
TX	Primary tumor thickness cannot be assessed.	Not applicable
T0	No evidence of primary tumor.	Not applicable
Tis	Melanoma in situ.	Not applicable
T1 T1a T1b	≤ (not more than) 1.0 mm. < (less than) 0.8 mm. < (less than) 0.8 mm. 0.8 – 1.0 mm.	Unknown or unspecified Without ulceration With ulceration With or without ulceration
T2 T2a T2b	> (more than) 1.0 – 2.0 mm. > (more than) 1.0 – 2.0 mm. > (more than) 1.0 – 2.0 mm.	Unknown or unspecified Without ulceration With ulceration
T3 T3a T3b	> (more than) 2.0 – 4.0 mm. > (more than) 2.0 – 4.0 mm. > (more than) 2.0 – 4.0 mm.	Unknown or unspecified Without ulceration With ulceration
T4 T4a T4b	> (more than) 4.0 mm. > (more than) 4.0 mm. > (more than) 4.0 mm.	Unknown or unspecified Without ulceration With ulceration
Node (N)		
N Category	**Number of tumor-involved regional lymph nodes**	**Metastases status***
NX	Regional nodes not assessed.	No
N0	No regional metastases detected.	No
N1 N1a N1b N1c	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes. One clinically occult. One clinically detected. No regional lymph node disease.	 No No Yes
N2 N2a N2b N2c	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node. Two or three clinically occult. Two or three, at least one of which was clinically detected. One clinically occult or clinically detected.	 No No Yes
N3 N3a N3b N3c	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases. Four or more clinically occult. Four or more, at least one of which was clinically detected, or presence of any number of matted nodes. Two or more clinically occult or clinically detected and/or presence of any number of matted nodes.	 No No Yes
* In-transit metastases occur more than 2 cm from the primary melanoma (both on the surface of the skin or below the surface of the skin) to the regional lymph nodes. Satellite metastases occur on or below the skin within 2 cm of the primary melanoma. Microsatellite metastases in the skin or in the deeper layer of the dermis near or deep within the skin of the primary melanoma is detected upon microscopic examination.		
Metastasis (M)		
M Category*	**Anatomic site**	**LDH level**
M0	No evidence of distant metastasis.	Not applicable
M1 M1a M1a(0) M1a(1) M1b M1b(0) M1b(1) M1c M1c(0) M1c(1) M1d M1d(0) M1d(1)	Evidence of distant metastasis. Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node. Distant metastasis to lung with or without M1a sites of disease. Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease. Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease.	See below Not recorded or unspecified Not elevated Elevated Not recorded or unspecified Not elevated Elevated Not recorded or unspecified Not elevated Elevated Not recorded or unspecified Normal Elevated
*Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.		

TREATMENT OPTIONS

Immunotherapy is changing the way doctors treat melanoma. Some of the very first types of immunotherapy approved were for melanoma, and research continues to find that it, in particular, responds well to it.

The immune system is a complex network of organs, cells and tissues working together to protect the body from germs (see *About Melanoma and the Immune System,* page 1). Likewise, research has discovered multiple ways to harness the potential of the body's own immune system and enable it to recognize and eliminate cancer cells. There are several types of immunotherapy approved to treat melanoma, and all are a result of the research done in clinical trials (see *Exploring Clinical Trials,* page 9). These treatments are first tested on metastatic melanomas (Stage IV). If they show success, they are tested on Stage III melanomas and possibly earlier stages.

Clinical trials also help determine if the treatment is appropriate for first-line therapy or second-line therapy. First-line therapy, also known as induction therapy, primary therapy and primary treatment, is the first treatment given and is usually part of the standard of care. Second-line therapy is treatment given after the primary treatment (first-line therapy) doesn't work or stops working. For melanoma, the first-line therapy is frequently surgery, and immunotherapy is used after surgery as second-line therapy for Stages II through IV.

The treatment depends on the stage of the melanoma (see *Staging Melanoma,* page 4). For early (or low) stage melanoma, treatment usually involves surgery only. For more advanced (higher) stage melanoma, additional treatment may be necessary to prevent recurrence or treat melanoma that has spread. Most immunotherapy strategies for melanoma are second-line treatments, often given after surgery (adjuvant treatment) with the goal of reducing the risk of disease recurrence. However, immunotherapy has evolved to become a first-line treatment for some types. One immune checkpoint inhibitor is approved as a first-line therapy for previously untreated melanoma that does not have a *BRAF* (pronounced bee-raff) V600 mutation (see *The Rising Importance of Biomarkers in Melanoma*). Clinical trial research is ongoing to test already approved types of immunotherapy on other melanoma stages as well as to identify new immunotherapy.

The following types of immunotherapy are approved to treat melanoma.

CYTOKINES

Cytokines were the first type of immunotherapy approved for melanoma. Cytokine immunotherapy aids in immune cell communication and plays a big role in the full activation of an immune response. This approach works by introducing large amounts of laboratory-made cytokines to the immune system to promote specific immune responses. It is also considered a non-specific immune stimulator. Three types of cytokines are used in immunotherapy.

1. **Interleukins** help regulate the activation of certain immune cells. Interleukin-2 was the first immunotherapy approved for metastatic melanoma. It is approved for unresectable (cannot be removed by surgery) Stage III and IV melanoma.
2. **Interferons** boost the ability of certain immune cells to attack cancer cells. Two types of interferon are approved as adjuvant therapy (given after primary treatment) for Stage II and III melanoma, and one is approved for metastatic melanoma after surgery.
3. **Granulocyte-macrophage colony stimulating factors** (GM-CSFs) stimulate the bone marrow, promoting the growth of immune and blood cells and the development of dendritic cells, which become antigen-presenting cells (cells that show the antigens to T-cells). Although GM-CSF alone has not been useful in treating melanoma, an oncolytic virus that includes the GM-CSF cytokine to help activate a strong immune response is approved for treatment.

FDA-APPROVED MELANOMA IMMUNOTHERAPIES

CYTOKINES
- interferon alfa-2b (Intron A)
- interleukin-2 (aldesleukin [Proleukin])
- pegylated interferon alfa-2b (PEG-Intron, Sylatron)

IMMUNE CHECKPOINT INHIBITORS
- ipilimumab (Yervoy)
- nivolumab (Opdivo)
- pembrolizumab (Keytruda)

ONCOLYTIC VIRUS THERAPY
- talimogene laherparepvec (Imlygic/T-VEC)

COMBINATION
- ipilimumab (Yervoy) + nivolumab (Opdivo)

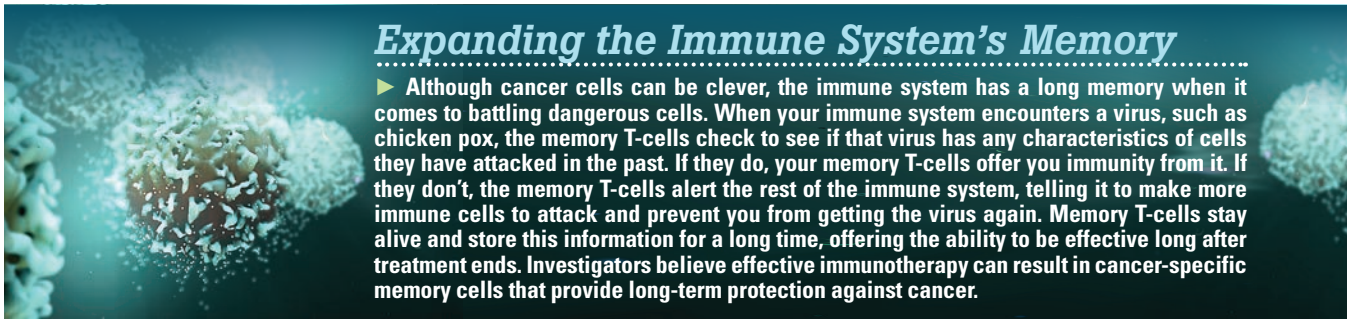
As of 12/14/18

IMMUNE CHECKPOINT INHIBITORS

This type of immunotherapy was first approved in 2011 for melanoma. There are some immune checkpoint inhibitors approved to treat melanoma, and some of them are also approved to be used in combination for certain types and stages of melanoma.

To understand how immune checkpoint inhibitors work, it is helpful to know how the immune system works in general. Since one of the primary functions of the immune system is to determine which cells or substances are self (normal) or non-self (abnormal or stressed), the immune system contains cells, called B-cells and T-cells, that can recognize abnormal or stressed cells. These cells are part of the white blood cells that fight infections and eliminate cancer cells in the body. To prevent attack on normal cells, the immune system has a complex process that regulates the activity of B-cells and T-cells. The immune cells are rapidly activated to clear an infection or kill a cancer cell. However, to prevent an attack on normal cells, the immune system must slow down. It does this through the use of checkpoints.

Checkpoints keep the immune system "in check" by turning off immune cells or killing the immune cells. This may be normal after an



Expanding the Immune System's Memory

Although cancer cells can be clever, the immune system has a long memory when it comes to battling dangerous cells. When your immune system encounters a virus, such as chicken pox, the memory T-cells check to see if that virus has any characteristics of cells they have attacked in the past. If they do, your memory T-cells offer you immunity from it. If they don't, the memory T-cells alert the rest of the immune system, telling it to make more immune cells to attack and prevent you from getting the virus again. Memory T-cells stay alive and store this information for a long time, offering the ability to be effective long after treatment ends. Investigators believe effective immunotherapy can result in cancer-specific memory cells that provide long-term protection against cancer.

infection has been cleared, but, in cancer, this may occur prematurely, allowing the cancer to continue to grow. In addition to checkpoints found on immune cells, other cells called regulatory T-cells may also turn down activated immune cells (see *About Melanoma and the Immune System,* page 1). When the correct checkpoint proteins and cell receptors connect, a series of signals is sent to the immune system to slow down once an immune response is finished. Three checkpoint receptors that slow down the immune system have been identified for their roles in cancer treatment.

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

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

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

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

Checkpoint inhibiting drugs prevent connections between checkpoints. This prevents the immune response from slowing down, which allows the immune cells to continue fighting the cancer. When an immune checkpoint inhibitor is given, it's as if the immune system develops X-ray vision and can see through the cancer cell's camouflage. This helps the immune system recognize cancer cells as foreign cells.

The following immune checkpoint inhibitors are currently approved as cancer treatments.

- **Anti-CTLA-4 antibodies** allow T-cells to continue fighting cancer cells instead of shutting down.
- **Anti-PD-1 drugs** allow for the continued or increased production of T-cells and enable them to continue fighting cancer.
- **Anti-PD-L1 molecules** allow the T-cells to see through some tumor cells' disguises. They recognize them as the enemy and then attack them.

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

Laboratory-made antibodies that are designed to target specific tumor targets, such as antigens or other proteins found on the cancer cell, can work in different ways, including flagging targeted cancer cells for destruction, blocking growth signals and receptors, and

THE RISING IMPORTANCE OF BIOMARKERS IN MELANOMA

Biomarkers are substances, such as genes, proteins or molecules, produced by cancer cells or other cells in the body. Biomarkers are also known as tumor markers, molecular markers, biological markers or serum markers.

Biomarkers may be prognostic, predictive or diagnostic. A prognostic biomarker provides information about a person's overall cancer outcome, regardless of therapy, while a predictive biomarker gives information about the effect of a specific treatment approach. Diagnostic biomarkers help determine the type of tumor.

With many advancements in understanding the genetics of cancer and how cancers grow, the use of biomarkers as prognostic, predictive and diagnostic tools is becoming more widespread. Research is ongoing to find new melanoma biomarkers that may offer more information for making treatment decisions and to identify more precise tests. Many biomarker tests have been created, but there is no official standard test recognized by the medical community.

Doctors are using these biomarkers to determine which patients may respond to immunotherapy. Several biomarkers have emerged as useful in melanoma, and they show potential for more widespread use, but they require more testing. Lactate dehydrogenase (LDH) is the only accepted serum biomarker tested for melanoma, and it was recently added to the American Joint Committee on Cancer (AJCC) TNM staging system's M category for melanoma (see *Staging Melanoma,* page 4). It is tested to determine if a person has an elevated risk for metastasis.

Not all patients who receive immunotherapy respond, and research is ongoing to find out why. Scientists are looking for biomarkers that will indicate whether a patient is a good candidate for immunotherapy. Biomarkers are expected to be used more commonly in the future so that immunotherapy is not given to someone who may not respond to it.

The following biomarkers are currently being used by some doctors to make immunotherapy treatment decisions.

- **PD-L1 expression** may be tested to determine if the tumor cells or immune cells in the tumor's microenvironment contain a higher level, which may mean that a patient could be a good candidate for immune checkpoint inhibitors.
- **Tumor mutational burden** (TMB) is an assessment of the number of genetic mutations in a tumor. It can help doctors determine if a patient will respond to immunotherapy. It is believed that the higher the TMB level is, the more likely the patient will respond to immunotherapy.

Doctors are also genetically testing melanoma tumors to identify subtypes and certain genetic mutations. This information aids your doctor in making treatment decisions. *BRAF* (pronounced bee-raff) is the most well-known genetic mutation of melanoma. Research shows that approximately 50 percent of melanomas have a mutation in the *BRAF* gene. Between 10 and 25 percent have an *NRAS* (pronounced en-rass) mutation and about 14 percent have an *NF1* mutation. Targeted therapies have been developed to treat melanomas with specific *BRAF* mutations, and more are expected in the future.

Advancements in research are expected to increase the importance of genetic testing. Current research is focused on identifying new biomarkers, making the current testing methods standardized for everyone, developing tests that are more sensitive and creating multi-gene tests to speed up diagnosis and guide treatment options.

delivering other therapeutic agents directly to targeted cancer cells. They can also be created to carry cancer drugs, radiation particles or laboratory-made cytokines (proteins that enable cells to send messages to each other) directly to cancer cells. 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. This direct form of radiation delivery typically damages only the targeted cells.

ONCOLYTIC VIRUS IMMUNOTHERAPY

An oncolytic virus immunotherapy was approved for melanoma in 2015. Oncolytic viruses attack and kill only cancer cells. They use viruses that directly infect tumor cells to cause an immune response against the infected cells. The oncolytic virus currently approved uses a weakened version of the herpes simplex virus. It has been changed from the original and contains the cytokine GM-CSF. The virus targets cancer cells, infects them and duplicates itself continuously within the cell until it ruptures. This rupture kills the cell and releases the GM-CSF cytokine produced by the virus to promote an overall immune boost against the cancer. This process increases the chance that the attack can also begin killing cancer cells that have not been infected with the virus. Other viruses are being evaluated as potential cancer treatments. ■

QUESTIONS TO ASK YOUR DOCTOR

- Why is immunotherapy the best treatment for me?
- Do you have experience treating melanoma patients with immunotherapy?
- Where will I receive treatment? In a hospital or doctor's office?
- Will the treatment be given as a pill, through an IV or something else?
- How often will I receive treatment?
- How long will it take for a treatment to be given?
- How long will I be on treatment?
- How will you know if the treatment is working?
- Will I be able to receive other treatments after being on immunotherapy?
- Will I be given other treatment options along with immunotherapy?
- Should I consider a clinical trial?
- What side effects can I expect, and how serious could they be?

GLOSSARY

B-cells – Immune cells (lymphocytes) that make proteins called antibodies to mark specific foreign substances for other immune cells to destroy. B-cells can potentially become plasma cells.

Clinical trial – A research study that assigns people in a specified manner to one or more interventions to determine how it affects a health or behavioral problem. Your doctor and the study team must explain participation requirements for the clinical trial, procedures involved, how the experimental drug is thought to work, possible side effects that are known, how many patients will participate, length of the trial, reasons to stop treatment, any associated costs to you and alternative options. You must sign an Informed Consent form before you can participate in the clinical trial. You have the right to stop participating usually at any time, although it is important to let your doctor 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.

Cytokines – Proteins secreted by certain immune cells so they can communicate with each other. These chemical messengers work alone and together to regulate different functions in the immune system. Cytokines can also be made in a laboratory for cancer-fighting immunotherapies.

Dermis – The inner layer of the two main layers of the skin. The dermis has connective tissue, blood vessels, sebaceous (oil) and sweat glands, nerves, hair follicles, and other structures.

Epidermis – The outer layer of the two main layers of the skin.

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

Immune-related adverse events (IRAEs) – The immune system's overreaction to immunotherapy. In rare cases, IRAEs can rapidly become life-threatening without medical attention.

Interferon – A cytokine that interferes with cancer cell division and slows tumor growth, boosting the body's immune response. A laboratory version is used as a type of cancer immunotherapy.

Interleukin – Part of a group of proteins (cytokines) that some immune cells make. Interleukin helps regulate certain functions in the immune system. A laboratory version is used in a type of cancer immunotherapy.

In-transit metastasis – A type of metastasis in which skin cancer spreads through a lymph vessel and begins to grow more than 2 centimeters away from the primary tumor but before it reaches the nearest lymph node.

Lactate dehydrogenase (LDH) – One of a group of enzymes found in the blood and other body tissues involved in energy production in cells. An increased amount in the blood may be a sign of tissue damage and some types of cancer, such as melanoma, or other diseases.

Lymphocyte – A type of immune cell (white blood cell) in lymph tissue and blood. The main types are B-lymphocytes (B-cells) and T-lymphocytes (T-cells), which both help the immune system fight cancer.

Microsatellite tumor – A small group of tumor cells in an area beside or below, but separate from, the primary (original) melanoma. Microsatellite tumors can only be seen with a microscope.

Monoclonal antibodies (mAbs) – Laboratory-made proteins created to target and bind with specific proteins or molecules on the surface of cancer cells. In cancer immunotherapy, mAbs are used to stimulate an immune response and may do so by activating a stimulatory receptor on an immune cell or by blocking checkpoint receptors that cause T-cells to shut down.

Oncolytic virus – A naturally occurring virus also manufactured as a cancer immunotherapy. It targets certain cancer or tumor cells, infects them and multiplies to cause cell death. The virus can also induce an immune response.

PD-1 (programmed cell death-1) – A receptor that binds with another protein (PD-L1) to help keep the body's immune response in check. A type of cancer immunotherapy involving checkpoint inhibitors blocks PD-1 receptors, in effect "releasing the brakes" on the immune system.

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

Radioimmunotherapy – A combination of radiation therapy and immunotherapy links a radioactive substance to a monoclonal antibody and injects it into the body. Radiation from the substance may kill cancer cells.

Receptors (immune receptors) – Surface molecules on immune cells that bind to the surface of other immune cells. This typically causes the cell to produce signals that regulate specific functions in the immune system.

Satellite tumor – A group of tumor cells in an area near the primary (original) tumor. In melanoma, satellite tumors occur within 2 centimeters of the primary tumor, on or under the skin, and can be seen without a microscope.

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

T-cells – White blood cells (immune cells) that play a significant role in the immune system's fight against infection and disease. T-cell activity and activation are primary focuses of immunotherapy research.

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

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

SITC Guidelines: The Society for Immunotherapy of Cancer (SITC) offers guidelines for medical professionals regarding the recommended use of immunotherapy treatments. Guidelines for melanoma and several other cancers are currently available at → **www.sitcancer.org/guidelines**

EXPLORING CLINICAL TRIALS

A significant focus of cancer research and drug development today is on immunotherapy agents, alone and in combination, to treat melanoma. Knowledge gained from these medical research studies continues to fuel promising advances in melanoma treatment, particularly for advanced melanoma. Such progress is a key reason to ask your doctor if you may be eligible for a clinical trial.

Current melanoma clinical trials are evaluating the effectiveness of new treatments such as chimeric antigen receptor T-cell (CAR T-cell) therapy, tumor necrosis factor therapy, therapeutic vaccines and immunotherapy combinations. Researchers are also trying to identify biomarkers to indicate which patients will benefit from immunotherapy and investigating how age may affect patient response to checkpoint inhibitors.

As you discuss clinical trials with your doctor, health care team and loved ones, keep in mind the following:

- They may offer access to leading-edge treatments that aren't yet available and may be more effective or better tolerated than current therapies.
- At minimum, the treatment you receive will be equivalent to standard of care.
- You may leave the trial at any time, for any reason, and switch to standard of care.
- Additional monitoring and care, including increased testing, visits and reporting, will occur throughout and may continue after the trial.
- There are no guarantees that participation in a clinical trial will work for you, but you will have the opportunity to help research and other patients. ■

ADDITIONAL RESOURCES

- **Society for Immunotherapy of Cancer:** www.sitcancer.org
- **Center for Information & Study on Clinical Research Participation:** www.searchclinicaltrials.org
- **ClinicalTrials.gov:** www.clinicaltrials.gov
- **Melanoma Research Foundation:** www.melanoma.org *Participate in a Clinical Trial*
- **My Clinical Trial Locator:** www.myclinicaltriallocator.com *Melanoma*
- **TrialCheck:** www.trialcheck.org

SEARCH ONLINE FOR CLINICAL TRIALS

Being an active participant in your cancer care includes doing your own research for melanoma clinical trials, in addition to talking with your doctor. The Internet provides access to clinical trial information, but using online search tools may be challenging. The screenshots below of a mock search site give you an idea of what to expect.

Start by having handy your exact diagnosis, pathology report and details about previous treatments. Then follow the instructions using different search sites (see *Assistance & Support Resources,* page 12). New clinical trials are continually added, so keep checking if you don't find a good fit at first. If you're interested in one that is closed to new participants, talk with your doctor about appealing for expanded access, also called "compassionate use."

[STEP 1] FILL IN YOUR INFORMATION

Enter Your Diagnosis
For example, type "melanoma." For more options, you can search for "advanced melanoma" to compare results.

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

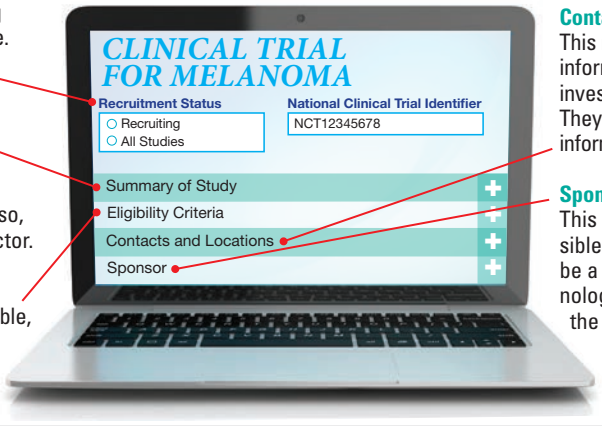
Other Terms
You can refine your search by adding a treatment type such as "immunotherapy," a specific drug name or a National Clinical Trial identifier. An NCT identifier is assigned to each clinical trial. Identifiers begin with the letters "NCT" followed by eight numbers.

[STEP 2] READ YOUR SEARCH RESULTS

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

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

Eligibility Criteria
This outlines the criteria you must meet to be eligible, such as the stage of disease, sites of metastasis, overall health requirements, age range and previous treatments that may affect your eligibility.



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

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

Partnering with your health care team to manage your care is very important. The better you feel, the better able you'll be to complete your treatment.

Most types of treatment cause side effects but, because immunotherapy tends to affect only cancer cells, people sometimes experience fewer and milder side effects than with other standard cancer treatments. Everyone, however, responds differently.

Before you begin treatment, talk with your doctor about both short-term and long-term effects. Ask for a list of symptoms specific to the immunotherapy you will receive so you'll know what to watch for, how to respond, and when to contact your doctor's office or seek emergency medical attention. Keep in mind that you may experience additional side effects if immunotherapy is combined with another type of cancer treatment or with another immunotherapy.

Side effects from immunotherapy can sometimes indicate your immune system is too active, putting you at risk for an autoimmune disorder. If a side effect is very severe, you may need to stop your treatment for a period of time or permanently. However, prompt recognition and early management of it can often result in rapid resolution and allow you to stay on treatment longer. Thus, it is important to report any side effects to your doctor or nurse as soon as possible, no matter how trivial or ordinary they may seem. Your health care team will depend on you for frequent communication.

Side effects may develop weeks or even months after treatment ends. Remain alert for symptoms and report them for at least 6 to 12 months following treatment.

Always seek immediate treatment for medical emergencies such as difficulty breathing, high fever, inflammation, swelling or severe abdominal pain. Inform all medical personnel that you're receiving immunotherapy.

IMMUNE-RELATED ADVERSE EVENTS (IRAES)

Serious side effects from immunotherapy are rare, but they can occur. Known as immune-related adverse events (IRAEs), they can develop rapidly and become life-threatening without immediate treatment. If immunotherapy overstimulates your immune system, immune cells can begin attacking healthy tissue as well as cancer cells. Left untreated, an IRAE can damage organs, intestines, nerves and other parts of the body, including the brain.

Some potentially serious IRAEs and their symptoms follow. Contact your health care team immediately if you experience any of these symptoms.

- **Cardiovascular** (cardiomyositis): chest pain, shortness of breath, leg swelling, rapid heartbeat, changes in EKG reading
- **Endocrine** (endocrinopathies): hyperthyroidism, hypothyroidism, extreme fatigue, persistent or unusual headaches
- **Gastrointestinal** (colitis): diarrhea with or without bleeding, abdominal pain, bowel perforation
- **Liver** (hepatitis): yellow skin or eyes (jaundice), nausea, abdominal pain, fatigue, fever
- **Nervous system** (neuropathies): tingling, numbness, a burning sensation or a loss of feeling in the hands or feet, pain, sensory overload, sensory deprivation
- **Neurologic** (encephalitis): confusion, hallucinations, seizures, mood or behavior changes, neck stiffness, extreme light sensitivity
- **Pulmonary/lung** (pneumonitis): chest pain, shortness of breath

SURVIVOR VOICE

"Joint pain was a problem, but the more I kept moving, the better I felt — thus my desire to work out almost every day."

~ ***Heather S.,***
melanoma survivor

- **Renal/kidneys** (nephritis): decreased urine output, blood in urine, swollen ankles, loss of appetite
- **Skin** (dermatitis): rash, skin changes (itching, blisters, painful sores)

Cytokine release syndrome is an IRAE associated with monoclonal antibodies and adoptive T-cell therapies. Reactions are usually mild but can be severe and even life-threatening. Symptoms include headache, fever, nausea, rash, low blood pressure, rapid heartbeat and difficulty breathing.

COMMON SIDE EFFECTS

Constipation can become very uncomfortable and even lead to serious medical issues, such as bowel obstructions. Eat high-fiber foods, drink plenty of fluids and establish regular bowel habits. It's important to discuss this condition with your doctor to get help for managing it.

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

Diarrhea is common with immune checkpoint inhibitors and cytokines. When severe, it can lead to dehydration and electrolyte imbalance, so contact your health care team immediately about severe abdominal cramping, frequent episodes or diarrhea that keeps you housebound. Stay well-hydrated, avoid dairy products and spicy or greasy foods, and consider a temporary diet of clear liquids.

Edema (swelling) in the legs results from fluid buildup in the tissues. Contact your doctor immediately about swelling, stiffness or a heavy feeling in your legs, and recent weight gain.

Fatigue is the most common side effect reported from immunotherapy. Cancer-related fatigue is more intense and longer-lasting than regular tiredness. Balance activity with rest each day, conserving energy for the activities that are most important to you.

PAIN RELIEF OPTIONS

→ Not all people who have melanoma experience pain. Although it can occur after a surgical procedure, it usually resolves as the body heals. Pain related to the melanoma itself, however, can result if cancer has metastasized, or spread, to other tissues or organs. If you have pain, contact your doctor or another member of your health care team right away because supportive care is available throughout treatment to address and treat pain as soon as it begins.

Mild pain may be managed with over-the-counter pain relievers. More severe pain may be controlled with prescription drugs, such as opioids. It's important to take opioids exactly as your doctor prescribes – the right medication at the right dosage at the right time – to get the maximum benefit, instead of taking them on an as-needed basis. If you are taking opioids, your doctor will monitor you closely throughout treatment so don't let the fear of addiction keep you from relieving your pain. Share your concerns with your doctor and, together, you will determine the best pain relief option for you.

Flu-like symptoms may occur with cytokines and oncolytic virus therapy. These include fever, chills, aches, headaches, drowsiness, nausea, vomiting, loss of appetite and blood pressure changes.

Heart palpitations may occur with certain types of immunotherapy. Contact your doctor immediately about abnormal heart rhythm, dizziness or light-headedness.

Infertility risks (for both women and men) should be discussed with your doctor before beginning treatment, if possible, even if you're undecided about having biological children in the future. For fertility preservation options, ask to be referred to a reproductive specialist experienced with cancer patients.

Infusion-related reactions include mild itching, skin rash, fever or chills. More serious symptoms are shaking, chills, low blood pressure, dizziness, trouble breathing and irregular heartbeat. Your doctor may give you the drug more slowly or stop it, or recommend analgesics, antihistamines or corticosteroids.

Mouth sores are much more easily managed when caught early, so report symptoms right away. Switch to a soft-bristled toothbrush, eat soft foods and drink plenty of fluids.

Muscle and joint pain ranges from mild to severe, affecting your entire body or certain areas. Pain typically resolves when treatment ends. If pain persists or worsens, discuss pain management options with your doctor.

Nausea and vomiting are more likely when immunotherapy is combined with chemotherapy, targeted therapy or other drug therapies. Eat smaller, more frequent meals and drink plenty of fluids. Your health care team may recommend antiemetics.

Skin reactions, such as bumpy or itchy red rashes, are common, but be alert for changes in skin color, hives, pale patches or redness. Your doctor may recommend a corticosteroid or numbing medicine or prescribe an antihistamine, medicated creams or antibiotics. ■

ADDITIONAL RESOURCES

- **Society for Immunotherapy of Cancer:** www.sitcancer.org
- **American Cancer Society:** www.cancer.org
  Cancer Treatment Side Effects
  Coping With Cancer
- **American Society of Clinical Oncology:** www.cancer.net
  Side Effects of Immunotherapy
- **Cancer Support Community:** www.cancersupportcommunity.org
  Immunotherapy for Melanoma
- **National Cancer Institute:** www.cancer.gov
  Feelings and Cancer
  Immunotherapy for Cancer

Take care of your emotional well-being

The feelings that accompany cancer treatment can be overwhelming. Following are common emotions and suggestions for managing them. You may also consider talking with a mental health professional. Don't be embarrassed or hesitant to ask your cancer treatment team for a referral to a therapist experienced in working with people who have cancer. Being emotionally healthy will help you better cope with cancer-related issues, including managing side effects.

Anger is common before, during and after cancer treatment. To avoid expressing bottled-up anger in unhealthy ways, find safe alternatives. Explain your feelings to a trusted friend. Yell at the top of your lungs while you are alone, hit a pillow with your fists or a foam bat, or participate in intense physical activity.

Anxiety and worry may make it challenging to cope with treatment or function day-to-day, or difficult for your body to properly heal. Explore relaxation techniques such as deep breathing, meditation, muscle relaxation or yoga. Share your anxieties with a good listener.

Depression is most likely to occur for people with cancer during times of unrelieved symptoms and is a side effect of some types of immunotherapy. It's important to talk with your doctor about feeling sad, "numb," hopeless, helpless or worthless if the feelings last more than a few days. Seek medical attention immediately if you have thoughts of death or suicide, or suicide attempts.

Emotional overload is common for people with cancer because everything you're dealing with seems overwhelming, and life feels as if it's spinning out of control. Try taking charge of the things you can control and becoming an expert on your treatment plan to know what to expect. Ask loved ones to handle routine decision-making.

Fear is a common reaction because you can't predict how you'll respond to treatment and the future seems uncertain. You may also fear possible changes in your appearance, sexuality or how others feel about you. Try learning all you can about your treatment, talk with others undergoing similar treatment and explore relaxation techniques.

Grief is an emotion many people with cancer don't expect. But you may mourn the loss of your health or of a future without the cloud of cancer recurrence. Give yourself permission to grieve, feel a full range of emotions and turn to loved ones for support.

Guilt may plague you if you blame yourself for getting cancer due to health-related actions you did or didn't take, or if you feel you're upsetting or being a burden to loved ones. You may even feel guilty if you have a negative attitude. Give yourself a break on bad-attitude days, share your feelings with other cancer survivors or consider seeing a counselor.

Loneliness may occur if you feel no one understands your feelings, or if a friend or family member stops visiting or calling because he or she doesn't know how to act. Consider reaching out to the absent person for conversation that isn't cancer-related. Check out a support group meeting in your area or find one online.

ASSISTANCE & SUPPORT RESOURCES

CANCER EDUCATION

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

CAREGIVERS & SUPPORT

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

CLINICAL TRIALS

ACCESS ..... cantria.com/access
AccrualNet ..... accrualnet.cancer.gov
ACT (About Clinical Trials) ..... www.learnaboutclinicaltrials.org
Center for Information & Study on Clinical Research Participation ..... www.searchclinicaltrials.org
CenterWatch ..... www.centerwatch.com
ClinicalTrials.gov ..... www.clinicaltrials.gov
Lazarex Cancer Foundation ..... www.lazarex.org
LIVESTRONG Foundation ..... www.livestrong.org
My Clinical Trial Locator ..... myclinicaltriallocator.com
National Cancer Institute ..... www.cancer.gov/clinicaltrials
NCI Contact Center (cancer information service) 800-422-6237
TrialCheck ..... www.trialcheck.org

FERTILITY & CANCER

Alliance for Fertility Preservation ..... www.allianceforfertilitypreservation.org
American Society for Reproductive Medicine ..... www.reproductivefacts.org
LIVESTRONG Foundation ..... www.livestrong.org
RESOLVE The National Infertility Association ..... www.resolve.org
SaveMyFertility ..... www.savemyfertility.org

FINANCIAL ASSISTANCE

BenefitsCheckUp ..... www.benefitscheckup.org
Bringing Hope Home ..... www.bringinghopehome.org
Cancer*Care* ..... www.cancercare.org/financial
Cancer Financial Assistance Coalition ..... www.cancerfac.org
HealthWell Foundation ..... www.healthwellfoundation.org
Hope Lodge ..... www.cancer.org/treatment/supportprogramsservices/hopelodge
Medicare.gov ..... www.medicare.gov
NeedyMeds ..... www.needymeds.com
Partnership for Prescription Assistance ..... www.pparx.org
Patient Access Network Foundation ..... www.panfoundation.org
Patient Advocate Foundation ..... www.patientadvocate.org
Patient Services, Inc. ..... www.patientservicesinc.org
RxAssist ..... www.rxassist.org
RxHope ..... www.rxhope.com
Social Security Administration ..... www.ssa.gov
Social Security Disability Resource Center ..... www.ssdrc.com
State Health Insurance Assistance Programs ..... www.shiptacenter.org

IMMUNOTHERAPY

The Answer to Cancer ..... www.theanswertocancer.org
Cancer Research Institute ..... www.cancerresearch.org
Society for Immunotherapy of Cancer ..... www.sitcancer.org

MELANOMA

A Cure in Sight (ocular melanoma) ..... acureinsight.net
AIM at Melanoma Foundation ..... www.aimatmelanoma.org
American Academy of Dermatology ..... www.aad.org
Melanoma Hope Network ..... www.melanomahopenetwork.org
Melanoma International Foundation ..... www.melanomainternational.org
Melanoma Research Alliance ..... www.curemelanoma.org
Melanoma Research Foundation ..... www.melanoma.org
Mollie's Fund ..... molliesfund.org
Ocular Melanoma Foundation ..... www.ocularmelanoma.org
Outrun the Sun ..... www.outrunthesun.org
The Skin Cancer Foundation ..... www.skincancer.org
Skin of Steel ..... skinofsteel.org
SunWise ..... www.neefusa.org/sunwise

MENTAL HEALTH SERVICES

American Psychosocial Oncology Society Helpline 866-276-7443

NUTRITION

American Cancer Society ..... www.cancer.org
Cancer*Care* ..... www.cancercare.org

LIVESTRONG Foundation ..... www.livestrong.org
OncoLink ..... www.oncolink.org
PearlPoint Nutrition Services ..... www.pearlpoint.org

PAIN MANAGEMENT

American Chronic Pain Association ..... theacpa.org
American Society of Anesthesiologists ..... www.asahq.org
Cancer Pain Research Consortium ..... www.cancerpainresearchconsortium.org
LIVESTRONG Foundation ..... www.livestrong.org
The Resource Center of the Alliance of State Pain Initiatives ..... www.trc.wisc.edu
U.S. Pain Foundation ..... uspainfoundation.org

PRESCRIPTION EXPENSES

Cancer*Care* Co-Payment Assistance Foundation ..... www.cancercarecopay.org, 866-552-6729
Cancer Financial Assistance Coalition ..... www.cancerfac.org
Foundation for Health Coverage Education ..... www.coverageforall.org
GoodDays ..... www.mygooddays.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
Patient Access Network Foundation ..... www.panfoundation.org, 866-316-7263
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
RxOutreach ..... www.rxoutreach.com, 888-796-1234
Singlecare ..... www.singlecare.com, 844-234-3057
Together Rx Access ..... www.togetherrxaccess.com, 800-444-4106

REIMBURSEMENT & PATIENT ASSISTANCE PROGRAMS

Amgen Assist 360 ..... www.amgenassist360.com/patient, 888-427-7478
Bayer Patient Assistance Program 866-575-5002
Bristol-Myers Squibb Access Support ..... www.bmsaccesssupport.bmscustomerconnect.com/patient, 800-861-0048
Bristol-Myers Squibb Patient Assistance Foundation ..... www.bmspaf.org, 800-736-0003
Imlygic Co-Pay and Reimbursement Resources ..... www.imlygic.com/savings-and-support, 888-657-8371
Intron A Patient Assistance Program www.merckhelps.com/intron%20%20a, 800-727-5400
Keytruda Patient Assistance ..... www.merckaccessprogram-keytruda.com/hcc/, 855-257-3932
Merck Access Program ..... www.merckaccessprogram.com/hcc/, 855-257-3932
Merck Helps ..... www.merckhelps.com, 800-727-5400
Opdivo with You ..... www.patientsupport.bmscustomerconnect.com/opdivo-with-you-registration, 855-673-4861
Pfizer Oncology Together ..... www.pfizeroncologytogether.com/patient, 877-744-5675
Pfizer RxPathways ..... www.pfizerrxpathways.com, 844-989-7284
Prometheus IV Bolus Proleukin Inpatient Reimbursement Hotline 877-776-5385
Sylatron Patient Assistance ..... www.merckhelps.com/sylatron, 800-727-5400

STOPPING TOBACCO USE

American Cancer Society ..... www.cancer.org
BecomeAnEx ..... www.becomeanex.org
National Cancer Institute Smoking Quitline 877-448-7848
PLAN MY QUIT ..... www.planmyquit.com
QuitSTART ..... teen.smokefree.gov/sftapps.aspx
Quitter's Circle ..... www.quitterscircle.com
Smokefree.gov ..... smokefree.gov
SmokefreeTXT ..... smokefree.gov/smokefreetxt

sitc
Society for Immunotherapy of Cancer

SITC Cancer Immunotherapy connectED

Your free resource for cancer immunotherapy patient education from the Society for Immunotherapy of Cancer (SITC)

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Access the following free online activities to learn about cancer immunotherapy:

- Download disease specific resources for patients and caregivers (available in English and Spanish)
- Engage in online companion activities for the *Understanding Cancer Immunotherapy* Patient Resource Guides to learn about cancer immunotherapy side effects, immunotherapy in clinical trials and more
- Hear from a cancer survivor and an expert in the field about how the immune system can be harnessed to fight cancer in *The Global Promise of Immunotherapy* webinar

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