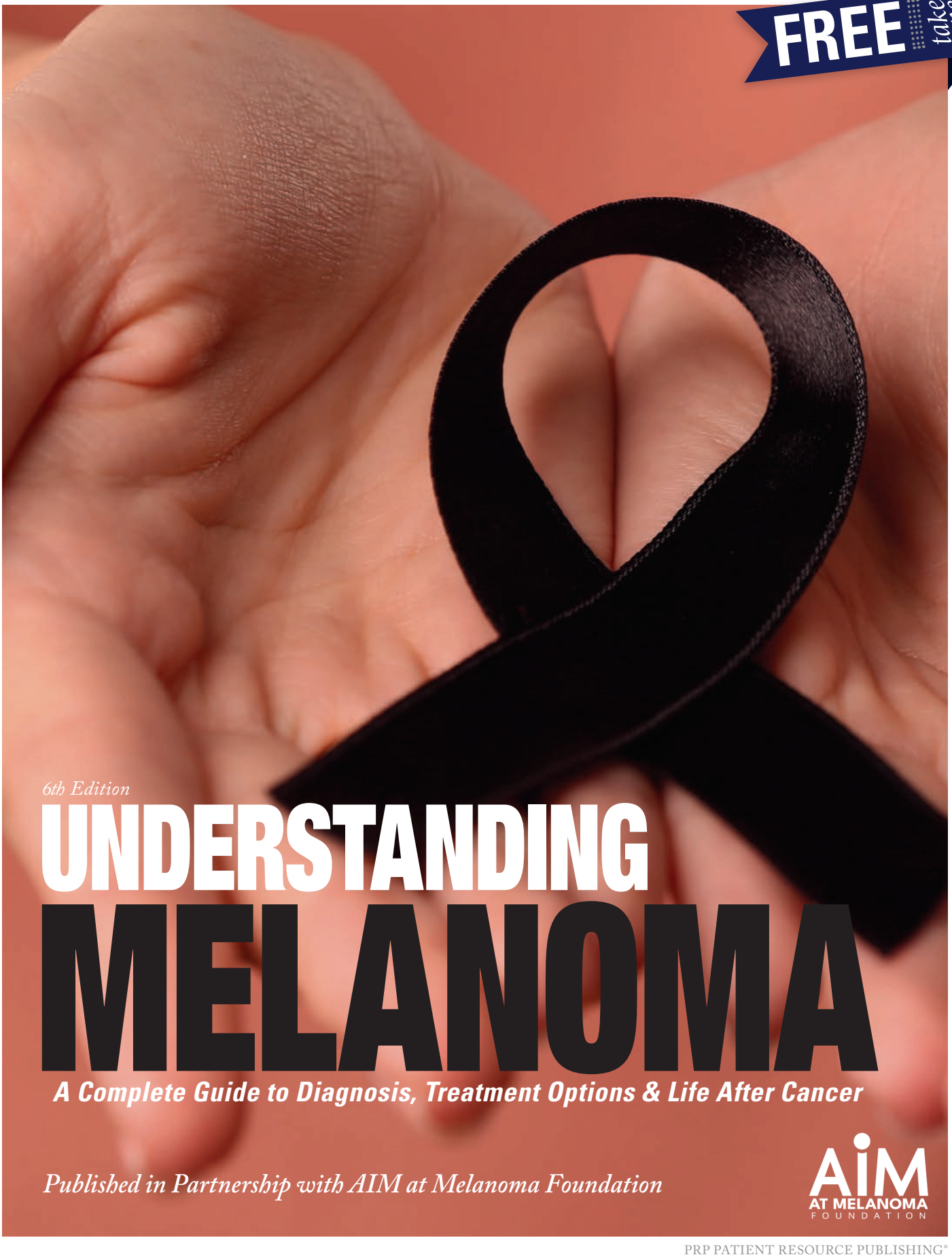
PATIENT RESOURCE

FREE take one



6th Edition

UNDERSTANDING MELANOMA

A Complete Guide to Diagnosis, Treatment Options & Life After Cancer

Published in Partnership with AIM at Melanoma Foundation

AIM AT MELANOMA FOUNDATION

PRP PATIENT RESOURCE PUBLISHING®

AIM AT MELANOMA FOUNDATION

HERE FOR YOU

AIM at Melanoma Foundation is one of the top resources for melanoma patient support, education, research, and advocacy. We strive to provide patients and their caregivers— both the newly diagnosed as well as those looking to gain a greater understanding of their disease—with a full suite of tools to guide them along their treatment journey.

Melanoma Support

Our melanoma medical expert provides accurate answers to a wide range of melanoma questions

Melanoma Education

Our educational symposiums provide patient-friendly information by internationally renowned medical experts

Melanoma Resources

Our website provides reliable, relevant, and current information about all aspects of melanoma

AIM at Melanoma knows that a melanoma diagnosis can be confusing, but no one has to handle it alone.

www.AIMatMelanoma.org

6th Edition

UNDERSTANDING MELANOMA

A Complete Guide to Diagnosis, Treatment Options & Life After Cancer

Scan to download

IN THIS GUIDE

AIM AT MELANOMA FOUNDATION

Published in Partnership with
AIM at Melanoma Foundation
www.aimatmelanoma.org

EDITOR-IN-CHIEF

Charles M. Balch, MD, FACS, FASCO

Professor of Surgery, The University of Texas MD Anderson Cancer Center

Editor-in-Chief, Patient Resource LLC

Former Executive Vice President & CEO, American Society of Clinical Oncology

Past President, Society of Surgical Oncology

PATIENT RESOURCE

Chief Executive Officer	**Mark A. Uhlig**
Editor-in-Chief	**Charles M. Balch, MD, FACS, FASCO**
Senior Vice President	**Debby Easum**
Managing Editor	**Colleen Scherer**
Medical Writer	**Dana Campbell**
Art Director	**Brett McGuire**
Medical Illustrator	**Todd Smith**
Vice President, Business Development	**Amy Galey**
Proofreader	**Lori McCabe**
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 Understanding Melanoma Guide,* visit PatientResource.com, call 913-725-1600, or email orders@patientresource.com.

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

Knowing more about your diagnosis can be empowering

Receiving a melanoma diagnosis can feel shocking and overwhelming. Take a deep breath and learn as much as possible about your diagnosis. Once you have digested the news that you have cancer, make a plan to move forward confidently. The medical professionals caring for you will be a valuable source of information and support. The more you know about the type of melanoma you have, the more empowered you are to make the best decisions for you.

WHAT IS MELANOMA?

Melanoma is a rare type of skin cancer. Also known as cutaneous melanoma, it is the most serious type because it can easily spread into deep layers of the skin as well as to lymph nodes and other organs. Melanoma begins in the cells known as melanocytes, which produce melanin. This substance colors the skin and eyes. Regardless of skin color, anyone can get melanoma, even people who don't ever burn in the sun.

The skin has multiple layers: the epidermis (outer layer), dermis (inner layer) and hypodermis (subcutaneous tissue). Melanoma typically develops in the epidermis (see Figure 1). The neck and face are common sites for melanoma of the skin.

Cutaneous melanoma has four main types:

- Superficial spreading melanoma, the most common type, usually develops from an existing mole.
- Nodular melanoma usually appears suddenly as a bump on the skin.
- Lentigo maligna melanoma typically begins on the face, ears, neck and arms that have been exposed to the sun for long periods of time.
- Acral melanoma (ALM) is found on the palms of the hands, soles of the feet or under the nail bed.

HOW MELANOMAS SPREAD

When DNA in the skin is damaged, it can cause the melanocytes to grow abnormally. When melanocytes grow out of control, they form a tumor and become a melanoma. As melanoma cells form, they can spread to nearby lymph nodes and enter the bloodstream and travel to other parts of the body. Early treatment can stop melanoma before it spreads to nearby lymph nodes or to distant organs. This is why early detection and treatment are important.

Melanoma has two main stages of growth. The first is known as the radial growth phase. This is when the melanoma grows horizontally across the skin and stays within the upper level of the skin (epidermis). At this growth phase, melanomas are not likely to metastasize (spread to other areas).

In the next phase, the vertical growth phase, the melanoma begins to grow down into deeper layers, such as the dermis and hypodermis, as well as up into the epidermis, and the risk for metastasis increases. This occurs because the lymphatic vessels are in the lower dermis and hypodermis. The melanoma cells can use these vessels to spread to lymph nodes. Because of this, the thickness of a melanoma is the most important factor in determining the prognosis.

To predict the risk of spreading, melanomas are classified as:

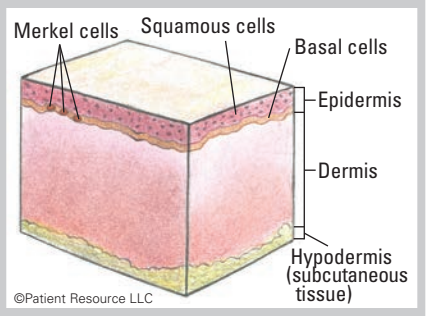
- Thin (less than 1 millimeter, or about the thickness of a credit card)
- Intermediate (1 to 4 mm)
- Thick (more than 4 mm)

For more information about how melanoma is staged, see *Staging*, page 4.

RARE TYPES OF MELANOMA

Besides the skin, melanomas can also occur in mucosal linings, such as the mouth, genitals and anal area, and in the eye. These are rare compared with melanoma of the skin.

FIGURE 1
ANATOMY OF THE SKIN



The eye is composed of several layers of tissues, including the iris, ciliary body and choroid (see Figure 2). Two types of melanoma can form in the eye.

- Uveal melanoma affects the middle layer of the eye, developing in the choroid, iris or ciliary body.
- Conjunctival melanoma develops in the conjunctiva, the clear tissue that covers the white part of the eye and inside the eyelids. Conjunctival melanoma is more rare than uveal melanoma.

In addition, some melanomas may be amelanotic, which lacks pigmentation (color), and desmoplastic, which contains certain cell types.

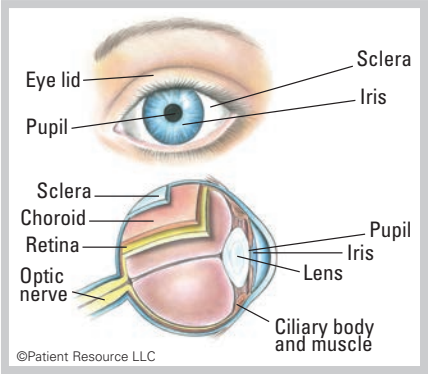
Mucosal melanoma is also rare. It develops in the mucosal lining of the body (a membrane that covers many body cavities and passageways). Because it often begins in concealed areas and causes no specific symptoms, many cases are diagnosed only after they have progressed to an advanced stage. These areas in the body have moist mucosal linings:

- The respiratory tract, in areas such as the sinuses, nasal passages and mouth. Head and neck mucosal melanoma is the most common type.
- The gastrointestinal tract, including the anus and rectum (anorectal).
- The female genital tract, including the vagina and vulva.

Although melanoma can affect the eye and mucosal linings, this guide focuses specifically on cutaneous melanoma, its treatment, side effects and survivorship.

If possible, find a doctor who specializes in diagnosing and treating melanoma. Also consider seeking a second opinion as another specialist may be aware of different treatment strategies and clinical trials. ■

FIGURE 2
ANATOMY OF THE EYE



Survivor advocates melanoma prevention to young adults

Diagnosed at 23 with Stage III melanoma, Mindi Helmandollar-Armatas never imagined she could get cancer at such a young age. The diagnosis left her feeling alone and isolated from her peers. After years of off-and-on treatments, including a few recurrences, she is doing all she can to help prevent anyone from feeling the way she did. Today, Mindi advocates for the importance of melanoma education, prevention and support.

When I was in high school and college, I was a cheerleader. Back then, believe it or not, we were expected to look tan at games. In college, we were even offered free tanning bed sessions to encourage it. I didn't think anything of it because everyone was doing it. And, when you are young, no one thinks about the potential risks of tanning. Many younger people think cancer is an older person's disease, but I quickly learned that melanoma can strike at any age.

After I graduated from college, a mole on the left side of my chest started bleeding. The dermatologist recommended observation for a couple of months. If it didn't go away by then, he said to return. His suggestion did not sit well with me, so I sought a second opinion. The second dermatologist decided it would be best to remove it. When the results came back from pathology, I was stunned. I had Stage III melanoma. I was only 23 years old.

Receiving a melanoma diagnosis left me feeling very alone. Although I had the support of my family, I couldn't talk about it with anyone my age because they couldn't relate.

After having the melanoma removed, I faithfully had scans every three to six months and kept follow-up appointments. At the time, no additional treatment was needed. After five years, I "graduated" from cancer. Although my doctor thought my risk of a recurrence was low, I kept up with my annual skin checks.

Eight years after my original diagnosis, new symptoms emerged. I developed vitiligo on my back. Vitiligo is a disorder that causes patches of skin to lose pigment or color. My eyelashes and eyebrows turned white, and I had a cough that wouldn't go away.

New scans showed a tumor on my lung. Pathology confirmed that the original tumor had metastasized to my lung. My diagnosis was upgraded to Stage IV melanoma.

The lower left lobe of my lung was removed where the tumor was found. Unlike five years earlier, additional post-surgery treatments were available. I decided to try an immunotherapy. Unfortunately, while I was on it, I developed a new tumor in my leg. The drug treatment was not controlling the cancer, so my doctor switched to a targeted therapy. I did not tolerate it well, so we tried a different targeted therapy combination and, fortunately, it worked really well. I then had five and a half good years with very few side effects until a new tumor was found on my right ovary. I had surgery to remove my right ovary and fallopian tube.

I didn't realize it, but a portion of the tumor that was removed from my lung years before had been saved. Therefore, they were able to compare it with this tumor and learned they were a match, which confirmed this was another metastasis from the original melanoma.

Following surgery, I began a new immunotherapy combination. After three treatments, I developed side effects that worsened quickly. The doctor immediately stopped one of the immunotherapies with the hope I could still tolerate the other. So far, I am, and the plan is for me to continue this treatment for another two years.

Everything I've been through has made me want to give back. I feel that educating young people about preventing future melanomas is critical. I use the teaching degree I earned to work with a local teaching hospital to design a curriculum for high school students warning of the dangers of spending too much time in the sun and using tanning beds.

I also partner with AIM at Melanoma to be a mentor to others and provide support. When I was first diagnosed, it was challenging to find resources for people my age, so I'm really happy to be able to help others who find themselves in that situation. I hope to reach all generations and educate them about melanoma prevention.

Today, I am more careful about being in the sun. I wear clothing that is 50 SPF, which is specially designed to block ultraviolet light from the sun. It's amazing the styles available from dresses to work clothes. I also wear a wide-brimmed hat.

My advice to anyone diagnosed with melanoma is to put one foot in front of the other. You cannot look back at what you did or didn't do, and you shouldn't fear the future. You must stay fully in the present. Advocate for yourself. You know your body best. Speak up if you notice something strange, and don't be afraid to get a second or third opinion. I tell everyone, skin safety now can save your life in the future. ■

Treatment options determined after staging melanoma

Your doctor will order a variety of tests to diagnose and learn about the melanoma. The diagnostic tests provide information about the tumor's location and size, whether it has spread to lymph nodes or other organs, any biomarkers and the type or subtype of the cancer.

TABLE 1

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.		

This information will be documented in a pathology report, which includes a description of cells and tissues made by a pathologist based on microscopic evidence. The results allow your doctor to stage your cancer. Staging provides essential information to your medical team. It defines the extent of the disease and helps the team predict outcomes (prognosis, or chance of recovery) as well as determine the best treatment plan for you.

Melanoma is usually staged twice. First, your doctor considers the results of your physical exam and skin biopsy to assign a clinical stage. During a more extensive procedure, the lesion (or as much of it as possible) is removed along with some healthy tissue surrounding it. In a different procedure, some lymph nodes may be removed (see *Sentinel Lymph Node Mapping*, page 6). After reviewing these specimens with and without a microscope and noting key characteristics, a pathologist also considers results from lymph node biopsies and other tissue that was examined. Then a pathologic stage is assigned. Because the pathologic stage is based on more details about the melanoma, this staging is the most accurate and is important in determining appropriate treatment options for your diagnosis.

Both the clinical and pathologic stages of melanoma are classified according to the tumor, node, metastasis (TNM) system developed by the American Joint Commit-

TABLE 2

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.

tee on Cancer (AJCC) (see Tables 1 and 2). This system uses the size and extent of the tumor (T), whether cancer cells are found in nearby lymph nodes (N) and whether the cancer has metastasized, or spread, to other parts of the body (M). The thickness of the primary melanoma is used to classify the melanoma in the T category. Additionally, 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 or present. The node (N) classification is used to describe how many lymph nodes contain melanoma cells.

Be aware that the stage of your cancer may change. If your cancer returns after treatment, diagnostic tests may be repeated to reassess your stage. This is known as restaging. If a new stage is assigned, it is often preceded by an "r" to denote that it has been restaged.

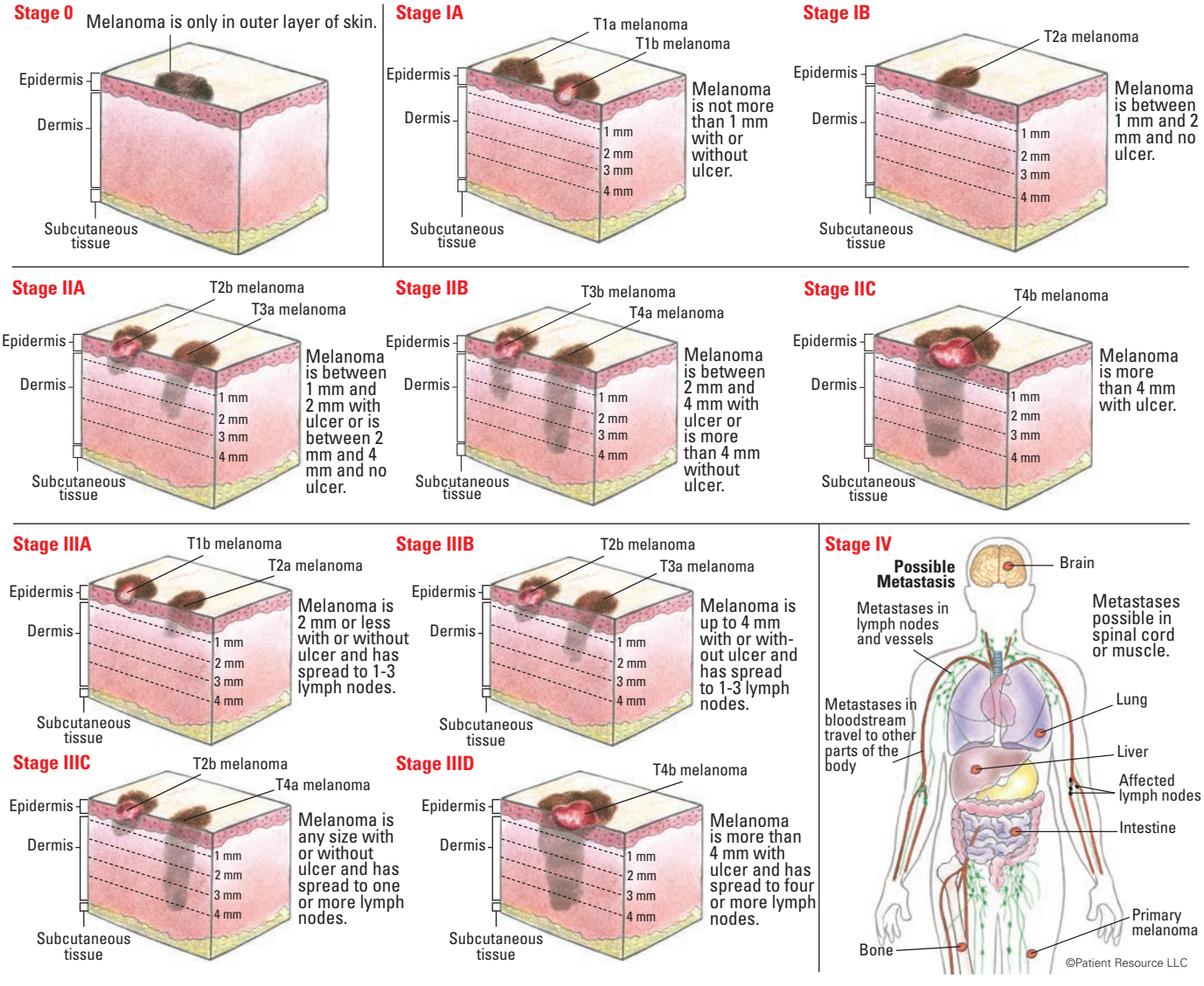
UNDERSTANDING PATHOLOGY TERMS

The results of the diagnostic tests are included in a pathology report that your doctor can share with you. Learning these terms will help you understand your stage of melanoma.

- ***Location:*** where the tumor is found
- ***Thickness:*** the total measurement of the melanoma growth depth beneath the epidermis and the height above the skin
- ***Mitotic rate:*** a measure of how fast cancer cells are dividing and growing
- ***Ulceration status:*** a microscopic evaluation to determine whether the tumor's top skin layer over the melanoma is present and intact (not ulcerated) or broken or missing (ulcerated)
- ***Dermal mitotic rate:*** how many melanoma cells are actively growing and dividing
- ***Peripheral margin status:*** the presence or absence of cancer cells in the normal-looking tissue that was removed from around the tumor
- ***Deep margin status:*** the presence or absence of cancer cells in the normal-looking tissue that was removed from underneath the tumor
- ***Microsatellitosis:*** the presence of tiny satellite tumors in the lymphatic channels that have spread to skin near the first melanoma tumor that can only be seen with a microscope
- ***Vertical growth phase:*** evidence of tumor growth deeper into the skin
- ***Angiolymphatic invasion:*** melanoma cells have grown into blood or lymph vessels
- ***Neurotropism:*** the presence of melanoma cells in or around the nerves in the skin ■

FIGURE 1

ILLUSTRATIONS SHOWING SOME SPECIFIC STAGES OF MELANOMA OF THE SKIN



Test results offer great insight

Melanoma can only be confirmed with a biopsy. However, every melanoma diagnosis is not the same. Because of that, it is extremely important for you and your medical team to learn as much as possible about your type of melanoma. To do that, you will undergo other tests in addition to a biopsy. The results will be crucial in helping your doctors determine the most appropriate treatment plan for you. Understanding your diagnosis begins with being aware of the tests you may have and know why they are important.

BIOPSY

The biopsy you have will depend on the size and location of the melanoma. An excisional biopsy removes an entire lump or suspicious area. An incisional biopsy removes a portion of a lump or suspicious area. A punch biopsy removes a small round piece of tissue about the size of a pencil eraser. A shave biopsy removes a skin abnormality and a thin layer of surrounding skin.

After the biopsy sample is removed, a pathologist, a doctor who has special training in identifying diseases by studying cells and tissues under a microscope, examines it for these and other characteristics:

- The type and subtype of melanoma
- The thickness of the melanoma
- Whether the top skin layer is intact or broken (ulcerated)
- How fast the melanoma cells are growing (mitotic rate)
- Whether the melanoma has spread to lymph vessels, blood vessels, lymph nodes or other organs.

The information obtained from your biopsy will be noted in a pathology report, which is the description of cells and tissues made by a pathologist based on microscopic evidence. It will be used to diagnose and stage your melanoma, and it will guide your doctor in selecting treatment options (see *Staging*, page 4). You may request a copy of your pathology report at any time.

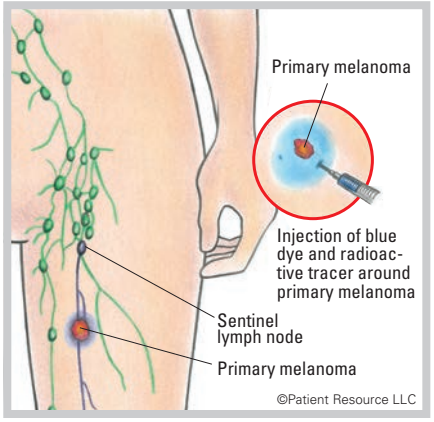
SENTINEL LYMPH NODE MAPPING

In cases where there is an increased risk that the primary melanoma may have spread to nearby lymph nodes, sentinel lymph node (SLN) mapping is recommended (see Figure 1). This procedure tracks the exact path of the bodily fluid (lymph) that carries white blood cells as it drains from the skin surrounding the melanoma to the nearest lymph node. The draining lymph node closest to the melanoma is called the sentinel lymph node.

Accurately identifying which lymph node is the SLN is important for many reasons. The decision to remove lymph nodes often depends on whether melanoma has spread to an SLN. It also helps determine the stage as well as the need for genomic testing, which in turn, guides treatment.

SLN mapping uses lymphoscintigraphy, a special type of imaging technique done in a hospital's nuclear medicine department. Ideally, it is performed on the same day as surgery to remove the melanoma. A radioactive tracer is injected into the skin around the site of the melanoma, and an imaging device that detects radioactivity makes a series of images that show the path of the radioactive material as it travels to the nearest group of lymph nodes. The surgeon injects a special dye into the skin around the site of the melanoma to visually identify the SLN. The surgeon then makes a small incision in the area of the lymph nodes and removes the SLN. The node(s) are carefully examined by a pathologist for the presence of melanoma cells. Because the SLN is the first place to which lymph drains from the site of the melanoma, it is highly unlikely the melanoma will have spread to any other lymph nodes if no cancer cells are found in the SLN.

FIGURE 1
SENTINEL LYMPH NODE MAPPING



GENOMIC TESTING

Many cancers are caused by genetic mutations, which are changes that occur in DNA. While examining your biopsy sample under a microscope, the pathologist may perform genomic, or molecular, testing to check certain genes, proteins or other molecules for mutations. This information could indicate the cancer's behavior, how aggressive it might be and whether it will metastasize (spread). With that knowledge, doctors can choose more personalized treatment options. In certain cancers, for example, mutations have been discovered that can be treated with targeted therapy, a type of treatment specifically designed for certain mutations or determine whether you may qualify for immunotherapy.

Mutations

These and other mutations enable melanoma to be classified into distinct subtypes:

- *BRAF* (pronounced BEE-raff, roughly half of all melanomas contain these mutations)
- *NRAS* (pronounced EN-rass)
- *NF-1*
- *KIT*
- *MEK1* and *MEK2* (pronounced meck, these mutations increase the growth of cancer cells)
- *NTRK* (pronounced EN-track)

Several targeted therapies, such as *BRAF* inhibitors, *MEK* inhibitors, *KIT* inhibitors and tumor-agnostic therapies, are approved by the U.S. Food and Drug Administration

TABLE 1

UNDERSTANDING BIOMARKERS

Type of Biomarker	Findings related to ...
Predictive	Whether a certain treatment approach may be appropriate
Diagnostic	The type of tumor
Others	How aggressive (fast growing) a tumor is; a prediction of long-term survival

to treat some of these mutations (see *Treatment Planning*, page 8). Clinical trials are testing treatments that target other mutations. It is important to understand that not all melanomas have actionable mutations. However, in that case, other treatment options are available.

Biomarkers

Biomarkers, also called tumor markers, biological markers or molecular biomarkers, are produced by cancer cells or other cells in the body in response to cancer. Genomic testing may be used to detect biomarkers such as genes or molecules that can be measured in the blood, plasma, urine, cerebrospinal fluid or other body fluids or tissues. Multiple types of biomarkers offer different information. For example, predictive biomarkers indicate whether an approved drug is appropriate for treating a person's melanoma. Companion diagnostic tests for molecular biomarkers, such as *BRAF* or *KIT*, may indicate that the person may be eligible for future clinical trials. (see Table 1).

Certain cancers are routinely tested for some biomarkers. Your doctor may test for the following.

- Lactate dehydrogenase (LDH) is the accepted serum (blood test) biomarker for melanoma. It is a prognostic biomarker that is measured to determine whether a person has an elevated risk for metastasis. Elevated LDH may indicate the cancer has progressed. A decrease in LDH has been associated with response to immunotherapy because it is released when melanoma cells are damaged or die.
- PD-L1 expression (also called the combined positive score or CPS) may be measured to determine whether the tumor cells or immune cells in the tumor's microenvironment contain a higher level of PD-L1, which may mean that a patient could be a good candidate for immune checkpoint inhibitors (see *Treatment Planning*, page 8). However, testing for this biomarker alone is not sufficient to determine a therapeutic response to immunotherapy in patients with melanoma or other skin cancers.
- Tumor mutational burden (TMB) is an assessment of the number of genetic mutations in a tumor. It can help doctors determine whether a patient may respond to immunotherapy. It is believed that the higher the TMB level, the more likely the patient may be to respond.
- Tumor-infiltrating lymphocytes (TILs) are a type of immune cell that has moved from the blood into a tumor. TILS can recognize and kill cancer cells. Melanomas with higher numbers of TILs and those with TILs inside the tumor have been shown to have a better prognosis and may respond better to therapy. In addition, some treatments result in higher TILs, and they may be a biomarker for response with these therapies. ■

SURVIVOR VOICE ›› Shelly Polak

"Regardless of the type of cancer you have, do your research. Be an advocate for yourself. It's ok if you don't agree with your doctor but look for one that listens to you and treats you as one of the family."

TERMS TO KNOW

Following are melanoma-related words you may hear. If a member of your health care team uses a term you are unfamiliar with, simply ask them to explain. It is important to understand everything you can about your diagnosis and treatment options.

Cutaneous: Related to the skin.

Dermatologist: A doctor specially trained to diagnose and treat skin problems.

In-transit metastasis: A type of metastasis in which the cancer spreads from the primary tumor through a lymphatic vessel and begins to grow in the lymphatic vessel before it has reached the nearest lymph node.

Lymphocyte: A type of immune cell (white blood cell) in lymph tissue and blood that helps the immune system fight infections and cancer. The main types are B-lymphocytes (B-cells) and T-lymphocytes (T-cells).

Melanocytes: A cell in the skin and eyes that produces and contains the pigment called melanin, which gives the skin its tan or brown color. Melanin protects the deeper layers of the skin from some harmful effects of the sun.

Microsatellite tumor: Cells that have spread very near the primary tumor that can be seen only with a microscope.

Pigment: A substance that gives color. In the body, the pigment melanin gives color to the skin, eyes and hair.

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

Sun protection factor (SPF): A rating scale for sunscreen products indicating how long the product provides protection against sunburn. The higher the SPF number, the more protection it provides.

Topical: Refers to medication applied to the skin or mucous membranes, usually as an ointment, cream, gel, etc.

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

Ultraviolet (UV) radiation: Invisible rays from the sun, tanning beds and sun lamps that can cause sunburn, premature aging of the skin, melanoma and other skin cancers and eye problems.

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

Progress in research is leading to better outcomes

The landscape of treating melanoma has changed dramatically in the past 10 years. Research and clinical trials have led to more effective treatment options, offering patients more hope. People are surviving longer after a melanoma diagnosis and enjoying a higher quality of life.

Understanding the options available to treat your melanoma is essential. Working closely with your medical team to learn about your choices while having honest conversations about each option and the potential side effects will help you feel more comfortable with the treatment decisions you make.

TREATMENT BASICS

Treatment for melanoma focuses on whether the treatment is local (confined to one area) or systemic (which travels somewhere else in the body), whether it's given by injection, infusion or orally as a pill, whether it's given before or after surgery and the order in which it is given.

- Local treatments target specific areas of the body and include surgery and occasionally radiation therapy. Some treatments involve injecting the drug directly into the lesion or topical application to the skin close to a melanoma.
- Systemic treatments, including drug therapies such as targeted therapy, immunotherapy and chemotherapy, travel through the bloodstream. They can help destroy melanoma cells that may be hiding in other places, such as the liver, lungs or bones. These hidden cancer cells are usually too small to detect with laboratory testing or imaging studies.
- Oral treatment is given in pill form.
- Neoadjuvant treatment is given before surgery to shrink a tumor so it can be more easily or safely removed with surgery.
- Adjuvant treatment is given after primary treatment, which is usually surgery.
- First-line therapy is the first treatment given.
- Second-line therapy is given when the first-line therapy doesn't work, is no longer effective or has side effects that are not well tolerated.

Most people will receive more than one type of treatment. Following are descriptions of some common types of treatment.

SURGERY

Surgery is usually the first treatment used for early stage local and regional melanomas and is also used for some metastatic melanomas. Often, surgery is the only treatment needed.

The two main types of surgery for melanoma include the following:

- A wide excision is used to remove the melanoma and an additional portion of normal-looking tissue, which is called a surgical margin (see Figure 1). The thicker the melanoma is, the larger the surgical margin needed. The tissue removed from the margin will be carefully examined by a pathologist under a microscope to determine whether any cancer cells remain. More surgery may be needed if the margins contain cancer cells.
- A lymph node dissection is a type of surgery that is sometimes performed to remove lymph nodes in the region after a biopsy if pathology results show a melanoma spread (metastasis) in the sentinel lymph node (see *Understanding Your Diagnosis*, page 6). At the end of the procedure, the surgeon will likely place drains into the area to collect any blood or fluid from the region where the lymph nodes were removed. The incision will then be closed, and the wound will be covered by a dressing. Your health care team will give you information for incision and drain care, if applicable.

DRUG THERAPY

Drugs are a type of systemic therapy used to destroy cancer cells, prevent progression or slow the cancer's growth. Drug therapy may be given intravenously (IV) through a vein, subcutaneously into the skin, or orally, and it may be used alone or in combination with other drug therapies or other treatment options (see Figure 2).

Most drug therapies are approved for unresectable (inoperable) and metastatic melanoma, which has spread to other organs. However, progress has been made with treating earlier stages of melanoma as well such as Stages II and III. Drug therapies are approved as first-line and second-line therapy. When and which drug therapy is used depends on the stage of the melanoma, the risk of recurrence, whether there was previous treatment and whether there was neoadjuvant or adjuvant treatment. Immunotherapy and targeted therapies may now be used as second-line therapy for Stages II and III.

The drug therapies used to treat melanoma are the following.

Targeted therapy uses drugs or other substances to identify and attack specific types of cancer cells. Unlike chemotherapy, which attacks healthy cells as well as cancer cells, targeted therapy is designed to affect only

FIGURE 1

RECOMMENDED SURGICAL MARGINS

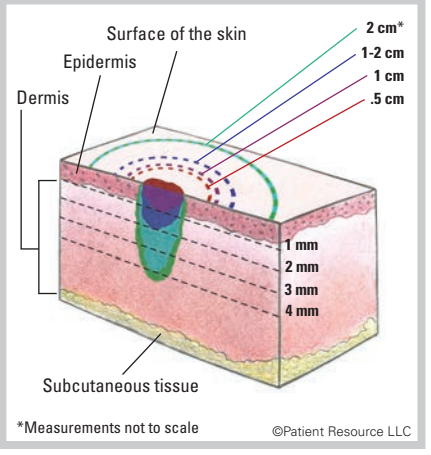
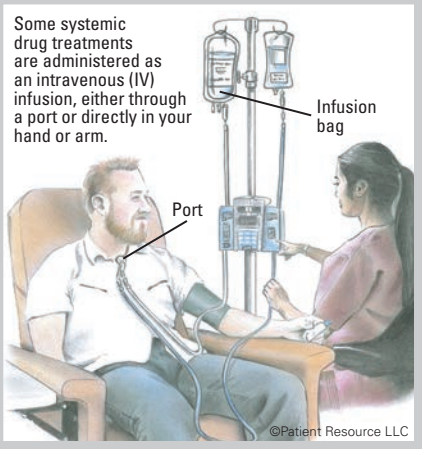


FIGURE 2

SYSTEMIC DRUG THERAPY



cancer cells. Targeted therapy drugs approved for melanoma are known as signal transduction inhibitors, which block signals passed between one molecule and another. Blocking the signals can kill some cancers. Targeted therapy drugs may be given alone or in combination with other drug therapies. Taken orally, targeted therapies may be used to treat both Stage III and Stage IV melanomas that are inoperable or metastatic.

Several mutations (abnormalities) in genes and proteins have been found in melanoma for which targeted therapies have been approved. A mutation in the *BRAF* gene has been found in many patients with melanoma. This mutation can cause melanoma cells to produce proteins that help cancer cells to grow. A type of targeted therapy known as a *BRAF* inhibitor can be used as part of a regimen to treat melanomas with this mutation. *BRAF* inhibitors attack the *BRAF* protein directly and can shrink or slow the growth of tumors in melanoma that has spread or can't be completely removed.

Another target is the *MEK* protein. Drugs that block *MEK* proteins are called *MEK* inhibitors and can also be used as part of a regimen to treat melanomas with *BRAF* mutations.

For patients with a *BRAF* mutation, doctors could prescribe a combination of a *BRAF* and *MEK* inhibitor.

Another mutation found in some melanomas is the *NTRK* gene. The treatment approved for this mutation is considered tumor-agnostic because it is approved to treat the *NTRK* fusion regardless of the type of cancer or where it is in the body.

In some rare melanomas, a mutation in the *KIT* gene has been found and these can be treated with *KIT* inhibitors.

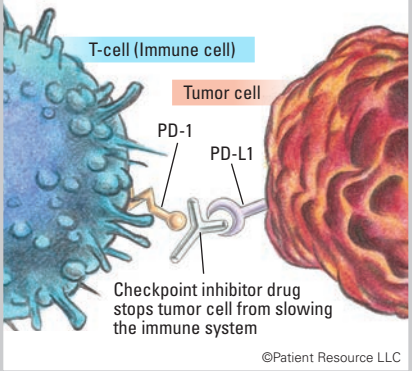
Immunotherapy helps the body's own immune system recognize and destroy cancer cells. By training the immune system to respond to cancer, this strategy has the potential for a response that can extend beyond the end of treatment. Most are given intravenously (IV), but some may be used as local treatment that is topical. Immunotherapy can be given as the primary treatment, also known as first-line therapy, for melanomas that cannot be removed surgically or that are metastatic. Some immunotherapy drugs may be combined and used as second-line treatment for patients who have not responded well to initial immunotherapy.

Immunotherapies approved by the U.S. Food and Drug Administration include monoclonal antibodies (mAbs), such as immune checkpoint inhibitors, as well as cytokines, immunomodulators, oncolytic viruses, tumor-infiltrating lymphocyte (TIL) therapy and a bispecific T-cell engager.

FIGURE 3

IMMUNE CHECKPOINT INHIBITORS

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



Monoclonal antibodies (mAbs) are antibodies made in a laboratory that target specific tumor antigens found on cancer cells. Some mAbs mark cancer cells so that the immune system will better recognize and destroy them. Other mAbs bring T-cells, a type of white blood cell, close to cancer cells, helping the immune cells kill the cancer cells. They can also carry cancer drugs, radiation particles or laboratory-made cytokines (proteins that enable cells to send messages to each other) directly to cancer cells.

Immune checkpoint inhibitors are a type of mAb that helps the immune system better recognize that melanoma cells are foreign to the body, which allows the immune cells to better destroy the cancer (see Figure 3). The immune checkpoint inhibitors are monoclonal antibodies that block the receptors of PD-1 (programmed cell death protein 1), PD-L1 (programmed cell death-ligand 1) and CTLA-4 (cytotoxic lymphocyte antigen 4), and thereby inhibit their activating signal to the cell. They may be given intravenously or by subcutaneous injection.

Cytokines are substances secreted by certain cells of the immune system that boost the whole immune system. They can be used alone or in combination with other treatments to produce increased and longer-lasting immune responses. Cytokines aid in immune cell communication and play a big role in the full activation of an immune response. This approach works by introducing large amounts of laboratory-made cytokines to the immune system to promote nonspecific immune responses as a systemic therapy.

Interleukins help control the activation of certain immune cells to better destroy the cancer.

Oncolytic virus immunotherapy uses viruses that directly infect tumor cells to cause an immune response. It is typically given as a local treatment by injection directly into the tumor.

Tumor-infiltrating lymphocyte (TIL) therapy is in a class of immunotherapy known as adoptive cellular therapy. It uses a patient's own lymphocytes (a type of white blood cell) as treatment for cancer. Some lymphocytes can recognize a tumor as abnormal and penetrate it. TIL therapy removes these specific lymphocytes from a patient's tumor. They are multiplied in a

Continued on page 10

Stay on time taking your medication

Some melanoma patients have the option of taking targeted therapy medications in the comfort of their home. These therapies are typically oral medications that you are responsible for taking on time, every time, also known as medication adherence. Correctly taking your medication is important because it can influence the effectiveness of the therapy and the management of side effects.

If your medications are not taken exactly as prescribed, the consequences can lead to unnecessary or unrelieved side effects, physician visits, hospitalizations and even cancer progression. Talk with your doctor before treatment begins about how and when to take your medication. It can be challenging to remember to take your medications, especially if you feel overwhelmed or confused by your treatment plan. Don't be afraid to ask for help managing your treatment at home.

lab and given back to the patient to help kill cancer cells. It is approved as second-line therapy for melanoma that can't be removed by surgery or metastatic melanoma that was previously treated with an immune checkpoint inhibitor.

A bispecific T-cell engager was recently approved for inoperable or metastatic uveal melanoma. It targets the human leukocyte antigen (HLA) and attaches to a T-cell, which is part of your immune system (see Figure 4). This treatment helps the immune system better find and kill cancer cells.

Chemotherapy uses powerful drugs to kill rapidly multiplying cells throughout the body. It is rarely used alone. When used, it is typically part of a combination of other drug therapies or if all other drug therapies have failed. A new chemotherapy has been approved for uveal melanoma that has spread to the liver.

RADIATION THERAPY

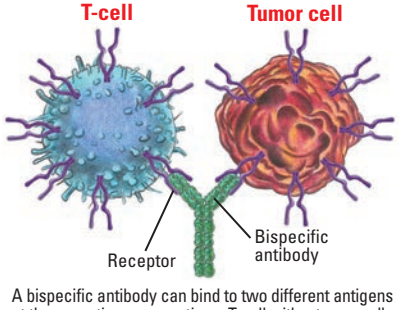
Radiation therapy uses high-energy radiation to destroy cancer cells and shrink tumors. Though radiation therapy is not typically used to treat the original melanoma, it may be given to areas where lymph nodes were surgically removed or after surgery to remove the melanoma if the risk of recurrence is considered to be high.

It may also be given to relieve symptoms related to the spread of melanoma, particularly to the bones or brain. When given to the brain, whole-brain radiation therapy or localized stereotactic radiation therapy may be used. Stereotactic radiation is given to a specific area of the body in a high dose.

Types of radiation used include external-beam radiation therapy, which uses a machine outside the body to send radiation toward the cancer, intensity-modulated radiation therapy, image-guided radiation therapy and stereotactic radiosurgery or stereotactic radiotherapy.

FIGURE 4

BISPECIFIC T-CELL ENGAGER



A bispecific antibody can bind to two different antigens at the same time, connecting a T-cell with a tumor cell. A T-cell is a type of white blood cell, which is part of the immune system. Normally, a T-cell can only interact with a tumor cell if it finds an antigen on a tumor cell and connects to it. A bispecific antibody skips this step and brings the T-cell directly to the tumor cell to release chemicals or other therapeutics to attack the tumor cell.

CLINICAL TRIALS

The advances in treating melanoma are due to clinical trials. New therapies are continually being researched and clinical trials need volunteers. Ask your doctor if you should consider this option as a first-line treatment or at any other time during your treatment (see *Clinical Trials*, page 11).

UNDERSTANDING RESISTANCE

Recent advances in therapies have been game-changers in treating melanoma. However, it is known that cancer can become resistant to these therapies. This means the disease may stop responding after treatment has been underway for a length of time.

Resistance is believed to develop when some cancer cells survive after being treated. The surviving cells recover and begin to grow and divide again, often with new genetic changes that the initial treatment is not designed to target. Research is underway to understand how and why resistance develops and to find ways to prevent it or slow it down to extend the effectiveness of the original therapy.

If resistance has occurred, new tests may be performed to determine whether new genetic alterations have developed. If they have, a different drug may be available to treat it. Talk with your doctor about the possibility of developing resistance to any immunotherapies or targeted therapies you may take.

RECURRENCE OR SECONDARY MELANOMA

Despite successful treatment, melanoma can return months or years later. Known as a recurrence, melanoma can return to the same area as the original melanoma, in surrounding skin or tissues, in lymph nodes or at other sites in the body (known as distant recurrence).

Once you've had melanoma, you are at risk of having a second melanoma. A new melanoma can appear anywhere on your body not related to the original melanoma. Keeping follow-up appointments and doing skin exams are important for detecting a recurrence early so that treatment may begin as soon as possible (see *Follow-up Care*, page 14). ■

SURVIVOR VOICE ›› Kathy Sallee

"My best advice to others diagnosed with skin cancer is to understand your disease and available treatments so you can make good decisions for yourself. And, of course, I advise everyone to stay out of the sun without protection and avoid tanning beds. It's not worth risking your life for a good tan."

WORDS TO KNOW

Some of the treatment terms your medical team uses may be confusing. These explanations may help you feel more informed as you make the important decisions ahead.

First-line therapy is the first treatment used.

Second-line therapy is given when the first-line therapy does not work or is no longer effective.

Standard of care refers to the widely recommended treatments known for the type and stage of cancer you have.

Neoadjuvant therapy is given to shrink a tumor before the primary treatment (usually surgery).

Adjuvant therapy is additional cancer treatment given after the primary treatment (usually surgery or radiotherapy) to destroy remaining cancer cells and lower the risk that the cancer will come back.

Local treatments are directed to a specific organ or limited area of the body and include surgery and radiation therapy.

Systemic treatments travel throughout the body and are typically drug therapies, such as gene therapy, targeted therapy and immunotherapy.

In situ refers to the cancer's original place. For example, with carcinoma in situ (stage 0 cancer), abnormal cells are found only in the place where they first formed. They have not spread.

Progression the cancer is growing or spreading without going away after treatment.

Progression-free survival is the length of time during and after the treatment of cancer that a patient lives with the disease, but without worsening.

Partial response means the cancer responded to treatment but is still present.

Complete response is the disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured.

Nodal recurrence happens when the melanoma returns in lymph nodes.

Overall survival is the amount of time a patient survives after their diagnosis or the start of treatment.

Understanding the basics of clinical trials

Every advance in melanoma treatment is the result of a clinical trial. Known as treatment trials, these research studies evaluate how well an intervention, such as a drug or combination of drugs, device, procedure, delivery system or strategy, works compared to the current standard of care. Along with having access to a treatment that otherwise may not be available, participants who volunteer for clinical trials are doing a great service. They are contributing to the future of cancer care.

As with any cancer treatment, those used in clinical trials present potential risks. Before you consider clinical trials as a treatment option, it is essential to learn about them so you can feel well-informed.

SAFETY

Clinical trials are designed with strict safety measures in place that were established and are enforced by the U.S. Food and Drug Administration. Although many trials are focused on the development of new treatments, the majority of cancer clinical trials include treatments that are already approved, sometimes alone and sometimes in combination with new therapies. Additionally, multiple guidelines and regulations are followed to ensure that all clinical trial participants are protected throughout the process. This is done through several levels of safeguards and a set of rules called a protocol. All participating clinics, hospitals, universities, cancer centers and medical offices, regardless of their size or location, must follow the same protocol.

TIMING

Clinical trials are often thought of as a last-ditch effort, something that is tried only after all other treatments have failed. That is not true. Depending on the diagnosis, a clinical trial may be considered as a first-line treatment. If your doctor has not talked with you about clinical trials yet, bring it up. You deserve to know about all of your treatment options.

SEARCHING FOR A TRIAL

Many clinical trials take place at the same time, making it difficult for your doctor to know about all of them. While your health care team is exploring potential trials, you can look for them online. Before you begin, have your exact diagnosis, pathology report and details of your current or prior cancer treatments on hand to help determine whether you meet the basic eligibility criteria. Then, start by using the list of clinical trial sites below. Your doctor may recommend additional sites. If you find a trial that interests you, discuss it with your health care team.

LOCATION

You do not have to live near a major cancer center to be involved in a clinical trial. Actually, trials take place all around the country — in nationally known cancer centers in major cities, university medical centers, regional hospitals and even oncologists' offices. And, thanks to advances in technology, many trials today use telehealth so you do not always have to travel for appointments or sign the Informed Consent form in person.

INFORMED CONSENT

If you find a trial, you will be given a document called Informed Consent. Informed Consent explains the protocol for that clinical trial in detail, including the trial's eligibility criteria, the tests and procedures, the medications and dosages, possible side effects, the schedule to accommodate the tests and appointments that are required for the trial, and the length of the study. You will be asked to read and sign the Informed Consent form before moving forward with the trial. It is important to note that even after you sign and begin the trial, you can withdraw at any time, for any reason.

Great strides in treating melanoma continue to be made through these studies, and ongoing research is essential to learning more about prevention and a cure. Melanoma-focused clinical trials researching targeted therapies, immunotherapies, CAR T-cell therapy, vaccines and more are currently underway. Ask your doctor if you should consider a clinical trial at any time during your treatment. ■

SURVIVOR VOICE » Bob Heffernan

"Never be afraid of research, especially if you have a rare cancer type. The researchers all talk to each other, and they know more about what's in the pipeline way before your oncologist does. You need to keep going as long as you can because you never know when that next breakthrough will be discovered. I joined NIH's clinical trial for a revolutionary treatment that involved tumor-infiltrating lymphocytes (TIL), which are immune cells that move from the blood into a tumor to try to attack it."

MYTHS vs FACTS

Myths about clinical trials can easily influence a person's decision when exploring this potential treatment option. See some myths debunked below.

MYTH: Participants may receive a placebo ("sugar pill").

FACT: Placebos are rarely used in cancer clinical trials. Participants will never receive a placebo instead of treatment.

MYTH: Participants are treated like "guinea pigs."

FACT: Most clinical trial participants report they had a good experience with clinical trials and felt they were treated with respect and dignity.

MYTH: Clinical trials are a last resort.

FACT: It is common for many people to feel this way, but trials today are open to patients at every stage of disease. Depending on the diagnosis, a clinical trial may be considered as a first-line treatment.

MYTH: The treatment cost of a clinical trial is not covered by health insurance.

FACT: Many insurers cover the normal costs of treatment in cancer clinical trials, and some states have mandatory coverage. And, Medicare covers most of the costs of care in a clinical trial.

CLINICAL TRIAL RESOURCES

- **Clinicaltrials.gov** ..... www.clinicaltrials.gov
- **National Cancer Institute** ..... www.cancer.gov/clinicaltrials, 800-422-6237

Be proactive about side effect management

One of the most common fears people have about cancer treatment is the potential side effects. Although most cancer and its treatments cause side effects, you will be surrounded by a health care team who will help you manage the symptoms from the moment you receive your diagnosis. You are encouraged to talk with your medical team before treatment begins about possible side effects and what to do if they occur.

Communicating honestly about how you feel, both physically and emotionally, is an important step you can take. The sooner you share your concerns, the quicker they can be managed. It's also important to be honest with your family, caregiver and medical team about the side effects you have and their level of severity.

COMMON PHYSICAL SIDE EFFECTS

Some physical side effects can be disruptive while others are an annoyance (see Table 1). Ask your doctor how you can recognize symptoms, when they might occur and ways you can help manage them. Managing side effects allows you to stay on treatment without interruption, making it easier for your body to handle treatment and generally improves your well-being.

It may comfort you to know that people often respond differently to the same treatments, so it is important to discuss with your doctor which side effects you may experience. Keeping track of your side effects helps your doctor to better manage them.

POTENTIALLY SEVERE SIDE EFFECTS

Some of the drug therapies used may be accompanied by side effects that can become serious and potentially life-threatening. Make sure you know whom to contact and how, especially after hours. Contact the appropriate person immediately if you experience any symptoms. Prompt treatment is necessary to keep these symptoms from becoming fatal.

TABLE 1

SOME COMMON SIDE EFFECTS OF MELANOMA TREATMENT*

Side Effect	Description or Symptoms
Abdominal pain	Cramping, dull aches
Constipation	Difficulty passing stools or having less frequent bowel movements compared to usual bowel habits
Decreased appetite	Eating less than usual, feeling full after minimal eating, not feeling hungry
Diarrhea	Frequent loose or watery bowel movements that are commonly an inconvenience but can become serious if left untreated
Edema	Swelling caused by excess fluid in body tissues
Fatigue	Tiredness that is much stronger and harder to relieve than the fatigue an otherwise healthy person has
Fever	Raised body temperature that could signal an infection
Hypertension	Abnormally high blood pressure
Hypotension	Abnormally low blood pressure
Lymphedema	Fluid buildup from lymph node removal that causes swelling
Nausea and vomiting	The feeling of needing to throw up and/or throwing up
Neutropenia	Low white blood cell count that increases the risk of infection
Pain	Pain and aches that occur in the muscles, bones, tendons, ligaments or nerves
Photosensitivity	A condition in which the skin becomes very sensitive to sunlight or other forms of ultraviolet light and may burn easily
Respiratory problems	Shortness of breath (dyspnea) with or without cough, upper respiratory infections
Skin reactions	Rash, redness and irritation, or dry, flaky or peeling skin that may itch
Sleep problems	Inability to fall asleep or stay asleep, excessive sleepiness
Weight loss	Losing weight without trying

*These are not all the possible symptoms or side effects of treatment for melanoma. Talk to your doctor about any side effects you experience.

Not all potentially severe side effects are ones you can recognize. Some are identified only on lab work and imaging results, so it is crucial to stay on schedule with your follow-up appointments for monitoring. Some potentially severe side effects include the following:

Immune-related adverse events (irAEs) are associated with certain immunotherapy drugs. They can occur if the immune system becomes overstimulated by treatment and causes inflammation in one or more organs or systems in the body (see Table 2). Some irAEs can develop rapidly, becoming severe and even life-threatening without swift medical attention.

Some irAEs can be detected early during routine laboratory and imaging tests even before you can feel symptoms, which makes it crucial to stay on schedule with all medical appointments. Contact your medical team if symptoms arise between appointments and remain alert to the possibility of irAEs for up to two years after completing immunotherapy.

Infection can occur as a result of surgery, a low white blood cell count (neutropenia/leukopenia) or other factors. Contact your doctor immediately – do not wait until the next day – if you have any of these symptoms: oral temperature over 100.4°F, chills or sweating; body aches, chills and fatigue with or without fever; coughing, shortness of breath or painful breathing; abdominal pain; sore throat; mouth sores; painful, swollen or reddened skin; pus or drainage from an open cut or sore; pain or burning during urination; pain or sores around the anus; or vaginal discharge or itching.

Infusion-related reactions most frequently occur with drug therapies, including im-

Resources for Side Effect Management

AIM at Melanoma provides side effect management sheets so patients and caregivers can recognize and manage their symptoms.

For Symptom & Side Effect Management Resource Guides, go to:

www.aimatmelanoma.org/melanoma-learning-center/side-effect-management-guides

munotherapies that are given intravenously (IV) through a vein in your arm or through a port, usually soon after exposure to the drug. Reactions are generally mild, such as itching, rash or fever. Other symptoms, such as shaking, chills, low blood pressure, dizziness, throat tightness, skin rash or flushing, breathing difficulties and irregular heartbeat, can be serious or even fatal without rapid medical intervention.

Cytokine release syndrome (CRS) occurs when immune cells are stimulated by treatment and release too many cytokines into the blood stream. A cytokine is a type of protein that is made by certain immune and non-immune cells, and it is a part of a healthy immune system. These small proteins help control the growth and activity of your blood cells and immune cells. Some cytokines stimulate the immune system and others slow it down. CRS can lead to high fever, inflammation, fatigue and nausea that can be severe and damage multiple organs. Without swift medical treatment, CRS can be fatal. ■

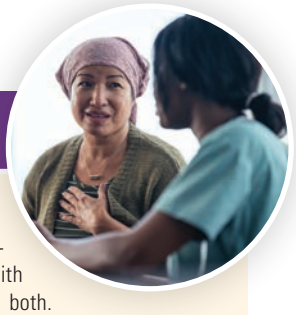
TABLE 2

IMMUNE-RELATED ADVERSE EVENTS (IRAES)*

Side Effect	irAE	Symptoms & Signs
Cardiovascular	**Myocarditis**	Chest pain, shortness of breath, leg swelling, rapid heartbeat, changes in EKG reading, impaired heart pumping function
Endocrine	**Endocrinopathies**	Hyperthyroidism, hypothyroidism, diabetes, extreme fatigue, persistent or unusual headaches, visual changes, alteration in mood, changes in menstrual cycle
Gastrointestinal	**Colitis**	Diarrhea with or without bleeding, abdominal pain or cramping, bowel perforation
Liver	**Hepatitis**	Yellow/orange-colored skin or eyes (jaundice), nausea, abdominal pain, fatigue, fever, poor appetite
Nervous system	**Neuropathies**	Numbness, tingling, pain, a burning sensation or loss of feeling in the hands or feet, sensory overload, sensory deprivation
Neurologic	**Encephalitis**	Confusion, hallucinations, seizures, changes in mood or behavior, neck stiffness, extreme sensitivity to light
Pulmonary (lungs)	**Pneumonitis**	Chest pain, shortness of breath, unexplained cough or fever
Renal (kidneys)	**Nephritis**	Decreased urine output, blood in urine, swollen ankles, loss of appetite
Skin	**Dermatitis**	Rash, skin changes, itching, blisters, painful sores

*Body systems listed in alphabetical order. Talk to your doctor about what to expect.

Managing Emotional Side Effects



Receiving a cancer diagnosis can be so unsettling that it affects your mental health. You may go from being scared or angry to anxious to depressed, sometimes all in a day. Don't be surprised at the frequency of your mood changes or by how intense your feelings are. Everything you feel is normal, and it is important to approach these emotional side effects as you would physical side effects. Before you become overwhelmed, find out how to get relief and remember that you're not alone.

Take advantage of the resources around you, starting with your family, friends and community. Your supportive care team can connect you with support groups, advocacy organizations, counselors, psychologists, psychiatrists and other specialists. Some organizations offer one-on-one buddy programs that pair you with another person who has your type of melanoma. It can be comforting to share your feelings with people who can relate.

Many people believe that having a positive attitude makes a difference. Even with the best intentions, be aware that some days will be more difficult than others. Be kind to yourself and accept that it is okay to have the occasional down day.

Following are some of the common emotions you may experience and suggestions for ways to feel better. However, it is critical to notify your health care team if you are unable to follow treatment due to extreme emotional distress; have excessive crying or continued feelings of hopelessness or despair; are unusually angry or irritable; are withdrawing and isolating yourself from family and friends; or feeling worthless. Get immediate medical attention for thoughts of death or suicide.

Anxiety can begin as soon as you receive your diagnosis and may ebb and flow. Moderate to severe anxiety is often treated with medication, therapy or a combination of both. Share your feelings with a trusted friend or by journaling.

Depression is a psychological reaction to your situation as a whole. Certain ongoing treatments, can cause or contribute to depression. Don't avoid talking to your doctor about it because you think depression is just part of having cancer — it isn't. Talk with a member of your health care team if you feel hopeless, helpless or numb.

Doubt about the meaning of life and your purpose may arise. Some people find strength from family, friends, the community or spirituality. It may also help to open up to a counselor or support group.

Fear about the treatment, side effects and your prognosis is common. Making plans may become difficult because every ache and pain triggers a concern. Surround yourself with a medical team you trust and a solid support system, and do your best to take it one day at a time.

Guilt may occur if you feel you've been a burden to loved ones or if you wonder why you survived when others with similar conditions didn't. Rely on the support of non-judgmental close friends and family members, and consider talking with a therapist about these feelings.

Scanxiety is a word that describes the anxiety that can happen when you are awaiting results from imaging scans, laboratory tests or examinations. Scanxiety can be extremely stressful, and it may help to find ways to manage it. Set expectations with your medical team so you can know when to expect results instead of being left waiting and wondering. Keep your mind occupied with things you enjoy, such as reading, exercising, social activities or meditation. Staying busy gives you less time to worry.

Stay in tune with your skin health

Completing treatment for your primary melanoma is a triumph. You have partnered with your health care team and made it through treatment to reach this milestone. Although it is a reason to celebrate, it is important to realize that your journey isn't over. You are at risk for a recurrence or a new melanoma, which makes follow-up care a necessary and critical part of your life.

Recurrence is when melanoma cells go undetected and survive treatment, then multiply enough to form a tumor. Your original diagnosis may offer some insight into your overall risk for recurrence. For example, early-stage (thin) melanomas generally tend to recur less often but over a longer period of time. Later-stage melanomas recur more often and over a shorter time period. For all stages, the risk of recurrence generally decreases over time, though it is never gone completely.

A new melanoma is different from a recurrence. Referred to as a new primary melanoma, this is one that appears somewhere on your body that is not related to the original melanoma. It is not uncommon to have a second melanoma of the skin due to the same risk factors that caused the first melanoma.

You can be proactive about your skin health in the following ways. Share this information with your friends and family also as everyone needs to monitor their skin.

SELF-EXAMS

Performing self-exams involves checking yourself on a regular basis for any moles or spots that change shape, size or color. To confidently notice things that look or feel out of the ordinary, you have to know your body. Some places are impossible to see on your own. Ask a loved one or your doctor to check out those hard-to-see areas.

Keep in mind that although you will be familiar with what the melanoma from your original diagnosis looked like, a recurrence or new melanoma may not look the same. The images on the "ABCDE" rule will help you identify the common differences between a melanoma and a mole that is harmless (benign) (see Figure 1).

Melanoma can spread to lymph nodes, so a self-exam also includes feeling around for any abnormal lumps.

If you are unsure of anything or something concerns you, contact your doctor right away. Don't wait until your next regularly scheduled doctor's appointment.

PREVENTIVE MEDICAL APPOINTMENTS

Your doctor should provide you with a schedule to help you stay on track with follow-up appointments. The frequency of visits will be customized for you, based on the following:

- Your previous diagnosis and stage
- Type of treatment you received
- National recommended guidelines
- Your risk factors, such as a fair complexion, light-colored eyes, blonde or red hair, a history of blistering sunburns, a tendency to burn or freckle, large moles or many small moles and a family history of melanoma

During these check-ups, your doctor will conduct a thorough physical examination, paying special attention to your skin, watching for long-term side effects (called late effects) and any areas of concern that you mention. Because melanoma can spread to lymph nodes, your doctor will check those closely, too.

Blood tests, regular X-rays and other imaging studies are not usually done for earlier-stage melanoma follow-up, but they may help if you have signs or symptoms of a possible recurrence. If you are at a higher risk of having your melanoma return, your doctor may order one or more of these imaging studies:

- Chest X-ray
- Computed tomography (CT)
- Positron emission tomography (PET)
- Combined PET/CT
- Magnetic resonance imaging (MRI) of the brain

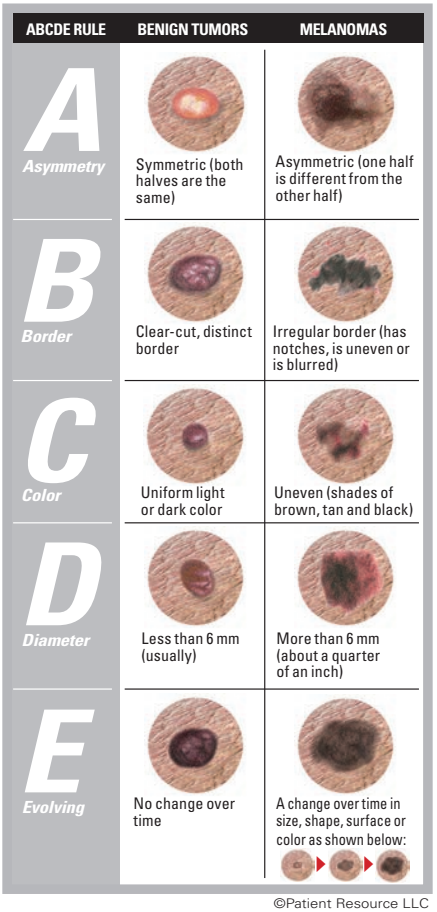
HEALTHY HABITS

Making skin cancer prevention a lifelong habit is a smart idea. As your scheduled follow-up visits get further apart in the future, you can continue to be mindful of your risks and ways you can help prevent a recurrence. A few key things to remember:

- Prevention is important regardless of the color of your skin. Although the risk is greater for people with a fair complexion, everyone is at risk for melanoma.

FIGURE 1

ABCDE RULE: HOW TO DETECT A MELANOMA



- The biggest risk factor is ultraviolet (UV) light, and it primarily comes from the sun.
- Indoor tanning is a dangerous source of UV rays, particularly for younger people.

Here are ways to protect your skin:

1. Choose a sunscreen and a lip balm with an SPF of at least 30 that protects against both UVA and UVB rays. Labels on sunscreen should say "broad spectrum" or "multi-spectrum" and should include ingredients such as titanium dioxide or zinc oxide. Apply sunscreen liberally on all exposed skin, and reapply at least every two hours (sooner if swimming or sweating). Don't forget your ears, the back of your neck and exposed parts of your scalp.
2. Limit sun exposure from 10 a.m. to 4 p.m. That is when the UV rays are the most powerful.
3. Wear protective clothing. If you sunburn easily, consider clothes with a rated ultraviolet protection factor (UPF).
4. Wear a wide-brimmed hat and sunglasses to protect against UV rays. Though a ball cap won't cover your ears or neck, it offers some protection, and some is better than none. ■

Prevention and early detection can save lives

Now that you have experienced a melanoma diagnosis, consider joining the many other survivors who advocate for melanoma awareness. It doesn't take a grand gesture. By simply talking about ways to lower the risks and how to screen, you may contribute to a better outcome for your friends and family members. Moving forward begins with being educated about melanoma.

KNOW THE RISKS

It's hard for many to believe that the sun can be so dangerous, but it is. It is the main source of ultraviolet (UV) rays, and it is crucial for all of us to avoid excessive exposure.

However, melanoma doesn't just develop on skin that is exposed to the sun. It can develop in the mucosal lining of the body, a membrane covering many body cavities and passageways. The body's moist mucosal linings are in the respiratory tract; sinuses, nasal passages and mouth; gastrointestinal tract, including the anus and rectum; and female genital tract, including the vagina and vulva.

Melanoma and other skin cancers may run in families, so encourage your family members to pay special attention to the following.

WHO NEEDS SUNSCREEN?

That's easy. Everyone. A common misconception is that only people with fair skin need to wear sunscreen. Although it is particularly important for people with a fair complexion, light-colored eyes, blonde or red hair and a tendency to burn or freckle with exposure to the sun, all people regardless of skin color are at risk.

Although darker skin has more melanin (the pigment that gives skin its color), which offers some protection from harmful UV rays, it is still vulnerable and sunscreen should be worn. Research shows that when people with dark skin are diagnosed with melanoma, it is often at a later stage because many people simply aren't aware that they are at risk. If you have dark skin and are aware of the risk but don't like the white residue sunscreen leaves on your skin, you're in luck. Different tints are now available for different skin tones, which helps avoid that filmy residue after each application.

To get the benefit of sunscreen, you must use it correctly.

- Choose a sunscreen with a sun protection factor (SPF) of at least 30. A higher SPF may be necessary to avoid burning.
- Look for "blocks UVA and UVB" or "broad spectrum" on the label.
- Use sunscreen anytime you plan to be in the sun for more than 15 minutes, even when it's cloudy.
- Apply liberally (minimum of 1 ounce, about the same amount as in a shot glass) at least 30 minutes before sun exposure. If you use spray sunscreen, be sure to cover all exposed skin.
- Apply to your ears, scalp, lips, neck, tops of feet and backs of hands.
- Reapply at least every 2 hours and each time you get out of the water or sweat heavily.
- Apply underneath your makeup and lip balm, even if they already contain SPF.
- Apply sunscreen first and bug spray second. Sunscreen may need to be reapplied more often.
- Use sunscreen in all seasons, even when it is cloudy. Snow reflects up to 80 percent of the sun's rays.
- Check the expiration date on your sunscreen or throw it away 1 to 2 years after opening it.
- Avoid indoor tanning.
- Ask your dermatologist for sunscreen recommendations if you have allergies or skin conditions.

Remember, wearing suncreen does not mean you should spend more time in the sun. And, don't rely on the sun to increase your vitamin D levels. To ensure you get enough vitamin D, your doctor may check your blood levels and may suggest an oral supplement.

Sunburn is just one risk to keep in mind. Some medicines can make your skin more sensitive to the sun, which may increase your risk of melanoma. Lesser-known risks include certain medical conditions, scars, skin conditions, skin ulcers and a high level of exposure to arsenic.

SELF-EXAMS ARE A MUST ESPECIALLY WITH TATTOOS

Early detection may be key to a better outcome from a melanoma diagnosis. It takes very little effort on your part. All you have to do is look at your skin. For those hard-to-see places, ask a loved one or a dermatologist for their help. If anything looks out of the ordinary, contact your doctor. It sounds simple enough, but it's not always easy to tell if something doesn't look right. To help you identify an abnormal mole or spot, see the ABCDE rule on page 14.

If your skin has certain characteristics, such as dark pigment, scars, constantly irritated areas or tattoos, you should be extra diligent about performing self-exams because these can make it more difficult to detect a mole or spot that doesn't look right.

For this reason, tattoo artists tend to avoid inking over existing moles or problem areas. However, that isn't always possible. Some tattoos are elaborate in color and size, such as a sleeve, which is a tattoo that runs from your wrist to your shoulder and often incorporates multiple colors.

If you have one or more tattoos or areas that may easily hide an irregularity, be sure to perform regular self-exams and see a dermatologist for preventive checks. ■

SELF-EXAMS

To conduct a thorough self-exam, use a mirror to examine these key checkpoints: neck, chest, torso, arms, legs, groin and face, including the skin around your eyes, ears and inside your nose and mouth. Don't forget these often overlooked areas:

Scalp | Soles of feet | Between the toes | Back / between buttocks | Underarms

Make a lifelong plan for your best health

Survivorship is the term many use to describe the journey that begins with a cancer diagnosis and lasts for the rest of your life. After you complete treatment, your path changes. It is one that concentrates on maintaining your physical health as well as your mental well-being. Develop and follow a survivorship plan to help you focus on these priorities.

WHAT IS A SURVIVORSHIP PLAN?

You can think of it as a life wellness plan. You may question whether you need a plan. You managed to live without one before, right? This really is different because there are many parts of your life that have changed since you were diagnosed with melanoma. A melanoma survivorship plan includes resources that can help you cope with long-term physical and emotional effects from treatment; manage your risk for recurrence or a second melanoma; address social and financial concerns; find support and community resources and improve your quality of life.

Your doctor may provide you with a survivorship plan. Some cancer centers offer survivorship programs. If neither are available to you, you can create a survivorship plan on your own. This information can help doctors who are unfamiliar with your care provide you the best possible care in the future.

Medical history. You may be able to fill in most of the information on your own, but it is important to follow up with your health care team about each part of the plan. Include the following components.

- Your cancer diagnosis, including the date of diagnosis and the type, stage and location of your cancer, as well as a full medical history.
- Your medical treatments, including drug names, dosages, dates and any side effects; include ongoing maintenance therapy.
- Your diagnostic test results.
- Your symptoms.
- Supportive care you have received, such as emotional counseling.
- Your family's medical history, including any history of cancer.

Health care team. Include the name, title, phone number, email and address of all members. Also note the role each person had in your care.

Late effects. Late effects are side effects that may last or show up weeks, months or even years after your treatment ends. Be sure to ask your health care team about the possible signs and symptoms so you can detect and manage them early.

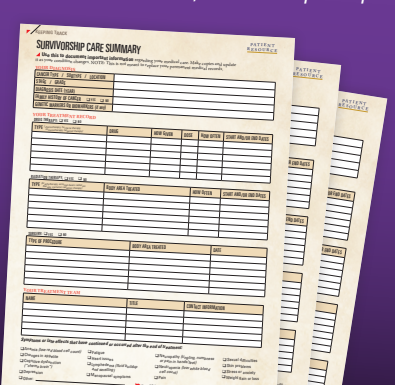
Risk for recurrence. Ask about your risk for cancer coming back and the symptoms that may signal a recurrence (see *Follow-up Care*, page 14).

Follow-up schedule. This may include information about future appointments, diagnostic tests and exams to monitor for signs of a recurrence or another cancer. Include any other procedures, such as reconstruction, that are part of your overall treatment plan. If you had a larger tumor removed, for example, a plastic surgeon may repair it with reconstructive techniques. It is important to conduct self-exams in between follow-up appointments. Putting them on your plan will serve as a reminder to do them.

If your doctor doesn't tell you how often to come back for checkups, ask. Your survivorship plan needs to be complete to be effective (see *Follow-up Care*, page 14). ■

DOWNLOAD A SAMPLE SURVIVORSHIP AND FOLLOW-UP CARE PLAN AT

PatientResource.com/SurvivorshipPlan.pdf



Re-entering the world

The idea of getting back to a pre-cancer life may be exciting, but it may also be somewhat scary. Following are suggestions to help you during the transition.

Healthy Lifestyle. Staying healthy and being active is an important part of survivorship. Eating right and exercising continue to offer multiple health benefits and help you build a solid foundation for going forward. Consider the following:

- Work with a dietitian to create healthier eating habits
- Maintain or start an exercise plan. Be sure to discuss your plan with your doctor
- Quit smoking and stop using tobacco products
- Wear sunscreen every time you go outside (see *Follow-up Care*, page 14).

Returning to work. You may have altered your work schedule or taken a leave of absence during treatment. Consider resuming your former responsibilities as they were or explore changes that could make it easier or more comfortable for you. Work with your supervisor and refer to the Americans with Disabilities Act to know your rights in the workplace. You may have long-term effects that could require some short-term changes such as these:

- A flexible schedule or reduced hours
- A redesigned workstation
- The ability to work from home
- Different responsibilities

Going back to class. Stay in touch with the faculty so they know when to expect you back. Consider stopping by before returning full-time to see if any accommodation, such as extra time between classes, having two sets of textbooks so you can keep one set at home, and being excused from a physical education class, can be made.

You may have anxiety about going back, and that is normal. Your school or workplace may offer emotional and social support resources to help with your transition.

THIS IS **LIVING WITH** CANCER™

This Is Living With Cancer™ is a program developed by Pfizer Oncology that includes resources designed for all people living with cancer, regardless of cancer type or stage of disease. This program is available to anyone in the United States, whether they're currently on a Pfizer treatment or not.

Advocacy resources

Encouragement, education and tools to help patients navigate their treatment journey.

Nutrition, exercise and wellness tips

Articles about healthy living, exercise and dietary considerations, as well as resources on managing depression, anxiety, pain and more.

Inspiration

Hear the real stories of people living with cancer. Their journeys may be different, but they all share strength, resilience and inspiration.

Personalized support

Whether you're a patient or a caregiver, **This Is Living With Cancer™** is here to provide personalized support and resources that fit your needs.

Find tools to help live life beyond your diagnosis at **ThisIsLivingWithCancer.com**

Pfizer

Funding and Support by: