

## Immunotherapy and Melanoma

Immunotherapy is rapidly emerging as an important approach to treating many forms of cancer. For people with melanoma, the news is particularly promising. Several approaches to immunotherapy, using the body's own natural defenses to fight cancers, have contributed to changing the outlook for many people with advanced or metastatic melanoma. Many studies are now underway to test new drugs and agents, and to learn how best to use the immunotherapy that exists today. This fact sheet provides a basic explanation of immunotherapy and how it is used to treat melanoma.

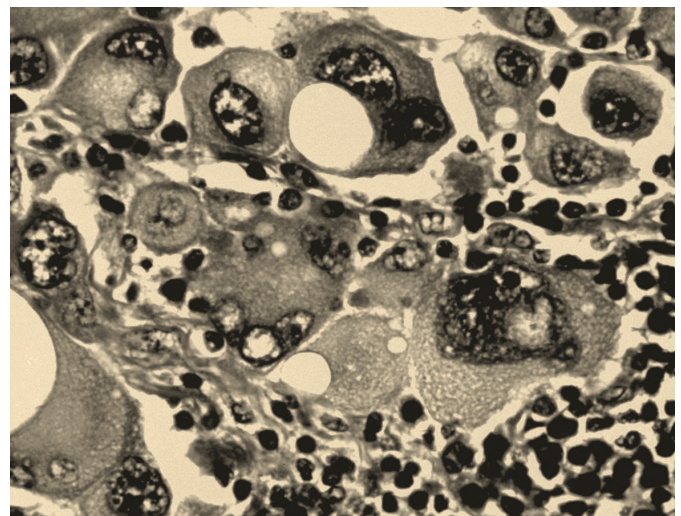
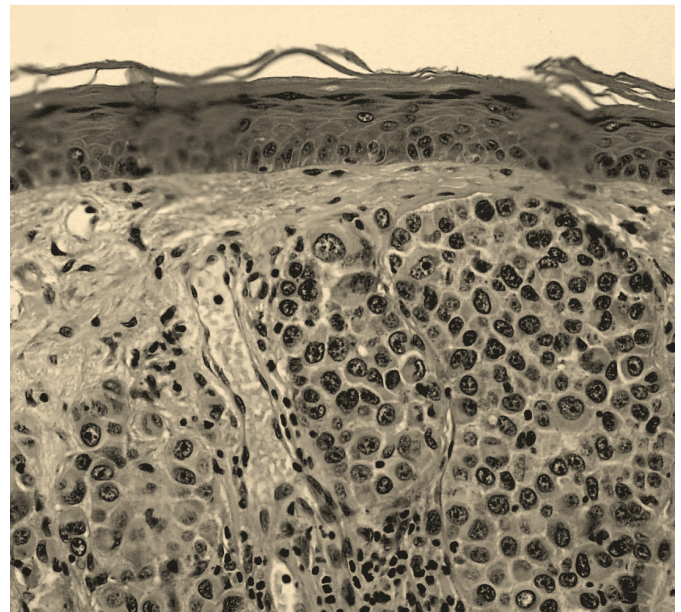


## KEY TAKEAWAYS:

- *Immunotherapy is a very promising approach to treating advanced melanoma—those that have spread or metastasized to different sites in the body.*
- *Several types of immunotherapies are used to treat melanoma. These include compounds such as cytokines, monoclonal antibodies, adoptive cell therapy and vaccines.*
- *In some people, immunotherapy can provide long lasting responses.*
- *All of these treatments have side effects. For many people the side effects from monoclonal antibodies against PD-1 are less severe than those from traditional chemotherapy.*
- *Immunotherapy is a rapidly changing approach to treating melanoma with many new drugs and clinical trials underway.*
- *Many clinical trials are now being done to determine which patients benefit from specific immunotherapies and in what sequence to use the available approaches.*
- *In the future, new and emerging approaches to immunotherapy may be used to treat melanoma patients who are at high risk for recurrence, as well as those who have advanced disease.*

## About Melanoma

Melanoma is a cancer that usually occurs on the skin. Melanomas that are detected and diagnosed early can often be cured with surgery. Unlike most skin cancers, however, melanomas have the potential to spread from the place where they begin to other organs of the body. Once it has spread, melanoma becomes a systemic disease, meaning that the cancer cells can be anywhere in the body. For that reason, it often can't be treated effectively with surgery and will require additional systemic treatment.



METASTATIC MELANOMA CELLS

“They pump you up with this drug that helps your own body fight the cancer—and it did it well.”

— Steve, living with metastatic melanoma

For many years, the outlook for people with advanced or metastatic melanoma was not good. There were a few drugs available to treat this disease, but a relatively small percentage of people responded to these therapies, and the responses often did not last long.

That has changed dramatically in the last five years. One major treatment advance came with the discovery that many people with melanoma have specific gene mutations that can be targeted with a new category of drugs. The introduction of these “targeted therapies” has meant that more people are living longer and enjoying a better quality of life. Targeted therapies produce high rates of tumor shrinkage and do so very quickly in a number of people with advanced melanoma. Only about half of melanoma patients have these mutations, and in those who do, the cancers become resistant to the treatment and progress. The goal—and the great hope—is to optimize the use of these targeted therapies and find new therapies that result in lasting responses.

The second source of excitement in treating advanced melanoma is immunotherapy. Doctors have known for a long time that there was a relationship between melanoma and the immune system. The immune system recognizes melanoma and tries to stop the growth of the tumor. A very small percentage of people have their tumors disappear without any treatment. Pathologists have evidence that when T cells, critical components of the immune system, are found in melanomas, those patients have a better prognosis.





# Types of Immunotherapy

There are a number of approaches to using immunotherapy to treat melanoma. Basically, all of them involve activating T cells, white blood cells that are the body's "soldiers," to kill cancer cells. There are two ways to do this. The first approach boosts the body's overall immune response in a general way. The second is based on emerging knowledge of how the immune system interacts with cancer cells. These newer approaches block the ability of cancer cells to turn off the immune system and de-activate the T cell response. Many researchers compare these two approaches to driving a car. Boosting the immune system is like putting your foot on the gas pedal, while the newer approaches are more like taking your foot off the brake.

■ **CYTOKINES:** Older approaches to immunotherapy attempted to boost the body's natural defense system in a general way. Interferon is a drug that is prescribed to people who have had the melanoma removed and have no evidence of disease, as a way to decrease the

## TARGETED THERAPIES:

- *Work for people who have specific gene mutations*
- *Have a high response rate—most people with the mutation will respond*
- *Produce a rapid response—people feel better*
- *Usually stop working after a period of time—not "durable"*
- *Combination strategies using targeted and immunotherapies are promising*

## CHECKPOINT BLOCKADE IMMUNOTHERAPY:

- *About one third of people respond to ipilimumab*
- *Responses may be delayed—take weeks or months to occur*
- *Responses have the potential to be durable*
- *PD-1 inhibitors may have higher response rates, fewer side effects*
- *Combination strategies using targeted and immunotherapies are available in clinical trials*

risk for recurrence. This is called adjuvant treatment. Interleukin-2 is prescribed to people with advanced melanoma and it shrinks tumors in about 10-20% of melanoma patients, and leads to complete remission in about 6% of patients. Although responses are small, they can be durable. The side effects of interferon are very much like having a severe case of the flu—fever, chills, tiredness, drowsiness and body aches. The side effects of interleukin-2 can be more severe. Side effects for cytokines, in general, can be resolved with stoppage of medicine. Today's approaches to immunotherapy for melanoma are based on a new understanding of how the immune system works and how cancer cells are able to evade the body's efforts to find and destroy these abnormal cells.

■ **IPILIMUMAB (YERVOY®):** The introduction of ipilimumab or ipi was a huge step forward in treating advanced melanoma. A brake/pedal analogy has been used by many to explain how it works. The immune system, which is activated to kill cancer cells, is similar to having the foot on the gas pedal. There are also

signals that stop the immune system, so that much like a car, it has a brake and doesn't keep moving forward. Ipilimumab is a monoclonal antibody that works by removing those brakes so that the immune system can continue to attack cancer cells. Large studies have shown that approximately 25% of people benefit from ipilimumab therapy. Often, responses to therapy can be long lasting. Researchers are now doing clinical trials with other drugs to see if combining ipilimumab with other therapies can increase the number of people that benefit.

One unusual characteristic of ipilimumab and similar drugs is that a response to treatment can be delayed, in fact, scans may look worse before they get better. Existing tumors sometimes grow before the positive response takes place. This delayed response can pose difficult challenges for people who want to know if their treatment is working or not. Positive responses can not only be delayed but often continue for long periods after the treatment is finished. Although response to treatment is usually defined as having the tumor shrink or disappear, ipilimumab can produce a long period of time in which the cancer is stable—it doesn't get smaller or larger. It is important for patients and their doctors to understand that these drugs work differently than standard chemotherapy, and often take longer before their effects are seen.

The common side effects of ipilimumab include fatigue, diarrhea, skin rash and itching. Some people have more serious side effects that occur when the immune system attacks the body's own tissues and organs.

■ **PD-1 INHIBITORS:** There is tremendous excitement about an emerging category of drugs called PD-1 inhibitors. PD-1 has been shown to be expressed on activated T cells, the blood cells that attack foreign or abnormal cells. Researchers have learned that cancer cells, including melanoma cells, can produce, or express PD-L1, which then binds to PD-1 on the T

cell and inactivates it. Doing this allows them to hide from the body's immune response.

Clinical trials using PD-1 inhibitors have shown very promising results in people with advanced melanoma because they restore the ability of T cells to recognize and attack cancer cells. The common side effects of PD-1 inhibitors are relatively mild and include fatigue, rash, itching and diarrhea, though potentially serious side effects can occur.

In 2014, the U.S Food and Drug Administration (FDA) approved two PD-1 inhibitor for use with people who have advanced melanoma and are no longer responding to other drugs. The drugs are pembrolizumab (Keytruda®) and nivolumab (Opdivo®).

■ **CANCER VACCINES:** Vaccines for melanoma are used for people who have advanced disease or are at risk for having their melanomas spread. The goal of this kind of therapy is to teach the immune system to attack and

*Most side effects of immunotherapy result from an activated immune system that attacks normal cells. Many of these side effects can be treated effectively—but it is very important to let your doctor know immediately if they occur. The most common side effects are:*

- *Rashes*
- *Extreme sensitivity to the sun*
- *Diarrhea and other gastrointestinal problems*
- *Problems with your thyroid or other endocrine glands*

destroy cancer cells. Although there are a number of different kinds of vaccines being tested, they all work by stimulating immune cells to recognize antigens on the surface of the cancer cells and react to them. Clinical trials of vaccines have shown that these treatments usually do not have major side effects, but to date have not in most instances demonstrated significant improvements in survival. A small trial testing a melanoma vaccine produced better outcomes than expected in people with advanced disease. However there is a need for larger, randomized trials to establish whether vaccines can improve survival, which patients benefit and when to give these treatments. To date, there is no FDA approved vaccine for routine therapy for melanoma.

■ **ADOPTIVE T CELL THERAPY:** Adoptive T Cell Therapy is a form of immunotherapy. This approach uses T cells taken from the patient's own body. These cells are then grown, re-engineered and injected back into the patient, often in combination with Interleuken-2. The goal is to create a large number of T cells activated to attack the cancer cells. Adoptive T cell therapy can only be done at this time in highly specialized cancer centers and as part of a clinical trial. Early trials using adoptive T cell therapy have produced excellent, lasting results in more than 50% of a small number of people with advanced melanoma. There are many trials underway now to improve the anti-tumor activity of these treatments and to boost the response rates in people with metastatic disease. While this approach is still new, it offers genuine promise for the future.

“I would recommend having someone with you at the appointment, at least initially, to help digest information and take notes on treatments, because it does tend to be overwhelming.”

— Matthew, living with metastatic melanoma



# Who Gets Immunotherapy for Melanoma?

Right now, the newer immunotherapies targeting CTLA-4 and PD-1 for melanoma are given to people whose tumors have spread or metastasized. Clinical trials are already underway studying these drugs in people who have melanomas that are at very high risk for recurring or spreading as a way of preventing that from happening.

Most people with advanced melanoma are eligible for immunotherapy treatment. Your doctor will assess your health situation and talk to you about these treatments and any side effects you can expect.

Ipilimumab, pembrolizumab and nivolumab are now approved by the FDA and are available to people in any cancer center or doctor's office where they are being treated. They are considered part of the standard of care for people with advanced melanoma. Many other new drugs are available only by participating in clinical trials. These studies compare the best known treatments (known as "standard of care") to novel approaches and are essential to understanding which regimen is more effective. Since there is no current cure for advanced melanoma, and due to the rapid pace in knowledge about immunotherapy and melanoma biology, clinical trials are always taken into consideration as a treatment option. In addition to studying the overall response rates to immunotherapy

drugs in people with melanoma, researchers are also very interested in learning:

- *Which patients benefit from immunotherapy?*
- *Why do some people not respond?*
- *When is the best time to give immunotherapy in the treatment plan?*
- *How can immunotherapy be combined with other drugs and treatments?*
- *How long should treatments continue?*
- *What are the long term effects of immunotherapy?*

These are all important questions that can only be answered in clinical trials by doctors and researchers who have expertise and experience in treating melanoma.

If you would like more information about how to participate in a clinical trial, ask your doctor or go to [www.clinicaltrials.gov](http://www.clinicaltrials.gov). If you would like help preparing for an upcoming doctor's visit at which you expect to be making a decision regarding your treatment, contact CSC about our Open to Options™ program.

## An Exciting Future

The field of immunotherapy for treating people with melanoma, especially those with widespread disease, is moving very fast. New developments are emerging all the time. Many melanoma experts now regard immunotherapy as critical to treating advanced melanoma. In the next few years, expect to see significant progress in the use of immunotherapy to give new hope to patients and families with what just a few years ago was a cancer that was almost impossible to treat.



# Resources for Information & Support

AIM at Melanoma [www.aimatmelanoma.org](http://www.aimatmelanoma.org)

American Cancer Society 1-800-227-2345 [www.cancer.org](http://www.cancer.org)

CancerCare 1-800-813-4673 [www.cancercare.org](http://www.cancercare.org)

Cancer.net 1-888-651-3038 [www.cancer.net](http://www.cancer.net)

Melanoma Research Alliance [www.curemelanoma.org](http://www.curemelanoma.org)

Melanoma Research Foundation 1-800-673-1290 [www.melanoma.org](http://www.melanoma.org)

National Cancer Institute 1-800-422-6237 [www.cancer.gov](http://www.cancer.gov)

Patient Advocate Foundation 1-800-532-5274

## CANCER SUPPORT COMMUNITY RESOURCES

The Cancer Support Community's (CSC) resources and programs are available free of charge. To access any of these resources below call 1-888-793-9355 or visit [www.cancersupportcommunity.org](http://www.cancersupportcommunity.org).

## CANCER SUPPORT HELPLINE ®

Whether you are newly diagnosed with cancer, a longtime cancer survivor, caring for someone with cancer or a health care professional looking for resources, CSC's toll-free Cancer Support Helpline (1-888-793-9355) is staffed by licensed CSC Helpline Counselors available to assist you Mon-Fri 9 am-9pm ET.

## OPEN TO OPTIONS™

If you are facing a cancer treatment decision, Open to Options™ is a research-proven program that can help you prepare a list of questions to share with your doctor. In less than an hour, our Open to Options specialists can help you create a written list of specific questions about your concerns for your doctor. Appointments can be made by calling the Helpline or by visiting the CSC website to locate a CSC affiliate offering this service near you.

A special thanks to our contributors and reviewers: April K.S. Salama, MD, Duke University; Grace Cherry, NP, University of California Los Angeles; Ellen Levine, MSW, LCSW, OSW-C, Cancer Support Community Central New Jersey; Louise Perkins, PhD, Melanoma Research Alliance; Shelby Moneer, Melanoma Research Foundation; Valerie Guild, AIM at Melanoma.

The Cancer Support Community and its partners provide this information as a service. This publication is not intended to take the place of medical care or the advice of your doctor. We strongly suggest consulting your doctor or other health care professionals to answer questions and learn more.

## THIS PROGRAM WAS MADE POSSIBLE THROUGH AN UNRESTRICTED EDUCATIONAL GRANT FROM:



© March 2015 Cancer Support Community. All rights reserved.

Design by Yolanda Cuomo Design, NYC; Cover Illustration © Anthony Russo

## FRANKLY SPEAKING ABOUT CANCER ®

CSC's landmark cancer education series provides sound medical and psychological information for cancer patients and their loved ones. Information is available through books, online and in-person programs.

## AFFILIATE NETWORK SERVICES

Over 50 locations plus more than 100 satellites around the country offer on-site support groups, educational workshops, and healthy lifestyle programs specifically designed for people affected by cancer at no cost to the member.

## CANCER EXPERIENCE REGISTRY

The Cancer Experience Registry is a community of people touched by cancer. The primary focus of the Registry is on collecting, analyzing and sharing information about the experience and needs of patients and their families throughout the cancer journey. For more information or to join, visit [www.CancerExperienceRegistry.org](http://www.CancerExperienceRegistry.org).

**FRANKLY SPEAKING ABOUT CANCER:** Your Immune System & Melanoma Treatment Program Partners:

