

TREATMENT UPDATE:

Advanced Skin Cancer and Melanoma

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EDITOR

Gregory A. Daniels, MD, PhD

Associate Clinical Professor of Medicine, University of California San Diego, Rebecca and John Moores Cancer Center

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One in five people in the United States will develop skin cancer over the course of their lifetime.

If found early, skin cancer can usually be treated with a relatively simple surgery. Basal cell skin cancer is the most common type of skin cancer, followed by squamous cell skin cancer and melanoma.

Treatment Approaches for Advanced Basal Cell and Squamous Cell Skin Cancer

At the time of diagnosis, most basal cell (BCC) and squamous cell (SCC) skin cancers have not spread from their original location and are managed with local treatments, including resection (removal) of the tumor and the use of topical (applied to the skin) medications. While less common, radiation therapy may be considered for some cases, in which neither resection nor topical medications is an option.

In advanced cases of BCC and SCC, the tumor spreads and affects other parts of the body. Resection may be more difficult or even impossible, and radiation may not be an option. It is in these situations that a medical oncologist may become part of your health care team, and the use of oral or intravenous (through the vein) drugs will be considered as a way to destroy the cancer. Drugs differ based on whether the cancer is basal cell or squamous cell.

Advanced Basal Cell Skin Cancer

Several years ago, researchers discovered that more than 70 percent of BCCs have certain gene mutations (changes) in what is called the “Hedgehog pathway.” These changes activate the growth of the cancer cells and allow for their survival. Finding the mutations meant that drugs could be designed to target those pathways.

Vismodegib (Erivedge) is a Hedgehog pathway inhibitor. It was approved by the U.S. Food and Drug Administration (FDA) in 2012 to treat BCC that has spread to other parts of the body, comes back after surgery, or cannot be treated with surgery or radiation. Vismodegib is a targeted therapy taken in capsule form.

In 2015, the FDA approved the targeted therapy sonidegib (Odomzo) for the treatment of people with locally advanced BCC that has recurred following surgery or radiation therapy and for people with BCC who are not candidates for surgery or radiation therapy.

The development and approval of vismodegib and sonidegib has launched additional research efforts, which may lead to the creation of new drugs to treat basal cell cancers.

Advanced Squamous Cell Skin Cancer

Advanced squamous cell skin cancer is rare, and until recently there have been few clinical trials. There is much more data available on squamous cell cancer of the head and neck, and the FDA has approved the targeted therapy cetuximab (Erbix) for those cancers; it is also approved for the treatment of certain types of colorectal cancer. Cetuximab, given intravenously, can block one of the signals that tells a tumor to grow by attaching to a structure on the cell called the epidermal growth factor receptor (EGFR).

Clinical trials now show that cetuximab is also effective in treating advanced SCC of the skin. If a drug has been approved for one use, doctors may choose to use the drug for other conditions, if they believe it may be helpful. Doctors are already prescribing cetuximab for some patients with advanced SCC of the skin whose tumors cannot be surgically removed or treated with radiation.

Chemotherapy drugs are sometimes used to treat advanced cases of SCC. These drugs, given orally or intravenously, can slow the spread of the cancer and relieve some symptoms. In some cases, they may shrink tumors enough so that other treatments, such as surgery or radiation, can be used.

In April 2018, the FDA granted a priority review for a biologics license application to the immunotherapy cemiplimab as a treatment for locally advanced SCC that cannot be treated by surgery and for advanced SCC.



Treatment Approaches for Melanoma

Melanoma is the most serious type of skin cancer. It develops in the cells that produce melanin, the pigment that gives color to skin, hair and eyes. Most cases of melanoma are diagnosed at an early stage, with a tumor—often a single thin spot or lesion—appearing on the skin. In the majority of people, the melanoma is effectively treated by the removal of the tumor.

Advanced (or metastatic) melanoma has spread from where it originated to another part of the body. Deciding what treatment option is best is based on factors unique to the individual person—including their health history, energy level, where the cancer appeared initially and where it appears currently. As there are a number of treatment options for advanced melanoma, it's important for people to ask their health care team questions to understand what treatment may be most effective for them.

Immunotherapies in the Treatment of Advanced Melanoma

Immunotherapy is treatment that uses certain parts of the immune system to fight illnesses, including cancer. There are several immunotherapies approved to treat advanced melanoma:

- **Interferon (Intron A, Sylatron).** In 1995, the FDA approved interferon as an adjuvant (post-surgery) therapy for patients whose advanced melanoma tumors were removed surgically. The use of interferon in these circumstances may stop the growth and spread of any remaining melanoma cells.

- **Aldesleukin (interleukin-2, Proleukin).** Since the late 1990s, aldesleukin has been approved as a standard treatment for advanced melanoma. Given through a vein, aldesleukin helps the body's immune system shrink and destroy tumors more effectively. Aldesleukin is not used as commonly today as it was in the past, because there are newer and more effective treatments.
- **Ipilimumab (Yervoy).** Ipilimumab was approved by the FDA in 2011 for treatment of advanced melanoma. This drug, given through a vein, helps the immune system in a different way from aldesleukin. Ipilimumab seeks out and locks onto CTLA-4, a protein that normally helps keep immune system cells (called T-cells) in check. By blocking the action of CTLA-4, ipilimumab is thought to help the immune system destroy melanoma cells.
- **Pembrolizumab (Keytruda).** Pembrolizumab was approved for the treatment of advanced melanoma in 2014. Given intravenously, pembrolizumab blocks a cellular pathway known as PD-1. The PD-1 pathway restricts the body's immune system from attacking melanoma cells.
- **Nivolumab (Opdivo).** Like pembrolizumab, nivolumab works by blocking the PD-1 pathway and is also given intravenously. Nivolumab was approved for treatment of advanced melanoma in 2014. In December 2017, the approval was extended as a post-surgery treatment of completely resected melanoma that is either advanced or has lymph node involvement.
- **Talimogene laherparepvec (Imlygic).** Talimogene laherparepvec is injected directly into the melanoma lesions, where it causes cancer cells to rupture and die. Talimogene also appears to improve the immune system's response to cancer.

Additionally, the combination of ipilimumab and nivolumab is approved for the treatment of people with advanced melanoma. This combination treatment, given simultaneously, is designed to block the actions of CTLA-4 and the PD-1 pathway.

Targeted Therapy in the Treatment of Advanced Melanoma

Targeted therapies are designed to inhibit specific cell mechanisms important for the growth and survival of tumor cells. Patients who may benefit from targeted therapies have specific DNA changes (called driver mutations) that allow cancers to develop and grow.

A number of targeted therapies have been approved by the FDA for the treatment of melanoma:

- **Vemurafenib (Zelboraf).** In 2011, the FDA approved vemurafenib, a drug that inhibits the “signal transduction” pathway in people with a BRAF gene mutation. Vemurafenib can help slow or stop the spread of melanoma cells and can shrink tumors in areas of the body such as the liver, bowel and bone.
- **Dabrafenib (Tafinlar).** In 2013, the FDA approved dabrafenib, which targets the BRAF gene mutation in the same way vemurafenib does.



- **Trametinib (Mekinist).** In 2013, trametinib was approved as a single agent to treat people with metastatic melanoma that cannot be removed by surgery. In 2014, the FDA approval was extended to include treatment in combination with dabrafenib. Trametinib blocks a protein called MEK, which is “switched on” by BRAF. In April 2018, the combination of dabrafenib and trametinib was granted FDA approval for the post-resection treatment of advanced melanoma with a BRAF V600E or V600K mutation.
- **Cobimetinib (Cotellic).** In 2015, the FDA approved cobimetinib for the treatment of patients with unresectable (unable to be removed) or advanced melanoma with a BRAF V600E or V600K mutation, to be used in combination with vemurafenib.
- **Encorafenib (Braftovi) and binimetinib (Mektovi).** In 2018, the FDA approved the combination treatment of encorafenib (a BRAF inhibitor) and binimetinib (a MEK inhibitor) for the treatment of people with unresectable or advanced melanoma with a BRAF V600E or V600K mutation.



Clinical Trial Research for the Treatment of Advanced Melanoma

Researchers are currently investigating therapies for the treatment of advanced melanoma, including:

- **Additional targeted therapies.** About 3 percent of melanomas have mutations in a gene called C-KIT, a type of receptor found on the surface of many different types of cells. The results of clinical trials are showing that targeted therapies, including imatinib and sunitinib (both of which are FDA-approved to treat other cancers) can block the mutated C-KIT receptor.
- **Combination of immunotherapy treatments.** There are a number of ongoing clinical trials whose purpose is to study ways to combine different types of immunotherapy, which may be more effective than monotherapy (only one type of therapy) in the treatment of melanoma.
- **Vaccines.** Melanoma cells (or parts of cells) that have been killed can be used in a vaccine to stimulate the immune system in an effort to destroy melanoma cells in the body. Using vaccines in combination with other immune therapies is also a promising approach currently being explored.
- **Adoptive cell transfer therapy (ACT).** An experimental type of immunotherapy, ACT modifies a person's own immune cells to activate the immune system against melanoma. The treatment uses tumor-infiltrating lymphocytes (TIL) cells from the person's surgically-removed tumor, which are then modified in a laboratory to increase their number and potency. The person then receives the modified TIL cells intravenously.

The Importance of Clinical Trials

Clinical trials are the standard by which we measure the worth of new treatments and the quality of life of individuals as they receive those treatments. For this reason, doctors and researchers urge people with cancer to take part in clinical trials.

Your doctor can guide you in making a decision about whether a clinical trial is right for you. Here are a few things that you should know:

- Often, people who take part in clinical trials gain access to and benefit from new treatments.
- Before you participate in a clinical trial, you will be fully informed as to the risks and benefits of the trial, including any possible side effects.
- Most clinical trials are designed to test a new treatment against a standard treatment to find out whether the new treatment has any added benefit.
- You can stop taking part in a clinical trial at any time for any reason.

Treatment Side Effects

All cancer treatments can cause side effects. It's important that you report any side effects that you experience to your health care team so they can help you manage them. Report them right away—don't wait for your next appointment. Doing so will improve your quality of life and allow you to stick with your treatment plan. It's important to remember that not all patients experience all side effects, and patients may experience side effects not listed here.

Side Effects of Chemotherapy

The side effects of chemotherapy depend on the type and dose of drugs given and the length of time they are used. They can include:

- Fatigue
- Nausea or vomiting
- Hair loss
- Increased risk of infection (from having too few white blood cells)
- Easy bruising or bleeding
- Changes in memory or thinking
- Peripheral neuropathy (numbness or tingling in hands and feet)

Side Effects of Radiation Therapy

Changes to the skin are the most common side effects of radiation therapy; those changes can include dryness, swelling, peeling, redness and blistering. If a reaction occurs, contact your health care team so the appropriate treatment can be prescribed. It's especially important to contact your health care team if there is any open skin or painful areas, as this could indicate an infection. Infections can be treated with an oral antibiotic or topical antibiotic cream.

Side Effects of Targeted Therapy

Common side effects of BRAF and MEK targeted therapy can include fever, skin rash, sun sensitivity, headache and joint pain.

Side Effects of Immunotherapy

Immunotherapy acts to enhance your immune system's response to cancer. Because it may attack healthy cells as well as cancer cells, certain side effects may be experienced, including fatigue, decreased appetite and digestive tract symptoms. The management of these potential side effects is discussed in the next section of this booklet.

Managing General Side Effects

There are certain side effects that may occur across different treatment approaches. Following are tips for managing these side effects. Your health care team may have additional guidance for your specific treatment type.

Digestive Tract Symptoms

Nausea and vomiting

- Avoid food with strong odors, as well as overly sweet, greasy, fried or highly seasoned food.
- Eat meals cold or at room temperature, which often makes food more easily tolerated.
- Having something in your stomach when you take medication may help ease nausea.

Diarrhea

- Drink plenty of water. Ask your doctor about using drinks such as Gatorade that provide electrolytes as well as liquid. Electrolytes are body salts that must stay in balance for cells to work properly.
- Choose foods that contain soluble fiber, such as beans, oat cereals, oranges and flaxseeds. Foods high in pectin (a fiber found in fruits) such as peaches, apples, oranges, grapefruit, bananas and apricots can also help to avoid diarrhea.
- Low fat food choices are less likely to cause diarrhea than fatty, greasy or fried foods. The fats you eat should come from healthy sources, such as olive oil, canola oil, avocado, olives, nuts and seeds.



Managing Loss of Appetite

- Eating small meals throughout the day is an easy way to take in more calories and maintain your weight. Try to include protein in every meal.
- Keep high-calorie, high-protein snacks on hand such as hard-boiled eggs, peanut butter, cheese, ice cream, granola bars, liquid nutritional supplements, puddings, nuts, canned tuna or trail mix.
- If you are struggling to maintain your appetite, talk to your health care team about whether appetite-building medication could be right for you.

Managing Fatigue

Fatigue (extreme tiredness not helped by sleep) is one of the most common side effects of many cancer treatments. If you are taking a medication, your doctor may delay or lower the dose of the drug, as long as it does not make the treatment less effective. If you are experiencing fatigue, talk to your doctor about whether taking a smaller dose is right for you.

There are a number of other tips for reducing fatigue:

- Take several short naps or breaks.
- Take short walks or do some light exercise, if possible.
- Try easier or shorter versions of the activities you enjoy.
- Ask your family or friends to help you with tasks you find difficult or tiring.

There are also prescription medications that may help, such as modafinil. Your health care team can provide guidance on whether medication is the right approach for your individual circumstances.

Managing Pain

Both cancer itself and the side effects of treatment can sometimes cause pain. There are a number of options for pain relief, including prescription and over-the-counter medications. It's important to talk to a member of your health care team before taking any over-the-counter medication to be sure it is safe and will not interfere with your treatments.

Physical therapy, acupuncture and massage may also be of help in managing your pain. Other techniques, such as mindfulness meditation, deep breathing exercises and yoga may also be helpful. Consult with a member of your health care team before beginning any of these activities.



Communicating with Your Health Care Team

As you manage your cancer, it's important to remember that you are a consumer of health care. The best way to make decisions about health care is to educate yourself about your diagnosis and the members of your health care team, including doctors, nurses, nurse practitioners, physician assistants, dietitians, social workers and patient navigators.

Here are some tips for improving communication with your health care team:

Start a health care journal. Having a health care journal or notebook will allow you to keep all of your health information in one place. You may want to write down the names and contact information of the members of your health care team, as well as any questions for your doctor. Keep a diary of your daily experiences with cancer and treatment. You can separate your journal or notebook into different sections to help keep it organized.

Prepare a list of questions. Before your next medical appointment, write down your questions and concerns. Because your doctor may have limited time, you should ask your most important questions first, and be as specific and brief as possible.

Bring someone with you to your appointments. It's always helpful to have support when you go to your appointments. The person who accompanies you can serve as a second set of ears. He or she may also think of questions to ask your doctor or remember details about your symptoms or treatment that you may have forgotten.

Write down your doctor's answers. Taking notes will help you remember your doctor's responses, advice and instructions. If you cannot write down the answers, ask the person who accompanies you to do that for you. If you have a mobile device, like a tablet or smartphone, ask if you can use it to take notes. Writing notes will help you review the information later.

Record your visit if your doctor allows it. Recording the conversation with your doctor gives you a chance to hear specific information again or share it with family members or friends.

Incorporate other health care professionals into your team.

Your medical oncologist is an essential member of your health care team, but there are other health care professionals who can help you manage your diagnosis and treatment:

- Your primary care physician should be kept updated about your cancer treatment and any test results.
- Your local pharmacist is a great source of knowledge about the medications you are taking. Have all of your prescriptions filled at the same pharmacy to avoid the possibility of harmful drug interactions.
- Make sure your oncologist knows of any other medical conditions you have, or any pain you are experiencing, so that he or she can consult with your primary care physician or your specialist if needed.
- Ask your oncologist to send a summary of your visits to your primary care physician and all doctors involved in your care.

Remember, there is no such thing as over-communication.

CancerCare's Free Support Services and Programs

It can be very difficult to receive a diagnosis of cancer, and adjusting to the necessary changes in your life can be challenging.

CancerCare can help. We are a national nonprofit organization providing free, professional services to anyone affected by cancer. Our licensed oncology social workers can provide support and education, help in navigating the complicated health care system, and provide information on support groups and other resources.

To learn more about how CancerCare helps, call us at 800-813-HOPE (4673) or visit www.cancercares.org.

You will likely also build your own personal support network comprised of family and friends. In doing so, it's best to take some time to think about the people in your life and how they are best suited to help. Match the task to their strengths—ask a family member who loves to shop to pick up something for you at the store; ask a friend who's a good listener to come over for a chat.



Frequently Asked Questions

Q: Can you explain what the “ABCDEs” of melanoma are and why they’re important?

A: If you have any moles with the following features, ask your doctor to check them out. Such changes in the appearance of a mole may be the first signs of melanoma. There is a high likelihood of a successful outcome if the melanoma is recognized and treated at an early stage.

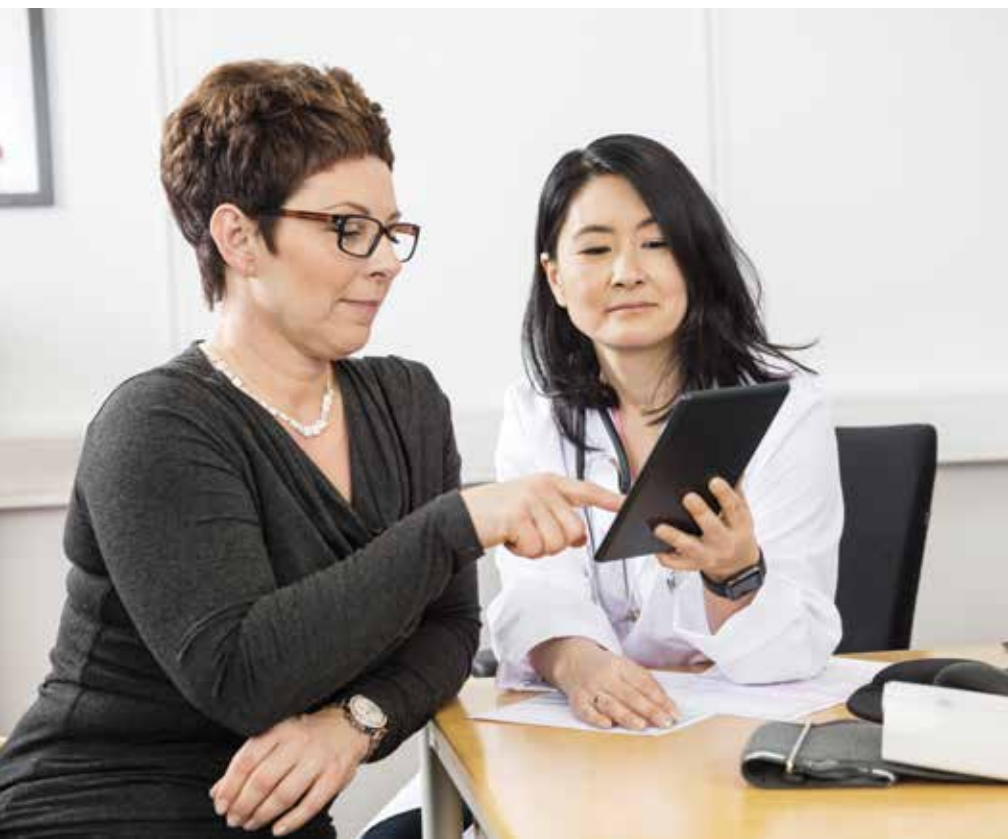
- **Asymmetrical:** One side of the mole looks different from the other
- **Border:** Irregular or vaguely defined borders
- **Color:** Uneven coloring or multiple colors
- **Diameter:** Larger than a pencil eraser or growing in size
- **Evolution:** Growing or changing in any way

Q: I was treated with immunotherapy for my melanoma, and it has now recurred. Can I be treated with another immunotherapy?

A: More than likely, yes. Different types of immunotherapy work in different ways. It may even be that the immunotherapy you were treated with initially may work. This is an area of ongoing research. On a related topic, it is important to note that there is no known reason to undergo multiple treatment types at the same time, and that approach has never been investigated.

Q: Are melanomas genetic?

A: Most melanomas occur in patients where no family or genetic link can be found. However, there is a rare form of melanoma that arises in childhood, without sun exposure, which is thought to be genetic. In addition, it is important to provide your doctor with your family's cancer history, as melanoma can be caused by gene changes found in families; these changes also have risks for breast, colon and pancreatic cancers. For melanomas related to sun exposure, having a close relative with melanoma is a risk factor, but it's not clear if the link is genetic or behavioral. Annual screenings for melanoma are recommended if you have a close relative with melanoma.



Resources

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www.cancer.org

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www.cancer.net

National Cancer Institute

800-422-6237
www.cancer.gov

**Melanoma International
Foundation**

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www.melanomainternational.org

Melanoma Research Foundation

877-673-6460
www.melanoma.org

The Skin Cancer Foundation

212-725-5176
www.skincancer.org

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