

TREATMENT UPDATE:

Advanced Skin Cancer

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Treatment Update: Advanced Skin Cancer

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TABLE OF CONTENTS

- Introduction.....2
- Treatment Approaches for Advanced Basal Cell and Squamous Cell Skin Cancer.....2
- Treatment Approaches for Melanoma.....5
- Clinical Trial Research for the Treatment of Advanced Melanoma.....9
- Treatment Side Effects.....12
- Communicating With Your Health Care Team.....16
- CancerCare’s Free Support Services and Programs.....18
- Frequently Asked Questions.....19
- Resources.....21

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One in five people in the United States will develop skin cancer over the course of their lifetime. 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 cases of basal cell skin cancer (BCC) and squamous cell skin cancer (SCC) have not spread from their original locations and are managed with local treatments, including the use of topical medications (applied directly to the skin) such as fluorouracil (Efudex) or surgical removal of the tumor.

Imiquimod cream can be applied to the biopsy site of certain BCCs to treat any cancer cells that remain. This treatment is typically given 5 days a week for 6 weeks. The most common side effect is irritation at the site of application.

There are certain superficial types of BCC and SCC that can be treated by performing small in-office procedures, including electrodesiccation and curettage (sometimes called “scrape and burn”) for BCC and two cycles of cryotherapy (freezing) for SCC.

Mohs micrographic surgery, a precise surgical technique, is often used to treat BCC and SCC that appears on the head and neck. This is a skin-sparing technique, in which pieces of skin are progressively removed at the site of the tumor and examined under a microscope until only cancer-free tissue remains.

If surgery is not an option, radiation may be considered. Radiation may also be used after surgery if there is concern about the risk of the skin cancer recurring (coming back).

Even though these types of skin cancers are very common, relatively few evolve into cases that require more intensive treatment. In advanced cases of BCC and SCC, surgery or radiation may not be an option. In these situations, the use of oral (by mouth) or intravenous (through a vein) drugs is often considered.



Advanced Basal Cell Skin Cancer

More than 90 percent of BCCs have certain gene mutations (changes) in what is called the Hedgehog pathway. These changes activate the growth of cancer cells and allow for their survival. Drugs have been designed to target mutations in the Hedgehog pathway. The Hedgehog inhibitors approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced BCC are vismodegib (Erivedge) and sonidegib (Odomzo). Taken orally, these drugs are used in cases where the BCC has spread to other parts of the body, has recurred after surgery or cannot be treated with surgery or radiation. Hedgehog inhibitors are sometimes used before surgery to shrink the size of a tumor, making surgery an easier process and increasing its chance of success.

In February 2021, the FDA approved cemiplimab-rwlc (Libtayo) for the treatment of locally advanced or metastatic BCC that was previously treated with a Hedgehog inhibitor or for which a Hedgehog inhibitor is not appropriate.

Advanced Squamous Cell Skin Cancer

There are two immunotherapies used in the treatment of advanced SCC, both of which are given via intravenous infusion:

- In 2018, the FDA approved the immunotherapy cemiplimab-rwlc (Libtayo) for the treatment of people with metastatic or locally advanced SCC who are not candidates for surgery or radiation.
- In June 2020, the FDA approved the immunotherapy pembrolizumab (Keytruda) for the treatment of recurrent or metastatic SCC that is not curable by surgery or radiation. In July 2021, the approval was expanded to include treatment of locally advanced SCC that is not curable by surgery or radiation.

The targeted therapy cetuximab (Erbix) is sometimes prescribed to treat people whose SCC tumors cannot be surgically removed or treated with radiation. By attaching to a structure on the cell called the epidermal growth factor receptor (EGFR), cetuximab can block one of the signals that tells a tumor to grow.

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, after a tumor appears on the skin. In the majority of people, the melanoma is effectively treated by the surgical removal of the tumor.

If surgery does not remove all of the melanoma, imiquimod cream may be used to destroy the remaining cancer cells. It can also be used to treat patients for whom surgery is not an option.

Advanced (metastatic) melanoma has spread from where it originated to another part of the body, including lymph nodes or other organs. Deciding what treatment option is best is based on factors unique to the individual, including their health history, energy level, where the cancer appeared initially and where it appears currently. Factors specific to the melanoma itself, such as whether the tumor has a mutation in the BRAF gene, also influence treatment options.

As there are a number of options for treating advanced melanoma, it's important for people to consult with their doctor to understand what treatment may be most effective for them.

Immunotherapy in the Treatment of Advanced Melanoma

Our immune system is constantly working to keep us healthy. It recognizes and fights against danger, such as infections, viruses and growing cancer cells. In general terms, immunotherapy uses our own immune system as a treatment against cancer.

There are a number of immunotherapies approved to treat advanced melanoma:

- **Interferon (Intron A, Sylatron).** In 1995, the FDA approved interferon as an adjuvant (post-surgery) therapy for people whose advanced melanoma tumors were surgically removed. The use of interferon in these circumstances may stop the growth and spread of any remaining melanoma cells. Interferon is rarely used today, because newer and more effective treatments are now available.
- **Aldesleukin (interleukin-2, Proleukin).** Since the late 1990s, aldesleukin has been used as a treatment for advanced melanoma. Given intravenously, aldesleukin helps the body's immune system shrink and destroy tumors more effectively. As is the case with interferon, aldesleukin is not used as frequently today as a standalone treatment as it was in the past.
- **Ipilimumab (Yervoy).** Ipilimumab was approved by the FDA in 2011 for the treatment of advanced melanoma. Ipilimumab binds onto CTLA-4, a protein that inhibits immune system cells (called T cells). By blocking the action of CTLA-4, ipilimumab is thought to help the immune system destroy melanoma cells. Ipilimumab is given intravenously.

- **Pembrolizumab (Keytruda).** Given intravenously, pembrolizumab blocks the PD-1 cellular pathway (a pathway that inhibits the body's immune system from working properly). Pembrolizumab is approved for the treatment of melanoma that is advanced or unresectable (unable to be removed) and for post-surgery treatment of melanoma with or without lymph node involvement.
- **Nivolumab (Opdivo).** Nivolumab was approved for the treatment of advanced melanoma in 2014. In 2017, the approval was extended for the post-surgery treatment of melanoma that has lymph node involvement. Like pembrolizumab, nivolumab works by blocking the PD-1 pathway and is given intravenously.
- **Talimogene laherparepvec (Imlygic).** This drug, often referred to as TVEC, was approved by the FDA in 2015 for the treatment of advanced stage melanoma. TVEC is injected directly into the melanoma lesions, where it can cause the destruction of cancer cells. As TVEC may also improve the immune system's response to cancer, melanoma lesions that were not injected with the drug may also shrink or disappear.

There are also two combination immunotherapies approved for the treatment of advanced melanoma:

- **Ipilimumab plus nivolumab (Yervoy plus Opdivo).** Approved by the FDA in October 2020, this combination is designed to block the actions of both the CTLA-4 and PD-1 pathways.
- **Nivolumab plus relatlimab (Opdualag).** Approved in March 2022, this treatment combines a PD-1 inhibitor with a novel (new) therapy that blocks the LAG-3 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. People who may benefit from targeted therapies have tumors possessing specific DNA changes (mutations) that allow cancers to develop and grow.

Up to 50 percent of melanomas have a mutation called BRAF. A number of targeted therapies have been approved by the FDA for the treatment of melanoma with a BRAF mutation:

- **Vemurafenib (Zelboraf).** In 2011, the FDA approved vemurafenib, a drug that inhibits the “signal transduction” pathway in people with a BRAF gene mutation.
- **Dabrafenib (Tafinlar).** In 2013, the FDA approved dabrafenib, which targets the BRAF gene mutation in the same way as vemurafenib.
- **Trametinib (Mekinist).** Trametinib was approved by the FDA in 2013 to treat people with advanced melanoma that cannot be removed by surgery. In 2014, the approval was extended to include use in combination with dabrafenib. Trametinib blocks a protein called MEK, which is “switched on” by the BRAF gene mutation. In 2018, the combination of dabrafenib and trametinib was granted approval by the FDA for the treatment of melanoma that has spread to the lymph nodes and which has a BRAF mutation.
- **Cobimetinib (Cotellic).** In 2015, the FDA approved cobimetinib for the treatment of people with inoperable or advanced melanoma that has a BRAF mutation, for use 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.
- **Atezolizumab (Tecentriq) plus cobimetinib (Cotellic) and vemurafenib (Zelboraf).** In July 2020, the FDA approved atezolizumab (an immunotherapy) in combination with the targeted therapies cobimetinib and vemurafenib for the treatment of BRAF V600-positive advanced melanoma.

Clinical Trial Research for the Treatment of Advanced Melanoma

While there has been significant progress in the treatment of melanoma and other forms of skin cancer, much remains to be learned. Researchers are currently investigating a number of 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. Results from clinical trials have shown 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 studying ways to combine different types of immunotherapies, which may be more effective than monotherapy (only one type of therapy) in the treatment of advanced melanoma.

- **Vaccines.** Melanoma cells (or parts of those cells) that have been inactivated (destroyed) can be used in a vaccine to stimulate the immune system in an effort to destroy active melanoma cells in the body. Using vaccines in combination with other immunotherapies is also a promising approach.
- **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 lymphocyte (TIL) cells from the person's surgically-removed tumor, which are modified in a laboratory to increase their number and potency (strength). The person then receives the modified TIL cells intravenously, usually along with the immunotherapy aldesleukin to help stimulate the TIL cells.



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 patients 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 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. It's important to remember that not all people experience all side effects, and some people may experience side effects not listed here.

Side Effects of Radiation Therapy

Changes to the skin are the most common side effects of radiation therapy. The 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 area, as this could indicate an infection. Infections can be treated with an oral antibiotic or topical antibiotic cream. Other common side effects of radiation therapy include fatigue, hair loss and changes in skin color at the radiation site, or damage to salivary glands or teeth when treating cancers near these areas.

Side Effects of Immunotherapy

Immunotherapy helps to prompt an immune response throughout the body. Sometimes the immune system can attack healthy cells as well as cancer cells, and certain side effects may be experienced. The most common side effects are fatigue, decreased appetite and skin rash. Lightening of the skin (vitiligo) can also occur, and may be permanent. More rare and serious side effects of immunotherapy include inflammation in the lung (pneumonitis) which can cause difficulty breathing, or frequent diarrhea (colitis).

Immunotherapy can also affect the thyroid and other hormone-producing glands. Hormone levels are typically monitored while on treatment and replacement therapy may be necessary if levels are not within normal ranges.

Side Effects of Targeted Therapy

The potential side effects of targeted therapy depend on the type of drug given, and can include taste alteration, hair thinning, muscle cramps or joint pain, sun sensitivity, liver problems (such as hepatitis and elevated liver enzymes), nerve damage, high blood pressure and problems with blood clotting and wound healing.



General Side Effects

Some side effects may occur across treatment approaches. This section provides tips and guidance on how to manage these side effects should they occur.

Managing Digestive Tract Symptoms

Nausea and vomiting

- Eat smaller, more frequent meals.
- Avoid food with strong odors, as well as overly sweet, greasy, fried or highly seasoned food.
- Having something in your stomach when you take medication may help ease nausea.
- Talk to your healthcare team if nausea is persistent or worsening. They may prescribe medication to ease this side effect, such as ondansetron (Zofran) or prochlorperazine (Compazine).

Diarrhea

- Drink plenty of fluids. Ask your doctor about drinks such as Gatorade, which provide electrolytes. Electrolytes, body salts that must stay in balance for cells to work properly, can be lost when severe diarrhea is being experienced.
- Over-the-counter medicines such as loperamide (Imodium A-D and others) and prescription drugs are available for diarrhea but should be used only if necessary and with your health care team's knowledge and approval.
- Choose foods that contain soluble fiber, like beans, oat cereals and flaxseed, and high-pectin foods such as peaches, apples, oranges, bananas and apricots.
- Avoid food high in refined sugar and those sweetened with sugar alcohols such as sorbitol and mannitol. Avoid greasy or fried foods as well.

Loss of appetite

- Eating small meals throughout the day is an easy way to take in more protein and calories, which will help maintain your weight. Nutrition shakes or protein drinks are a way to add calories to your daily diet.
- To keep from feeling full early, avoid liquids with meals or take only small sips (unless you need liquids to help swallow). Drink most of your liquids between meals.
- Keep high-calorie, high-protein snacks on hand such as peanut butter, cheese, granola bars, liquid nutritional supplements, nuts, canned tuna and 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 Rash

- Gentle skin care is recommended. Take lukewarm showers, use products that do not contain dyes or fragrances that may irritate the skin, and moisturize with lotion after showering.
- Wear sun protective hats and clothing, and wear sunscreen with SPF 30 or above.
- Contact your health care team if a rash occurs, as they may need to prescribe topical creams to help manage the rash. Oral steroids are sometimes prescribed for more severe cases.

Managing Fatigue

Fatigue (extreme tiredness, or sleeping more than usual) is one of the most common side effects of many cancer treatments. If you are fatigued while on treatment, your doctor may lower the dose of the drug(s), as long as it does not make the treatment less effective. Your doctor may also conduct bloodwork testing to make sure that your fatigue is not due to another condition.

Communicating With Your Health Care Team

As you manage your skin 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 get to know all the members of your health care team.

Here are some tips:

Start a health care journal. Having a health care journal or notebook (either on paper or in a digital format) 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.

Prepare a list of questions and bring important documents.

Before your next medical appointment, write down your questions and concerns. Because your doctor may have limited time, ask your most important questions first and be as specific as possible. Also, bring important documents that you have in your possession, such as the results of biopsies or scans done at other locations.

Bring someone with you to your appointments or have them be present during telehealth sessions. Even if you have a journal and a prepared list of questions or concerns, it's always helpful to have support during your appointments. The other person can serve as a second set of ears. They 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. You can also ask the person who accompanies you to take notes for you, either in your journal or on a tablet or smartphone.

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 skin 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 when possible to minimize the possibility of harmful drug interactions.
- Make sure your oncologist and dermatologist know of any other medical conditions you have or any pain you are experiencing so that they can consult with your primary care physician or specialist as needed.



CancerCare's Free Support Services and Programs

It can be very difficult to receive a diagnosis of advanced skin 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 offer 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 composed 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, or ask a friend who's a good listener to come over for a chat.



MORE ABOUT ADVANCED SKIN CANCER

Frequently Asked Questions

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

A: A change in the appearance of a mole, described in words beginning with A, B, C, D and E, may be the first sign of melanoma. Consult with your doctor if you have any moles with the following features. 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. What is Gorlin syndrome?

A: Gorlin syndrome, also called basal cell nevus syndrome or nevoid basal cell carcinoma syndrome, is a rare inherited condition. People with Gorlin syndrome develop many basal cell carcinomas (BCC) over their lifetime, often starting in childhood or in their teen years. Unprotected exposure to ultraviolet (UV) radiation from the sun or indoor tanning can increase the incidence of these tumors. Sometimes people with Gorlin syndrome are put on Hedgehog inhibitor therapy to try to control the development or progression of BCC.

Q: Are melanomas genetic (inherited)?

A: Most melanomas occur in people where no family or genetic link can be found. However, there may be rare cases, not related to sun exposure, that have a genetic predisposition. 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 skin screenings for melanoma are recommended if you have a close relative with melanoma.

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 in some cases the immunotherapy you were treated with initially may be effective in treating the recurrence of the melanoma. This area is the subject of ongoing research.



Resources

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800-813-HOPE (800-813-4673)
www.cancercares.org

American Cancer Society
800-227-2345
www.cancer.org

Cancer.Net
Patient information from the American Society of Clinical Oncology
888-651-3038
www.cancer.net

National Cancer Institute
800-422-6237
www.cancer.gov

The Skin Cancer Foundation
212-725-5176
www.skincancer.org

Medicine Assistance Tool
www.medicineassistancetool.org

CLINICAL TRIALS WEBSITES

ClinicalTrials.gov
www.clinicaltrials.gov

EmergingMed
www.emergingmed.com

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