

TREATMENT UPDATE:

# Advanced Skin Cancer

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# Treatment Update: Advanced Skin Cancer

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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 (applied directly onto the skin) medications or surgical removal of the tumor.



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.

In certain cases, surgery may be difficult or impossible. Radiation therapy may be considered in certain situations; for example, if neither surgery nor a topical medication is an option, or if the skin cancer is in a cosmetically sensitive area, such as the face.

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 as a way to treat the cancer.

## **Advanced Basal Cell Skin Cancer**

Several years ago, researchers discovered that 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.

Vismodegib (Erivedge) and sonidegib (Odomzo) are Hedgehog pathway inhibitors approved by the U.S. Food and Drug Administration (FDA) to treat advanced BCC. These drugs are used in cases where the BCC has spread to other parts of the body, has recurred (returned) 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.

## Advanced Squamous Cell Skin Cancer

There have not been many clinical trials conducted on advanced SCC, as it is a rare condition. There is much more data available on squamous cell cancer of the mouth and throat, and the FDA has approved the targeted therapy cetuximab (Erbix) for those cancers. Cetuximab, which is given intravenously, is also approved for the treatment of certain types of colorectal cancer. 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.

If a drug has been approved by the FDA for one use, doctors may prescribe it for other conditions. As clinical trials have shown that cetuximab can be effective as a therapy for advanced SCC of the skin, it is sometimes prescribed to treat people whose tumors cannot be surgically removed or treated with radiation.

Chemotherapy drugs, given orally or intravenously, can slow the spread of advanced SCC. In some cases, they may shrink tumors enough so that other treatments, such as surgery or radiation, can be used. Side effects of chemotherapy can be significant, so it is generally used in cases where other treatments have failed or are not an option.

In 2018, the FDA approved the immunotherapy cemiplimab-rwlc (Libtayo) for the treatment of people with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for surgery or radiation. Cemiplimab-rwlc, an immunotherapy, is now often the first-line (initial) treatment for this type of skin cancer.

In June 2020, the FDA approved the immunotherapy pembrolizumab (Keytruda) for the treatment of recurrent or metastatic CSCC that is not curable by surgery or radiation.

# Treatment Approaches for Melanoma

Melanoma is considered to be 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 removal of the tumor.

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 not used as frequently today as it was in the past, 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).** In 2014, pembrolizumab was approved for the treatment of advanced or unresectable (unable to be removed) melanoma. In 2019, the FDA expanded the approval of pembrolizumab to include adjuvant (post-surgery) treatment of melanoma that has lymph node involvement. Given intravenously, pembrolizumab blocks the PD-1 cellular pathway (a pathway that inhibits the body's immune system from working properly).



- **Nivolumab (Opdivo).** Like pembrolizumab, nivolumab works by blocking the PD-1 pathway and is also given intravenously. Nivolumab was approved for the treatment of advanced melanoma in 2014. In 2017, the approval was extended for the adjuvant treatment of melanoma that has lymph node involvement.
- **Talimogene laherparepvec (Imlygic).** This drug, referred to as TVEC, is injected directly into the melanoma lesions, where it can cause cancer cells to rupture and die. As TVEC may also improve the immune system's response to cancer, melanoma lesions that were not injected with the drug also sometimes shrink or disappear.

Additionally, the combination of ipilimumab and nivolumab is approved for the treatment of people with advanced melanoma. This combination treatment is designed to block the actions of both 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. People who may benefit from targeted therapies have specific DNA changes (called driver mutations) that allow cancers to develop and grow. The most important known driver mutation in melanoma is the BRAF mutation, with up to 50 percent of melanomas having this mutation.

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. Vemurafenib can help slow or stop the spread of melanoma cells.
- **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 unresectable or advanced melanoma with 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 immunotherapy, 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 lymphocytes (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 Chemotherapy

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

- Achiness
- Nausea/vomiting
- Hair loss
- Increased risk of infection (from having too few white blood cells)
- Easy bruising or bleeding (from having too few platelets)
- 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. 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, and 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, and frequent diarrhea (colitis). Immunotherapy can also affect the thyroid gland, so thyroid levels are typically monitored while on treatment.

## 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. Blood work is monitored during the time people are taking targeted therapy.



## 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.
- Eat meals that are chilled, which often makes food more easily tolerated.
- Nibble on dry crackers or toast. These bland foods are easy on the stomach.
- 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, which can be lost with severe diarrhea. Electrolytes are body salts that must stay in balance for cells to work properly.
- 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.

### *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 care team, as they may need to prescribe topical creams to help manage the rash.



## Managing 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 determine if it is safe and will not interfere with your treatment. Many pain medications can lead to constipation. Your doctor can recommend over-the-counter or prescription medications that help to avoid or manage constipation.
- Physical therapy, acupuncture and massage may also be of help in managing your pain. Consult with a member of your health care team before beginning any of these activities.

## Managing Fatigue

Fatigue (extreme tiredness not helped by sleep) is one of the most common side effects of many cancer treatments. If you are very 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 monitor bloodwork, to make sure that your fatigue is not due to a more serious condition.

There are a number of other tips for reducing fatigue:

- Take several short naps or breaks during the day.
- Take 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.
- Make sure you are getting adequate nutrition and eating a balanced diet.

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

# 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 and get to know 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 (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.** 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.

**Bring someone with you to your appointments.** Even if you have a journal and a prepared list of questions or concerns, it's always helpful to have support when you go to your appointments. The person you bring 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 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 they can consult with your primary care physician or specialist as needed.

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 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.cancercare.org](http://www.cancercare.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.



## 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: 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.

### **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.



## Resources

### **CancerCare®**

800-813-HOPE (800-813-4673)  
[www.cancercares.org](http://www.cancercares.org)

### **American Cancer Society**

800-227-2345  
[www.cancer.org](http://www.cancer.org)

### **Cancer.Net**

Patient information from  
the American Society of  
Clinical Oncology  
888-651-3038  
[www.cancer.net](http://www.cancer.net)

### **National Cancer Institute**

800-422-6237  
[www.cancer.gov](http://www.cancer.gov)

### **AIM at Melanoma**

1-877-246-2635  
[www.aimatmelanoma.org](http://www.aimatmelanoma.org)

## **CLINICAL TRIALS WEBSITES**

### **EmergingMed**

[www.emergingmed.com](http://www.emergingmed.com)

### **National Cancer Institute**

[www.cancer.gov](http://www.cancer.gov)

### **Melanoma International Foundation**

866-463-6663  
[www.melanomainternational.org](http://www.melanomainternational.org)

### **Melanoma Research Foundation**

877-673-6460  
[www.melanoma.org](http://www.melanoma.org)

### **The Skin Cancer Foundation**

212-725-5176  
[www.skincancer.org](http://www.skincancer.org)

### **Medicine Assistance Tool**

[www.medicineassistancetool.org](http://www.medicineassistancetool.org)

This booklet is supported by Bristol Myers Squibb and an independent educational grant from Merck & Co. Inc.



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