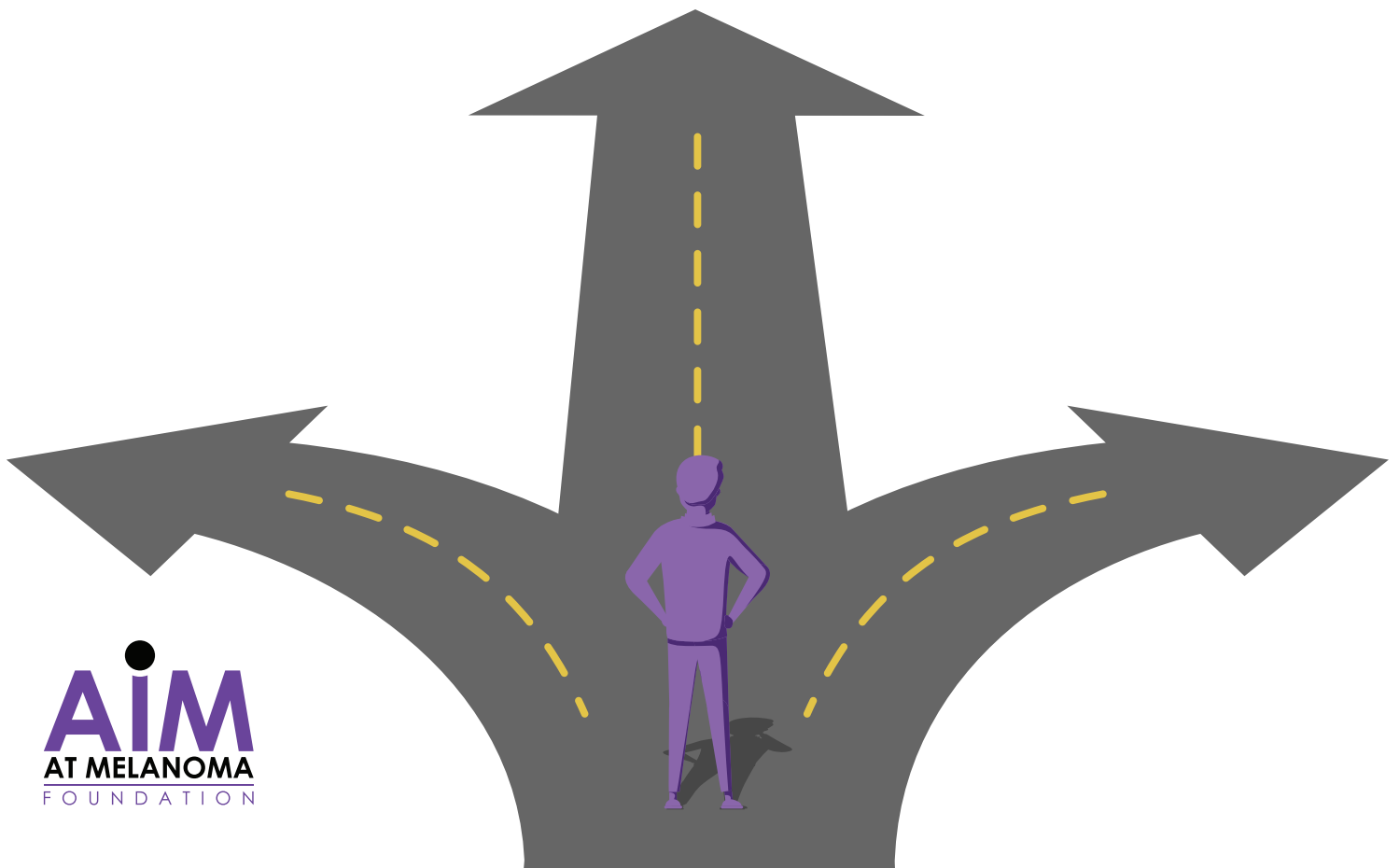


Options for Stage III Melanoma

Making the Decision That's Right for You



INTRODUCTION

You are reading this because you or someone you love has been diagnosed with Stage III melanoma. Dealing with a diagnosis of melanoma can be an overwhelming experience. You (or your loved one) may have already had surgery to remove the tumor. Still, the melanoma is considered at high risk to come back or spread.

The good news is that there are now multiple options available to you, including treatments that can help reduce the risk of your melanoma coming back. In addition to active surveillance, there are drugs that have been tested in melanoma patients with more advanced cancer than yours, so we have learned a lot about them. Additionally, they have been tested in patients with surgically removed Stage III melanoma—your stage, and those studies revealed that the new treatments help reduce the risk of melanoma coming back in those patients. ***This type of treatment is called adjuvant therapy because it is given after the primary treatment, in your case surgery, and it is a therapy (drug).***

This guide is organized to give you information on your disease, the options available, and how to weigh the options with your oncology team to make the decision that is right for you. It explores the following topics:

- UNDERSTANDING YOUR RISK 2
- WHY ARE STAGE III PATIENTS AT HIGH RISK FOR RECURRENCE, AND WHY SHOULD THEY CONSIDER TREATMENT? 4
- OPTIONS FOR STAGE III MELANOMA 5
 - Targeted Therapy 5
 - Immunotherapy 6
 - Active Surveillance 7
- HOW WELL THESE DRUGS WORK 8
- THE SIDE EFFECTS OF THE DRUGS 11
- OTHER CONSIDERATIONS 17
 - Drug Administration 17
 - Financial Issues 18
 - Fertility/Family Planning 19
- WEIGHING THE DIFFERENT OPTIONS 20
- MY RESOURCES 23
- FURTHER READING ON STAGING 25
- ACKNOWLEDGMENTS 31

UNDERSTANDING YOUR RISK

Your melanoma stage affects the expected course of your disease. The stages of melanoma can generally be divided into 4 groups:

Stage 0 is thin melanoma which has not penetrated (invaded) the deeper layers of the skin (*in situ*).

Stages I and II are melanomas that are limited to the skin. These melanomas vary in how thick they are and whether the skin covering the melanoma is **ulcerated** or not. Thicker melanomas and ulcerated melanomas have a higher risk of recurring.

Stage III is melanoma that has spread from the original site of your melanoma to 1 or more of the nearby **lymph nodes** or to the nearby skin/tissue in between. Stage III melanoma is divided into 4 groups, A, B, C, and D, as described below. For more information about how these groups are defined, see the section **FURTHER READING ON STAGING**.

Stage IV is melanoma that has spread farther than regional lymph nodes, to distant sites such as the lung, liver, or brain.

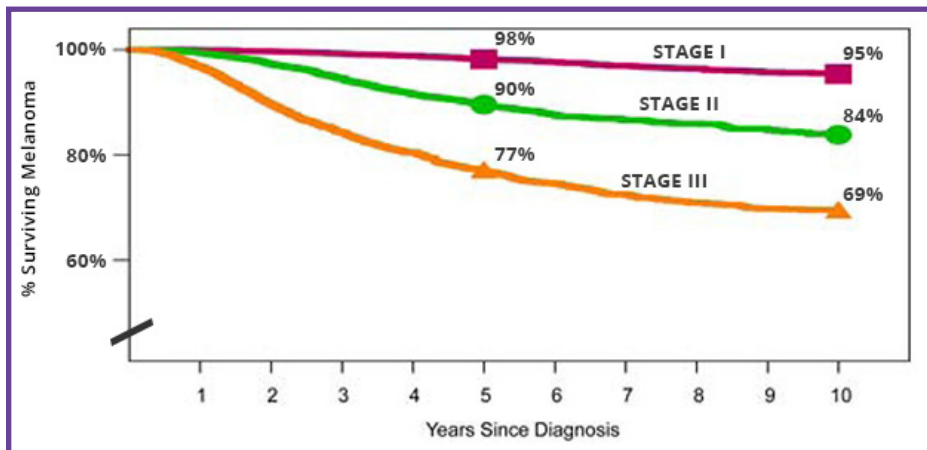
A survival curve shows how many people can be expected to still be alive, typically anywhere from 1 to 10 years, after their diagnosis. Graphics 1 & 2 show the likelihood of surviving melanoma for 5 or 10 years (melanoma-specific survival). Patients who die from other causes are not included in this number. Remember, survival rates are estimated averages based on past cases but do not necessarily predict your individual survival. Every person and case is different, and many factors contribute to survival. You can discuss these curves with your oncology team.

KEY TERMS:

Lymph nodes: Small, bean-shaped structures containing white blood cells that fight disease. These are located throughout the body but mainly in the armpit, groin, and neck.

Ulcerated: Term used to describe when the top layer of skin on a melanoma tumor is broken or missing.

Graphic 1. Differences in melanoma-specific survival rates between Stages I, II, and III melanoma. Adapted from Gershenwald et al. 2017.

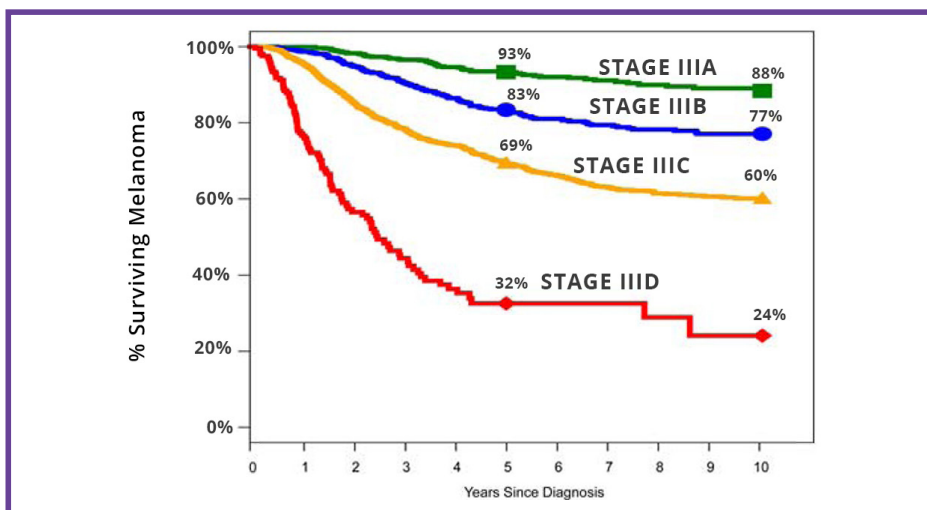


Graphic 1

As you can see from this graphic, after 10 years:

- 95% of Stage I patients are alive
- 84% of Stage II patients are alive
- 69% of Stage III patients are alive. Stage III has a relatively poor disease outcome compared with Stage I or II melanoma.

Graphic 2. Differences within Stage III, your stage. Stage III is divided into Stage IIIA, IIIB, IIIC, and IIID. Adapted from Gershenwald et al. 2017.



Graphic 2

Graphic 3. Highlights the differences in survival for different Stage III substages. Adapted from Gershenwald et al. 2017.

Stage	Melanoma-specific survival	
	5-Year	10-Year
Stage IIIA	93%	88%
Stage IIIB	83%	77%
Stage IIIC	69%	60%
Stage IIID	32%	24%

Graphic 3

Within the Stage III group, survival rates generally get worse as you go from Stage IIIA to Stage IIID. This is why it is important you and your oncology team discuss your individual stage and risk.

WHY ARE STAGE III PATIENTS AT HIGH RISK FOR RECURRENCE, AND WHY SHOULD THEY CONSIDER TREATMENT?

High-risk melanoma is a melanoma that has a high likelihood of **recurring** or spreading after the primary tumor has been surgically removed. **Overall, patients with Stage III melanoma have a 68% risk of their melanoma recurring within a 5-year period. That means 2 out of 3 people will have a recurrence of their melanoma.** For this reason, Stage III patients should consider adjuvant (additional) treatment.

The idea that your cancer might come back or spread may be confusing to you, since you may have been told that “we got it all.” Anything that could be seen has been removed. However, what may be left is what your medical team can’t see. Unfortunately, there is a chance that some melanoma cells may have broken away from the primary tumor and are still in your body. Although your medical team has done their best to remove all the cancer that is visible, it’s not possible to search your entire body for any breakaway cancer cells. Adjuvant therapy is designed to eradicate these breakaway cells—either by interfering with the cellular processes the cells use to grow and multiply or by helping your body’s immune system to hunt them down and destroy them. In this way, the cancer may be kept from spreading or coming back.

There is a long history of people using adjuvant therapy in other cancers, such as breast cancer. Adjuvant therapy has also been used in the treatment of melanoma for decades, but the older options were highly toxic and did not improve survival. That has changed. The good news is that now we have more options for Stage III melanoma, and they are more effective and generally have fewer side effects. The next sections provide you information about these options and, hopefully, can help guide you and your oncology team in deciding what is right for you.

KEY TERMS:

Recurrence: Melanoma that has returned after treatment.

OPTIONS FOR STAGE III MELANOMA

You will now be working with your oncology team to figure out what to do next. There are 3 possible options if you have Stage III melanoma. These are targeted therapy, immunotherapy, or active surveillance (no medication involved).

To determine if targeted therapy is an option for you, you will need to have your tumor tested for a marker called *BRAF*. If the *BRAF* test shows that your tumor has the *BRAF* mutation, you are eligible for targeted therapy. But if your tumor does **not** have the *BRAF* mutation, you are not eligible for targeted therapy.

The second option is immunotherapy. Immunotherapy uses medications that are designed to “awaken” your body’s own immune system to help fight any remaining cancer cells. You are eligible for immunotherapy regardless of your tumor’s *BRAF* status.

Finally, the third option is active surveillance, which means not taking any medication but watching your condition carefully with your oncology team in order to catch your melanoma early if it comes back.

Each of these options is discussed below, with a review of the potential plusses and minuses.

TARGETED THERAPY

Both *BRAF* and *MEK* kinases are key protein enzymes that help melanoma cells grow. About half of all melanoma patients have a mutated form of code for the *BRAF* protein in their tumors. This is called having a *BRAF* mutation.

For those patients with a *BRAF* mutation, there is the option to use a combination of oral (by mouth) drugs called Tafenlar[®] (dabrafenib) and Mekinist[®] (trametinib) as an adjuvant therapy. When given together, these drugs can help block these proteins and stop the melanoma from growing. Remember, these drugs only work in people who have the *BRAF* mutation.

KEY TERMS:

Mutation: Change in a structure of a gene that often leads to a change in a protein.

Tafinlar+Mekinist is approved for patients with Stage III melanoma that has been surgically removed and has tested positive for the *BRAF* mutation. It is not approved for patients who do not have the *BRAF* mutation (**wild-type** tumors). Therefore, knowing if you have this genetic mutation is critical before you choose a treatment.

Testing for the *BRAF* mutation requires that a sample of your melanoma tumor be processed in a specific way. Ideally, your melanoma should be tested for the *BRAF* mutation with an FDA-approved test to ensure that your healthcare team has access to the information needed and to aid in reimbursement. A list of these FDA-approved tests is available at <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>.

Because using Tafinlar+Mekinist for adjuvant therapy is still a relatively new treatment option, your medical team may not have ordered the test. You should check with them to see if it has been ordered. If not, you should ask to be tested for the *BRAF* mutation before sitting down with your oncologist to discuss your options. Occasionally, there is not enough tumor available to complete the test. If this happens, your oncologist will discuss what happens next.

IMMUNOTHERAPY

Immunotherapy is a treatment that gives your immune system more power to fight your cancer. Every day, our immune system recognizes dangerous things—cancer cells, foreign invaders like bacteria and some viruses—and hunts them down and destroys them. However, some cancer cells (including some melanoma cells) have ways evading/putting the brakes on your immune system, preventing it from doing its job. In fact, the immune system may not even recognize these cancer cells, which might explain why they can keep growing and multiplying.

Immune checkpoint inhibitors take the brakes off the immune system, allowing it to identify and destroy cancer cells. PD-1 inhibitors and CTLA4 inhibitors are types of immune checkpoint inhibitors. PD-1 inhibitors generally produce fewer and less severe side effects compared with CTLA4 inhibitors, such as Yervoy® (ipilimumab). Additionally, in a clinical trial Opdivo® (nivolumab) did a better job of preventing recurrence of Stage III cancer compared with Yervoy. Opdivo is a PD-1 inhibitor approved for use in the adjuvant setting for melanoma. Keytruda® (pembrolizumab), another PD-1 inhibitor, was recently approved by the FDA for adjuvant therapy as well.

ACTIVE SURVEILLANCE

In some cases, you and your oncologist may decide that **active surveillance** is the best course of action for you. Active surveillance is a way of monitoring you closely for melanoma recurrence rather than treating you right away to prevent the melanoma from coming back. Perhaps your tumor has a relatively low risk of recurring, or you have had health problems and are concerned you will not be able to tolerate treatment. Under active surveillance, you won't receive adjuvant treatment but will have regular follow-up exams and tests to detect any spread or recurrence of your cancer.

Follow-ups may include:

- Physical exams several times a year focusing on your skin and lymph nodes
- Imaging scans such as an **ultrasound**, an x-ray, a **computed tomography (CT)**, a **PET/CT**, or **magnetic resonance imaging (MRI)** to see if there are any signs of melanoma in your lymph nodes or other areas of your body
- Your oncology team may recommend genetic testing if you have had 3 or more invasive melanomas or someone in your family has had melanoma. This testing may allow your provider to further define an appropriate follow-up strategy for you.

KEY TERMS:

Active surveillance: A disease management plan that involves watching a patient's condition closely and doing exams and tests on a regular schedule to determine if the condition is progressing. Treatment would be considered if the disease progresses (in this case, the melanoma recurs or spreads).

Ultrasound: An imaging scan that uses sounds or vibrations to create an image of internal parts of the body.

Computed tomography (CT): An imaging scanning technique that uses x-rays from different angles to make a 3-dimensional picture of the inside of the body.

Positron emission tomography (PET)/CT: An imaging method that combines CT with another nuclear imaging test (PET) to provide detailed information about both the structure (CT) and the function (PET) of cells and tissues in the body. This test is helpful in finding and grading tumors.

Magnetic resonance imaging (MRI): A scanning technique that uses magnets and radio waves to generate images of the organs in the body.

HOW WELL THESE DRUGS WORK

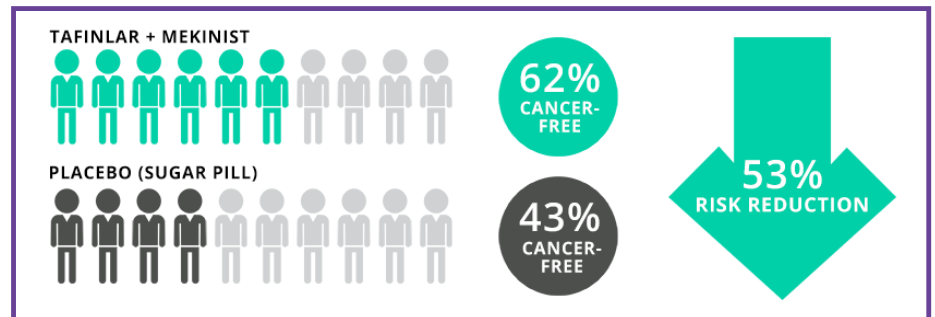
Oncologists have different ways of looking at how well cancer drugs work. First, they typically look at how many people are still alive after 5 years and after 10 years. This is called the **overall survival** benefit, meaning how long a person will live if he or she takes one of these treatments, regardless of whether the cancer has come back or not. The other way is to look at **relapse-free survival** (or disease-free survival), which means how long a person may live without having a recurrence of their cancer. It's important to keep in mind that targeted therapy has not been compared directly (head-to-head) with immunotherapy for Stage III melanoma.

TARGETED THERAPY

For targeted therapy, a trial compared the Tafenlar+Mekinist combination with a placebo (sugar pill). This trial enrolled 870 patients with Stage III melanoma who had the *BRAF* mutation. Half of the patients received the combination therapy, and half received a placebo.

As shown in Graphic 4, after 2.8 years, 62% of patients receiving the combination were melanoma free, compared with 43% of patients receiving the placebo. Overall, there was a 53% reduction in the risk of the melanoma coming back in patients treated with the combination as compared with the placebo.

Graphic 4. Results of the adjuvant trial of Tafenlar+Mekinist vs placebo in patients whose melanoma tumors have been surgically removed and who are at a high risk of recurrence. Adapted from Long et al. 2017.



Graphic 4

This benefit is ongoing—recent results show that after 4 years, 54% of the patients treated with the combination were still melanoma free, compared with 38% of those who received the placebo. In addition, this combination also improved overall survival rates. At the 3-year timepoint, 86% of patients in the combination arm were alive, compared with 77% of those who received the placebo. Even though this was not considered statistically significant by the criteria set up in the study, it was considered a clinically meaningful improvement.

IMMUNOTHERAPY

Opdivo

For the Opdivo approval, a trial compared Opdivo with Yervoy. This trial enrolled 906 people who had melanoma in their lymph nodes (Stage III, but excluding Stage IIIa) or distant metastases (Stage IV) that was removed by surgery.

As shown in Graphic 5, after 18 months, 66% of the patients treated with Opdivo were melanoma free, compared with 53% of patients receiving Yervoy. Overall, there was a 35% reduction in the risk of the melanoma coming back in patients treated with Opdivo as compared with Yervoy. It's important to remember that this study compared Opdivo with a drug already known to work in this setting (Yervoy) and not with a placebo. There were also people in this study who had Stage IV melanoma, which is a more advanced disease. More time is needed to see if there will be an improvement in overall survival with Opdivo as compared with Yervoy.

Graphic 5. Results of the trial of Opdivo vs Yervoy in patients with completely surgically removed melanoma that are at high risk of recurrence. Adapted from Weber et al. 2017.

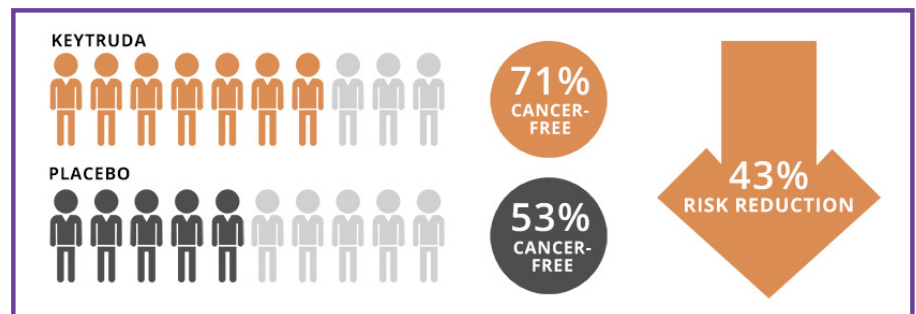


Graphic 5

Keytruda

For the Keytruda approval, a trial compared Keytruda with a placebo (sugar pill). This trial enrolled 1,019 people who had melanoma in the lymph nodes (some Stage IIIa patients as well as those with more severe Stage III disease) that was removed by surgery. As shown in Graphic 6, at 18 months, 71% of patients treated with Keytruda were cancer free, while 53% of patients treated with the placebo were cancer free. Overall, there was a 43% reduction in the risk of the melanoma coming back in patients treated with Keytruda as compared with the placebo.

Graphic 6. Results of the trial of Keytruda vs placebo in patients with completely surgically removed Stage III melanoma. Adapted from Eggermont 2018.



Graphic 6

DECISION-MAKING POINTS:

- If you have the *BRAF* mutation, you may be eligible for either targeted therapy or immunotherapy. We don't know if it is better for Stage III patients to receive targeted therapy or immunotherapy
- For both immunotherapy and targeted therapy, we don't yet know which patients will respond well to these drugs and which ones won't
- Opdivo has received FDA approval for all patients with Stage III melanoma that has been surgically removed, although the clinical trial did not include Stage IIIA
- Keytruda has received FDA approval for all patients with Stage III melanoma that has been surgically removed. It was tested in some Stage IIIA melanomas as well as more severe Stage III disease
- It is important not to simply look at the snapshots of the data we have given you and try to compare the treatments. These trials were done in different groups of people at different times, and these trials were set up differently. We are also only showing you a portion of the data. It's important to have a conversation with your oncology team about the data and what it means for you

THE SIDE EFFECTS OF THE DRUGS

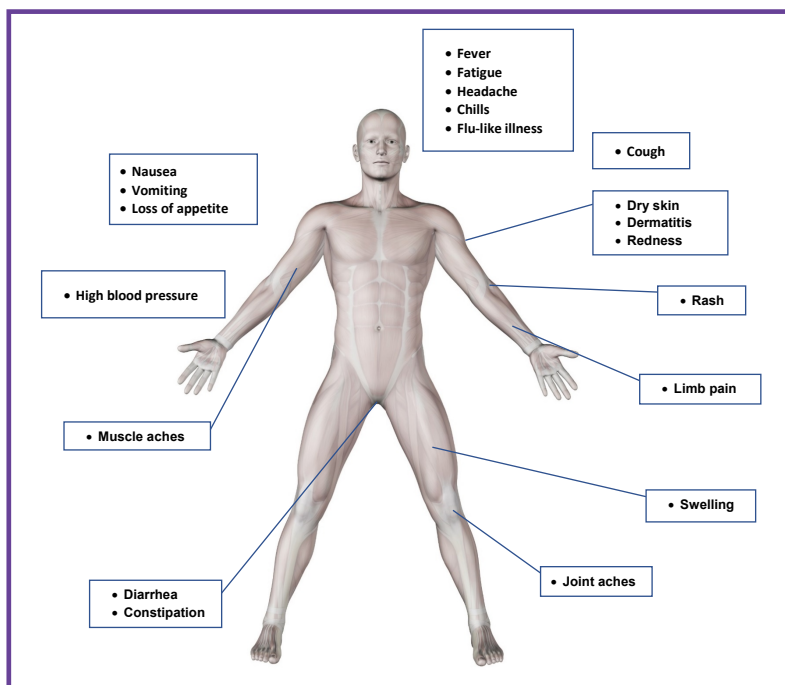
TARGETED THERAPY

Targeted therapy is associated with a range of side effects. In the clinical trial that led to Tafinlar+Mekinist approval in the adjuvant setting, 97% of patients who received Tafinlar+Mekinist reported having at least 1 side effect. Common side effects of Tafinlar+Mekinist are shown in Graphic 7 and Graphic 8.

Graphic 7. Common side effects associated with Tafinlar+Mekinist and the percentage of patients experiencing them in the clinical trials. These side effects are listed in descending order from the most common to the least common. From the manufacturer's prescribing information.

Common side effects of Tafinlar+Mekinist		
• Fever (63%)	• Vomiting (28%)	• Dry skin (13%)
• Fatigue (59%)	• Joint aches (28%)	• Acne-like dermatitis (12%)
• Nausea (40%)	• Muscle aches (20%)	• Constipation (12%)
• Headache (39%)	• Cough (17%)	• High blood pressure (11%)
• Chills (37%)	• Flu-like illness (15%)	• Loss of appetite (11%)
• Rash (37%)	• Limb pain (14%)	• Redness (11%)
• Diarrhea (33%)	• Swelling (13%)	

Graphic 7



Graphic 8. Body image showing common side effects associated with targeted therapy.

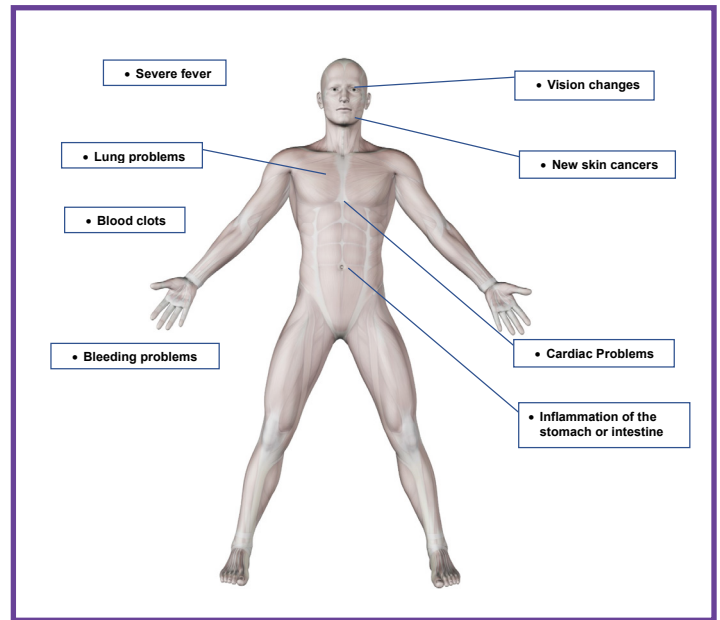
Graphic 8

Targeted therapies tend to cause “nuisance” side effects, not typically as serious as those associated with immunotherapies but nonetheless challenging (eg, fevers can make the patient very uncomfortable). However, some of the side effects—particularly cardiac side effects and vision problems—can be very serious and must be reported right away. The range of serious side effects is shown in Graphic 9 and Graphic 10 below. Of note, the fever commonly associated with Tafenlar+Mekinist can get worse and lead to serious complications if it is not treated promptly.

Serious side effects associated with targeted therapy

- Bleeding problems (19%)
- Severe fever (17%)
- High blood sugar (hyperglycemia) (<6% severe or life-threatening)
- Heart problems (including heart failure and heart rhythm problems) (3%)
- Blood clots (2%)
- Eye problems (2%)
- New skin cancers (<2%)
- Lung problems (<1%)
- Tears of the stomach or intestine (0.3%)
- Breakdown of red blood cells (anemia) in people with a relatively rare condition called glucose-6-phosphate dehydrogenase deficiency

Graphic 9



Graphic 10

Graphic 10. Body image showing serious effects associated with Tafenlar+Mekinist.

Graphic 9. Serious side effects associated with Tafenlar+Mekinist and the frequency of their occurrence in the adjuvant setting. Adapted from the manufacturer’s prescribing information.

HOW ARE THESE SIDE EFFECTS MANAGED?

With targeted therapy, sometimes an individual side effect can be managed with specific medications (for example, acetaminophen for fever) and supportive care (increasing fluids in patients with fever). Other times, these side effects can be managed with either a decrease in the dosage or by briefly stopping one or both of the drugs and then resuming the drug(s) after the symptoms go away. Sometimes when the drug or drugs are resumed, it is at a lower dosage. In some rare cases, the drug may need to be permanently discontinued. Once patients stop taking the drugs, the drugs wash out of the body within a few months and the symptoms typically stop.

A safety concern of targeted therapy is the potential for drug-drug interactions, since these drugs are broken down by a common enzyme that breaks down other medications as well. If you are on other medications, that is something to consider. This is especially important if you are taking any medications that may cause heart arrhythmias or you are on hormonal contraceptives, since this can cause drug-drug interactions with the targeted therapy. Drug-drug interactions are less of an issue with immunotherapies, since they are not broken down by the same enzymes acting on most prescription drugs.

IMMUNOTHERAPY

Immunotherapy is associated with a range of side effects. In the Opdivo and Keytruda clinical trials, most patients had side effects that could be linked to the therapy. Severe or life-threatening side effects occurred in less than 20% of patients. Graphic 11 lists the common side effects associated with Opdivo, Graphic 12 shows those associated with Keytruda, and Graphic 13 shows a body image with these side effects.

Graphic 11. Common side effects associated with immunotherapy and the percentage of patients experiencing them in the clinical trials. These side effects are listed in descending order from the most common to the least common. Adapted from the manufacturer's prescribing information.

Common side effects associated with Opdivo		
• Feeling tired (57%)	• Headache (23%)	• Joint pain (19%)
• Diarrhea (loose stools) (37%)	• Nausea (23%)	• Low thyroid function (12%)
• Rash (35%)	• Upper respiratory tract infection (22%)	• Dizziness (11%)
• Pain in muscles, bones (32%)	• Stomach pain (21%)	• Shortness of breath (10%)
• Itchy skin (28%)	• Cough (19%)	• Constipation (10%)

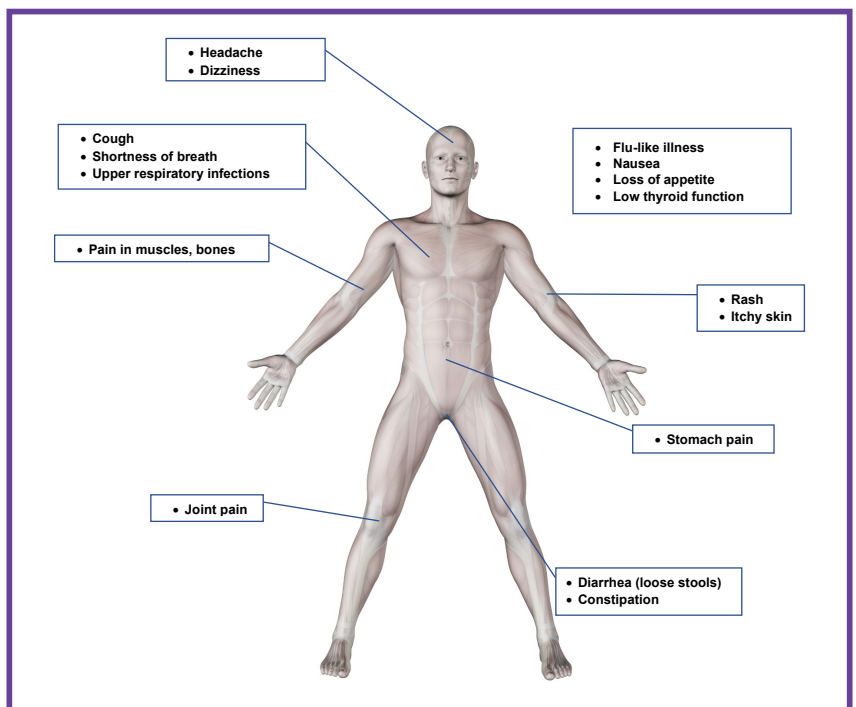
Graphic 11

Graphic 12. Common side effects associated with Keytruda and the percentage of patients experiencing them in the clinical trials. These side effects are listed in descending order from the most common to the least common. Adapted from the manufacturer's prescribing information.

Common side effects associated with Keytruda
• Diarrhea (loose stools) (28%)
• Itchy skin (19%)
• Nausea (17%)
• Joint pain (16%)
• Low thyroid function (15%)
• Cough (14%)
• Rash (13%)
• Muscle weakness (11%)
• Flu-like illness (11%)
• Weight loss (11%)
• Hyperthyroidism (10%)

Graphic 12

Graphic 13. Body image showing common side effects associated with immunotherapy.



Graphic 13

As mentioned earlier, immunotherapy works by unleashing the body's immune system to fight the cancer. For that reason, the immune system may get revved up and attack any organ or tissue. This means if you receive immunotherapy, you can have a range of side effects affecting any part of your body. Also, because these side effects are caused by changes in your immune system and not directly by the drug, they can happen at any time during treatment or even after treatment has ended.

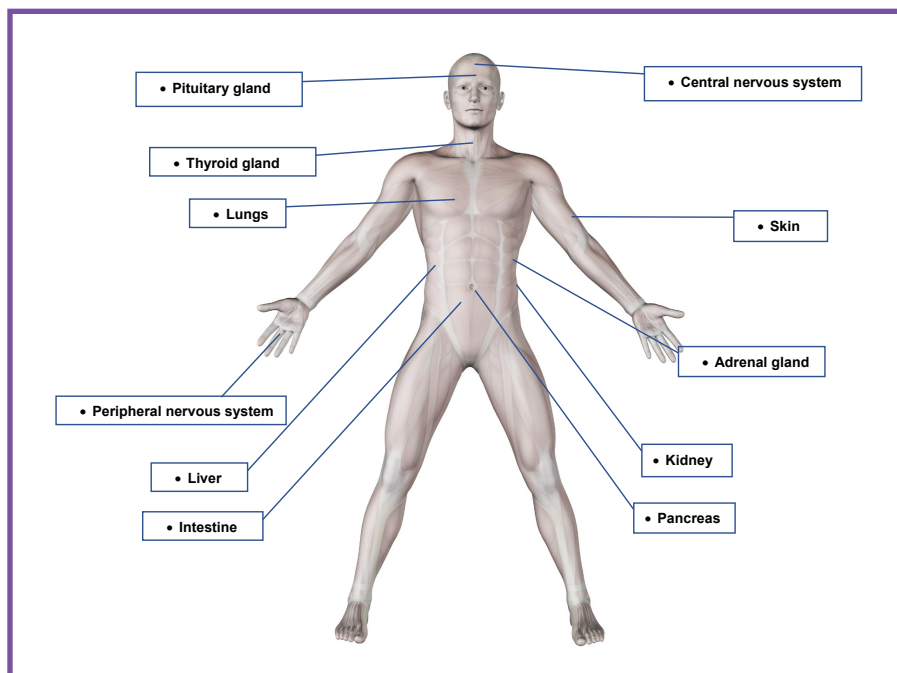
Potentially serious side effects of immunotherapy can become life-threatening. These side effects are shown in Graphic 14. Graphic 15 shows a body image with the organs and organ systems that can be affected. This list is not complete—as mentioned above, any organ or body system can be affected.

Graphic 14. Serious side effects that can occur with immunotherapy. Rates of adverse events are listed from clinical trials; they may be higher in the real-world setting. These are generally grouped from most common to least common.

Potentially serious side effect	Overall occurrence rate (% of patients affected)	Severe or life-threatening occurrence rate (% of patients affected)
Skin problems (such as rash and itching)	Up to 40%	Less than 2%
Intestinal problems		
Diarrhea , which can lead to dehydration	8% to 20%	Less than 2%
Colitis (inflammation of the colon)	1% to 3%	Less than 1%
Hormonal problems		
Thyroid (most common)	3% to 10%	Less than 1%
Other endocrinopathies involving the pancreas (diabetes), adrenal glands, or pituitary (control center of the brain)	Less than 3%	Less than 3%
Liver problems	Less than 10%	Less than 1%
Lung problems (called pneumonitis)	1% to 6%	1% to 2%
Neurologic problems (including inflammation of the brain)	Less than 3%	Less than 1%
Kidney problems	Less than 2%	Less than 1%

Graphic 14

Graphic 15. Organs and organ systems affected by immunotherapy. The result can be serious side effects.



Graphic 15

HOW ARE THESE SIDE EFFECTS MANAGED?

With immunotherapy, reducing the dosage is not generally recommended. The management of these side effects typically involves stopping immunotherapy and then managing the side effect. In many cases, corticosteroids are used to quiet the immune system, after which immunotherapy can be restarted. But in severe cases, the drug may need to be discontinued.

DECISION-MAKING POINTS:

- Immunotherapy may cause hormonal side effects that are manageable, but you may need to stay on hormone replacement for life. Many of the other side effects are reversible, although there are some cases in which patients have permanent problems with the liver, kidneys, or other organs. Also, side effects can occur long after the immunotherapy regimen is completed

OTHER CONSIDERATIONS

DRUG ADMINISTRATION

For targeted therapy, you will be taking capsules/tablets twice a day as long as you are tolerating the combination and the melanoma doesn't come back, for up to 1 year.

Opdivo is given as an intravenous (IV) infusion into your arm, typically at your oncologist's office. The drug is usually given every 2 weeks (but can be given every 4 weeks) and will be continued as long as you tolerate it and the melanoma doesn't come back, for up to 1 year. The infusion lasts for 30 minutes.

Keytruda is given as an IV infusion into your arm, typically at your oncologist's office. The drug is usually given every 3 weeks and will be continued as long as you tolerate it and the melanoma doesn't come back, for up to 1 year. The infusion lasts for 30 minutes.

Now that you have a better understanding of how each treatment is given, here are some factors you may want to consider in choosing your treatment option:

Targeted Therapy

- How do you feel about having to take "pills" every day?
- Will you remember to take your medication twice a day, every day?
- The MEKINIST® (trametinib) component of targeted therapy must be refrigerated. Would this be an issue for you (for example, having to keep the medication at the proper temperature when traveling)?
- How diligent will you be about taking these pills? They need to be taken on an empty stomach (at least 1 hour before or 2 hours after a meal)

Immunotherapy

- Are you willing to go to an infusion center every 2, 3, or 4 weeks?
- Do you have the transportation and the means to get to the infusion center?
- Can you arrange your schedule to be at the infusion center every 2, 3, or 4 weeks?

Many patients expect that pills will have fewer side effects than IV drugs, but that's not always the case. You can get rashes or feel achy with oral drugs just as you do after an IV infusion, and you may be less mentally prepared for side effects from an oral drug than from an infusion.

FINANCIAL ISSUES

Immunotherapy and targeted therapies are innovative medicines and are generally costlier than chemotherapy. Before sitting down to make your treatment decision, you should ask your oncologist's office to contact your health insurance company to find out whether these medications are covered by your insurance and if you will be responsible for paying for any part of the bill. You can also look into this on your own. Several things to consider include the following:

- 1. If you have commercial insurance.** With commercial insurance, you generally can receive co-pay assistance from the drug manufacturer. Financial assistance information for targeted therapy (Novartis) and immunotherapy (Bristol-Myers Squibb or Merck & Co, Inc.) is shown below under My Resources.
- 2. If you have insurance from a federal/state program (such as Medicare, Medicaid, or Tricare).** If you have insurance through a federal/state insurance program, you can't receive financial assistance from the drug manufacturer, but you may be eligible for co-pay assistance from an independent charitable foundation. <https://panfoundation.org/index.php/en/patients/assistance-programs/melanoma>
- 3. If you are not insured.** If you are not insured, you may be eligible for free medications through either the drug manufacturers or charitable organizations, depending on your income.

For information on financial resources and assistance for Tafinlar+Mekinist, check out: <https://www.us.tafinlarmekinist.com/advanced-melanoma/patient-support/cost-support>

For information on financial resources and assistance for Opdivo, check out: <http://www.bmsaccesssupport.bmscustomerconnect.com/patient/financial-support>

For information on financial resources and assistance for Keytruda, check out: <https://www.merckaccessprogram-keytruda.com>

To find additional financial assistance through charitable organizations, check out the Patient Access Network Foundation: <https://panfoundation.org/index.php/en/patients/assistance-programs/melanoma>

- 4. Which therapy you are considering (IV at office vs oral at home).** For insurance purposes, oral drugs such as Tafinlar+Mekinist may be treated differently than an IV drug such as Opdivo or Keytruda. If you are on Medicare, oral drugs such as Tafinlar+Mekinist will most likely be covered under Medicare Part D, which is the prescription drug benefit, and Opdivo or Keytruda will most likely be covered under Medicare part B.
- 5. Whether you will be able to work.** Here are some questions to ask yourself:
 - Are you able to miss work during treatment, either to receive infusions or because of the side effects of therapy?
 - Does your work require you to travel?
 - If you work full time, can you arrange a flexible schedule to meet your treatment requirements? It is important to consider these factors and find out your legal protections under the Family and Medical Leave Act. The Patient Advocate Foundation www.patientadvocate.org (800.532.5274) can assist in this process.

FERTILITY/FAMILY PLANNING

Pregnancy Prevention

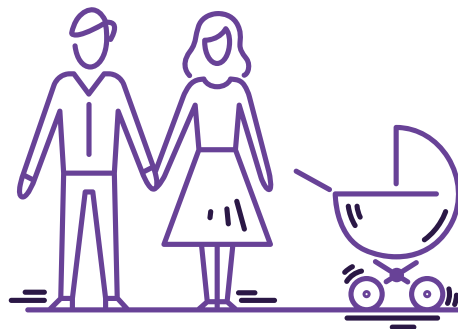
Whether you are a woman of childbearing age or a man who is sexually active, it is important that you use effective birth control while on treatment and for the specified time thereafter. These medications can cause fetal harm. People taking Tafinlar+Mekinist should use an effective nonhormonal birth control method such as a condom, diaphragm, or spermicide during treatment and for 4 months after the last dose. Hormonal birth control (pills) is not recommended because of the potential for interaction with this drug combination. For Opdivo or Keytruda, you should use an effective method of birth control during treatment and for 6 months after the last dose of therapy.

Fertility/Family Planning

Fertility and family planning can be important issues to consider. Little is specifically known about the impact of these drugs on fertility. What is known is that once targeted therapy is discontinued, there are generally no long-term side effects, and the drugs are out of your system relatively quickly. If you use effective birth control and don't conceive for 4 months after you stop treatment, it is unlikely the medication would have a long-term effect on fertility.

With immunotherapy, fertility questions are more complex because of the potential of long-term impact on the immune system from these drugs in both men and women. Side effects could occur (including hormonal changes such as pituitary or thyroid problems) that could impact fertility, but this has not been well studied. Again, at the very least, you should avoid trying to conceive for at least 6 months after you stop treatment.

It's important to have a frank conversation with your oncology team about your family planning issues prior to starting treatment. You might also want to consider seeing a fertility specialist who is familiar with these issues in cancer patients. You may wish to discuss whether you can freeze some of your eggs/sperm before treatment if you are considering trying to conceive later. Your oncology team might have some names of specialists who can help.



WEIGHING THE DIFFERENT OPTIONS

The following worksheets are intended for you and your medical oncologist to use to evaluate whether targeted therapy, immunotherapy, or active surveillance is the best approach for your melanoma that is at high risk of recurrence. These worksheets will help you weigh the potential pros and cons of each option.

Worksheet 1: Targeted Therapy

Factor to Consider	My Thoughts	Weighing of Factor to You				
My tumor status (<i>BRAF</i>)		1	2	3	4	5
Effectiveness of the drug		1	2	3	4	5
Side effects		1	2	3	4	5
Convenience of receiving the treatment		1	2	3	4	5
Quality of life		1	2	3	4	5
Financial considerations		1	2	3	4	5
Fertility/family planning		1	2	3	4	5
Other factors		1	2	3	4	5

Not At All Important Slightly Important Important Fairly Important Very Important

Worksheet 2: Immunotherapy

Factor to Consider	My Thoughts	Weighing of Factor to You				
My tumor status (<i>BRAF</i>)		1	2	3	4	5
Effectiveness of the drug		1	2	3	4	5
Side effects		1	2	3	4	5
Convenience of receiving the treatment		1	2	3	4	5
Quality of life		1	2	3	4	5
Financial considerations		1	2	3	4	5
Fertility/family planning		1	2	3	4	5
Other factors		1	2	3	4	5

Not At All Important

Slightly Important

Important

Fairly Important

Very Important

Worksheet 3: Active Surveillance

Factor to Consider	My Thoughts	Weighing of Factor to You				
		1	2	3	4	5
My tumor status (<i>BRAF</i>)		1	2	3	4	5
No treatment side effects		1	2	3	4	5
Anxiety/concern about not having treatment		1	2	3	4	5
Likelihood that the cancer might come back		1	2	3	4	5
Quality of life		1	2	3	4	5
Financial considerations		1	2	3	4	5
Fertility/family planning		1	2	3	4	5
Other factors		1	2	3	4	5

Not At All Important Slightly Important Important Fairly Important Very Important

Final Thoughts

We hope you found this guide to be helpful in evaluating your options for your Stage III melanoma. Our goal has been to empower you to work with your oncology team to make the best decision for you. We have included in the list below other resources that you may want to consult as you evaluate your options. Being informed puts you in the best position to have an active role in this important decision.

MY RESOURCES

FINANCIAL RESOURCES

BRISTOL-MYERS SQUIBB

BMS Access Support; BMS Oncology Co-Pay Assistance Program
1-800-861-0048

MERCK

The Merck Access Program
1-855-257-3932

NOVARTIS

Novartis Patient Assistance Foundation, Inc.
1-800-245-5356

Patient Assistance Now Oncology
1-800-282-7630

INFORMATION RESOURCES

AIM at Melanoma
<https://www.aimatmelanoma.org>

American Cancer Society. Working During Cancer Treatment. <https://www.cancer.org/treatment/survivorship-during-and-after-treatment/staying-active/working-during-and-after-treatment/working-during-cancer-treatment.html>

National Comprehensive Cancer Center Patient and Caregiver Resources. NCCN Guidelines for Patients. Melanoma. 2018. Available at <https://www.nccn.org/patients/guidelines/melanoma>

Patient Resources. Melanoma: Classifying and Staging Melanoma of the Skin. Available at https://www.patientresource.com/Melanoma_Staging.aspx

US Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Available at <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>.

IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE

Eggermont AMM, Robert C, Suci S. Adjuvant pembrolizumab in resected stage III melanoma. *N Engl J Med*. 2018;379:593-595.

Gershenwald JE, Scolyer RA, Hess KR, et al; for members of the American Joint Committee on Cancer Melanoma Expert Panel and the International Melanoma Database and Discovery Platform. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. *CA Cancer J Clin*. 2017;67:474-492.

Keung EZ, Balch CM, Gershenwald JE, Halpern AC. Key changes in the AJCC eighth edition melanoma staging system. *Melanoma Lett*. 2018;36:1-10.

Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *N Engl J Med*. 2017;377:1813-1823.

Weber J, Mandala M, Del Vecchio M, et al; for the CheckMate 238 Collaborators. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med*. 2017;377:1824-1835.

FURTHER READING ON STAGING

YOUR STAGE

How do doctors determine how advanced your melanoma is? The process your health care team uses to determine how far your cancer has advanced is known as staging and is based on a system developed by the American Joint Committee on Cancer (AJCC). This staging system was last updated in 2017. Staging helps doctors identify the best treatments for your cancer.

Your stage is determined by looking at both clinical and pathologic information. Clinical information is made up of a physical examination of your entire body, including a full body skin exam and any tests you might take, such as x-rays, CT scans, etc. Pathologic information includes the results of your original biopsy (a microscopic examination of the tissue sample from your original melanoma), and the biopsy of the lymph nodes closest to the tumor site if they were surgically removed.

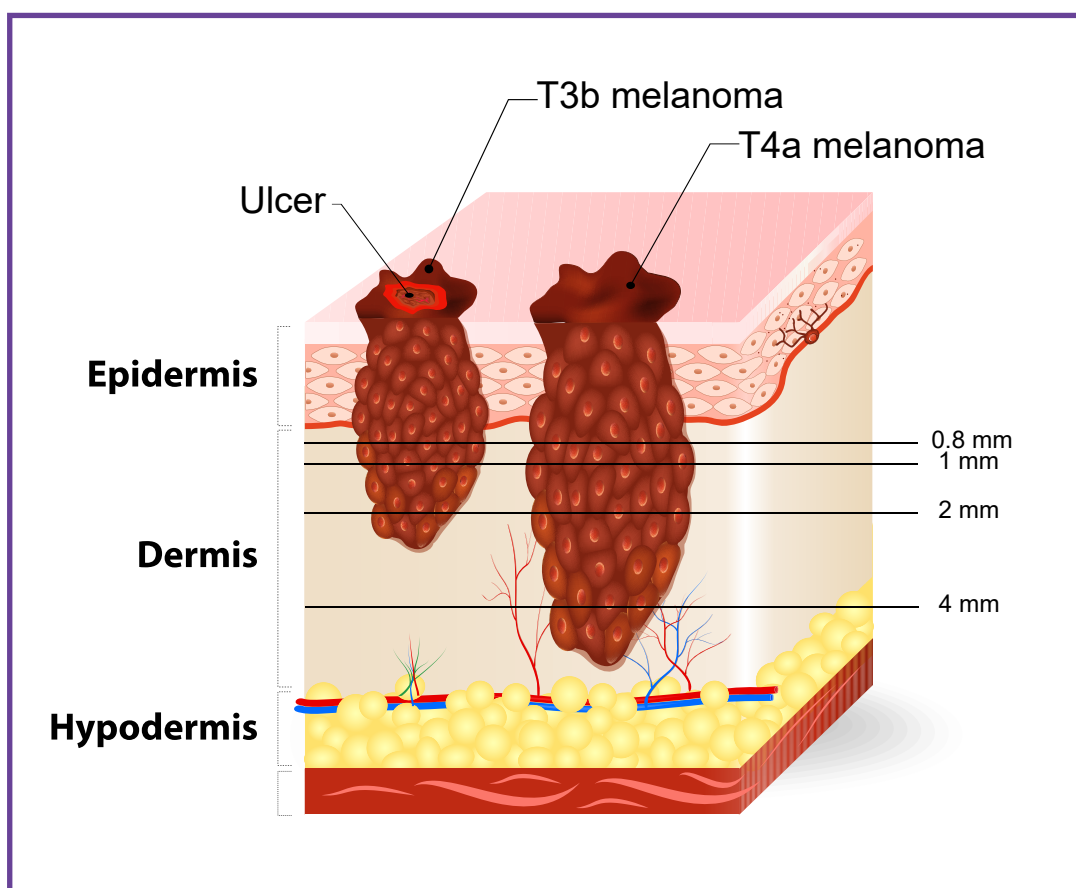
The most widely used way of determining one's cancer stage is called the TNM (Tumor-Node-Metastasis) system. A number of clinical and pathological factors determine the stage of the melanoma.

T = TUMOR CLASSIFICATION

Tumor classification in melanoma is determined by 2 factors, tumor thickness, and ulceration. The thicker the tumor, the further the melanoma has penetrated into the deeper layers of the dermis, and the more likely it is to spread. There are 5 T designations: the first is *in situ*, then there are 4 additional designations, each of which is subdivided.

The other primary factor in tumor classification is ulceration. As illustrated in Graphic 16, an ulcer is a breakdown (an open wound) of the skin. It may cover part or most of the melanoma, and it may have a scab around the edges. It typically does not heal. Ulceration is a key part of the newly revised AJCC staging system because it's been shown that ulcerated melanomas are more likely to spread and are associated with poorer survival rates as compared with melanomas that aren't ulcerated. Ulceration is determined by the pathologist when looking at your biopsy under the microscope.

Graphic 15. Example of the T classification of a localized melanoma.



Graphic 16

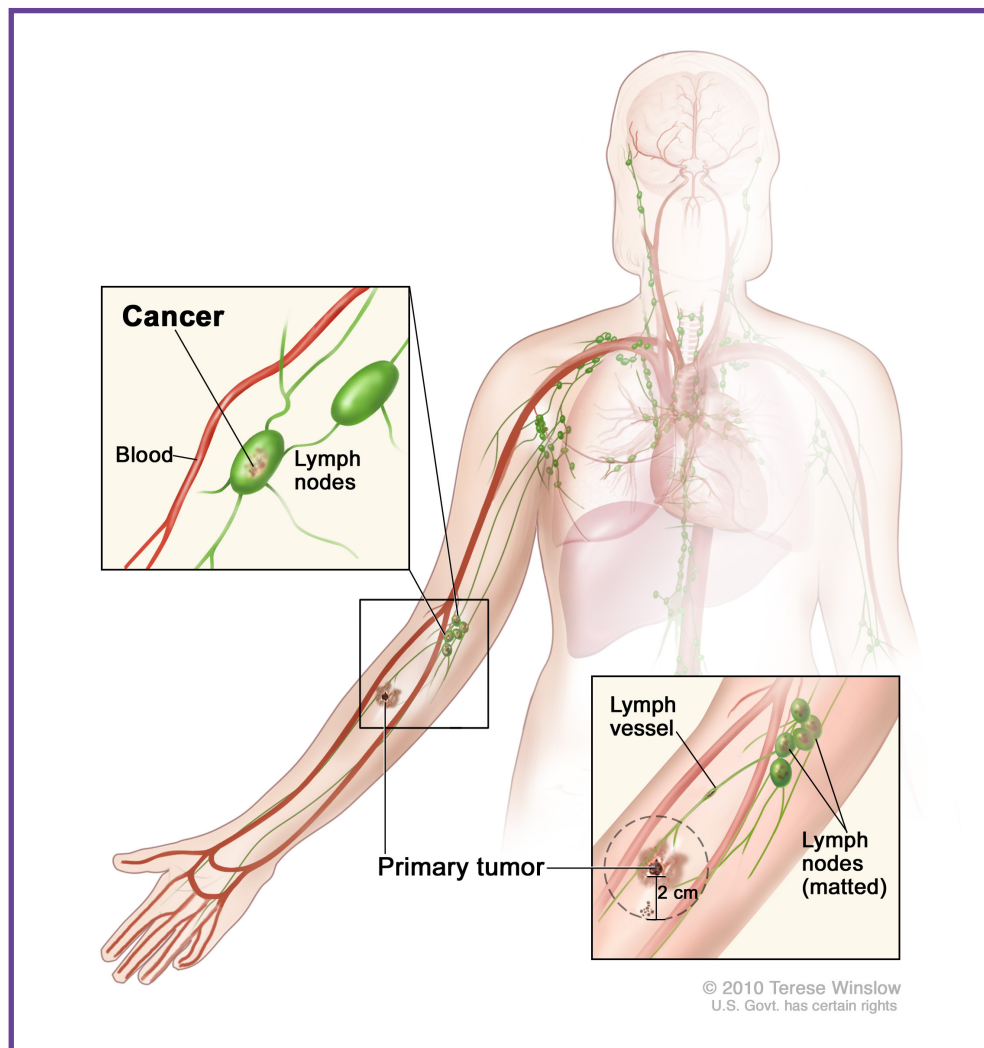
N= NODAL CLASSIFICATION

The **nodal** classification in melanoma tells you if any of the melanoma cells have spread from the primary tumor to nearby (regional) lymph nodes or skin/lymphatics. As shown in Graphic 17, lymph nodes are small, seed-shaped structures that contain clusters of immune cells. Their function is to filter the lymphatic fluid. They are found throughout the body, notably in the neck, armpit, and groin. As discussed earlier, cancer cells typically spread from the primary tumor to the nearest lymph node before traveling to other parts of the body.

Lymph node involvement is rated according to a number of factors. One factor is how many lymph nodes, when biopsied, are found to have melanoma cells. There are 4 N designations: N0 means there is no lymph node involvement, while N1-3 designations are used for 1 to greater than 4 involved nodes. There are more subgroupings based on whether the nodes are visible to the naked eye/palpable (which means they can be felt by the hand). Some involved nodes are not visible/palpable and are only found by a sentinel lymph node (SLN) biopsy.

SLNs are the first nodes (or a single node) to which lymph fluid flows and to which cancer may move when it leaves the dermis. To perform an SLN biopsy, a doctor will inject a radioactive tracer or dye (marker) into the area near the primary tumor location; the marker will travel via the lymphatics to the sentinel node(s), and this will help the surgeon visualize/identify them. The SLN(s) will then be removed and examined for cancer cells. Lymph nodes that are identified as having melanoma cells in them, only by performing a SLN biopsy, are classified as occult, since they are not palpable or visible to the naked eye. Generally speaking, when lymph node involvement is occult vs visible or palpable, it marks a better disease course.

Finally, the N classification includes evaluation of satellites, in-transit metastases, and microsattelites. While they may be labeled with different terms, these are all grouped together as intralymphatic regional metastases and are considered regional disease. They all represent small metastases that are close to but separate from the primary tumor. They have not reached the regional (nearby) lymph node. As shown in Graphic 17, when the nodes are “clumped/matted,” meaning the process of spreading has attached them together, that is also a marker of more advanced disease.



Graphic 16

Graphic 17. Stage III melanoma. The figure shows the nodes in relationship to the primary melanoma as well as the lymphatics that drain the tissue surrounding the tumor. In the inset, several of the lymph nodes are clumped/matted, which is a marker of more advanced disease. Used with permission from Terese Winslow, LLC.

M = METASTASIS (DISTANT)

The **M** (metastasis, distant) classification addresses what other site(s) the cancer has spread to in the body—to either far away lymph nodes or the lungs, brain, or other organs, known as **distant metastases**. Stage III disease would be classified as M0 (no distant metastases). M1 means the cancer has spread to distant sites in the body beyond the regional lymph nodes, which is Stage IV disease. M1 can be broken down by the location of the distant metastases, to include the skin, soft tissue or muscle, other lymph nodes, the lungs, the viscera (digestive system organs such as the small and large intestine—the gut), and the brain/spinal cord (central nervous system).

Having been diagnosed with Stage III melanoma, you can work with your oncology team using the Graphic 18 to identify the factors that determined what your substage is (IIIA, IIIB, IIIC, or IIID). You may want to ask your doctor to circle the tumor and nodal factors that places you in that particular substage.

Graphic 18. Stage III Melanoma Substaging Criteria.

Primary Tumor, T Category with Thickness, Ulceration	Nodal Category	Stage	Melanoma-Specific Survival	
			5-Year	10-Year
T1a or T2a: Less than 2.0 mm, <i>not ulcerated</i> OR T1b: Less than 0.8 mm, <i>ulcerated</i> OR 0.8 – 1.00 mm, <i>regardless of ulceration</i>	N1a: 1 node found, not visible or palpable (detected by SLN biopsy) OR N2a: 2-3 nodes found, not visible or palpable (detected by SLN biopsy)	Stage IIIA	93%	88%
T3a: 2.1 - 4.0 mm, <i>not ulcerated</i> OR T2b: 1.1-- 2.0 mm, <i>ulcerated</i>	N1a: 1 node found, not visible or palpable (detected by SLN biopsy) OR N2a: 2-3 nodes found, not visible or palpable (detected by SLN biopsy)	Stage IIIB	83%	77%
T1a-T3a: Less than 4.0 mm, <i>not ulcerated</i> OR T1b, T2b: Less than 2.0 mm, <i>ulcerated</i>	N1b: 1 node visible/palpable OR N1c: In-transit, satellite, or microsatellite metastases but no disease in the regional lymph node OR N2b: 2-3 nodes, at least 1 visible/palpable			
T0: Primary melanoma not found	N1b: 1 node visible/palpable OR N1c: In-transit, satellite, or microsatellite metastases but no disease in the regional lymph node			
T1a-T3a: Less than 4.00 mm, <i>not ulcerated</i> OR T1b-T2b: Less than 2.00 mm and <i>ulcerated</i>	N2c: 1 node not visible or palpable (detectable by SLN biopsy) or 1 node visible/palpable with In-transit, satellite, or microsatellite metastases OR N3a: 4 or more nodes, not visible or palpable (detected by SLN biopsy) OR N3b: 4 or more nodes, at least 1 visible or palpable, or any clumped nodes OR N3c: 2 or more nodes, either visible/palpable or not visible/palpable and/or any clumped nodes plus in-transit, satellite, or microsatellite metastases	Stage IIIC	69%	60%
T3b: 2.1 – 4.0 mm, <i>ulcerated</i> OR T4a: More than 4.0 mm, <i>not ulcerated</i>	Any N1, N2, or N3 (any nodal involvement or in-transit, satellite, or microsatellite metastases)			
T4b: More than 4.00 mm, <i>ulcerated</i>	N1a-N2c: Up to 3 involved nodes, regardless of whether visible/palpable or in-transit, satellite, or microsatellite metastases without regional nodal involvement or only 1 regional node detected			
T0: Unknown primary	N2b: 2-3 nodes, at least 1 visible/palpable OR N2c: 1 node not visible or palpable (detected by SLN biopsy) or 1 node visible or palpable with In-transit, satellite, or microsatellite metastases OR N3b: 4 or more nodes, at least 1 visible or palpable, or any clumped nodes OR N3c: 2 or more nodes, either visible/palpable or not visible or palpable (detected by SLN biopsy) and/or any clumped nodes plus in-transit, satellite, or microsatellite metastases			
T4b: More than 4.00 mm, <i>ulcerated</i>	N3a: 4 or more nodes, not visible or palpable (detected by SLN biopsy) OR N3b: 4 or more nodes, at least 1 visible or palpable, or any clumped nodes OR N3c: 2 or more nodes, either visible/palpable or not visible or palpable (detected by SLN biopsy) and/or any clumped nodes plus in-transit, satellite, or microsatellite metastases	Stage IIID	32%	24%

ACKNOWLEDGMENTS

This pamphlet was produced through a collaboration between the AIM at Melanoma Foundation and Terranova Medica, LLC.

We wish to thank our consultant faculty for directing and reviewing the content:

- Dr Eric D. Whitman, MD, FACS; Medical Director of Atlantic Health System's Oncology Service Line; Morristown, New Jersey
- Janice M. Mehnert, MD; Regional Phase 1 Clinical Program Director; Medical Oncologist; Rutgers Cancer Institute; New Brunswick, New Jersey
- Lisa A. Kottschade, APRN, MSN, CNP; Coordinator, Outpatient Oncology Melanoma Practice; Mayo Clinic; Rochester, Minnesota

The development of this pamphlet was supported by unrestricted educational grants from Bristol-Myers Squibb; Merck & Co., Inc; and Novartis Pharmaceuticals Corporation.

About AIM at Melanoma

AIM at Melanoma is globally engaged and locally invested in advancing the battle against melanoma through innovative research, legislative reform, education, and patient and caregiver support. Founded in 2004, AIM at Melanoma is the largest international melanoma foundation seeking the cure for melanoma. We are dedicated to:

Innovation in Melanoma Research

We believe that the cure for melanoma will be found more quickly by bringing together leading global researchers and funding their collaborative research. Our three paradigm-shifting global research initiatives, including the Melanoma Tissue Bank Consortium, are poised to reshape the future of melanoma.

Legislation, Policy & Advocacy

We are the respected voice of melanoma across the nation. When drugs are approved, legislation is drafted, and research is assessed, AIM is at the table, speaking loudly and clearly on behalf of patients and their families. We are trusted advisors for pharmaceutical companies, medical boards, and government agencies on critical topics that affect melanoma patients.

Information & Resources

Both in the U.S. and on a global level we provide comprehensive, easy-to-access melanoma information and resources to patients and healthcare professionals.

For more information about AIM at Melanoma, please go to www.AIMatMelanoma.org.

