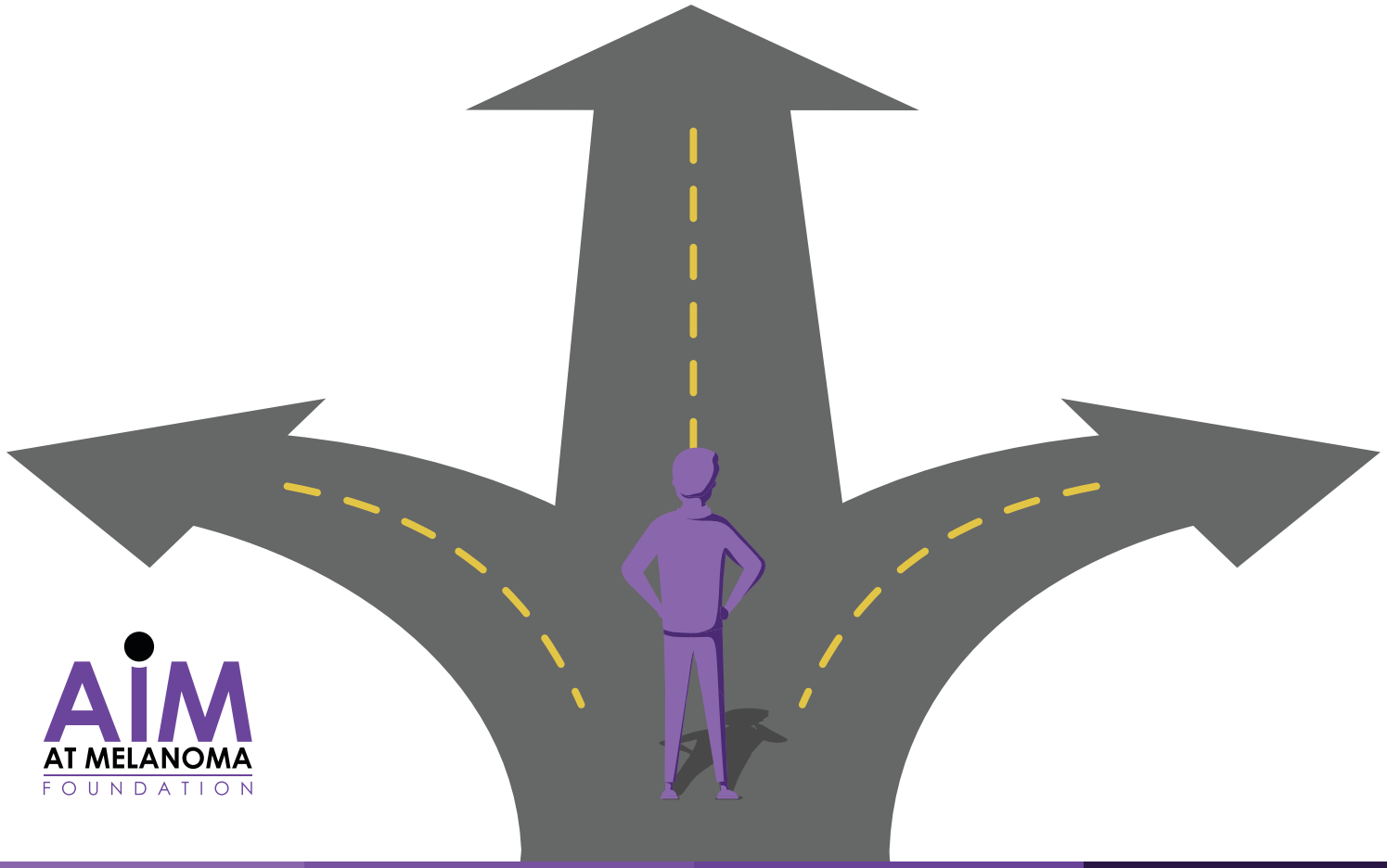
Options for Stage III Melanoma

Making the Decision That's Right for You



AIM AT MELANOMA FOUNDATION

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

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:

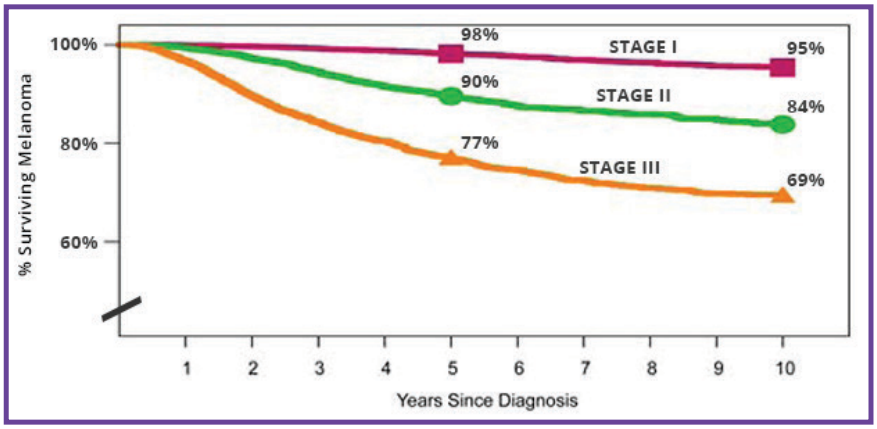
Lymph nodes: Small, bean-shaped structures containing white blood cells that fight disease. These are located throughout the body but mainly in the armpit, groin, and neck.

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

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

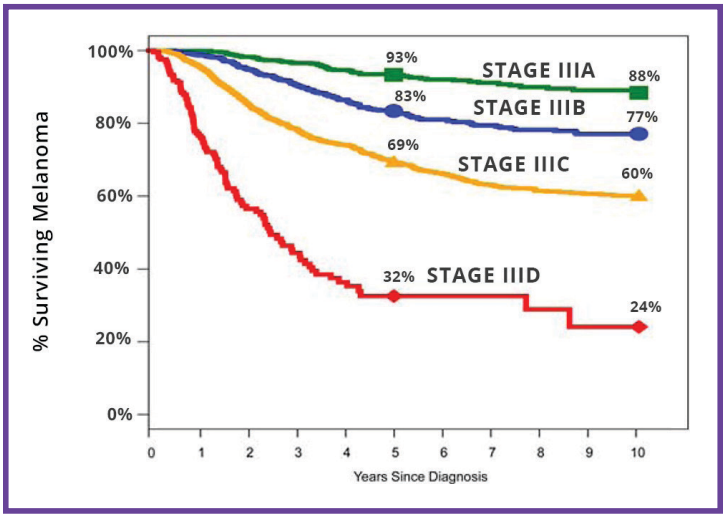
- 95% of Stage I patients are alive
- 84% of Stage II patients are alive
- 69% of Stage III patients are alive.

With increasing disease stage, the melanoma-specific survival rate decreases.



Graphic 1

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



Graphic 2

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.

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

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

Recently, a German study from the Central Malignant Melanoma Registry (CMMR) evaluated survival rates for 1553 patients with a Stage III melanoma diagnosis from 2000 to 2012. The investigators found generally lower survival rates for patients in this group (and other European groups) as compared with those reported by the AJCC by stage. For example, in the CMMR vs the AJCC group, 5-year survival for Stage IIIa was 80% vs 93%. For Stage IIIb, it was 75% vs 83%. Similar results were seen for 10-year survival and for Stage III in general and in the more advanced substages.

Within the Stage III group, survival rates generally decrease as you go from Stage IIIA to Stage IIID. This is why it is important that you and your oncology team discuss your individual substage 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 dabrafenib and 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.

Dabrafenib + trametinib 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 your tumour has 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 approved test to ensure that your healthcare team has access to the information needed and to aid in reimbursement.

Because using dabrafenib + trametinib 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. Oncology teams have become more adept at handling these challenging situations with more experience and testing options.

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 ipilimumab. Additionally, in a clinical trial nivolumab did a better job of preventing recurrence of Stage III cancer compared with ipilimumab. Nivolumab is a PD-1 inhibitor, while Pembrolizumab is another PD-1 inhibitor.

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

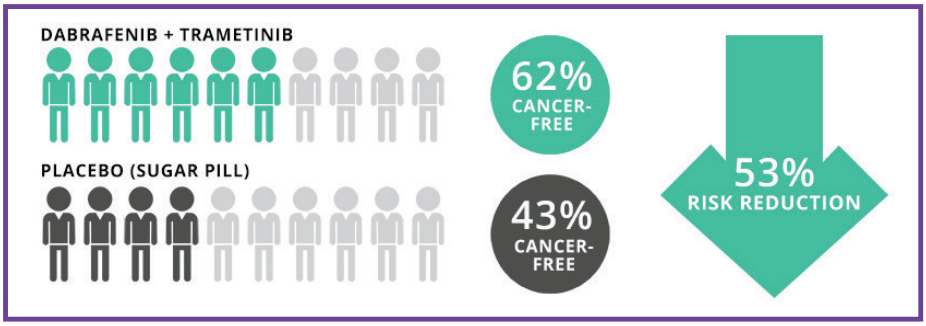
Oncologists have different ways of looking at how well cancer drugs work. First, they typically look at how many people are still alive after 5 years and after 10 years. This is called the ***overall survival*** benefit, meaning how long a person will live if he or she takes one of these treatments, 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 dabrafenib + trametinib 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 dabrafenib + trametinib 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 5-years, 52% of the patients treated with the combination were still melanoma-free, compared with 36% of those who had received placebo. However, the investigators were not able to make a definitive statement on the effect on long-term survival, since there were not enough events (deaths) to draw a conclusion.

IMMUNOTHERAPY

Nivolumab

For the nivolumab approval, a trial compared nivolumab with ipilimumab. 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 nivolumab were melanoma free, compared with 53% of patients receiving ipilimumab. Overall, there was a 35% reduction in the risk of the melanoma coming back in patients treated with nivolumab as compared with ipilimumab. It's important to remember that this study compared nivolumab with a drug already known to work in this setting (ipilimumab) 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 nivolumab as compared with ipilimumab.

Graphic 5

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

At the 4-year follow-up, 52% of the nivolumab-treated patients were cancer free, while 41% of the patients receiving ipilimumab were cancer free.

IMMUNOTHERAPY (CONTINUED)

Pembrolizumab

For the pembrolizumab approval, a trial compared pembrolizumab 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 pembrolizumab 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 pembrolizumab as compared with the placebo.

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

Graphic 6

At a 3-year follow-up, the effect was sustained: 64% of patients treated with pembrolizumab were cancer free, compared with 44% for those who were treated with placebo. Overall survival was not reported.

DECISION-MAKING POINTS:

- If you have the *BRAF* mutation, you may be eligible for either targeted therapy or immunotherapy. In terms of which approach might be better, we are still learning about the long-term benefits of these drugs
- Experts are still conducting studies to figure out which patients are likely to respond well (or not respond well) to these different groups of drugs
- 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

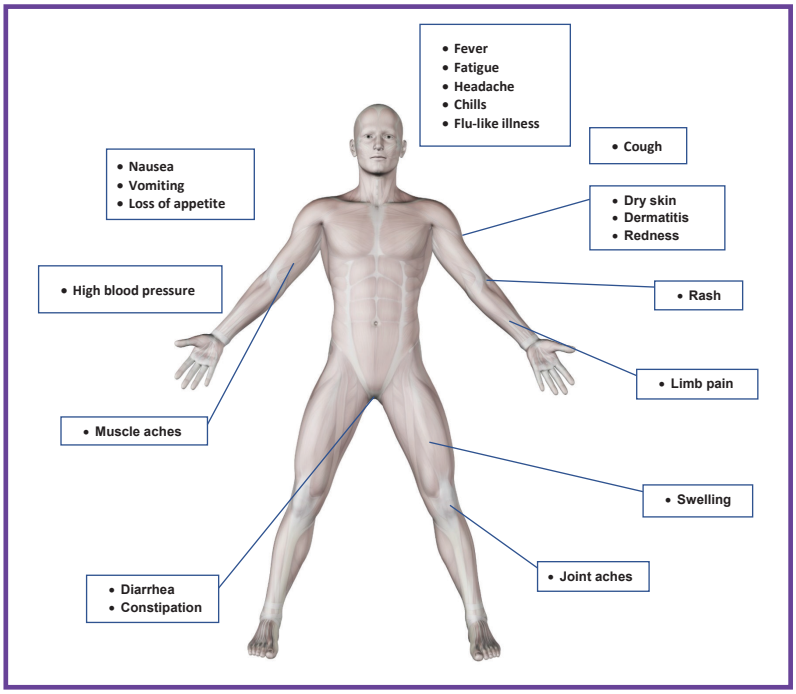
Targeted therapy is associated with a range of side effects. In the clinical trial that led to dabrafenib + trametinib approval in the adjuvant setting, 97% of patients who received dabrafenib + trametinib reported having at least 1 side effect. Common side effects of dabrafenib + trametinib are shown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

Graphic 7. Common side effects associated with dabrafenib + trametinib 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 dabrafenib + trametinib

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

Graphic 7



Graphic 8

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

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 dabrafenib + trametinib can get worse and lead to serious complications if it is not treated promptly.

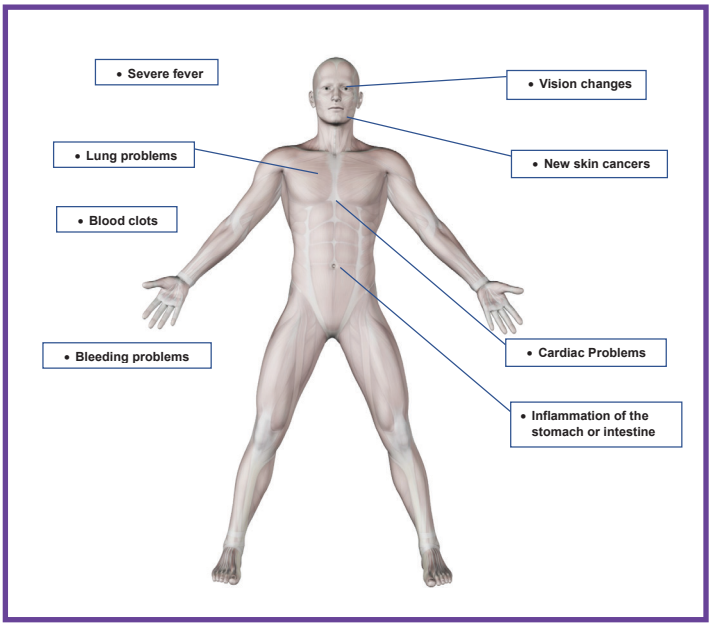
In the follow-up study of the dabrafenib/trametinib combination used for adjuvant therapy, there were no differences in the incidence or severity of serious side effects between the combination and placebo-treated patients.

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 9. Serious side effects associated with dabrafenib + trametinib and the frequency of their occurrence in the adjuvant setting. Adapted from the manufacturer's prescribing information.



Graphic 10

Graphic 10. Body image showing serious effects associated with dabrafenib + trametinib.

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 arrythmias 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 nivolumab and pembrolizumab 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 nivolumab, Graphic 12 shows those associated with pembrolizumab, and Graphic 13 shows a body image with these side effects.

Graphic 11. Common side effects associated with nivolumab 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 nivolumab

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

Graphic 11

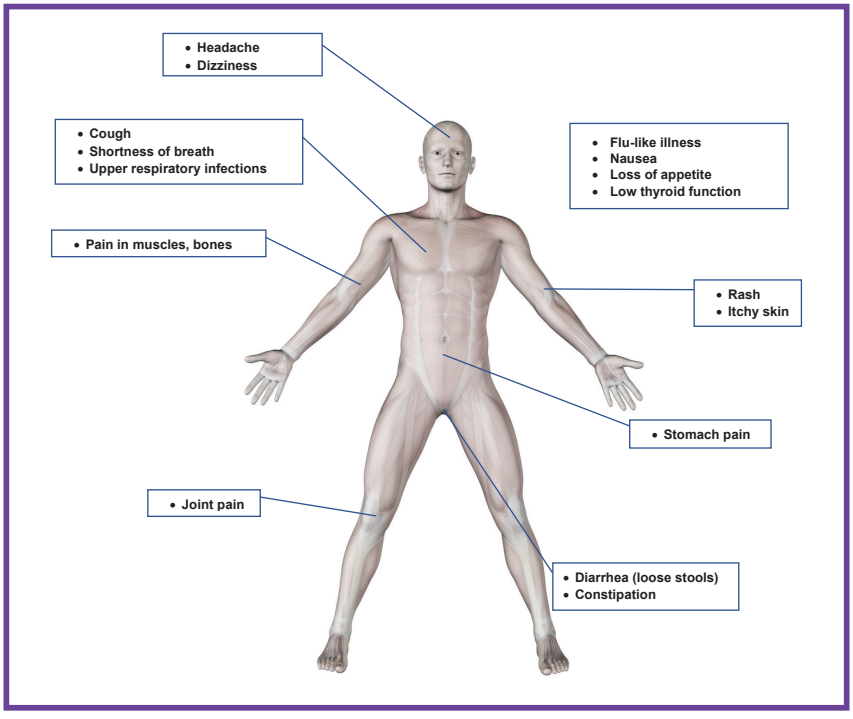
Graphic 12. Common side effects associated with pembrolizumab and the percentage of patients experiencing them in the clinical trials. These side effects are listed in descending order from the most common to the least common. Adapted from the manufacturer's prescribing information.

Common side effects associated with pembrolizumab

- 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.

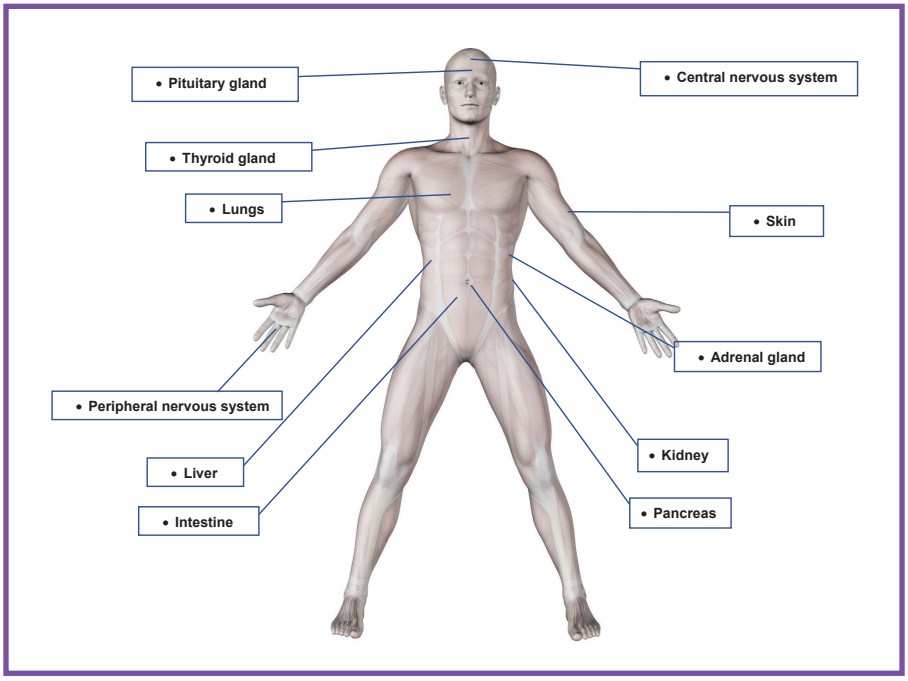
Potentially serious side effects of immunotherapy can become life-threatening. These side effects are shown in Graphic 14. Graphic 15 shows a body image with the organs and organ systems that can be affected. This list is not complete—as mentioned above, any organ or body system can be affected.

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.

Nivolumab 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.

Pembrolizumab 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 when discussing with your physician and 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 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/ACCESS ISSUES

- Immunotherapy and targeted therapies are innovative medicines and are generally costlier than chemotherapy. When sitting down with your physician to discuss treatment options, it is important to ask if there will be any out-of-pocket cost to you
- Another financial consideration is the impact of therapy on your ability to earn a living. 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
- If for any reason you have difficulty accessing testing or therapies in Canada, or you need emotional and/or financial support, please visit Save Your Skin Foundation Patient Support. https://saveyourskin.ca/patient-support-webinars/

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 dabrafenib + trametinib 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 nivolumab or pembrolizumab, 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.

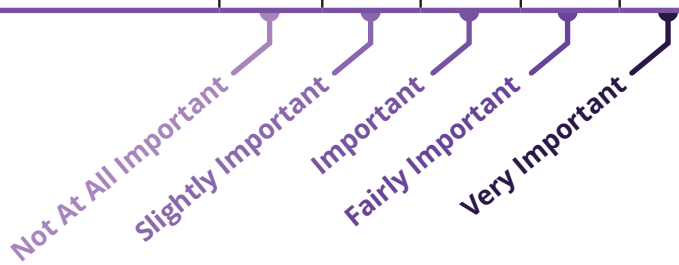
It's important to have a frank conversation with your oncology team about your family planning issues prior to starting treatment. You might also want to consider seeing a fertility specialist who is familiar with these issues in cancer patients. You may wish to discuss whether you can freeze some of 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.

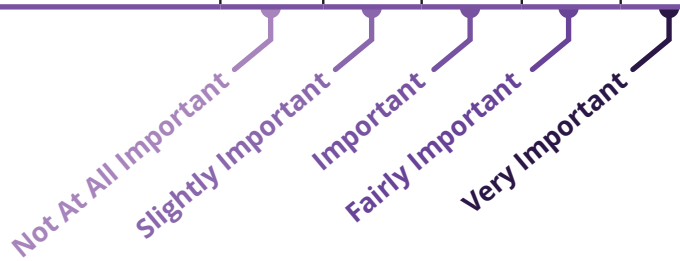
Worksheet 1: Targeted Therapy

Factor to Consider	My Thoughts	Weighing of Factor to You				
My tumor status (*BRAF*)		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



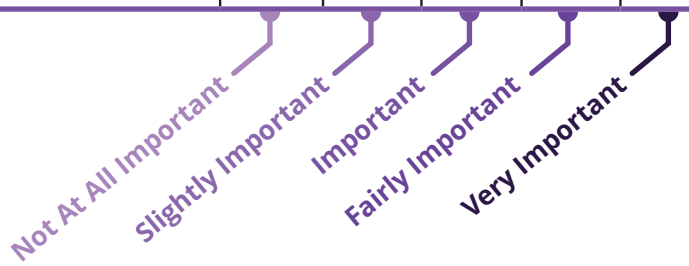
Worksheet 2: Immunotherapy

Factor to Consider	My Thoughts	Weighing of Factor to You				
My tumor status (*BRAF*)		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



Worksheet 3: Active Surveillance

Factor to Consider	My Thoughts	Weighing of Factor to You				
My tumor status (*BRAF*)		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



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

INFORMATION RESOURCES

Save Your Skin Foundation
https://saveyourskin.ca
1-800-460-5832

AIM at Melanoma

General information: https://www.aimatmelanoma.org

For caregivers: https://www.aimatmelanoma.org/support-resources/caregiving

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

IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE

Ascierto PA, Del Vecchio M, Mandalá M, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2020;21:1465-1477.

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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.

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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.

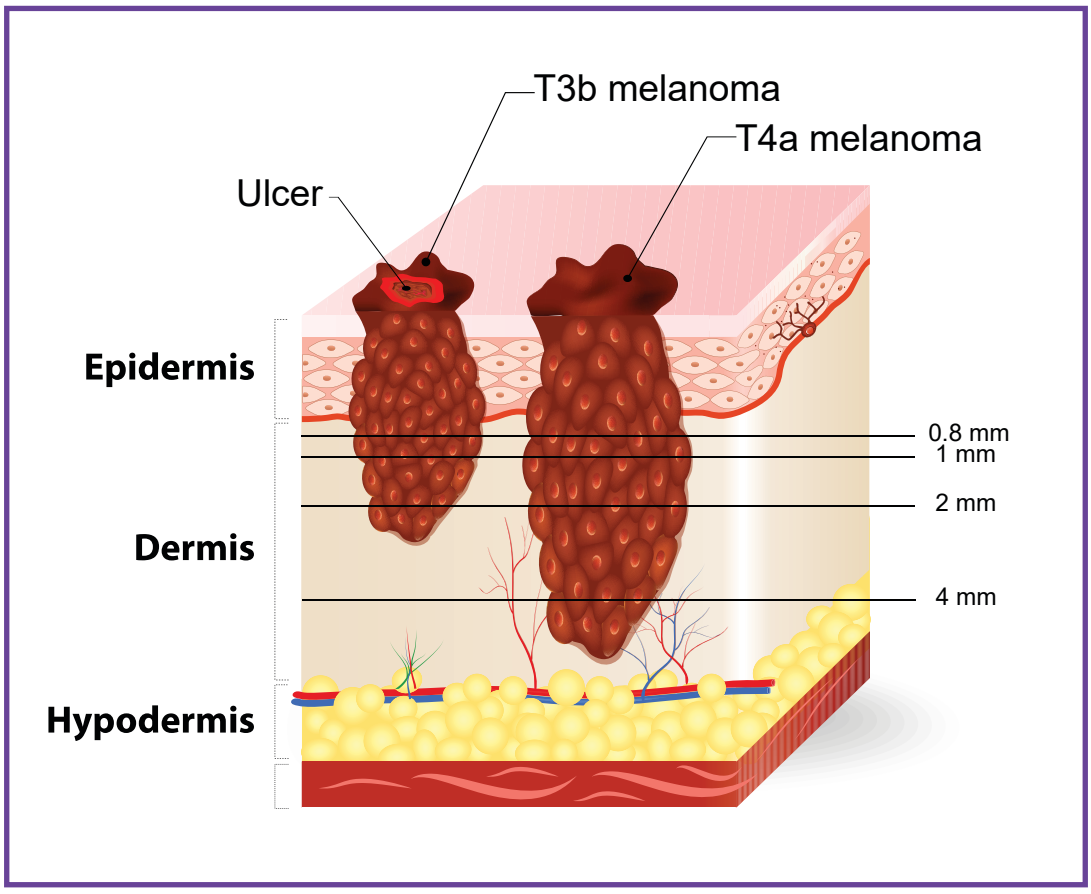
The most widely used way of determining one's cancer stage is called the TNM (Tumor-Node- Metastasis) system. A number of clinical and pathological factors determine the stage of the melanoma.

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 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 16. Example of the T classification of a localized melanoma.



Graphic 16

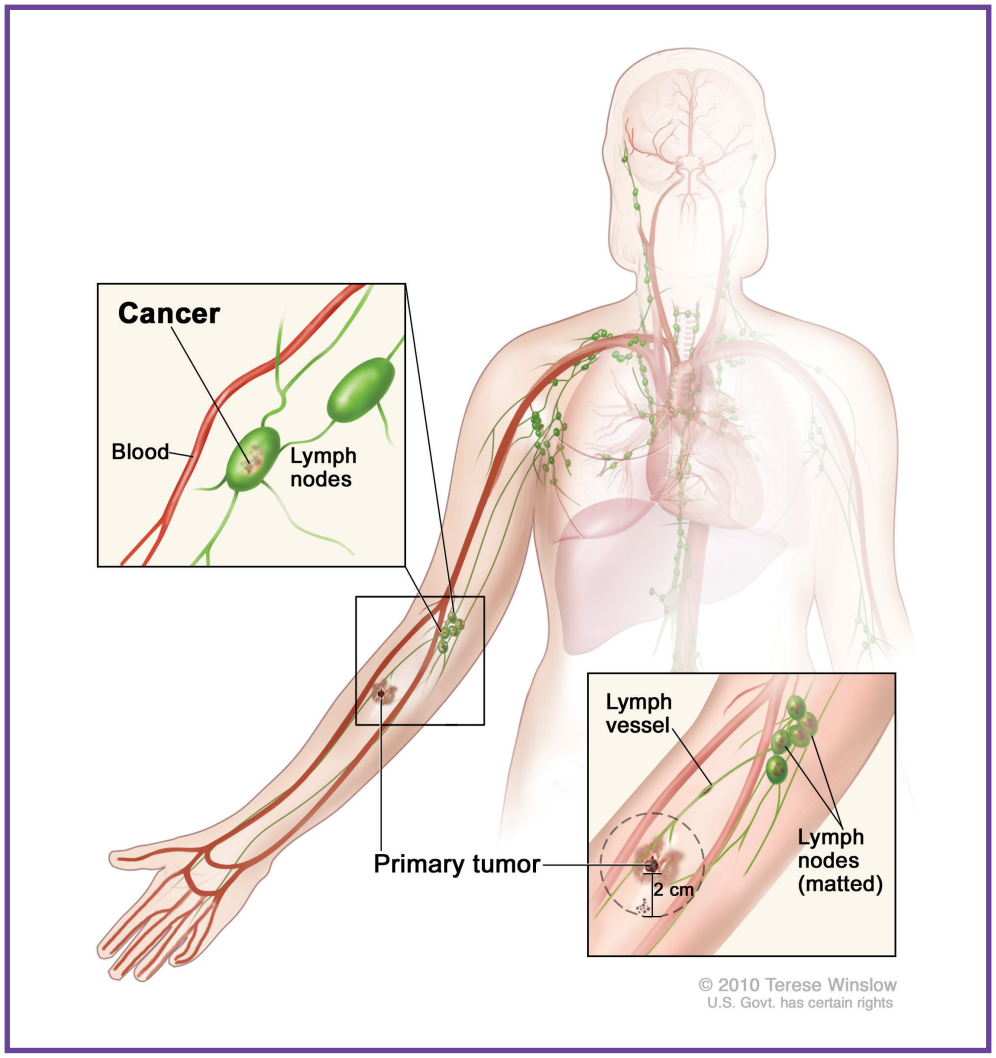
N= NODAL CLASSIFICATION

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 microsatellites. 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 17

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, ***not ulcerated*** OR **T1b**: Less than 0.8 mm, ***ulcerated*** OR 0.8 – 1.00 mm, ***regardless of ulceration***	**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, ***not ulcerated*** OR **T2b**: 1.1-- 2.0 mm, ***ulcerated***	**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, ***not ulcerated*** OR **T1b, T2b**: Less than 2.0 mm, ***ulcerated***	**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, ***not ulcerated*** OR **T1b-T2b**: Less than 2.00 mm and ***ulcerated***	**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, ***ulcerated*** OR **T4a**: More than 4.0 mm, ***not ulcerated***	**Any N1, N2, or N3** (any nodal involvement or in-transit, satellite, or microsatellite metastases)			
T4b: More than 4.00 mm, ***ulcerated***	**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, ***ulcerated***	**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%

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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:

This pamphlet was reviewed and acculturated for Canadian English by Save Your Skin Foundation.

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Save Your Skin Foundation
https://saveyourskin.ca
1-800-460-5832

Save Your Skin Foundation (SYSF) is a patient-led not-for-profit organization dedicated to the fight against non-melanoma skin cancers, melanoma, and ocular melanoma through education, advocacy, and awareness initiatives across Canada. SYSF provides a community of oncology patient and caregiver support throughout the entire continuum of care, from prevention and diagnosis to survivorship. www.saveyourskin.ca

AIM AT MELANOMA FOUNDATION

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