This is a companion piece for the guide, *Options for Stage III Melanoma: Making the Decision That’s Right for You*, which can be downloaded here: [https://aimwithimmunotherapy.org/canada/](https://aimwithimmunotherapy.org/canada/).

This companion piece was developed based on the answers to questions posed by real patients who attended a Facebook Live review of the guide. We hope you find this information helpful to you as you navigate your way through your Stage III melanoma diagnosis.
Questions and answers

What is stage III melanoma?

Stage III melanoma is melanoma that has spread (metastasized) from the primary tumour to the regional area. This is in contrast to melanoma that has spread far away to a distant location. In Stage III, melanoma has spread from the original location to the region right around it, or a little further toward the lymph nodes in the region, or to the regional lymph nodes.

You may be familiar with the lymph nodes in your neck, armpit, and groin. As an example, let’s say you had a primary melanoma on your upper arm. The lymph nodes that the melanoma would typically travel to first would be under the armpit. If those tested positive for melanoma, it would be considered Stage III disease. You could also have other forms of regional (Stage III) disease. For example, an in-transit metastasis would show up somewhere in the little lymphatic channels that travel away from the primary tumour location but not quite as far as the lymph nodes in the armpit. It would also be Stage III disease if the melanoma spread to the area right around the original primary tumour. This type of spread is sometimes picked up when your doctor performs the wide local excision and is called a microsatellite. So you may hear different terms—nodal disease, satellite, microsatellite, or in-transit disease—to describe melanoma that has spread in the region (Stage III disease).

Guide Notes: The last part of the guide contains an in-depth discussion of melanoma staging. Pages 27-28 explain regional (Stage III melanoma) in text and pictures under the heading N (nodal classification).

N= NODAL CLASSIFICATION

The N classification in melanoma tells you if any of the melanoma cells have spread from the primary tumour to nearby lymph nodes or skin/lymphatics. As shown in Graphic 17, lymph nodes are oval, bean-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 tumour to the nearest lymph node before traveling to other parts of the body. Lymph node involvement is rated according to a number of factors. The key 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, N1 designations are used for 1 involved node, N2 designations are used for 2 or more involved nodes. N3 designations are used for 3 or more involved nodes. There are 6 subgroupings based on whether the nodes are visible/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 releasing when it leaves the dermis. To perform an SLN biopsy, a doctor will inject a radioactive tracer or a dye into the area near the primary tumour location; the marker will travel via the lymphatics to the sentinel nodes(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 an 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 described with different terms, these are all grouped together as extranodal regional metastases and are considered regional disease. They all represent small metastases that are close but separate from the primary tumour. They have not reached the regional lymph nodes. As shown in Graphic 17, when the nodes are identified, screening the process of spreading has attached them together, that is also a marker of more advanced disease.
Why should I know what specific substage of Stage III melanoma I have?

Stage III melanoma encompasses a wide range of conditions. You may have only one or multiple lymph nodes that contain cancer. Your lymph nodes may be enlarged to the point that your healthcare provider can see or feel them. Or the affected lymph nodes may not be readily apparent—they may only have been detected when the lymph node was biopsied, and the cancer was visible under the microscope. It could be that you had matted or clumped lymph nodes. Alternatively, you may have melanoma in the region between the primary tumour location and the lymph nodes. Your specific substage of Stage III melanoma is also affected by the characteristics of your primary melanoma—how thick it was and whether or not it was ulcerated, which means part of the upper layer of skin is broken on the top of the melanoma. Ulcerated melanomas have a different disease course (prognosis) than nonulcerated melanomas.

It’s important to know this information and which substage of Stage III disease you have, whether it is Stage IIIA, IIIB, IIIC, or IIID. The prognosis differs with each substage.

Guide Notes: In addition to pages 27 and 28 of the guide, which explain all of the different elements of the nodal classification system, page 30 contains a table that helps you understand how the primary tumour characteristics and the nodal characteristics can be used to determine your substage. The table also shows the 5-year and 10-year survival rates associated with each substage at the time that the staging system was published.

Your healthcare provider can use this table to help you understand how he/she arrived at your substage and what it means for the predicted course of your disease (prognosis). However, it is important to remember that survival rates do not predict an individual’s outcome. Every person and every case are different, and many factors contribute to an individual’s survival. It’s also important to remember that new and successful treatments have emerged over the last few years, and survival rates are increasing in Stage III melanoma.
Surgery for stage III disease is sometimes not enough. In Stage III patients, the risk of the disease coming back (recurring) can be high enough that surgical removal of the tumour(s) is not enough. When a lymph node is positive, the melanoma can have access to the rest of the body. It can spread throughout the lymphatic system. The lymphatic system is closely tied to the bloodstream, which travels everywhere throughout the body. So even though the melanoma may have started on your hand, if it gets into the lymphatics, it can spread more easily. Overall, Stage III patients have about a two-thirds chance of recurrence over 5 years. Thus, there can be a strong rationale for taking medication to prevent the disease from coming back. The higher your substage of Stage III, the greater the risk of recurrence from the disease.

Options for Stage III Melanoma: Making the Decision That’s Right for You, Companion Piece.

Questions and answers, continued

Why is surgery sometimes not enough?

Your melanoma stage affects the expected course of your disease. The stages of melanoma are generally divided into 4 groups: Stage I, Stage II, Stage III, and Stage IV. Stage I is melanoma which has not penetrated (invaded) the deeper layers of the skin (in situ). Stage II melanomas 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. Stage III melanomas and ulcerated melanomas have a higher risk of recurring. Stage IV melanoma is melanoma that has spread farther than regional lymph nodes, to distant sites such as the lung, liver, or brain. Stage IV melanoma may have started on your hand, if it gets into the lymphatics, it can spread more easily. Overall, Stage III patients have about a two-thirds chance of recurrence over 5 years. Thus, there can be a strong rationale for taking medication to prevent the disease from coming back. The higher your substage of Stage III, the greater the risk of recurrence from the disease.

Guide Notes: On pages 2-4, the guide addresses the risk for recurrence with Stage III melanoma. It shows survival curves that help you understand why Stage III melanoma is considered high risk and how the risk increases with progressive substages (Stage IIIA, Stage IIIB, Stage IIIC, Stage IIID). It also explains how the tumour can come back even when the surgeon removed all the visible tumour.
What do I need to know before I go to the oncologist?

There are a few pieces of information that your oncology team will need in order to evaluate the options to treat your high-risk melanoma.

First, the team needs all the details about your stage—this can include the pathology report from the original primary as well as all the information from the assessment of your lymph node (example, sentinel lymph node biopsy, surgery, needle biopsy, etc.). They will also need staging scans (imaging) to make sure that the melanoma has not already metastasized farther, meaning it has spread past the lymph nodes to other parts of the body such as in the lung, liver, or bone. Such staging scans could include the use of a positron emission tomography/computer tomography (PET/CT) combination scan, magnetic resonance imaging (MRI), or a CT scan alone. If there are distant metastases, then you would be staged as Stage IV and you and your oncologist would then discuss therapy options specific for that stage.

Another important piece of the puzzle is your BRAF status. BRAF is a mutation that is present in approximately 50% of cutaneous (skin) melanomas that are tested. If you have melanoma on your hands/feet, your mucosa, or in your eye, different mutations can be involved—we will not be discussing those types of melanoma in this guide. For cutaneous melanoma, the reason it’s important to know your BRAF status is that there are drug treatments, BRAF/MEK inhibitor combinations, that are an option for adjuvant therapy if you have the BRAF mutation. But those drugs don’t work if you don’t have the BRAF mutation.

To be tested for the BRAF mutation, your pathologist, surgeon, dermatologist, or oncologist must order the test. If your healthcare provider has not ordered the test, you will want to talk with either your surgeon, dermatologist, or oncologist about ordering it.

Guide Notes: The guide provides a discussion of BRAF testing and treatment for BRAF-positive melanoma (pages 5-6).

OPTIONS FOR STAGE III MELANOMA

You will now be working with your oncology team to figure out what to do next. There are three 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 BRAF (BRAFV600E) mutation. If the BRAF test shows that your tumor has a 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 reawaken 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 waiting to see if your melanoma returns if it comes back.

TARGETED THERAPY

Both BRAF and MEK inhibitors are key protein enzymes that help melanoma cells grow. About half of all melanoma patients have a mutated form of codon 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 are approved for adjuvant therapy if you have the BRAF mutation (wild-type tumors). Therefore, knowing if your tumor has the BRAF 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 well before you have a local recurrence so 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 can still help you determine your best treatment options while you continue following up and handling these challenging situations with more experience and testing time.

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 melanoma cells) have ways of evading the brakes on your immune system, providing it from doing its job. In fact, the immune system may, in some cases, actually help the cancer grow. By blocking immune checkpoint inhibitors, the brakes on the immune system are released, allowing it to identify and destroy cancer cells.

PD-1 inhibitors and CTLA4 inhibitors are types of immune checkpoint inhibitors that are used for Stage IV melanoma. These medications are most likely to work if your tumor has the BRAF mutation. However, if you have a BRAF mutation, you do not have to have an approved test to ensure that your healthcare team has access to the information needed and to aid in reimbursement.

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What are the options for Stage III melanoma?

There are three options for managing Stage III melanoma: targeted therapy, immunotherapy, and active surveillance. Each are briefly discussed below.

Targeted therapy is a combination of oral medications—a BRAF/MEK inhibitor combination that can be used in patients who have the BRAF mutation. Together, these drugs block key protein enzymes that help the melanoma grow.

Immunotherapy treatments give your immune system more power to fight cancer. Currently, immune checkpoint inhibitors—PD-1 inhibitors and CTLA4 inhibitors—are used as adjuvant immunotherapy for melanoma.

Another option is called active surveillance. With active surveillance you are not taking any medicine to prevent the melanoma from coming back, but you are keeping a close eye out for any recurrence. You would go back to your oncologist on a regular basis for monitoring, which would include examination of your skin, a clinical examination to feel for lymph nodes, and additional imaging scans to see if the melanoma has spread further. You might consider active surveillance if you and your oncologist feel like your risk for recurrence is relatively low or if the adjuvant medications are not good options for you.
How long is drug treatment?

Targeted therapies and PD-1 inhibitors can be given for up to a year—as long as you tolerate the side effects and the melanoma has not come back.

**Guide Notes:** See page 17 for a discussion of how the drugs are given.

### Other Considerations

**Drug Administration**

For targeted therapy, you will be taking capsules/tablets once a day or 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 once every 2 weeks. This trial enrolled 906 people who had melanoma in their lymph nodes (Stage III, excluding Stage IIIa) or distant metastases (Stage IV) that was removed by surgery.

For pembrolizumab, you will be getting an IV infusion every 3 weeks. This trial enrolled 1,019 people who had melanoma in the lymph nodes (some Stage IIIa patients were included in this trial). 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 from these trials to help you understand what it means for you.

**Immunotherapy**

**Nivolumab**

For the nivolumab approval, a trial compared nivolumab with ipilimumab. Over a 4-year follow-up, 52% of the nivolumab-treated patients were cancer-free, while 41% of the ipilimumab-treated patients were cancer-free (see Graphic 4). This trial enrolled 1,230 people who had melanoma in the lymph nodes (Stage III, excluding Stage IIIa) or distant metastases (Stage IV) that was removed by surgery.

For pembrolizumab, you will be getting an IV infusion every 3 weeks. This trial enrolled 2,056 people who had melanoma in the lymph nodes (some Stage IIIa patients were included in this trial). 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 from these trials to help you understand what it means for you.

**Immunotherapy (cont.)**

**Pembrolizumab**

For the pembrolizumab approval, a trial compared pembrolizumab with a placebo (sugar pill) in 1,787 people who had melanoma in the lymph nodes (Stage III, excluding Stage IIIa). This trial enrolled 870 people with Stage III melanoma who had the BRAF mutation. Half of the patients received the combination therapy, and half received a placebo.

**Decision-Making Points:**

- If you have the BRAF mutation, you are likely 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.
- It is important to keep in mind that the expectations of the data we have don’t mean you and they do not mean you should 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 is important to have a conversation with your oncology team about the data and what it means for you.

**Questions and answers, continued**

**Do the drug treatments work?**

These drugs are effective at reducing your risk of recurrence and improving survival rates in melanoma patients. We are continuously learning about the long-term benefits of these drugs on survival.

**Guide Notes:** See pages 8-10 for a discussion of the data on each of the adjuvant therapies.
What are the side effects of these drugs?

With the BRAF/MEK inhibitors, about 97% of patients will have some kind of side effect. So although it’s easy to take this combination at home, you may experience side effects of some kind. The most common are fevers—and they can be pretty high, in the 103°F range; fatigue; and nausea. An itchy rash can develop. Other side effects as described in the guide. Your oncologist can adjust the medicine and reduce the dose if some of these side effects tend to be more severe.

With immunotherapy, the most common side effect is fatigue. The drugs work by revving up the immune system, so you can develop autoimmune problems, like an inflammation of the colon, a rash, liver inflammation, endocrine problems, pulmonary issues, etc. These can happen any time during the course of your therapy or even after your therapy, and they can progress and become serious. But they can generally be treated quite effectively. So it’s important to inform your care team about any changes in how you feel because some of the immune-related side effects can start off very subtly. It’s best to treat them early.

Guide Notes: See pages 11-16 for a discussion of the side effects of the drugs.
Will these drugs affect my ability to have children?

These drugs may cause fetal harm. Therefore, the general recommendation is for couples to avoid pregnancy while one of them is taking any of these medicines—whether it’s a man or a woman. So while you’re on therapy, make sure that you’re using two birth control methods. These can be condoms, female contraceptive, whatever that is for you. However, if you are a woman taking targeted therapy, you need to be careful with oral contraceptives because they may interact with your medicine. While experts don’t believe these drugs have a direct long-term effect on fertility, the immunotherapies may affect the hormone system long term because of a potential hormonal effect, so some patients have described difficulty getting pregnant for the year or so after they stopped treatment.

Most clinics will tell you not to conceive until at least six months after immunotherapy is stopped. Now, targeted therapy clears from your system a little bit faster, and the manufacturer recommends that you don’t get pregnant for at least four months after therapy.

Before considering any next steps in family planning, consult your health care team.

Guide Notes: See page 19 for a discussion of fertility/family planning with these therapies.
Is one approach better than the other?

Not necessarily. Your oncologist will work with you on deciding your specific treatment plan. A lot of factors will be considered:

- Your substage and risk for recurrence
- Your \textit{BRAF} status
- Any existing autoimmune conditions
- Your overall health
- The safety of the drugs
- Convenience/quality of life
- Fertility/Family planning

\textbf{Guide Notes:} See pages 20-22 for the worksheets to help you weigh your options. You can complete these worksheets with your healthcare team to evaluate the options and select the approach that is best for you.