Stage IV Melanoma Treatment Options

Making the Decision That's Right for You

AIM AT MELANOMA FOUNDATION

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MELANOMA & SKIN CANCER ADVOCACY NETWORK

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INTRODUCTION

If you are reading this booklet, likely you (or someone close to you) has been diagnosed with or is being evaluated for Stage IV melanoma.* Stage IV is advanced melanoma, meaning it has spread from its original site to a distant location in the body. While this diagnosis can be overwhelming, it is important to know that Stage IV melanoma does not mean "end-stage melanoma." Fortunately, in the last 10 to 15 years, we have come a long way in treating this stage of melanoma. There are now several effective treatments available, and many more are being investigated. Patients with Stage IV melanoma can live long, productive lives because of these advances.

This document is designed to help you understand your treatment options and identify the different considerations you care about in deciding your treatment course. Using this guide, you and your team can weigh the options to make the decision that is right for you.

*This document has been developed to support decision making for Stage IV cutaneous melanoma, specifically the type that occurs on sun-exposed skin. There are other types of melanoma—ocular, mucosal, and acral lentiginous—that are not discussed here. For more information about these other types of melanoma and their treatment, please see https://www.aimatmelanoma.org/melanoma-101/types-of-melanoma/.

Document Released June 10, 2022.

DIAGNOSING AND MONITORING STAGE IV MELANOMA

INTRODUCTION

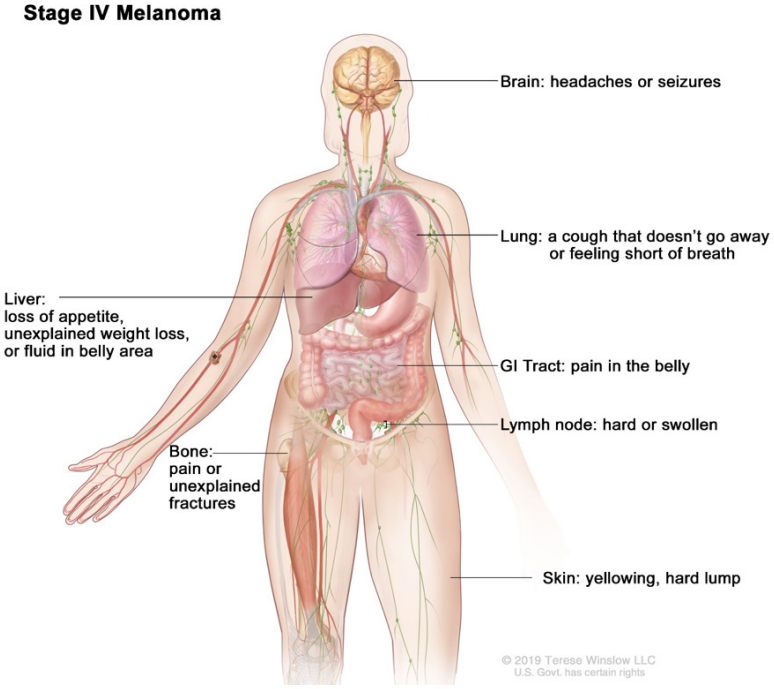
This section discusses some of the ways in which your oncologist will diagnose and evaluate Stage IV melanoma. Once a patient is diagnosed with Stage IV disease, many of these tests can also be repeated during the monitoring phase.

CLINICAL SIGNS OF STAGE IV DISEASE

Stage IV melanoma may be suspected based on imaging tests, or you may have had symptoms that made your healthcare team concerned. These symptoms could include:

- Hard or swollen lymph nodes
- Hard lump on the skin
- Fatigue
- Weight loss
- Yellowing of the skin
- Fluid build-up in the belly area
- Stomach pain

Specific symptoms can be associated with melanoma that has spread to certain regions of the body. For example, difficulty catching your breath or a cough that does not go away may be related to lung metastases. A severe headache or seizures may result from melanoma that has spread to your brain. Therefore, it's important to stay in close communication with your healthcare team about new (and unexplained) symptoms after you have been diagnosed with melanoma, regardless of the stage. Some of these symptoms associated with specific areas of cancer spread are shown in Graphic 1.



Graphic 1. Specific symptoms associated with melanoma that has spread to different regions of the body. Adapted with permission from Terese Winslow.

Beyond clinical assessment, your oncology team will use imaging and a range of pathology tests to determine the extent of cancer and its characteristics.

IMAGING

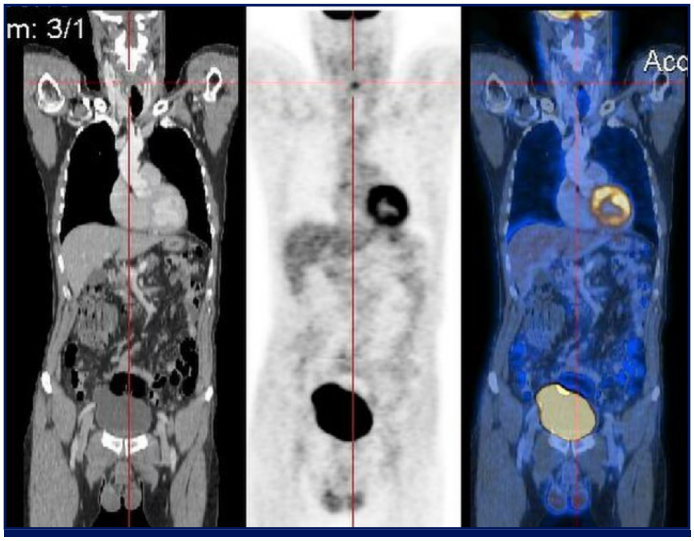
Imaging involves taking pictures of what is going on inside your body. Imaging tests are very important tools that your oncology team will use to diagnose and monitor Stage IV melanoma. These tests are helpful to look for and evaluate metastases. Here we provide a brief overview of some of these imaging tests.

Computed tomography (CT) or computerized axial tomography (CAT) scan is an imaging scanning technique that uses X-rays from different angles to make a 3-dimensional picture of the inside of your body. CT scans can be used with or without a material called contrast. **Contrast materials** are substances that help make certain body areas or structures stand out. This helps make the pictures the radiologist sees easier to interpret. We can think of CT scans as helping us find tumours and figure out their structure.

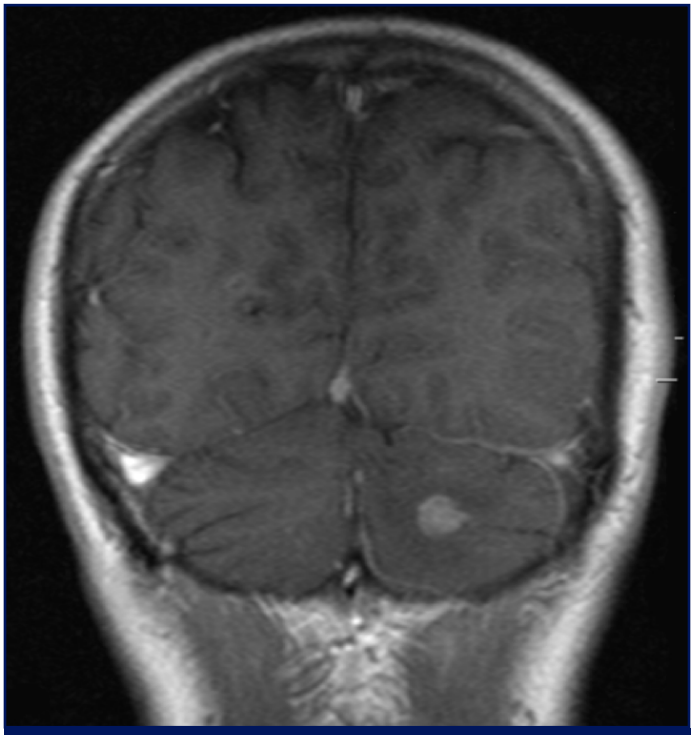
Positron emission tomography (PET scan) is a test that uses a radioactive drug (a tracer). The tracer is injected into a vein and settles in parts of the body that are using a lot of sugar to grow. We can think of this as testing the function (activity) of cells. An area that "lights up" on a PET scan might be an area that has cancer or an area that is inflamed from arthritis or injury. Because this test might pick up other things that are not cancer, it is often used together with a CT scan as described below.

PET/CT is an imaging method that combines CT with PET to provide detailed information about both the structure (CT) and the function (PET) of cells and tissues in the body. The overlaying helps the radiologist be confident that a region of concern is cancer, such as when the CT and PET images line up. An example of a PET/CT overlay is shown in Graphic 2.

Magnetic resonance imaging (MRI) is a scanning technique that uses magnets and radio waves to generate images of the organs in the body (see Graphic 3). It does not use X-rays. Sometimes the test is used with contrast. Other times it is not. MRI is the best test for imaging the brain. **Because melanoma often spreads to the brain, all patients with Stage IV melanoma should have an MRI of the brain, if possible.** However, some people cannot receive MRI tests because of metals in their bodies or for other reasons. These people should then get a CT of the brain if needed. MRI can also be used to image other areas of the body where there are soft tissues to be evaluated. There is no radiation associated with an MRI test.



Graphic 2. CT (left most panel), PET scan (centre panel), and PET/CT (right panel) showing the overlain results. Reproduced from Wikimedia Commons, courtesy of Creative Commons Attribution.



Graphic 3. Brain MRI showing metastases (white areas). From Wikimedia Commons, courtesy of Nevil Dilmen.

BIOPSY

If your imaging or clinical examination suggests you have Stage IV melanoma, a biopsy will most likely be used to confirm it. The biopsy can also be used to obtain tissue for further analysis by a pathologist. The types of biopsies that may be undertaken are discussed below.

Skin biopsy: If you have a suspected metastases in your skin far from your primary, you will undergo a skin biopsy. This involves cutting the spot or lump out and sending it to the laboratory to be tested.

Fine needle biopsy: This is where the doctor uses a thin, hollow needle to remove a small piece of tissue to see if the cancer is there. It is often used to evaluate lymph nodes or other structures. A local anaesthetic is sometimes used to numb the area. If you need to check a structure away from the body surface, such as liver or lung, an imaging test such as an **ultrasound** (imaging test using sound waves) or CT scan can be used to guide the needle into place.

Core-needle biopsy: This biopsy uses a needle that has a wider diameter than a fine-needle biopsy. This type of biopsy is typically used to sample larger tumours. With this procedure, the doctor removes a small cylinder of tissue (maybe 2 mm in diameter and 1 cm long).

Excisional or incisional biopsy: In this type of biopsy, the entire tumour (**excisional** biopsy) or a small part of a large tumour (**incisional** biopsy) are removed. This type of biopsy often can be performed using local or regional anaesthesia. However, if the tumour is inside the chest or abdomen (belly) it might require **general anaesthesia**, which means drugs that put you into a deep sleep.

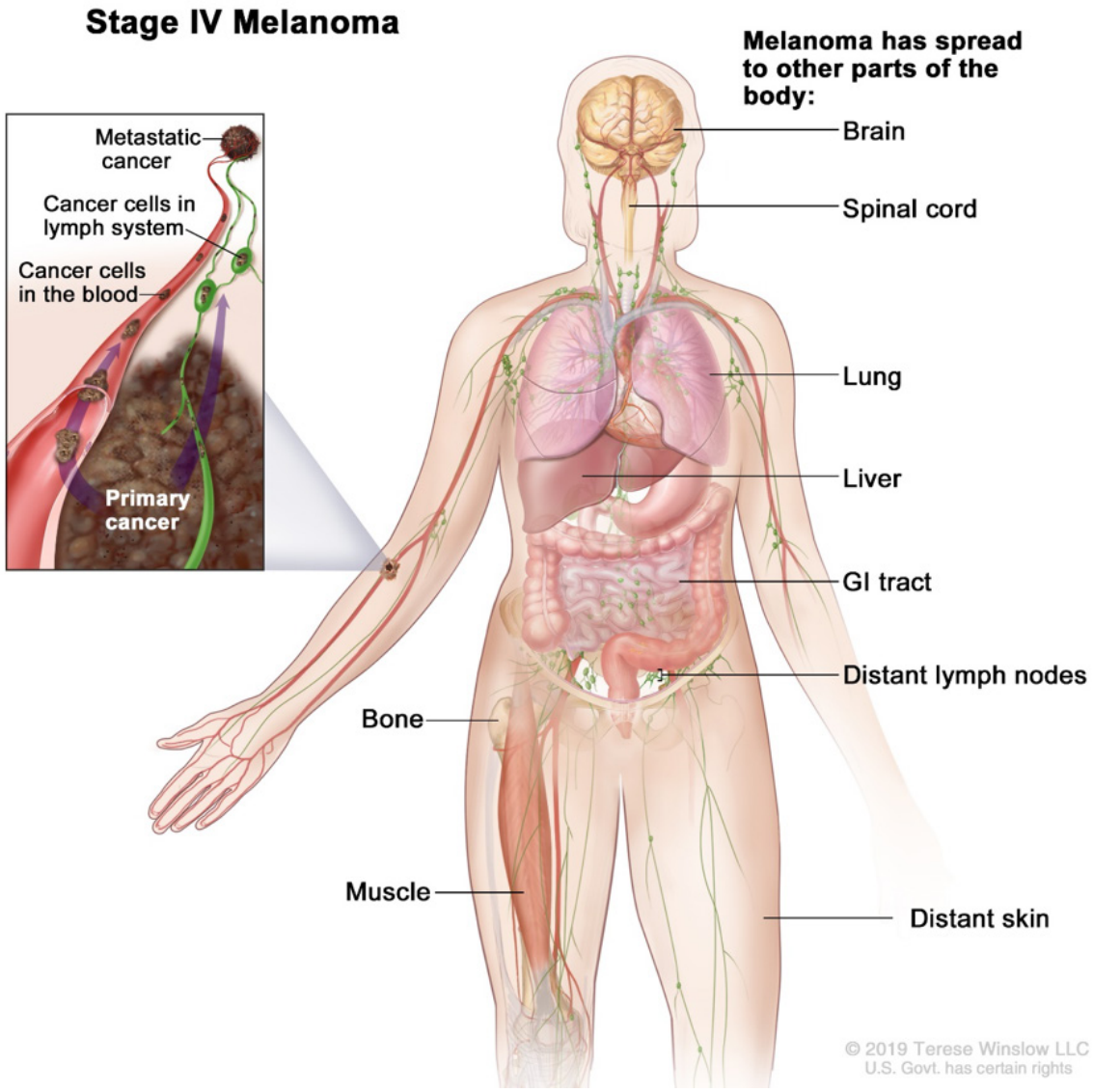
Lymph node excisional biopsy (surgical removal): In this biopsy technique, an entire enlarged lymph node is removed. It's sometimes used when the lymph node's large size suggest that the melanoma has taken over the whole lymph node.

Endoscopic biopsy: This is a procedure in which the doctor uses a thick flexible lighted tube (an **endoscope**) to look inside different parts of the body. The endoscope can then be used to sample tissue that might be cancer. This type of biopsy might be used to obtain a sample from your oesophagus, lungs, or intestines.

Laparoscopic, thoracoscopic, and mediastinoscopy biopsies: These types of biopsies are used to reach areas that an endoscope can't reach. For these types of biopsies, the surgeon cuts into the region and then passes a tube to look inside and take a biopsy. The term before the scope explains what part of the body is being sampled (e.g., thoracoscopic biopsy is taken from the thorax).

OVERVIEW OF STAGE IV MELANOMA

Stage IV melanoma is melanoma that has spread (**metastasised**) to sites away from the spot where it first started (the **primary melanoma**). As shown in Graphic 4, these distant sites can include the lung, liver, brain, bone, or even the skin or lymph nodes far away from the primary (original) site of the melanoma. By contrast, Stage III melanoma means the cancer has spread only to the closest lymph nodes or the skin region right around the primary melanoma.



Graphic 4. Visual representation of Stage IV melanoma. Adapted with permission from Terese Winslow.

TREATMENT PLANNING FOR STAGE IV DISEASE

Below is a discussion of some of the tests and other factors that will be considered in making your treatment plan. This guide will assist you in understanding the rationale for decision making that is best for you.

TESTING

To evaluate Stage IV melanoma, your oncology team will order a series of pathology or laboratory tests, some on the tumour, others on blood. The tumour is sampled through a biopsy. You will most likely also undergo some imaging scans.

Some of the tests your oncology team will order are checking for **biomarkers**, which are substances in your tissue, blood, body fluid, or the tumour itself that tell us key information about your cancer. A biomarker might tell us how aggressive your cancer is, whether it will respond to a specific therapy, or how your body is responding to the presence of the cancer. We discuss some key melanoma biomarkers below.

Pathology Tests on the Tumour

When the tumour from the biopsy gets to the pathology laboratory, the pathologist will run specific tests on the tumour tissue to learn more about it. *BRAF* testing is an important biomarker to test for. See the APPENDIX for more detail about this test. Programmed death ligand 1 (PD-L1) is being studied as a biomarker to guide therapy in some melanoma clinical trials.

At some melanoma centres, patients are getting a test known as targeted exome sequencing. This test gives their oncologist a readout of hundreds of genes in the tumour, including some rare mutations. Melanomas that contain some of these less common mutations are important to identify because they may be treated differently, as outlined below. Less common mutations include a neurotrophic tropomyosin receptor kinase (NTRK) fusion, which would be treated with a therapy specific to that mutation. Another mutation that the test might find is a mutation in the c-KIT gene. c-KIT is a protein that is also involved with growth of cancers. c-KIT is more commonly mutated in other cancers and in noncutaneous melanomas (like those in the mucous membranes). In cutaneous melanoma, *c-KIT* mutations are more common in melanomas arising in chronically-sun damaged skin. *c-Kit*—mutated melanoma may respond to specific types of therapy described below.

If your oncologist conducts the targeted exome sequencing test, it's helpful to discuss those results and how the information is going to be used to guide treatment.

Blood Tests

Blood tests will tell your oncology care team about your general health as well as some more specific information about the cancer and how your body is fighting it.

Some biomarkers are tested in the blood. Such tests are often helpful for following your cancer (and your body's response to the cancer) over time.

Lactate dehydrogenase (LDH)

LDH levels in your blood serum may be tested. LDH is a protein that is used to turn sugar into energy to fuel your cells. It is used in different parts of your body. Cancer cells need a lot of this protein because they need a lot of energy, and it helps them survive in low oxygen environments. When cells, such as cancer cells, are damaged, they release LDH into the blood, which is why higher levels of LDH in the blood serum are found when cancer cells are spreading rapidly. LDH levels may be related to the amount of melanoma present. LDH levels have also been associated with outcomes to treatment.

Circulating tumour DNA (ctDNA)

One monitoring test being studied is ctDNA. ctDNA are small pieces of DNA released from tumour cells that make their way into the bloodstream. ctDNA is a sensitive test that helps determine if you have any tumours in your body—even if the tumours are not visible on scans (a state known as no evidence of disease). This remains an experimental test in melanoma and is currently not widely used to guide treatment decisions or monitoring.

FACTORS FOR DECISION MAKING

Once your oncology team has gathered the information about your melanoma from the different tests, they will have a clearer picture of what is happening. They will assess a number of items about your disease.

Extent, Pace, and Location of Disease

It's important to recognise that Stage IV melanoma can take many forms. You may have a single metastasis (one site), or you may have metastases in many parts of your body. The extent of the disease affects what treatments are considered. So understanding the **extent** of the disease is important.

Your oncology team may also look at how quickly the melanoma has spread (the **pace of disease**) based on prior scans and tests as well as how many sites are involved. If the tumour is spreading quickly, your team may recommend a more aggressive approach to treatment.

The **location** of the disease is also important. Some therapies can reach throughout the body but are not effective when there is melanoma in the brain. Others can work effectively in the brain. Sometimes, melanoma spreads to distant sites on the skin and in the lymph nodes and can be cut out or injected with medication, so location is also important to consider when selecting therapy.

OTHER ASPECTS OF TREATMENT PLANNING

While the above factors have to do with your melanoma, you—your general health and your goals—are also important considerations.

Your Fitness

You and your oncology team will consider your general health in selecting therapy and in evaluating what kind of support you need. Your oncology team will most likely use a standardized performance-status scale to assess the level of your functioning. This assessment evaluates how much energy you have and your ability to do daily activities (for example, paid work, housework, shopping, and self-care such as bathing, dressing, and eating).

Your Goals for Therapy

Your oncology team will be working with you to meet your goals for therapy. It's important that you think through how aggressive you want to be in fighting the cancer and how you value that aggressiveness vs the possible trade-offs in terms of convenience, quality of life, and other factors that matter to you. Each therapy has its plusses and minuses in terms of how well it works, the side effects, how it is given (and how convenient that is for you), cost, and impact on family planning. These are all points to consider, and the rest of this document provides much more information on these topics.

WEIGHING ALL THE FACTORS

In order to make decisions about treatment, you and your oncology team will take into consideration all of the factors described above: your scans and test results; the extent, pace and location of your cancer; your overall health; and your goals. Additionally, you and your team will consider what we know about how well each treatment works, the costs, and the side effects. Graphic 5 shows some questions you and your oncology team will consider in this process.

Graphic 5. Factors to consider in the Stage IV decision-making process.

Extent and Location of Disease
How many sites (and which locations) has the tumour spread to?
Is it in the brain?
Are there tumours in or under the skin or in the lymph nodes that can be injected?
Pace of Disease
Is the disease progressing quickly?
Is the cancer causing pain and other symptoms? If so, how bad are these symptoms?
Is the cancer making you very sick?
What is the LDH level?
Other Tumour Characteristics
What is your *BRAF* status?
Does the tumour carry any rare mutations that could be targeted?
Prior Therapy
Did you receive **adjuvant therapy** (therapy given after surgical removal to prevent the cancer from coming back)?
Have you received therapy before for Stage IV disease?
Have you received corticosteroids recently?
Therapy Considerations
How well is a therapy likely to work for you?
What are the side effects of the therapy and how well are you likely to tolerate them?
How is the therapy administered?
What will the therapy cost you?
Personal Considerations
How convenient is each therapy for you?
How much are you willing to trade off in terms of other factors (side effects, etc) for a therapy that works well?

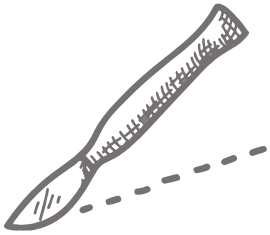
THERAPEUTIC OPTIONS FOR STAGE IV MELANOMA

This section starts with an overview of the different types of therapies used to treat Stage IV melanoma. We then drill down in detail on the medications used to treat melanoma: how well they work, their side effects, how they are given, financial and access issues, as well as pregnancy and family-planning considerations. Our goal here is to cover all of these considerations to provide the information you need to support the shared decision-making process.

OVERVIEW OF THERAPIES

In this subsection, we review therapies based on in the order in which they are typically considered or offered as options to you: surgery (if possible), medications, and radiotherapy. We then discuss specific therapies for managing brain metastases, since they stand alone. We end with clinical trials, because clinical trials may involve any of these treatment types.

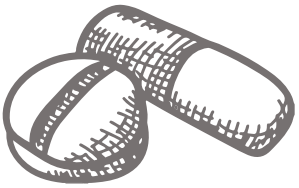
Surgery



In some cases, your cancer may have spread from the primary melanoma to one or just a few sites, and it can be removed surgically. If the visible cancer can be removed entirely, then your status becomes **no evidence of disease (NED)**. Once the surgery is complete, your team will determine if you are NED. If all of the melanoma has been surgically removed, **adjuvant therapy**, which is therapy provided to prevent the disease from coming back, will be offered. If the surgery is not successful in removing all of the tumour, the extent of cancer left will be determined. If more surgery is feasible, you may be offered that. However, most likely, at that point you will be offered medication, usually given systemically to fight the cancer.

Currently, many studies are underway to investigate the role of medications given before surgery. These **neoadjuvant** therapies may shrink or kill the tumour and make it more operable. So it's worth discussing neoadjuvant clinical trials, if appropriate, with your surgeon and medical oncologist.

Medications for Stage IV Disease



Here we provide an overview of the medications that are used in Stage IV melanoma. We have organised these by how the medications work, which is a common way that oncologists classify them and present them to patients. Many of these medications are considered **systemic therapies**, meaning they work throughout the body to fight the melanoma.

Targeted Therapies

Targeted therapies are medications that "target" certain processes or proteins in melanoma cells. We will start with the BRAF/MEK targeted therapies, since they are the most common targeted therapies used in melanoma.

As mentioned previously, BRAF is a key protein that helps melanoma cells grow. Patients whose melanoma carries a mutated BRAF gene are eligible for therapy targeted to BRAF that helps block the protein and slow the growth of melanoma. This is relevant for around 40% of patients.

Researchers discovered that when a BRAF inhibitor was combined with a MEK inhibitor, which targets a protein further down in the same cellular pathway, the combination was better at slowing melanoma growth and eliminated or reduced some of the troublesome side effects that were associated with BRAF inhibitors alone. It was as if the combination of medications hit melanoma with a more effective one-two punch.

BRAF/MEK inhibitors are oral (by mouth) drugs. For patients with a BRAF mutation, the BRAF/MEK inhibitor targeted therapies are available for management of Stage IV disease that can't be managed surgically (unresectable).

The available BRAF/MEK targeted therapies are:

- Dabrafenib (TAFINLAR®) + trametinib (MEKINIST®)
- Vemurafenib (ZELBORAF®) + cobimetinib (COTELLIC®)
- Encorafenib (BRAFTOVI®) + binimetinib (MEKTOVI®)

Patients who have tumors that carry less common mutations may be eligible for clinical trials evaluating drugs specifically targeted to those mutations. For patients who have melanomas that carry NTRK fusions, drugs such as larotrectinib (VITRAKVI®) and entrectinib (ROZLYTREK®) are available. These drugs are not specifically approved in melanoma, but your oncologist can prescribe one for you if s/he feels it's appropriate. NTRK fusions are often identified by broad genetic screens. For *c-KIT* mutations, inhibitors such as imatinib (GLEEVEC®), nilotinib (TASIGNA®), dasatinib (SPRYCEL®), and sunitinib (SUTENT®) have been evaluated in small studies. Combination approaches, including strategies involving c-KIT-directed therapy plus immunotherapy, are being investigated in clinical trials.

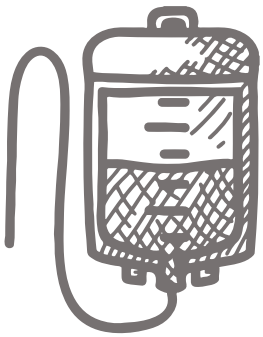
Immunotherapy

Immunotherapy is a treatment that gives your immune system more power to fight your cancer. Every day, our immune system recognises dangerous substances—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 your immune system, preventing it from doing its job. In fact, the immune system may not even recognise these cancer cells, and so they can keep growing and multiplying.

Currently, the immunotherapies we will discuss below are given intravenously, with the exception of talimogene laherparepvec, which is given intralesionally (intra-tumourally, or directly into the tumour).

Checkpoint Inhibitors

Checkpoint inhibitors are monoclonal antibody drugs that target specific pathways in the immune system. Monoclonal antibodies are large proteins with multiple parts. Therefore, they are challenging to manufacture an must be given in the vein (intravenously). Checkpoint inhibitors "take the brakes off" the immune system, allowing it to identify and destroy cancer cells. Currently for melanoma, there are a number of checkpoint inhibitors available in Australia:



PD-1 inhibitors:

- Pembrolizumab (KEYTRUDA®)
- Nivolumab (OPDIVO®) (given alone or in combination with YERVOY®)

CTLA4 inhibitors:

- Ipilimumab (YERVOY®) (given alone and in combination with OPDIVO®)

PD-1 and CTLA-4 inhibitors are types of checkpoint inhibitors. PD-1 inhibitors generally produce fewer and less severe side effects compared with CTLA-4 inhibitors, such as ipilimumab. Nevertheless, the combination of the PD-1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab is considered highly effective when a strong response is needed, although the use of this combination is associated with a more severe side-effect profile.

It's also important to mention that the CTLA-4 inhibitor ipilimumab became commercially available in 2011, before the PD-1 inhibitors. It was the first new treatment approved for melanoma in decades, and it ushered in a new era of melanoma research and treatment. However, as you will see below in **How Well These Therapies Work**, the PD-1 inhibitors have a better efficacy and safety profile. Therefore, ipilimumab is rarely prescribed as a single-agent therapy. Instead, it is more frequently used in combination with nivolumab. For this reason, we will not spend time discussing ipilimumab as a single-agent therapy.

A Note on Corticosteroids

Corticosteroids are sometimes used to reduce swelling in the brain from melanoma metastases or surgery. Patients who are receiving corticosteroids are sometimes not eligible for immunotherapy right away. Therefore, corticosteroid use is an important factor to consider in choice of therapy.

Cytotoxic Therapies (Chemotherapy)

Chemotherapy does not work very well in melanoma, unlike other tumors. For this reason, it is rarely used. Chemotherapy can be considered for patients with Stage IV melanoma who are not appropriate candidates for immune-based therapy, BRAF/MEK-inhibitors, or clinical trials or for whom these other approaches have not been effective.

Radiation Therapy

Radiation therapy has a clear role in managing brain metastases, as discussed below. Radiation therapy can sometimes be used as adjuvant therapy after surgery for high-risk melanoma in lymph nodes. It can also be used for specific indications, such as control of bleeding, or to improve symptoms, such as pain from melanoma in the bone. The possible side effects of radiation therapy may include skin breakdown (ulcers), pain, redness at the site of irradiation, as well as fatigue.

Localized Treatments for Brain Metastases

Neurosurgery

Surgery of the **central nervous system** (the brain and spinal cord) is performed by a specialised neurosurgeon. Surgery for brain metastases is usually restricted for specific circumstances:

- Patients with fewer than three metastases.
- Patients who are not candidates for radiation therapy (because the metastases are too large).
- Patients with significant symptoms or bleeding from the tumour.
- Patients whose tumours regrow after radiation therapy.

To perform brain surgery, a **craniotomy** is required. In this procedure, the neurosurgeon makes an opening in the skull to access the tumour. The neurosurgeon typically tries to remove the tumour or reduce its size to make other treatments more effective. The tumour tissue is usually evaluated to determine the best treatments (see biomarker discussion above). Usually, after neurosurgery, additional treatments are required, including radiation and systemic therapies, as described below.

Complications during or after any type of surgery can include bleeding, infections, or reactions to anaesthesia, although these are not common. A major concern after surgery is swelling in the brain. Anti-inflammatory drugs called corticosteroids are typically given before and for several days after surgery to help lessen this risk. As mentioned previously, use of corticosteroids can affect the choice of systemic therapy.

Radiation Therapy for Brain Metastases

Stereotactic surgery (SRS) is a computer-guided treatment that provides highly focused radiation to tumours in the brain. In Australia, the most common type of stereotactic surgery is delivered via a linear accelerator (LINAC) machine, which delivers focused x-rays (eg, CyberKnife). There is no incision or knife. The term reflects the precise way radiation is used like a knife. Less commonly, stereotactic surgery can be delivered as focused gamma rays (Gamma Knife).

Whole Brain Radiation Therapy (WBRT) is a process in which the entire brain is treated with radiation. It is typically reserved for the following situations:

- Too many metastases for surgery or stereotactic surgery.
- Patients with leptomeningeal disease, in which the melanoma has spread to the cerebrospinal fluid, the fluid that bathes the brain and the spinal cord.
- After stereotactic surgery, if the tumours continue to grow.
- After trying immunotherapy, if the tumours continue to grow.

Radiation therapy to the brain can cause a range of side effects. WBRT is associated with more side effects than SRS because it is used more broadly. Side effects can include headaches, hair loss, nausea & vomiting, fatigue, hearing loss, and trouble with memory and speech.

Clinical Trials/Emerging Approaches

Many patients think clinical trials are an option of last resort, but this belief is a misconception. Robust research is regularly bringing forth new treatments, so clinical trials can offer good options, regardless of where you are on your cancer journey. You should discuss clinical trial options with your oncologist before making any treatment decision—even your very first treatment decision—because some trials are designed to test therapies in patients who have not yet received treatment. These study drugs are being evaluated to see if they are the best option for "first-line" therapy or even before surgery (**neoadjuvant therapy**).

Another misconception about clinical trials is that you have a 50% risk getting the placebo (sugar pill). This is not true. Today, most melanoma studies compare the investigational therapy with standard of care. So, with the possible exception of studies in melaoma that has been through multiple lines therapy (and for which there is no standard of care), you are guaranteed to receive some type of therapy in melanoma clinical trials.

A benefit of participating in a clinical trial is that you will be monitored very closely by an expert in the field. However, a downside is that clinical trials can sometimes require additional time and inconvenience for tests, appointments, and other monitoring.

To search for clinical trials available in Australia, please see www.australianclinicaltrials.gov.

Emerging approaches for melanoma are evolving in real-time. Strategies that are far along in development and show great promise at the time of this writing include:

- **LAG-3 and PD-1 inhibitor combination therapy**. Researchers have recently identified another immune checkpoint called lymphocyte activation gene-3 (LAG-3). As a checkpoint, LAG-3 blocks the growth and activity of certain types of T cells, which are white blood cells that help protect the body from cancer and other threats. LAG-3 is a different target than PD-1/PD-L1, and so when both pathways are inhibited, T cells are unleashed and the cancer killing effect is magnified. Relatlimab is the most advanced LAG-3 inhibitor in development. Recent studies have shown that the combination of relatlimab + the PD-1 inhibitor nivolumab prevent disease progression better than PD-1 inhibitor nivolumab alone in late-stage clinical trials for patients with Stage IV melanoma.
- **Oncolytic viruses**. One oncolytic virotherapy being studied is talimogene laherparepvec (IMLYGIC®, T-VEC) is an immunotherapy made by modifying a herpes virus to increase its ability to home in on tumour cells. When T-VEC is delivered to the tumour, viral reproduction in the tumour cells causes them to burst (**lyse**). T-VEC also causes the production of proteins that stimulate the immune system to come to the tumour location and kill additional cells. T-VEC is an intralesional therapy—it's injected directly into the melanoma tumour on the skin, below the skin, or in the lymph node that can't be easily removed with surgery. As mentioned, T-VEC stimulates the body's immune system to go to the site and attack the melanoma. It also treats tumours away from the site of injection because it causes a local and body-wide immune response. One oncolytic intralesional therapy that is being developed takes advantage of the patient's own immunity to polio. Using a modified polio vaccine to target a protein that is shared on the polio virus and cancer cells (thus directing your immune system to attack the melanoma), this therapy, PVSRIPO, has shown a benefit in patients with difficult-to-treat Stage IV melanoma.

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HOW WELL SYSTEMIC THERAPIES WORK

In this section, we review data from clinical trials of therapies for use in Stage IV melanoma. In addition to all of the other factors that you will weigh in your treatment decision, the efficacy of each drug is an important consideration.

Endpoints, or outcomes measures, help researchers objectively determine whether the treatment being studied is beneficial or not. The outcomes results are the most important information that a trial provides. Here are some of the outcomes that you are typically reported in studies:

- **Overall survival (OS)**: The length of time from start of treatment that cancer patients live, regardless of whether their cancer spreads, grows, shrinks, disappears, or stays the same size. OS is occasionally reported as a median, which is the middle value in a list of values. Often, OS is reported as percentage of people alive at a specific time point. Below, we have provided the latest survival data available at specific study time points. OS statistics are calculated based on any deaths that occur in the study, not necessarily only the deaths caused by melanoma.
- **Progression-free survival (PFS)**: The length of time cancer patients live without their cancer growing or spreading. Like overall survival, progression-free survival might be reported as a median, but it also can be reported as a percentage of people experiencing progression-free survival at a specific timepoint (such as three years). While we do not typically report PFS below, it can be found in study reports.
- **Overall Response Rate (ORR)**. The percentage of patients whose tumours shrink substantially (by 30% or more) or disappear altogether as a result of treatment. A **Complete Response (CR)** means the tumour(s) completely disappear, while a **Partial Response (PR)** occurs when tumours have shrunk by at least 30% but have not completely disappeared. ORR = CR + PR. Even if the treatment works by shrinking or stabilizing tumours that are growing, in a clinical trial, a patient is only considered to have had a "response" if the measurable tumours shrink by at least 30% or more. **This means the objective response rate underestimates the proportion of patients for whom the treatment is effective**.

We provide data on outcomes for specific subgroups of patients, which may also be helpful for you and your team in projecting the likelihood of response based on what subgroup you belong to.

As you review the following information, it's important to keep in mind that these studies were done at different times and involved different groups of people and control groups, which means it's not appropriate to compare results across the studies. Nonetheless, each study yields information on the efficacy of each of the treatments tested.

BRAF/MEK Inhibitors

Remember that BRAF/MEK inhibitors are only given to patients whose melanoma is *BRAF*-positive, so the following information is relevant only to those patients. If your melanoma is *BRAF*-negative, you may want to skip to the next section, **Immunotherapy**.

The BRAF/MEK inhibitors have been studied in a range of clinical trials vs single-agent BRAF inhibitors, which served as the active control group. As mentioned previously, single-agent targeted therapies are rarely used, so it's more important to see how these combinations performed overall rather than how they compared to the single agents.

The other point to consider is that all three of these targeted therapy combinations have been found effective. It's important to remember that we don't know which combination is the best. If you and your oncologist decide to use targeted therapy, you can look at the overall profiles of these different combinations and see which one best suits you.

Dabrafenib + Trametinib

This BRAF/MEK inhibitor combination was evaluated in several studies. If you would like to review these studies, please see the Long 2015, Robert 2015a, and Robert 2019a citations listed in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**. Survival outcomes are shown in Graphic 6 below.

Graphic 6. Dabrafenib + trametinib overall survival outcomes at 5 years.

Outcomes for Specific Subgroups

In the long-term outcomes report, dabrafenib + trametinib outcomes were better in certain subgroups of patients.

- **Patients with low tumour burden**: In this study, the investigator classified patients as having low tumour burden when the baseline LDH was below or at the upper limit of normal and there were no more than three organ sites with metastases. Patients with low tumour burden did well: 55% were alive at five years, compared with 34% for the study group overall.
- **Complete responders**: For the 109 patients who had a complete response to therapy, the overall survival rate was 71% at five years.

Vemurafenib + Cobimetinib

This combination was evaluated in several studies. If you would like to review these studies, please see the Ribas 2014, Larkin 2014, and Ribas 2019 citations listed in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**. Survival outcomes are shown in the Graphic 7 below.

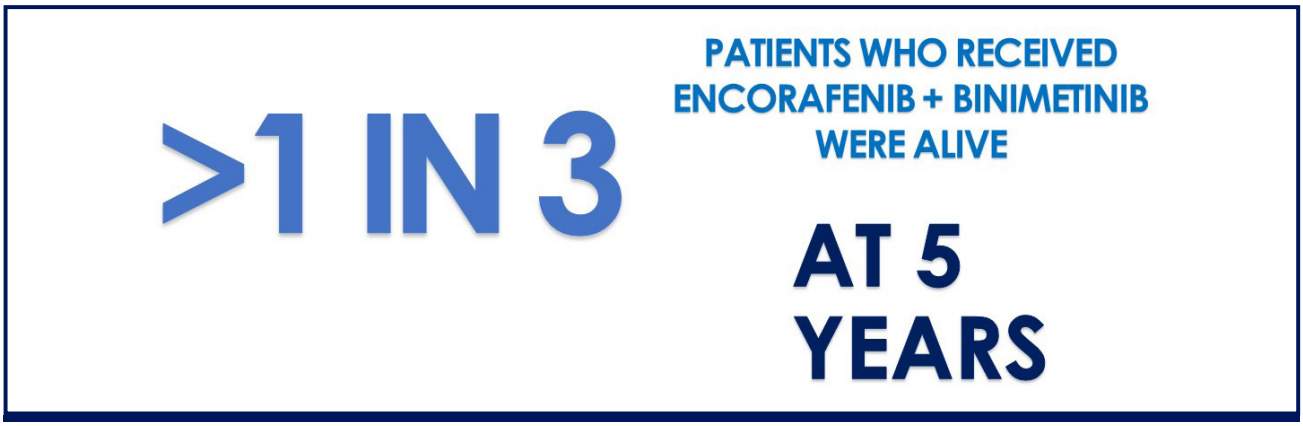
Graphic 7. Vemurafenib + cobimetinib outcomes at 5 years.

Outcomes for Specific Subgroups of Patients

Patients with normal LDH levels and a tumour diameter ≤45 mm had a three-year survival rate of 53% with the combination therapy, compared with a survival rate of <10% for patients with an LDH greater than two times the upper limit of normal.

Encorafenib + Binimetinib

Please see the Dummer 2018, Ascierto 2020, and Dummer 2021 citations listed in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**. Survival outcomes are shown in Graphic 8 below.



Graphic 8. Encorafenib and binimetinib outcomes at 5 years.

Outcomes for Specific Patient Subgroups

In the follow-up study, rates of overall survival and progression-free survival were similar across subgroups. However, patients elevated LDH levels did not do as well as patients with normal LDH levels, as was seen with other BRAF/MEK inhibitors.

Other Targeted Therapies

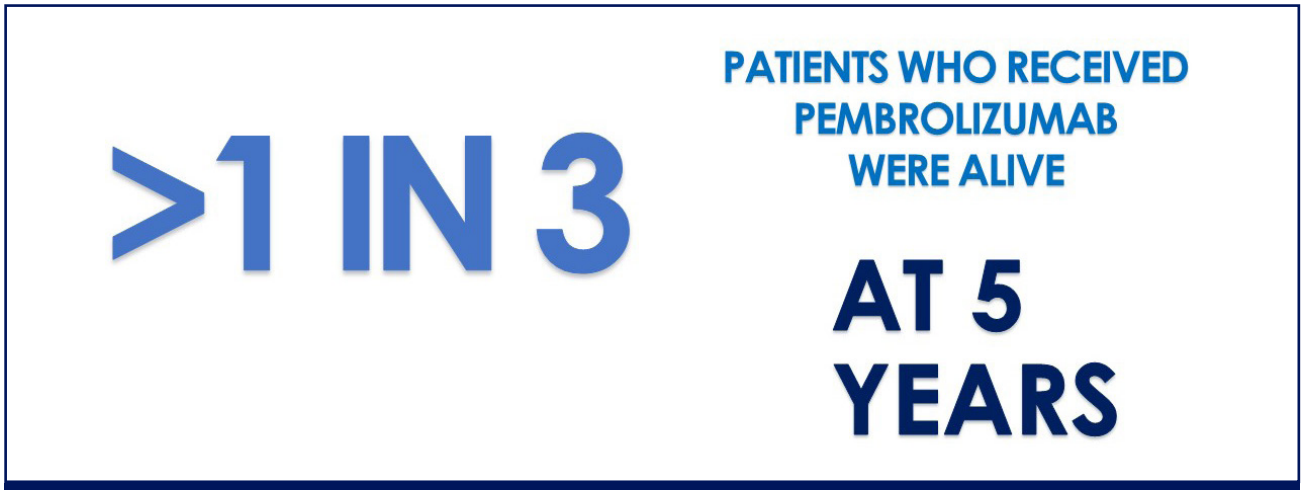
Imatinib or nilotinib, inhibitors of mutated *c-KIT*, have been studied in a small number of cases. For metastatic melanoma, these therapies can be considered as second-line therapy (after immunotherapy) for tumours with mutations of *c-KIT*. While these agents do produce overall response rates up to 30%, the responses tend to be short-lived. Therefore, imatinib or nilotinib are recommended as second-line or subsequent therapy. Similarly, larotrectinib or entrectinib are recommended for NTRK-gene fusion-positive tumours in the second-line setting. These drugs are not readily available in Australia, but they may be considered as part of a clinical trial.

Checkpoint Inhibitor Immunotherapy

The content below shows data for the checkpoint-inhibitor monotherapy and combination regimens. Ipilimumab is a comparator arm for many of these studies since it was commercially available and the standard of care when the PD-1 inhibitors were being studied. As the data shows, single-agent PD-1 inhibitors have better efficacy than single-agent ipilimumab. For this reason, ipilimumab is not frequently used as monotherapy anymore, and we will not review the studies on it. However, ipilimumab is still used commercially as part of combination immunotherapy. This gives us two different checkpoint inhibitor approaches—single-agent PD-1 inhibitor therapy and combination immunotherapy—which is considered a more aggressive approach.

Pembrolizumab

Pembrolizumab monotherapy has been evaluated in several studies. We will focus on the data from the KEYNOTE-006 study that compared pembrolizumab to ipilimumab in patients with advanced melanoma who had up to one prior therapy. For a review of this study, see Robert 2015b and Robert 2019b in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**. Survival outcomes are shown in Graphic 9 below.



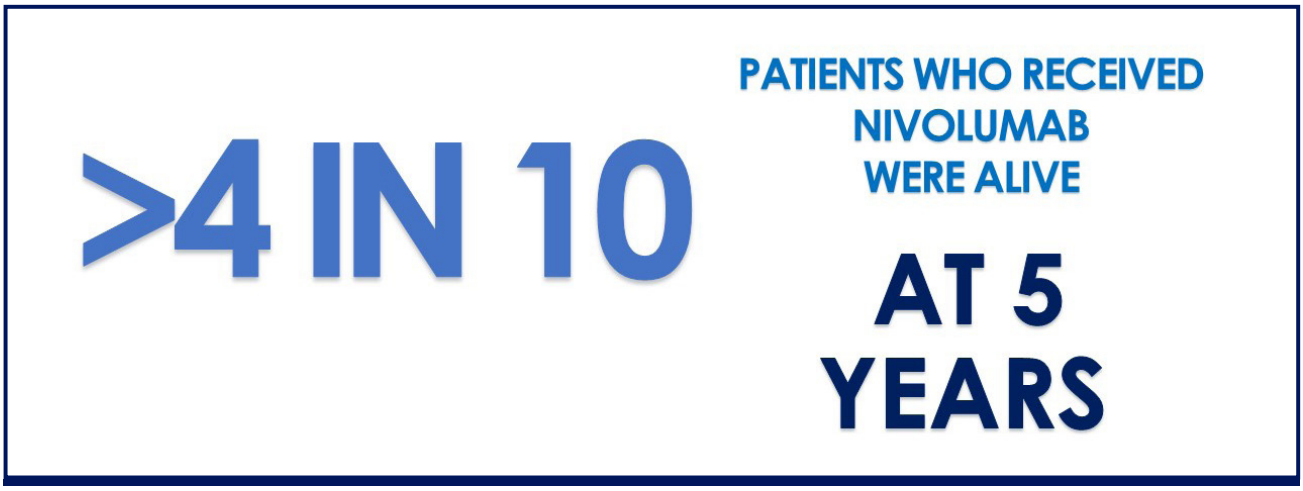
Graphic 9. Overall survival rate at five years with pembrolizumab for the KEYNOTE-006 study.

Outcomes for Specific Subgroups

- **PD-L1 levels**: In the KEYNOTE-006 study, subgroups performed well, except for a small subgroup that had negative PD-L1 levels. However, the small number of people in that group make the data hard to interpret. Researchers continue to evaluate the role of PD-L1 levels and response. But for now, testing of PD-L1 levels is not required for checkpoint inhibitor therapy.
- **Prior therapy**: In an additional pembrolizumab study (KEYNOTE-001), the overall response was higher in the subgroup of patients without prior treatment (called treatment-naïve patients) than in the overall group of patients. This result is expected, given that disease that progresses through treatment is generally more difficult to treat.

Nivolumab

Nivolumab monotherapy has been evaluated in several studies. We will focus on the data from the long-term report of the CheckMate 067 study (which evaluated nivolumab alone or nivolumab + ipilimumab in comparison with ipilimumab alone). If you would like to review this study, please see the Larkin 2019 citation listed in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**. Survival outcomes are shown in the Graphic 10 below.



Graphic 10. Proportion of patients alive at five years who received nivolumab in the Checkmate 067 study.

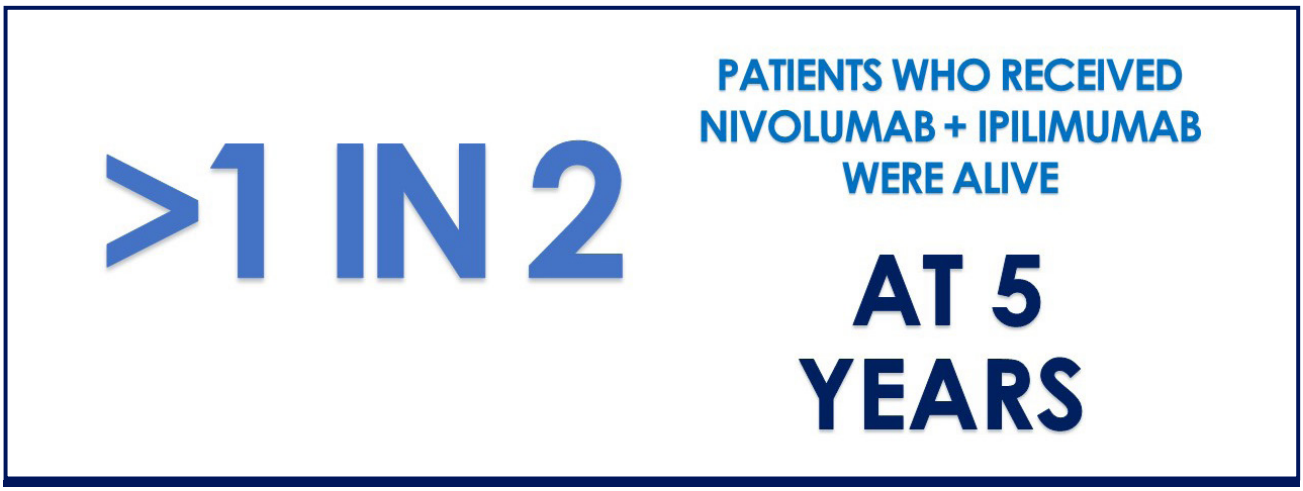
As reported at the 2021 American Society of Clinical Oncology (ASCO) meeting, this effect is sustained. At 6.5 years, 42% of nivolumab-treated patients were alive.

Outcomes for Specific Subgroups

- ***BRAF* status**: Overall survival at five years in nivolumab + ipilimumab-treated patients was higher in BRAF-positive patients (60%) vs BRAF-negative (48%).
- **LDH**: Overall survival at five years was higher in patients who received the combination with normal LDH levels (60%) vs survival for patients with elevated LDH (38%).
- **PD-L1 expression**: PD-L1 expression alone did not affect outcomes.

Combination Immunotherapy (nivolumab + ipilimumab)

This combination was evaluated in several studies. We will focus on the data from the long-term report of the CheckMate 067 study (which evaluated nivolumab + ipilimumab with nivolumab alone or ipilimumab alone). If you would like to review this study, please see the Larkin 2019 citation listed in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**. Survival outcomes are shown in Graphic 11 below:



Graphic 11. Proportion of patients alive at five years who received nivolumab + ipilimumab in the Checkmate 067 study.

This effect was sustained. At 6.5 years, 49% of patients who received the combination were alive (ASCO 2021).

Outcomes for Specific Subgroups

- ***BRAF* status**: Overall survival at five years in nivolumab + ipilimumab-treated patients was higher in *BRAF*-positive patients (60%) vs *BRAF*-negative (48%).
- **LDH**: Overall survival at five years was higher in patients who received the combination with normal LDH levels (60%) vs survival for patients with elevated LDH (38%).
- **PD-L1 expression**: PD-L1 expression alone did not affect outcomes.

Cytotoxic therapies

The cytotoxic therapies (chemotherapies) such as dacarbazine, temozolomide, paclitaxel, and albumin-bound paclitaxel can help some patients (~20%) with melanoma. They remain an option for patients who have failed other therapies or who cannot tolerate other therapies.

Medications for Brain Metastases

Many of the initial studies of the treatments discussed above excluded patients with brain metastases. However, additional studies have been conducted that help us tease out the role of different therapies for brain metastases. A review of the data supporting the use of these agents for brain metastasis reveals some caveats:

- BRAF/MEK inhibitor combinations do have activity against brain metastases, but the response rates are lower than for disease outside the brain (**extracranial disease**). These agents still work in patients who are BRAF positive who have symptomatic disease that required corticosteroids.
- Checkpoint inhibitors, alone or in combination, have efficacy against brain metastases. Many of the studies are ongoing. However, because corticosteroids can interfere with the activity of checkpoint inhibitors, their use in patients receiving corticosteroids for symptomatic brain metastases is limited.
- Some experts propose that checkpoint inhibitors—particularly combined therapy—should be used in combination with SRS in patients with a few or a single-brain metastases. For patients with brain disease that is symptomatic or rapidly progressing, BRAF/MEK inhibitor therapy can be used in patients who are BRAF positive.

SIDE EFFECTS OF STAGE IV SYSTEMIC THERAPIES

The side effects of the drugs to manage Stage IV melanoma are shown below. For each type of therapy, we describe the common side effects experienced by 10% or more of patients, regardless of how serious they are. We also list separately the serious side effects—those that are considered severe or life threatening. In listing of the common side effects, we focused on signs (objective evidence of the side effect that someone else can observe, such as a lump) and symptoms (the subjective experience of the side effect you experience, such as fatigue) rather than laboratory abnormalities, such as liver enzyme elevations. However, we did consider laboratory abnormalities in the discussion of serious side effects, where they are grouped by organ systems (for example, kidney and liver issues).

Targeted Therapies

Targeted therapy is associated with a range of side effects.

In the 5-year analysis from the studies of dabrafenib + trametinib, 98% of patients who received the combination reported side effects. Common side effects of dabrafenib + trametinib are shown in Graphic 12.

Graphic 12. Common side effects with dabrafenib + trametinib (occurring in 10% or more of patients).

Common side effects associated with dabrafenib + trametinib				
• Fever (58%)	• Headache (35%)	• Vomiting (31%)	• Rash (28%)	• Muscle aches (18%)
• Nausea (37%)	• Fatigue (35%)	• Joint aches (29%)	• Cough (25%)	
• Diarrhea (36%)	• Chills (34%)	• High blood pressure (29%)	• Swelling (19%)	

Graphic 13. Common side effects with vemurafenib + cobimetinib (occurring in 10% or more of patients).

Common side effects/laboratory abnormalities associated with vemurafenib and cobimetinib		
• Rash (73%)	• Joint aches (38%)	• Decreased appetite (20%)
• Diarrhea (61%)	• Fever (29%)	• Hair loss (17%)
• Photosensitivity (48%)	• Eye or vision problems (27%)	• Decreased heart function (usually temporary) (12%)
• Nausea (43%)	• Vomiting (26%)	• Skin thickening (10%)

In the study of vemurafenib + cobimetinib, 99% of patients reported side effects. In the 18-month follow-up study, common side effects of cobimetinib and vemurafenib were found as shown in Graphic 13. We did not include laboratory abnormalities here.

Graphic 14. Common side effects with encorafenib + binimetinib (occurring in 10% or more of patients).

Common side effects associated with encorafenib + binimetinib	
• Fatigue (43%)	• Rash (22%)
• Nausea (41%)	• Constipation (22%)
• Diarrhea (37%)	• Headache (22%)
• Vomiting (30%)	• Vision problems (20%)
• Abdominal pain (28%)	• Fever and chills (18%)
• Joint pain/swelling (26%)	• Dry skin (16%)
• Muscle problems (23%)	• Hair loss (14%)
• Thickening skin (23%)	• Itchiness (13%)

In the study of encorafenib + binimetinib, side effects occurred in a large proportion of patients. The most common side effects are shown in Graphic 14.

It's important to consider the serious side effects of targeted therapies.

In the dabrafenib/trametinib product information, there is a warning about the following serious side effects:

- Risk for new skin cancers, bleeding problems, stomach or intestinal problems; blood clots; heart problems; eye problems; lung problems; severe fever; serious skin problems; increased blood sugar; breakdown of red blood cells (anaemia) in people with a condition called G6PD deficiency; harm to a developing fetus.

For vemurafenib/cobimetinib, there is a warning about the following serious side effects:

- Risk for new skin cancers, bleeding problems, allergic reactions, serious skin reactions, heart rhythm problems, liver problems, eye problems, muscle problems, photosensitivity; worsening the side effects from radiation treatment, connective tissue problems (thickening of the flesh of your hands/feet).

For encorafenib/binimetinib, there is a warning about the following serious side effects:

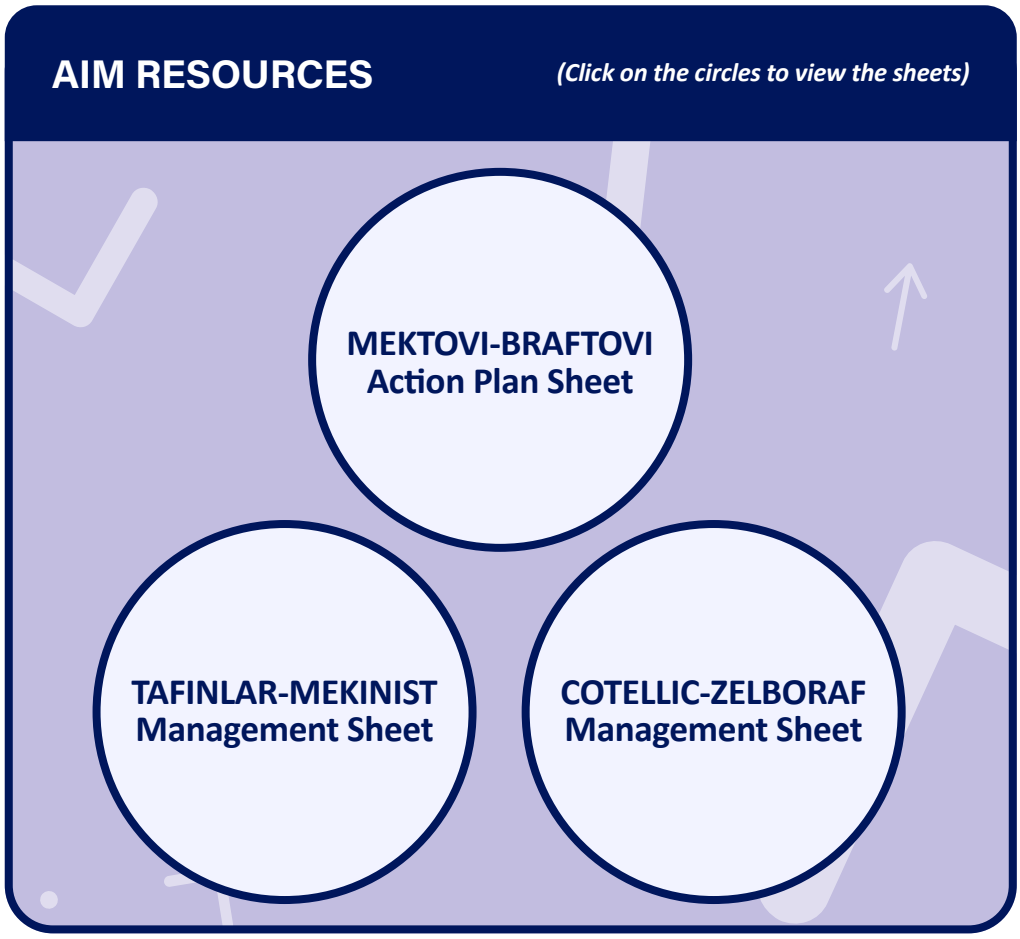
- Risk for new skin cancers, heart problems (including heart failure), blood clots, bleeding problems, eye problems, lung or breathing problems, liver problems, muscle problems, changes in your heart rhythm, harm to a developing fetus.

How are the Side Effects of Targeted Therapies Managed?

With targeted therapy, sometimes an individual side effect can be managed with specific medications (for example, paracetemol for fever) and supportive care (for example, 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 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, with the goal of eliminating the side effect or reducing its impact. 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, discuss this subject with your oncologist. This safety concern is especially important if you are taking any medications that may cause heart arrhythmias or you are on hormonal contraceptives, since these two types of drugs 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.

AIM has developed side-effect management sheets for these targeted therapies. They help you recognise the side effects and know what to do about them. See below:



Immunotherapy

Immunotherapy is associated with a range of side effects. Some of these are directly related to the medication; others are caused by the immune system's activation by the drug.

Checkpoint Inhibitors

Because checkpoint inhibitors work by unleashing the body's immune system to fight the cancer, the immune system may get revved up and attack any organ or tissue. 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.

In the pembrolizumab and nivolumab clinical trials, most patients had side effects that could be linked to the therapy. Severe or life-threatening side effects generally occurred in less than 20% of patients. Graphic 15 lists the common side effects associated with pembrolizumab, Graphic 16 those associated with nivolumab, and Graphic 17 those associated with nivolumab + ipilimumab.

In the KEYNOTE 006 study, 98% of patients treated with pembrolizumab experienced at least one side effect related to treatment. See below for the most common.

Graphic 15. Common side effects associated with pembrolizumab (occurring in 10% or more of patients).

Common side effects associated with pembrolizumab	
• Feeling tired (26%)	• Nausea (14%)
• Itchy skin (21%)	• Joint pain (14%)
• Diarrhea (loose stools) (19%)	• Weakness (13%)
• Vitiligo (loss of pigment) (13%)	• Rash (17%)

Graphic 16. Common side effects associated with nivolumab (occurring in 10% or more of patients).

Common side effects associated with nivolumab	
• Feeling tired (36%)	• Nausea (13%)
• Rash (24%)	• Joint pain (11%)
• Itchy skin (23%)	• Decreased appetite (11%)
• Diarrhea (22%)	• Low thyroid (10%)

In the analysis of the CheckMate 067 study, 87% of patients who received nivolumab alone had side effects related to treatment. The most common side effects are shown in Graphic 16.

In the analysis of the CheckMate 067 study, 96% of patients who received nivolumab/ipilimumab had side effects related to treatment. The most common side effects are shown in Graphic 17.

Graphic 17. Common side effects associated with nivolumab/ipilimumab (occurring in 10% or more of patients).

Common side effects associated with nivolumab/ipilimumab	
• Diarrhea (45%)	• Vomiting (15%)
• Feeling tired (38%)	• Joint pain (14%)
• Itchy skin (36%)	• Inflammation of the colon (13%)
• Rash (30%)	• Shortness of breath (12%)
• Nausea (28%)	• Flat and raised rash (12%)
• Fever (19%)	• Overactive thyroid (11%)
• Weakness (10%)	• Headache (11%)
• Low thyroid (17%)	• Decreased appetite (19%)

*Rates of side effects are listed from clinical trials or product reports, which may include longer-term data. Rates may be higher in the real-world setting. Side effects are generally grouped from most common to least common.

AIM has developed side-effect management sheets for checkpoint inhibitors. They help you recognise the side effects and know what to do about them. See below:

AIM RESOURCES

(Click on the circles to view the sheets)

KEYTRUDA Side-effect Management Sheet

OPDIVO Side-effect Management Sheet

OPDIVO-YERVOY Side-effect Management Sheet

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 reduce the immune response, after which immunotherapy can be restarted. But in severe cases, the drug may need to be discontinued.

How the Drugs Are Given

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 progress.

Pembrolizumab is given as an intravenous (IV) infusion into your arm at an infusion centre. The drug is usually given every three weeks (but can be given every six weeks) and will be continued for as long as you tolerate it, or your oncologist may discuss stopping it if your melanoma has responded very well to the treatment. The infusion lasts for 30 minutes.

Nivolumab is given as an IV infusion into your arm, typically at your oncologist's office. The drug is usually given every two weeks (but can be given every four weeks) and will be continued for as long as you tolerate it, or your oncologist may discuss stopping it if your melanoma has responded very well to the treatment. The infusion lasts for 30 minutes.

When nivolumab and ipilimumab are given in combination, both drugs are given by IV. Nivolumab is given over a 30-minute period. Ipilimumab is given over 90 minutes. They will be given every three weeks for a total of four doses. After that, nivolumab is usually given alone every two or four weeks. The therapy is usually given for as long as you tolerate it, or your oncologist may discuss stopping it if your melanoma has responded very well to the treatment.

For vemurafenib + cobimetinib + atezolizumab, the administration includes a period with just the targeted therapies (which is capsules/tablets twice a day) for 28 days. This is followed by the triple combination approach, which includes 28 days with targeted therapy along with atezolizumab every two, three, or four weeks given as an intravenous infusion into your arm (over a 60-minute period for the first dose and, if tolerated, over 30 minutes thereafter), typically at the oncologist's office. The triple drug combination will be continued for as long as you tolerate it, and the melanoma doesn't progress.

Now that you have a better understanding of how each treatment is given, here are some questions you may want to ask yourself that will help you consider which treatment option is best for you:

Targeted Therapy

Targeted therapy is generally delivered orally (by mouth).

- 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 travelling)?
- How diligent will you be about taking these pills? What if your medications require taking them on an empty stomach (at least 1 hour before or two hours after a meal)?
- For the triple combination, are you willing to take medication every day and go to an office for an infusion as well?

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.

Immunotherapy

Immunotherapy is typically delivered via infusion at an infusion centre.

- Are you willing to go to an infusion centre every two, three, four, or six weeks?
- Do you have transportation and the means to get to the infusion centre?
- Can you arrange your schedule to be at the infusion centre every two, three, four, or six weeks?

FINANCIAL/ACCESS ISSUES

Immunotherapy and targeted therapies are innovative medicines. Since treatment costs are covered by PBS, the maximum out-of-pocket payments you would need to make would be $41.30 (or $6.60 if you have a concession card) per each medication per cycle. You will need to also consider whether there are any additional costs for transportation and the impact of your treatment on your ability to work.

You may want 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?

PREGNANCY, FERTILITY, AND 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. Each medication varies in its warnings related to fetal harm and use of birth control.

Targeted Therapies

- People taking dabrafenib + trametinib should use an effective nonhormonal birth control method such as a condom, diaphragm, or spermicide during treatment and for four months after the last dose. Hormonal birth control is not recommended because of the potential for interaction with this drug combination.
- People taking vemurafenib + cobimetinib should use an effective nonhormonal birth control method such as a condom, diaphragm, or spermicide during treatment and for two weeks after the last dose. Hormonal birth control is not recommended because of the potential for interaction with this drug combination.
- People taking encorafenib + binimetinib should use an effective nonhormonal birth control method such as a condom, diaphragm, or spermicide during treatment and for one month after the last dose. Hormonal birth control is not recommended because of the potential for interaction with this drug combination.

Immunotherapies

- For nivolumab or pembrolizumab or the combination of nivolumab + ipilimumab, you should use an effective method of birth control during treatment and for six months after the last dose of therapy

FERTILITY/FAMILY PLANNING

There are many considerations with regards to family planning and it's important to have a frank conversation with your oncology team 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.

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 four 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 due to the need for additional hormone supplementation. Again, at the very least, you should avoid trying to conceive for at least six months after you stop treatment.

SHARED DECISION MAKING

The following worksheets can be used to evaluate your treatment options based on the different factors that are important to you. There is a sheet for targeted therapy, immunotherapy, and more aggressive immunotherapeutic options (including combination approaches).

Worksheet 1: Targeted Therapy

Factor to Consider	My Thoughts	Weighing of Factor to You
My tumour status (*BRAF*)		1 2 3 4 5
Effectiveness of the therapy expected for my situation		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

1 – Not At All Important
2 – Slightly Important
3 – Important
4 – Fairly Important
5 – Very Important

Worksheet 2: Single-agent PD-1 directed therapy (for example, nivolumab or pembrolizumab)

Factor to Consider	My Thoughts	Weighing of Factor to You
My tumour status (*BRAF*)		1 2 3 4 5
Effectiveness of the therapy expected for my situation		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

1 – Not At All Important
2 – Slightly Important
3 – Important
4 – Fairly Important
5 – Very Important

Worksheet 3: Aggressive Immunotherapy Approach (example, Combination Immunotherapy)

Factor to Consider	My Thoughts	Weighing of Factor to You
My tumour status (*BRAF*)		1 2 3 4 5
Effectiveness of the therapy expected for my situation		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

1 – Not At All Important
2 – Slightly Important
3 – Important
4 – Fairly Important
5 – Very Important

Final Thoughts

We hope you found this guide to be helpful in evaluating your options for your Stage IV 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 additional resources. Being informed puts you in the best position to have an active role in this important decision.

Document Released June 10, 2022.

INFORMATION RESOURCES

Melanoma & Skin Cancer Advocacy Network (MSCAN)
https://mscan.org.au/

IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE

Ascierto PA, Dummer R, Gogas HJ, et al. Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. *Eur J Cancer*. 2020;126:33-44.

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ABOUT AIM AT MELANOMA

By directing and funding paradigm-shifting research initiatives; educating patients, healthcare professionals, and the public; and advocating for survivors and their families, AIM at Melanoma's goal is to end this disease in our lifetime while improving the lives of those it affects. Founded in 2004, AIM at Melanoma is a global foundation dedicated to finding more effective treatments and, ultimately, the cure for melanoma.

AIM at Melanoma is 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 paradigm-shifting global research initiatives, including the International 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 government agencies, medical boards, and pharmaceutical companies on critical topics that affect melanoma patients.

Information & Support

Both in the United States and on a global level we provide comprehensive, easy-to-access melanoma resources for patients and health care professionals. AIM's patient, family, and caregiver support offerings—such as our Ask an Expert service, which allows patients to contact a melanoma physician assistant with their questions, and our Peer Connect program, which matches newly diagnosed patients with melanoma veterans—serve as models for other cancer foundations.

About MSCAN

The Melanoma & Skin Cancer Advocacy Network (MSCAN) provides a new, innovative approach to tackle Australia's national cancer. We have the highest incidence of skin cancer in the world. It's time for Australia to get skin serious.

MSCAN's mission is to listen to, represent, and inform the melanoma/skin cancer community with a focus on three key areas:

- Innovation in Cancer Research
- Advocacy and Policy
- Resources & Information

MSCAN is a globally engaged, independent, Australian organisation, and we are here for you.

AIM AT MELANOMA FOUNDATION

MSCAN
MELANOMA & SKIN CANCER ADVOCACY NETWORK

APPENDIX

BRAF Testing

One of the most important tumour biomarker tests the pathologist will conduct is the test for the *BRAF* mutation. *BRAF* (pronounced "Bee-Raf") is a gene that makes a protein called BRAF, which is involved in sending signals in cells and in cell growth. Everyone has this gene in their normal body cells, but some tumours carry a mutated (or changed) form of *BRAF*. When *BRAF* is altered, it changes how the melanoma grows. About half of all cutaneous melanomas from sun-exposed skin carry this mutation. These melanomas are called *BRAF* positive. Melanomas that don't have this mutation are called wild-type or *BRAF* negative. If a *BRAF* mutation is found, it does not mean your melanoma is genetically inherited or that you are at risk of passing along a melanoma susceptibility gene related to *BRAF* to first-degree relatives, like children. It simply means there is an abnormal protein in your melanoma cells.

It is important to make sure your oncology team has obtained your *BRAF* testing as soon as possible, since this will help determine which therapy options are available to you. *BRAF* testing is strongly recommended for all patients with Stage III and Stage IV melanoma, so you may have already had your tumour tested. If not, you should speak with your oncologist about getting the *BRAF* test done. Currently, *BRAF* testing requires tumour tissue. Your oncologist's office will see what tumour tissue is available to test. DNA will be extracted from the tissue to look for the mutation. To ensure an adequately sized sample, additional biopsies may be necessary.