

# Stage IV Melanoma Treatment Options

Making the Decision That's Right for You



# TABLE OF CONTENTS

---

INTRODUCTION .....	1
OVERVIEW OF STAGE IV MELANOMA .....	2
TREATMENT PLANNING FOR STAGE IV MELANOMA .....	3
Testing .....	3
Disease Factors for Decision Making.....	6
Patient Factors for Decision Making .....	7
Weighing All the Factors .....	8
THERAPEUTIC OPTIONS FOR STAGE IV MELANOMA .....	10
Overview of Therapies .....	10
How Well Systemic Therapies Work .....	19
Side Effects of Stage IV Systemic Therapies .....	32
How the Drugs Are Given .....	40
Financial/Access Issues .....	42
Pregnancy, Fertility, and Family Planning .....	42
SHARED DECISION MAKING .....	44
SURVIVORSHIP AND ADVANCED CARE PLANNING .....	47
INFORMATION RESOURCES .....	47
IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE .....	48
ACKNOWLEDGMENTS .....	51
APPENDIX: DIAGNOSING AND MONITORING STAGE IV MELANOMA .....	53
Clinical Signs of Stage IV Disease .....	53
Imaging .....	54
Biopsy .....	56



# INTRODUCTION

---

If you are reading this booklet, likely you (or someone you love) have been diagnosed with Stage IV melanoma or are being evaluated for it.\* 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.

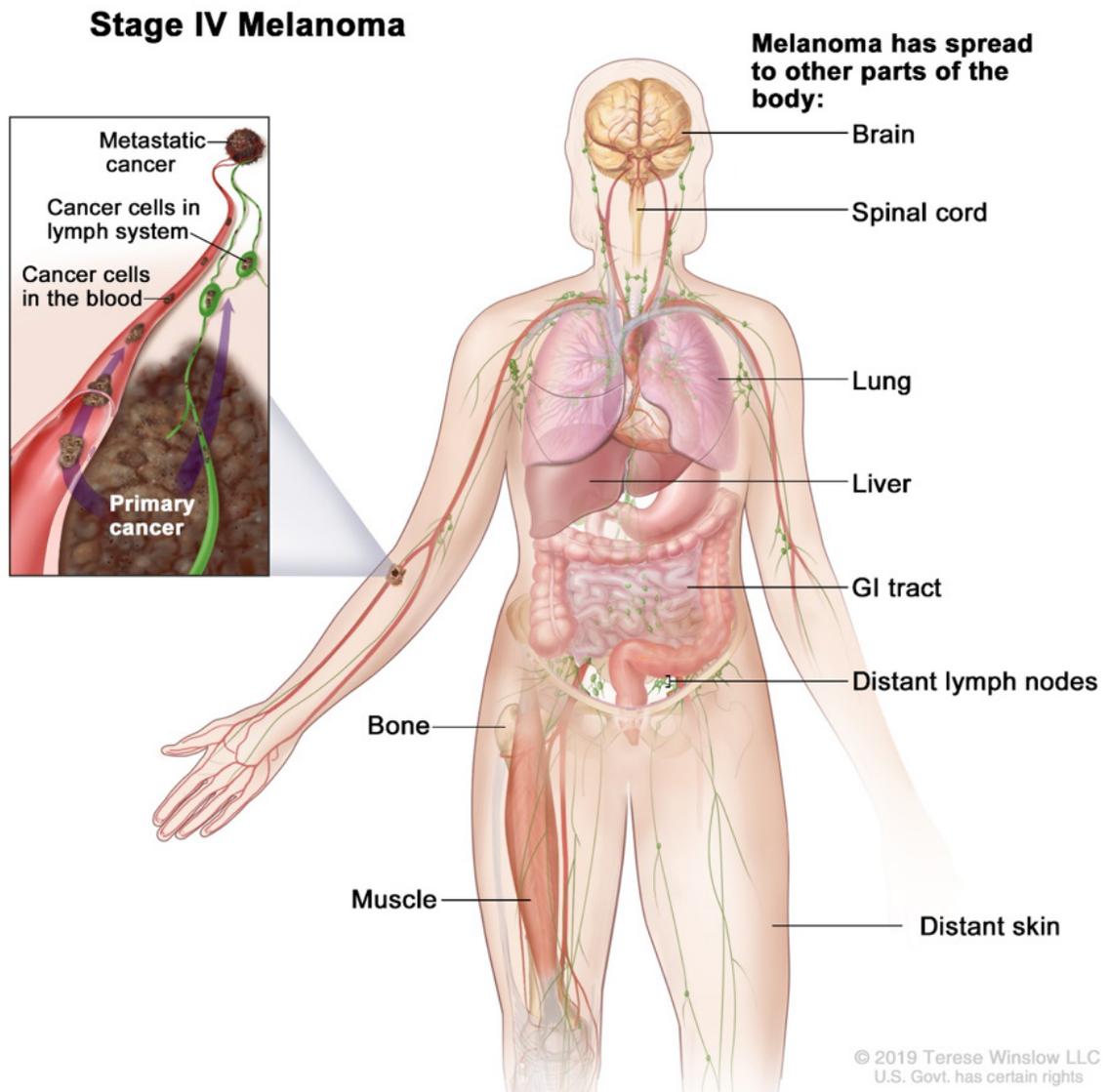
This document is designed to help you and your oncology team evaluate treatment options and identify the different considerations you care about in deciding your treatment course. Using this guide, you and your team can weigh the options to make the decision that is right for you.

For people who have already been diagnosed with Stage IV melanoma, we recommend that you begin your review at the beginning of this document, which starts with treatment planning. If you are still being evaluated for Stage IV melanoma (and want to learn more about imaging and biopsy techniques) we suggest that you first go to the Appendix entitled **DIAGNOSING AND MONITORING STAGE IV MELANOMA**. This backgrounder provides detail about the tests you will undergo to arrive at a diagnosis.

\*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/>.

# 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 1, 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 1. 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 and your healthcare team in assessing these factors so that, together, you can make the decision 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. The details of different types of biopsies and the imaging scans are discussed in the Appendix.

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.

### KEY CONSIDERATION

Take charge of your health. You will most likely be very busy undergoing pathology, laboratory, and imaging tests during your evaluation for Stage IV melanoma. When you sit down with your oncologist to make treatment decisions, it's best to have as many of your test results available as possible. **At the very least, make sure your oncologist has the results of the *BRAF* testing, because that is key to knowing all of your treatment options.** The details of the *BRAF* test are described in the text on the next page.

## Pathology Tests on the Tumour

When the sample from the biopsy gets to the pathology laboratory, the pathologist will run specific tests on the tumour tissue to learn more about it.

### ***BRAF***

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. Less than 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 there is enough tumour material for the test to be performed, additional biopsies may be necessary.

### ***PD-L1***

If you are taking part in a clinical trial, your oncologist may have you take a test to measure your programmed cell death ligand 1 (PD-L1) levels. PD-L1 is what is called an immune checkpoint—a protein that acts to “put the brakes on” the immune system—which can allow cancer to grow unchecked. Checkpoint inhibitors are a type of immunotherapy drug that “take the brakes off” the immune system so it can fight the cancer. For some cancers, it is important to test for PD-L1 to help predict if the checkpoint inhibitor will work. Currently, in everyday practice, the checkpoint inhibitors used in melanoma do not require testing for PD-L1 levels. But as we mentioned, use of PD-L1 levels to guide therapy is being studied in some melanoma clinical trials. You may also hear about this test being required for other types of cancer being treated with checkpoint inhibitors.

## Other mutations

Currently, some patients with melanoma 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 could 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. While the test can pick up less common mutations for which there are specific therapies, many times the results show different mutations of uncertain significance or that doctors do not yet know how to treat. So it's important that your team has a plan for how to sift through all the results and best use the information from the test.

## 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 enzyme that is involved in the conversion of 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 may be why higher levels of LDH in the blood serum are found when cancer cells are spreading rapidly. LDH levels have also been associated with outcomes to treatment.

### *Circulating tumour DNA (ctDNA)*

ctDNA levels may also be tested. 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 tumour cells 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.

# DISEASE 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 factors 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. Understanding the extent of the disease is important because it can affect what treatments are considered.

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.

# PATIENT FACTORS FOR DECISION MAKING

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. Oncologists like to use objective criteria when evaluating fitness. One scale that is used is the Eastern Co-Operative Oncology Group/World Health Organization (ECOG/WHO) system for **performance status**. This system ranks your ability to perform tasks on a scale of 0-5. Graphic 2 shows an overview of the ECOG/WHO performance status scale.

Graphic 2. ECOG/WHO Performance Status.

Performance Status	Description
0	Fully active, no restrictions on activities. A performance status of 0 means no restrictions in the sense that someone is able to do everything they were able to do prior to their diagnosis.
1	Unable to do strenuous activities but able to carry out light housework and sedentary activities. This status basically means you can't do heavy work but can do anything else.
2	Able to walk and manage self-care, but unable to work. Out of bed more than 50% of waking hours. In this category, people are usually unable to carry on any work activities, including light office work.
3	Confined to bed or a chair more than 50% of waking hours. Capable of limited self-care.
4	Completely disabled. Totally confined to a bed or chair. Unable to do any self-care.
5	Dead

## *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 tradeoffs in terms of convenience, quality of life, and other factors that matter to you. Each therapy has its pluses 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.

Beyond the immediate decision making regarding your treatment, you have a lot of other decisions to make about your future. To learn more about this type of planning, see the **SURVIVORSHIP AND ADVANCED CARE PLANNING** section at the end of this document.

## **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 3 shows some questions you and your oncology team will consider in this process.



Graphic 3. Factors to consider in the Stage IV decision-making process.

<b>Extent and Location of Disease</b>
<p>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?</p>
<b>Pace of Disease</b>
<p>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?</p>
<b>Other Tumour Characteristics</b>
<p>What is your <i>BRAF</i> status?          Does the tumour carry any rare mutations that could be targeted?</p>
<b>Prior Therapy</b>
<p>Did you previously receive adjuvant therapy (therapy given after surgical removal to prevent the cancer from coming back)?          Have you received therapy for Stage IV disease before?          Have you received corticosteroids recently?</p>
<b>Therapy Considerations</b>
<p>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? How often?</p>
<b>Personal Considerations</b>
<p>How will the choice of therapy affect your family planning, if that's an important consideration?          How convenient is each therapy for you?          How much are you willing to compromise in terms of other factors (side effects, etc) for a therapy that works well?</p>

# 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 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)**. But even if the surgery is not able to remove all of the cancer, it can still reduce the amount of tumour in your body (**burden of disease**), which may be helpful. Many of the medications that your oncologist can offer you work better when the burden of disease is low.

So surgical management may make sense, if it's possible. Only you and your treatment team can determine if your tumour(s) can be surgically removed safely. Tumours found in the brain are discussed in the section below.

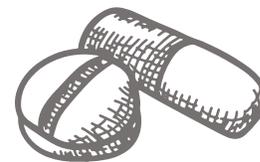


Once the surgery is complete, your team will determine if you are NED. If all of the melanoma has been surgically removed, **adjuvant therapy**, which is therapy provided to prevent the disease from coming back, will be offered. If the surgery is not successful in removing all of the tumour, the extent 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 (i.e., throughout the body, such as by oral or intravenous administration) 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. In a study published in March, 2023, patients with Stage III or IV melanoma that could be removed surgically were provided either immunotherapy prior to and after surgery (neoadjuvant and adjuvant) or just after surgery (adjuvant). Those who were assigned to neoadjuvant plus adjuvant therapy experienced lower rates of melanoma-associated events (including progression before surgery, recurrence after surgery, and death) compared to those assigned to adjuvant therapy alone. So it's worth discussing this option with your surgeon and medical oncologist. If you would like to review this study, please see the Patel 2023 citation listed in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**.

## 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 mutated BRAF protein and slow the growth of melanoma. When "BRAF inhibitors" were first introduced and used alone, they were not very good at slowing melanoma growth and had some problematic side effects. The limited efficacy was caused by the melanoma cells figuring out ways to work around the blocked BRAF in the cellular signalling pathway. 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 both adjuvant treatment and management of Stage IV disease that can't be managed surgically (unresectable).

The available BRAF/MEK targeted therapies are:

- Dabrafenib (TAFINLAR®) + trametinib (MEKINIST®) —for adjuvant therapy and advanced disease
- Vemurafenib (ZELBORAF®) + cobimetinib (COTELLIC®) —for advanced disease
- Encorafenib (BRAFTOVI®) + binimetinib (MEKTOVI®) —for advanced disease

As we mentioned, the BRAF and MEK inhibitors work best when combined. For this reason, although these drugs are commercially available for use alone, they are rarely used this way. Typically, they are only used alone if someone has a contraindication or cannot tolerate the other drug in the combination. We will, therefore, not spend additional time discussing the use of these drugs as single agents. If you, for some reason, require single-agent therapy, your oncologist will help you evaluate that treatment option.

There are other therapies that target less common mutations that occur in melanoma. NTRK fusions are rare alterations that may be identified by broad genetic screens; participation in an extended genomic testing study may be required to access these tests. For patients who have melanomas that carry NTRK fusions, drugs such as larotrectinib (VITRAKVI®) and entrectinib (ROZLYTREK®) may be useful. These drugs are not specifically approved or subsidised in melanoma, but your oncologist may discuss options to access one for you if they feel it's appropriate. For melanoma harbouring *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. While these agents are also not approved or subsidised for use in melanoma, your oncologist may discuss them with you if appropriate.

## ***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 (T-VEC), which is given intralesionally (intra-tumourally, or directly into the tumour).

## Checkpoint Inhibitors

Checkpoint inhibitors “take the brakes off” the immune system, allowing it to identify and destroy cancer cells. Currently in melanoma, there are several checkpoint inhibitors either approved or in late-stage development for melanoma:



PD-1 inhibitors:

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

CTLA4 inhibitors:

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

LAG-3 inhibitors:

- Relatlimab (given in combination with OPDIVO as OPDUALAG™)

PD-1, PD-L1, CTLA4, and LAG-3 inhibitors are types of checkpoint inhibitors. PD-1 and PD-L1 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. LAG-3 inhibitors work together with PD-1 inhibitors to provide strong response as well but are associated with a milder side-effect profile than ipilimumab plus nivolumab in clinical studies to date.

It's also important to mention that the CTLA-4 inhibitor ipilimumab became commercially available in 2011, before the PD-1 and PD-L1 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, unless the melanoma has failed to respond to other types of therapy first. 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. Some patients may be on corticosteroids to manage unrelated inflammatory disorders. 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.

## Interleukin-2 Therapy

Another immunotherapy that has been used for decades to treat melanoma is high-dose interleukin-2 (IL-2). Interleukin-2 is a naturally occurring protein that increases the growth and activity of a variety of immune cells. When used as a high-dose therapy for melanoma, IL-2 enhances the ability of cells in the immune system to target and kill cancer cells. High-dose IL-2 is a very powerful therapy that must be given in the hospital setting because it causes some severe side effects. For a small subset of patients, IL-2 therapy can cause the cancer to go away for a very long period of time. However, due to its low likelihood of benefit and high risk of significant toxicity, IL-2 therapy has been rarely used for well over a decade. As discussed below under clinical trials, IL-2 is also being studied in an engineered form to make it more effective at killing cancer cells while decreasing its toxicity. It is also being studied in combinations with checkpoint inhibitors and in combination with tumour infiltrating lymphocyte (TIL) therapy (described in the clinical trial section below).

## Oncolytic Virotherapy

Talimogene laherparepvec (IMLYGIC<sup>®</sup>, 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. Unlike the other immunotherapies mentioned above, 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. T-VEC stimulates the body's immune system to go to the site of injection and attack the melanoma. It can also treat tumours away from the site of injection because it causes a local and body-wide immune response. Although not approved in Australia, T-VEC has been used for Stage III melanoma (in-transit disease) and in patients with Stage IV melanoma that has spread to the skin, subcutaneous tissues, or nodes away from the original tumour (remote nodes).

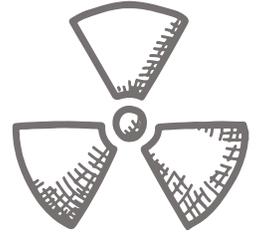


## Cytotoxic Therapies (Chemotherapy)

Chemotherapy drugs generally work by interfering with cell division. Most chemotherapy drugs have the biggest impact on rapidly-dividing cells. While that includes the cancer cells, it also includes other rapidly dividing cells in the body. Because it works broadly, chemotherapy is not classified as targeted therapy. 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. The chemotherapeutic agents tested in melanoma that have the best evidence are combinations of carboplatin and paclitaxel or single-agent temozolomide. Other agents that also may be considered for use include dacarbazine (also known as DTIC), nanoparticle albumin-bound paclitaxel (ABRAXANE<sup>®</sup>), or the combination of cisplatin/vinblastine/dacarbazine (CVD).

## Radiation Therapy

Radiation therapy has a clear role in managing brain metastases, as discussed below. Radiation therapy can also be used as adjuvant therapy after surgery for high-risk melanoma in lymph nodes and to improve symptoms in patients with Stage IV melanoma, such as pain from melanoma in the bone. The side effects of radiation therapy include skin breakdown (ulcers), pain, redness at the site of irradiation, as well as fatigue.



## Localized Treatments for Brain Metastases

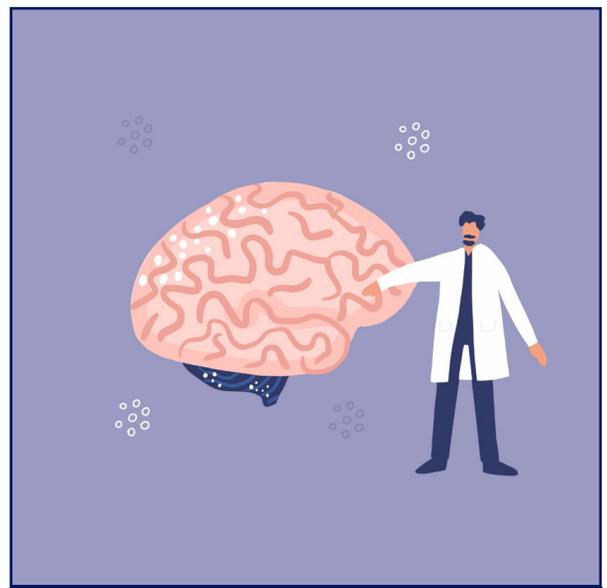
### Neurosurgery

Surgery of the **central nervous system** (the brain and spinal cord) is performed by a specialized 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 or when residual brain tissue breaks down late after radiation therapy (called radionecrosis).

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 or timing of systemic therapy.



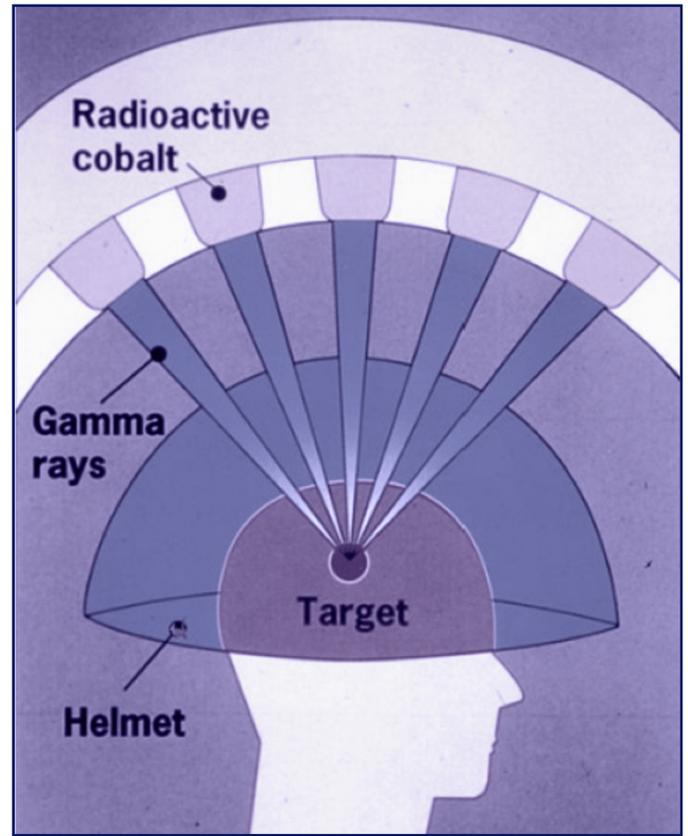
## Radiation Therapy for Brain Metastases

**Stereotactic surgery (SRS or Gamma Knife)** is a computer-guided treatment that provides highly-focused radiation to tumours in the brain. There is no incision or knife. The term reflects the precise way radiation is used like a knife. In the procedure, as shown in Graphic 4, a boxed-shape frame is placed over your head and keeps the target aligned. The frame is fastened to your head with pins. An intravenous line is placed, and a contrast agent is infused in your vein so that the tumour is seen. Most patients are awake for this procedure. Imaging is then done with the frame in place. Your neurosurgeon/radiation oncologist will then plan the dose and location of treatment. The gamma knife then delivers the treatment.

**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 meninges, the tissue that lines the surface of the brain and spinal cord, sometimes leading to release of melanoma cells into the cerebrospinal fluid that bathes the brain and 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 affects a greater amount of brain tissue. Side effects can include headaches, hair loss, nausea & vomiting, fatigue, hearing loss, and trouble with memory and speech.



Graphic 4. Set up for gamma knife for treatment of brain metastases. Reproduced from Wikimedia Commons, courtesy of NRC.

## 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 may risk getting only the placebo (sugar pill) if you don't receive the study drug. This is not true. Unlike clinical trials of the past, there are no trials in Stage IV melanoma in which one of the groups receives only a placebo. If you are not in the group receiving the study drug, you are guaranteed to receive therapy that is the standard of care.

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.



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.** As mentioned earlier, the first combination of LAG-3 and PD-1 inhibitors, Opdualag™, has been FDA approved in melanoma, but is not yet approved in Australia. A range of additional LAG-3 inhibitors, including fianlimab, which is in late-stage trials, are being studied alone or in combination in melanoma.

**Personalised cancer therapies.** Several different approaches can be taken for personalised cancer therapies. In T-cell transfer therapies (adoptive cell therapies), your immune cells are isolated, often from a tumour sample obtained by biopsy or surgery, and grown in the laboratory typically with a degree of selection to enrich for the cells best able to attack the melanoma. The T-cell product is then given back to you either in greater numbers or with enhancements to fight cancer. Tumor-infiltrating lymphocyte (TIL) therapy is adoptive cell therapy using T cells isolated from your tumour specimen. At the time of this writing, lifileucel is the TIL therapy furthest along in clinical development. Another type of T-cell transfer is chimeric antigen receptor (CAR) T-cell therapy, in which your own T cells are genetically altered in the lab so that they better attack certain proteins on the surface of cancer cells. These super T cells are grown to large numbers and then returned to you to fight the cancer. There are several CAR T-cell therapies approved for blood cancers, and this therapy is being studied in melanoma.

In addition, there are now cancer vaccines in late stage development for melanoma. These involve taking part of your tumour and designing a vaccine specific to the proteins expressed on it. When you receive the vaccine, your body develops an immune response specific to the protein on your tumour. This kind of vaccine (a therapeutic vaccine) is being studied in combination with immunotherapy to boost the immune response.

- **Oncolytic viruses.** As already described for T-VEC, this type of immunotherapy uses viruses to infect and destroy cancer cells. 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, lerapolturev, has shown a benefit in patients with difficult-to-treat Stage IV melanoma
- **Next generation IL-2-based therapies.** As discussed, high-dose IL-2 can produce long-lasting responses in a subset of patients, but with a safety trade off. IL-2 binds to different receptors to cause its effects: one receptor is associated with its cancer-killing activity and another with its side effects and an actual reduction of the immune response. Investigators are working on next-generation IL-2-based therapies to more specifically activate only the receptor responsible for the cancer-killing activity of IL-2, such as the re-engineered IL-2 therapy nemvaleukin, which is in late-stage clinical development, over the receptor associated with the side effects and the reduction in the immune response. A re-engineered IL-2 therapy (nemvaleukin) is in late-stage clinical development that “selects” for the receptor providing anti-tumor activity preferentially.

## HOW WELL SYSTEMIC THERAPIES WORK

In this section, we review data from clinical trials of therapies approved 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.

Although these are the newest data available, some of these statistics are already likely outdated since they reflect longer term outcomes from patients diagnosed more than five years ago. Overall survival, especially, is expected to be better for patients diagnosed now compared to the survival rates reported in the studies below.

**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. Wherever possible, we provide data on the following important endpoints:

- **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.***

Many times, decisions about your therapy are based on such “objective” tumours criteria because they give us a short-term snapshot of how the drug is working. For this reason, where possible, we provide both these tumour response data and survival outcomes for each drug. Additionally, 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.

Researchers are beginning to collect data from studies comparing the sequence of therapies. For example, the DREAMSeq study compared therapy with dabrafenib + trametinib to the combination of nivolumab + ipilimumab as initial therapy for *BRAF*-positive patients with Stage IV disease. Patients were then switched to the alternative therapy if their disease progressed. In this study, 72% of patients who began with combination immunotherapy were alive at two years, compared with only 52% of those who started with dabrafenib + trametinib. Based on these findings, the DREAMSeq study supports the consideration of combination immunotherapy as a potential starting regimen for patients with Stage IV disease. If you would like to review this study, please see the Atkins 2023 citation listed in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**.

Of course, other factors besides efficacy should be considered, as are discussed in this resource.

## 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, Checkpoint Inhibitor 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.

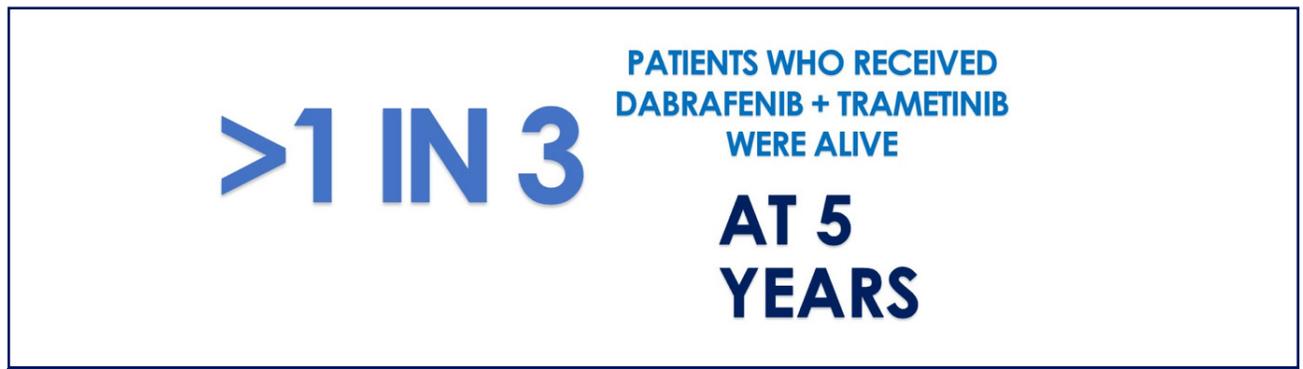
The other point to consider is that all three of these targeted therapy combinations have been found effective. It’s important to remember that we don’t know which combination is the best. If you and your oncologist decide to use targeted therapy, you can look at the overall profiles of these different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

## Dabrafenib + Trametinib

This BRAF/MEK inhibitor combination was evaluated in several studies. We will focus on the data from the COMBI-d study (which compared dabrafenib + trametinib to dabrafenib + placebo), the COMBI-v study (which compared dabrafenib + trametinib to the BRAF-inhibitor vemurafenib) as well as a follow-up study that looked at long-term (five-year) outcomes from both 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

As shown in Graphic 5, in the most recent update from the clinical studies, more than one in three (34%) of patients treated with dabrafenib + trametinib were alive at five years. Nearly one in five did not have disease worsening (were in PFS) at the five-year mark.



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

### Tumour Response Outcomes

As shown in Graphic 6, derived from the early report of the COMBI-d study, the overall response rate was higher for the combination—69% of the trial participants who received dabrafenib + trametinib saw a partial or complete response vs dabrafenib alone (53%).

Advantage in overall response rate was also seen with dabrafenib + trametinib vs vemurafenib (the COMBI-v study). The overall response rate was significantly higher for patients receiving dabrafenib + trametinib (64%) than for those receiving vemurafenib (51%).

	PR (tumour shrinks by 30% or more)	CR (tumour disappears)	ORR (PR + CR)
Dabrafenib + trametinib	53%	16%	69%
Dabrafenib	40%	13%	53%

Graphic 6. Tumour responses in the COMBI-d study.

ORR = overall response rate; CR = complete response; PR = partial response.

## Outcomes for Specific Subgroups

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

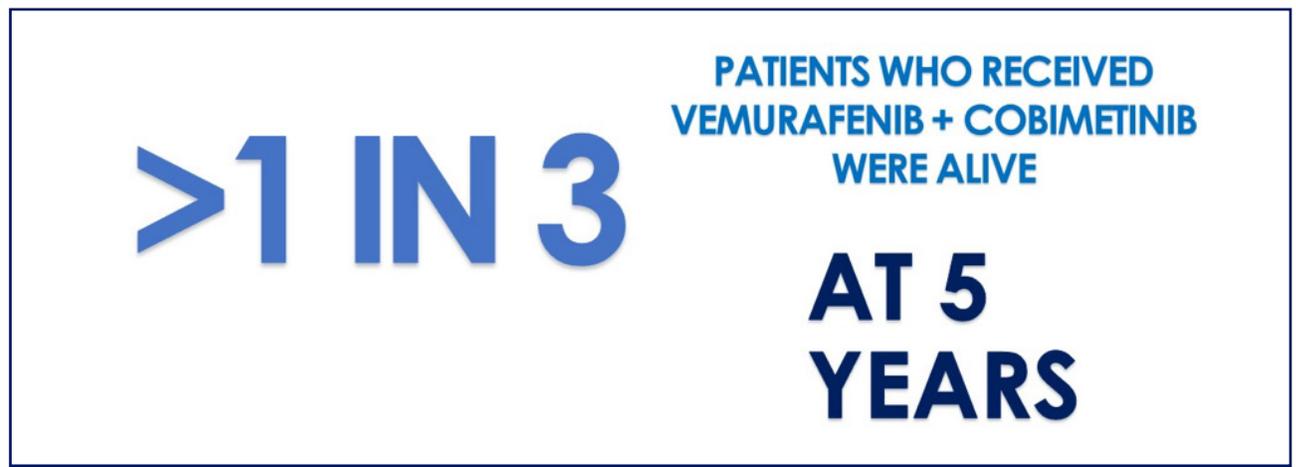
- **Patients with low tumour burden:** In this study, the investigator classified patients as having low tumour burden when the baseline LDH was below or at the upper limit of normal and there were no more than three organ sites with metastases. Patients with low tumour burden did well: 55% were alive 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. We will focus on the data from the CO-BRIM study (which compared vemurafenib + cobimetinib to vemurafenib + placebo), the BRIM-7 study (which evaluated vemurafenib + cobimetinib in individuals who had never received BRAF inhibitors to individuals who had recently progressed on vemurafenib), as well as a follow-up study that looked at long-term (five-year) outcomes from the BRIM-7 study. 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

As shown in Graphic 7, over one in three (39%) patients treated with vemurafenib + cobimetinib were alive at the five-year landmark. This proportion was the same as at the four-year mark, suggesting that a subset of patients experience a favourable long-term outcome.



Graphic 7. Vemurafenib + cobimetinib overall-survival outcomes at 5 years.

## Tumour Response Outcomes

As shown in Graphic 8 from the CO-BRIM study, the overall response rate was 68% for those receiving the combination therapy, which was significantly higher compared to that for the patients receiving BRAF inhibitor alone (45%).

### 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.

	PR (tumour shrinks by 30% or more)	CR (tumour disappears)	ORR (PR + CR)
Vemurafenib + cobimetinib	57	10	68
Vemurafenib + placebo	40	4	45

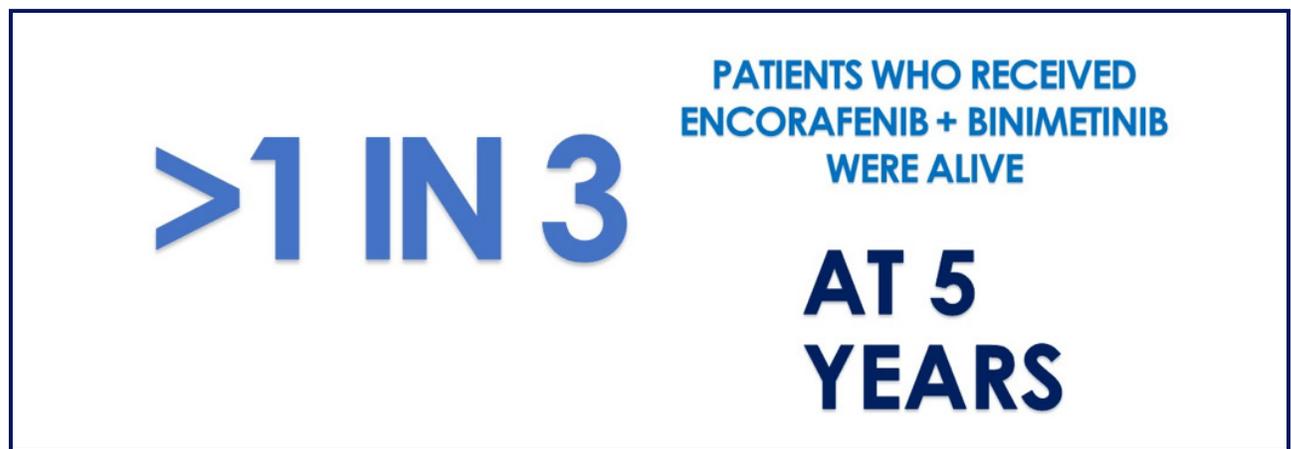
Graphic 8. Tumour responses in the CO-BRIM study.  
ORR = overall response rate; CR = complete response; PR = partial response.

### Encorafenib + Binimetinib

For the encorafenib + binimetinib combination, we will focus on the data from the COLUMBUS study (which compared encorafenib + binimetinib to encorafenib alone and vemurafenib alone), as well as a follow-up study that looked at long-term (five-year) outcomes. If you would like to review these studies, please see the Dummer 2018, Ascierto 2020, and Dummer 2021 citations listed in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**.

### Survival Outcomes

As shown in Graphic 9, at five years, more than one third (35%) of patients treated with encorafenib + binimetinib were alive.



Graphic 9. Encorafenib + binimetinib overall survival outcomes at 5 years.

## Tumour Response Outcomes

In the COLUMBUS study, the overall response rate was significantly higher for encorafenib + binimetinib (64%) vs encorafenib (52%) or vemurafenib (41%), as shown in Graphic 10.

	PR (tumour shrinks by 30% or more)	CR (tumour disappears)	ORR (PR + CR)
Encorafenib + binimetinib	51%	13%	64%
Encorafenib	45%	7%	52%
Vemurafenib	33%	8%	41%

Graphic 10. Tumour responses in the COLUMBUS study.  
ORR = overall response rate; CR = complete response; PR = partial response.

## 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 agents are not currently approved for use in melanoma in Australia.

## Checkpoint Inhibitor Immunotherapy

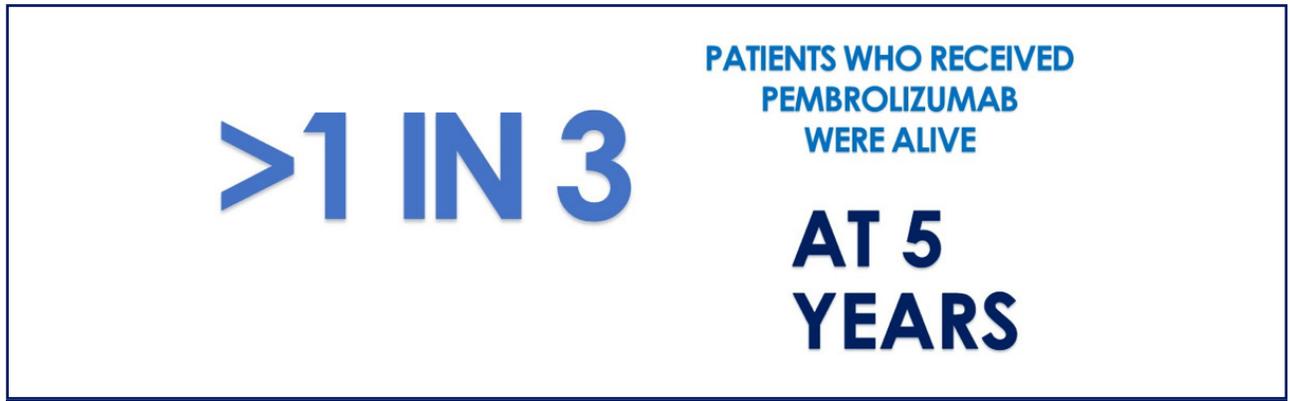
The content below shows data for the checkpoint-inhibitor monotherapy and combination regimens. Ipilimumab is a comparator arm for many of these studies since it was commercially available and the standard of care when the PD-1 inhibitors were being studied. As the data shows, single-agent PD-1 inhibitors 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. The combination of nivolumab + ipilimumab has greater efficacy than nivolumab or ipilimumab alone. 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

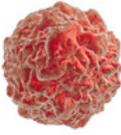
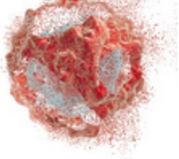
In the KEYNOTE-006 study, over one in three (39%) of all patients with advanced melanoma treated with pembrolizumab monotherapy were alive at five years of follow-up (Graphic 11).



Graphic 11. Overall survival rate at five years with pembrolizumab for the KEYNOTE-006 study.

### Tumour Response Outcomes

As shown in Graphic 12 from the KEYNOTE-006 study, the overall response rate was significantly higher in patients who received pembrolizumab than in patients who received ipilimumab.

	PR (tumour shrinks by 30% or more)	CR (tumour disappears)	ORR (PR + CR)
			
Pembrolizumab (every 2 weeks)	29%	5%	34%
Pembrolizumab (every 3 weeks)	27%	6%	33%
Ipilimumab	10.4%	1.4%	12%

Graphic 12. Tumour responses in the KEYNOTE-006 study.

ORR = overall response rate; CR = complete response; PR = partial response.

## Outcomes for Specific Subgroups

- **PD-L1 levels:** In the KEYNOTE-006 study, subgroups performed well, except for a small subgroup that had PD-L1 non-expressing tumours. 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 previous treatment is generally more difficult to control with subsequent lines of therapy.

## 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 and Hodi 2022 citations listed in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**.

## Survival Outcomes

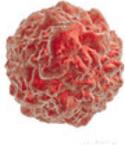
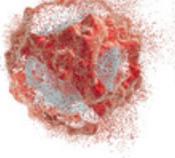
As shown in Graphic 13, more than four out of ten patients who received nivolumab alone (44%) were alive at five years. This percentage is higher than the percentage in patients who received ipilimumab alone (26%). As reported at the 2022 American Society of Clinical Oncology (ASCO) meeting, this effect is sustained. At 7.5 years, 42% of nivolumab-treated patients were still alive.



Graphic 13. Proportion of patients alive at five years who received nivolumab in the Checkmate 067 study.

## Tumour Response Outcomes

As shown Graphic 14 from the Checkmate 067 study, the overall response rate was significantly higher in patients who received nivolumab alone (45%) as compared with that in patients who received ipilimumab alone (19%).

	PR (tumour shrinks by 30% or more)	CR (tumour disappears)	ORR (PR + CR)
			
Nivolumab	26%	19%	45%
Ipilimumab	13%	6%	19%

Graphic 14. Tumour responses in the CheckMate-067 study.  
ORR = overall response rate; CR = complete response; PR = partial response.

## Outcomes for Specific Subgroups

- **BRAF Status:** Overall survival at five years in nivolumab-treated patients was similar but slightly higher in patients with *BRAF*-positive melanoma (46%) vs *BRAF* negative (43%)
- **LDH:** Overall survival at five years for patient receiving nivolumab was higher in patients with normal LDH levels (53%) vs survival for patients with elevated LDH levels (28%)
- **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 and Hodi 2022 citations listed in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**.

### Survival Outcomes

As shown in Graphic 15, over one half (52%) of patients treated with nivolumab + ipilimumab were alive at five years of follow-up, compared to 44% of patients who received nivolumab alone and 26% of patients who received ipilimumab alone. This was sustained. This was sustained. At 7.5 years, 48% of patients who received the combination were alive.



Graphic 15. Proportion of patients alive at five years who received nivolumab + ipilimumab in the Checkmate 067 study.

### Tumour Response Outcomes

As shown in Graphic 16 from the CheckMate 067 study, the overall response rate was significantly higher in patients who received nivolumab + ipilimumab compared to the response in patients who had received nivolumab or ipilimumab alone.

	PR (tumour shrinks)	CR (tumour disappears)	ORR (PR + CR)
Nivolumab + ipilimumab	46%	12%	58%
Nivolumab	35%	9%	44%
Ipilimumab	17%	2%	19%

Graphic 16. Tumour responses in the CheckMate 067 study. ORR = overall response rate; CR = complete response; PR = partial response.

### 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.

## Nivolumab + Relatlimab

This combination was compared with nivolumab alone in patients with previously untreated Stage III or Stage IV melanoma that could not be managed surgically. We will focus on the RELATIVITY-047 study. If you would like to review this study, please see Tawbi 2022 and Long 2022 in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE** document.

### Survival Outcomes

The primary outcome of the study was progression-free survival (PFS). At 12 months, PFS was 48% for the combination compared with 36% for nivolumab alone. Overall survival rates at 24 months were 64% for nivolumab + relatlimab vs 58% for nivolumab alone.

### Tumor Response Outcomes

The tumor response outcomes are shown in Graphic 17 below.

	PR (tumor shrinks by 30% or more)	CR (tumor disappears)	ORR (PR + CR)
Nivolumab + relatlimab	27%	16%	43%
Nivolumab	19%	14%	33%

Graphic 17. Tumor responses in the RELATIVITY-047 study.  
ORR = overall response rate; CR = complete response; PR = partial response.

### Outcomes for Specific Subgroups

The outcomes of the RELATIVITY-047 study suggest that the combination of nivolumab + relatlimab is favored across key prognostic subgroups, regardless of LAG-3 expression, BRAF mutational status, AJCC stage, LDH level, and tumor burden.

## High-Dose IL-2 Immunotherapy

High-dose IL-2 provides long-lasting responses in a small proportion of patients. The overall response rate is around 16%, with 6% of patients experiencing complete responses. For patients who experienced a complete response, it often lasted; 60% of patients who had a complete response maintained that response from 3.5 to 10 years. Some are expected to stay in complete response for even longer periods of time.

## Intralesional Immunotherapy Plus Checkpoint-Inhibitor Therapy

Several studies have or are evaluating T-VEC in combination with checkpoint inhibitors for patient with both injectable and non-injectable metastases. If you would like to review the studies, please see the Gogas 2021 and Chesney 2018 citations listed in the **IN-DEPTH READING FROM THE SCIENTIFIC LITERATURE**.

The combination of T-VEC plus pembrolizumab was compared with pembrolizumab alone in patients with advanced melanoma. While median progression-free survival was 14.3 months for the combination as compared with 8.5 months for pembrolizumab alone, this was not a significant difference. Overall survival was not expected to achieve statistical significance at the planned analysis. The overall response rate was 48.6% for the T-VEC + pembrolizumab group as compared with 41.3% for the pembrolizumab group, which was also not statistically different. Therefore, this was considered a negative study.

The combination of T-VEC plus ipilimumab was compared with ipilimumab alone in patients with advanced melanoma. The primary endpoint of this study was overall response rate, which was significantly improved in the T-VEC plus ipilimumab arm (39%) as compared with the ipilimumab arm (18%). This study did not report data for overall survival, as patients were still being followed at the time of its publication. However, progression-free survival data was improved with the T-VEC + ipilimumab combination (8.2 months), as compared with the ipilimumab group (6.4 months).

While studies are still ongoing, these data are not encouraging. In clinical practice, T-VEC is not likely to be widely used in conjunction with checkpoint inhibitor therapy and has not been approved for use either alone or in combination with checkpoint inhibitors in Australia.

## Cytotoxic therapies

The cytotoxic therapies (chemotherapies) such as dacarbazine (DTIC), temozolomide, paclitaxel, and nanoparticle 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 have shown activity in patients who are *BRAF* positive who have symptomatic brain metastases that required corticosteroids
- Checkpoint inhibitors, alone or in combination, have efficacy against brain metastases. However, they are generally less effective against brain metastases than against disease outside the brain. Combination ipilimumab + nivolumab is significantly more effective against intracranial disease than anti-PD-1 therapy alone and is usually considered the treatment of choice for melanoma brain metastases whenever feasible. Many of the studies are ongoing. However, because corticosteroids can interfere with the activity of checkpoint inhibitors, checkpoint inhibitor use in patients receiving corticosteroids for symptomatic brain metastases is associated with lower response rates
- 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; however, whether and when SRS should be recommended for such patients remains the subject of ongoing clinical trials.

# SIDE EFFECTS OF STAGE IV SYSTEMIC THERAPIES

Before we get into the details about the adverse effects of therapies, we want to mention 2 points.

1. The adverse events reported in clinical trials typically report any event that happened to a patient and do not necessarily imply they are caused by the treatment; these symptoms or signs could be related to other health conditions, other medications, or the cancer itself
2. Which side effects are most likely to occur and most relevant/impactful to a patient is complex, and requires a thorough discussion with the treating team
3. AIM at Melanoma's convention is to refer to these adverse events as side effects for simplicity sake. However, they are not necessarily caused by the drugs.

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 18.

In the study of vemurafenib + cobimetinib, 99% of patients reported side effects. In the 18-month follow-up study, common side effects of vemurafenib and cobimetinib were found as shown in Graphic 19. We did not include laboratory abnormalities here.

Graphic 18. Common side effects with dabrafenib + trametinib (occurring in 10% or more of patients).

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

Graphic 19. 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%)	• Retinal problems (27%)
• Diarrhea (61%)	• Vomiting (26%)
• Photosensitivity (48%)	• Decreased appetite (20%)
• Nausea (43%)	• Hair loss (17%)
• Joint aches (38%)	• Decreased heart function (12%)
• Fever (29%)	• Skin thickening (10%)

In the study of encorafenib + binimetinib, side effects occurred in a large proportion of patients. The most common side effects are shown in Graphic 20.

Graphic 20. 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%)

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?

First, your treatment team will discuss with you what side effects may occur and will provide education and materials about how to avoid, minimise, or manage them.

With targeted therapy, sometimes an individual side effect can be managed with specific medications (for example, paracetamol 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 symptoms typically stop quickly (within a few days to weeks).

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 to view sheets.

### AIM RESOURCES

*(Click on the circles to view the sheets)*

- MEKTOVI-BRAFTOVI Action Plan Sheet
- TAFINLAR-MEKINIST Management Sheet
- COTELLIC-ZELBORAF Management Sheet

## Immunotherapy

Immunotherapy is associated with a range of effects. Many of the side effects 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 21 lists the common side effects associated with pembrolizumab, Graphic 22 those associated with nivolumab, and Graphic 23 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 Graphic 22 for the most common.

Graphic 21. 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%)

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 22.

Graphic 22. 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%)	• Thyroid underactivity (10%)

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 23.

Graphic 23. Common side effects associated with nivolumab/ipilimumab (occurring in 10% or more of patients).

<b>Common side effects associated with nivolumab + ipilimumab</b>	
• 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%)
• Thyroid underactivity (17%)	• Decreased appetite (19%)

In the RELATIVITY-047 study of relatlimab + nivolumab, 97% of patients had a side effect. The most common side effects are shown in Graphic 24.

Graphic 24. Common side effects associated with relatlimab/nivolumab (occurring in 15% or more of patients).

<b>The most common side effects associated with relatlimab + ipilimumab</b>	
• Pain in the muscles or skeletal system (45%)	• Headaches (18%)
• Feeling of tiredness (39%)	• Nausea (17%)
• Skin rash (28%)	• Thyroid underactivity (17%)
• Itching (25%)	• Decreased appetite (15%)
• Diarrhoea (24%)	• Cough (15%)

Potentially serious side effects of checkpoint inhibitors can become life-threatening. These side effects are shown in Graphic 25. This list is not complete—as mentioned previously, any organ or body system can be affected. For instance, myocarditis (inflammation of the heart muscle) is an immune-related adverse event that can occur with immune checkpoint inhibitors that experts are becoming more aware of. The table can include side-effects noted in longer-term data.

Graphic 25. Overall and serious side effects with checkpoint inhibitors.\*

Potentially serious side effect	Occurrence Rate (% of Patients Affected) Overall			Severe or Life-Threatening Occurrence Rate (% of Patient Affected)		
	PD-1 inhibitor alone (such as nivolumab or pembrolizumab)	Combination therapy (nivolumab + ipilimumab)	Combination therapy (nivolumab + relatlimab)	PD- 1 inhibitor alone (such as nivolumab or pembrolizumab)	Combination therapy (nivolumab + ipilimumab)	Combination therapy (nivolumab + relatlimab)
<b>Skin problems</b>						
Rash	9% to 40%	53%	28%	1% or less	15%	1%
Itching	14% to 27%	39%	25%	0%	2%	1%
<b>Intestinal problems</b>						
<b>Diarrhea</b> , which can lead to dehydration	15% to 36%	54%	24%	2.5% to 5%	11%	1%
<b>Colitis</b> (inflammation of the colon)	1% to 4%	25%	5%	3% or less	14%	1%
<b>Hormonal problems</b>						
<b>Thyroid</b> (most common)	10% to 11%	20% or more	17%	1% or less	1% or less	0%
<b>Other endocrinopathies</b> involving the pancreas (diabetes), adrenal glands, or pituitary (control centre of the brain)	Less than 3%	Less than 0%	7%	Less than 1%	Less than 3%	<2%
<b>Liver problems</b>	Less than 5%	25%	6%	1% to 2%	15%	4%
<b>Lung problems</b> (called pneumonitis)	1% to 5%	7% to 10%	4%	1% to 2%	1% to 2%	Less than 1%
<b>Neurologic problems</b> (including headache & peripheral neuropathy)	6%	12%	20%	Less than 1%	Less than 1%	Less than 1%
<b>Kidney problems</b>	1%-5%	4% to 5%	2%	Less than 1%	Less than 1%	1%

\*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 to view sheets.

**AIM RESOURCES** (Click on the circles to view the sheets)

**KEYTRUDA**

**Side-effect  
Management  
Sheet**

**OPDIVO-YERVOY**

**Side-effect  
Management  
Sheet**

**OPDUALAG**

**Side-effect  
Management  
Sheet**

## IL-2

Aldesleukin (IL-2) is a very powerful medicine that can only be administered at select institutions because of its toxicity and the potential requirement for admission to an intensive care unit. Certain patients are potential candidates for this therapy, specifically those who have

- No infection
- No autoimmune or inflammatory disorders
- No lung, heart, kidney, or brain or spinal cord issues
- No organ transplants
- No cancer that has spread to the brain or spinal cord.

The most common side effects are low blood pressure (71%), diarrhea (67%), chills (52%), vomiting (50%), difficulty breathing (43%), rash (42%), and high bilirubin (40%). The symptoms that were life threatening that occurred in more than 1% of patients are shown in Graphic 26.

Graphic 26. Serious side effects associated with aldesleukin.

Potentially serious side effect	Overall occurrence rate (% of patients affected)	Life threatening occurrence rate (% of patients affected)
Hypotension	71%	3%
Diarrhea	67%	2%
Elevated bilirubin (liver problem)	40%	2%
Serious respiratory disorders (eg, requiring a ventilator)	11%	3%
Coma	Not common	2%
Low urine output	63%	6%
No urine output	Not common	5%

## T-VEC

The most common side-effects with T-VEC (happening in more than 20% of patients) are flu-like symptoms such as pyrexia, chills, fatigue, as well as nausea, injection-site pain, and vomiting. T-VEC contains a live herpes virus; therefore, there are a range of safety precautions that have to be taken to prevent other people from contracting the herpes virus. For detailed discussion of T-VEC side effects and safety precautions, see <https://1pgozz2wgm3s1zpoz1y808b-wpengine.netdna-ssl.com/wp-content/uploads/AIM-IMLYGIC-MULTIPAGE.pdf>. When T-VEC is used in combination with checkpoint inhibitors, early results from the combined approach showed no new unexpected side effects; the most common side effects were fatigue, rash, chills, fever, and joint pain. Immune-related side effects did occur.

### *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.

With IL-2, the side effects are managed through close intensive care in the hospital. T-VEC side effects are managed like the flu, and specific safety precautions are taken to prevent spread of the herpes virus.

## 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 IV infusion into your arm or other access point to a vein (eg, a port), typically at your treating hospital. The drug can be given either every three or six weeks and will be continued for as long as you tolerate it, and the melanoma doesn't progress. The infusion lasts for 30 minutes.

Nivolumab is given as an intravenous (IV) infusion into your arm, typically at your treating hospital. The drug can be given every two or four weeks and will be continued for as long as you tolerate it, and the melanoma doesn't progress. 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 also given over 30 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, and the melanoma doesn't progress for a maximal treatment time of two years.

Relatlimab and nivolumab are given together in a premixed formulation. The combination is given by IV over a 30-minute period. The combination will be given every four weeks. The therapy is given for as long as you tolerate it, and the melanoma doesn't progress. Your doctor will determine how many treatments you need.

Ipilimumab is given as an IV infusion over 30 minutes. It is usually given every three weeks for a total of four cycles.

As mentioned, IL-2 is given in the hospital and requires hospital stays of five to seven days per course, most often in an intensive care or bone marrow transplant setting. The infusion itself is given by an intravenous line for a treatment course of two cycles, each given three times per day for five days. So you take a two-week break before the second cycle. A month after the second cycle, the scans are done to see if the cancer is shrinking. If it is working you can receive up to a total of six cycles of IL-2.

T-VEC is injected directly into the tumour in the physician's office or clinic. As mentioned, T-VEC is made with a herpes virus so you will need to be careful with dressing changes and potential exposure to people who you are in close contact with, particularly those who are immunocompromised or pregnant. The injections are at the initial visit, then three weeks later, and then every two weeks while you have the tumour to inject. You can be treated for six or more months.

**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 until it is opened. 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 or hospital.

- 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?
- Will infusion treatments interfere too much with your other work and life commitments?

## High-Dose IL-2

IL-2 requires hospitalisation, and you don’t know in advance how many cycles it requires.

- Is there an IL-2 infusion centre near you? If not, are you willing to travel for it?
- Are you prepared to stay in the hospital for your IL-2 treatments?
- Since you don’t know how many cycles you will tolerate, can you be flexible in your plans for several months?

## T-VEC

T-VEC involves lesion injections at the doctor’s office, and you have safety precautions to consider at home.

- Does your oncologist’s office perform T-VEC injections? If not, where is the nearest centre and are you willing to travel to it?
- Are you prepared to go into the office for injections every 2 weeks (and potentially more if you are receiving additional immunotherapy)?
- Do you have anyone pregnant or immunocompromised in your house?
- Do you have the support you need at home to handle dressing changes and disposal of waste?

## FINANCIAL/ACCESS ISSUES

Intravenous therapy will need to be taken at the hospital, while you can take the oral medicine at home. These medications may be treated differently in terms of reimbursement.

A financial consideration is the impact of therapy on your ability to earn a living. Are you able to miss work during treatment, either to receive infusions or because of the side effects of therapy? Does your work require you to travel? If you work full time, can you arrange a flexible schedule to meet your treatment requirements? It is important to consider these factors and find out your legal protections.

## 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 non-hormonal 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 non-hormonal 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 non-hormonal 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, the combination of nivolumab + ipilimumab, or the combination of nivolumab + relatimab, you should use an effective method of birth control during treatment and for six months after the last dose of therapy
- For T-VEC, you should use an effective method of birth control during treatment and for 30 days after the last administration. Sexual intercourse without a latex condom should be avoided. A patient who received T-VEC should wait three months before becoming pregnant. Special care needs to be made to avoid exposing a pregnant woman to the herpes virus since it can be transmitted to the baby during birth. Close contacts who are pregnant should avoid changing dressings and coming in contact with fluids of the patient during the course of therapy
- For IL-2, the benefits of therapy need to be weighed against potential fetal harm.

## FERTILITY/FAMILY PLANNING

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

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



# 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				
<b>My tumour status (<i>BRAF</i>)</b>		1	2	3	4	5
<b>Effectiveness of the drug</b>		1	2	3	4	5
<b>Side effects</b>		1	2	3	4	5
<b>Convenience of receiving the treatment</b>		1	2	3	4	5
<b>Quality of life</b>		1	2	3	4	5
<b>Financial considerations</b>		1	2	3	4	5
<b>Fertility/family planning</b>		1	2	3	4	5
<b>Other factors</b>		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 ( <i>BRAF</i> )		1	2	3	4	5
Effectiveness of the drug		1	2	3	4	5
Side effects		1	2	3	4	5
Convenience of receiving the treatment		1	2	3	4	5
Quality of life		1	2	3	4	5
Financial considerations		1	2	3	4	5
Fertility/family planning		1	2	3	4	5
Other factors		1	2	3	4	5

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

**Worksheet 3:** Aggressive Immunotherapy Approach (example, combination immunotherapy, IL-2)

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

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

# SURVIVORSHIP AND ADVANCED CARE PLANNING

---

Patients with melanoma are living longer than ever before, and it's important to think about the impact of the disease and therapies on your life in general. You will need to address the emotional and physical effects of treatment. Given the challenges you face, you may want to connect with other patients in the community who are sharing your cancer journey. Professional help might be warranted to address the anxiety or other strong emotions associated with your Stage IV diagnosis. Perhaps you will do well with therapy but you may have anxiety about the disease coming back. You can work with your oncology care team to develop a survivorship care plan. This plan will help you be proactive about maintaining your health and assuring proper cancer follow-up care after treatment. For more on this topic, see AIM's page: <https://www.aimatmelanoma.org/support-resources/survivorship/>

While your oncology team is working to achieve the best outcomes possible, it's impossible to determine if, and when, things may not go as hoped. For advanced care planning, it's best to explore different scenarios so you can make sure that your wishes are met as much as possible during your cancer journey. Advanced care planning can include everything from choosing a healthcare proxy, to making an advanced directive, to addressing your will, to assessing under what circumstances you would want to withdraw care and move on to hospice.

This kind of planning is best done when you are feeling well—if you postpone this type of planning too long, you may not be well enough to make the decisions thoughtfully. Or you may not get a chance to do any planning at all, which can lead to unnecessary additional stress and confusion for yourself and your loved ones during a difficult time. A resource from the American Society of Clinical Oncology (ASCO) on advanced planning is included in the **INFORMATION RESOURCES** section at the end of this document.

## 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 other resources that you may want to consult as you evaluate your options. Being informed puts you in the best position to have an active role in this important decision.

## 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.

Ascierto PA, Long GV, Robert C, et al. (2019). Survival outcomes in patients with previously untreated BRAF wild-type advanced melanoma treated with nivolumab therapy: three-year follow-up of a randomized phase 3 trial. *JAMA Oncol*. 2019;5:187–194.

Ascierto PA, McArthur GA, Dréno B, et al. (2015). coBRIM: a phase 3, double-blind, placebo-controlled study of vemurafenib versus vemurafenib + cobimetinib in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma (NCT01689519). *J Transl Med*. 2015;13(Suppl 1):O4.

Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol*. 1999;17:2105-2116.

Atkins MB, Lee SJ, Chmielowski B, et al. Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: The DREAMseq Trial-ECOG-ACRIN EA6134. *J Clin Oncol*. 2023;41(2):186-197. doi: 10.1200/JCO.22.01763.

Chesney J, Puzanov I, Collichio F, et al. Randomized, open-label phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced, unresectable melanoma. *J Clin Oncol*. 2018;36:1658-1667.

Daud A, Pavlick AC, Ribas A, et al. Extended follow-up results of a phase 1B study (BRIM7) of cobimetinib (C) and vemurafenib (V) in BRAF-mutant melanoma. *J Clin Oncol*, 2016;34(15 suppl):9510.

Dréno B, Ribas A, Larkin J, et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. *Ann Oncol*. 2017;28:1137-1144.

Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19:1315-1327.

Dummer R, Flaherty KT, Robert C, et al. 5-year update on COLUMBUS: A randomized phase III trial of encorafenib (enco) + binimetinib (bini) versus enco or vemurafenib (vem) In patients(pts) with BRAF V600-mutant melanoma. Abs 1041MO. Presented at the ESMO Congress 2021, September 20, 2021.

Elias ML, Behbahani S, Maddukuri S, John AM, Schwartz RA, Lambert WC. Prolonged overall survival following metastasectomy in stage IV melanoma. *J Eur Acad Dermatol Venereol*. 2019;33:1719-1725.

Gogas HJ, Flaherty KT, Dummer R, et al. Adverse events associated with encorafenib plus binimetinib in the COLUMBUS study: incidence, course and management. *Eur J Cancer*. 2019;119:97-106.

Gogas HJ, Ribas A, Chesney J. MASTERKEY-265: A phase III, randomized, placebo (Pbo)-controlled study of talimogene laherparepvec (T) plus pembrolizumab (P) for unresectable stage IIIB-IVM1c melanoma (MEL). Abstract 10370. Presented on September 18, 2021. ESMO 2021.

Gutzmer R, Vordermark D, Hassel JC, et al. Melanoma brain metastases- interdisciplinary management recommendations 51 Stage IV Melanoma Treatment Options • Making the Decision That's Right for You Copyright © 2023 AIM at Melanoma Foundation and Terranova Medica, LLC. All Rights Reserved. Document Released January 26, 2022. Updated April 15, 2023. 2020. *Cancer Treat Rev.* 2020;89:102083. doi: 10.1016/j.ctrv.2020.102083.

Hamid O, Robert C, Daud A, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Ann Oncol.* 2019;30:582–588.

Hauschild A, Larkin J, Ribas A, et al. Modeled prognostic subgroups for survival and treatment outcomes in BRAF V600- mutated metastatic melanoma: pooled analysis of 4 randomized clinical trials. *JAMA Oncol.* 2018;4:1382-1388.

Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol.* 2018;19:1480-1492.

Hodi FS, Corless CL, Giobbie-Hurder A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. *J Clin Oncol.* 2013;31:3182-3190.

Hodi FS, Chiarion-Sileni V, Lewis KD, et al. Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. *J Clin Oncol.* 2022;40(16)suppl, 9522-9522. doi:10.1200/JCO.2022.40.16\_suppl.9522

Larkin J, Ascierto PA, Dréno B, et al. (2014). Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med.* 2014;371:1867-1876.

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. (2015). Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med.* 2015;373:23-34.

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med.* 2019;381:1535-1546.

Long GV, Flaherty KT, Stroyakovskiy D, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. *Ann Oncol.* 2017;28:1631-1639.

Long GV, Hodi FS, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in previously untreated metastatic or unresectable melanoma: overall survival and response rates from RELATIVITY-047 (CA224-047). *J Clin Oncol.* 2022;40(36) suppl, 360385-360385. doi:10.1200/jco.2022.40.36\_suppl.360385

Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAFmutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet.* 2015;386:444-451.

National Cancer Institute SEER Database Program. Cancer Stat Facts: Melanoma of the Skin. <https://seer.cancer.gov/statfacts/html/melan.html>. Accessed September 7, 2021.

Patel SP, Othus M, Chen Y, et al. Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma. *N Engl J Med*. 2023;388(9):813-823. doi: 10.1056/NEJMoa2211437

Pavlick AC, Ribas A, Gonzalez R, et al. Extended follow-up results of phase Ib study (BRIM7) of vemurafenib (VEM) with cobimetinib (COBI) in BRAF-mutant melanoma. *J Clin Oncol*. 2015;33(15\_suppl):9020.

Ribas A, Daud A, Pavlick AC, et al. Extended 5-year follow-up results of a phase Ib study (BRIM7) of vemurafenib and cobimetinib in BRAF-mutant melanoma. *Clin Cancer Res*. 2020;26:46-53.

Ribas A, Dummer R, Puzanov I, et al. Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy. *Cell*. 2017;170:1109-1119.e10. doi: 10.1016/j.cell.2017.08.027. Erratum in: *Cell*. 2018 Aug 9;174(4):1031-1032.

Ribas A, Gonzalez R, Pavlick A, et al. Combination of vemurafenib and cobimetinib in patients with advanced BRAF(V600)-mutated melanoma: a phase 1b study. *Lancet Oncol*. 2014;15:954-965. doi: 10.1016/S1470-2045(14)70301-8. Epub 2014 Jul 15. Erratum in: *Lancet Oncol*. 2014;15:417.

Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory 52 Stage IV Melanoma Treatment Options • Making the Decision That's Right for You Copyright © 2023 AIM at Melanoma Foundation and Terranova Medica, LLC. All Rights Reserved. Document Released January 26, 2022. Updated April 15, 2023. melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol*. 2015;16:908-918.

<sup>a</sup>Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015;372:30-39.

<sup>b</sup>Robert C, Schachter J, Long GV, et al. KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372:2521-32.

<sup>a</sup>Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med*. 2019;381:626-636.

<sup>b</sup>Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol*. 2019;20:1239-1251.

Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med*. 2022;386:24-34. doi:10.1056/NEJMoa2109970

# ACKNOWLEDGMENTS

---

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

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

**Anna Pavlick, BSN, MSc, DO, MBA**

Professor of Medicine, Division of Hematology &  
Medical Oncology  
Weill Cornell Medicine College  
New York, New York

**Michael A. Postow, MD**

Co-Lead, Melanoma Disease Management Team  
Memorial Sloan Kettering Cancer Center  
Assistant Professor of Medicine  
Weill Cornell Medical College  
New York, New York

The development of this pamphlet was supported by unrestricted educational grants from Alkermes; Amgen; Bristol Myers Squibb; and Novartis Pharmaceutical Corporation.

## 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.

This pamphlet was reviewed and acculturated for Australia by Melanoma & Skin Cancer Advocacy Network.

## ABOUT MSCAN

The Melanoma & Skin Cancer Advocacy Network (MSCAN) is an independent, consumer-led, national charity established in 2020 to spearhead the battle against Australia's national cancer - skin cancer.

MSCAN takes an innovative approach in listening to, representing and informing the skin cancer community on skin cancer prevention, early detection through to coping with a serious diagnosis. MSCAN champions equitable access to healthcare, and works hard to encourage more funding for research, clinical trials and a committed advocacy approach. MSCAN is passionate about working with government and the medical, research, consumer, and business communities.

MSCAN's activities are anchored to the following three pillars:

- Advocacy and Health Policy
- Innovation in Care and Research
- Information and Resources for people affected by a diagnosis.

MSCAN is a globally engaged and is a member of the Melanoma International Patient Advocates Coalition (MI-PAC).



# APPENDIX: 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

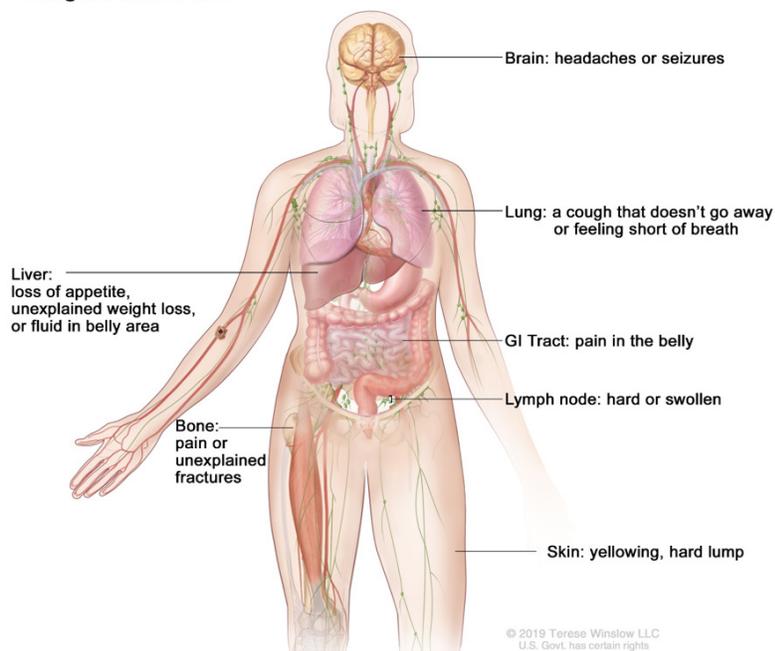
Stage IV melanoma may be suspected based on imaging tests, or you may have had symptoms that made your healthcare team concerned. These symptoms could include:

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

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 A.

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

**Stage IV Melanoma**



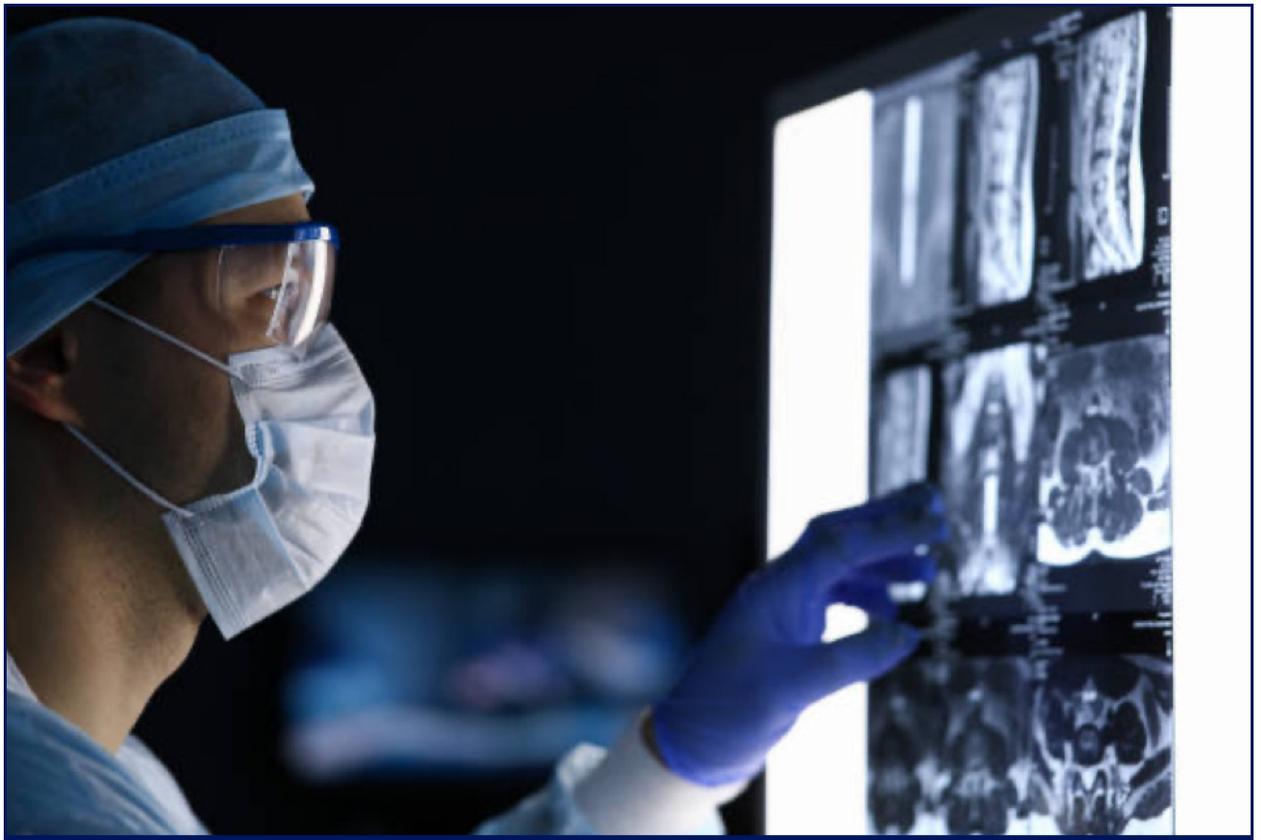
Graphic A: Specific symptoms associated with melanoma that has spread to different regions of the body. Adapted with permission from Terese Winslow.

## 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.

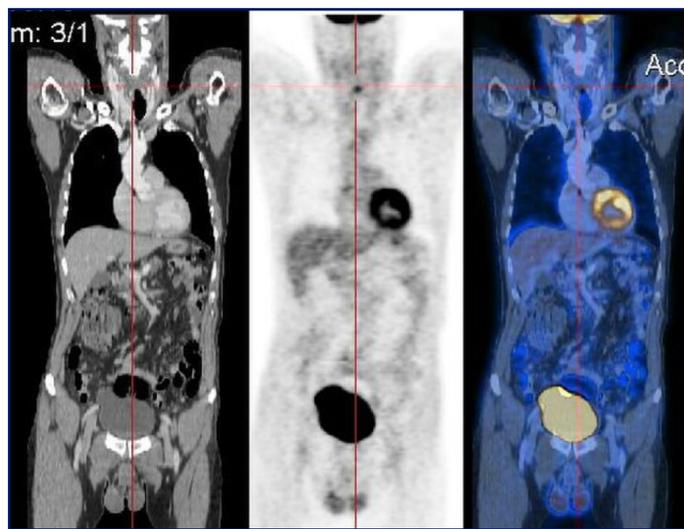
**Computed tomography (CT) or computerized axial tomography (CAT) scan** is an imaging scanning technique that uses X-rays from different angles to make a 3-dimensional picture of the inside of your body. CT scans can be used with or without a material called contrast. **Contrast materials** are substances 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.

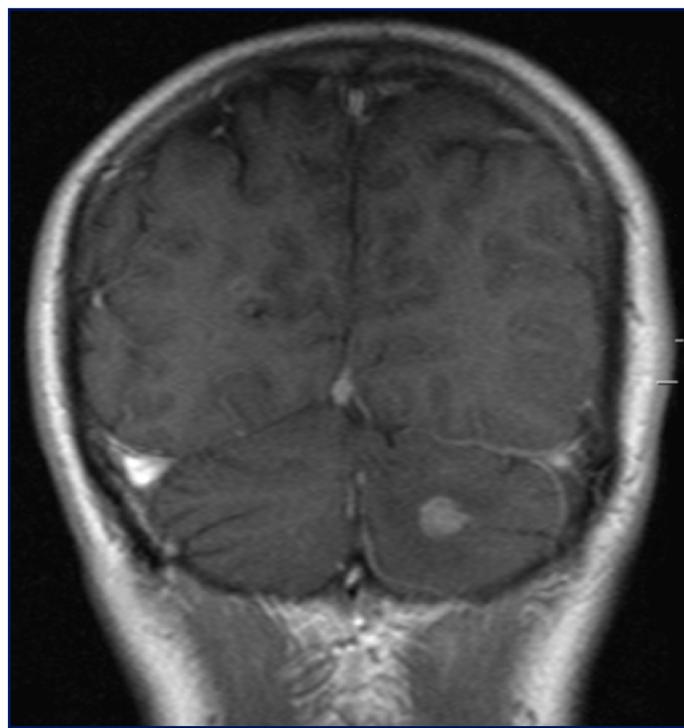


**PET/CT** is an imaging method that combines CT with PET to provide detailed information about both the structure (CT) and the function (PET) of cells and tissues in the body. The overlaying helps the radiologist be confident that a region of concern is cancer, such as when the CT and PET images line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

**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 C). 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 B. 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 C. Brain MRI showing metastases (white areas). Reproduced from Wikimedia Commons, courtesy of Creative Commons Attribution.

# 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 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 1/16 inch in diameter and a half inch 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 esophagus, 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).