Melanoma. Let’s get under the skin of it

Understanding the BRAF mutation
About this guide

This guide has been developed for people who have recently been diagnosed with melanoma. It aims to provide information about melanoma gene mutations – in particular, to the BRAF gene – and the relevance of these mutations in making treatment decisions.

It is important to talk to your doctor about getting tested for the mutation to the BRAF gene as soon as possible after diagnosis. Once you know if you have this mutation, you and your doctor will be better informed to explore treatment options.
Melanoma is a cancer of the skin that occurs when skin cells called melanocytes change and grow uncontrollably. Melanomas can occur anywhere on the body but are most commonly found on the chest and legs. The most common sign of melanoma involves the appearance of a new mole however, in approximately 30% of cases they appear on the site of existing moles. Melanoma is classified by clinical stages 1, 2, 3, and 4, on the basis of the extent of the disease. Depending on the stage of the melanoma, there are a range of treatment options, including surgery, radiation therapy, and drug therapy.

Gene mutations in melanoma

Sometimes, changes occur within the DNA of melanoma cells. These changes are called ‘mutations’. Multiple gene mutations can play a role in the progression of melanoma. The three most common mutations in melanoma are to the BRAF, NRAS and c-KIT genes. However, the only mutation for which targeted therapy is available is for the BRAF gene.
Who should be tested for BRAF and why

Approximately 40-50% of people with skin melanoma have a mutation to the BRAF gene.\textsuperscript{7,8}

Everyone has the BRAF gene, but in some people this gene is mutated. This means the tumour sends continuous signals, causing cells to grow and divide too fast.\textsuperscript{9}

Knowing whether you have a mutation to the BRAF gene can help you better understand your available treatment options. Getting tested to see if your melanoma is BRAF positive is simple and getting these test results may expand your treatment options. Drugs that target mutations in the BRAF gene, known as BRAF inhibitors, are available, and they have been shown to be effective in treating melanoma.\textsuperscript{10}
BRAF mutation testing

The entire testing process – from biopsy to obtaining results – can take anywhere from three to five days to several weeks. However, this can take anywhere from 3-5 days to several weeks, depending on the laboratory and type of test. In some limited cases, biopsies that test for BRAF mutation will need to be repeated if a sufficient sample of the tumour is not collected.

How do they test for a mutation to the BRAF gene?
- Your doctor will collect a small biopsy (tissue sample) from your melanoma or some cells from your lymph nodes to send to a laboratory.
- A pathologist at the laboratory will test your melanoma cells to see if they are BRAF positive or negative and send a report to your doctor.
- Your doctor will review the report and let you know if your melanoma is BRAF positive or not.

If you test negative for BRAF, also called wild type, your doctor may propose other molecular tests or (non-targeted) treatment. Currently, there are only molecular tests for BRAF, GNA11, GNAQ, KIT, and NRAS genes.
Therapy options

Individuals with stage 1-3 melanomas typically undergo surgery to remove the melanoma. In cases where surgery is not suitable, other treatments are considered. Most people diagnosed with melanoma will have further surgery after the area of affected skin has been removed. This surgery is known as a wide local excision. It is done to make sure that all the melanoma cells in the area have been removed, where the mole previously was, to reduce the chances of the melanoma coming back.

Adjuvant therapy is treatment given after the primary treatment for melanoma, usually surgery. Adjuvant therapy is given to try to reduce the risk of melanoma returning.

There are two types of drugs used to treat advanced melanoma: targeted therapies and immunotherapies.

Your doctor may decide to treat you with one of these treatments before changing to another. Studies have not established which order of drug treatments is the most effective. The table below summarises how both types of therapies work and their effectiveness in treating advanced melanoma, as well as how they are taken and any potential side effects.

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<td>A BRAF mutation causes melanoma cells to grow and spread. Targeted therapies prevent this by switching off these BRAF mutations¹⁹</td>
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<td>BRAF inhibitors (drugs that work to stop BRAF mutations from causing tumours to spread further) were developed specifically to treat melanomas that have the BRAF mutation</td>
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# Targeted therapies at a glance

- These medicines are tablets or capsules that are taken by mouth (orally)\(^2\)

# Immunotherapies at a glance

- There are a number of different types of immunotherapies available, each have different approaches and different effects
  - CTLA-4 inhibitors and PD-1 inhibitors are two examples

## How do you take them

- Targeted therapies may be taken alone or in combination with other targeted therapies
- They are often oral therapies that can be taken at home

- They often must be given as an intravenous (IV) infusion every few weeks at your doctor’s office

## Are there any side effects?

- Just as there are with any kind of treatment, there are side-effects related to targeted therapies, with the symptoms dependent on the particular medicine your doctor prescribes you. If you experience severe side effects, therapy may need to be interrupted or stopped completely

- Just like with any kind of treatment, there are specific side effects that come with the use of immunotherapy. In some cases, immunotherapy can cause the body to develop an immune reaction against its own tissues. When this happens, therapy may need to be interrupted or stopped completely

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In advanced melanoma, targeted therapies are an option for the roughly 40-50% of patients whose melanoma is driven by the BRAF mutation. They are designed to 'switch off' the uncontrolled signalling that is caused by a mutated gene.\(^7,8\)

Testing for a mutation to the BRAF gene is the only way you can know if targeted therapy is an option for you. Once your doctor knows if you have the BRAF mutation, you can begin to discuss targeted therapy as a treatment option.
Summary

— Depending on the type of melanoma and stage of the disease, your cancer may be treated with surgery, radiation therapy, and/or drug therapy
— A biomarker for melanoma (the BRAF mutation) has been identified for which targeted therapies are available
— If you have tested positive for a mutation to the BRAF gene, your doctor may discuss with you available targeted therapies that may help fight your tumour

Where to find further information

Melanoma: Let’s Get Under the Skin of It
For more information about staging, please refer to our Understanding Melanoma guide.

For more information about patient-doctor consultations, please refer to our Patient Consultation Guide and Checklist.

Alongside speaking to your doctor about your melanoma, you may find some of the links / websites listed below useful in finding out more information:

Melanoma UK:
www.melanomauk.org.uk

British Skin Foundation:
https://www.britishskinfoundation.org.uk/melanomaskincancer

Cancer Research UK:
www.cancerresearchuk.org/about-cancer/melanoma

Macmillan Cancer Support:
https://www.macmillan.org.uk/information-and-support/melanoma
References


Adverse events should be reported. Reporting forms and information can be found at www.yellwcard.mhra.gov.uk/ (UK)