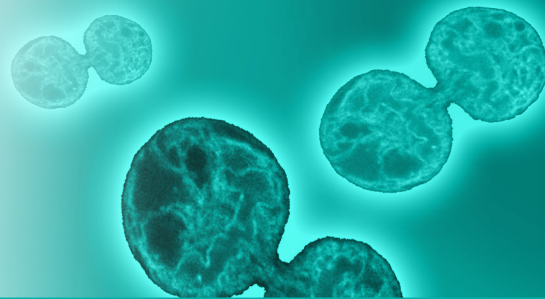


Melanoma information card

Melanoma statistics



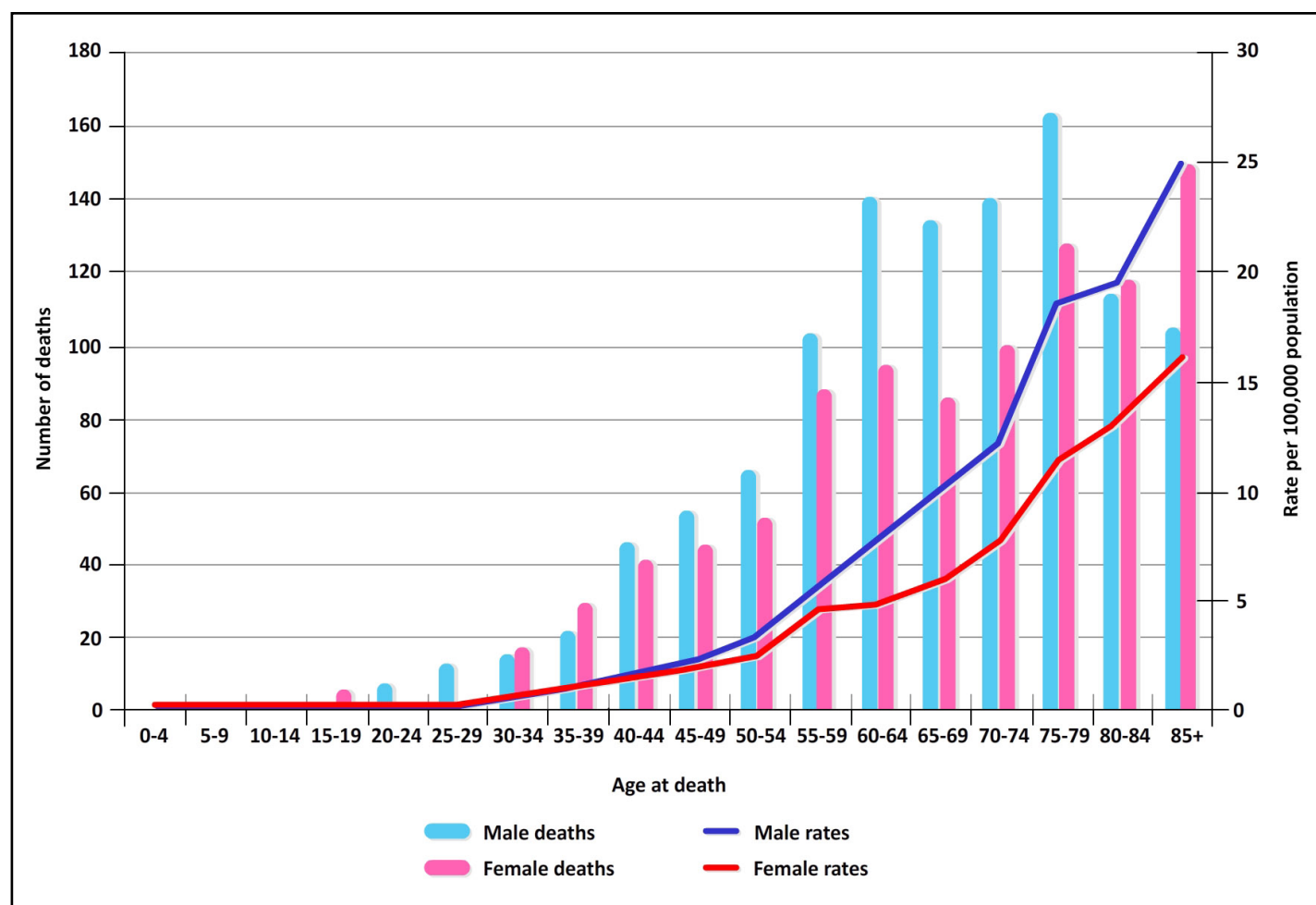
Malignant melanoma is estimated to represent 4% of all skin cancers and is responsible for 80% of deaths from skin cancer. (Cancer Research UK, Miller and Mihm, 2006)

	Malignant melanoma	Non-melanoma
Cases of skin cancer diagnosed and registered in the UK in 2008	11,767	98,800*
Deaths from skin cancer in the UK in 2009	2,081	552

* Please note that not all non-melanoma skin cancer has to be registered so the actual number of incidence is estimated to be over 100,000.

Source: Cancer Research UK (<http://info.cancerresearchuk.org/cancerstats/types/skin/>)

Number of deaths from malignant melanoma, by sex, UK, 2008

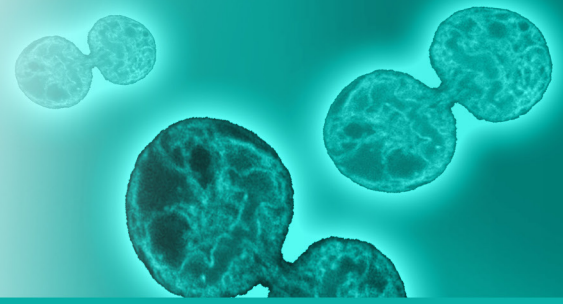


Source: Cancer Research UK (<http://info.cancerresearchuk.org/cancerstats/types/skin/mortality/>)

The survival rate for patients with metastatic malignant melanoma is low with only 10-20 % of patients surviving for two years or more. Most patients live for an average of 6-15 months after diagnosis.

Melanoma information card

Melanoma progression

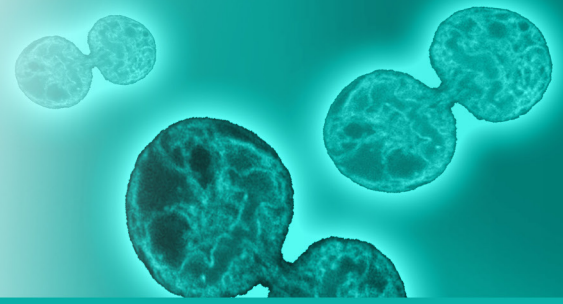


Stage	Benign Nevus	Dysplastic Nevus	Radial-growth Phase	Vertical-growth Phase	Metastatic Melanoma
<p>Epidermis</p> <p>Basement membrane</p> <p>Dermis</p> <p>Subcutaneous tissue and blood vessels</p>					<p>Metastasis to other tissues</p>
Key features	<ul style="list-style-type: none"> • Common mole. • Melanocytes increase in number to form a naevus or mole. • Uniform colour and edges. • Benign, rarely progresses to cancer. 	<ul style="list-style-type: none"> • Atypical mole. • Melanocytes grow abnormally. • Mole is larger with irregular edges and colouration. • May arise from benign nevi or as new lesion. • Premalignant stage. Increased risk of cancer progression. 	<ul style="list-style-type: none"> • Primary malignant stage. • The melanocytes begin to spread outwards (laterally) through the epidermis layer. • Some cells begin to invade the dermis layer. 	<ul style="list-style-type: none"> • Invasive stage where melanoma cells spread vertically, penetrating the basement membrane, invading and growing within the dermis layer. • The tumour has the potential to spread to other parts of the body (metastasise) as it infiltrates blood (vascular) and lymphatic systems. • The depth of the melanoma will determine treatment. 	<ul style="list-style-type: none"> • The melanoma is malignant and cells break away from the primary tumour and invade other body parts such as the lung, liver or brain via the blood (vascular) or lymphatic system. • Once the cancer has spread to other organs, prognosis is poor. Patients live for an average of 8–18 months after diagnosis.

Adapted from: Miller AJ and Mihm MC. Melanoma. The New England Journal of Medicine 2006; 355: 51-65.

Melanoma information card

Melanoma treatment



Stage	Benign Nevus	Dysplastic Nevus	Radial-growth Phase	Vertical-growth Phase	Metastatic Melanoma
<p>Epidermis</p> <p>Basement membrane</p> <p>Dermis</p> <p>Subcutaneous tissue and blood vessels</p>					<p>Metastasis to other tissues</p>
Treatment options		<ul style="list-style-type: none"> • Surgical removal of affected tissue. 	<ul style="list-style-type: none"> • Surgical removal of affected tissue. • Sentinel lymph node sampling, a process that uses radioactive solution and dye to identify which lymph nodes near the melanoma could contain or receive cells from the primary malignant melanoma. If the test results are positive the lymph nodes around the melanoma are removed. 	<ul style="list-style-type: none"> • Surgical removal of affected tissue. • Sentinel lymph node sampling. • Removal of lymph nodes near the melanoma. • Chemotherapy, e.g. dacarbazine (if tumour returns after surgical removal). • Targeted drug therapy e.g. vemurafenib (if patient's tumour has <i>BRAF</i>^{V600E} mutation). 	<ul style="list-style-type: none"> • Surgical removal of affected tissue (if possible). • Chemotherapy, e.g. dacarbazine. • Radiotherapy • Immunotherapy, e.g. ipilimumab. • Targeted drug therapy, e.g. vemurafenib (if patient's tumour has <i>BRAF</i>^{V600E} mutation).

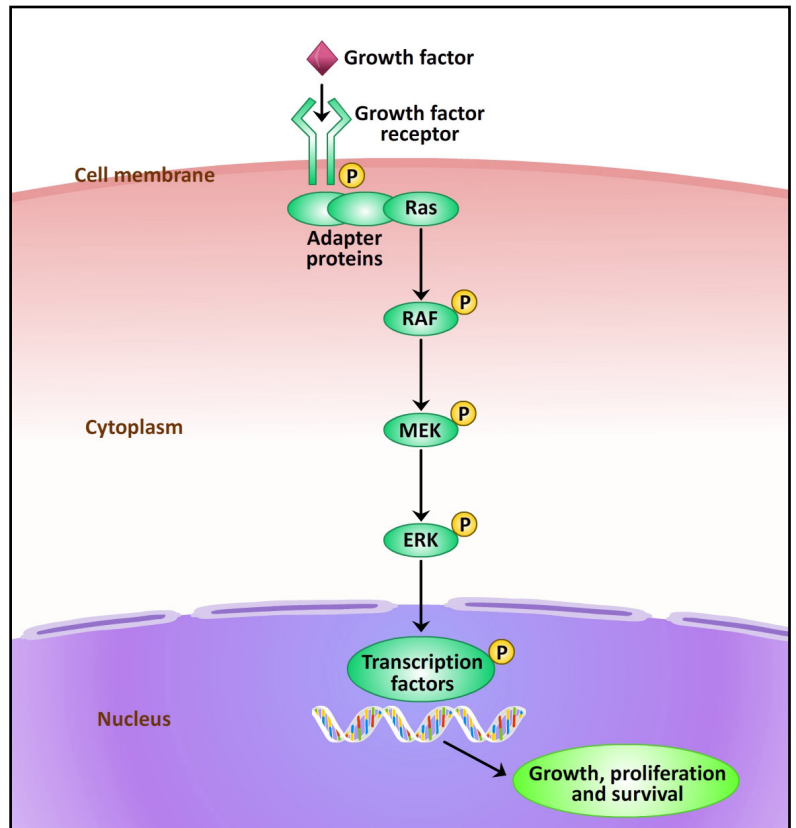
Adapted from: Miller AJ and Mihm MC. Melanoma. The New England Journal of Medicine 2006; 355: 51-65.

Melanoma information card

BRAF mutations in cancer

***BRAF* function**

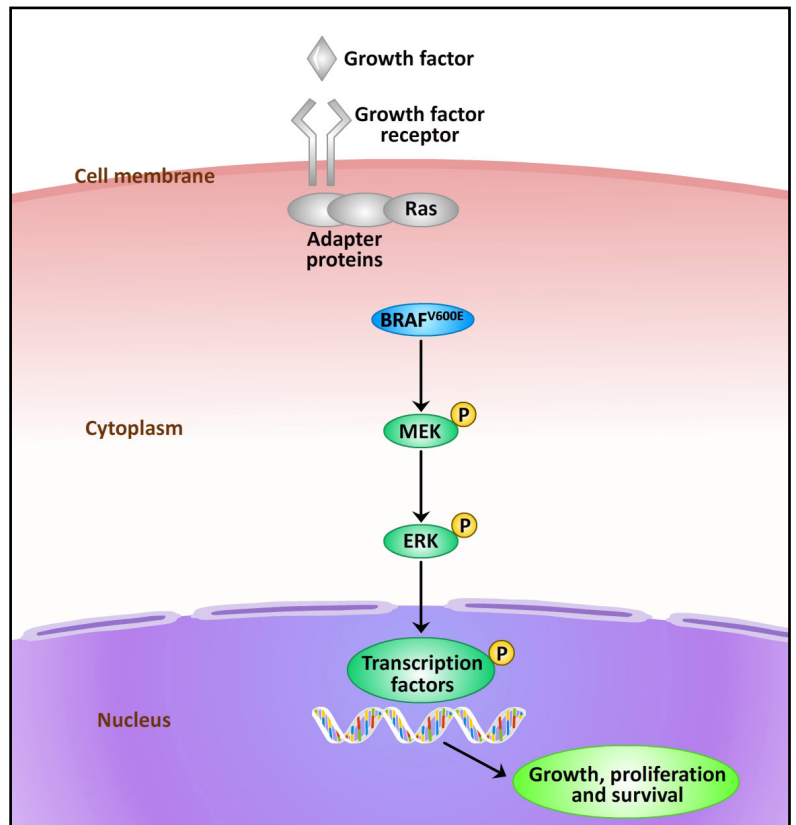
The *BRAF* gene encodes the BRAF protein, a protein kinase that is part of a key cellular pathway known as the MAPK-ERK cascade. This pathway is responsible for sending signals to the nucleus for cell growth and division. A simplified MAPK-ERK pathway is shown on the right.



Mutations in *BRAF*

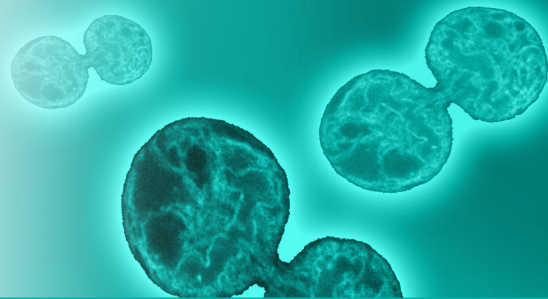
The most common mutation of the *BRAF* gene is V600E. This mutation occurs in the 600th codon in the gene and causes the amino acid to change from valine (V) to glutamic acid (E). The BRAF^{V600E} protein is permanently activated and continually sends signals for cell growth to proteins downstream of it. It does this without activation from other proteins upstream of it in the signalling pathway (see diagram).

BRAF mutations are found in approximately 50% of melanomas, 30-70% of thyroid cancers, 30% of ovarian cancers and 10% of colorectal cancers.



Melanoma information card

Gene alterations in melanoma



The table below shows different types of mutations associated with malignant melanoma (MM)

Gene type	Gene	Percent of malignant melanoma patient samples with mutation	What does the protein normally do?
Proto-oncogenes	<i>BRAF</i>	50-70% mutated	BRAF is involved in sending signals within the cell (signal transduction). It functions like an on-off switch. Once activated it starts sending signals to other proteins in the cell that control cell division. Once inactivated it stops sending these signals.
	<i>NRAS</i>	15-30% mutated	NRAS is involved in sending signals within the cell (signal transduction). It functions like an on-off switch. Once activated it starts sending signals to other proteins (including BRAF) in the cell that control cell division. Once inactivated it stops sending these signals.
	<i>AKT3</i>	Up to 70% overexpressed	AKT3 plays an important role in cell survival. When activated the protein prevents cell death by inhibiting the action of proteins that signal for cell suicide (apoptosis).
	<i>Cyclin D1</i>	6-44% amplified	Cyclin D1 plays a role in driving forward the cell cycle. It interacts with other proteins to inactivate the retinoblastoma (Rb) protein. The Rb protein controls progression of the cell cycle at the checkpoint between G1 phase and S phase, when the DNA is replicated.
Tumour suppressors	<i>CDKN2A</i>	30-70% deleted, mutated or silenced	CDKN2A plays an important role in controlling the cell cycle. It suspends cell division, allowing time for damaged DNA to be repaired and can initiate cell suicide (apoptosis) if cells are too badly damaged to be repaired. These actions prevent the formation of tumours.
	<i>PTEN</i>	5-20% deleted or mutations	PTEN plays an important role in controlling the cell cycle. It normally acts to prevent uncontrolled cell division by sending signals to the cell to stop dividing. It can also tell cells to undergo cell suicide (apoptosis).
	<i>p53</i>	10% lost or mutated	P53 is known as the “guardian of the genome”. It can control the cell cycle by suspending cell division, allowing time for damaged DNA to be repaired. It can activate DNA repair proteins when DNA has been damaged and if the cell is too badly damaged to be repaired it can initiate cell suicide (apoptosis).

Adapted from Gray-Schopfer V, Wellbrock C and Marais R. Melanoma biology and new targeted therapy. *Nature* 2007; 445: 851-857

Melanoma information card

Chemotherapy treatment

Mode of action

Chemotherapy treatments use cytotoxic drugs (drugs that are toxic to cells) to destroy cancer cells. The drugs target rapidly dividing cells and “kill” them. This treatment destroys cancer cells but also destroys other rapidly dividing cells such as hair cells. This is why hair loss is a common side effect of chemotherapy treatment.

Dacarbazine, also known as DTIC, is the most commonly prescribed chemotherapy for advanced malignant melanoma. It damages the DNA of cancer cells by adding an alkyl group to the DNA. This damage to the DNA is detected by the cell and triggers programmed cell death (apoptosis).

Dacarbazine is given by injection into a vein. It is often used as a single treatment for metastatic melanoma that has spread to other parts of the body. It is also given after surgery to remove melanomas if the disease is believed to have spread to the lymph nodes.

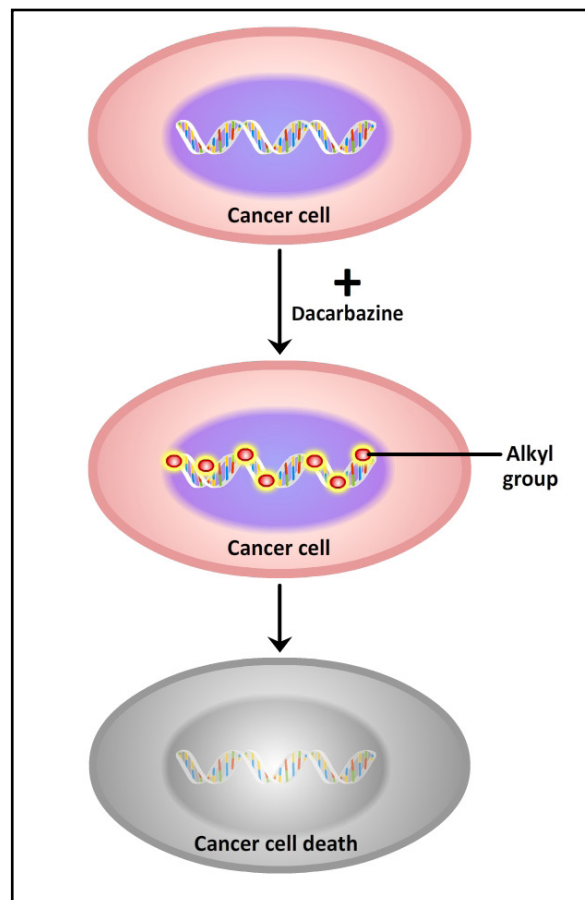
Side effects

Chemotherapy can cause side effects including:

- decrease in white blood cells resulting in an increased risk of infection
- decrease in red blood cells resulting in tiredness and anaemia
- nausea
- hair thinning or loss
- sore mouth and mouth ulcers.

Effectiveness

Studies have shown that dacarbazine causes tumour shrinkage in 7-12% of patients, offering an overall survival of 5 to 7 months.



Melanoma information card

Radiotherapy treatment

Mode of action

Radiotherapy uses high energy X-ray beams to target tumour cells. The X-rays damage the DNA of the cancer cells which is detected by the cell and leads to cell death (apoptosis). Radiotherapy is delivered once a day in short sessions for several weeks.

When the cancer has spread to other areas of the body, radiotherapy can be used to reduce tumour size and help to improve the symptoms of advanced melanoma.

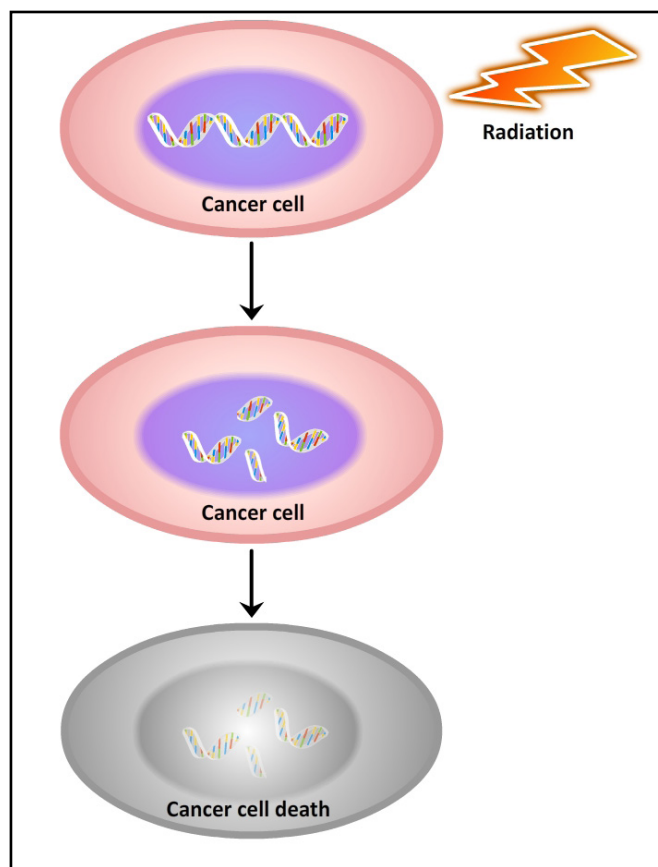
Side effects

Radiotherapy can cause side effects including:

- fatigue/tiredness
- red and sore skin
- nausea
- hair loss (if treating secondary brain tumours).

Effectiveness

Radiotherapy can be used after surgical removal of tumours for patients with advanced melanoma. For patients with metastatic melanoma that cannot be removed by surgery, radiotherapy alone is a treatment therapy. Radiotherapy after surgery may reduce the rate of local recurrence of melanoma, a tumour that develops in or near the site where the first tumour was completely removed, however it does not prolong overall survival compared to surgery alone.



Melanoma information card

Immunotherapy treatment

Mode of action

Ipilimumab, also known as Yervoy, is a monoclonal antibody treatment that blocks the activity of a protein called cytotoxic T-lymphocyte antigen 4 (CTLA-4). This protein is found on T-cells, a type of white blood cell that “kills” tumour cells by inducing programmed cell death (apoptosis). CTLA-4 is a negative regulator of T-cells. This means it sends signals to stop the T-cells destroying cancer cells. Ipilimumab blocks the action of CTLA-4 so that the immune system is activated and T-cells “kill” the tumour cells leaving normal, non-cancerous cells unaffected.

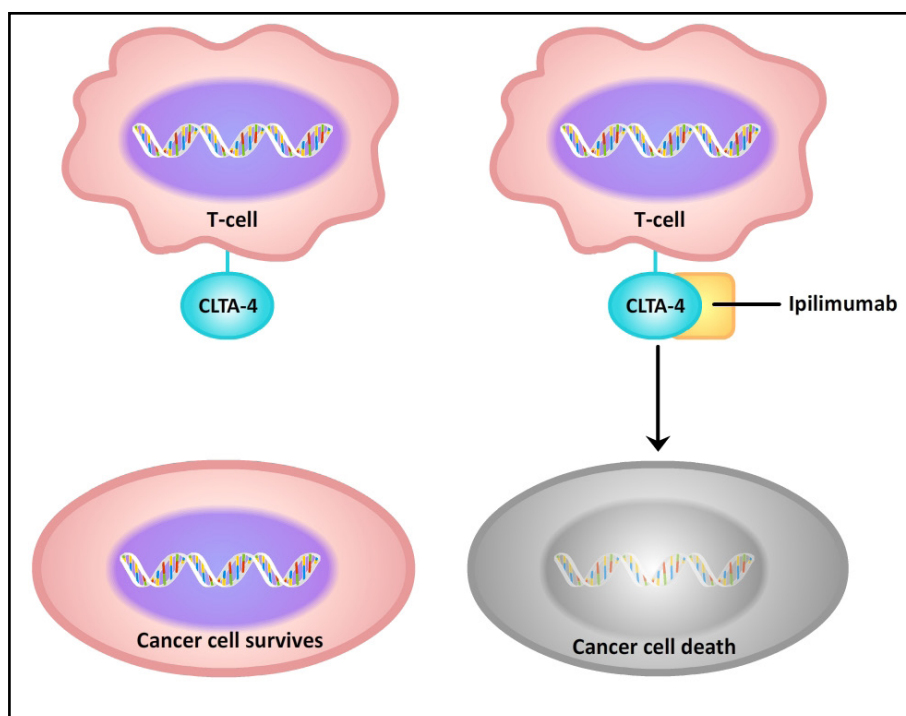
Side effects

Ipilimumab can cause side effects including:

- diarrhoea
- skin rash
- fatigue
- liver failure
- hormone problems
- inflammation of the intestines (colitis)
- red sore skin.

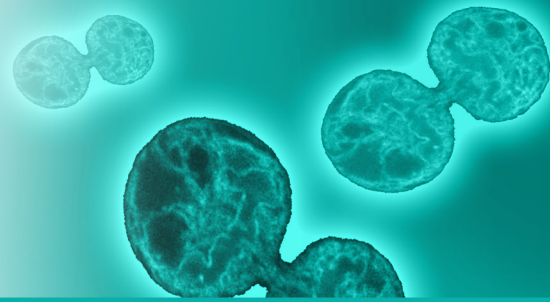
Effectiveness

Clinical studies have shown that using ipilimumab in combination with dacarbazine (chemotherapy) increases survival in patients with metastatic melanoma compared with treatment with dacarbazine alone. Overall patients treated with ipilimumab and dacarbazine survived for a median of 11.2 months compared to 9.1 months with dacarbazine and a placebo.



Melanoma information card

Targeted $BRAF^{V600E}$ inhibitor drug



Mode of action

Vemurafenib, also known as Velboraf, is a drug used to treat metastatic melanoma patients whose tumours have the $BRAF^{V600E}$ mutation. Approximately 50% of melanoma patients have the $BRAF^{V600E}$ mutation. The drug is given in tablet form and was approved for use in the USA in 2011 and in Europe in 2012.

The drug targets cells that carry the $BRAF^{V600E}$ mutation and inhibits signalling through the mutated BRAF protein. This prevents unregulated cell growth and ultimately leads to apoptosis (cell death) of the tumour cells. Vemurafenib is able to distinguish between cancer cells and normal healthy cells and as a result only targets the tumour cells.

Side effects

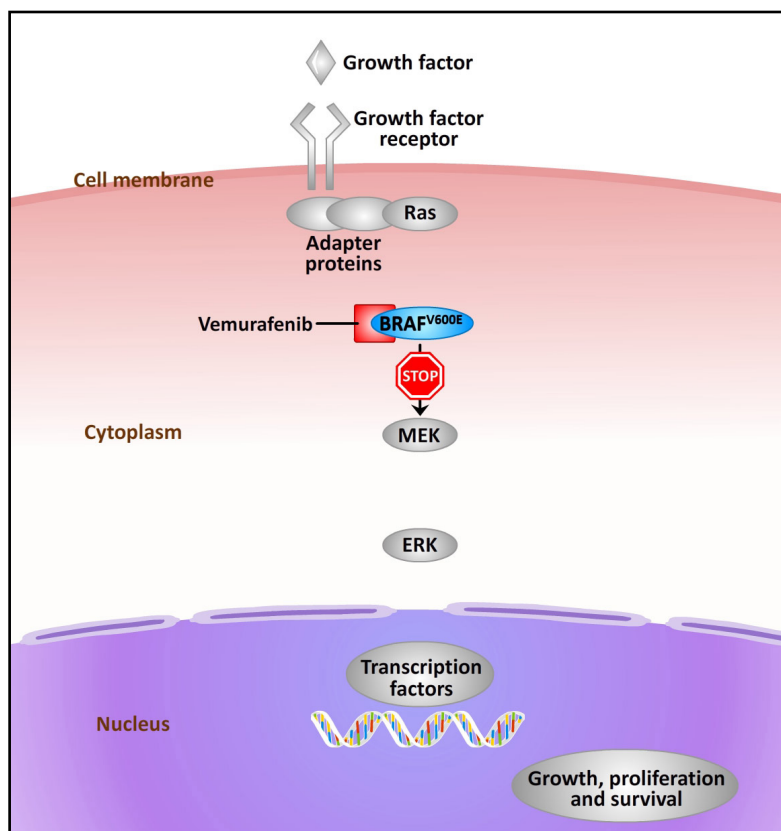
Vemurafenib can cause side effects including:

- fatigue/tiredness
- nausea
- rash or adverse skin reaction
- hair loss
- joint pain
- development of squamous cell carcinoma, a type of non-melanoma skin cancer that can be removed by simple surgery.

Effectiveness

The drug is only appropriate for use in patients that have the $BRAF^{V600E}$ mutation. Diagnostic tests are now available that can identify whether tumours carry the mutation. This ensures that vemurafenib is only prescribed to patients for whom the treatment is likely to be effective.

In clinical trials, vemurafenib has been shown to significantly reduce the risk of the disease progressing and improves overall short term survival for patients with the $BRAF^{V600E}$ mutation. Of the patients who took vemurafenib 84% were still alive 6 months after treatment. This compared with 64% who were treated with dacarbazine (chemotherapy). On average vemurafenib-treated patients experienced a median of 5.3 months without their cancer progressing, i.e. they lived with the disease but it didn't get any worse. This compared to a median of 1.6 months for patients treated with dacarbazine.



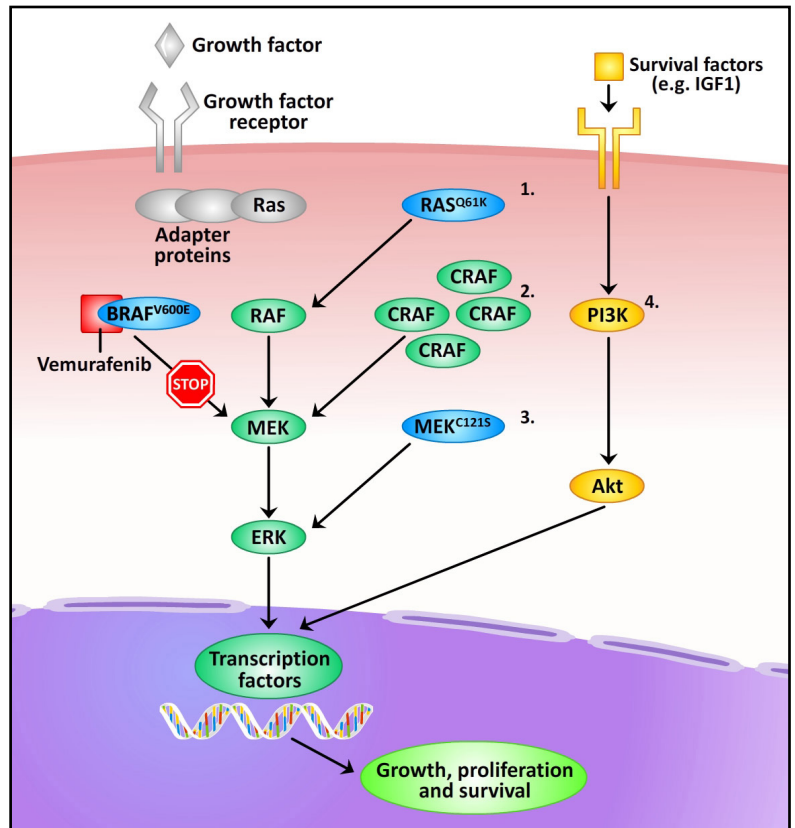
Melanoma information card

BRAF^{V600E} inhibitor drug resistance

Resistance mechanisms

Studies have identified the mechanisms that enable tumour cells to become resistant to vemurafenib. These “escape” pathways are shown below:

1. Mutations of the NRAS protein upstream of BRAF in the MAPK-ERK pathway. This “reactivates” the pathway leading to unregulated cell growth.
2. Over expression (producing too much) of other proteins in the MAPK-ERK pathway, e.g. CRAF. This over expression leads to cell growth and division.
3. Mutations in the MEK protein in the MAPK-ERK pathway. This mutation occurs downstream of BRAF in the MAPK-ERK pathway. This reactivates the pathway leading to uncontrolled cell growth.
4. Activation of receptors at the cell surface membrane allows signalling through alternative pathways leading to unregulated cell division and tumour survival.



Combining therapies

Studies are investigating whether combining BRAF inhibitors with other targeted drug therapies, such as MEK inhibitors, will prevent drug resistance from emerging. Early clinical trials have shown that combining BRAF inhibitors and MEK inhibitors resulted in reduction in tumour size and reduced melanoma growth. It is hoped that combining two therapies will prevent resistance developing and prolong patient survival, improving the results seen with current, single drug therapies. These studies are ongoing.

Combining radiotherapy and the immunotherapy ipilimumab has also been shown to significantly reduce tumour size in a melanoma patient.