What is melanoma?

Let us explain it to you.
MELANOMA: A GUIDE FOR PATIENTS

PATIENT INFORMATION BASED ON ESMO CLINICAL PRACTICE GUIDELINES

This guide for patients has been prepared by the Anticancer Fund as a service to patients, to help patients and their relatives better understand the nature of melanoma and appreciate the best treatment choices available according to the subtype of melanoma. We recommend that patients ask their doctors about what tests or types of treatments are needed for their type and stage of disease. The medical information described in this document is based on the clinical practice guidelines of the European Society for Medical Oncology (ESMO) for the management of melanoma. This guide for patients has been produced in collaboration with ESMO and is disseminated with the permission of ESMO. It has been written by a medical doctor and reviewed by two oncologists from ESMO including the lead author of the clinical practice guidelines for professionals. It has also been reviewed by patient representatives from ESMO’s Cancer Patient Working Group.

More information about the Anticancer Fund: www.anticancerfund.org

More information about the European Society for Medical Oncology: www.esmo.org

For words marked with an asterisk, a definition is provided at the end of the document.
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*This text was written by Dr. Gauthier Bouche (Anticancer Fund) and reviewed by Dr. Svetlana Jezdic (ESMO), Prof. Reinhard Dummer (ESMO), and Prof. Lorenz Jost (ESMO's Cancer Patient Working Group).*

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**DEFINITION OF MELANOMA**

This definition comes from and is used with the permission of the National Cancer Institute (NCI) of the United States of America.

A form of cancer that begins in melanocytes*. Melanocytes* are cells that make the pigment melanin. It may begin in a mole (skin melanoma), but can also begin in other pigmented tissues, such as in the eye or in the intestines.

![Anatomy of the skin](image)

Anatomy of the skin, showing the epidermis*, dermis*, and subcutaneous* tissue. Melanocytes* are located in the layer of basal cells at the deepest part of the epidermis.

**IS MELANOMA FREQUENT?**

Worldwide, cases of melanoma occur most frequently in Australia and New Zealand where it is 3 times more frequent than in Europe. On the other hand, melanoma is very rare in African and Asian countries.

In Europe, about 1 in every 100 people will develop melanoma at some point in their life, but important variations exist from one country to another. About 15 in every 100,000 people are diagnosed with melanoma annually. This number is increasing in almost all European countries. Melanoma is slightly more frequent in females than in males. Melanoma is more frequent in Switzerland, the Netherlands and the Scandinavian countries (Norway, Sweden and Denmark) where about 20 out of 100,000 people are diagnosed each year with melanoma. It is less frequent in Mediterranean countries where 3 to 5 out of 100,000 are diagnosed with melanoma each year.
WHAT CAUSES MELANOMA?

Today, it is not clear why melanoma occurs. Some risk factors* have been identified. A risk factor* increases the risk that cancer occurs, but is neither necessary nor sufficient to cause cancer. A risk factor is not a cause in itself.

Some people with these risks factors will never develop melanoma and some people without any of these risk factors* will develop melanoma.

The main risk factors* of melanoma are:

- **Skin type:** people with fair skin have a higher risk of developing melanoma than people with darker skin. The highest risk concerns people with red hair and freckles. Melanoma is actually very rare in black or Asian people. When it does occur it is usually a special type of melanoma called acral lentiginous melanoma occurring on the palms, soles or under the nails.

- **Naevi:** a naevus* is the medical term for a mole. The majority of moles will never turn into cancer, but the presence of many (more than 100) moles or unusual moles indicates an increased individual risk of developing melanoma.
  - Having multiple common naevi* (like the one in the picture on the right) increases the risk of developing melanoma. The risk increases with the number of naevi* and is particularly high when the number of naevi* is above 100.
  - Having 3 or more atypical naevi* increases the risk of developing melanoma. An atypical naevus* is defined as a naevus* presenting at least 3 of the ‘ABCD’ characteristics: Asymmetry in its shape, Border irregularity or a border which is ill-defined, Colour varying from one area to another and Dynamic evolution over time regarding its shape, colour or size.
  - Congenital naevi* are moles that are present from birth. Large (>5cm) congenital moles are at risk of turning into melanoma. Persons with large congenital naevus* should be followed up on a regular basis.

- **Sun exposure:** natural exposure to ultraviolet (UV)* radiation emitted by the sun is an important risk factor* for melanoma. The following factors increase the risk at every stage of life but are worse when exposure occurs in early childhood.
  - Intermittent sun exposure, usually for recreational purposes, increases the risk of developing melanoma.
  - Sunburn increases the risk of developing melanoma, especially sunburns during childhood.
  - Using sunscreen may reduce the risk of developing melanoma. It should be associated with other simple rules such as avoiding being in the sun between 11 am and 3 pm, and covering up with clothes, a broad hat and sunglasses when exposed to the sun.

- **Sun bed use:** exposure to artificial UV light to get a tan increases the risk of developing melanoma especially when sun beds are used before the age of 30.

- **History of melanoma**
  - Having had melanoma increases the risk of having another melanoma at a different location.
Having a first-degree relative (parents, siblings and children) who had melanoma increases the risk of having melanoma. Some inherited gene mutations* are known, such as the CDKN2A mutation*, but gene mutations* are found in less than 50% of the melanoma families.

- **Age**: the risk of melanoma increases with age although melanoma is less associated with aging than other types of cancer and it can occur in people who are under the age 30.
- **Gender**: in North-America, Oceania and Israel men have a higher risk of developing melanoma while in Europe the risk is slightly higher in women.
- **Immune suppression**: people with lowered immunity are at a higher risk of developing melanoma. Immunity can be lowered because of a disease such as AIDS or because of drugs given after an organ transplant.
- **Xeroderma pigmentosum**: it is a rare and inherited disease in which the ability to repair damage caused by ultraviolet light* is impaired. For these people, the risk of developing all types of skin cancers including melanoma is extremely high.

Other factors, such as exposure to pesticides or having Parkinson’s disease are suspected to be associated with an increased risk of melanoma, but evidence of and reasons for these associations remain unclear.
**HOW IS MELANOMA DIAGNOSED?**

Melanoma is usually diagnosed after a suspicious mole is noticed by the patient, a relative or a doctor. This can happen during a screening or routine skin examination, especially for people with fair skin, red hair, a tendency to burn in the sun and multiple naevi*.

The diagnosis of melanoma is based on the following examinations:

1. **Clinical examination***
   The doctor asks the patient questions, especially regarding possible risk factors*, and about the evolution of the suspicious mole(s). Examination of the suspicious mole(s) and of the rest of the skin is also done. As mentioned above, a suspicious mole presents the ‘ABCD’ characteristics:
   - Asymmetry in its shape
   - Border irregularity or a border which is ill-defined
   - Colour varying from one area to another
   - Dynamics

   Not all melanomas present the 4 characteristics altogether. There are even melanomas without dark colors that present as reddish pimples. In addition, the doctor also feels the lymph nodes* in the groin, armpit, neck, etc. depending on the location of the suspicious mole(s).

2. **Dermoscopy**
   This consists of using a small device called dermoscope or dermatoscope which illuminate and magnify the spots on the skin for a more precise examination. Even if examination with a dermoscope is not always necessary, it enhances the accuracy of diagnosis when performed by an experienced doctor trained to use this technique.

3. **Histopathological* examination after removal of the whole mole.**
   A histopathological* examination is the laboratory examination of the tumor cells by dissecting the tumor. This will confirm the diagnosis of melanoma. The tumor has to be cut out completely and then sent to the laboratory. This is called a skin biopsy* and is done manually by the doctor. First, a local anaesthetic* is injected into the area that is going to be removed. Then, the suspicious mole is removed ensuring a certain margin of normal tissue around and under the tumor is also removed. It is very important that both removal of the mole and laboratory examination are performed by professionals with experience in the treatment of melanoma.
WHAT IS IMPORTANT TO KNOW TO GET THE OPTIMAL TREATMENT?

Doctors will need to consider many aspects of both the patient and the cancer in order to decide on the best treatment.

Relevant information about the patient

- Personal medical history
- History of melanoma in relatives
- Results from the clinical examination* by the doctor including the skin examination, palpation of the lymph nodes* in the relevant area(s) according to the localisation of the melanoma, and any other sign or symptom, which could be related to the local or distant spread of the tumor.
- General well-being

Relevant information about the cancer

- Results of the biopsy*

As mentioned before, the tumor is cut out completely and this skin biopsy is then sent to the laboratory. This laboratory examination is called histopathology*. It is very important that this examination is done in a laboratory experienced with histopathology of melanoma. If the melanoma was not completely removed during the biopsy, the doctor will need to remove the remaining tumor and a second histopathological* examination will then be performed. A histopathological examination of the lymph nodes* possibly removed by surgery will also be performed. It is very important to confirm the results of the biopsy and to provide more information on the cancer. Results of the examination of the biopsy should include:

- **Maximum thickness or Breslow thickness**
  Maximum thickness indicates how deep the tumor has invaded into the skin. It is measured in mm. The following thickness categories are used in the planning of the treatment: less than 1 mm, from 1.01 to 2 mm, from 2.01 to 4 mm and more than 4 mm. The greater the thickness, the worse the prognosis*.

- **Mitotic rate in case of thickness of less than 1mm**
  The mitotic rate indicates how fast the melanoma cells divide. The division of a cell into two new cells is called mitosis. The pathologist counts under the microscope how many of the cells in 1 mm² are actually dividing. This is done a few times on different mm². If, on average, 1 or more cells are dividing per mm², the prognosis* is worse than if less than 1 cell per mm² is dividing.

- **Presence or absence of ulceration**
  Ulceration* means that the melanoma invades the overlying skin. This can be visible to the naked eye, for example when the lesion is bleeding. But this is also checked under a microscope during the laboratory examination. The prognosis* is better when there is no ulceration*.
Presence and extent of tumor regression
In some cases, the pathologist observes signs indicating that the tumor previously regressed in some areas of the biopsy*. This is called tumor regression and means that, previously, the tumor was larger. Little satellites of tumor are groups of cancer cells found close to the tumor, but separated from it by normal tissue. These micro-satellites can also be found as a consequence of this regression phenomenon. Tumor regression might sound like good news at first. Unfortunately it indicates that the tumor was previously larger and may have spread to lymph nodes*.

Positive or negative margins*
The pathologist checks whether the whole tumor has been removed by analysing if the tumor is totally surrounded by normal tissue. This is reported either as negative margins* of resection (meaning that it is very likely that the whole tumor has been removed) or as positive margins* of resection (meaning that it is very likely that the whole tumor has not been removed). For the margins* following the resection of the tumor by surgery, minimal values of margins* are defined and they are described in the following text.

Additional information may be given by the pathologist, such as:

Lymphovascular invasion
The presence of lymphovascular invasion means that tumor cells are found in the blood vessels and in the lymph vessels of the biopsy*. Finding tumor cells in these vessels means that it is more likely that tumor cells have spread to the lymph nodes*, or to other organs.

Tumor-infiltrating lymphocytes*
The presence of lymphocytes* in the tumor, called tumor-infiltrating lymphocytes*, is a sign of an active immune response against the tumor. An active immune response against the tumor is usually associated with a better prognosis*.

Analysis of the mutation(s) present in tumor cells (mutational testing)
For patients whose melanoma has spread to lymph nodes or organs at a distance from the primary tumor, a metastasis is analysed in order to verify the presence or absence of BRAF mutation*. If the BRAF gene is mutated, a treatment with targeted therapy which inhibits the mutation is recommended (for more information see the section on treatment options). Other mutations can be analysed too (NRAS, c-kit), given that this information is important for a possible participation in clinical trials. Analysis of these mutations must be performed in specialized laboratories.

Staging*

Doctors use staging* to assess the spread of the cancer and the prognosis* of the patient. The TNM staging* system is commonly used. The combination of size of the tumor and invasion of nearby tissue (T), involvement of lymph nodes*(N) and metastasis, spread of the cancer to other organs of the body (M), will classify the cancer into one of the following stages as presented in the table below.

The stage is fundamental for the decision on treatment. The more advanced the stage, the worse the prognosis*. Staging* is performed by combining results of clinical examination*, histopathological* examination and sometimes radiological examination which is performed if clinical or histopathological* examinations indicate that the cancer cells may have spread to other places than
the initial skin tumor. Staging* may be done a second time after the results of the histopathological* examination of the lymph nodes* removed by surgery.

The table below presents the different stages for melanoma. The definitions are somewhat technical so it is recommended to ask doctors for more detailed explanations.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Stage 0</td>
<td>The tumor is limited to the epidermis* and has not spread to the dermis* (see picture used in the definition). In addition, no tumor cell is found in the lymph nodes*. Stage 0 melanoma is also called in situ melanoma.</td>
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</table>
| Stage I | The thickness of the tumor is:  
  - Either less than 2 mm in diameter without ulceration*  
  - Or less than 1 mm in diameter but has ulceration* or has invaded the lower layer of the dermis, called reticular dermis or the subcutaneous* fat  
In addition, no tumor cell is found in the lymph nodes*.  
Stage I is divided into stages IA and IB according to the combination of thickness, depth of invasion in the dermis and ulceration*. |
| Stage II | The thickness of the tumor is:  
  - Either more than 1 mm in diameter with ulceration*  
  - Or more than 2 mm in diameter (with or without ulceration*)  
In addition, no tumor cell is found in the lymph nodes*.  
Stage II is divided into stages IIA, IIB and IIC according to the combination of thickness and presence or absence of ulceration*. |
| Stage III | Regardless of tumor thickness and presence of ulceration*, the tumor has spread to the lymph nodes* (lymph node metastasis) or groups of tumor cells are found less than 2 cm away from the initial tumor (satellite metastasis) or on the way from the initial tumor to the lymph nodes* (in-transit metastasis).  
Lymph node, satellite and in-transit metastases are called loco-regional metastasis.  
Stage III is divided into stage IIIA, IIIB and IIIC according to the location, the number and the extent of loco-regional metastases*. |
| Stage IV | The tumor has spread:  
  - Either beyond the regional lymph nodes* to the skin or other lymph nodes*  
  - Or to other organs such as the liver, lungs or brain |
WHAT ARE THE TREATMENT OPTIONS?

Surgery is the main treatment for the vast majority of patients. This is also the only treatment performed for patients with stage 0, stage I and most types of stage II melanomas. Other treatment options include chemotherapy*, immunotherapy*, radiotherapy* and targeted therapies*, either alone or combined.

The extent of the treatment will depend on the stage of the cancer, on the characteristics of the tumor and on the risks for the patient.

Treatments listed below have their benefits, their risks and their contraindications. It is recommended that patients ask their doctors about the expected benefits and risks of every treatment in order to be informed about the consequences of the treatment. For some treatments, several possibilities are available and the choice should be discussed according to the balance between benefits and risks.

Treatment plan for in situ melanoma (Stage 0)

An in situ melanoma is limited to the epidermis* and has not spread beyond it. The treatment consists of removing the tumor.

After the diagnosis has been confirmed by the biopsy*, an excision of the tumor (called wide excision) is performed in order to achieve appropriate safety margins* for a malignant tumor. After injection of a local anaesthetic* around the tumor, the tumor is removed with a margin of 0.5 cm of normal tissue around and below the tumor.

It is sometimes possible that the biopsy performed to make the diagnosis succeeds in removing the complete tumor with the appropriate margins. The biopsy is then called excisional biopsy and no further intervention is needed.

Treatment plan for stage I to stage III melanoma

Stage I and stage II melanomas do not spread to the lymph nodes* while stage III melanomas do. The most important treatment consists of a complete removal of the melanoma and of the lymph nodes* where cancer cells have spread. When the clinical and radiological examinations* do not show spreading of the cancer to the lymph nodes* or when it is unclear, a procedure called sentinel lymph node biopsy* is usually needed and performed during the same surgical intervention.

Surgery

After the diagnosis has been confirmed by the biopsy, an excision with a safety margin of the tumor (called wide excision) is performed in order to achieve appropriate safety margins* for a malignant tumor. When the clinical and radiological examinations* do not show spreading of the cancer to the lymph nodes* or when it is unclear, a procedure called sentinel lymph node biopsy* is usually performed during the same surgical intervention. When it is clear that the cancer has spread to the
lymph nodes*, the removal of all regional lymph nodes* is performed during the same surgical intervention. The operation is usually performed under general anaesthesia* but can sometimes be performed under local anaesthesia* depending on the location of the melanoma and on the decision of the anaesthesiologist and surgeon.

**The tumor is removed**

- with a margin of 1 cm of normal tissue around and below the tumor when the tumor thickness is 2 mm or less;
- with a margin of 2 cm of normal tissue around and below the tumor when the tumor thickness is more than 2 mm. The margins* may be smaller when the melanoma is located on the face (for aesthetic reasons) or on other places like palm, sole of the foot or under the nail for reasons related to the healing of wounds.

**One or several lymph nodes* may be removed**

**Sentinel lymph node biopsy** is a procedure performed for all stage I and stage II patients, except for patients whose tumors are 1 mm thick or less.

After injection of a marker near the tumor, the marker will naturally be led to lymphatic vessels and then to lymph nodes*. With the help of a probe*, the surgeon will be able to identify in which lymph node(s) the marker is located. Since the tumor cells (if they were to spread) would also first be led to these lymph nodes, the surgeon will remove the lymph node(s) to check if cancer cells are present. A rapid examination of the lymph nodes* will be made while the patient is still in surgery. If cancer cells are found in the lymph node(s), the surgeon will remove other lymph nodes* in the same area.

This sentinel lymph node biopsy* helps doctors to be more accurate in defining the stage of the cancer, but there is no evidence that it has any therapeutic role.

**Extensive lymph node dissection** of the surrounding lymph node region(s) is performed for patients for whom it is suspected according to the clinical or radiological examination that the tumor spread to the lymph nodes*. This consists of removing all lymph nodes* in the region(s) towards which the lymph vessels around the tumor are directed.

**Adjuvant* therapy**

An adjuvant* therapy is a therapy given in addition to surgery. No adjuvant* therapy is needed for stage I and stage II A.

**Adjuvant* therapy when surgical removal of tumor and lymph nodes* involved is complete**

For patients with stage IIB, stage IIC and stage III melanoma for which the surgery removed all lymph nodes*, there is no standard adjuvant* therapy. The only adjuvant* therapy option today is a synthetic form of interferon-alfa*. Interferon-alfa* is a natural substance produced by the white blood cells and involved in the immune response against viruses, bacteria and tumor cells. Interferon-alfa* used as a treatment is a synthetic interferon* produced in the laboratory. It is injected into the body with the goal of improving the immune response, in this case, against tumor cells. Interferon-alfa is not suitable for long-term therapy (maximum 1 year) but another form, called
peg-interferon-alfa* has been shown to be more suitable (up to 5 years). High-dose interferon-alfa as well as peg-interferon-alfa can delay the time before the cancer comes back. An impact on life expectancy of the patients has been shown for patients with an ulcerated melanoma at diagnosis or with micrometastases in the lymph nodes. Therefore, it can be recommended when high-dose interferon-alfa or peg-interferon-alfa is well tolerated.

Without documented metastases to organs, chemotherapy*, mistletoe extracts and hormone therapies are not beneficial. Immunotherapy* with interleukin-2*, cancer vaccines*, BRAF-inhibitors or any combination are experimental and not to be used outside of controlled clinical trials. In general, since there is no consensus on what the best adjuvant* therapy, if any, could be, adjuvant* therapies should be preferentially given in the context of clinical trials* in specialised centres.

**Additional treatments when surgical removal is not complete**

In some cases, it is not possible to remove the whole tumor and all loco-regional metastases* by surgery. In such a situation, other therapies can help to kill the remaining cancer cells still present locally. This can be done by radiotherapy* or by local application of high dose chemotherapy* if the melanoma is located on the arm or leg.

Radiotherapy* uses radiation to damage and kill cancer cells. Radiation is produced by an external source and then directed at the tumor at the lymph nodes*. There are two main situations where radiotherapy* can be used to control the (re-)growth of the tumor when surgery could not remove all tumor cells:

1. Lentigo maligna melanoma is a special type of melanoma, usually large and occurring in the elderly. Either because patients are too old or because the melanoma is too large, complete removal may not be feasible.
2. Incomplete removal of loco-regional metastases* (satellite, in-transit or lymph nodes*) because they are too large or there are too many of them. However, studies have failed to show that radiotherapy in such situations provides a benefit in extending survival. Control of the growth of the local tumor can, however, be improved by radiotherapy.

Isolated limb perfusion is a surgical technique aiming at injecting a high dose of chemotherapy* into the limb (arm or leg) where the melanoma is located. This requires a temporary derivation of the blood circulation to and from the limb by surgery. Different drugs can be injected into the isolated limb and the most common are melphalan, TNF-alfa or both. Thanks to this technique, high concentrations of these drugs can be obtained in the limb with very limited diffusion to the rest of the body. This therapy is complicated and should be restricted to experienced centres.

**Treatment plan for stage IV melanoma**

*Stage IV melanomas have spread either beyond the regional lymph nodes* to the skin or other lymph nodes* (for example, spreading to the skin of the abdomen for an initial melanoma on the leg) or to distant organs, such as the liver, lungs or brain.*

Patients with stage IV melanoma should be treated in centres with broad experience in dealing with this disease. Whenever possible, they should be treated in the context of clinical trials*. In the recent years, several drugs showed a clear benefit for some patients with stage IV melanoma. Two drugs are
now approved in Europe, namely ipilimumab* and vemurafenib*. There are continuously new experimental treatment options for patients with metastatic melanoma being made available.

The treatment options for patients with stage IV melanoma depend on the number and type of metastases* and on the presence or absence of BRAF mutation*. It is recommended that the decision for treatment is based on discussion in an inter-disciplinary team of medical professionals. This meeting of different specialists is called multidisciplinary opinion* or the tumor board review. In this meeting, the planning of treatment will be discussed according to the relevant information about the patient, about the extent of the cancer and about previous treatments. The written decision of the tumor board must be accessible to the patient.

Single metastasis

A single metastasis may be removed by surgery, especially in the brain, the lung and the liver. This requires that the person is in good health. A single metastasis in the brain can also be treated by a special type of radiotherapy* that targets precisely the metastasis to avoid radiation reaching the normal brain tissue around the tumor. This is called stereotactic radiosurgery. Depending on the location of the brain metastasis, it can sometimes be preferred over neurosurgery. When surgery is not feasible, another option is the use of a combination of chemotherapy* and immunotherapy*, if possible within a clinical trial*. The drugs available are listed in the following sections.

Multiple metastases*

When there are multiple metastases* in the body, surgery is rarely possible. It may be appropriate for some people who are in good shape and depending on the location and extent of the metastases*, but this treatment is rarely feasible or useful. Therefore, the goal of the treatment is to target the cancer cells all over the body. This is done with targeted therapy*, immunotherapy* which helps the immune system to recognise and destroy cancer cells, or chemotherapy* which is directly toxic to cancer cells.

Targeted therapy

When analysis of the tumor has shown that the tumor cells presented a BRAF mutation*, vemurafenib*, an inhibitor of BRAF, is the preferred first option in patients with metastases. Vemurafenib gives a high chance for a rapid response including improvement of the quality of life. Vemurafenib can also be used safely in patients with brain metastases, where in some cases it shows some effectiveness. Vemurafenib seems to be effective even after the immunotherapy treatment with ipilimumab* (described further in this text).

Chemotherapy* and immunotherapy*

If clinical trials or recently approved targeted therapies are not available, the following drugs can generally be used in the first place:

- Chemotherapy: dacarbazine*, temozolomide*, paclitaxel*, fotemustine*, carboplatin*, cisplatin* and vindesine*
- Immunotherapy using cytokines: interleukin-2* and interferon-alfa*.

Dacarbazine is still considered a reference drug in this situation. If the melanoma is spreading rapidly and cause many symptoms, the use of combination of paclitaxel and carboplatin, or cisplatin,
Vindesine and dacarbazine can help to decrease or even stop the spreading of the cancer. Some centers still use interleukin-2 alone as the first treatment option when the tumor volume is small, even if there is no large randomized clinical trial that has evaluated its efficacy.

In case a first treatment using one or a combination of the abovementioned options failed, ipilimumab* or participation in clinical trials are the main options. Other chemotherapies and immunotherapies mentioned above can also be used but are of limited usefulness.

Ipilimumab is an antibody which, once injected, helps the white blood cells to recognize and attack cancer cells. In Europe, it can be used to treat patients with advanced melanoma that cannot be surgically resected, yet only after a first chemotherapy or immunotherapy treatment has failed.

**Radiotherapy**
External radiotherapy* can be used to relieve the symptoms and pain caused by brain or bone metastases*.

### New promising therapies
Several other drugs have shown promising results, even though they are not yet available in the clinic. Access to these drugs can only be obtained within clinical trials.

- Combination of treatment with BRAF inhibitor* dabrafenib* and MEK inhibitor* trametinib* has shown that it can delay resistance to the treatment in patients with a BRAF mutated* melanoma.
- Imatinib has shown it could decrease the size of the tumor or stabilize the disease in some patients with melanoma harbouring a c-kit mutation.
- Immunotherapy using anti-PD1 antibodies* has demonstrated antitumor activity in early phase of clinical trials.
- Nanoparticle* albumin-bound paclitaxel* is a chemotherapeutic drug that showed promising activity in patients with advanced melanoma.

It seems that patients with metastatic melanomas carrying NRAS mutation* could benefit from MEK inhibition* therapy but more research is needed to confirm these findings.
WHAT ARE THE POSSIBLE SIDE EFFECTS OF THE THERAPIES?

All targeted*, chemotherapy* and immunotherapy* drugs have frequently side effects.

**Side effects of chemotherapy**

Side effects of chemotherapy* are very frequent. They will depend on the drug(s) administered, on the doses and on individual factors. Combinations of different drugs usually lead to more side effects than the use of a single drug.

The most frequent side effects of the drugs used for chemotherapy* are hair loss and decreased blood cell count. Decreased blood cell count can result in anaemia*, bleeding and infections. Once the chemotherapy* is over, the hair grows back and the blood cell count returns to normal.

Other frequent side effects include:

- allergic reactions, such as flushing and rash
- nerve problems affecting the hands and/or feet (peripheral neuropathy), which can cause tingling feelings in the skin, numbness and/or pain
- temporary loss of or changes in your eyesight
- ringing in the ears or changes in your hearing
- low blood pressure
- nausea, vomiting and diarrhea
- inflammation of areas such as the lining of the mouth
- loss of sense of taste
- lack of appetite
- slow heart beat
- dehydration
- mild changes in nails and skin which soon disappear
- painful swelling and inflammation where the injection is given
- muscle or joint pain
- seizures
- tiredness

Other less frequent but more serious side effects can occur. These include especially, stroke, myocardial infarction and damage to the function of the kidneys and liver.

Any of these symptoms should be reported to a doctor.

**Side effects of vemurafenib***

Side effects of vemurafenib are frequent. The most common symptoms are:

- joint pain
- severe sensitivity to sunlight – therefore a strong UV protection must be applied
- reduced Hair growth
- rash
- skin itching
- skin cancers including new squamous cell carcinomas and rarely new skin melanomas
- warts
- feeling tired
- headache
- nausea
- diarrhea

Other less common side effects include:

- dry skin
- redness of the skin
- loss of appetite
- weight loss
- vomiting
- constipation
- muscle pain
- back pain
- fever
- swelling in the hands or feet
- weakness
- changes in taste
- cough
- sunburn
- abnormal blood test results of the liver function
- inflammation in veins
- numbness or tingling in the hands or feet

Rare but severe side effects include allergic reactions, severe skin reactions, changes in heart rhythm and eye problems.

Patients treated with vemurafenib should be carefully followed with special attention to skin and other secondary cancers.

**Side effects of immunotherapy**

**Side effects of interleukin-2* and interferon-alpha**
The following symptoms are very frequent with these therapies. Their occurrence mainly depends on the dose administered.

- fever and chills or flu-like symptoms. The severity decreases over time, particularly in low-dose regimens.
- generalized flushing (redness) of the face and body, or skin rash.
- nausea or vomiting
- fatigue
- lowered blood pressure
- diarrhea
- low white blood cells, red blood cells and platelets counts, resulting in an increased risk for infection, anemia or bleeding, respectively
- changes in mental status, such as confusion, drowsiness or memory loss
- fast or irregular heartbeats
- lowered urine output
- changes in liver function
- temporary low calcium, high glucose, or high triglyceride levels
- generalized aches and pains
- swelling of the face, ankles or legs
- hair loss (only with interferon-alfa)

The following are less common (occurring in 10 to 29%) side effects:
- breathing difficulty
- itching
- mouth sores
- poor appetite
- taste changes (only with interferon-alfa)
- depression
- weight gain or loss
- infection
- dizziness
- dry or peeling skin
- injection site reactions when administered under the skin (sub-cutaneous)
- anxiety and irritability

A serious, but very uncommon side effect of interleukin-2* in high doses is "capillary leak syndrome" or "vascular leak syndrome." Capillary leak syndrome is a potentially serious condition in which fluids within the veins and capillaries leaks into the tissue outside the bloodstream. This results in low blood pressure and poor blood flow to the internal organs.

Your doctor will monitor these things carefully. You should notify your doctor immediately if you notice dizziness, sudden swelling or rapid weight gain, little or no urine output (for 8-12 hours), shortness of breath, difficulty breathing, irregular heartbeats, chest pain or if you feel unexpectedly depressed.

**Side effects of ipilimumab**

During the treatment with ipilimumab, a unique set of adverse events may occur called immune-related adverse events. Early recognition of immune-related adverse events and initiation of treatment are critical to reduce the risk of sequelae*.

These side effects are most likely to begin during treatment; however, side effects can show up months after the last infusion.

- Inflammation of the intestines (colitis) that may even very infrequently cause tears or holes (perforation) in the intestines. Signs and symptoms of colitis may include diarrhea, blood in the stools, stomach pain or tenderness.
- Inflammation of the liver (hepatitis) that can lead to liver failure. Signs and symptoms of hepatitis may include yellowing of your skin or the whites of your eyes, dark urine (tea colored), nausea or vomiting, pain on the right side of the stomach and bleeding or bruise more easily than normal.
- Inflammation of the skin that can lead to severe skin reaction (toxic epidermal* necrolysis). Signs and symptoms of skin reactions may include skin rash with or without itching, mouth sores, skin blisters and/or peels.
- Inflammation of the nerves that can lead to paralysis. Symptoms of nerve problems may include unusual weakness of legs, arms, or face, numbness or tingling in hands or feet.
- Inflammation of hormone glands (especially the pituitary, adrenal, and thyroid glands) that may affect how these glands work. Signs and symptoms that your glands are not working properly may include persistent or unusual headaches, unusual sluggishness, feeling cold all the time, weight gain, changes in mood or behaviour such as decreased sex drive, irritability, or forgetfulness, dizziness or fainting.
- Inflammation of the eyes. Symptoms may include blurry vision, double vision, or other vision problems, eye pain or redness.

Contact the responsible doctor who is leading the therapy if you have any of these signs or symptoms or if they get worse. Do not try to treat symptoms yourself. Other physicians may not be familiar with the peculiar side effects of this drug.

Getting medical treatment right away may keep the problem from becoming more serious. Your doctor should order blood tests, such as liver and thyroid function tests, before starting and during treatment with ipilimumab. Your oncologist may decide to delay or stop ipilimumab.
WHAT HAPPENS AFTER THE TREATMENT?

Follow-up* with doctors

After the treatment has been completed, doctors propose a follow-up* program consisting of consultations on a regular basis and aiming to:

- detect possible recurrence* at an early stage
- recognize new skin tumors, melanoma as well as non-melanoma tumors since they share the same main risk factors*
- evaluate treatment-related complications and treat them
- provide psychological support and information to enhance returning to normal life

Follow-up* visits with the oncologist should include history-taking and clinical examination*. No radiological examination or blood tests are necessary for the majority of patients, especially for those patients treated for a thin melanoma. According to the stage of the cancer or to the results of the clinical examination*, additional radiological exams may be performed. Ultrasound* of lymph nodes, computed tomography (CT)* or whole body positron emission tomography scans (PET)* or PET–CT scans may lead to an earlier diagnosis of relapses, in patients at higher risk of relapse, i.e. patients with an initial thick primary melanoma or patients treated for metastases. However, an impact of these examinations on the life expectancy has not been demonstrated yet. Tests measuring the level of S-100 protein* and lactate dehydrogenase (LDH)* in the blood are sometimes used to detect recurrence* of the cancer, but it is unclear whether it really helps or not.

Return to normal life

It can be hard to live with the idea that the cancer can come back. Based on what is known today, there are a few simple rules that are recommended:

- To reduce the risk of recurrence* after completion of the treatment:
  - Avoid sunburn
  - Avoid unprotected solar exposure
  - Avoid artificial ultraviolet light
- To detect early any suspicious moles or recurrence* of the melanoma
  - Regular self-examinations of the skin for the rest of one’s life
  - Regular self-examinations of the lymph nodes* for the rest of one’s life

As a consequence of the cancer itself and of the treatment, the return to normal life may not be easy for some people. Questions related to body image, sexuality, fatigue, work, emotions or lifestyle may be a concern. Discussing these questions with relatives, friends or doctors may be helpful. Support from ex-patients’ groups or telephone information and helplines is available in many countries.

It is also important to inform members of the family (parents, siblings and children) who are at an increased risk of developing melanoma. A regular examination of their skin by themselves and by a
doctor should be organized to detect and remove any suspicious moles as early as possible. Genetic testing is not needed.

What if the cancer comes back?

If the cancer comes back, it is called a recurrence* or relapse. The treatment depends on the extent of the recurrence*. The extension of the recurrence* should be fully evaluated through physical examination, radiological examination and blood tests.

The treatment options will depend on the extent of the recurrence*. Discussion of treatment options should be done in a multidisciplinary meeting.

If it comes back as a local recurrence* on the skin or in the lymph nodes*

The treatment decision will be based on the same elements as the first time, especially the extent of the cancer in the skin and in the lymph nodes*. The treatment will follow the same recommendations as previously described.

If it comes back as a recurrence* with distant metastasis

The treatment plan for this type of recurrence* will be discussed according to what is presented in the paragraph ‘Treatment plan for stage IV melanoma’.

If it comes back as another melanoma

About 8% of people who have had a melanoma develop a second melanoma within 2 years of the diagnosis of the first one. When a second melanoma occurs, the treatment depends mainly on its extent, as described previously. It will be treated as if it is a first melanoma.

If it comes back as another skin cancer

Basal cell cancer and squamous cell cancer of the skin are more frequent than melanomas and share approximately the same risk factors* as melanoma. Exposure of fair skin to UV light is a common risk factor*. These two types of cancer are less aggressive than melanomas and usually grow slowly, but if they are left untreated, they can cause serious damage locally and may rarely involve lymph nodes* and other organs. They can be easily treated if they are diagnosed at an early stage, by removing them by surgery, cryosurgery* or several other local therapies.

Since treatment with vemurafenib* increases the risk of developing these types of skin cancer, patients treated with vemurafenib should be carefully followed up to detect early any new skin lesion.
DEFINITIONS OF MEDICAL TERMS

Adjuvant
The term adjuvant in cancer refers to a therapy that helps another therapy to reach its ultimate goal and reinforces its effect. For example radio and/or chemotherapy assist a surgery in accomplishing its goal of eliminating a cancerous tumor. In contexts other than oncological ones it can also be an agent added to vaccines to stimulate the immune system’s response to the antigen.

Anaemia
Condition characterized by the shortage of red blood cells or hemoglobin, the iron that contains the hemoglobin carries oxygen from the lungs to the whole body, this process is diminished in this condition.

Anaesthesia
A reversible state of loss of awareness in which the patient feels no pain, has no normal reflexes, and responds less to stress, induced artificially by the employment of certain substances known as anaesthetics. It can be complete or partial and allows patients to undergo surgery.

Anti-PD1 antibody
Antibody that targets proteins in human cells called PD1 (Programmed death 1). Blocking PD1 has been studied as an immune system booster. PD1 blockade has been shown to have antitumor activity.

Biopsy
The removal of cells or tissues for examination by a pathologist. The pathologist may study the tissue under a microscope or perform other tests on the cells or tissue. There are many different types of biopsy procedures. The most common types include: (1) incisional biopsy, in which only a sample of tissue is removed; (2) excisional biopsy, in which an entire lump or suspicious area is removed; and (3) needle biopsy, in which a sample of tissue or fluid is removed with a needle. When a wide needle is used, the procedure is called a core biopsy. When a thin needle is used, the procedure is called a fine-needle aspiration biopsy.

BRAF mutation
A specific mutation (change) in the BRAF gene, which makes a protein that is involved in sending signals in cells and in cell growth. This BRAF gene mutation may be found in some types of cancer, including melanoma and colorectal cancer. It may increase the growth and spread of cancer cells. Checking for this BRAF mutation in tumor tissue may help to plan cancer treatment.

Cancer vaccine
A vaccine used to help the immune system to recognize and attack cancer cells. It can either be used to prevent the development of cancer (preventive vaccine) or to treat the cancer (therapeutic vaccine).

Carboplatin
A drug that is used to treat advanced ovarian cancer that has never been treated or symptoms of ovarian cancer that has come back after treatment with other anticancer drugs. It is also used with other drugs to treat advanced, metastatic, or recurrent non-small cell lung cancer and is being
studied in the treatment of other types of cancer, as it is the case of melanoma. Carboplatin is a form of the anticancer drug cisplatin* and causes fewer side effects in patients. It attaches to DNA in cells and may kill cancer cells. It is a type of platinum compound.

CDKN2A mutation
CDKN2A (or p16, or MTS-1) gene is a gene that encodes a tumor suppressor protein called cyclin-dependent kinase inhibitor 2A. Mutations or abnormal changes in this gene increase the risk of developing a variety of cancers, notably melanoma.

Chemotherapy
A type of cancer treatment using drugs that kill cancer cells and/or limit their growth. These drugs are usually administered to the patient by slow infusion into a vein but can also be administered orally, by direct infusion to the limb or by infusion to the liver, according to cancer location.

Cisplatin
A drug used to treat many types of cancer. Cisplatin contains the metal platinum. It kills cancer cells by damaging their DNA and stopping them from dividing. Cisplatin is a type of alkylating agent.

Clinical examination
The examination of the body to search for signs of disease.

Clinical trial
A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called a clinical study.

Computed tomography (CT scan)
A form of radiography in which body organs are scanned with X-rays and the results are synthesised by a computer to generate images of parts of the body.

Cryosurgery
A minimally invasive treatment that uses extreme cold to freeze and destroy diseased tissue, including cancer cells.

Dabrafenib
Anticancer drug used to treat melanoma considered unresectable or metastatic melanoma with BRAF mutation*. It might inhibit the proliferation of tumor cells that have BRAF mutations. It inhibits the mutation of the BRAF gene, which normally, when it is not mutated, plays a role in the regulation of cell growth.

Dacarbazine
A drug that is used to treat Hodgkin lymphoma and malignant melanoma and is being studied in the treatment of other types of cancer. It attaches to DNA in cells and may kill cancer cells. It is a type of alkylating agent.

Dermis
The inner layer of the two main layers of the skin. The dermis has connective tissue, blood vessels, oil and sweat glands, nerves, hair follicles, and other structures. It is made up of a thin upper layer called the papillary dermis, and a thick lower layer called the reticular dermis.
Epidermis
The outer layer of the two main layers of the skin.

Follow-up
Monitoring a person's health over time after treatment. This includes keeping track of the health of people who participate in a clinical study or clinical trial for a period of time, both during the study and after the study ends.

Fotemustine
A substance used in the treatment of some brain tumors and metastatic melanoma. It is approved in some European countries including France and Belgium.

Histopathology
The study of diseased cells and tissues using a microscope.

Immunotherapy
Treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases. Also used to lessen certain side effects that may be caused by some cancer treatments. Agents used in immunotherapy include monoclonal antibodies, growth factors, and vaccines. These agents may also have a direct antitumor effect. Also called biological response modifier therapy, biological therapy, biotherapy, and BRM therapy.

Interferon
A protein made by lymphocytes and involved in the communication between immune cells. A biological response modifier (a substance that can improve the body's natural response to infections and tumor cells). There are several types of interferons, including interferon-alpha, -beta, and -gamma. The body normally produces these substances. They are also made in the laboratory to treat cancer and other diseases.

Interferon-alpha
A type of interferon* which is a protein made by lymphocytes and involved in the communication between immune cells. It is a biological response modifier (a substance that can improve the body's natural response to infections and tumor cells). The body normally produces this substance. It is also made in the laboratory to treat cancer and other diseases.

Interleukin-2
One of a group of related proteins made by leukocytes (white blood cells) and other cells in the body. Interleukin-2 is made by a type of T lymphocyte. It increases the growth and activity of other T lymphocytes and B lymphocytes, and affects the development of the immune system. Aldesleukin (interleukin-2 made in the laboratory) is being used as a biological response modifier to boost the immune system in cancer therapy. Interleukin-2 is a type of cytokine. Also called IL-2.

Ipilimumab
A drug used to treat melanoma that has spread to other parts of the body or that cannot be removed by surgery. It is also being studied in the treatment of other types of cancer. Ipilimumab binds to a substance called CTLA-4, which is found on the surface of T cells (a type of white blood cell). Ipilimumab may block CTLA-4 and help the immune system kill cancer cells. It is a type of monoclonal antibody.
Lactate dehydrogenase (LDH)
One of a group of enzymes found in the blood and other body tissues and involved in energy production in cells. An increased amount of lactate dehydrogenase in the blood may be a sign of tissue damage and some types of cancer or other diseases. Also called lactic acid dehydrogenase.

Lymphocyte
A type of white blood cell that is essential in the immune system. The three major types of lymphocyte are T cells, B cells and natural killer (NK) cells which all have their own roles in the immune system.

Lymph node
A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Lymph nodes* filter lymph and they store lymphocytes*. They are located along lymphatic vessels. Also called lymph gland.

Margin
The edge or border of the tissue removed in cancer surgery. The margin is described as negative or clean when the pathologist finds no cancer cells at the edge of the tissue, suggesting that all of the cancer has been removed. The margin is described as positive or involved when the pathologist finds cancer cells at the edge of the tissue, suggesting that all of the cancer has not been removed.

MEK inhibitor
A substance being studied in the treatment of several types of cancer. MEK inhibitor blocks proteins needed for cell growth and may kill cancer cells. It is a type of protein kinase inhibitor.

Melanocyte
A type of cell located in the bottom layer of the skin, in the eyes, and in other parts of the body. Melanocytes* produce melanine, a substance that is important for skin and eye colour.

Metastasis
The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a metastatic tumor or a metastasis. The metastatic tumor contains cells that are like those in the original tumor.

Multidisciplinary opinion
A treatment planning approach in which a number of doctors who are experts in different specialties (disciplines) review and discuss the medical condition and treatment options of a patient. In cancer treatment, a multidisciplinary opinion may include that of a medical oncologist (who provides cancer treatment with drugs), a surgical oncologist (who provides cancer treatment with surgery), and a radiation oncologist (who provides cancer treatment with radiation). Also called tumor board review.

Mutation
A change in the sequence of base pairs in the DNA that makes up a gene. Mutations* in a gene do not necessarily change the gene permanently.

Nanoparticle
A microscopic particle with at least one dimension less than 100 nm.
Naevus
The medical term for a mole.

NRAS mutation
Abnormal change in the gene NRAS. This mutation activates a reaction in cells that results in proliferation and promotion of tumor growth.

Paclitaxel
A drug used to treat breast cancer, ovarian cancer, and AIDS-related Kaposi sarcoma. It is also used together with another drug to treat non-small cell lung cancer. Paclitaxel is also being studied in the treatment of other types of cancer. It blocks cell growth by stopping cell division and may kill cancer cells. It is a type of antimitotic agent.

Peg-interferon-alfa
It is interferon-alfa* linked to a substance called PEG, which makes the drug stay longer in the body.

Positron emission tomography (PET) scan
A procedure in which a small amount of radioactive glucose (sugar) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is used. Because cancer cells often use more glucose than normal cells, the pictures can be used to find cancer cells in the body.

Probe
It is a long and thin instrument used to explore wounds, cavities or body passages.

Prognosis
The likely outcome or course of a disease; the chance of recovery or recurrence*.

Radiotherapy
A therapy in which radiation is used in the treatment of cancer always oriented to the specific area of the cancer.

Recurrence
Cancer or disease (usually auto-immune) that has come back, usually after a period of time during which the cancer or disease was not present or could not be detected. This may happen at the same location as the original (primary) tumor or to another location in the body. Also called recurrent cancer or disease.

Risk factor
Something that increases the chance of developing a disease. Some examples of risk factors* for cancer are age, a family history of certain cancers, use of tobacco products, being exposed to radiation or certain chemicals, infection with certain viruses or bacteria, and certain genetic changes.

S-100 protein
A protein that is made by many different types of cells and is involved in processes that take place both inside and outside of the cell. It is produced in larger amounts in patients with inflammatory diseases such as rheumatoid arthritis, and in patients with some types of cancer.
**Sentinel lymph node biopsy**
Removal and examination of the sentinel node(s) (the first lymph node(s) to which cancer cells are likely to spread from a primary tumor). To identify the sentinel lymph node(s), the surgeon injects a radioactive substance, blue dye, or both near the tumor. The surgeon then uses a probe* to find the sentinel lymph node(s) containing the radioactive substance or looks for the lymph node(s) stained with dye. The surgeon then removes the sentinel node(s) to check for the presence of cancer cells.

*Sentinel lymph node biopsy* of the skin. A radioactive substance and/or blue dye is injected near the tumor (first panel). The injected material is detected visually and/or with a probe* that detects radioactivity (middle panel). The sentinel nodes (the first lymph nodes to take up the material) are removed and checked for cancer cells (last panel).

**Sequelae**
The consequences of a particular condition or therapeutic intervention.

**Staging**
Performing exams and tests to determine the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. It is important to know the stage of the disease in order to plan the best treatment.

**Subcutaneous**
Beneath the skin.

**Temozolomide**
Temozolomide belongs to a group of anticancer medicines called alkylating agents. In the body, temozolomide is converted to another compound called MTIC. MTIC binds to the DNA of cells while they are reproducing, which stops cell division. As a result, the cancer cells cannot divide, slowing down the growth of tumours.

**Trametinib**
Anticancer drug used to treat unresectable or metastatic melanoma with BRAF mutation*. It is administered orally as a single agent. Trametinib is not indicated in patients that have previously received BRAF inhibitor therapy.
Ulceration
The development of an ulcer which is a break on the skin, in the lining of an organ, or on the surface of a tissue.

Ultrasound
A procedure in which high-energy sound waves are bounced off internal tissues or organs and make echoes. The echo patterns are shown on the screen of an ultrasound machine, forming a picture of body tissues called a sonogram. Also called ultrasonography.

Ultraviolet light (UV)
Ultraviolet light is electromagnetic radiation with a wavelength shorter than that of visible light, but longer than X-rays, in the range of 400 to 100 nm.

Vemurafenib
Vemurafenib is an inhibitor of BRAF, a protein involved in stimulating cell division. In melanoma tumours with the BRAF V600 mutation of the BRAF gene, an abnormal form of the BRAF protein is present which plays a role in the development of the cancer by allowing uncontrolled division of the tumour cells. By blocking the action of the abnormal BRAF protein, vemurafenib helps to slow down the growth and spread of the cancer. Vemurafenib is only given to patients whose melanoma tumours are caused by the BRAF V600 mutation.

Vindesine
An anticancer drug that belongs to the family of plant drugs called vinca alkaloids. It prevents cancer cells from dividing.
The ESMO / Anticancer Fund Guides for Patients are designed to assist patients, their relatives and caregivers to understand the nature of different types of cancer and evaluate the best available treatment choices. The medical information described in the Guides for Patients is based on the ESMO Clinical Practice Guidelines, which are designed to guide medical oncologists in the diagnosis, follow-up and treatment in different cancer types. These guides are produced by the Anticancer Fund in close collaboration with the ESMO Guidelines Working Group and the ESMO Cancer Patient Working Group.

For more information please visit www.esmo.org and www.anticancerfund.org