STAGE 4 MELANOMA

What are the aims of this leaflet?

This leaflet provides some general information on melanoma skin cancer. In particular it tells you what stage 4 melanoma is and what might be the investigations/treatments. This leaflet will be relevant to the majority of patients with stage 4 melanoma but not necessarily all. Details on where to find out more information are provided at the end of the leaflet.

What is melanoma?

Melanoma is a type of skin cancer, which arises from the pigment cells (melanocytes) in the skin. One of the most important causes of melanoma is exposure to too much ultraviolet light in sunlight. The use of artificial sources of ultraviolet light, such as sunbeds, also increases the risk of getting a melanoma.

Melanocytes make a brown/black pigment (known as melanin), and often the first sign of a melanoma developing is a previous mole changing in colour or a new brown/black lesion developing on the skin. Most frequently there is darkening in colour but occasionally there is loss of pigmentation with pale areas or red areas developing. Occasionally melanomas have no pigment and appear just a pink/red colour. The development of this melanoma on the skin is known as the primary melanoma.

Melanoma is considered to be the most serious type of skin cancer because it is more likely to spread (metastasise) from the skin to other parts of the body than other types of skin cancer. If melanoma has spread to other parts of the body, those deposits are known as secondary melanoma (secondaries/metastases).

What is stage 4 melanoma?

The AJCC (American Joint Committee on Cancer) system is currently used in the UK to stage melanoma from 1 to 4. Stage 1 is the earliest melanoma and stage 4 is the most advanced.

Stage 1 and 2 melanomas are present in the skin only and have not spread elsewhere in the body. Stage 3 have spread towards or have reached the draining lymph glands (nodes) and Stage 4 melanomas are those that have spread beyond the closest draining lymph glands to other parts of the body.

Stage 4 melanoma is a form of secondary melanoma where melanoma has spread to distant skin sites, distant lymph nodes (glands) and/or internal organs such as the liver, lungs, bones and brain (distant metastases).

What are the symptoms?

When stage 4 melanoma is diagnosed after a scan, there may be no symptoms at all, and it can be difficult to believe the cancer has spread. However, people with stage 4 melanoma may have a very wide range of symptoms. People who have melanoma diagnosed in the brain are told not to drive.

What tests are carried out for stage 4 melanoma?

Blood tests

These are used to monitor general health and treatment effects. The tests usually include full blood count (to look for anaemia) and tests of liver function.

Scans

Scans such as ultrasound, CT *(computerised tomography)*, MRI *(magnetic resonance imaging)*, PET *(positron emission tomography)* and bone scans are used to monitor any further spread of the cancer. Your melanoma team will explain why they have chosen a particular type of scan - each type has particular advantages. Further details on what these scans may involve can be found on the links provided at the end of the leaflet.

Biopsies and genetic testing

These are used to confirm the presence of deposits of melanoma in other parts of the body. A biopsy may involve the removal of a lump or the taking of a sample with a needle (fine needle biopsy/core biopsy). The sample is then sent to a laboratory for a doctor called a pathologist to examine under a

microscope. A sample of your melanoma will also be sent for genetic testing, in particular to look for a specific gene mutation (a change in the arrangement of the building blocks of your melanoma), known as a BRAF mutation. This gene mutation makes an altered BRAF protein which makes the melanoma cells grow. Around 50% of melanomas will have a BRAF mutation.

If you have changes in the BRAF gene, your melanoma is described as BRAF positive or mutant. If you don't have changes, then your melanoma is BRAF negative or wild type. This information will help plan future treatment with drug therapies.

Multidisciplinary Team (MDT) Meetings

Test results will be discussed at a skin cancer multi-disciplinary team (MDT) meeting. Following this you may be referred to a specialist melanoma MDT, which may be at another hospital. The specialist melanoma MDT will include a number of specialists including dermatologists, surgeons, pathologists, radiologists, oncologists and also specialist nurses. Following a diagnosis of stage 4 melanoma, you will be seen in clinic by an oncologist, a doctor who specialises in cancer care. He/she will explain your treatment options and discuss which is the best treatment plan for you.

What is the treatment for stage 4 melanoma?

The aims of treatment for stage 4 melanoma are to shrink and control the melanoma to relieve any symptoms, and to prolong life. There have been many developments in the treatment for stage 4 melanoma in the last decade and this is an evolving area with new treatments and regimens being developed. The treatments may cause side effects. The advantages and disadvantages of each treatment, and of having no treatment at all, will be discussed with you by your own doctor. Some of the treatments that may be discussed with you are outlined below.

1. ***Surgery***

   Melanoma lumps in the skin can sometimes bleed or cause discomfort. Similarly, melanoma within lymph nodes can become uncomfortable and painful. It may be possible to remove the lumps or nodes with surgery. If the melanoma has spread to the internal organs, but only as one or two small deposits, it may be possible to remove them with surgery. If melanoma is present in several organs, or there are multiple deposits in one organ, then surgery is usually not a suitable option.

2. ***Radiotherapy***

Radiotherapy involves the use of high energy X-rays to destroy cancer cells. This can be helpful for melanoma in the bones or brain. Unfortunately, the radiotherapy will not cure the melanoma but it may reduce or remove symptoms. For melanoma that has spread to the brain, steroid tablets may also be given, reducing any swelling around the tumour.

3. *Targeted Therapies*

If your melanoma is shown to have a BRAF mutation when it is sent for genetic testing, then targeted therapy with a BRAF inhibitor drug will be suitable for you and works by inhibiting the growth of the melanoma cells. These are tablets or capsules which are taken twice a day. This treatment is not a cure but may help to shrink down or slow the growth of the melanoma cells. BRAF inhibitor drugs do not work unless you have a BRAF mutation. Side effects of these drugs include rashes, joint pain, high temperature (fever), liver strain, and ECG changes,

BRAF inhibitor drug are usually given in combination with a MEK inhibitor drug. The combination treatments have been shown to produce longer responses than the single BRAF inhibitor agents alone in the clinical studies done so far. MEK inhibitors may cause high blood pressure, changes in eyesight, and weakness of the heart muscle. You will generally carry on taking targeted treatment for as long as it is working.

4. *Immunotherapy*

The body's own defences, the immune system, may act on the melanoma cells to slow their growth. Immunotherapy is treatment that encourages this action of the body to fight against the melanoma. This can cause a number of side effects so the doctors will discuss this with you in more detail. There are a number of immunotherapy drugs (known as immune checkpoint inhibitors) available which are outlined below.

Ipilimumab is a drug that blocks a protein on the surface of T-cells, called CTLA-4, thereby activating T-cells (which are part of the immune system) to destroy melanoma cells. It is given as a drip into a vein (intravenous infusion) every three weeks for up to four treatments. Side effects can include diarrhoea, skin reactions, tiredness, feeling sick, loss of appetite, liver upset, changes in gland function (e.g. thyroid and adrenals), joint pain, and eye inflammation.

Pembrolizumab and *Nivolumab* are drugs that binds to PD1 protein which is another protein found on T cells. This activates the T cells to produce an immune response against melanoma cells. They are given as an intravenous infusion for as long as they keep the cancer under control; pembrolizumab is given every 3 weeks, and nivolumab may be given every 2 or 4 weeks. Side effects can include diarrhoea, skin reactions, tiredness, feeling sick, loss of appetite, liver upset, changes in gland function (e.g. thyroid and adrenals), joint pain, and eye inflammation. These side-effects are the same as the side-effects of ipilimumab, but are less common than with ipilimumab, and less likely to be severe.

The combination of *Nivolumab* and *Ipimilumab* can also be used. Combination therapy is more effective against the melanoma cancer than using a single immunotherapy agent, but the side effects of treatment are increased.

All immune checkpoint inhibitors have the potential to cause autoimmune conditions, which are conditions where your immune system reacts against normal body tissues. If you already have such a condition, such as rheumatoid arthritis or ulcerative colitis, immunotherapy treatment may make this condition worse. Your doctor would advise whether this treatment is suitable in those circumstances.

5. *Chemotherapy*

Chemotherapy is the use of anti-cancer drugs to destroy cancer cells. There are several drugs that have be used to treat melanoma cancer cells such as *Dacarbazine* (also known as DTIC) and *Temozolomide,* but these would generally be used if you are unable to have a BRAF inhibitor or an immunotherapy.

6. *Talimogene laherparepvec*

Talimogene laherparepvec (or T-VEC) is a genetically modified virus that is designed to infect and kill melanoma cells. It has to be injected directly into tumours, so is only suitable for people who have lumps that can be felt (e.g. skin lumps or lymph nodes). It is considered for those patients with no signs of internal organ involvement and when surgery and other systemic immunotherapies are not an option. Ultrasound guidance may be needed to make the injection safer. If melanoma cells are killed by the virus, this can stimulate the immune system, so tumours elsewhere in the body may also shrink or stop growing. Side-

effects of T-VEC include pain at the injection site and rashes. You should keep the injection site covered for 48 hours after treatment, and discard dressings in the bin provided by the hospital.

7. Clinical trials

Significant progress is being made in the treatment of metastatic melanoma. Ask your melanoma team what clinical trials are available in your area.

Self care (What can I do?)

. Top sun safety tips:

- Protect your skin with clothing, and don't forget to wear a hat that protects your face, neck and ears, and a pair of UV protective sunglasses.
- Spend time in the shade between 11am and 3pm when it's sunny. Step out of the sun before your skin has a chance to redden or burn.
- When choosing a sunscreen look for a high protection SPF (SPF 30 or more) to protect against UVB, and the UVA circle logo and/or 4 or 5 UVA stars to protect against UVA. Apply plenty of sunscreen 15 to 30 minutes before going out in the sun and reapply every two hours and straight after swimming and towel-drying.
- Keep babies and young children out of direct sunlight.
- The British Association of Dermatologists recommends that you tell your doctor about any changes to a mole or patch of skin. If your GP is concerned about your skin, make sure you see a Consultant Dermatologist – an expert in diagnosing skin cancer. Your doctor can refer you for free through the NHS.
- Sunscreens should not be used as an alternative to clothing and shade, rather they offer additional protection. Sunscreens do not provide 100% protection.

Vitamin D advice

The evidence relating to the health effects of Vitamin D blood levels, sunlight exposure and Vitamin D intake remains inconclusive. Avoiding all sunlight exposure if you suffer from light sensitivity, or to reduce the risk of melanoma and other skin cancers, may be associated with Vitamin D deficiency.

Patients diagnosed with melanoma are advised to have their Vitamin D level checked by their hospital team. If levels are low they are advised to consider taking vitamin D3, 10-20 micrograms (400-800IU) per day, and increasing their intake of foods high in Vitamin D such as oily fish, eggs, meat, fortified margarines and cereals. Vitamin D3 supplements are widely available from supermarkets and chemists. Specific advice will be given by your doctor depending on your level of Vitamin D.

Having had a melanoma may impact on future applications for life or health insurance, particularly for the first five years after diagnosis. Equally you may be able to make a claim against any critical illness insurance, you may have taken out prior to the diagnosis of melanoma. If you have particular concerns about this, you should seek financial advice.

Where can I get more advice, support & information about melanoma?

Coping with stage 4 melanoma can be a tremendous challenge for you as well as your family and friends. The website links below contain interviews with melanoma patients talking about their experiences having been diagnosed with stage 4 melanoma and how they have coped. You may find this helpful.

When you are diagnosed with stage 4 melanoma, you will be given a lot of information. All this information at once can be hard to take in. If you are not clear about anything during your treatment, please don't be afraid to ask.

Web links to detailed leaflets:

British Association of Dermatologists

- Information on early detection and prevention of melanoma
  http://www.bad.org.uk/for-the-public/skin-cancer/melanoma-leaflets
- Information on sun-safety
  http://www.bad.org.uk/for-the-public/sun-awareness-campagin
  http://www.bad.org.uk/for-the-public/skin-cancer/sunscreen-fact-sheet
- Information on Vitamin D
  http://www.bad.org.uk/for-the-public/skin-cancer/vitamin-d

Cancer Research UK (CRUK)

- cancerhelp.cancerresearchuk.org/type/melanoma/living/advanced/

GenoMEL: The Melanoma Genetics Consortium

- http://www.genomel.org/secondary_melanoma/toolkit.html

Melanoma Focus

- *Patient Decision Aid*
  https://pda.melanomafocus.com/
- *Sentinel Node Consensus*
  https://melanomafocus.com/wp-content/uploads/2019/01/SNB-Consensus-Final-1.pdf
- *Video Immunotherapy Treatment for Patients*
  https://vimeo.com/252355507/00d629311d

Macmillan Cancer Support

- www.macmillan.org.uk/Cancerinformation/Cancertypes/Melanoma/TreatingadvancedmelanomaTreatingadvancedmelanoma.aspx
- Financial support
  http://www.macmillan.org.uk/HowWeCanHelp/FinancialSupport/FinancialguidanceFinancialguidance.aspx

Links to patient support groups:

Melanoma UK
Web: https://www.melanomauk.org.uk/

Melanoma Action and Support Scotland (MASScot)
17 Cairnhill Road
Bearsden
East Dunbartonshire
Glasgow, G61 1AU

Tel: 0773 823 1260
Email: leigh@masscot.org.uk
Web: www.masscot.org.uk

For details of source materials used please contact the Clinical Standards Unit (clinicalstandards@bad.org.uk).

This leaflet aims to provide accurate information about the subject and is a consensus of the views held by representatives of the British Association of Dermatologists: individual patient circumstances may differ, which might alter both the advice and course of therapy given to you by your doctor.

This leaflet has been assessed for readability by the British Association of Dermatologists' Patient Information Lay Review Panel

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