Masitinib for advanced or metastatic malignant melanoma with a c-kit juxtamembrane mutation

LAY SUMMARY

Melanoma is a type of skin cancer that can appear anywhere on the body and usually begins with a mole. The back, legs and face are commonly affected areas of the body. Melanoma is the fifth most common cancer in the UK with a third of people diagnosed under the age of 55. Treatment of melanoma is often successful at first, but may begin to fail as the cancer spreads and enters end-stage disease.

Masitinib is a new drug for the treatment of melanoma which is given as a tablet. Some studies have suggested masitinib may be helpful for people whose melanoma has one particular type of genetic mutation and whose disease has spread. More studies are now aiming to show how well it works and that it is safe to use.

If masitinib is licensed for use in the UK, it could be a new treatment option that may improve survival in patients with end-stage disease.

NIHR HSRIC ID: 5780
TARGET GROUP

Malignant melanoma: unresectable or metastatic end stage disease; with c-Kit juxtamembrane mutation.

TECHNOLOGY

DESCRIPTION

Masitinib (AB1010, masitinib mesilate, masitinib mesylate) is a highly selective tyrosine kinase inhibitor that targets the c-Kit, Lyn and Fyn signalling pathways. By combined targeting of these different pathways, masitinib is particularly efficient in controlling mast cell survival, differentiation and degranulation.\(^1\)

In a phase III clinical trial, masitinib is administered orally at 7.5mg/kg daily.

Masitinib is currently being developed in 13 phase III indications; seven in oncology, three in inflammatory diseases, and three in neurodegenerative diseases. A range of phase II clinical trials are also ongoing, mainly in oncology.

Masitinib does not currently have any Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, masitinib will provide an additional oral treatment option for patients with unresectable or metastatic end-stage malignant melanoma with c-Kit juxtamembrane mutation.

DEVELOPER

AB Science.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Malignant melanoma is a type of cancer that arises from melanocytes. It most commonly occurs in the skin, but can also be found in the uveal tract, upper digestive tract, anal canal, rectum and vagina.\(^2,3\) Activating mutations and/or gene amplification of c-KIT have been found in 28% of cutaneous melanomas that arise in chronically sun damaged skin.\(^4\) C-Kit mutations occur in a subgroup of cutaneous melanomas where the more likely mutation is BRAF, however they are more likely to occur in mucosal and acral melanomas, which are less likely to have BRAF mutations, and therefore pose an unmet need for new targeted therapies.\(^5\)

\(^{a}\) Expert personal opinion.
About half of all melanomas start with a change in previously normal-looking skin. As the abnormal melanocytes start to spread into the surrounding epidermis, they begin to look like a dark spot or mole (nevus) on the skin. Other melanomas may develop from existing nevi. Signs of melanoma arising from previously existing nevi may include asymmetry, change of shape, change in colour and/or diameter, or an evolving appearance (including the area becoming raised or dome-shaped), itchiness, pain, bleeding or crustiness. The main risk factor for developing melanoma is exposure to ultraviolet radiation from natural or artificial sources, e.g. the sun or sunbeds. People with very fair skin, sun-sensitive skin, large numbers of nevi, dysplastic nevi, reduced immunity, or a family history of malignant melanoma, have an increased risk of disease. Metastatic melanoma describes disease which has spread to other parts of the body, most commonly the lungs, liver, brain, bones, or to distant lymph nodes or areas of the skin.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

Over the last thirty years, rates of malignant melanoma in the UK have risen faster than any of the current ten most common cancers. Around 13,500 new cases of malignant melanoma were diagnosed in 2012 in the UK. More than one-third of all cases occur in people aged under 55. Malignant melanoma is almost twice as common in young women (up to 34 years of age) as in young men, but more men than women die from it. The annual incidence of malignant melanoma is estimated at 0.02% in England, equating to 10,773 people. At presentation, 10% of cutaneous melanomas are metastatic; metastatic disease is associated with extremely poor survival with a median survival of 6-10 months. Approximately 70% of people diagnosed with metastatic or unresectable melanoma may be suitable to receive chemotherapy and active therapy. Somatic mutations in c-Kit have been found in 2-8% of all malignant melanoma though they are relatively more common in certain subgroups.

In 2014-15, there were 15,820 hospital admissions for malignant melanoma of the skin (ICD-10 C43), resulting in 12,500 bed days and 16,269 finished consultant episodes. 2,237 deaths from malignant melanoma of the skin were registered in England and Wales during 2013 (ICD-10 C43).
NICE Guidance

- NICE technology appraisal in development. Melanoma (advanced and metastatic) – temozolomide [ID316]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Melanoma (metastatic) – paclitaxel albumin-bound nanoparticles (1st line) [ID570]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Melanoma (resected stage IV, high risk stage III) – ipilimumab (adjuvant) [ID721]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Melanoma (BRAF V600, advanced, unresectable, metastatic) – cobimetinib (with vemurafenib) [ID815]. Expected October 2016.
- NICE technology appraisal in development. Melanoma (untreated, advanced, unresectable, metastatic) – nivolumab (with ipilimumab) [ID848]. Expected September 2016.
- NICE technology appraisal. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab (TA357). October 2015.
- NICE technology appraisal. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA321). October 2014.
- NICE technology appraisal. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269). December 2012.
- NICE technology appraisal. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). December 2012.

- NICE public health guidance. Skin cancer prevention: information, resources and environmental changes (PH32). January 2011.

Other Guidance

- American Society of Clinical Oncology. Sentinel lymph node biopsy for melanoma: ASCO and SSO joint clinical practice guideline. 2012\textsuperscript{16}.
- European Society for Medical Oncology. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2012\textsuperscript{17}.
- American Academy of Dermatology (AAD). Guidelines of care for the management of primary cutaneous melanoma. 2011\textsuperscript{18}. 
CURRENT TREATMENT OPTIONS

Non-surgical modalities, including immunotherapy, chemotherapy, radiation therapy, or a combination of these treatments may be offered for inoperable stage III and IV disease (locally advanced or metastatic disease)\(^22\). Treatment options include\(^23,24,25,26,27,28\):

- **Biological therapy:**
  - Vemurafenib for inoperable stage III and IV BRAF mutant melanoma.
  - Dabrafenib for inoperable stage III and IV BRAF mutant melanoma.
  - Checkpoint inhibitors
    - Ipilimumab for unresectable stage III or IV malignant melanoma.
    - Pembrolizumab for unresectable stage III or IV malignant melanoma.

- **Chemotherapy – dacarbazine remains standard first line chemotherapy for wild-type BRAF melanoma, and is the most commonly used chemotherapy in the UK. Other options include:**
  - Temozolomide.
  - Cisplatin or carboplatin.
  - Vinca alkaloids – vindesine.
  - Paclitaxel.
  - Nitrosoureas – carmustine.
  - Carboplatin and paclitaxel in combination.
  - Dacarbazine and a vinca alkaloid in combination.

- **Immunotherapy – interferon-alpha and interleukin-2.**

- **Radiotherapy may be used to palliate locally advanced or metastatic disease where the main goal is symptom control or adjuvantly for high risk lymph node basins. Stereotactic radiosurgery may be offered for low volume oligometastatic brain metastases\(^b\).**

- **Surgery – excision of the primary tumour, affected lymph nodes and in transit recurrent disease. Metastasectomies.**

- **Other:**
  - Imiquimod for lentigo maligna.
  - Isolated limb perfusion – with melphalan, for recurrent disease within a limb.
  - Electrochemotherapy (with bleomycin) – palliative for recurring in-transit metastases and also for fungating lesions.

Efficacy and Safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>AB08026, NCT01280565; masitinib vs dacarbazine; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>AB Science.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry(^29), manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (not UK) and USA.</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
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</table>

\(^b\) Expert personal opinion.
Participants
n=112; aged 18 years and older; histologically or cytologically confirmed non-resectable or metastatic stage III or stage IV melanoma; c-Kit juxtamembrane mutation confirmed by DNA or RNA sequencing; measurable disease according to RECIST; Eastern Cooperative Oncology Group (ECOG) performance score of ≤2.

Schedule
Randomised to oral masitinib 7.5mg/kg per day; or intravenous dacarbazine 1,000mg/m² once every 3 weeks.

Follow-up
Active treatment period 24 weeks or until disease progression without clinical benefit, limiting toxicity or patient consent withdrawal. Follow-up of patients exiting the study for tumour progression or toxicity, every 12 weeks until death.

Primary outcome
Objective response rate.

Secondary outcomes
Overall progression-free survival, overall survival, ECOG performance status, EORTC QLQ-C30.

Expected reporting date
Primary completion date reported as December 2017.

ESTIMATED COST and IMPACT

COST

The cost of masitinib is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers
☑ Reduced mortality/increased length of survival ☑ Reduced symptoms or disability ☐ Other: ☐ No impact identified

Impact on Health and Social Care Services
☐ Increased use of existing services ☐ Decreased use of existing services ☐ Re-organisation of existing services ☐ Need for new services ☐ Other: ☐ None identified

Impact on Costs and Other Resource Use
☑ Increased drug treatment costs: *likely to be more expensive than dacarbazine. The relative cost-effectiveness of masitinib compared to ipilimumab or pembrolizumab would be of interest*. ☑ Reduced drug treatment costs ☐ Other increase in costs: ☐ None identified ☐ Other: ☐ Other reduction in costs:

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* The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.
* Expert personal opinion.
Clinical uncertainty or other research question identified: a lot of the literature looking at Kit inhibition in melanoma suggest that the mutation type does not reliably predict response. This needs to be considered in further detail.

REFERENCES


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29 ClinicalTrials.gov. A phase 3 study to compare efficacy and safety of masitinib to dacarbazine in the treatment of patients with non-resectable or metastatic stage 3 or stage 4 melanoma carrying a mutation in the juxta membrane domain of C-Kit.  
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