Masitinib for gastrointestinal stromal tumours – second line

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Masitinib for gastrointestinal stromal tumours – second line

Target group
- Gastrointestinal stromal tumours (GIST): unresectable and/or metastatic – second line, after progression with imatinib.

Technology description
Masitinib (AB-1010; masitinib mesylate) is an orally active tyrosine kinase inhibitor which selectively inhibits the stem cell factor receptor (c-Kit), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and to a lesser extent focal adhesion kinase (FAK). It also inhibits mast cell degranulation. About 95% of GIST are positive for c-Kit expression, and 85–90% of GIST have a gain-of-function mutation of either c-Kit or PDGFRα. Masitinib is intended to substitute sunitinib for the second-line treatment of patients with unresectable and/or metastatic GIST that has progressed despite imatinib. It is administered orally at 12mg/kg/day, in a divided dose taken twice daily.

Masitinib is in phase III clinical trials for the treatment of asthma, malignant melanoma, mastocytosis, multiple myeloma and pancreatic cancer. It is also in phase II/III clinical trials for the treatment of multiple sclerosis and rheumatoid arthritis, and phase II clinical trials for Alzheimer’s disease.

Innovation and/or advantages
If licensed, masitinib would provide an additional treatment option for this patient group whose therapeutic options are limited.

Developer
AB Science.

Availability, launch or marketing dates, and licensing plans
In phase II clinical trials.

NHS or Government priority area
This topic is relevant to Improving Outcomes: A Strategy for Cancer (2011).

Relevant guidance
- NICE technology appraisal. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours. Part review of NICE technology appraisal guidance 86. 2010².
- NICE technology appraisal. Imatinib for the adjuvant treatment of gastrointestinal stromal tumours. 2010³.
- NICE technology appraisal. Sunitinib for the treatment of gastrointestinal stromal tumours. 2009⁴.
- NICE technology appraisal. Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours. 2004⁵.
- Allum WH, Blazeby JM, Griffin SM et al. Guidelines for the management of oesophageal and gastric cancer. 2011⁶.
Clinical need and burden of disease
Gastrointestinal stromal tumours are the most common mesenchymal tumours of the gastrointestinal (GI) tract, expressing the proto-oncogene protein CD117 (also known as c-Kit)\textsuperscript{10}. GIST can occur anywhere in the GI tract, but the majority arise in the stomach (60–70%) and small bowel (25–35%)\textsuperscript{5}. Although GIST can occur at any age, the mean age of presentation is between 50 and 70 years\textsuperscript{10}. Many people with GIST are asymptomatic during early stages of the disease, but once tumours reach a large size they may rupture and bleed or obstruct the GI tract\textsuperscript{2}. Prognosis depends on the resectability of the tumour\textsuperscript{10}. Approximately half of new cases of GIST are likely to be unresectable and/or metastatic on first presentation\textsuperscript{7}. Ten-year survival for resectable/non-metastatic tumours is 30-50\textsuperscript{10}, but prognosis for people with unresectable and/or metastatic GIST is poor, with few, if any people surviving beyond 5 years\textsuperscript{5}.

GIST is rare cancer and accounts for less than 1% of all cancers of the GI tract\textsuperscript{10}. The annual incidence of GIST is estimated to be around 15 per million, which equates to approximately 900 new cases per year in the UK\textsuperscript{7}. The number of new cases of unresectable and/or metastatic GIST is estimated to be around 240 people per year\textsuperscript{11}. Approximately 30-50 patients experience primary resistance to imatinib, and around 60-100 patients develop a reduced response at a later stage\textsuperscript{11}. Following failed imatinib treatment and in the absence of further treatment, survival is usually less than 1 year\textsuperscript{11}. Sunitinib therapy is also limited by the development of secondary resistance\textsuperscript{12}.

Existing comparators and treatments
Surgical resection is the treatment of choice for resectable GIST\textsuperscript{10}. Imatinib is licensed but not recommended by NICE for the adjuvant treatment of patients with GIST, who are at significant risk of relapse after surgery\textsuperscript{3,10}. Surgery for advanced or metastatic GIST is not recommended unless there is an immediate clinical need\textsuperscript{2}. Advanced or metastatic GIST is resistant to conventional cytotoxic chemotherapy and radiotherapy\textsuperscript{2}.

NICE guidelines recommend\textsuperscript{4,5}:
- Imatinib 400mg/day for the first line treatment of people with unresectable and/or metastatic GIST.
- Sunitinib for the second line treatment of people with unresectable and/or metastatic GIST, resistant or intolerant to imatinib.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01506336, AB07001; masitinib or sunitinib; phase II.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>AB Science.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{13}, manufacturer\textsuperscript{14}.</td>
</tr>
<tr>
<td>Location</td>
<td>France.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
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<tr>
<td>Participants and schedule</td>
<td>n=44; adults; histological proven GIST; c-Kit positive; metastatic or locally advanced; non-operable; resistant to imatinib at 400mg to 800mg per day. Randomised to masitinib at 12mg/kg/day or sunitinib at 50mg/day.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment until disease progression.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Overall progression free survival.</td>
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</tbody>
</table>
**Secondary outcome** | Overall survival.
---|---
**Key results** | After 17 months median follow-up, the updated median overall survival was not reached for masitinib versus 16 months for sunitinib (Hazard Ratio: 0.27 [95% CI, 0.09-0.78]). After 18 months, 82% [95% CI, 59%-93%] of patients treated with masitinib were still alive versus 33% [95% CI, 8%-62%] for patients treated with sunitinib.

**Adverse effects (AEs)** | Most common AEs observed in masitinib group were nausea/vomiting, diarrhoea and asthenia. Patients receiving masitinib experienced longer safety event free survival (p≤0.001) and a lower occurrence of severe AEs. Masitinib was well tolerated, with 17% of patients reporting treatment related grade 3 AEs, and no treatment related grade 4 AEs.

**Expected reporting date** | Study expected to complete by December 2012.

**Estimated cost and cost impact**

The cost of masitinib is not yet known. The cost of sunitinib (Sutent, Pfizer) at 50mg once daily is around £3138.80 for 28 days.\(^{15}\)

**Claimed or potential impact – speculative**

**Patients**

- ☑ Reduced mortality or increased length of survival
- ☑ Reduction in associated morbidity or improved quality of life for patients and/or carers
- ☑ Quicker, earlier or more accurate diagnosis or identification of disease
- ☑ None identified

**Services**

- ☑ Increased use
- ☑ Service organisation
- ☑ Staff requirements
- ☑ None identified

**Costs**

- ☑ Increased unit cost compared to alternative
- ☑ Increased costs: more patients coming for treatment
- ☑ Increased costs: capital investment needed
- ☑ Other: uncertain unit cost compared to comparator

**Other issues**

- ☑ Clinical uncertainty or other research question identified:
- ☑ None identified

**References**


10 Hislop J, Quayyum Z, Elders A et al. Clinical effectiveness and cost effectiveness of imatinib dose escalation for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours that have progressed on treatment at a dose of 400 mg/day: a systematic review and economic evaluation review and economic evaluation. Health Technology Assessment 2011;15(25).


