National Horizon Scanning Centre

Imatinib (Glivec) for adjuvant therapy in gastrointestinal stromal tumours

August 2008

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Imatinib (Glivec) for adjuvant therapy in gastrointestinal stromal tumours

Target group
Gastrointestinal stromal tumours (GISTs) - post surgical resection adjuvant therapy in patients with a tumour size greater than 3cm.

Technology description
Imatinib (Glivec) is an oral selective inhibitor of the BCR-ABL, PDGFr, ARG and c-KIT kinases. Imatinib inhibits proliferation and induces apoptosis in GISTs expressing an activating kit mutation. In the registration trial imatinib is administered at 400mg once a day for 1 year post surgical resection, subsequent ongoing trials administer imatinib for 2 or 3 year intervals.

Imatinib is licensed in the EU for the following indications:
- Adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant GIST.
- Adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (Ph+ CML) for whom bone marrow transplantation is not considered as the first line of treatment.
- Adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- Adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements.
- Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFR rearrangement.
- Adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

Innovation and/or advantages
If licensed, imatinib would be the first adjuvant targeted treatment for GIST.

Developer
Novartis Pharma AG Ltd.

NHS or Government priority area:
This topic is relevant to the Cancer Reform Strategy (2007).

Relevant guidance
- NICE technology appraisal in development. Sunitinib malate for the treatment of gastrointestinal stromal tumours refractory to imatinib. Issue date to be confirmed\(^1\).
- NICE technology appraisal. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours. 2004\(^2\).
- NICE cancer service guidance. Improving outcomes for people with sarcoma. 2006\(^3\).
Clinical need and burden of disease

Gastrointestinal stromal tumours are gastrointestinal mesenchymal tumours expressing a proto-oncogene protein called CD117 (also known as c-KIT). Although GISTs can occur along the length of the gastro-intestinal (GI) tract, the majority arise in the stomach (60–70%), small bowel (25–35%), colon and rectum (5%) and, to a lesser extent, the oesophagus. Many people with GISTs are asymptomatic during early stages of the disease until tumours reach a large size, at which time the tumours can rupture and bleed or obstruct the GI tract.

Estimates of GIST incidence vary widely from 4 to 40 cases per million of the population, which corresponds to between 200 and 2,150 new cases per year in England and Wales. Approximately one quarter of new cases of GIST are likely to be metastatic and/or unresectable on first presentation. Tumours that are greater than 3cm could be categorised as ‘high risk’ or ‘intermediate risk’ and approximately half of all resected tumours would be included within this. The estimated eligible population for adjuvant therapy in England and Wales is therefore between 75 and 807 people per annum.

Although GIST can occur at any age, the mean age of presentation is between 50 and 70 years and it is more common in men than women. The disease specific survival rate range is 69% - 97% at 1 year and 35% - 76% at 5 years. Recurrence occurs in 40% of patients and survival rates in patients after complete resection are 88% at 1 year and 54% at 5 years.

Existing comparators and treatments

Complete surgical excision is the treatment of choice for localised GISTs. There are currently no licensed drugs for adjuvant therapy.

**Efficacy and safety**

<table>
<thead>
<tr>
<th>Trial code</th>
<th>NCT00041197: Z9001; primary GIST; imatinib vs. placebo; phase III.</th>
<th>NCT00025246; Z9000; primary GIST; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>American College of Surgeons; National Cancer Institute.</td>
<td>American College of Surgeons; National Cancer Institute.</td>
</tr>
<tr>
<td>Status</td>
<td>Published abstract.</td>
<td>Published abstract.</td>
</tr>
<tr>
<td>Location</td>
<td>USA</td>
<td>USA</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, double-blind, placebo control.</td>
<td>Single arm, open label.</td>
</tr>
<tr>
<td>Participants in trial.</td>
<td>n=708; adults; primary GIST; tumour at least 3cm in diameter; no peritoneal or distant metastases; complete gross resection in past 14-70 days; CD117 positive; no objective evidence of residual disease. Randomised to: Imatinib 400mg or placebo once a day for 1 year. Upon recurrence patients could cross over to imatinib from placebo, or go to 800mg daily.</td>
<td>n=107; adults; high-risk primary GIST; complete gross resection in past 70 days; Kit positive; no residual disease on CT or MRI. All patients received 400mg imatinib daily for 1 year.</td>
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<tr>
<td>Follow-up.</td>
<td>1 year (treatment); 10 year follow-up.</td>
<td>1 year (treatment); 10 year follow-up.</td>
</tr>
<tr>
<td>Primary outcome.</td>
<td>Recurrence-free survival (RFS).</td>
<td>OS.</td>
</tr>
<tr>
<td>Secondary outcomes.</td>
<td>Overall survival (OS)</td>
<td>Recurrence rate at 2 and 5 years.</td>
</tr>
<tr>
<td>Key results.</td>
<td>Interim analysis - patients assigned to</td>
<td>OS rate at 1, 2 and 3 years was 99%, 97%</td>
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</tbody>
</table>
imatinib had a 1 year RFS of 97% vs. 83% for placebo (HR 0.325; 95% CI 0.198-0.534; p=0.0000014). and 97% respectively. RFS was 94%, 73% and 61% respectively.

**Adverse effects.** Imatinib therapy was well tolerated by most patients. At 1 year no grade 4 or 5 toxicity. 19 (17%) patients had grade 3 toxicity: neutropenia (2%), dermatitis (2%), or increased ALT (2%). The most frequent toxicities of any grade were oedema (55%), fatigue (43%), nausea (42%), diarrhea (42%), and dermatitis (27%).

<table>
<thead>
<tr>
<th>Trial code.</th>
<th>NCT0010316810; EORTC 62024: intermediate or high risk; phase III.</th>
<th>NCT0011693511; SSG XVIII/A1: 12 months vs. 36 months adjuvant; high risk; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
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<tr>
<td>Location</td>
<td>Europe (including UK), Australia New Zealand, Singapore.</td>
<td>Scandinavia, Germany.</td>
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<tr>
<td>Design</td>
<td>Randomised, open label, active control.</td>
<td>Randomised, open label, active control.</td>
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<tr>
<td>Participants in trial.</td>
<td>n=750 (planned); adults; localised GIST; complete resection of primary tumour within last 2-12 weeks; at intermediate to high risk of relapse; CD117 positive; no distant metastases. Randomised to imatinib 400mg daily for 2 years or no additional therapy.</td>
<td>n=400 (planned); adults; complete resection within last 2-12 weeks; CD117 positive; high risk of tumour recurrence – combination of tumour size, mitotic counts and tumour spillage at surgery. Randomised to: imatinib 400mg daily for 12 months or 36 months.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>5 years.</td>
<td>5 years.</td>
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<tr>
<td>Primary outcome.</td>
<td>OS.</td>
<td>RFS.</td>
</tr>
<tr>
<td>Secondary outcomes.</td>
<td>RFS, safety.</td>
<td>OS, adverse effects.</td>
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</table>

**Estimated cost and cost impact**

A 400mg, 30-tab pack of imatinib costs £1,604.08. This would equate to an annual treatment cost of around £19,500.

**Potential or intended impact – speculative**

**Patients**

☑ Reduced morbidity ☑ Reduced mortality or increased survival ☐ Improved quality of life for patients and/or carers

☐ Quicker, earlier or more accurate diagnosis or identification of disease ☐ Other: ☐ None identified

**Services**

☑ Increased use ☐ Service reorganisation required ☐ Staff or training required

☐ Decreased use ☐ Other: ☐ None identified

**Costs**
Increased unit cost compared to alternative
☑ New costs: No existing treatment.
☑ Increased costs: more patients coming for treatment
☑ Increased costs: capital investment needed
☐ Savings:
☐ Other:

References

1 National Institute for Health and Clinical Excellence. Sunitinib malate for the treatment of gastrointestinal stromal tumours refractory to imatinib. Technology appraisal in development. Issue date to be confirmed.


5 Novartis. Market research - conducted May 2008 - (DOF GLI0001-1).


Clinical Trials. Imatinib mesylate or observation only in treating patients who have undergone surgery for localized gastrointestinal stromal tumor. NCT00103168. Available at: http://clinicaltrials.gov/ct2/show/NCT00103168?term=NCT00103168&rank=1&show_locs=Y#locn (Accessed 08/08/08).


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