

National Horizon Scanning Centre

Imatinib (Glivec) for adjuvant therapy in gastrointestinal stromal tumours

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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 confirmed¹.
- NICE technology appraisal. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours. 2004².
- NICE cancer service guidance. Improving outcomes for people with sarcoma. 2006³.
- Association of Upper Gastrointestinal Surgeons of GB & Ireland. Care Guideline. Guidelines for the management of gastrointestinal stromal tumours (GISTs). 2005⁴.

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 tract².

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 Wales². 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 this⁵. 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 years⁶.

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

Trial code	NCT00041197: Z9001; primary GIST; imatinib vs. placebo; phase III.	NCT00025246; Z9000; primary GIST; phase II.
Sponsor	American College of Surgeons; National Cancer Institute.	American College of Surgeons; National Cancer Institute.
Status	Published abstract ⁷ .	Published abstracts ^{8,9} .
Location	USA	USA
Design	Randomised, double-blind, placebo control.	Single arm, open label.
Participants in trial.	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.	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.
Follow-up.	1 year (treatment); 10 year follow-up.	1 year (treatment); 10 year follow-up.
Primary outcome.	Recurrence-free survival (RFS).	OS.
Secondary outcomes.	Overall survival (OS)	Recurrence rate at 2 and 5 years.
Key results.	Interim analysis - patients assigned to	OS rate at 1, 2 and 3 years was 99%, 97%

	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%), diarrhoea (42%), and dermatitis (27%).

Trial code.	NCT00103168 ¹⁰ ; EORTC 62024: intermediate or high risk; phase III.	NCT00116935 ¹¹ ; SSG XVIII/A1: 12 months vs. 36 months adjuvant; high risk; phase III.
Sponsor	European Organization for Research and Treatment of Cancer.	Scandinavian Sarcoma Group.
Status	Ongoing.	Ongoing.
Location	Europe (including UK), Australia New Zealand, Singapore.	Scandinavia, Germany.
Design	Randomised, open label, active control.	Randomised, open label, active control.
Participants in trial.	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.	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.
Follow-up.	5 years.	5 years.
Primary outcome.	OS.	RFS.
Secondary outcomes.	RFS, safety.	OS, adverse effects.
Expected reporting.	Study started July 2004; final analysis expected 2013.	Study started February 2004; final analysis expected 2014.

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

- | | | |
|---|---|--|
| <input checked="" type="checkbox"/> Reduced morbidity | <input checked="" type="checkbox"/> Reduced mortality or increased survival | <input type="checkbox"/> Improved quality of life for patients and/or carers |
| <input type="checkbox"/> Quicker, earlier or more accurate diagnosis or identification of disease | <input type="checkbox"/> Other: | <input type="checkbox"/> None identified |

Services

- | | | |
|---|--|---|
| <input checked="" type="checkbox"/> Increased use | <input type="checkbox"/> Service reorganisation required | <input type="checkbox"/> Staff or training required |
| <input type="checkbox"/> Decreased use | <input type="checkbox"/> Other: | <input type="checkbox"/> None identified |

Costs

- | | | |
|---|--|---|
| <input type="checkbox"/> Increased unit cost compared to alternative | <input type="checkbox"/> Increased costs: more patients coming for treatment | <input type="checkbox"/> Increased costs: capital investment needed |
| <input checked="" type="checkbox"/> New costs: No existing treatment. | <input type="checkbox"/> Savings: | <input type="checkbox"/> Other: |

References

- ¹National 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.
- ²National Institute for Health and Clinical Excellence. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours. Technology appraisal TA86. October 2004.
- ³National Institute for Health and Clinical Excellence. Improving outcomes for people with sarcoma. Cancer service guidance. March 2006.
- ⁴Association of Upper Gastrointestinal Surgeons of GB & Ireland. Guidelines for the management of gastrointestinal stromal tumours (GISTs). Care Guideline. July 2005.
- ⁵Novartis. Market research - conducted May 2008 - (DOF GLI0001-1).
- ⁶Saconato H, El Dib RP, Atallah AN. Imatinib mesylate for gastrointestinal stromal tumours (GISTs). (Protocol) Cochrane Database of Systematic Reviews 2007 (3). Art. No: CD006584. DOI: 10.1002/14651858.CD006584.
- ⁷DeMatteo R, Owzar K, Maki R, et al. Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumor (GIST): North American Intergroup phase III trial ACOSOG Z9001. J Clin Oncol 2007; 25 (Suppl 18):A-10079.
- ⁸DeMatteo RP, Owzar K, Antonescu CR et al. Efficacy of adjuvant imatinib mesylate following complete resection of localized, primary gastrointestinal stromal tumor (GIST) at high risk of recurrence: the U.S. Intergroup phase II trials ACOSOG Z9000. American Society of Clinical Oncology Gastrointestinal Cancers Symposium. January 2008.
- ⁹DeMatteo RP, Antonescu CR, Chadaram V, et al. Adjuvant imatinib mesylate in patients with primary high risk gastrointestinal stromal tumor (GIST) following complete resection: Safety results from the U.S. Intergroup phase II trial ACOSOG Z9000. Journal of Clinical Oncology 2005; 23 (Suppl 16): A-9009, 818s.
- ¹⁰Clinical 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).
- ¹¹Clinical Trials. Study comparing 12 months versus 36 months of imatinib in the treatment of gastrointestinal stromal tumor (GIST). NCT00116935. Available at: <http://clinicaltrials.gov/ct2/show/NCT00116935?term=NCT00116935&rank=1> (Accessed 08/08/08)

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