Imatinib for the treatment of patients with unresectable and/or metastatic gastro-intestinal stromal tumours – a systematic review and economic evaluation (Commercial-in-confidence [CIC] data removed)

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Produced by: West Midlands Health Technology Assessment Collaboration, Department of Public Health and Epidemiology, The University of Birmingham

Authors:

Jayne Wilson,	Systematic reviewer[1]
Martin Connock,	Systematic reviewer[1]
Fujian Song	Senior research fellow[1]
Guiqing Yao,	Health economist[2]
Anne Fry-Smith	Information specialist[1]
Prof James Raftery	Health economist[2]
David Peake	Consultant Clinical Oncologist[3]

1. Department of Public and Epidemiology, The University of Birmingham.

2. Health Economics Facility, Health Services Management Centre, The University of Birmingham.

3. University Hospitals, Birmingham NHS Trust, Edgbaston, Birmingham.

Correspondence to: **Ms Jayne Wilson (J.S.Wilson.1@bham.ac.uk)**

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Notes: This is the version in which data from an unpublished study (Goss et al) is removed (except summary results from the Goss study).

Where type is red, this data was supplied by Novartis in their industry submission to the TAR team. This data is not commercial in confidence.

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ABOUT "HOME UNIT"

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produces rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands NHS and the NCCHTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

CONTRIBUTIONS OF AUTHORS

Jayne Wilson and Fujian Song developed and all commented on the review protocol. Anne Fry-Smith designed the search strategies and searched the electronic databases. Jayne Wilson and Martin Connock reviewed effectiveness studies. Fujian Song and Martin Connock reviewed prognostic studies. Fujian Song and Martin Connock assessed and modified Novartis model. Guiquing Yao and James Raftery developed the new Birmingham model. Jayne Wilson, Martin Connock and Fujian Song wrote the report. David Peake provided clinical advice. All authors commented on the draft manuscript.

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David Peake has been paid by Novartis to give one lecture on GIST and was sponsored to attend the Third International Symposium on GIST. Other than this members of the review team at the University of Birmingham have no any pecuniary relationship with sponsors, specific or non-specific.

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Objectives

To assess the clinical and cost effectiveness of imatinib in the treatment of unresectable and/or metastatic, KIT positive, gastrointestinal stromal tumours (GISTs), relative to current standard treatments.

Methods

Electronic literature databases and the references of identified studies were searched for relevant studies. The searches were not restricted by language or publication status. Because there were no randomised trials that have directly compared imatinib with the current standard treatment in patients with advanced GIST, this review included non-randomised controlled studies, cohort studies, and case series that reported effectiveness results of treatment with imatinib and/or other interventions in patients with advanced GIST. The effectiveness assessment was based on the comparison of results from imatinib trials and results from studies of historical control patients.

Economic evaluation was mainly based on an assessment and modification (when judged necessary) of a model submitted by Novartis. The results from a new model confirmed the findings from the modified Novartis model.

Effectiveness assessment

Two trials and 8 case studies were identified from the published literature, and four ongoing trials and a case series were identified, which have reported data in abstract form only. Evidence from published uncontrolled trials involving 187 patients, and from abstracts reporting similar uncontrolled trials involving 1700 patients, indicate that approximately 50% of imatinib-treated individuals with advanced GIST experience a dramatic clinical response in terms of at least a 50% reduction in tumour mass. At present, although useful data are accumulating, it is not possible to predict which individuals might respond in this way. Fifteen studies where possible GIST patients had been treated with therapies other than imatinib or BSC were also identified. Because of the problems of in particular diagnosis an indirect comparison using these studies was not possible, therefore the results of these studies will not be compared to the imatinib trials in the following section.

All imatinib treated patients experienced adverse effects, although the adverse events were relatively mild.

Overall imatinib was reported well tolerated. The most common serious events included unspecified haemorrhage and neutropenia. Skin rash, oedema, and peri-orbital oedema were the common adverse events observed. Patients on the highest dose regime (1000 mg/day in one trial) may experience dose-limiting drug toxicity.

A systematic review of prognostic studies confirmed a large number of patients with advanced GIST will die within a few years of diagnosis, but some patients may survive for many years. The evidence from modelling suggested that the patients in the imatinib trial

were relatively comparable to all patients with recurrent or metastatic GIST in an unpublished study [text related to this study is commercial in confidence and has been removed].

Cost-effectiveness

Novartis has submitted an economic evaluation of imatinib for unresectable and/or metastatic GIST. After a structured assessment of the Novartis model, we found that it was clearly presented and well-written; the model structure and input data were transparent; and the level of simplification was reasonable in terms of the objectives and data availability. However, the original Novartis model overestimated the cost-effectiveness of imatinib because of (1) disproportion of survival and time-to-treatment failure in the imatinib arm, and (2) the use of a possibly biased survival curve for patients in the control arm.

The original Novartis model was modified so that the two important shortcomings were corrected. The modified Novartis model became less sensitive to the choice of the survival curve for the control patients. According to the modified Novartis model, the estimated cost per QALY was £85,224 (from £51,515 to £98,889) after 2 years, £41,219 (from £27,331 to $44,236) after 5 years, and £29,789 (from £21,404 to £33,976) after 10 years. The results from a new Birmingham model were also within the range of estimates from the modified Novartis model.

Conclusions

Evidence from uncontrolled studies indicates that the treatment with imatinib brings about clinically significant shrinkage of tumour mass in about half of patients with unresectable and/or metastatic, KIT positive GIST. Results of modelling based on data from uncontrolled studies suggest that imatinib treatment improves survival in patients with unresectable and/or metastatic GIST. The economic evaluation modelling suggests that the cost per QALY gained ranges from £51,515 to £98,889 after 2 years, from £27,331 to £44,236 after 5 years, and from £21,404 to £33,976 after 10 years. The estimates after 2 years are of great uncertainty because they were based on the extrapolation beyond the trial data. The conclusions are based on the existing evidence, and uncontrolled trials in progress will provide additional data from more imatinib-treated patients and/or data of longer follow-up.

ABBREVIATIONS

BSC	Best supportive care (more recently termed “Active Symptom Control”)
CML	Chronic Myloid Leukaemia
CPMP	Committee for Proprietary Medicinal Products
CR	Complete response
CT	Computed tomography
CTC	Common toxicity criteria
EPAR	European Public Assessment Report
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FDG	^{18}F 2-fluoro 2-deoxyglucose
FDGP	2-fluoro deoxyglucose 6 phosphate
GIST	Gastrointestinal stromal tumours
ICC	Interstitial Cells of Cajal
IH	Immunohistological
KM	Kaplan Meier
PD	Progressive disease
PET	Positron emission tomography
PM	Performance Measure
PR	Partial response
QoL	Quality of Life
RCT	Randomised Controlled Trial
RECIST	Response evaluation criteria in solid tumours
SCF	Stem Cell Factor
SD	Stable disease
SUV	Standard Uptake Value
SWOG	Southwest Oncology Group
TTF	Time to Treatment Failure

1. AIMS AND BACKGROUND

1.1 Aims

This systematic review seeks to assess the clinical and cost effectiveness of imatinib in the treatment of unresectable and/or metastatic, KIT positive, gastrointestinal stromal tumours (GISTs), relative to current standard treatments.

1.2 Description of underlying health problem

1.2.1 Gastrointestinal stromal tumours – definition

In the last 3 decades the meaning of the term GIST has evolved as gastrointestinal tumours have been studied by increasingly more sophisticated investigative techniques. These have included:

- morphological characterisation evident from light microscopic examination coupled with conventional tissue staining methods
- detailed descriptions of ultra structure available with the use of the electron microscope
- profiling of tumours using immuno-histochemical methods so as to determine presence and absence of marker antigens
- detection and analysis of mutation in oncogenes
- most recently and in the future molecular characterisation of gene-expression by application of cDNA arrays to determine mRNA expression in tumour cells (methods first applied to other more common tumour types).

The term "stromal gastrointestinal tumour", later to become "gastrointestinal stromal tumour" (GIST), appears to have been first used by Schaldenbrand and Appelman (1984)[1] while "gastric stromal tumour" was introduced by Mazur and Clark (1983).[2] GISTs then encompassed GI tract tumours that were judged to have developed from GI stroma cells of mesenchymal origin. GISTs were thus separated from epithelium-derived tumours. Soon the term came into wide usage but it's meaning has shifted in line with the knowledge and opinion that accrued with application of the newer techniques of investigation. [3]

Many cell types in the GI stroma are potentially capable of becoming tumours and there are several GI stromal phenotypes toward which tumours might differentiate or partially differentiate. These include[4] :

- smooth muscle cells and their progenitors
- autonomic neurons of the myenteric plexi
- fibroblasts and fibroblast-like cells
- neuron sheath cells (Schwann cells)
- pace-maker cells (Interstitial Cells of Cajal, ICC) and their progenitors
- adipocytes

- mast cells
- other mesenchymal cells

Some of these are specific to the GI tract while others occur at other sites where they also may give rise to tumours that in turn may metastasize to new sites.

GISTs were first thought to derive from smooth muscle cells in the GI wall or to differentiate toward a muscle phenotype. However it became evident that GIST appearance (cellularity, nuclear shape, eosinophilia), propensity to metastasize, and response to potential therapies, differed from muscle tumours at other sites. With the advent of electron microscopy neural features were observed in some GISTs and a spectrum of subgroups began to be recognised including muscle types (leiomyomas), neural types (plexosarcomas, Schwannomas) and others of apparently mixed "myo-neural" character.

The era of immuno-histochemical investigations has eventually led to the realisation that a distinct group of tumours formerly identified as GISTs, and representing a large proportion of such tumours, were characterised by expression of the surface antigen CD 117, the product of the c-kit proto-oncogene. Positive immunochemical reaction for CD117, shared morphological features, and a claimed common positive immuno-reaction for the CD34 antigen, led to the notion that these GISTs were derived from the Interstitial Cells of Cajal (ICC), or, because c-kit positive tumours arise at sites where ICC are not found (GI mesentery and omentum), from multipotent cells that are precursors of ICC. These findings have driven reappraisals of the classification of GI "mesenchymal" tumours.[4-6]

A consensus view [5]and that expressed in the WHO classification of Gastrointestinal tumours[7] (published 2000) is that the term GIST should be reserved for KIT positive tumours, while the rarer GI-associated muscle-derived myosarcomas (immuno-positive for actin and desmin) and Schwannomas are viewed as separate entities. Nevertheless the current literature accepts the concept of the rare CD117 negative GIST; these resemble CD117 positive forms in all respects other than immunoreactivity for CD117. These tumours do not express cKIT and around 5% are now known to be due to mutations in the PDGFRA gene, which encodes a related tyrosine kinase. Some of these tumours may also respond to imatinib.[8] Tumours formerly classified as GANTs (gastrointestinal autonomic nerve tumours) are now included as GISTs and the term GANTs may no longer warrant designation as a separate entity.

Most CD117 positive GISTs are also immuno-positive for Nestin [9] and for the CD34 antigen, a result that was judged consistent with their origin from ICCs because these also were considered CD34 positive. However recent dual staining [10-12] of GI tissue from human, mouse and other species revealed that CD34 was absent from most or all CD117 positive cells and mostly resided in fibroblast-like cells, similarly branched to ICCs, that form a network in close association with the ICC network. One recent investigation[13]of human small bowel claimed that about 14% ICCs are dually positive (CD117 and CD34) and that this small subpopulation could be the source of most GISTs.

1.2.2 Symptoms

GIST can cover a spectrum of disease. Patients can present with single small primary tumours or have advanced disease or reoccurrences. Patients with single small primary tumours are often asymptomatic with tumours being detected incidentally. If symptoms are present they vary depending on the size and location of the tumour. The most common symptoms are vague abdominal discomfort or pain, a feeling of abdominal fullness, and presence of a palpable mass. Secondary symptoms such as anaemia can occur and are caused by the tumour bleeding.

1.2.3 Diagnosis

The definite diagnosis is made from biopsy. Morphology of the tissue sample is examined by a pathologist. A raft of immuno-histochemical (IH) tests are undertaken to characterise the cell type and aid elimination of certain other types of tumours. The recent immuno-histochemical test for the cKIT protein has become adopted as the strongest indicator that a tumour, with an appropriate morphology and site, is in fact a GIST. This test is seen by many as the final arbiter in the diagnostic process and has been described by some as the diagnostic 'gold standard' for GIST.[14] However, as discussed elsewhere (Appendix 3, page 83) the reproducibility and validity of the test are yet to be fully established. If treatment options partly depend on pathologists' interpretation of IH test results for c-kit and on surgeons judgements regarding unresectability then it can be appreciated there may be considerable latitude for subjectivity.

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1.2.4 Epidemiology and occurrence.

Incidence estimates range from 4 to 40 cases per million.[15, 17]In the UK it has been estimated that 10 per million (i.e. 500 to 1,000) patients a year are affected[18] however this incidence estimate may eventually be found to be higher as more patients are tested for CD117. The majority of tumours occur in the stomach (60 – 70%), with the small bowel (25 to 35%), colon and rectum (5%) and oesophagus being affected.[15] Isolated cases have been found in the appendix and tumours have also been found in the omentum, mesenteries and retroperitoneum.[15] GISTs can occur at any age, including very rare[19]occurrences in children, however, the average age at presentation is between 50 and 70 years old.[20] GISTs range in size from a few millimetres to 40 cm in diameter. Over 95% of patients present with a solitary primary tumour, with up to 40% of these directly invading the surrounding organs.

1.2.5 Prognosis

Prognosis of patients with GISTs greatly depends on whether the tumour is resectable. If resectable the size and mitotic activity of the tumour can be used to estimate prognosis with the location and tumour stage at presentation also being influential.[14,20] Prognosis for unresectable and/or metastatic GIST is generally seen as poor. For example, Conlon [21] described a 5 year survival of 0% in patients who did not have complete tumour resection in contrast to 40% in patients who underwent complete resection.[22] In metastatic

disease a median survival rate of only 19 months was reported in 94 patients with metastatic GIST.[23] It must be borne in mind that prognosis for KIT positive GIST is uncertain because of the recent change in the definition of GIST and recent introduction of immuno-histological testing. Prognosis estimates that date from before IH testing was introduced may have included patients who did not have KIT positive GIST and prognosis estimates from studies after 2000 may not have had time to mature.

1.3 Current service provision

Surgery is the treatment of choice in patients presenting with disease amenable to surgery, but options are limited if a tumour is unresectable or if metastases are present. In practice some patients receive chemotherapy or radiotherapy but their benefits remain uncertain.[18] Treatment of people with unresectable and /or metastatic GIST currently comprises symptom relief and best supportive care (BSC). Imatinib was granted a licence in the UK in 2002 and is beginning to be used in patients with advanced unresectable and/or metastatic GIST. Recent guidelines for its use from a group of UK investigators/practitioners have been developed and published .[18] The guidelines recommend that imatinib should be considered as the treatment of choice in patients with advanced unresectable or metastatic GIST and patients should be managed in an appropriate multidisciplinary setting, ideally within a Multidisciplinary Sarcoma Team, where close monitoring of treatment should be undertaken. They recommend an initial dose of 400mg daily, taken orally with food, with the option of proceeding to higher doses in the event of a poor response or relapse. However the drug should not be continued beyond 8 weeks in the absence of a clear cut clinical or radiological benefit. The guideline authors state that there is still much to be learned about the drug and their recommendations may be modified in the light of more mature data from ongoing phase III trials.

1.4 Description of new intervention

Imatinib (Glivec in Europe, Gleevec in the USA, formerly STI 571 *[signal transduction inhibitor 571]*) is a derivative of 2-phenylaminopyrimidine that specifically inhibits certain tyrosine kinases by binding to their ATP binding domain. It is available in tablet form and is administered orally. Imatinib is a protein-tyrosine kinase inhibitor (ATC code: L01XX28) developed by Novartis Pharmaceuticals UK Ltd. As previously described recent molecular research has found that the majority of GISTs are positive for the KIT protein, a plasma membrane receptor normally stimulated by stem cell factor (SCF) to become an active protein tyrosine kinase. The KIT gene is a proto-oncogene whose product participates in cell signalling that controls cell division and apoptosis. The KIT mutations in GIST cause the receptor to become phosphorylated in the absence of SCF and to gain constitutive protein tyrosine kinase activity. Imatinib works by inhibiting the tyrosine kinase activity of the KIT protein and so shifting the balance toward re-establishing control over apoptosis and cell division.[23,24] Imatinib was first used in patients with chronic myeloid leukaemia (CML).[29]

Dosage and administration

The Novartis website has detailed information regarding prescribing practice. (http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf [accessed 17.9.03])

The following information is a short summary:
Novartis recommends that therapy should be initiated by a physician experienced in the treatment of patients with gastrointestinal stromal tumors. They recommend a dose of imatinib of 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day. The drug is available in tablet form, as 100mg tablets or 400mg tablets. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

Drug interactions

CYP3A4 is the major enzyme responsible for metabolism of imatinib with other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, playing a minor role in its metabolism. Caution is recommended when administering imatinib with inhibitors of the CYP3A4 family, these drugs may increase imatinib plasma concentrations, or conversely drugs that are inducers of CYP2A4 activity may decrease imatinib plasma concentrations. In addition drugs with CYP3A4 substrates should also be administered with caution (for further details and contraindications details, see the product information at: (http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf [accessed 17.9.03]).

1.4.1 Licensing

The FDA approved imatinib in the USA in February 2002 for the treatment of GIST[25] and is licensed for the treatment of adult patients with KIT (CD117) positive unresectable and/or metastatic malignant GIST. In Europe, the European Commission Committee for Proprietary Medicinal Products (CPMP), in a European Public Assessment Report (EPAR), issued a Marketing Authorisation on 24th May 2002 for imatinib to be used in the treatment of adult patients with KIT (CD117) positive unresectable and /or metastatic malignant GIST. The licence was issued on the basis of a single phase II, open-label, randomised, uncontrolled multinational study that was conducted in 147 patients (B2222). The primary evidence for efficacy in these patients with unresectable and/or metastatic GIST was based on the objective response rate of tumour size from a Phase II trial.[26] "The Committee for Proprietary Medicinal Products (CPMP) recommended that the Marketing Authorisation should be granted under exceptional circumstances because the indications for which the medicinal product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the quality, safety and efficacy of the medicinal product".[27,28] In addition the EPAR states that "Given the outstanding activity observed and in view of the applicant's commitment to complete the identified programme of studies laid out as specific obligations, the results of which shall form the basis of an annual reassessment of the benefit/risk profile, the CPMP considered that an approval under exceptional circumstances could be recommended".[28] Imatinib is also licenced for use in patients with Chronic Myeloid Leukaemia.[29]

1.4.2 Anticipated costs

In 2002 The National Horizon Scanning Centre analysed evidence pertaining to the use of imatinib as a new and emerging technology for the treatment of GIST.[30] According to this report, if imatinib were used in patients within its licensed indication, then around 300 patients each year would be eligible for treatment with imatinib. At an estimated cost of £1,557 to £3,115 per month per patient (depending upon dose), this would result in a cost to the NHS (England and Wales) of between £5.6M to £11.2M per year. Little additional service impact was envisaged because imatinib can be used on an outpatient basis.

2. SYSTEMATIC REVIEW METHODS

2.1 Methods for reviewing effectiveness

2.1.1 Problems envisaged in determining imatinib effectiveness.

According to our scoping search it was thought unlikely that there are published RCTs or any controlled trials that directly compare imatinib with current standard treatment for unresectable and/or metastatic GIST. If this proves to be the case after systematic searching an indirect comparison of imatinib and standard treatment will be attempted. This will be done by conducting searches for studies that have investigated standard care or experimental treatments and comparing the results of these studies with the results of the uncontrolled imatinib trials. As well as the usual problems of heterogeneity of study quality, and comparability of studies using completely different treatments, the major problem specific to this review is the changing definition of GIST over the last 20 years or so. Whilst the advent of molecular analysis, has recently clarified the definition of GIST, before these techniques were available the term GIST encompassed many different pathologies, which means that patients in studies undertaken before these techniques were available may or may not have GIST as judged by current criteria. This will cause difficulties with the validity of any indirect comparisons used in the evidence synthesis. To try and flag this up throughout the report, when results tables are given, patient diagnoses are repeatedly described. This recent shift in the definition of GIST will also have implications for development a model for economic analysis because one important component of the model will be an understanding of the natural course of the disease in the absence of treatment. Studies that have been undertaken before molecular/ KIT based diagnosis of GIST came on stream, may well have included patients who were not suffering from GIST (as currently defined), making the use of these natural histories of GIST extremely problematical. Conversely because the diagnosis of GIST through molecular techniques is so recent, < 4 years, a full understanding of the progression of KIT positive disease will not be possible.

These issues have important implications for the conduct of the review, in particular the search strategy, inclusion criteria and quality assessment.

2.1.2 Search strategy

The search strategy was divided into 6 parts and aimed to look for trials of imatinib (with or without standard treatment comparators), trials of alternative/experimental treatments, studies that had observed patient prognosis without treatment (to enable a comparison of disease progression should trials without comparators be available) and diagnostic papers in order to gain an insight into the uncertainty of GIST diagnosis and possible consequences of treating false positives. In addition ongoing trials were sought, as imatinib is a very recent drug. A search for economic evaluation of treatments for GIST was also conducted.

The searches were not restricted by language. Published and unpublished studies were sought. Databases were searched from inception. Searches (except for ongoing trials) were undertaken between 25 April and 15 May 2003.

Electronic Search

The following databases were searched:

Effectiveness of Imatinib for treating GISTs.

The following sources were searched:
- Bibliographic databases: Cochrane Library (CENTRAL) 2003 Issue 2; MEDLINE (Ovid) 1966 – Week 3 April 2003; EMBASE (Ovid) 1980 – Week 16 April 2003; SCI Search (Web of Science) 1981 – April 2003; CancerLit (PubMed) 1966 – May 2003, and CINAHL (Ovid) 1982 – Week 3 April 2003.

CancerLit was listed as a separate database in the review protocol. However, since then it has been subsumed by PubMed and can be searched by choosing the 'Cancer' subset as a 'limit'

Effectiveness of alternative treatments

The following sources were searched:
- Bibliographic databases as follows: Cochrane Library (CENTRAL) 2003 Issue 2; MEDLINE (Ovid) 1966 – Week 4 April 2003; EMBASE (Ovid) 1980 – Week 19 May 2003; SCI Search (Web of Science) 1981 – May 2003; CancerLit (PubMed) 1966 – May 2003, and CINAHL (Ovid) 1982 – Week 4 April 2003.

Where appropriate, searches were restricted to systematic reviews and clinical trials (see Appendix 1 page 68 for detail)

Prognosis/natural history of GISTS

- Bibliographic databases: MEDLINE (Ovid) 1966 – Week 3 April 2003; EMBASE (Ovid) 1980 – Week 17 April 2003; CINAHL (Ovid) 1982 – Week 3 April 2003.

Diagnosis of GISTs

The following sources were searched:
- Bibliographic databases: MEDLINE (Ovid) 1966 – Week 3 April 2003; EMBASE (Ovid) 1980 – Week 17 April 2003; CINAHL (Ovid) 1982 – Week 3 April 2003.

Ongoing trials

- Trials registers: m*eta*Register of Controlled Trials (*m*RCT), National Research Register 2003 Issue 2, ClinicalTrials.gov (National Institutes of Health), International Cancer Research Portfolio, Current Trials (MRC Clinical Trials Unit), UKCCCR National Register of Cancer Trials, CancerBACUP, Cancer.gov (National Cancer Institute). Searches were carried out 8-9 July 2003. Unless otherwise stated the registers were searched using the drug terms Imatinib, Glivec, Gleevec, STI 571 and the results browsed for references to the relevant population.

Economic evaluation / models

The searches for clinical effectiveness were extended to identify any existing models on treating GISTs and information on costs, cost effectiveness and quality of life from the following sources:

- Bibliographic databases; MEDLINE (Ovid) 1985 – July 2003, EMBASE (Ovid) 1980 – July 2003, Cochrane Library (NHS EED) 2003 Issue 2, Cochrane Library (DARE) 2003 Issue 2, HEED June 2003
- Internet sites of national economic units: University of York Centre for Health Economics, Health Economics Research Unit, Health Economics Research Group.

Since very broad searches of MEDLINE and EMBASE had already been conducted on effectiveness, prognosis and diagnosis, additional searches of these databases focussed on specific searches for costs and quality of life of the condition [see Appendix 1 for detail]

2.1.3 Inclusion and exclusion criteria

A three stage sorting process was instigated to look through the yield of the search.

Stage 1 - including or excluding studies.

Two reviewers independently assessed papers for inclusion/exclusion using the title and where available the abstract. The following inclusion criteria were applied:

Inclusion criteria

Study design: Relevant RCTs, non-randomised controlled studies, cohort studies, and case series that reported effectiveness results of treatment with imatinib and/or other interventions in patients with GIST.

Population: Ideally patients diagnosed cKIT positive unresectable and/or metastatic GISTs (including primary or recurrent tumours). Not so ideal but still included were patients histologically diagnosed with GIST. In trials older than 1999 patients who were diagnosed with gastrointestinal leiomyosarcoma or soft tissue sarcoma that appeared to behave as GIST (e.g. tendency to metastasize in the liver), were included. Early terms for GIST[4] could include: - oesophageal leiomyosarcoma; gastric leiomyoma; gastric leiomyoblastoma; small intestinal leiomyoma and leiomyosarcoma; colonic and rectal leiomyoma and leiomyosarcoma; gastrointestinal autonomic nerve tumour (GANT); leiomyoma and leiomyosarcoma of omentum and mesentery; retroperitoneal leiomyosarcoma.

Intervention: Imatinib. Oral dosage – any dose. (Where imatinib = STI 571, Glivec, Gleevec, or CGP57148).

Comparators: The ideal comparator was the current standard treatment (symptom-relief and best supportive care), or placebo. If there were no trials with these comparators, data from trials that investigated experimental treatments in

patients with GIST were sought, so that an indirect comparison could be made.

Outcomes: The following outcomes were considered whenever available: Quality of life (most preferred), mortality (overall survival and median survival times), morbidity and tumour response. (Tumour response could be measured using CT scans, MRI scans or PET scans).

Disagreements were resolved by discussion. Inclusion/exclusion decisions were made prior to detailed scrutiny of the results and study quality assessment. Foreign language publications were screened using English abstracts where available.

Stage 2 Consensus meeting.

Because the initial systematic search and sort at stage 1 had yielded in excess of 1000 papers using the above criteria, it was felt that tighter criteria were needed to eliminate papers that could not add substantial value to the review. In particular a large yield had come from prognosis/natural history papers and diagnostic papers. It was therefore agreed that the following inclusion criteria were to be applied:

Imatinib effectiveness - any patient with GIST (at any stage) who has been treated with imatinib. Ignore reviews and case studies of single patients published in abstract form only.

Other treatments – any patient with GIST (at any stage) who has been treated with drugs other than imatinib, also include other procedures e.g. surgery, radiotherapy, brachytherapy. Exclude papers that compare surgical laparoscopy vs. open surgery.

Prognosis – papers describing primary research that involved the prognosis of 10 or more patients where clinical outcomes are described. Ignore reviews.

Diagnosis – papers describing primary research that involved 10 or more patients with clinical outcomes reported. Major reviews on diagnostic accuracy or diagnostic criteria of GIST, especially those describing advanced disease were included.

Three reviewers (MC, FS, JW) applied the criteria on the papers selected at stage 1, and disagreements were resolved by discussion.

Stage 3

Full paper copies of studies identified in stage 2 were obtained for detailed examination. At this stage, additional papers were excluded as and when detailed study of the methods revealed that the paper did not meet the inclusion criteria, usually this was because the wrong populations had been used, in particular some papers on examination had used patients with primary disease that was treatable with surgery and was not metastatic. Translations were also obtained on full papers where necessary or where possible. Translations were not obtained for 4 case studies included in the review, as it was not felt that a translation would add value to the review.

2.1.4 Data extraction strategy

Two reviewers independently extracted data using a pre-designed data extraction form (see Appendix 2 page 81). Disagreements were resolved by discussion, consulting with a third party where necessary. Where there was missing information and time constraints allowed the authors were contacted. Data from studies with multiple publications were reported as a single study but the source of the publications was noted.

2.1.5 Quality assessment strategy

Quality of studies was assessed using the York CRD criteria[16] for experimental and observational studies (Appendix 11, page128). These criteria were tested and revised where necessary. The following quality issues were felt to be of paramount importance: study design, patient characteristics, (in terms of GIST diagnosis, disease severity, length of time with GIST), and any possible sources of biases in patient selection, treatment provided, and outcomes measured, where found these were reported.

2.1.6 Methods of analysis/synthesis

A descriptive analysis of each individual included study was undertaken with the relevant evidence categorised and summarised in tables. Summary tables of survival, tumour response, adverse events and quality of life were constructed. Where appropriate, results from individual studies were quantitatively pooled by meta-analysis. Identified research evidence was interpreted according to the assessment of methodological strengths and weaknesses and the possibility of potential biases.

2.1.7 Handling the company submissions

The industry dossier was used as a source of data for studies that met the inclusion criteria. A detailed analysis of the industry model, including the strengths and weaknesses and the implications of different assumptions was undertaken.

Any ‘commercial in confidence’ data has been shaded in this TAR report (followed by an indication of the relevant company name e.g. in brackets) so that the NICE secretariat can negotiate (before and during the Institute’s consultation process) with industry the subsequent inclusion of such data in the HTA monograph publication or subsequent peer-review publications. In addition “academic in confidence” data has also been shaded, where data has been used from unpublished work, in this case the Goss et al study.

3. RESULTS OF EFFECTIVENESS ASSESSMENT

Because of the absence of data from RCTs that had directly compared imatinib and standard treatment for patients with advanced kit +ve GIST, the following assessment was based on data from uncontrolled trials, case series, or single case studies.

3.1 Quantity and quality of research available

3.1.1 Number of studies identified

Although systematic searching yielded a very large number of publications very few of these reported clinical outcomes of imatinib treatment for unresectable and/or metastatic GIST. Table 1shows how many studies were identified from the systematic search.

Table 1 Yield of search strategy

Stage	Imatinib search	Alternative treatments	Prognosis	Diagnosis
Stage 0 – electronic search	166	842	2155	2880
Stage 1	92	190	267	446
Stage 2	34 full papers + 5 abstracts + 1 unpub*	64 + 1 unpub*	48 + 1 unpub	109
Stage 3 - included	10 (1 trial = 2 publications); + 4 ongoing trials with interim results published in abstract only, + 1 retrospective case series published in abstract only.	15	14 including 1 unpub*	Not sorted further systematically

* unpublished study of Goss et al included in industrial submission

3.1.2 Number and type of studies excluded, with reasons for specific exclusions

At stage two, 24 published full papers out of 34 potential imatinib studies were excluded after scrutiny of the full publications. These together with the unpubished study are listed and reasons for exclusion provided in Table 19 (page 122). Of a total of 64+1 papers describing possible alternative treatments that were scrutinized using the full paper copy, 49 were excluded for the reasons given Table 20 (page 123). A total of 49 papers were scrutinized regarding prognosis data, of these 35 papers were excluded because no survival data was available. These are listed in Table 21 (page 126).

3.1.3 Number and types of study included.

This section describes the characteristics of the included studies that have reported on imatinib treatment or alternative treatments for advanced GIST.

Imatinib treatment

Two uncontrolled trials and 8 single case studies that treated cKIT positive patients with unresectable and/or metastatic GIST with imatinib were published as full papers and were included from the systematic search. The main characteristics of these studies are shown in Table 2 together with information on 4 trials and one case series published in abstract form only.

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Table 2 Included studies reporting Imatinib treatment of c-kit positive advanced GIST.

Study ID [trial recruitment]	No: in study	Age [median] (range) gender	Previous treatments	Stage of disease [Time to treatment of advanced disease]	Imatinib dose/day [follow up]	Outcomes sought
Uncontrolled Trials (published in full)						
Demetri 2002 [26] [July 2000 to April 2001] Status - ongoing	147	[54 yr] (18 – 83) 57% ♂	Surg 98% Chemo 51% Radio 15%	Unres 100% Mets 100% Reocc 51%	400 mg or 600 mg [9 mths]	Mortality: K-M Tu: response: MRI/CT QoL/PM:(ECOG) Adverse events: CTC 2.0
van Oosterom 2002 [31] [Aug 2000 to Dec 2000] Status - ongoing	40	[53 yr] (29 – 69) 62.5%♂	Chemo 60% Radio 10%	Mets (liver) 75%	400, 600, 800, or 1000 mg [9-13 mths]	Mortality: described Tu: response: MRI/CT/PET (RECIST criteria) Adverse events: CTC 2.0
Uncontrolled Trials (interim results published in Abstract only)						
Verweij 2003 [32] [Feb 2001 to Feb 2002] Status - ongoing	946	[59] (18-91) 61%♂	Surg 85% Chemo 67% Radio 7%	Mets (liver) 71%	400 mg or 800 mg [median 8.4 mths]	Progression-free survival Tu: response: (RECIST criteria) Adverse events
Benjamin 2003 [33] [Dec 2000 to Sept 2001] Status - ongoing	746	NR	NR	'advanced'	400 mg or 800 mg [median 14 mths]	Progression-free survival Tu: response: (RECIST criteria) Adverse events
Ryu 2003 [34] [June 2001 to Oct 2002] Status - ongoing	33	[52] (33-73) NR	NR	Mets or unres 100%	400 mg or 600 mg [median 19 mths]	Tu: response. Side effects
Judson 2003 [35] [NR] Status - ongoing	28 GIST of 51	[55]	Chemo 73%	NR	800 mg	Tu: response: (RECIST criteria) Adverse events
Case series (published in Abstract only)						
Jankilevich 2003 [36] Status - ongoing	17	NR	NR	NR	NR	Tu: response Toxicity
Case studies						
Joensuu 2001 [37]	1	54 ♀	Surg, Chemo (*thalidomide*)	Mets (4 yr)	400 mg [11 mths]	QoL/PM: WHO performance status Tu: response: MRI/PET Biopsy. Adverse events: CTC 2.0
Hogenauer 2003[38]	1	51 ♂	Surg Chemo	Mets (1 yr)	400 mg [7 mths]	QoL/PM: QLQ-C30 test Tu: response: MRI/PET Biopsy *(by IH)* Adverse events: described
Brooks 2002 [39]	1	75 ♂	Surg	Mets (many sites). (0)	800 mg [4 mths]	QoL/PM: ECOG Tu: response: CT/MRI
*Miyagawa 2002[40]	1	62 ♂	Surg	Unres Mets (4 yr)	300 mg [12 mths]	Tu: response: MRI Adverse events: described
*Terashima [41]	1	32 ♀	Surg	Meta (4 mths)	400 mg [7 wks]	Tu: response: CT Adverse events: described
*Mukaide	1	45	Surg	Unres	400 mg	Tu: response: described

2002[42]		♀		Mets (0)	[9 mths]	
*Omori 2002 [43]	1	64 ♀	Surg	Mets (0)	400 mg [2 mths]	QoL/PM: described Tu: response: CT Morbidity: described
*Fujimoto 2002[44]	1	59 ♂	Surg	Mets (0)	400 mg [9 mths]	

* Published in Japanese – information from abstract only. ♂, male; ♀, female; NR, not reported; Mets, metastatic disease; Unres, unresectable disease; Reocc, reoccurrent disease; Surg, surgery; Radio, radiotherapy; Chemo, chemotherapy; yr, years; mths, months; wks, weeks; Tu: tumour; QoL, quality of life; PM, Performance measure; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; K-M, Kaplan Meier. ECOG, Eastern Cooperative Oncology Group; CTC, Common Toxicity Criteria; RECIST, Response Evaluation Criteria in Solid Tumours.

Alternative treatments

Eleven published trials and 4 single case studies were identified from the systematic review. The characteristics of these studies are shown in Table 3. None of the trials prospectively tested patients for cKIT as they commenced before the test was available. A retrospective analysis of patients for cKIT was undertaken in Ryan.

Table 3 Included studies reporting non-imatinib treatment of GIST.

Study ID	Diagnosis	No: in study (Dates of study)	Age [median] (range) gender	Previous treatments	Stage of disease	Intervention [follow up]	Outcomes sought
RCT							
Judson 2001[45]	Soft tissue sarcoma. Some GIST by retro d	94; 21 GIST (NG)	52 (19 – 80) 48% ♂	Surg 61% Radi 29% Chem 0%	Adv mets	CAELYX vs. doxorubicin [?]	Mortality. Tu: response: Adverse events: CTC
Uncontrolled trials							
Ryan 2002[46]	HC GIST 16/20 cKIT +ve by retro d	20 (August 1999-?)	44 (22 – 77) 77% ♂	Surg 95% Radi 20% Chem 45%	Adv	ET-743 [?]	Mortality: K-M Tu: response: CT Adverse events: CTC
DePas 2003[19]	"GI sarcomas"	67 (1979-1999)	Not stated	N/A	Adv mets 95%, reocc 5%	STS therapy [?]	Mortality: K-M. Tu: response.
Rajan 2001[47]	HC mets sarcomas	16 (1993 – 2000)	Not stated 50% ♂	Chem 44%	Mets	Chem-embo [3 yrs]	Mortality: K-M. Tu: response: WHO criteria. Adverse events.
Mavligit 1995[48]	HC LMS	14 (1991 – 1994)	(30 – 75) 86% ♂	Surg 100%, Radi 7% Chem 36%,	Mets (liver)	Chem-embo [3 yrs]	Tu: response: CT. Adverse events.
Chen 1998[49]	HC LMS	11 (1984 – 1995)	56 (30 – 69) 18%♂	Surg 100%, Radi + chem 9%	Mets (liver)	Resection of liver mets [39 mths]	Mortality.
Bramwell 2002[50]	HC GIST or LMS	26; 11 GIST. (NG)	51.7 58% ♂	?	Locally adv or mets	VX-710 + doxorubicin [?]	Mortality: KM Tu: response: Adverse events: CTC
Edmonson	Stromal	39;	55	None	Adv	DTIC with	Mortality: KM.

2002[51]	tumours 18 LMS†	21 GIST (1994 – 1998)	(39 – 69) 62% ♂			MAP [?]	Tu: response. Adverse events.
Patel 2001[52]	HC soft tissue sarcoma	56 (1998 – 2000)	54 (28 – 76) 48% ♂	Chem 29%	Adv mets	Gemcitabine [?]	Tu: response. Adverse events. Time to progression: K-M
Cohort study							
Eilber 2000[53]	GIST	46 (13 control) (1988-1998)	Not stated	Not stated	Reocc & mets††	IP chem [mean 19 mths]	Mortality. Reoccurrence. Adverse events.
Case series							
Carson 1994[54]	Gastric LMS or leiomyobl-astoma	32 (1970 – 1991)	57 (13 – 81) 75% ♂	N/A	Primary or mets	Chem, radi, or surgery [?]	Mortality. Tu: response.
Case studies							
Shioyama 2001[55]	Retro d cKIT +ve GIST	1 (1993)	75 ♀	Surg	Reocc	Chem, radi, immuno [6 yrs]	Tu: response: CT/PET.
Pollock 2001[56]	CD34 +ve GIST	1 (NG)	77 ♀	None	Unres	Radi [2 yrs]	Tu: response. Adverse events
Kamoshita 2002[57]	cKIT +ve GIST	1 (NG)	56 ♀	None	Mets (liver)	Surg + ethanol inject'n therapy [8 mths]	Tu: response: CT
Miyauchi 2002[58]	CD34 +ve GIST	1 (NG)	82 ♀	None	Unres	Self-expandable stent [12 mths]	Mortality

† of non GI origin. †† not beyond liver or peritoneum. HC, histologically confirmed; LMC, leiomyosarcoma; ♂, male; ♀, female; Mets, metastatic disease; Unres, unresectable disease; Reocc, reoccurrent disease; Surg, surgery; Radi, radiotherapy; Chem, chemotherapy; Immuno, immunotherapy; yr, years; mths, months; wks, weeks; Tu: tumour; QoL, quality of life; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; K-M, Kaplan Meier; ECOG, Eastern Cooperative Oncology Group; CTC, Common Toxicity Criteria; RECIST, Response Evaluation Criteria in Solid Tumours.

3.1.4 Quality of included studies and evidence rating

Quality of studies and evidence rating.

Quality was assessed using the York CRD checklist[16] for case studies (see Appendix 11 page 128). This checklist helps identify selection bias and study conduct. Quality was assessed on all trials, a detailed analysis of the imatinib trials and a summary of the alternative treatments is given below, for further details see Appendix 12, page 131.

Demetri 2002[26]:
In this trial eligibility criteria were explicit i.e. all patients had to have cKIT positive GIST and all were in a similar state of their disease progression. It is unclear how the sample was selected and therefore how representative it was. With regard to study conduct all the outcomes were assessed using standard criteria where these were available, for example, the SWOG criteria was used for tumour response measurement and CTC was used for adverse

events. Unfortunately in reporting of the CTC scale grades 3 and 4 were combined. In addition 2 patients were withdrawn with reasons not given. Blinding of assessors to patient treatment was likely but not explicitly stated. Follow up was long enough for tumour response and short-term adverse events to be assessed but at write up median survival had not been approached. The trial is still ongoing. Overall this trial was well conducted however the fundamental problem of no control group means that it represents evidence of grade C according to the York CRD criteria.[16]

Van Oosterom 2001-2002 [31,59]
Quality was assessed using the York CRD criteria. Two publications reported data on this trial at different stages. The number of patients with cKIT was reported differently in separate publications (35 vs. 36). For this reason data used in this review came from the latest publication that offered more mature data. Eligibility criteria were explicit (all patients cKIT positive GIST) but the representativeness of the sample is uncertain. It was unclear if all patients were in a similar state of disease progression. With regard to study conduct, outcomes were assessed using standard criteria for tumour response and adverse events. Adverse events were not clearly reported, for example, grades for orbital oedema were not reported, and grades were compressed for reporting diarrhoea. The manner of adverse events reporting makes intra- and inter- trial comparisons difficult. Follow up was adequate for assessment of short-term adverse events and tumour response to be assessed but was not long enough for median survival to be reached. Overall this trial was well conducted, the major problem being its uncontrolled design so that it represents grade C evidence according to the York CRD criteria.[16]

Alternative treatments.
In all the trials of alternative treatments, it was difficult to ascertain if the sample was representative as details of patient recruitment were not given and in all but 4 trials it was difficult to ascertain disease status. Most trials however did have explicit inclusion criteria but because of the ambiguity of terms for GIST these may not be too helpful. Follow up was long enough in most cases for important events to occur with many of these trials reaching maturity. Most trials used objective criteria for outcome evaluation, but none mentioned blinding of assessment. All but 2 were uncontrolled trials, which makes interpretation of treatment effectiveness difficult. In the only RCT found, GIST patients contributed a small proportion (21/94) but these were not cKIT tested. The cohort study used control patients who were ineligible for the trial, which may make these controls different from the cases. In summary, whilst these trials were reasonably well conducted in most cases, because of trial design and difficulty in identification of GIST, the data that they contribute to understanding the relative effectiveness of imatinib for GIST should be viewed with caution.

3.2 Results reported in Imatanib included studies

Two uncontrolled trials published in full, Demetri 2002[26] and van Oosterom 2002[31], reported clinical outcomes for patients (187 in total) with advanced GIST treated with Imatinib. These trials are summarised below.

Demetri trial

Demetri 2002[26] (study CSTI571-B2222[60]) is an ongoing multicentre trial sponsored by Novartis to evaluate imatinib for advanced GIST. Recruitment of 147 patients occurred between July 2000 and April 2001; of these 135/137 tested positive for c-kit with10 samples were unavailable for analysis. Two kit negative patients were judged ineligible. Patient characteristics are listed in Table 2 (page 21); all patients had advanced (metastatic and unresectable) GIST with a mean total tumour area of 173 cm^2 . Patients were randomly assigned to receive orally a single dose of 400 mg (n=73) or 600 mg (n=74) Imatinib (100 mg capsules). Disease progression and clinical condition warranted dose increase from 400 mg to 600 mg in 9 patients. Patients whose disease progressed were withdrawn from treatment; these plus withdrawals for any other reason and those that died were classified as treatment failures.

The main outcome measures in this study were mortality, tumour response to treatment as an indicator of disease progression, time to treatment failure and adverse events (recorded daily in patient diaries). In addition a quality of life measure ("performance status" ECOG), PET scan (44% of patients), biopsy of selected patients, and plasma monitoring of imatinib were implemented. Tumour response was determined by CT or MRI at 1, 3 and 6 months then every 6 months according to SWOG criteria. Four categories of tumour response were defined: CR = complete response (disappearance of detectable and evaluable disease); PR = partial response (≥50% reduction in sum of products of perpendicular diameters of all measurable lesions); SD = stable disease (neither CR, PR or disease progression); DP = disease progression (≥50% increase OR 10 cm increase in sum of products of perpendicular diameters of all measurable lesions, OR worsening of an evaluable lesion, OR reappearance of a lesion OR appearance of a new lesion OR failure to attend for evaluation due to disease progression). All responses were confirmed by repeated imaging within 1 to 4 months.

Results of survival analysis and tumour responses observed in the Demetri 2002 trial are summarised in table Table 4 and in Table 5.

Table 4 Survival of patients treated with imatinib in Demetri trial.

Study	Diagnosis (no:)	survival from start of treatment			survival from diagnosis‡		
		median	1 yr	2 yr	median	2.66 yr	4 yr
Demetri 2002[26,61]	GIST 91% c kit+ve (147)	not reached	88%	78%	not reached	88%	77%

‡ For most of the time since diagnosis most patients were not receiving Imatinib. ‡‡ at 9-12 months. NR, not reported.

Table 5 Tumour responses to Imatinib observed in Demetri trial*

Study	Unevaluable	Complete response	Partial response	Stable Disease	Disease Progression
Demetri‡ n=147 [at 21 months[61]]	4.8%† [5%]	0%† [0%]	53.7%† [66%]	27.9%† [17%]	13.6%† [12.2%]

* SWOG criteria. ‡ all doses. †median follow up 9 months. commercial in confidence

Approximately 65% of patients remained without treatment failure up to 60 weeks (15 months) of treatment.[61]

A proportion (n=64, 44%) of patients in the Demetri trial received PET scans. PET results correlated with subsequent evidence of tumour response determined by CT or MRI and in particular PET showed increases in ^{18}F-deoxy glucose uptake or new sites of uptake in those patients that experienced disease progression. More detailed results summarising PET observations obtained at one study centre (n=25) at 21 months after start of treatment are provided in the industrial submission.[61]

ECOG performance status results observed in the Demetri trial are summarised in Table 6 and adverse events in Appendix 6 page 98. All patients experienced an adverse event of some sort suspected to be related to treatment. In the first interim analysis (median follow-up at 288 days) a total of 144 patients (98%) had an adverse event of some kind with 31 patients (21.1%) having a serious adverse event classed at grade 3 or 4. In the second interim analysis (316 days later) all the patients (100%) had an adverse event of some kind. Of these 37.4% were classed as grade 3 and 15% were classed as grade 4, giving a total of adverse events at grade 3 and 4 as 52.4%.[61]The most common serious events at the early interim analysis appear to be an unspecified haemorrhage (7 patients) and neutropenia (7 patients). In the later analysis GI symptoms such as nausea, vomiting, abdominal pain and diarrhaea become slightly more frequent, but the numbers are very small (7 or less). Overall imatinib was reported well tolerated.

Table 6 ECOG performance status results in Demetri 2002 trial

performance status[61]	month of visit						
	screening	2	4	7	14	19	25
0	42%	56%	64%	69%	69%	69%	77%
1	39%	30%	22%	21%	19%	20%	13%
2	18%	9%	5%	4%	3%	1%	3%
3	1%	1%	0%	1%	0%	0%	0%
4	0%	0%	1%	0%	0%	1%	0%
unknown	0%	3%	8%	5%	9%	9%	6%
N	147	147	144	130	121	103	31

van Oosterom trial

The van Oosterom 2002[31,62] study is an ongoing 3-centre Phase I (dose-determining) study of imatinib that recruited 40 patients, 35 with kit +ve GIST, between August and December 2000. Eligible patients were required to have evidence of disease progression less than 6 weeks prior to starting imatinib treatment. Daily doses ranged from 400 mg (in one dose, n=8), 600 mg (in two doses, n=8), 800 mg (in two doses, n=16), to 1000 mg (in two doses,

n=8). Dose escalation and dose reduction were permitted. The main outcome measures were tumour response (according to RECIST criteria http://www3.cancer.gov/bip/RECIST.htm), toxicity (CTC version 2), and PET-determined tumour function according to EORTC criteria (see Appendix 4, page 87) in a subgroup of patients (n=16) at a centre able to undertake PET analysis.

The results of survival analysis and tumour responses observed are summarised in Table 7 and Table 8.

Table 7 Survival in van Oosterom trial

Study	Diagnosis (no:)	survival from start of treatment			survival from diagnosis‡		
van Oosterom 2002[31]	GIST 88% c kit+ve (40)	NR	90%‡‡	NR	NR	NR	NR

‡‡ at 9-12 months. NR, *not reported.*.

Table 8 Tumour response* to Imatinib in van Oosterom trial†

Study	Unevaluable	Complete response	Partial response	Stable Disease	Disease Progression
van Oosterom[31] n=35‡	8% no longer on treatment	0%	51%	31%	8.5%

* RECIST criteria. ‡ c-kit +ve patients only. † Five non-GIST patients had disease progression, results as of Sept 2001.

Tumour function determined by ^{18}F-deoxy glucose uptake observed by PET was evaluable in 14/16 patients. Response was monitored on day 0, then at day at 8, and again at day 28 for confirmation of any functional change seen at day 8. EORTC criteria classify 4 categories of response (see Appendix 4, page 87): - complete response, partial response, stable disease (no change), and disease progression. Results are summarised in Table 9. Survival data from this trial is shown in Table 7.

Table 9 Tumour functional status by PET in 14 patients treated with Imatinib.

Response	CR day 28	PR day 28	NC day 28	DP day 28
CR day 8	**8**	-	-	-
PR day 8	**2**	-	-	-
NC day 8	**1**	-	-	-
DP day 8	-	-	-	**3**

CR, complete response; PR, partial response; NC, no change; DP, disease progression.

Adverse events observed in the van Oosterom[31] study are tabulated in Appendix 6 page 98. Five of the 8 patients on the highest dose regime experienced dose-limiting drug toxicity. Skin rash, oedema, and peri-orbital oedema were the commonest adverse events observed.

Single case studies

In addition to the two uncontrolled trials, 8 case studies of imatinib for advanced GIST were included.[37-44] They describe patients treated between March 2000 and June 2002. Six patients received 400 mg / day, one 2 x 400 mg / day and another 300 mg /day. Time to treatment after metastases ranged from 4 years to 0 months. All patients survived to time of

analysis (range 7 weeks to 12 months) and all experienced considerable reductions in tumour size after treatment (90% reduction in one case). Adverse events were either unreported or described as not severe. Further details of case studies are provided in Appendix 5 (page 91) and further details can be found in Appendix 9.

Interim results published in Abstract format only

Interim results of 4 ongoing trials and a case series reported in Abstract form only are incorporated into summary tables (Table 10 and Table 11). For further details see Appendix 9.

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3.3 Results reported in studies of alternative treatments

Fifteen studies[19,45-57] were included (of which 9 were trials, one controlled) that reported on treatments other than imatinib for advanced GIST. In only one small study was cKIT status analysed (retrospectively, Ryan[46]). Studies date from 1970 to 1999. The median age was in the fifth decade and both sexes were represented. All of the trials looked at patients with advanced disease. Diagnosis were described as leiomyosarcoma, gastrointestinal leiomyosarcoma, gastrointestinal sarcoma and GIST. Whilst some patients may have had GIST as we define it today, others may have had leiomyosarcoma, or other GI sarcomas therefore the usefulness of these studies as historical controls is very limited.

In most of these studies patients had had surgery for primary disease, with 4 reporting prior chemotherapy in about a third of patients and 3 reporting prior radiotherapy in a small proportion of patients. Interventions were heterogeneous, 3 trials (Judson[45], Ryan[46] and Patel[52]) describe novel strategies of chemotherapy, whereas 3 trials examined standard sarcoma chemotherapy, either alone (DePas[19]) or with enhancement of additional drugs (Bramwell[63], Edmonson[51]). A single study looked at intraperitoneal (IP) therapy (Eilber[53]) whilst 2 tested the effect of hepatic chemoembolization for liver metastases. Finally 2 studies reported the effect of surgery on metastatic disease (Chen[49], Carson[54]).

The results (Table 10 and Table 11) observed in these intervention studies in general did not promise patient benefit. Seven studies reported median survival (range 8 months to 24 months). Survival probability was about 72% at 1 year (range 18% to 100%), reducing at 2 years to about 40% (range 30 – 66%) and to 16% at 3 years (range 0 – 40%). Of the trials (n=9) that measured tumour response only 1 patient (unlikely a true GIST) had a complete response (Carson[54]). In terms of tumour response 13 patients (5%) out of a total of 258 cases achieved a partial response whilst 24% were described as having stable disease (64/258). Adverse events were only described in 8 trials. In the trial by Judson[45], doxorubicin gave the most serious haematological adverse events with 47% of patients suffering grade 4 neutropenia. In Ryan[47], patients treated with ET 743, again tended to suffer from haematological problems in particular leukopenia, neutropenia and anaemia. Of the two trials in which patients were treated with chemoembolization, pain seems to have been significant in a number of patients. Bramwell[63] found alopecia was the most common adverse event, whilst Edmonson[51] described toxicity as being significant with 33% of patients experiencing grade 3 vomiting. Finally Patel[52] again found that haematological symptoms were the most common events suffered by the patients treated. None of the trials measured quality of life.

Because of problems of diagnosis, considerable heterogeneity of hopeful treatments attempted, small number of patients investigated and uncontrolled study design in nearly all studies it is difficult to draw firm conclusions from much of the data reported. It was felt that these trials did not offer suitable data for indirect comparison, in particular because of the problems with diagnosis. Further details of these studies are provided in the (Appendix 7, page 103).

Table 10 Summary of tumour response in studies of treatment for advanced GIST

Studies (in full or abstract)	Diagnosis (no) [treatment]	sub-groups	Tumour response				
			%CR	%PR	%SD	%DP	%NE
Uncontrolled Trials (published in full)							
Demetri 2002[26,61] **(in full)**	GIST (147) [imatinib]	median 9 mths follow up At 21 months	0 0	54 66	28 17	14 12	5 5
van Oosterom 2002[31] **(in full)**	GIST (40) [imatinib]		0	51	31	9	8
Uncontrolled Trials (interim results published in Abstract format only)							
Verweij 2003[32] **(abstract)**	GIST (946) [imatinib]	Low dose arm† High dose arm	3 2	48 49	33 33	26 26	
Benjamin 2003[33] **(abstract)**	GIST (746) [imatinib]	Low dose arm†† High dose arm	43 41		32 32	25 25	
Ruy 2003[34] **(abstract)**	GIST (33) [imatinib]		0	48	32	19	
Judson 2003 [35]**(abstract)**	28 GIST of 51	GIST‡	4	64	?	?	4
Case series (published in Abstract format only)							
Jankilevich 2003 [36] **(abstract)**	GIST (17) [imatinib]	13 of 17 evaluated	6	41	18	12	24
Included studies reporting non – imatinib treatment for GIST.							
Judson 2001[45] **(in full)**	STS retro GIST (21/94) [CAELYX /doxorub]	GIST patients only CAELYX doxorub	0 0	0 0	0 0	? ?	? ?
Ryan 2002[46] **(in full)**	[ET – 743] (18/20 patients 16/18 cKIT GIST)		0	0	11	89	0
DePas 2003[19] **(in full)**	GI sarcomas (67) [STS therapy]	Ifosfamide + antracyclin Other all	0 0 0	12 4 9	36 36 36	48 56 51	5 4 5
Rajan 2001[47] **(in full)**	Metastatic sarcomas (16) [chemoembolization]	(at 30 days after treatment)	0	13	69	19	0
Mavligit 1995[48] **(in full)**	LMS (14) [chemoembolization]		.	.	.	.	.
Bramwell 2002[63] **(in full)**	STS; GIST (26) LMS (18) [VX-710 + doxorub]	Non GIST GIST	0 0	13 0	47 9	40 91	0 0
Edmonson 2002[51] **(in full)**	GI "Stromal" (21) [DTIC with MAP]	GIST Leiomyosarcoma	0 0	2 61	NR NR	NR NR	NR NR
Patel 2001[52] **(in full)**	STS (56) [Gemcitabine]	GI leiomyosarcoma Non-GI, STS	0 0	0 18	0 0	100 82	0 0
Carson 1994[54] **(in full)**	LMS or LMB (32) [chem (25)]	chem *partial response duration less than 4 months*	4	16	0	80	0

Doxorub, doxorubicin; GI, gastrointestinal. CR, PR, SD, DP, NE, complete response, partial response, stable disease, disease progression, non-evaluable. ‡ Numbers calculated from Institute of Cancer Research submission to NICE assuming 27 patients evaluated. † 'Objective response' interpreted as CR + PR, data partly from Institute of Cancer Research submission to NICE, PD calculated by difference. †† 'rate of response + stable disease' interpreted as CR + PR + SD. SD by subtraction.

Table 11 Summary of patient survival in studies of treatments for advanced GIST

Study	Diagnosis (number of patients) [treatment]	survival from start of treatment			
Imatinib treated		**median**	**1 yr**	**2 yr**	**3 yr**
Demetri2002[26,6 1]	GIST (147) [imatinib]	not reached at 24 mths	88%	78%	Not reached
van Oosterom2002[31]	GIST (40) [imatinib]	NR	90%	NR	Not reached
Other treatments		**median**	**1 yr**	**2 yr**	**3 yr**
Eilber 2000[53]	GI stromal sarcomas (33 IP therapy) 13 controls no treatment)	[?]	75% IP 70%NT	42% 30%	20% 20%
Ryan 2002[46] [only non-imatinib patients]	GIST (7) [ET – 743]	8.6 mths	18%	NR	NR
Ryan 2002[46] [n = 18]	GIST (assume 18) [ET – 743]	Median survival not yet observed	71%	NR	NR
DePas 2003[19]	GI sarcomas (67) [STS therapy]	16 mths (range 2 –60)	61%	24%	15%
Rajan 2001[47] From time of treatment.	Metastatic sarcomas (16) [chemoembolization]	[?]	67%	50%	40%
Mavligit 1995[48]	Leiomyosarcoma (14) [chemoembolization]	18 mths	71%	66%	0%
Chen 1998[49]	Leiomyosarcoma (5) [Surg – incomplete resection]	24 mths	100%	40%	20%
Edmonson 2002[51]	GI Stromal tumours (21) [DTIC with MAP]	16.7 mths (CI 8.8 – 27.5)	63%	44%	17%
Carson 1994[54]	Leiomyosarcoma or leiomyoblastoma (32) chem.; radi; surg (tot / partial)	Surg tot (21/32) 40 mths Surg partial (11/32) 8 mths	NR	NR	34% (at 5 yrs)

3.4 Summary of effectiveness assessment

Two trials (still ongoing) and 8 case studies were identified from the published literature that reported on imatinib-treated KIT positive patients with advanced GIST. Four relevant ongoing trials and a case series were also identified which have reported data in abstract form only. Fifteen studies where possible GIST patients had been treated with therapies other than imatinib or BSC were also identified. Because of the problems of in particular diagnosis an indirect comparison using these studies was not possible, therefore the results of these studies will not be compared to the imatinib trials in the following section.

Two fully published uncontrolled trials (Demetri 2002[26] n=147, and van Oosterom 2002[31] n=40) provided information on the effects of imatinib treatment. A proportion of advanced GIST patients (8 and 14%, van Oosterom and Demetri trials) experience disease progression (>50% increase in tumour mass). Approximately one third (Demetri 28%, van Oosterom 31%) of patients experienced "stable disease" as determined by measures of tumour mass (CT or MRI). The definition of "stable disease" encompasses up to 50% increase or decrease in tumour load as determined by interpretation of CT or MRI scans. A complete response (disappearance of detectable tumour) was not observed in any trial patient, however approximately half of all patients (54% Demetri, 51% van Oosterom) did experience a "partial response" (> 50% reduction in tumour mass as determined by CT or MRI). More limited evidence (PET and biopsy) indicated that, at least in some instances amongst these partial responders, the functional competence of remaining tumour mass might be severely compromised. Information on tumour response provided only in abstracts (2 large trials, n=946 and n=746, 2 smaller trials, and a case series) was difficult to interpret. These results indicated that a few patients may experience a complete response and that overall tumour response rate was similar to that observed in the fully published trials. The abstracts lacked full details regarding disease status of patients in these studies.

Survival is an objective clinical outcome measure and was recorded in the Demetri trial. The estimation of any putative benefit of imatinib treatment on survival requires comparison with a suitable control group over an appreciable period of time. Unfortunately to date trial follow up time is limited and control group data is only available indirectly from historical studies in which judgments of diagnosis and of disease status may have been applied differently from the Demetri trial. The choice of comparator amongst those available might greatly influence estimates of survival benefit of imatinib. In studies of alternative treatments for advanced GIST median survival ranged from 8 to 24 months (or longer in one study that achieved complete surgical removal of tumour) and survival probability at 1, 2, and 3 years ranged from 18-100%, 24-66% and 0-40% respectively. Survival was better in the Demetri trial (median > 24 months, at 1 year 88%, at 2 years 78%), however it must be born in mind that patient groups were unlikely to be strictly comparable with regard to diagnosis and disease stage and that alternative unsuccessful treatments may theoretically worsened prognoses. In the following section (section 4, page 33) a review of all evidence pertaining to choice of survival probability of patients diagnosed with advanced GIST suitable for comparison with imatinib-treated patients is presented. This is provided so that any choices made regarding suitable comparators can be placed in their proper context.

Both trials of imatinib monitored and reported incidence of adverse events and both used the same CTC version for grading. Unfortunately in their published accounts both trials reported adverse events as combined grades (grade 3 with 4 by Demetri[26], and grade 2 with 3 by van Oosterom[31]). In a statement to us the NCI, who administer the CTC, said they "preferred that results be reported according to grade and not be combined". With a grade 2 event described as a "*moderate adverse event*" a grade 3 as "*severe and undesirable*" and grade 4 as "*life threatening and disabling*", the use of combined grades renders impossible any meaningful comparison between trials and the combination of data across trials problematical. The industrial submission provided further adverse event information from the Demetri trial reporting that 37% of patients experienced grade 3 adverse events and only 15 % grade 4 events. Despite the inconsistent reporting practice in the present instance, it is clear that virtually all imatinib-treated patients experience adverse events. These are mostly, but far from exclusively, of relatively mild grade of severity, which may contrast favourably with

adverse events reported for alternative treatments. In addition the relatively good treatment retention in patients in the Demetri trial is consistent with this assertion.

QoL was not measured directly. Measures of functional status in every-day life tasks (ECOG), which relate to some dimensions of health-related QoL, indicate modest improvement after imatinib treatment. Because of lack of a control, the short-term follow up time in trials, and the lack of direct measures of QoL, these measures are difficult to interpret in terms of effectiveness of imatinib

It is reasonable to assume that patients with unresectable and or metastatic GIST who remain untreated or are only administered BSC will experience tumour growth and disease progression eventually resulting in death. In this context the evidence available from uncontrolled trials (Demetri 2002[26]and van Oosterom 2002[31]) indicates some effectiveness of imatinib for some patients since large decreases in tumour mass with probable loss of functional integrity occur in about half treated patients.

The crucial question "*how extensive is the effectiveness of Imatinib?*" must necessarily be addressed for cost effectiveness analysis. Estimating the extent of effectiveness is problematical; it requires considerable extrapolation of survival data far beyond that provided in the available imatinib trials, comparison with survival probability of an appropriate control group (fraught with difficulties of heterogeneous diagnoses, and allocation of appropriate disease state with regards to unresectability and metastases), together with consideration of QoL experienced by compared groups of patients. These problems are addressed extensively in the Economic Analysis (section 5, page 44) part of this report and are not discussed further here.

4. PROGNOSTIC HISTORICAL CONTROL STUDIES.

To estimate the cost-effectiveness of imatinib for unresectable and/or metastatic GIST, the clinical outcomes of patients treated with imatinib were compared with those of patients with alternative interventions (current standard treatment). As there are no trials that directly compare imatinib with alternative treatments for patients with unresectable and/or metastatic GIST, the relative effectiveness of imatinib can only be estimated by an indirect comparison of outcomes of historical patients and outcomes of patients in imatinib clinical trials.

Survival is one of the most objective and important clinical outcomes. This section of the review aims to summarise data from primary studies that reported survival outcomes of patients with advanced GIST.

4.1 Methods

Studies were included if they were a) primary studies that (b) included more than 10 patients with unresectable and/or metastatic GIST and (c) reported survival outcomes. Because of the difficulty in defining unresectability, studies of patients with recurrent GIST and/or incompleted resection were also included. Clinical trials that evaluate imatinib are not the focus of this section of the review, although a few studies in which some patients subsequently received imatinib were considered. The included studies were assessed concerning patient characteristics, cKIT tested or not, treatment received, length of follow-up, and results of survival outcomes. In many included studies, printed survival curves were the only data source, and we used a ruler to obtain the results of survival outcome.

4.2 Main results

Fourteen papers were identified (Table 12). Histological confirmation of CD117 was provided in only two studies (Ryan et al[46] and an unpublished study by Goss et al[64][supplied on a commercial in confidence basis]). GIST patients usually received surgical treatment. Some patients (or all patients in two studies) were treated with various chemotherapies and/or radiation therapy; and in two studies (Ryan[46] and Goss[64]), some surviving patients finally received imatinib.

4.2.1 Median survival

Median survival was reported (or could be estimated) in 12 studies (with 983 patients in total) (Table 13 page 43). The reported median survival was different across studies and different patients groups (from 2 to 39 months). [Commercial in confidence text removed]

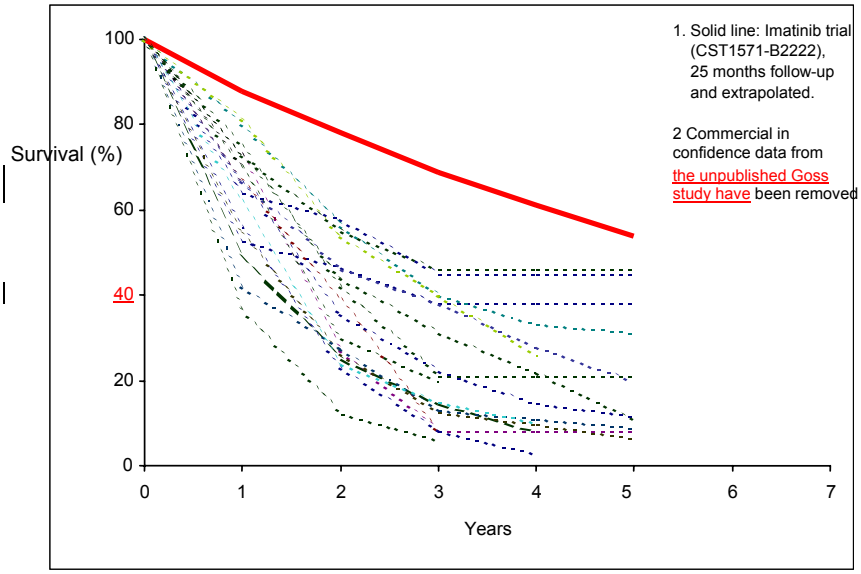
Two studies that included advanced or recurrent GIST (Edmonson et al[51], and Ng et al[65]) reported a median survival of about 16 months. The median survival of patients with incompletely resected

GIST was about 12 month or less, except in a study by Crosby et al[66] (median survival 20 months).

4.2.2 Survival curves

The survival curves from the included studies are presented in Figure 1. The survival rate was from 37% to 80% at year one, from 6% to 45% at year three, and from 0% to 45% at year five. It may not be a surprise to observe very different results, considering differences in patient diagnoses, start points of follow-up, and interventions received.

Figure 1 Survival curves from included prognostic studies



The survival curves based on the most relevant study (Goss et al[64]) [data removed – commercial in confidence] Figure 1. [Commercial in confidence text removed] ……. However, by excluding patients who received imatinib excludes many patients with good survival prognosis. In the Goss study, patients were studied between January 1996 and March 2001, and imatinib for GIST was available only from March 2000. Over the study period patients who died early had no or much less opportunity to be treated with imatinib than patients who survived longer [Commercial in confidence text removed]..... ……. Thus, the survival curve of patients never treated with imatinib greatly under-estimates the survival of patients with metastatic or recurrent GIST in the study by Goss et al[64] (also see Figure 2 [Removed]) because patients who have a longer survival over the study period, (i.e. those who go on to receive imatinib) are excluded.

The industry submission stated that the Goss et al[64] study overestimated the survival of patients with advanced GIST. However, they only used a worse scenario for sensitivity analysis, based on the result of patients with metastases plus incomplete resection in Clary et

al[67], which was inappropriate according to empirical data presented in Figure 1. In the following chapter of economic evaluation, we modified the Novartis submitted model, and confirmed that the patients included in the major imatinib trials (CSTB2222) were relatively comparable to all patients with metastatic and/or recurrent GIST in the Goss study[64].

Figure 2 Survival curves in metastatic or recurrent patients in the study of Goss et al.

Note: [Commercial in confidence data removed].

4.2.3 Long surviving patients

Although a large number of patients with advanced GIST will die within a few years of diagnosis, a small number of patients may survive for many years. For example, according to individual patient data from Novartis,[60] 21 of the 147 patients in the imatinib trial (CSTIB2222) had a disease history (from initial diagnosis) more than 241 weeks before the start of the study, and a recurrence history (from first recurrence) more than 129 weeks. It is interesting to note that the proportion of deaths was relatively low in patients with a very long history of disease or recurrence (Figure 3 and Figure 4). Thus, the imatinib trial may have overestimated the benefit of imatinib, by including a relatively large proportion of patients with very long disease history.

4.3 Remarks

It has been widely quoted that patients with advanced unresectable GIST have a gloomy prognosis; most of them will die soon after diagnosis with a median survival about 12 months. The empirical evidence summarised in Table 13 and Figure 1 indicated that the prognosis of patients with advanced GIST was indeed not good, but it was not homogeneous to all such patients. The reviewed evidence should be interpreted with great caution because of some limitations.

In the majority of the included prognostic studies, historical cases were reviewed retrospectively, and the diagnoses were not confirmed by CD117 (KIT) testing. There is uncertainty about the direction of the impact on the estimated survival dependent on the lack of CD117 confirmation.

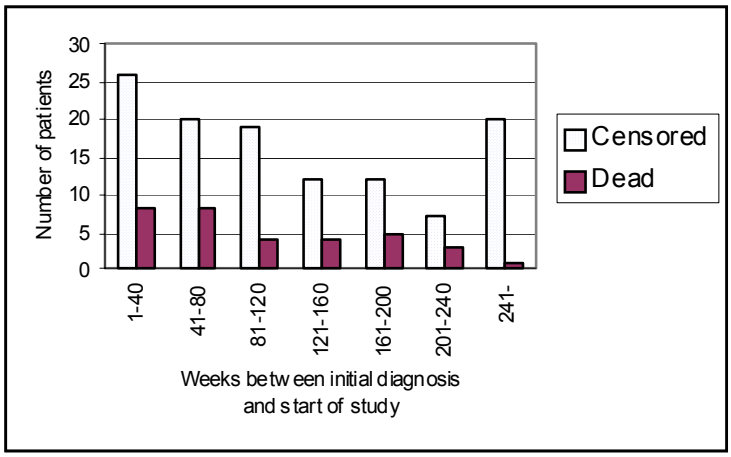
There may be general agreement about the diagnosis of metastatic GIST, nevertheless the prognosis of local and distant metastases may be very different. In addition it is more problematic to define unresectability. Presumably, if the surgical resection of GIST cannot be complete, patients may be defined as having unresectable GIST. It is possible that different surgeons, clinicians and even patients may use different criteria [56] (explicitly or implicitly) about unresectability, and the availability of alternative interventions (including imatinib) may influence the definition of unresectability. For these reasons, the broad spectrum of studies that included patients with incompletely resected, recurrent, or metastatic GIST was considered in this review of historical controls.

In two studies (Ryan [46] and Goss [64])some patients subsequently received imatinib. In the Novartis' submission, only data based on patients without imatinib were considered to be useful as a historical control. This is a biased approach, because patients in the two studies had to be good survivors to receive imatinib. Patients who had a worse prognosis and died early could not be treated with imatinib. If individual patient data in the Goss study[64] is available, the data should be re-analysed after censoring the patients at the time of imatinib treatment, rather than completely excluding such patients. Without individual patient data, the most valid method is to include all patients' data, no matter whether they finally received imatinib or not. The impact of imatinib in the Goss study[64] was likely to be small because it became available for a very late and short period.

Many patients in the historical control studies had received chemotherapy and/or radiation therapy. It has been suggested that results from these studies reflected the natural history of the disease since no interventions before imatinib proved effective. This suggestion fails to consider adverse effects from chemotherapy and radiation therapy. The global outcomes of patients treated with ineffective but potentially harmful chemotherapy and/or radiation therapy might be worse than that of patients without such therapies. It is possible (at least theoretically) that the use of such historical control may lead to an overestimate of the effectiveness of imatinib.

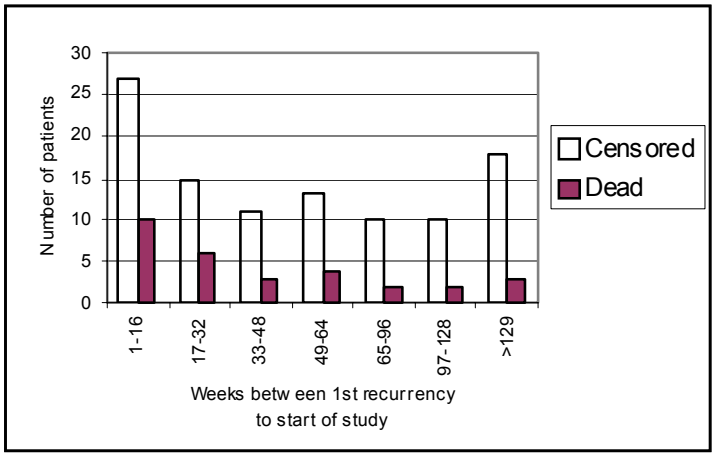
For the purpose of comparison, survival curves of patients treated with imatinib (based on data from the CSTIB2222 trial[60]) is also presented in Figure 1 (the thick solid line). There is little doubt that the treatment with imatinib has improved survival of patients with advanced GIST, though questions remain about (1) what is the most accurate estimation of survival in control groups (or what was the survival curve for patients included in the imatinib trials if they had not been treated with imatinib); and (2) validity of the long-term projection of survival beyond observed data.

Figure 3 Duration of disease (from initial diagnosis to the start of study) and death.



Patients in study CSTB2222 (censored=114, dead=33). Data from Novartis.[60]

Figure 4 Duration of recurrent disease and death.



Patients in study CSTIB2222 (censored=104, dead=30). Data from Novartis[60]

Table 12 Included prognostic studies: study characteristics and survival outcomes

Study, design, patients and treatment	Survival outcomes	Other
Chen et al 1998[49] - Patients with metastatic liver disease from leiomyosarcoma (between 1984 and 1995). - Hepatic resection of metastases. - Not KIT tested.	Median survival (n=11): 39 months.	Patients with a complete resection (n=6) had a significant longer survival than those who had incomplete resections (n=5).
Clary et al 2001[67] - Patients with GIST from 1982-99. Leiomyosarcoma arising within GI sites were classified as GIST. 8% with locally recurrent and 45% metastases disease. - Surgery. Some received AT and/or CT. - No kit test.	Overall 5yr survival (n=239): 28% Median survival Complete resection (n=136): 59 months Incomplete resection (n=100): 12 months Disease-specific survival (from Fig 3/4) 1yr, 3yr, 5yr Primary disease (n=112): 81%, 61%, 42% Primary incomplete resection (n=18): 64%, 45%, 45% Local recurrence (n=18): 53%, 38%, 38% Metastases (n=109): 66%, 22%, 12% Meets/incomplete resec (n=74): 50%, 14%, 7%(4yr)	**Note:** First 200 patients data used in DeMatteo et al 1999. Novartis used survival curve for patients with metastatic GIST and incomplete resection as the historical control in sensitivity analysis.
Crosby et al 2001[66] - A database created in 1989-98 was searched to identify patients with malignant GIST of the small intestine. - All cases independently reviewed by a single pathologist to confirm the diagnosis of GIST according to the most current pathologic standards. - 78% primary and 22% recurrence at the time of referral. 18% (n=9) presented with distant metastatic disease.	Disease-specific survival 1yr, 3yr, 5yr Overall (n=50): 84%, 51%, 41% Complete resect (n=35): 97%, 66%, 42% Incomplete resect (n=15): 73%, 8%, 8% Median (mean) survival Complete resect: 50 mths (mean 60, range 4.5-176) Incomplete resect: 20 mths (mean 29, range 1-157) Survival rate for stage III patients (multiple primary lesions or distant metastases at diagnosis, n=11; estimated from fig 4): 1yr: 73%; 2yr: 27%.	Data available about the extent of disease at presentation and rate of compete resection. 15 of the 35 patients with complete resection recurred at a median of 25 months (mean 25.5, range 4-81). In the 41 patients presenting without distant metastases, 24 (59%) developed metastases at a median of 21 months (mean 31,

- Surgery. About 20% received adjuvant treatment. - No kit test.		range 2-91).
DeMatteo et al 1999[23] - Patients with malignant GIST from 1982-98. Histological diagnosis was confirmed by pathologists at Memorial Hospital. 54% with metastatic or locally recurrent disease. - Surgery, with adjuvant and radiation therapy in some patients. - No kit test **Note:** Patient data also used in Clary et al 2001.	Disease-specific survival: 1yr, 3yr, 5yr Overall (n=200): 69%, 44%, 35% Median survival: Primary (n=93): 60 mths Metastatic (n=94): 19 mths Locally recurrent (n=13): 12 mths Survival outcomes after 1st recurrence in patients with primary disease and completed resection (estimated according to data in table 7) All recurrent patients (n=27): median 8 (mean 17.5, range 1-125) months. 1yr -41%; 2yr -14% Patients with metastasis (n=18): median 10.5 (mean 11.7, range 1-40) months. 1yr -44%; 2yr -6%	With a median follow up of 24 months (range 1-175), recurrence occurred in 40% (n=32) of 80 patients with primary disease who underwent complete resection.
De Pas et al 2003[19] - 76 patients with advanced GIST (between 1979 and 1999). - Systemic chemotherapy as adjuvant treatment (n=15) or for metastatic disease (n=67). - Not KIT test confirmed.	Median survival (n=67): 16 months (range: 2 to 60) Survival rate (n=67, Fig 1) 1yr, 2yr, 3yr, 4yr 62%, 24%, 15%, 10% (From the start of chemotherapy)	
Edmonson et al 2002[51] - A prospective phase II study of 21 patients with advanced histologically confirmed GIST between 1994-98; and no standard curative therapy was known. - Patients received intravenous chemotherapy (dacarbazine, mitomycin, doxorubicin, and cisplatin plut GM-SCF)	Median survival (n=21): 16.7 months (95%CI: 8.8 to 27.5) Survival rate (from Fig 1): 1yr, 2yr, 3yr 67%, 39%, 8%	Objective tumour regression was observed in one of 21 (1.8%) GIST. Time to disease progression was 7.3 months (95%CI: 4 to 8.5).

- No KIT test		
Howe et al 2001[68] - Data from the National Cancer Data Base for patients with primary small bowel sarcoma between 1985-95. Majority with leiomyocarcoma (75%). - Surgery, and radiotherapy, chemotherapy. - No kit test.	Disease-specific survival: 1yr, 3yr, 5yr Overall (n=590): 77.6%, 48.2%, 38.9% Leiomyosarcoma (n=456): 81.8%, 51.0%, 40.3% Stage local (n=214): 93.1%, 80.0%, 75.0% regional (n=172): 80.2%, 40.0%, 30.8% distant (n=146): 54.1%, 12.4%, 6.5%	
Pierie et al 2001[69] - A retrospective review of 70 GIST patients from 1973-1998. Metastatic disease at initial visit was present in 41% of patients. GIST defined as any sarcoma of the gut. - Surgery. - No kit test.	Survival 1yr, 3yr, 5yr Overall (n=69): 38%, 29%. Complete resection (n=41): 88%, 54%, 42% Incomplete resect (n=28): 42%, 13%, 9%	Recurrent disease occurred in 41% of 39 patients who had no distant disease, peritoneal seeding, or lymph node metastases at the time of diagnosis. The overall time to local and/or distant recurrence was 19 (range, 8-300) months.
McGrath et al 1987[70] - Patients with primary GI sarcomas from 1952-1984. Charts and histopathologic slides were reviewed. - Surgery. Some received radiation and/or chemotherapy. - No kit test.	Median survival Distant metastatic patients (n=28): 10 months Partial resection (n=21): 9 months Survival rate (Fig 1 and 4) 1yr, 2yr, 3yr, 4yr, 5yr Partial resection (n=21) 46%, 27%, 21%, 14%, 10% Adjacent spread (n=?) 67%, 46%, 38%, 28%, 20% Distant metastases(n=28) 36.5%, 12%, 6%	46% (12/26) recurrent after complete resection. Median interval from initial resection to detection of recurrence was 2 years (range 6-98 months).
Ng et al 1991[65] - Patients with GI leiomyosarcomas from 1957-87; diagnosis confirmed by a pathologist. - Surgery. plus chemotherapy in 76% and	Median survival All patients (n=191): 29 (range 1-284) months Recurrent patients after complete resection: 14-19 months. Peritoneal recurrence with metastasis: 9-13 months.	Patients who had relapses 18 months after surgery had a better survival outcome than those who relapsed before 18 months.

radiation therapy in 20% of the patients. - No kit test	Survival rate (Fig 6) 1yr, 2yr, 3yr, 4yr, 5yr Recurrent (>18mon, n=56): 73%, 44%, 31%, 22%, 11% Recurrent (<18mon,n=54): 56%, 23%, 8%, 3%, -	
Rajan et al 2001[47] - Patients (n=16) with histologically proven metastatic (to liver) sarcoma from Jan 1993 to Jan 2000. - Chemoembolization - Not KIT test confirmed	Median survival (n=16): 20 months Survival rate (n=16) 1yr, 2yr, 3yr, 4yr 81%, 54%, 40%, 26% (From time of diagnosis)	
Ryan et al 2002 [46] - A phase II trial of patients with unresectable advanced or metastatic GIST, which was proven histologically. - Cytotoxic agent: ecteinascidin 743 (ET-743). 11 patients subsequently received imatinib (but no data about the time and duration of treatment with imatinib). - KIT positive in 16/17 (3 unknown)	Overall 1yr survival rate (n=18): 71.1%. (The 1yr survival rate for those received imatinib (n=11) was 100% and for those who did not receive imatinib (n=7) was 18%. However, the comparison may not be valid because patients should be 'long survivors' in order to receive imatinib. The selection bias is therefore obvious. A further consideration is the toxicities from chemotherapy.)	
Yao et al 2000 [71] - Patients with primary gastrointestinal sarcomas from 1981-96. - Surgery. - No kit test.	Median survival All patients (n=55): 32 months Complete resection (n=35): 46 months Incomplete resection (n=17): 10 months Estimated 5 yr survival Complete resection: 28% Incomplete resection: 0%	
Goss et al[41] **(unpublished)** [commercial in confidence].	[commercial in confidence].	Patients were referred to the centre from 1996 to 2001, and the imatinib treatment was available from (July)

- A retrospective review of 143 patients with histological confirmation GIST; between 1996-2001. 132 patients had recurrent or metastatic GIST. - Various chemotherapy regimens. Some patients subsequently received imatinib. - CD117 (KIT) positive.		2000. Patients who survived long were more likely to receive imatinib than patients who died early. If only those with no imatinib included, then selection bias was likely.

Table 13 Median survival of patients with advanced GIST: findings from cohort studies

Study	Patients	No. of patients	Median survival (months)
Chen et al[49] 1998	Leiomyosarcoma liver metastasis	11	39
Clary et al[67] 2002	Incomplete resection (all)	100	12
	Primary+ incomplete resection	18	34
	Local recurrence + incomplete resec	8	2
	Metastases + incomplete resec	74	12
	Local recurrence (all)	18	23.2
	Metastases (all)	109	17.6
Crosby et al[66] 2001	Incomplete resection (small bowel)	15	20
De Pas et al[19] 2003	Advanced GIST	67	16
Edmonson et al[51] 2002	Advanced GIST	21	16.7
Goss et al [64] (un published)	All recurrence/metastasis	[CiC]	[CiC]
	Recurrence/metastases -no		
Howe et al[68] 2001	Small bowel sarcomas		
	regional stage	172	28.6
	distant stage	146	13.8
Pierie et al[69] 2001	Incomplete resection	28	10.4
McGrath et al[70] 1987	Incomplete resection	21	9
Ng et al[65] 1991	Recurrent GIST	110	16.5
Rajan et al[47] 2001	Sarcoma liver metastasis	16	20
Yao et al[71] 2000	Incomplete resection	17	10
Total		**983**	

5. ECONOMIC EVALUATION

In this chapter, we first assessed the model that Novartis submitted to NICE. We modified the Novartis model in response to the identified problems. A new, more sophisticated model was also developed to provide alternative estimates and if necessary to perform further analyses.

5.1 Assessment of the Novartis model

Novartis submitted a model for economic analysis of imatinib.[61] The main report and the model details (in the form of an Excel file) were provided. Based on the recommendations by the ISPOR Task Force on Good Research Practices-Modelling Studies,[72] the model assessment focuses on three areas: the model structure, data used, and model validation.

5.1.1 Objectives and perspectives

The Novartis model was developed to perform the full economic evaluation about the cost-effectiveness of imatinib in patients with unresectable and/or metastatic GISTs. The evaluation is from a UK NHS perspective. Costs were discounted at 6% and health benefit at 1.5% in the baseline scenario.[61]

5.1.2 Model structure

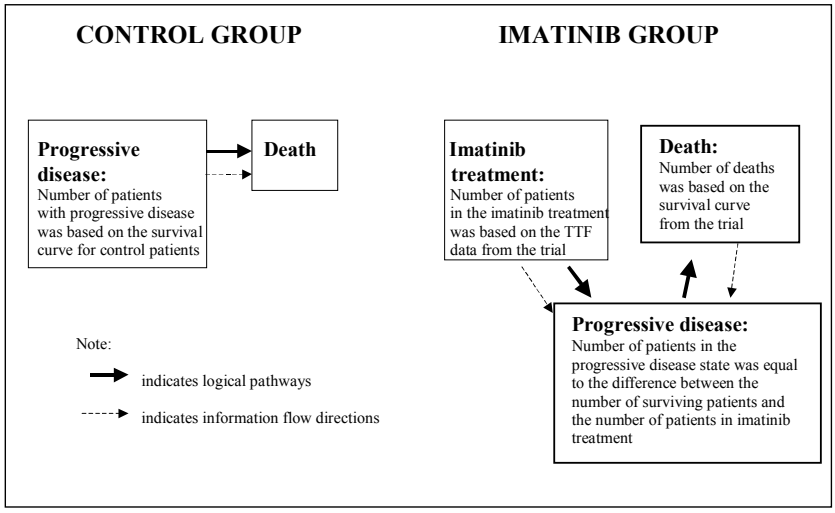
5.1.2.1 States in the model

The Novartis model is a state-transition model, and has two arms: the control and the imatinib treatment arm (Figure 5). The patients in the control arm have only two states in the model (progressive disease or death) based on the assumption that patients who do not receive imatinib have a gloomy prognosis. The patients in the state of progressive disease may remain in this state, or move to the state of death.

In the imatinib arm, a state of imatinib treatment is added into the model. Patients in the state of imatinib treatment include those who have a stable disease or who achieve a partial response, because evidence suggested that the cost and survival consequences were the same with the stable disease or partial response. At the beginning of the modelling, all patients in the imatinib arm are in the state of imatinib treatment. Patients in the imatinib group who fail to respond or whose disease progresses are moved to the state of progressive disease. Logically, patients in the state of progressive disease should have as poor survival prognosis as patients in the control arm, and many will soon be moved to the state of death (Figure 5).

The assumed states in the Novartis model are acceptable, considering the defined patient groups, and the available evidence on imatinib treatment.

Figure 5 States in the control and in the Imatinib arm: the original Novartis model



5.1.2.2 State-transitions in the Novartis model

The number of patients in each state is calculated every 4 weeks. The reported outcomes are up to 10 years, though the results after 2 years are of great uncertainty. In the control arm, the number of surviving patients (i.e., the number of patients in the state of progressive disease) over time is determined by the survival curve of historical patients who have not received imatinib treatment.

In the imatinib arm, surviving patients are separated into two states, imatinib treatment and progressive disease. Figure 5 shows the logical pathways of state transitions in the model. It should be noted that, in the imatinib arm, the directions of logical transition pathways are not the same as the directions of information flow in the actual model. First, the Novartis model estimates the number of surviving patients according to the survival curve from a clinical trial. Then it estimates the number of patients in the state of imatinib treatment, according to the Time to Treatment Failure (TTF) curve from the same trial. Finally, the number of patients in the state of progressive disease equals the difference between the number of surviving patients and the number of patients in the state of imatinib treatment.

An important weakness of the Novartis model is that the TTF and survival curves are independently calculated, and no efforts have been made to calibrate the outcomes of the two curves. As shown in Figure 6 (page 46), the small proportion of patients in the state of

imatinib treatment is disproportionate to the great proportion of surviving patients during the period of modelling. For example, the proportion of patients in the state of imatinib treatment and the overall survival are 44% and 79% respectively after 2 years; 13% and 55% respectively after 5 years; and 2% and 30% respectively after 10 years (baseline scenario). This is possible only if the progressive patients in the imatinib arm had a good survival prognosis, which is contrary to the assumption that the majority of patients in the state of progressive disease will die in two years (this point is further illustrated in Appendix 13, page 133).

Figure 6 Proportions in state "imatinib treatment" and overall survival (Novartis model).

[Commerical in confidence data removed]

5.1.3 Data used in the model

5.1.3.1 Input data required

To estimate relative effectiveness and utility of imatinib treatment for unresectable and/or metastatic GIST, the Novartis model requires input data on

- The proportion of survival over time in the control patients
- The proportion of survival over time in patients treated with imatinib

- Quality of life for patients who receive imatinib and for patients who receive the control intervention
- Time to treatment failure (TTF) for patients who receive imatinib.

The Novartis model requires the following cost data:

- Drug cost of imatinib treatment (about £20,000/year)
- Cost of outpatient visits including tests (£440/year)
- Cost of CT scans (£656 for imatinib patients and £82 for patients with progressive disease)
- Cost of GP visit (£40/year) and
- Cost of management of adverse events (on average £159/year, range 127.2 to 190.8).

5.1.3.2 Data on quality of life

The literature search identified no studies that have directly evaluated quality of life (QoL) using EQ-5D for patients with advanced GIST.[61] In the Novartis model, utility values for patients in the imatinib arm are estimated by a mapping of ECOG performance status to EQ-5D scores. ECOG data was from the CST1571-B2222 trial. A questionnaire was sent to nine clinicians to map the ECOG state to the EQ-5D score. Three completed questionnaires were received. Thus, the mapping was based on the subjective judgement from only three clinicians. The estimated utility value was 0.875 for patients in the state of progressive disease, and 0.935 for patients in the state of imatinib treatment. These estimates seem sensible, but are not convincing because of small number of clinicians involved.

5.1.3.3 Data on the survival of patients

The key input data for the effectiveness modelling was the relative survival benefit of imatinib treatment. Ideally, the difference in survival between patients treated with imatinib and patients who receive control treatments should be evaluated in large-scale randomised trials. However, there are no controlled trials that directly compared imatinib with current treatment for unresectable and/or metastatic GIST. Thus, results from cohort trials or case-series studies have to be used.

Survival data for imatinib treated patients

The Novartis model used data from a single trial (CSTI571-B2222)[60] to estimate survival curves for patients treated with imatinib. This open-label, multicentre trial compared two imatinib doses (400 mg or 600 mg/day) in 147 patients with malignant unresectable and/or metastatic GISTs. The advantage of using this trial is that it provides the most complete

available survival data for imatinib treated patients, with a follow-up of up to 25 months. The survival rate was 88% after one year and 78% after two years.

The median follow up of patients in the trial (CSTI571-B2222) was 25 months. The Novartis model used exponentially fitted curves to project the survival and the time to treatment failure for patients treated with imatinib (Figure 6, page 46) beyond the observed data. The exponential curves were fitted using data of the first 90 weeks for survival and data of the first 60 weeks for TTF because heavily censored data from longer follow-up was considered unreliable. According to the Novartis submission sensitivity analyses suggested no difference if all data available was used. As has been discussed earlier, the projected survival in the Novartis model was disproportionate to the estimated proportion of patients in the state of imatinib treatment (Figure 6, and Appendix 13, page 133).

Survival data for control patients

It is more problematic to obtain good survival data for control patients because of the following difficulties. Firstly, the molecular marker KIT was introduced in the diagnosis of GIST from 2000, but was not used in the previous studies. Other than by retrospective immuno-testing this makes it generally impossible to separate KIT positive GIST from other gastrointestinal sarcomas in older studies. A second problem is that there is a lack of objective definition of unresectability for the recurrent or metastatic GIST.

The authors of the Novartis submission identified five published studies that reported survival outcomes of patients with advanced GIST. It was reported that the median survival for patients with advanced GIST is about 12 months, ranging from 2 to 20 months. An unpublished study by Goss et al[64] employed histological confirmation of CD117 in the diagnosis of GIST, and may be considered the most relevant. In the Novartis model, the survival curve based on the unpublished Goss study (median survival [CiC removed]) was used in the baseline scenario, and survival curves from Clary et al[67] (median survival 12 months) was used for sensitivity analysis. The follow-up was over or close to [CiC removed] in the study by Goss et al and in the study by Clary et al[67]. The fitted exponential curves were well matched with the observed survival curves for the control patients.

Text related to the unpublished study by Goss et al is commercial in confidence and has been removed.

Figure 7 Survival curves for patients in the control arm.

[Data related to the unpublished study by Goss et al is commercial in confidence and has been removed]

5.1.4 Model validation

According to Weinstein et al (2003) [72], internal validation includes model verification (debugging) and calibration. An examination of the Novartis model found no programming problems.

Between model validation cannot be conducted because no other model was available from the literature. However, the results of the original Novartis model and the modified Novartis model will be compared in next section. A new model was also developed and the results of the new model, the original Novartis model and the modified Novartis models were compared.

The external and predictive validation cannot be carried out. There are no directly controlled trials that compare imatinib with alternative interventions for patients with unresectable and/or metastatic GIST.

5.1.5 Summary

- Because of lack of directly controlled trials, modelling is the only formal approach to estimate the cost-effectiveness of imatinib for patients with unresectable and/or metastatic GIST. The Novartis model is clearly presented. The model structure and input data are transparent. The model structure and level of simplification seems reasonable in term of model's objectives and data availability. The cost estimates seem reasonable.
- The original Novartis model[61] has overestimated the cost-effectiveness of imatinib for patients with unresectable and/or metastatic GIST because of (1) disproportion of survival and TTF in the imatinib arm, and (2) the survival curve for patients in the control arm may have been biased against long term survivors. Sensitivity analyses were carried out by using different input values for patient survival. However, these sensitivity analyses were designed in such a way so that the results tended to further exacerbate the overestimation of the cost-effectiveness for the imatinib treatment.
- In response to the identified shortcomings, we modified the Novartis model as presented below.

5.2 Modified Novartis models and results

The original Novartis model was modified first in terms of model structure (modified-A). Then the Novartis model was further modified by using more appropriate survival curve for patients in the state of progressive disease (modified-B).

5.2.1 Modified-A

To overcome the Novartis model's weakness that the state of imatinib treatment is independent from the survival, we made following modifications. (It is called Modified-A, to distinguish between different versions). First, the number of patients in the state of imatinib treatment is estimated according to the same TTF curves, as in the original Novartis model. It is assumed that all patients in the state of imatinib treatment are alive. Patients who fail to respond to imatinib are moved to the state of progressive disease, and start to follow the same survival process as the new control patients. The number of surviving patients over time is calculated as the sum of patients in the state of imatinib treatment and surviving patients in the state of progressive disease. That is, in the modified model, the survival outcome in the imatinib arm is determined by both the TTF curves and the survival curve for progressive patients. An important advantage with the Modified-A model is that both the imatinib arm and the control arm will use the same survival curve for patients in the state of progressive disease. This approach is more reasonable, and the modelling results will be less sensitive to

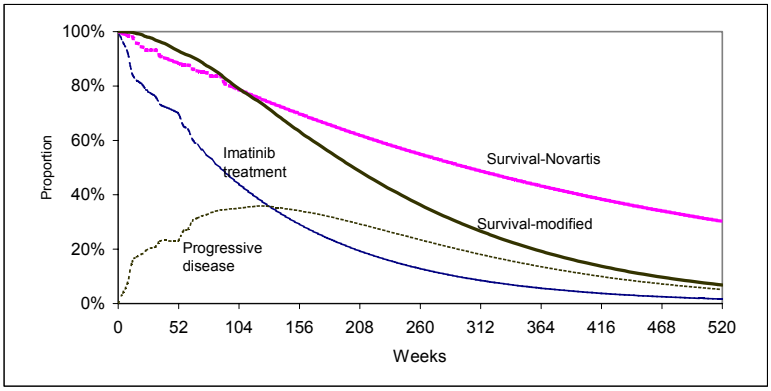
the selection of different survival curves for control patients (this will be further discussed later).

The assumption that all patients in the state of imatinib treatment are alive may lead to an overestimation of the benefit of imatinib treatment. Since the proportion of deaths from causes other than GIST was very small in this patient population, the overestimation may be negligible. In addition, patients whose disease progresses after imatinib treatment may have a different survival process from those who never receive imatinib. However it seems unlikely that prognosis after treatment failure would be better than that of the control patients, since the criterion for treatment failure (i.e. transition to a state of progressive disease) was an increase of at least 50% in tumour mass. The above two assumptions were adopted for reasons of simplicity in the Modified-A model.

Figure 8 compares the overall survival from the original Novartis model and the Modified-A model. It also shows the proportion of patients in the state of imatinib treatment, and the proportion of patients in the state of progressive disease. Clearly, the original survival curve has greatly over-estimated the survival benefit of imatinib treatment given the same survival curve for the control patients and for the progressive patients in the imatinib arm.

Table 14 presents the main outcomes of the original Novartis model and the modified models. Over the first 3 years, the estimated incremental cost-effectiveness ratios are similar between the Novartis model and the modified model-A. After about 3 years, the estimated cost per QALY is greater in the modified models than in the original Novartis model. For example, the estimated cost per QALY after 10 years is £21,949 in the modified-A model versus £14,072 in the original Novartis model.

Figure 8 The modified-A model: survival curves, proportion of patients in the state of imatinib treatment



Also shown are the proportion of patients in the state of "Imatinib treatment" and the proportion of patients in progressive disease (based on the modified-A model, baseline scenario). In the modified-B model the control survival curve used was different to, and more appropriate than, that used in the Novartis model (see section 5.2.2, page 52).

Table 14 Results of original Novartis model and the modified models

Year	Imatinib		Control		Cost/QALY
	QALYs	Costs	QALYs	Costs	
Novartis original					
2	1.63	£27,712	1.20	£2349	£59,013
3	2.28	£34,677	1.48	£2915	£39,781
5	3.33	£42,069	1.75	£3426	£24,441
10	4.99	£47,092	1.90	£3674	£14,072
Modified-A					
2	1.68	£27,727	1.20	£2349	£52,407
3	2.31	£34,849	1.48	£2915	£38,534
5	3.15	£42,399	1.75	£3426	£27,955
10	3.88	£47,086	1.90	£3674	£21,949
Modified-B					
2	1.73	£30,295	1.39	£1949	£85,224
3	2.42	£37,053	1.83	£2652	£58,690
5	3.45	£43,663	2.47	£3265	£41,219
10	4.85	£47,521	3.39	£4047	£29,789

Notes: **Modified-A**: The structure of the Novartis model was modified so that patients who failed to respond to imatinib follow the same survival prognosis as those in the control arm. **Modified-B**: with modifications (1) as in the Modified-A; (2) the survival curve for patients in the state of progressive disease was based on all metastatic or recurrent patients in the Goss study; (3) the exponential TTF curve based on all trial data (CST1571-B2222); (4) cost of imatinib as in the imatinib trial.

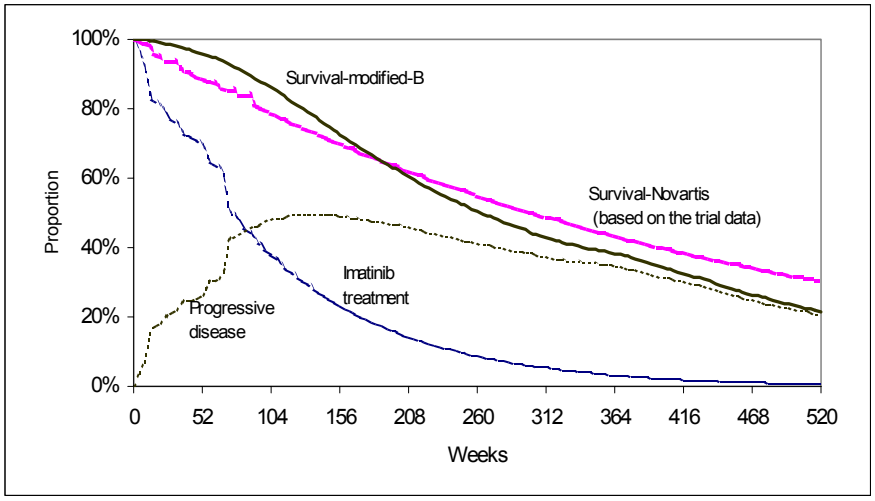
5.2.2 Modified-B

Since the survival curve for patients who never received imatinib in the Goss[64] study underestimated the survival of control patients, we further modified the Novartis model (additional to the change in Modified-A) by using the survival curve for all patients with metastatic or recurrent GIST in the Goss[64] study. In addition, we used exponential TTF curve and the imatinib dose based on all available data from the trial CST1571-B2222. The results of this further modification are also shown in Table 14, page 52). The cost per QALY gained is £85,224 after 2 years, £41,219 after 5 years, and £29,789 after 10 years. The results from the Modified-B model suggest a lower cost-effectiveness of imatinib than the results of the original Novartis model (Table 14).

The use of the survival curve for all patients in the Goss study resulted in a better survival not only for patients in the control arm but also for patients in the imatinib group (relative to that in the Modified-A). This is because, in the modified models, patients in the state of

progressive disease in the control arm had the same survival as patients in the state of progressive disease in the imatinib arm. Figure 9 shows the survival curve for patients in the imatinib arm from the imatinib trial (CST1571-B2222) and the curve estimated by the Modified-B model. The two curves are similar, although the estimated survival is better than the observed before about 190 weeks and then worse than the observed after 190 weeks. This evidence suggests that the patients in the imatinib trial are relatively comparable to all patients with recurrent or metastatic GIST in the Goss[64] study. Thus, the survival curve for the control patients used in Modified-B model (i.e., all patients data in the Goss[64] study) is a better estimate than the survival curve used in the original Novartis model. The use of the survival curve for all patients in the Goss[64] study will at least partially resolve the concern about the disproportion of patient survival and time to treatment failure in the original Novartis model.

Figure 9 Survival curves in the original Novartis model and modified-B model



Note: The two survival curves are similar, although the estimated survival is better than the observed before 190 weeks and then worse than the observed after 190 weeks. This evidence suggested that the survival curve for the control patients used in Modified-B model (i.e., all patients data in the Goss[64] study) may be a better estimate than the survival curve used in the original Novartis model. The use of the survival curve for all patients in the Goss[64] study will at least partially resolve the concern about the disproportion of patient survival and time to treatment failure in the original Novartis model.

5.2.3 Sensitivity analyses using the modified Novartis model

The original Novartis model has provided central, low and high estimates for relevant costs. In addition, the different curves had been fitted for the time-to-treatment failure for imatinib treated patients. We used the central, low and high estimates of input values in the modified Novartis model for sensitivity analyses. The input choices and the results of sensitivity analyses are presented in Table 15. The estimated cost per QALY ranged from £51,515 to £98,889 after 2 years, from £27,331 to £44,236 after 5 years, and from £21,404 to £33,976 after 10 years.

5.2.4 Summary

The best evidence (results from the modified model: Modified-B) suggested that the cost per QALY gained ranges from £51,515 to £98,889 at 2 years, from £27,331 to £44,236 at 5 years, and from £21,404 to £33,976 at 10 years (Table 15). This range of estimates may not fully reflect the uncertainty, since the estimates after 2 years are largely based on mathematical extrapolations beyond observed data.

Table 15 Results of modified Novartis model: cost-effectiveness of imatinib for unresectable and/or metastatic GIST

Parameter	Baseline	Low estimate	High estimate
Weekly cost of imatinib	Pooled trial data: £420.38	Pooled trial data: £420.38	400 mg/d start dose: £370.38
Other costs per imatinib treated patient	£1,136	£1,786	£570
Other costs per progressive patient	£562	£1,498	£233
Discount rate	Cost 6% QALY 1.5%	Cost 3% QALY 3%	Cost 6% QALY 1.5%
Fitted exponential TTF curve for imatinib treated patients (parameter)	All trial data: -0.0093	Change at 60 weeks: -0.0209	Use of 60 weeks data: -0.0079
Survival curve for patients in the state of progressive disease	[Goss study – CiC]	[Goss study – CiC]	[Goss study – CiC]
Utility value	Imatinib treated: 0.935 Progressive: 0.875	Imatinib treated: 0.900 Progressive: 0.875	Imatinib treated: 0.935 Progressive: 0.875
Costs/QALY			
2 year	£85,224	£98,889	£51,515
3 year	£58,690	£63,612	£37,789
5 year	£41,219	£44,236	£27,331
10 year	£29,789	£33,976	£21,404

Note: (1) Data were from the original Novartis model[61] (except survival curve for all patients in the Goss[64] study). (2) Low estimate of cost-effectiveness used high estimate of costs and low (or baseline) estimate of health benefit; high estimate of cost-effectiveness used low estimates of costs and high estimate of health benefit.

5.3 The Birmingham model

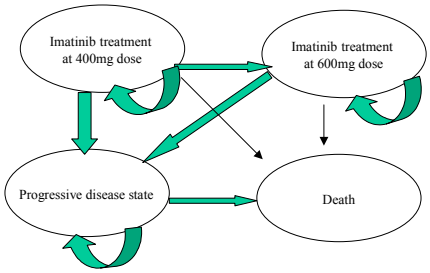
A new model was developed which differed from the Novartis model in four main ways:- by a Monte Carlo simulation to allow the uncertainty into the model, by having an additional state for the imatinib treatment arm, by allowing switches in the drug dosage, and by using a range of statistical distributions to extrapolate survival beyond the observed data.

5.3.1 Model structure

The aim of the Birmingham model is to predict costs and benefits of imatinib treatment compared with best support care. Four states apply to the imatinib treatment group: on imatinib treatment at 400mg dose, imatinib treatment at 600mg dose, progressive disease state and death. Two states apply to best support care group: progressive disease and death. Transitions between states are defined over 4 weeks cycles. The simulation length is 10 years (130 x 4-weeks).

The model was developed in DataPro. A Cohort of 10,000 patients was simulated for the analysis and Monte Carlo techniques were used to progress individuals through disease stages. It was assumed that all patients in the imatinib treatment group started at the imatinib treatment state (400mg daily). Patients could either respond or remain stable (no distinction was made between response and stable disease), or experience disease progression, or die. If patients responded (or remained stable), they continued on the imatinib treatment at 400mg dose. Patients whose disease progressed while being treated with imatinib at 400mg/day dose, or whose disease progressed after a period of response or stabilisation, were switched to the 600 mg dose. If their disease continued to progress at 600mg they were withdrawn from the treatment. When patients were withdrawn from imatinib treatment, they were assumed to be in the state of progressive disease. It was assumed that this state was the same as for those patients who had never received imatinib treatment. The pathways in the imatinib treatment group are shown in Figure 10.

Figure 10 Patient pathways in the imatinib arm, the new Birmingham model



In the best support care (BSC) group, only two states were defined (as in the Novartis model), the state of progressive disease state and death. All patients in this group started in

the progressive disease state, they could either remain in this state or die at the next cycle of the simulation.

In this Monte Carlo simulation a patient is randomly stepped through the Markov process based on transition probabilities for each patient's current state. Because only one individual is evaluated at a time, a tracker variable was used to record each individual path through the process. These tracker variables were used to dynamically modify the transition probabilities in the Markov process. After 10,000 times of simulation, we calculated expected cost and QALYs gained with BSC and imatinib treatment.

5.3.2 Assumptions used in modelling

In the imatinib arm, the transition probability from imatinib treatment to progressive state is derived from the survival curve for time to treatment failure (TTF). The relative hazard for treatment failure at time t, given the state of imatinib treatment at stage t-1, is given by:

$$h_t = \frac{(s_{t-1} - s_t)}{s_{t-1}}$$

For a patient who failed to respond to imatinib 400mg dose, a random number was generated to decide whether the patient was moved to 600mg dose treatment or to the sate of progressive disease. The probability that a patient will receive 600mg imatinib after failing at 400mg/day dose was estimated from the Demetri trial[26] in which it was reported that three of the nine patients who received the higher dose after evidence of disease progression was observed had a sustained partial response or stable disease after cross-over. Patients who moved to the state of imatinib 600 mg dose were assumed to have the same probability of progressing as patients in the state of 400mg dose imatinib treatment.

Deaths due to other causes rather than GIST during imatinib treatment were estimated by using mortality of the general population with similar age and gender characteristics to patients in the imatinib trial (STCB2222).[60] All patients entering into the progressive state, irrespective of whether they previously received 400mg or 600mg dose of imatinib or had not received imatinib (BSC arm), were assumed to have the same probability of staying in progressive state or of proceeding to death.

5.3.2.1 Input data for Cost and QALY

The cost and utility input data used in the Birmingham model was the same as that in the model proposed in the industrial submission by Novartis[61] and is shown in Table 16. Cost and QALY are discounted annually at 6% for cost and 1.5% for QALY.

Table 16 Input costs and QoL for modelling, adopted from the Novartis model

	4-weeks (28 days)	1-year
Cost of Adverse event	12.23	159
Cost of Imatinib at dose of 400mg	£1,453.54	18896
Cost of at dose of 600mg	£1,874.49	24368
Cost of no treatment (BSC)	£43.23	562
Cost of Terminal disease (death)	£2,730	£2,730
Discounted rate for Cost	0.0046154	0.06
Discounted rate for QALY	0.0011538	0.015
Other cost for Imatinib treatment patient	£87.38	£1,136
Utility at Imatinib treatment	0.935	0.935
Utility at progressive state	0.875	0.875

5.3.2.2 Survival curve for patients in the state of progressive disease

The Birmingham model (as in the modified Novartis models) assumed that patients leaving imatinib treatment had the same state of progressive disease as patients in the control arm. This means that any choice of control arm survival probability will affect both control and imatinib arm in the same direction. As been discussed in the modified Novartis model, the patients in the imatinib trial were relatively comparable to all patients with metastatic or reocurrent GIST in the Goss[64] study. Therefore, the base-case scenario in the Birmingham model used the Goss-All patient's survival for patients in the state of progressive disease in both control arm and the imatinib treatment arm.

[Text related to the Goss study is commercial in confidence and has been removed]…….

……The Birmingham model used data for the first 40 months to project long time survival for this group of patients (exponential fit). For sensitivity analysis we used the first 80 months of data instead of 40 months (Figure 11).

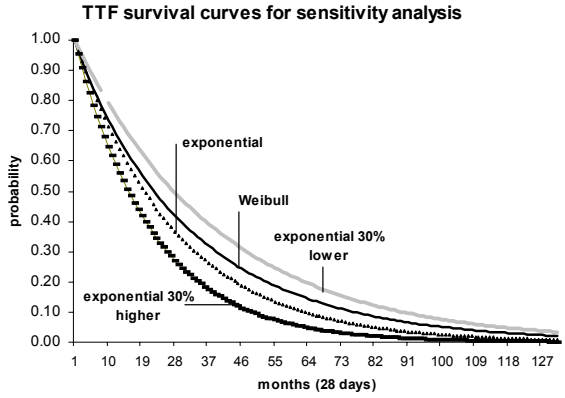
Figure 11 Exponential extrapolations of survival data for Goss-all patients

[Data related to the unpublished Goss study is commercial in confidence and has been removed].

5.3.2.3 Survival curve for time to treatment failure in Imatinib treatment

We used the same TTF data as in the Novartis model.[61] The TTF curve was an exponential function fitted to the Kaplan-Meier data of Study CST571-B2222. We used sensitivity analyses to explore the effects of different TTF curves to trial data. We used Weibull and exponential fitted curves and also lower and upper values around the fitted exponential curve (Figure 12).

Figure 12 Fitted curves for time to treatment failure.



5.3.2.4 Survival curves for imatinib arm

Survival curves for imatinib treated patients, calculated using various fitted curves for survival of untreated (progressive disease) patients and time to treatment failure (exponential curve), are shown in Figure 13. These survival curves were used to estimate the cost effectiveness of imatinib relative to BSC

Figure 13 Survival based on exponential curves fitted to Goss all patient data

[Data related to the unpublished Goss study is commercial in confidence and has been removed].

5.3.3 Results from the Birmingham model

Results for the four-state Markov model based on 10,000 patient-simulation over 10 years is shown in Table 17. The results for the base-case scenario were similar to that of the Modified-B Novartis model. The estimated cost per QALY gained by the imatinib treatment was £80884, £57106, £39526, and £27126 respectively at year 2, year 3, year 5 and year 10. Sensitivity analyses using different fitted curves for survival and TTF showed only small differences in estimated cost-effectiveness (data not shown). Further sensitivity analyses was not considered necessary.

Table 17 Results of base-case scenario from the Birmingham Model

Year	Imatinib		BSC		Cost/QoL
	Cost	QALY	Cost	QALY	
2	31079.2	1.77	1836.3	1.41	80884.6
3	40694.0	2.55	2476.4	1.88	57106.8
5	51995.1	3.78	3348	2.55	39525.8
10	63176.5	5.59	4333.1	3.42	27126.4
Note: The hazard for TTF used in the model was based on the exponential curve extrapolation from 60 weeks of data. Hazard of death in the progressive disease state was based on the exponential survival curve for Goss all patients extrapolated from 40 weeks of data					

5.4 Discussion

In the Novartis model[61] the proportion of patients in the disease progression state in the imatinib arm was calculated from the difference between the proportion of surviving patients and the proportion still in treatment (derived from the time to treatment failure survival curve). When extrapolated this generated a large proportion of patients in progressive disease state who exhibited prolonged survival. This large number of long-term survivors contrasted with the control arm where progressive disease state patients were associated with much poorer survival probability.

This incompatibility could result from at least 3 non-exclusive explanations: (1) The progressive disease state after treatment failure with imatinib differs from the progressive disease state in the patients never treated with imatinib (i.e. they have better survival probability); (2) The control arm patients had worse survival probability than the imatinib arm patients at the start of treatment (that is, the patients were not comparable between two arms); (3) Erroneous extrapolation beyond the observed data, especially in the TTF and overall survival curves in the imatinib arm. Explanation (1) is unlikely since a >50% increase in tumour load (from start of treatment) was required for transition from treatment to progressive disease state. Explanation (2) is likely since the historical control chosen for the Novartis model excluded patients with better survival (those that eventually received imatinib after July 2000) from the population of patients with advanced kit positive GIST. Explanation

(3) appears possible since it is impossible to be certain that the extrapolated estimate was valid.

The modified (B) version of the Novartis model (with a change in the model structure and employing a more suitable historical control group) resulted in less attractive estimates of the ICER of imatinib relative to BSC. According to the modified Novartis model, the estimated cost per QALY was £85,224 (from £51,515 to £98,889) after 2 years, £41,219 (from £27,331 to $44,236) after 5 years, and £29,789 (from £21,404 to £33,976) after 10 years. The results from the new Birmingham model were also within the range of estimates from the modified Novartis model.

6. DISCUSSION

6.1 General considerations

To estimate the effectiveness of imatinib for unresectable and/or metastatic and KIT positive GIST, the clinical outcomes of patients treated with imatinib need to be compared with those of patients treated with alternative interventions (current standard treatment). There are no trials that directly compare imatinib and alternative treatments for patients with unresectable and/or metastatic GIST. In this assessment, relative effectiveness of imatinib was estimated by an indirect comparison of outcomes of historical patients and outcomes of patients in imatinib clinical trials.

This review assessed the effectiveness and cost effectiveness of a recently developed drug for treatment of a rare but devastating disease for which diagnostic criteria have recently been redefined. Consequently the data on the treatment of GIST with imatinib has yet to mature and the trials that were available for assessment principally focussed on dosage and safety. Thus the relative effectiveness of imatinib in the treatment of unresectable and/or metastatic GIST had to be estimated by an indirect comparison of outcomes of historical patients and outcomes of patients in imatinib uncontrolled clinical trials. After analysis of potential historical control data the unpublished study of Goss et al that included retrospective cKIT testing was found to contain the most suitable comparator patients. Many other studies describing potentially useful historical patient groups were considered less appropriate because diagnoses predated and excluded cKIT testing.

Modelling is the only possible formal approach to extrapolating beyond observed data from the trials and incorporating data from diverse sources in order to arrive at an estimate of the cost effectiveness of imatinib. In this report we assessed the model developed by Novartis, and modifications were made in response to identified major shortcomings in the original Novartis model. In addition we proposed an alternative model for cost effectiveness that differed from the industrial submission in several respects.

6.2 Major results

6.2.1 Tumour response

Evidence from published uncontrolled trials involving 187 patients, and from abstracts reporting similar uncontrolled trials involving 1700 patients, indicate that approximately 50% of imatinib-treated individuals with advanced GIST experience a dramatic clinical response in terms of at least a 50% reduction in tumour mass. At present, although useful data are accumulating, it is not possible to predict which individuals might respond in this way.

Because advanced GIST is perceived as inexorably progressive it would be contrary to accepted dogma and common experience that such striking alterations in the progress of the disease would occur in the absence of imatinib treatment. Also there is no convincing evidence from studies of alternative treatments that such responses have previously been observed in this group of patients. However, it must be acknowledged that regular monitoring

of disease status in large numbers of individuals with good imaging techniques has probably not been a common practice previous to imatinib trials and such "spontaneous" changes, in theory, may have gone undetected. It is partly for this reason, but also because GISTs are designated slow growing and because of the likelihood of great variation in tumour growth rate between individuals, that trial results reporting that a further 30% or so of imatinib-treated patients experience "stable disease" are difficult to evaluate in terms of effectiveness of the drug.

6.2.2 Survival

Because of the immaturity of the data and trial design, evidence for survival has considerable uncertainties associated with it, which makes it difficult to answer the crucial question of how and if these clinical responses translate into patient benefit in terms of prolonged survival and quality of life.

It is clear from comparing the survival curve for patients in an imatinib trial (Demetri 2002[26], n=147) with curves from a variety of sources describing survival of similar groups of patients not treated with imatinib that imatinib does indeed confer survival benefit. However, estimating the extent of this benefit is fraught with difficulties particularly with regard to considerable extrapolation beyond available data for imatinib-treated patients and to the selection of the most appropriate "control" survival curve for comparison.

It has been widely quoted that patients with advanced unresectable GIST have a gloomy prognosis and that most of them will die soon with a median survival about 12 months. A review of prognostic studies confirmed this gloomy prognosis, but also showed it was not homogeneous to all such patients. Although a large number of patients with advanced GIST will die in a few years, some patients may survive for many years. For example, according to individual patient data from Novartis, 21 of 147 patients in the imatinib trial (Demetri 2002[26], CSTIB2222[60]) had a disease history (from initial diagnosis) of more than 241 weeks before the start of the study, and a recurrence history (from first recurrence) of more than 129 weeks. In addition, within this group of patients with a long history of disease or recurrence the proportion of deaths was relatively low.

Commonly quoted figures for median survival of potential "control" patients with advanced GIST are about 12 months for those with local recurrence and about 20 months for metastatic disease. These estimates stem from various studies (e.g. De Matteo et al 2000 [23]) that describe disease status variably as re-current (local or otherwise), metastatic, unresectable (or resection incomplete), that are based on diagnoses that did not include the c-kit test, and that included patients who had been administered various ineffective chemotherapies or radiotherapy.

To estimate the relative benefit of imatinib for unresectable and/or metastatic GIST, the patients included in the imatinib trials should be comparable to patients in the studies of [61]historical cases. Since no direct evidence was available, we used modelling approach, and concluded that patients in the imatinib trial (CSTB2222[61]) were comparable to all those patients (whether they subsequently received imatinib or not) with recurrent or metastatic GIST described in the unpublished study by Goss et al[64]. [Commercial in confidence data removed]…….. This group of patients in the Goss study had histologically confirmed

GIST, were c-kit positive and details of demography were similar to patients in the imatinib trial.

6.2.3 Quality of life

Anecdotal evidence[73-75] (www.liferaftgroup.org) indicates that imatinib-treated patients with a good clinical response (>50% reduction in tumour mass) experience relief from symptoms the benefit of which outweighs the variety of unpleasant side effects of treatment that are reported to occur in various combinations in virtually all patients. However QoL measures have not been reported for GIST patients and the impact of imatinib on patient quality of life is uncertain. The Demetri trial provided data showing that after imatinib treatment patients recorded an improvement in ECOG score (a measure of functional capacity in every-day life tasks). In the absence of results for a control group we need to assume these changes were imatinib- rather than time-dependent. The industrial submission[61] stated that these improvements were maintained up to at least 2 years and reported a mapping exercise that was undertaken to relate ECOG scores to QoL (EQ-5D). This exercise provides what may be reasonable estimates of QoL for imatinib-treated and control GIST patients; however, because it was rooted in a questionnaire addressed to clinicians (rather than patients) of whom only 3 out of 9 responded these estimates must be viewed with some caution and their uncertainty adds to the difficulty of determing the effectiveness of imatinib. It is possible serious long term adverse events might result from imatinib treatment; however it is probably a better choice for patients to be alive and at risk of these possible hazards than dead and not at risk through lack of treatment.

6.2.4 Cost-effectiveness

The structure of the industrial model (Novartis model)[61] for cost effectiveness and the data input in the submission were transparent. The model structure and level of simplification seem reasonable in terms of the model's objectives and data availability. However, the original Novartis model overestimated the cost-effectiveness of imatinib for patients with unresectable and/or metastatic GIST because: (1) given the time to treatment failure data and the assumed disease prognosis for the progressive state (i.e. the same survival probability as a progressive disease patient in the control arm) there was a disproportionate number of survivors in the imatinib arm; and (2) the use of a possibly biased survival curve for patients in the control arm.

We modified the Novartis model by employing a more valid estimate of survival probability for patients in the “progressive state” and by employing the time to treatment failure to determined the proportion of patients moving into the progressive state through time in the imatinib arm. The results of modified Novartis model suggested that the cost per QALY gained ranged from £51,515 to £98,889 at 2 years, from £27,331 to £44,236 at 5 years, and from £21,404 to £33,976 at 10 years (Table 15). This range of estimates may still not fully reflect the uncertainty, since the estimates after 2 years are largely based on mathematical extrapolations beyond observed data. The results from the new Birmingham model confirmed the findings from the modified Novartis model.

The budgetary impact to the NHS was estimated in the Novartis submission to NICE.[61] They used an incidence rate of 15 per million population, and assumed 10-30% of all GIST patients may have metastatic and/or unresectable disease. So the number of patients to be

treated with imatinib was between 80 and 240. The annual cost of imatinib treatment (including associated care) was estimated to be £20,400. Considering that some patients will fail to respond to imatinib and discounted annually at 6% over 10 years, the average cost to the NHS was between £2.4 million and £11.8 million per year. These estimates appear reasonable. Because of the approved effectiveness of imatinib, the use of imatinib may become less restricted over time, and the high estimate of the cost to the NHS may be more likely than the low estimate.

6.3 Uncertainties, limitations and future developments

The considerable uncertainties in the assessments presented in this report have been discussed in previous sections. In brief, because no directly controlled trials have been conducted and since only short follow-up period data is available, the current evidence to support estimates of the effectiveness of imatinib may not be conclusive. The questions that remain are (1) what is the most accurate estimation of survival in control groups; (2) what is an accurate long-term projection of survival and time-to-treatment failure beyond observed trial data; and (3) what potential biases can arise in the indirect comparison of survival of patients with and without imatinib. The results of on-going uncontrolled trials will only partially address these problems, and it seems that no data on QoL of "control" patients will ever become available and that RCTs to determine imatinib effectiveness are unlikely to be undertaken.

This report was limited to the analysis of effectiveness and cost effectiveness of imatinib for treatment of patients with unresectable and/or metastatic c-kit positive GIST. The timing of implementation of therapy for these patients is subject to vagaries of disease monitoring practices, the propensity of patients to consult when they experience symptoms, and upon the latitude implicit both in the judgement of c-kit positivity and in the judgements regarding unresectability. From this perspective the timing of implementation of therapy appears highly arbitrary. There is no current evidence bearing on what is the most effective time point in disease progression for introduction of imatinib. Similarly lacking is evidence bearing on the most appropriate dosage and whether treatment should be for the full duration of an objective response, although an adequately powered trial is underway that will distinguish between relative effectiveness of 400 and 600mg / day. Resolution of these questions clearly has cost implications bearing in mind the considerable expense of imatinib.

A recurrence-free survival rate in primary KIT positive GISTs treated with complete surgical resection has been found to be 49% +/- 8% at 5 years and 37% +/- 10% at 10 years with a median follow up for all patients free of reoccurrance at 48 months.[76] If the data from this small study (n = 48) is found to be typical this means that a large proportion of patients with GIST initially treated with complete surgical resection would therefore be expected to proceed to the stage where they would be eventually considered candidates for imatinib treatment under the licensed indication. In this context the timing of the intervention to coincide with the necessarily temporally variable diagnosis of the metastatic or non-resectable stage of disease again appears arbitrary. The possible use of imatinib as adjuvant therapy pre- or post-operatively is a question that may address some of the uncertainty regarding timing of the intervention. These aspects are currently the subject of investigation (see protocol ID RTOG-S-0132, ACOSOG-Z9000).

Experimental evidence indicates that mutation of the c-kit gene or its up regulation is probably a major driver of transformation in GIST. However it is probably not the only driver (e.g. mutation in the PDGF receptor is an alternative) nor is it the only signal transduction element that might be targeted for therapy. Currently several drugs in various stages of development and clinical trial are being considered as alternatives and/or supplements of imatinib therapy. For example an abstract (and a web site entry) reporting interim results indicates that Sugen (SU11248) a tyrosine kinase inhibitor produced by Pfizer, yields a partial response (i.e. tumour shrinkage and/or functional loss as developed by PET) in patients whose disease progresses under continued imatinib therapy. Future developments are thus likely to encompass combination therapies in an analogous manner to strategies for some other tumours (e.g. ovarian cancer). Overly prescriptive suggestions for future research would pre-empt such proximal developments, however, where ethical considerations permit, study designs adopted should be adequately powered RCTs encompassing intention to treat analysis of measures of objective clinical outcome. As the well being of the patient as well as survival is of paramount in importance in patients with advanced malignant disease estimates of patient centred QoL and adverse events should also be measured as a matter of course.

6.4 Conclusions

Evidence from uncontrolled studies indicates that the treatment with imatinib brings about clinically significant shrinkage of tumour mass in about half of patients with unresectable and/or metastatic, KIT positive GIST. Results of modelling based on data from uncontrolled studies suggest that imatinib treatment improves survival in patients with unresectable and/or metastatic GIST. The economic evaluation modelling suggests that the cost per QALY gained ranges from £51,515 to £98,889 after 2 years, from £27,331 to £44,236 after 5 years, and from £21,404 to £33,976 after 10 years. The estimates after 2 years are of great uncertainty because, for example, they were based on the extrapolation beyond the trial data and of the possible changes in the costs of treatments. The conclusions are based on the existing evidence, and uncontrolled trials in progress will provide additional data from more imatinib-treated patients and/or data of longer follow-up.

6.4.1 Recommendations for future research

- More emphasis should be placed on quality of life[77] within trials involving patients with advanced malignancy. Adverse events should be reported so that inter trial comparisons could be made. As the increase in grade 3 adverse events with longer-term use of imatinib reported in the industrial submission indicates, long term follow up of adverse events is needed.

- Patients diagnosed with GIST are a heterogeneous group. Patients may have primary disease (which could be resectable or unresectable), recurrent disease or metastatic. Most are cKIT positive GIST but a small proportion are cKIT negative. Patients may have undergone a number of surgical procedures and other treatments, may succumb to the disease quickly or survive for many months. Added to this GIST can affect all

parts of the GI tract therefore symptoms and consequences of the disease can be many and varied depending upon the disease site. Subgroup analysis of which if any patient types have a better or worse response to imatinib is needed. An exploratory analysis of individual patient data may be a good way of exploring these issues.

- There are many uncertainties surrounding imatinib prescription such as the length of time patients should be on imatinib, the dose, i.e. is it better to step up or step down, drug resistance and the optimum time in the disease course to give the drug. When the present ongoing trials have had time to mature, answers to some of these uncertainties may well be forthcoming and ongoing trials on adjuvant therapy in patients with primary disease may well answer the question of timing of imatinib therapy. Secondary research such as an update of this systematic review and a reassessment of the model is highly recommended when ongoing trials reach completion.

7. APPENDICES

Appendix 1 Search strategy details

Effectiveness of Imatinib for treating GISTs.

Database: MEDLINE (Ovid) 1966 to April Week 3 2003

1 gastrointestinal neoplasms/ (9112)
2 gastrointestinal stromal tumo?r$.ti,ab. (558)
3 gists$.ti,ab. (187)
4 cd 117 positive stromal tumo?r$.ti,ab. (0)
5 cd117 positive stromal tumo?r$.ti,ab. (0)
6 cd 117 antigen$.ti,ab. (0)
7 cd117 antigen.ti,ab. (13)
8 GI PACT.ti,ab. (0)
9 gipact.ti,ab. (3)
10 icc tumo?r$.ti,ab. (8)
11 gastrointestinal mesenchymal tumo?r$.ti,ab. (19)
12 mesenchymal tumo?r$.ti,ab. (1266)
13 mesenchymoma/ (1225)
14 kit signalling.ti,ab. (11)
15 gastrointestinal smooth muscle tumo?r$.ti,ab. (14)
16 smooth muscle tumo?r$.ti,ab. (667)
17 leiomyoma$.mp. (10579)
18 leiomyoblastoma$.ti,ab. (356)
19 leiomyosarcoma$.ti,ab. (4596)
20 leiomyosarcoma/ (5066)
21 gastrointestinal autonomic nerve tumo?r$.ti,ab. (66)
22 autonomic nerve tumo?r$.ti,ab. (71)
23 gant$.ti,ab. (816)
24 pacemaker cell tumo?r$.ti,ab. (9)
25 gastrointestinal pacemaker cell tumo?r$.ti,ab. (7)
26 ckit.ti,ab. (13)
27 c kit.ti,ab. (2530)
28 Protein-Tyrosine Kinase/ or Proto-Oncogene Protein c-kit/ (20663)
29 7 or 9 or 10 or 12 or 13 or 14 or 16 or 17 or 18 or 19 or 20 or 22 or 23 or 24 or 26 or 27 or 28 (40291)
30 1 and 29 (492)
31 1 or 2 or 3 or 11 or 15 or 21 or 25 or 30 (9379)
32 imatinib.mp. (627)
33 gleevec.mp. (138)
34 glivec.mp. (70)
35 sti 571.ti,ab. (155)
36 sti571.ti,ab. (415)
37 st1 571.ti,ab. (2)
38 st1571.ti,ab. (16)
39 cgp 57148.ti,ab. (15)
40 cgp57148.ti,ab. (12)
41 or/32-40 (903)
42 31 and 41 (136)

Database: EMBASE (Ovid)1980 to 2003 Week 16

1 gastrointestinal tumor/ (1615)
2 gastrointestinal stromal tumo?r$.ti,ab. (488)
3 gists$.ti,ab. (159)
4 gastrointestinal mesenchymal tumo?r$.ti,ab. (12)
5 gastrointestinal smooth muscle tumo?r$.ti,ab. (9)
6 gastrointestinal autonomic nerve tumo?r$.ti,ab. (62)
7 gastrointestinal pacemaker cell tumo?r$.ti,ab. (7)
8 or/1-7 (1823)
9 cd 117 positive stromal tumo?r$.ti,ab. (0)
10 cd117 positive stromal tumo?r$.ti,ab. (0)
11 cd 117 antigen$.ti,ab. (0)
12 cd117 antigen.ti,ab. (11)
13 GI PACT.ti,ab. (0)
14 gipact.ti,ab. (2)
15 icc tumo?r$.ti,ab. (7)
16 mesenchymal tumo?r$.ti,ab. (970)
17 mesenchymoma$.mp. (709)
18 kit signalling.ti,ab. (10)
19 smooth muscle tumo?r$.ti,ab. (535)
20 leiomyoma$.mp. (5055)
21 leiomyosarcoma$.mp. (4075)
22 leiomyoblastoma$.mp. (283)
23 autonomic nerve tumo?r$.ti,ab. (66)
24 gant$.ti,ab. (703)
25 pacemaker cell tumo?r$.ti,ab. (8)
26 c kit.ti,ab. (2326)
27 ckit.ti,ab. (18)
28 protein tyrosine kinase.mp. (18193)
29 proto-oncogene protein.mp. (55)
30 or/9-29 (30800)
31 1 and 30 (300)
32 8 or 31 (1823)
33 imatinib.mp. (886)
34 gleevec.mp. (316)
35 glivec.mp. (237)
36 sti 571.ti,ab. (109)
37 sti571.ti,ab. (256)
38 st1 571.ti,ab. (2)
39 st1571.ti,ab. (21)
40 cgp 57148.ti,ab. (8)
41 cgp57148.ti,ab. (8)
42 or/33-41 (1046)
43 32 and 42 (113)

Database: CINAHL (Ovid)1982 to April Week 3 2003

1 exp gastrointestinal neoplasms/ (1984)
2 gastrointestinal stromal tumo?r$.ti,ab. (6)
3 gists$.ti,ab. (2)
4 gastrointestinal mesenchymal tumo?r$.ti,ab. (0)
5 gastrointestinal smooth muscle tumo?r$.ti,ab. (0)
6 gastrointestinal autonomic nerve tumo?r$.ti,ab. (0)
7 gastrointestinal pacemaker cell tumo?r$.ti,ab. (0)
8 or/1-7 (1985)
9 cd 117 positive stromal tumo?r$.ti,ab. (0)

10 cd117 positive stromal tumo?r$.ti,ab. (0)
11 cd 117 antigen$.ti,ab. (0)
12 cd117 antigen.ti,ab. (0)
13 GI PACT.ti,ab. (0)
14 gipact.ti,ab. (0)
15 icc tumo?r$.ti,ab. (0)
16 mesenchymal tumo?r$.ti,ab. (4)
17 mesenchymoma$.mp. (3)
18 kit signalling.ti,ab. (0)
19 smooth muscle tumo?r$.ti,ab. (4)
20 leiomyoma$.mp. (180)
21 leiomyoblastoma$.ti,ab. (0)
22 leiomyosarcoma$.mp. (23)
23 autonomic nerve tumo?r$.ti,ab. (0)
24 gant$.ti,ab. (6)
25 pacemaker cell tumo?r$.ti,ab. (0)
26 ckit.ti,ab. (0)
27 c kit.ti,ab. (3)
28 protein tyrosine kinase.mp. (2)
29 proto-oncogene protein.mp. (0)
30 or/9-29 (218)
31 1 and 30 (6)
32 8 or 31 (1985)
33 imatinib.mp. (12)
34 gleevec.mp. (12)
35 glivec.mp. (0)
36 sti 571.ti,ab. (5)
37 sti571.ti,ab. (7)
38 st1 571.ti,ab. (0)
39 st1571.ti,ab. (0)
40 cgp 57148.ti,ab. (0)
41 cgp57148.ti,ab. (0)
42 or/33-41 (32)
43 32 and 42 (9)

Database: Cochrane Library (CENTRAL) 2003 Issue 2

Search terms: (Textwords) imatinib OR gleevec OR glivec OR sti 571 OR sti571 OR st1 571 OR st1571 OR cgp 57148 OR cgp57148.

Database: PubMed 1966 – April 2003

(Imatinib OR glivec OR gleevec) AND (gastrointestinal stromal tumor$ OR gastrointestinal stromal tumour$ OR CD117 OR GIST$ OR positive stromal tumor$ OR positive stromal tumour$)

Database: ISI SCI Search (Web of Science) 1981 – April 2003

The searches were undertaken in 3 iterations and the records downloaded as follows:
(Gleevec OR imatinib OR glivec) AND (GIST* OR gastrointestinal stromal tumor* OR gastrointestinal stromal tumour*)

(Gleevec OR imatinib OR glivec) AND (mesenchymal OR mesenchyma OR smooth muscle tumor* OR smooth muscle tumour* OR leiomyoma)

(Gleevec OR imatinib OR glivec) AND (leiomyoblastoma* OR leiomyosarcoma* OR autonomic nerve tumor* OR autonomic nerve tumour* OR gant* OR pacemaker cell tumor* OR pacemaker cell tumour* OR ckit)

Diagnosis of GISTs

Database: MEDLINE (Ovid) 1966 to April Week 3 2003

1 gastrointestinal neoplasms/ (9112)
2 gastrointestinal stromal tumo?r$.ti,ab. (558)
3 gists$.ti,ab. (187)
4 cd 117 positive stromal tumo?r$.ti,ab. (0)
5 cd117 positive stromal tumo?r$.ti,ab. (0)
6 cd 117 antigen$.ti,ab. (0)
7 cd117 antigen.ti,ab. (13)
8 GI PACT.ti,ab. (0)
9 gipact.ti,ab. (3)
10 icc tumo?r$.ti,ab. (8)
11 gastrointestinal mesenchymal tumo?r$.ti,ab. (19)
12 mesenchymal tumo?r$.ti,ab. (1266)
13 mesenchymoma/ (1225)
14 kit signalling.ti,ab. (11)
15 gastrointestinal smooth muscle tumo?r$.ti,ab. (14)
16 smooth muscle tumo?r$.ti,ab. (667)
17 leiomyoma$.mp. (10579)
18 leiomyoblastoma$.ti,ab. (356)
19 leiomyosarcoma$.ti,ab. (4596)
20 leiomyosarcoma/ (5066)
21 gastrointestinal autonomic nerve tumo?r$.ti,ab. (66)
22 autonomic nerve tumo?r$.ti,ab. (71)
23 gant$.ti,ab. (816)
24 pacemaker cell tumo?r$.ti,ab. (9)
25 gastrointestinal pacemaker cell tumo?r$.ti,ab. (7)
26 ckit.ti,ab. (13)
27 c kit.ti,ab. (2530)
28 Protein-Tyrosine Kinase/ or Proto-Oncogene Protein c-kit/ (20663)
29 7 or 9 or 10 or 12 or 13 or 14 or 16 or 17 or 18 or 19 or 20 or 22 or 23 or 24 or 26 or 27 or 28 (40291)
30 1 and 29 (492)
31 1 or 2 or 3 or 11 or 15 or 21 or 25 or 30 (9379)
32 "Sensitivity and Specificity"/ (98098)
33 sensitivity.ti,ab. (232754)
34 diagnosis/ (7204)
35 specificity.ti,ab. (157451)
36 (diagnosis or diagnostic).ti,ab. (647419)
37 or/32-36 (992340)
38 31 and 37 (1880)

Database: EMBASE (Ovid)1980 to 2003 Week 17

1 gastrointestinal tumor/ (1616)
2 gastrointestinal stromal tumo?r$.ti,ab. (491)
3 gists$.ti,ab. (160)
4 gastrointestinal mesenchymal tumo?r$.ti,ab. (12)
5 gastrointestinal smooth muscle tumo?r$.ti,ab. (9)
6 gastrointestinal autonomic nerve tumo?r$.ti,ab. (62)
7 gastrointestinal pacemaker cell tumo?r$.ti,ab. (7)
8 or/1-7 (1827)
9 cd 117 positive stromal tumo?r$.ti,ab. (0)
10 cd117 positive stromal tumo?r$.ti,ab. (0)
11 cd 117 antigen$.ti,ab. (0)
12 cd117 antigen$.ti,ab. (16)
13 GI PACT.ti,ab. (0)
14 gipact.ti,ab. (2)
15 icc tumo?r$.ti,ab. (7)

16 mesenchymal tumo?r$.ti,ab. (971)
17 mesenchymoma$.mp. (710)
18 kit signalling.ti,ab. (10)
19 smooth muscle tumo?r$.ti,ab. (535)
20 leiomyoma$.mp. (5057)
21 leiomyosarcoma$.mp. (4078)
22 leiomyoblastoma$.mp. (283)
23 autonomic nerve tumo?r$.ti,ab. (66)
24 gant$.ti,ab. (706)
25 pacemaker cell tumo?r$.ti,ab. (8)
26 c kit.ti,ab. (2331)
27 ckit.ti,ab. (18)
28 protein tyrosine kinase.mp. (18220)
29 proto-oncogene protein.mp. (55)
30 or/9-29 (30843)
31 1 and 30 (301)
32 8 or 31 (1827)
33 "sensitivity and specificity"/ (8363)
34 sensitivity.ti,ab. (198210)
35 exp diagnosis/ (1317329)
36 specificity.ti,ab. (127760)
37 (diagnosis or diagnostic).ti,ab. (475695)
38 or/33-37 (1719322)
39 32 and 38 (996)

Database: CINAHL (Ovid) 1982 to April Week 3 2003

1 exp gastrointestinal neoplasms/ (1984)
2 gastrointestinal stromal tumo?r$.ti,ab. (6)
3 gists$.ti,ab. (2)
4 gastrointestinal mesenchymal tumo?r$.ti,ab. (0)
5 gastrointestinal smooth muscle tumo?r$.ti,ab. (0)
6 gastrointestinal autonomic nerve tumo?r$.ti,ab. (0)
7 gastrointestinal pacemaker cell tumo?r$.ti,ab. (0)
8 or/1-7 (1985)
9 cd 117 positive stromal tumo?r$.ti,ab. (0)
10 cd117 positive stromal tumo?r$.ti,ab. (0)
11 cd 117 antigen$.ti,ab. (0)
12 cd117 antigen.ti,ab. (0)
13 GI PACT.ti,ab. (0)
14 gipact.ti,ab. (0)
15 icc tumo?r$.ti,ab. (0)
16 mesenchymal tumo?r$.ti,ab. (4)
17 mesenchymoma$.mp. (3)
18 kit signalling.ti,ab. (0)
19 smooth muscle tumo?r$.ti,ab. (4)
20 leiomyoma$.mp. (180)
21 leiomyoblastoma$.mp. (0)
22 leiomyosarcoma$.mp. (23)
23 autonomic nerve tumo?r$.ti,ab. (0)
24 gant$.ti,ab. (6)
25 pacemaker cell tumo?r$.ti,ab. (0)
26 ckit.ti,ab. (0)
27 c kit.ti,ab. (3)
28 protein tyrosine kinase.mp. (2)
29 proto-oncogene protein.mp. (0)
30 or/9-29 (218)
31 1 and 30 (6)

32 8 or 31 (1985)
33 "Sensitivity and Specificity"/ (3823)
34 sensitivity.ti,ab. (4227)
35 diagnosis/ (474)
36 specificity.ti,ab. (1790)
37 (diagnosis or diagnostic).ti,ab. (25510)
38 or/33-37 (31777)
39 32 and 38 (177)

Prognosis of GISTs

Database: MEDLINE 1966 to April Week 3 2003

1 gastrointestinal neoplasms/ (9112)
2 gastrointestinal stromal tumo?r$.ti,ab. (558)
3 gists$.ti,ab. (187)
4 cd 117 positive stromal tumo?r$.ti,ab. (0)
5 cd117 positive stromal tumo?r$.ti,ab. (0)
6 cd 117 antigen$.ti,ab. (0)
7 cd117 antigen.ti,ab. (13)
8 GI PACT.ti,ab. (0)
9 gipact.ti,ab. (3)
10 icc tumo?r$.ti,ab. (8)
11 gastrointestinal mesenchymal tumo?r$.ti,ab. (19)
12 mesenchymal tumo?r$.ti,ab. (1266)
13 mesenchymoma/ (1225)
14 kit signalling.ti,ab. (11)
15 gastrointestinal smooth muscle tumo?r$.ti,ab. (14)
16 smooth muscle tumo?r$.ti,ab. (667)
17 leiomyoma$.mp. (10579)
18 leiomyoblastoma$.ti,ab. (356)
19 leiomyosarcoma$.ti,ab. (4596)
20 leiomyosarcoma/ (5066)
21 gastrointestinal autonomic nerve tumo?r$.ti,ab. (66)
22 autonomic nerve tumo?r$.ti,ab. (71)
23 gant$.ti,ab. (816)
24 pacemaker cell tumo?r$.ti,ab. (9)
25 gastrointestinal pacemaker cell tumo?r$.ti,ab. (7)
26 ckit.ti,ab. (13)
27 c kit.ti,ab. (2530)
28 Protein-Tyrosine Kinase/ or Proto-Oncogene Protein c-kit/ (20663)
29 7 or 9 or 10 or 12 or 13 or 14 or 16 or 17 or 18 or 19 or 20 or 22 or 23 or 24 or 26 or 27 or 28 (40291)
30 1 and 29 (492)
31 1 or 2 or 3 or 11 or 15 or 21 or 25 or 30 (9379)
32 incidence/ (74549)
33 mortality/ (21952)
34 follow-up studies/ (264821)
35 prognos$.ti,ab. (155870)
36 predict$.ti,ab. (310339)
37 course.ti,ab. (226841)
38 natural history.ti,ab. (17733)
39 morbidity.mp. (99392)
40 disease progression.mp. (32112)
41 survival analysis/ (35563)
42 survival rate/ (57889)
43 or/32-42 (1081003)
44 31 and 43 (1647)

Database: EMBASE (Ovid)1980 to 2003 Week 17

1 gastrointestinal tumor/ (1616)
2 gastrointestinal stromal tumo?r$.ti,ab. (491)
3 gists$.ti,ab. (160)
4 gastrointestinal mesenchymal tumo?r$.ti,ab. (12)
5 gastrointestinal smooth muscle tumo?r$.ti,ab. (9)
6 gastrointestinal autonomic nerve tumo?r$.ti,ab. (62)
7 gastrointestinal pacemaker cell tumo?r$.ti,ab. (7)
8 or/1-7 (1827)
9 cd 117 positive stromal tumo?r$.ti,ab. (0)
10 cd117 positive stromal tumo?r$.ti,ab. (0)
11 cd 117 antigen$.ti,ab. (0)
12 cd117 antigen$.ti,ab. (16)
13 GI PACT.ti,ab. (0)
14 gipact.ti,ab. (2)
15 icc tumo?r$.ti,ab. (7)
16 mesenchymal tumo?r$.ti,ab. (971)
17 mesenchymoma$.mp. (710)
18 kit signalling.ti,ab. (10)
19 smooth muscle tumo?r$.ti,ab. (535)
20 leiomyoma$.mp. (5057)
21 leiomyosarcoma$.mp. (4078)
22 leiomyoblastoma$.mp. (283)
23 autonomic nerve tumo?r$.ti,ab. (66)
24 gant$.ti,ab. (706)
25 pacemaker cell tumo?r$.ti,ab. (8)
26 c kit.ti,ab. (2331)
27 ckit.ti,ab. (18)
28 protein tyrosine kinase.mp. (18220)
29 proto-oncogene protein.mp. (55)
30 or/9-29 (30843)
31 1 and 30 (301)
32 8 or 31 (1827)
33 incidence/ (41623)
34 MORTALITY/ (85409)
35 follow-up/ (107343)
36 prognos$.ti,ab. (127952)
37 predict$.ti,ab. (284989)
38 course.ti,ab. (173662)
39 natural history.ti,ab. (15091)
40 morbidity.mp. (93363)
41 disease progression.mp. (10407)
42 exp survival/ (116353)
43 or/33-42 (859310)
44 32 and 43 (453)

Database: CINAHL 1982 to April Week 3 2003

1 exp gastrointestinal neoplasms/ (1984)
2 gastrointestinal stromal tumo?r$.ti,ab. (6)
3 gists$.ti,ab. (2)
4 gastrointestinal mesenchymal tumo?r$.ti,ab. (0)
5 gastrointestinal smooth muscle tumo?r$.ti,ab. (0)
6 gastrointestinal autonomic nerve tumo?r$.ti,ab. (0)
7 gastrointestinal pacemaker cell tumo?r$.ti,ab. (0)
8 or/1-7 (1985)
9 cd 117 positive stromal tumo?r$.ti,ab. (0)
10 cd117 positive stromal tumo?r$.ti,ab. (0)

11 cd 117 antigen$.ti,ab. (0)
12 cd117 antigen.ti,ab. (0)
13 GI PACT.ti,ab. (0)
14 gipact.ti,ab. (0)
15 icc tumo?r$.ti,ab. (0)
16 mesenchymal tumo?r$.ti,ab. (4)
17 mesenchymoma$.mp. (3)
18 kit signalling.ti,ab. (0)
19 smooth muscle tumo?r$.ti,ab. (4)
20 leiomyoma$.mp. (180)
21 leiomyoblastoma$.mp. (0)
22 leiomyosarcoma$.mp. (23)
23 autonomic nerve tumo?r$.ti,ab. (0)
24 gant$.ti,ab. (6)
25 pacemaker cell tumo?r$.ti,ab. (0)
26 ckit.ti,ab. (0)
27 c kit.ti,ab. (3)
28 protein tyrosine kinase.mp. (2)
29 proto-oncogene protein.mp. (0)
30 or/9-29 (218)
31 1 and 30 (6)
32 8 or 31 (1985)
33 incidence/ (1963)
34 mortality/ (2633)
35 follow-up studies/ (24049)
36 prognos$.ti,ab. (2939)
37 predict$.ti,ab. (16755)
38 course.ti,ab. (8786)
39 natural history.ti,ab. (522)
40 morbidity.mp. (5523)
41 disease progression.mp. (1708)
42 survival analysis/ (1499)
43 survival rate/ (0)
44 or/33-43 (56607)
45 32 and 44 (271)

Effectiveness of alternative treatments for GISTs

Database: MEDLINE 1966 to April Week 4 2003

Search Strategy for reviews

1 gastrointestinal neoplasms/ (9126)
2 gastrointestinal stromal tumo?r$.ti,ab. (564)
3 gists$.ti,ab. (190)
4 cd 117 positive stromal tumo?r$.ti,ab. (0)
5 cd117 positive stromal tumo?r$.ti,ab. (0)
6 cd 117 antigen$.ti,ab. (0)
7 cd117 antigen.ti,ab. (13)
8 GI PACT.ti,ab. (0)
9 gipact.ti,ab. (3)
10 icc tumo?r$.ti,ab. (8)
11 gastrointestinal mesenchymal tumo?r$.ti,ab. (20)
12 mesenchymal tumo?r$.ti,ab. (1268)
13 mesenchymoma/ (1227)
14 kit signalling.ti,ab. (11)
15 gastrointestinal smooth muscle tumo?r$.ti,ab. (14)
16 smooth muscle tumo?r$.ti,ab. (669)

17 leiomyoma$.mp. (10591)
18 leiomyoblastoma$.ti,ab. (356)
19 leiomyosarcoma$.ti,ab. (4601)
20 leiomyosarcoma/ (5071)
21 gastrointestinal autonomic nerve tumo?r$.ti,ab. (66)
22 autonomic nerve tumo?r$.ti,ab. (71)
23 gant$.ti,ab. (820)
24 pacemaker cell tumo?r$.ti,ab. (9)
25 gastrointestinal pacemaker cell tumo?r$.ti,ab. (7)
26 ckit.ti,ab. (13)
27 c kit.ti,ab. (2539)
28 Protein-Tyrosine Kinase/ or Proto-Oncogene Protein c-kit/ (20695)
29 7 or 9 or 10 or 12 or 13 or 14 or 16 or 17 or 18 or 19 or 20 or 22 or 23 or 24 or 26 or 27 or 28 (40345)
30 1 and 29 (496)
31 1 or 2 or 3 or 11 or 15 or 21 or 25 or 30 (9395)
32 surgery/ (20175)
33 exp drug therapy/ (245034)
34 exp radiotherapy/ (70098)
35 hepatic arterial chemoembolization.ti,ab. (86)
36 (embolization therapeutic and hepatic artery).sh. (1046)
37 (doxorubicin or adriamycin or ifosamide or cyclophosphamide or dacarbazine).mp. or vincristine.ti,ab. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (65769)
38 (dactinomycine or dtic or mitomycin or cisplatin or gemcitabine).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (39686)
39 palliative care/ (20707)
40 or/32-39 (404413)
41 31 and 40 (1043)
42 (systematic adj review$).tw. (3990)
43 (data adj synthesis).tw. (2791)
44 (published adj studies).ab. (3820)
45 (data adj extraction).ab. (2513)
46 meta-analysis/ (4933)
47 meta-analysis.ti. (4168)
48 comment.pt. (242714)
49 letter.pt. (499936)
50 editorial.pt. (151241)
51 animal/ (3428453)
52 human/ (8011318)
53 51 not (51 and 52) (2662788)
54 41 not (48 or 49 or 50 or 53) (1006)
55 or/42-47 (17806)
56 54 and 55 (2)

Search strategy for trials:

Sets 1-41 of the above strategy were repeated and sets 42-56 replaced by the following terms:

51 clinical trial.pt. (353915)
52 exp clinical trials/ (144112)
53 (clin$ adj25 trial$).ti,ab. (89701)
54 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (72228)
55 placebos/ (22514)
56 placebo$.ti,ab. (77769)
57 random$.ti,ab. (257368)
58 research design/ (36800)
59 or/51-58 (616989)
60 59 not 49 (573877)
61 60 not 50 (303852)
62 50 or 61 (583332)

63 41 and 62 (274)

Database: EMBASE (Ovid) 1980 to 2003 Week 19

1 gastrointestinal tumor/ (1626)
2 gastrointestinal stromal tumo?r$.ti,ab. (501)
3 gists$.ti,ab. (163)
4 gastrointestinal mesenchymal tumo?r$.ti,ab. (12)
5 gastrointestinal smooth muscle tumo?r$.ti,ab. (9)
6 gastrointestinal autonomic nerve tumo?r$.ti,ab. (62)
7 gastrointestinal pacemaker cell tumo?r$.ti,ab. (7)
8 or/1-7 (1847)
9 cd 117 positive stromal tumo?r$.ti,ab. (0)
10 cd117 positive stromal tumo?r$.ti,ab. (0)
11 cd 117 antigen$.ti,ab. (0)
12 cd117 antigen$.ti,ab. (16)
13 GI PACT.ti,ab. (0)
14 gipact.ti,ab. (2)
15 icc tumo?r$.ti,ab. (7)
16 mesenchymal tumo?r$.ti,ab. (974)
17 mesenchymoma$.mp. (712)
18 kit signalling.ti,ab. (10)
19 smooth muscle tumo?r$.ti,ab. (539)
20 leiomyoma$.mp. (5068)
21 leiomyosarcoma$.mp. (4093)
22 leiomyoblastoma$.mp. (287)
23 autonomic nerve tumo?r$.ti,ab. (66)
24 gant$.ti,ab. (709)
25 pacemaker cell tumo?r$.ti,ab. (8)
26 c kit.ti,ab. (2342)
27 ckit.ti,ab. (18)
28 protein tyrosine kinase.mp. (18270)
29 proto-oncogene protein.mp. (55)
30 or/9-29 (30937)
31 1 and 30 (301)
32 8 or 31 (1847)
33 surgery/ (34090)
34 exp drug therapy/ (546204)
35 exp radiotherapy/ (104608)
36 hepatic arterial chemoembolization.ti,ab. (78)
37 (artificial embolism and hepatic artery).sh. (666)
38 (doxorubin or adriamycin or ifosamide or cyclophosphamide or dacarbazine or vincristine).mp. (93590)
39 (dactinomycine or dtic or mitomycin or cisplatin or gemcitabine).mp. (59769)
40 palliative therapy/ (6771)
41 or/33-40 (721541)
42 32 and 41 (295)
43 randomized controlled trial/ (74238)
44 exp clinical trial/ (270409)
45 exp controlled study/ (1567279)
46 double blind procedure/ (47654)
47 randomization/ (6177)
48 placebo/ (63095)
49 single blind procedure/ (4170)
50 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (94326)
51 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (67220)
52 (placebo$ or matched communities or matched schools or matched populations).mp. (103495)
53 (comparison group$ or control group$).mp. (99566)
54 (clinical trial$ or random$).mp. (450331)

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55 (quasiexperimental or quasi experimental or pseudo experimental).mp. (873)
56 matched pairs.mp. (1411)
57 or/43-56 (1892288)
58 42 and 57 (132)

Database: ISI SCI Search (Web of Science) 1981 – May 2003

(GIST* OR gastrointestinal stromal tumor* OR gastrointestinal stromal tumour*) AND (surgery OR chemotherapy OR radiotherapy OR hepatic arterial chemoembolization OR palliat*)

Database: PubMed 1966 – May 2003

(gastrointestinal stromal tumor$ OR gastrointestinal stromal tumour$ OR CD117 OR GIST$ OR positive stromal tumor$ OR positive stromal tumour$) AND ((all subject headings) surgery OR radiotherapy OR chemotherapy OR (textword) hepatic arterial chemoembolization).

The following 'Limits' were then applied in turn: 'Reviews', RCTs, clinical trials.

Database: Cochrane Library (CENTRAL) 2003 Issue 2

Sets 1-41 of MEDLINE strategy above were repeated.

Economic Evaluation / Model

Database: MEDLINE (Ovid) to July 2003

1 gastrointestinal neoplasms/ (9255)
2 gastrointestinal stromal tumo?r$.ti,ab. (612)
3 gists$.ti,ab. (206)
4 cd 117 positive stromal tumo?r$.ti,ab. (0)
5 cd117 positive stromal tumo?r$.ti,ab. (0)
6 cd 117 antigen$.ti,ab. (0)
7 cd117 antigen.ti,ab. (13)
8 GI PACT.ti,ab. (0)
9 gipact.ti,ab. (3)
10 icc tumo?r$.ti,ab. (8)
11 gastrointestinal mesenchymal tumo?r$.ti,ab. (20)
12 mesenchymal tumo?r$.ti,ab. (1293)
13 mesenchymoma/ (1242)
14 kit signalling.ti,ab. (11)
15 gastrointestinal smooth muscle tumo?r$.ti,ab. (15)
16 smooth muscle tumo?r$.ti,ab. (682)
17 leiomyoma$.mp. (10921)
18 leiomyoblastoma$.ti,ab. (356)
19 leiomyosarcoma$.ti,ab. (4690)
20 leiomyosarcoma/ (5154)
21 gastrointestinal autonomic nerve tumo?r$.ti,ab. (67)
22 autonomic nerve tumo?r$.ti,ab. (72)
23 gant$.ti,ab. (838)
24 pacemaker cell tumo?r$.ti,ab. (9)
25 gastrointestinal pacemaker cell tumo?r$.ti,ab. (7)
26 ckit.ti,ab. (16)
27 c kit.ti,ab. (2616)
28 Protein-Tyrosine Kinase/ or Proto-Oncogene Protein c-kit/ (21296)
29 7 or 9 or 10 or 12 or 13 or 14 or 16 or 17 or 18 or 19 or 20 or 22 or 23 or 24 or 26 or 27 or 28 (41435)

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30 1 and 29 (524)
31 1 or 2 or 3 or 11 or 15 or 21 or 25 or 30 (9546)
32 economics/ (25980)
33 exp "costs and cost analysis"/ (106972)
34 cost of illness/ (5373)
35 exp health care costs/ (20667)
36 economic value of life/ (7077)
37 exp economics medical/ (9854)
38 exp economics hospital/ (12419)
39 economics pharmaceutical/ (1241)
40 exp "fees and charges"/ (21234)
41 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (179846)
42 (expenditure$ not energy).tw. (7859)
43 (value adj1 money).tw. (326)
44 budget$.tw. (8231)
45 or/32-44 (283724)
46 31 and 45 (116)
47 value of life/ (7077)
48 quality adjusted life year/ (1750)
49 quality adjusted life.tw. (1167)
50 (qaly$ or qald$ or qale$ or qtime$).tw. (910)
51 disability adjusted life.tw. (175)
52 daly$.tw. (241)
53 health status indicators/ (7538)
54 health utilit$.ab. (199)
55 health$ year$ equivalent$.tw. (32)
56 quality of wellbeing.tw. (2)
57 exp quality of life/ (38954)
58 quality of life.tw. (36472)
59 life quality.tw. (1162)
60 health status.tw. (14355)
61 utilit$.tw. (38941)
62 or/47-61 (116711)
63 31 and 62 (174)
64 46 or 63 (276)
65 limit 64 to yr=1985-2002 (244)

Database: EMBASE 1980 to July 2003

1 cost benefit analysis/ (16032)
2 cost effectiveness analysis/ (30028)
3 cost minimization analysis/ (542)
4 cost utility analysis/ (856)
5 economic evaluation/ (1559)
6 (cost or costs or costed or costly or costing).tw. (103413)
7 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (48382)
8 (technology adj assessment$).tw. (967)
9 or/1-8 (153819)
10 gastrointestinal tumor/ (1666)
11 gastrointestinal stromal tumo?r$.ti,ab. (546)
12 gists$.ti,ab. (176)
13 gastrointestinal mesenchymal tumo?r$.ti,ab. (14)
14 gastrointestinal smooth muscle tumo?r$.ti,ab. (9)
15 gastrointestinal autonomic nerve tumo?r$.ti,ab. (63)
16 gastrointestinal pacemaker cell tumo?r$.ti,ab. (7)
17 or/10-16 (1923)
18 cd 117 positive stromal tumo?r$.ti,ab. (0)
19 cd117 positive stromal tumo?r$.ti,ab. (0)
20 cd 117 antigen$.ti,ab. (0)

21 cd 117 antigen$.ti,ab. (0)
22 gi pact.ti,ab. (0)
23 gipact.ti,ab. (2)
24 icc tumo?r$.ti,ab. (7)
25 mesenchymal tumo?r$.ti,ab. (988)
26 mesenchymoma$.mp. (721)
27 kit signalling.ti,ab. (11)
28 smooth muscle tumo?r$.ti,ab. (547)
29 leiomyoma$.mp. (5155)
30 leiomyosarcoma$.mp. (4148)
31 leiomyoblastoma$.mp. (287)
32 autonomic nerve tumo?r$.ti,ab. (67)
33 gant$.ti,ab. (719)
34 pacemaker cell tumo?r$.ti,ab. (8)
35 c kit.ti,ab. (2394)
36 ckit.ti,ab. (20)
37 protein tyrosine kinase.mp. (18549)
38 proto-oncogene protein.mp. (55)
39 or/18-38 (31413)
40 10 and 39 (308)
41 17 or 40 (1923)
42 9 and 41 (26)
43 exp quality of life/ (39963)
44 quality adjusted life.tw. (1043)
45 (qaly$ or qald$ or qale$ or qtime$).tw. (760)
46 disability adjusted life.tw. (153)
47 daly$.tw. (183)
48 health utilit$.ab. (184)
49 health$ year$ equivalent$.tw. (22)
50 quality of wellbeing.tw. (5)
51 life quality.tw. (1031)
52 health status.tw. (9344)
53 utilit$.tw. (36835)
54 or/43-53 (84200)
55 41 and 54 (45)
56 42 or 55 (67)
57 from 56 keep 1-67 (67)

Appendix 2 Data extraction form

Data extraction sheet – effectiveness of Imatinib for GIST and other treatments for GIST.

Review Date:…….

Ref ID of Study:…….

Study Title:……

Reviewer Name: FS, MJC, JW

Study Type:……

Author (first author):
……

Journal, Vol, Date
published:……

Is the paper: fully published: abstract: ongoing

Study Objectives:……

Any relationship of study to other trials included in the review? If so describe:

……

Study Characteristics

Years when trial was undertaken:……..

Population

Diagnosis – describe (e.g. GIST, leiomyosarcoma etc)

……
How diagnosed
……

No. patients
intervention……..
control……

Age
intervention……
control……..……
Percentage males
intervention……
control……..…….

Stage of disease
Unresectable primary tumour …….
Metastatic……
Reoccurrance……

Previous treatment/s……

Intervention/Comparator

	Intervention	**Comparator**
Name of treatment		
Dose		
Mode of administration		
Length of time on treatment		
Any adjuvant therapy?		
Follow up intervals		
Length of follow up		

Comments:

Outcomes

	Outcomes sought	**Intervention**	**Comparator**
1	Quality of life		

2	Mortality (overall survival, progression free survival)		
3	Response		
4	Partial response		
5	Morbidity		
6	Side effects/adverse events/toxicity		
7	Other		

How were outcomes measured?

……

Analysis

Statistical tests used:……

Power calculation?……

Subgroup analysis?……

Intention to treat analysis?……

Comments?

Results

No of patients at end of trial: ……

Results

	Outcomes sought	**Intervention**		**Comparator**	
	Please fill in details regarding outcomes	**Raw data (n/N)**	**Summary statistics**	**Raw data**	**Summary statistics**

Comments regarding results: ……..

Appendix 3 Immunohistochemical demonstration of cKIT

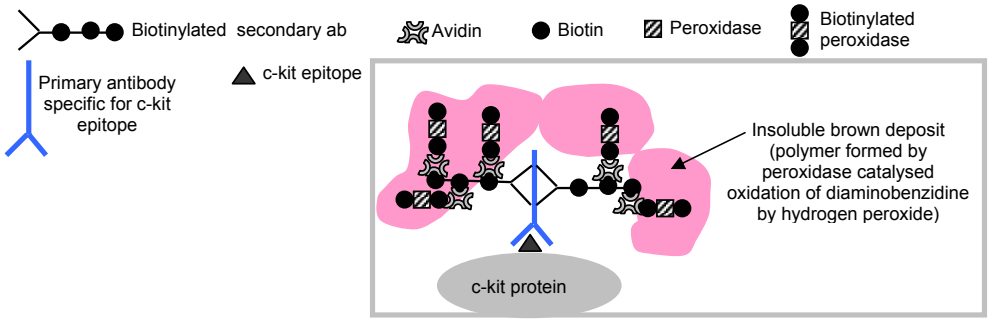
Method

Routine identification of c-kit (CD117) positive GISTS is made almost exclusively by using immunohistochemical (IH) test procedures. Test-use likely exceeds that implied by the incidence of GISTS because of utility in ruling out this diagnosis. Nevertheless because of the infrequency with which the test would be required not all histopathology laboratories in the UK would do it, in which case samples would likely be sent to a large centre that holds the appropriate reagents and has more extensive experience.

It is unlikely the test for c-kit would be carried out in isolation; rather a raft of immuno-techniques would be used including tests for CD 34, S100 (neural crest antigen), desmin, and smooth muscle actin.

The c-kit IH test is carried out using sections cut from paraffin embedded tissue. The test procedure results in the deposition of a dye (usually oxidised diaminobenzidine which is brown) at the sites of c-kit in the tissue section. The brown deposit of oxidised diaminobenzidine is visible by standard light microscopy (it can also be visualised in the electron microscope should such advanced methods be available or of interest).

An example of the sequence of events necessary for dye deposition is illustrated below and includes the following: -- Specific primary antibody binds to exposed



epitope(s) of the c-kit protein; biotinylated secondary antibody specific for the type of primary antibody employed then binds to the primary antibody; in a separate step avidin-bound biotinylated peroxidase binds to the secondary antibody via excess biotin binding sites on avidin. The tissue section is then immersed in a solution containing diaminobenzidine plus hydrogen peroxide and the enzyme action of peroxidase uses these substrates for the production of oxidised diaminobenzidine, which polymerises as an insoluble brown deposit at the sites of peroxidase in the tissue section thereby identifying and localising the sites of c-kit protein.

Because endogenous sources of peroxidase and biotin in the tissue section can give rise to false positive dye deposits (i.e. independent of c-kit) blocking procedures are often employed so as to eliminate these. Such sites may be considered unusual in alimentary tissue and blocking might be omitted. Sections tested are likely to contain c-kit positive mast cells and these act as an internal positive control; alternatively an external positive control might be included in the tissue block.

Because c-kit epitopes may be masked and initially undetectable by the primary antibody some workers employ "epitope retrieval" procedures prior to application of the IH test. These can involve exposure of the section to chelating solutions (citrate or ethylenediamine tetra acetic acid) and microwave treatment.

At least two preparations of polyclonal primary antibodies for c-kit are commercially available. These have been used in research and have not generated wholly concordant results in hands of different researchers.

Interpretation and quality assurance

A pathologist interprets sections submitted to an IH test for c-kit visually. The use of objective densitometry methods would be unlikely. Typically a subjective three-point scale employed to interpret a test for c-kit positivity might be: - 'positive', or 'problematical', or 'negative'. Problematic samples might be retested using an alternative tissue block (if available) and/or further sections from the same block.

Clinical Laboratories may avail themselves of the UK National External Quality Assessment Service (UKNEQAS). Recently "UKNEQAS Immunocytochemistry" reported on the performance by 38 participating laboratories in the immunocytochemical demonstration of CD117. [78]

Histopathology laboratories can apply for accreditation from Clinical Laboratory Accreditation (UK) Ltd (http://www.cpa-uk.co.uk) which recently formed a partnership with the United Kingdom Accreditation Service (UKAS).

Intermittently pathologists are subjected to a quality control in which it is determined to what degree their interpretation of prepared slides coincides with that of the consensus of a panel of expert pathologists. Such slides could include ones used in an IH test for c-kit but this is unlikely.

"Quality assurance for Immunocytochemistry; Approved Guideline" [79] published by the National Committee for Clinical Laboratory Standards (NCCLS) provides general guidelines for performing immunocytochemical procedures.

Result of c-kit test and subsequent implementation of imatinib treatment

The limited available evidence indicates that inter-laboratory and inter-observer reproducibility of IH tests in general may be limited (e.g. research and IH quality assessment data relevant to c-kit testing indicates that test results may vary from laboratory to laboratory). False negative test results (c-kit "activated cells not immunoreactive [18,80] might be obtained for many potential reasons. In view of the negligible cost of the IH test for c-kit relative to the high cost of imatinib treatment, the lack of alternative effective treatment options for non-resectable or metastatic c-kit positive GIST, and the significant possibility of error in the IH test, it would be sensible for the IH test on such samples to be carried out by at least two independent laboratories.

From the single perspective of identifying suitable candidate tumours for treatment with imatinib there are potential pitfalls in the use of the immuno-histochemical reaction for

CD117 as sole determinant of whether a patient might benefit from the putative effectiveness of imatinib. These include:

- a proportion of GISTs (possibly CD117 negative) may be driven by mutation in the PDGF receptor; this tyrosine kinase, like the SC receptor, is inhibited by imatinib and it would be reasonable to expect that such tumours would respond to imatinib treatment in a similar way to c-kit driven CD117 +v tumours.[81,82]
- it is possible that some mutations in the c-kit oncogene that drive transformation may alter the CD117 protein sufficiently for it to be no longer recognised by the antibodies used for the immuno-histochemical test, or other factors may be responsible for lack of c-kit immunoreactivity in c-kit "activated" cells.[18,80]
- the literature indicates that antigen retrieval of CD117, and therefore its demonstration by immuno-histochemistry, may depend strongly on the particular procedure adopted. Further, opinion is divided as to whether epitope retrieval should be attempted or not.
- CD117 immuno-histochemical responses of GISTs may vary according to the commercial polyclonal antibody preparation employed.
- lack of objective criteria for judgement of CD117 positivity. Although the presence of CD117 positive Mast cells in GI tissue affords a convenient and probably consistently staining positive control the intensity of staining and its distribution[‡] in tumour cells varies making arbitrary demands upon interpretation.

Inter-observer and inter-laboratory consistency and quality control of immuno-histochemical tests for CD117 [83] (and other tumour markers)[84] have not been widely practiced or investigated.[85] One study[86] carried out on the Ki67 marker (used as an index of proliferative activity) reported considerable variation between observers and laboratories, a result that points up the desirability that quality controls should be implemented in circumstances where the test result may determine eligibility for potentially effective but expensive therapy.

[‡] e.g. membrane-associated, diffuse cytoplasmic, punctate cytoplasmic.

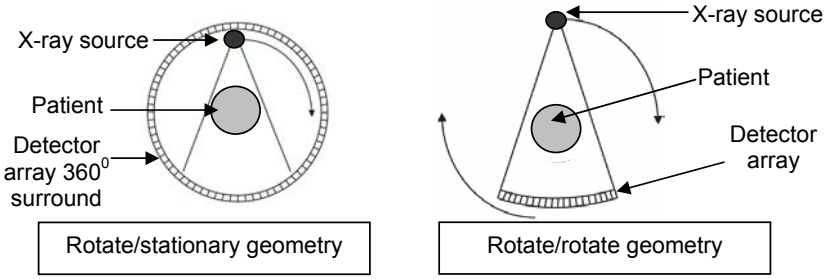
Appendix 4 Imaging methods for monitoring disease

CT scan

The CT scan (or computed axial tomography scan, CAT scan) uses X rays and advanced computer technology to generate highly detailed cross sectional (tomographic) images of the body. The technique is able to resolve objects of extremely small contrast and so discriminate between various soft tissues in ways not available from traditional X-ray techniques using film.

In CT a collimated (i.e. directed and confined) X-ray beam is passed through the patient whose different tissues absorb them to different extents (depending on their chemical make up, their physical density, and the energy in the X-ray photons). The transmitted and attenuated X-ray beam emerging from the patient reaches an array of detectors arranged on the opposite side of the patient from the X-ray source. The detectors are activated to an extent depending on the incoming X-ray energy. Electrical signals from the detector array are passed to the computer system for image generation.

In modern instruments the patient lies supine at the centre of the system and is moved continuously or in repeated small steps in an axial direction through the centre of the assembly while scanning is achieved by rotation in a circular path around the patient of either the X-ray source and detector array in fixed geometric relation to each other (rotate/rotate geometry), or of the X-ray source only concentrically with a complete array of detectors that surround the patient (rotate/stationary geometry). With the latter arrangement and continuous axial movement of the patient the source describes a helical path around the patient and X-rays are continuously generated resulting in faster acquisition of information for imaging.



The detector array consists of hundreds or thousands of separate detectors. Detectors are of two sorts. In one type scintillation crystals composed of solid materials (e.g. sodium iodide or cadmium tungstate crystals) that produce visible light on absorbing the energy of X-rays are coupled to a photoelectric converter (photelectrode plus photomultiplier system or a photodiode) that converts the light into electrical signals. The other type is a gaseous ionisation chamber containing gas under high pressure; as X ray energy is absorbed charge accumulates which is collected to generate an electric signal. Because X-rays give up less energy in a gas than a solid these detectors have a long path-length for collection of photons, and use a high atomic number gas (Xenon) under pressure (8 to 20 atmospheres) to raise physical density and increase the probability of interaction with the incoming X rays.

For some purposes contrast enhancing agents are used to increase resolution of structures of interest. These are administered orally or IV.

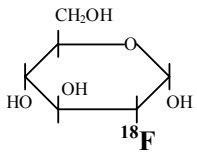
Recently PET / CT fusion scanners have been developed. These have the potential of combining the high resolution of CT scanning with the functional information derived from PET. These machines are not yet widely available for routine use.

Positron Emission Tomography (PET)

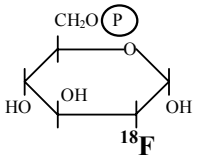
PET has been used to monitor the changes in tumour status that occur through time. Whereas CT and MRI provide purely morphological information PET has the potential of indicating functional changes in tissue masses. PET scans may be performed at various time intervals, e.g. 2 or 4 weeks or longer, and the images compared and quantified. A recent meta-analysis [87] of non-invasive imaging methods used to screen for hepatic metastases from GI cancers found FDG-PET to be superior to contrast-enhanced CT, contrast enhanced MR, and to ultra-sound methods. On the other hand a recent study of 30 consecutive patients[88] compared PET and dynamic enhanced MRI for the evaluation of liver metastases found the latter slightly superior.

The PET technique depends on the use of the radioactive glucose analogue ^{18}F 2-fluoro 2-deoxyglucose (FDG) which is injected into the blood stream. FDG is then taken up by those cells that transport and metabolise glucose. Like glucose itself FDG undergoes the first reaction of glycolysis (becoming phosphorylated by action of the enzyme hexokinase) but unlike glucose the phosphorylated form of FDG (2-fluoro deoxyglucose 6 phosphate, FDGP) cannot proceed through the remaining reaction steps of glycolysis; also FDPG cannot be transported out of the cell and it is resistant to dephosphorylation and consequently it accumulates inside the cells that take up FDG.

In general cancer cells rely more heavily on the uptake and utilisation of glucose‡ than do normal cell [7,89,90] and as a result they often take up and accumulate much more radioactive FDG than surrounding tissues.



^{18}F-labelled 2-fluoro deoxyglucose



^{18}F-labelled 2-fluoro deoxyglucose 6 phosphate

The unstable radioactive ^{18}F atom undergoes decay by emitting a positron. Almost immediately the emitted positron will collide with a nearby electron resulting in the mutual annihilation of both particles and the conversion of their rest mass energy (0.511 MeV each)

‡ Cancer cells may often be situated in a relatively anoxic environment and therefore must rely on glycolysis; also, unlike normal cells, cancer cells often fail to express a normal "Pasteur effect" in which glycolysis typically is greatly reduced in response to aerobic conditions.

into back-to-back gamma rays that pass out of the body and can be detected by an external array of gamma cameras. The signals received by the camera array are computed to generate an image of the anatomical sites of FDGP accumulation and a quantitative estimate of the radioactivity (FDGP) accumulated at these sites. These images and quantities can be compared between scans done at different times.

Because FDGP accumulation depends on the time that the tissues are exposed to the FDG it is important that compared scans are performed at a standard or fixed and specified time after injection. Also, since blood glucose concentration varies and because FBG uptake and glucose uptake compete, it is important that injection of FDG is given when blood glucose level is stable and within a known and specified range.

The European Organization for Research and Treatment of Cancer (EORTC) PET Study Group has proposed a method of analysing PET scan results for purposes of determining tumour status.[91] This proposal depends on several measures: -
a] Standard Uptake Value (SUV);
b] longest dimension of uptake site;
c] the appearance of previously undetectable uptake sites.

The SUV is an estimate of FDGP accumulation at a site and is given by: -
$(Q_t \times BSA) / Q_i$; where Q_t is radioactivity detected at the uptake site, Q_i is radioactivity injected, and BSA is body surface area.

On the basis of these measures four categories of change from one scan to a later one have been defined as follows: -

- Progressive Disease; ≥ 25% increase in SUV, **OR** ≥20% increase in longest dimension, **OR** appearance of ≥1 new lesion.
- Stable Disease; ≤ 25% increase and ≤15% decrease in SUV, and not more than 20% increase in longest dimension.
- Partial Response; a decrease of a minimum of 15 to 25% in SUV after one cycle of chemotherapy **AND** a decrease in SUV of more than 25% after >1 cycle (decrease in longest dimension not required).
- Complete Response; Tumour volume no longer distinguishable from surrounding tissue.

Because imatinib is administered daily rather than in cycles a partial response would sensibly be interpreted as a ≥ 25% decrease in SUV. In addition a “non-specific” response (stable disease or partial response) would be interpreted as any result that was neither progressive disease nor a complete response (according to the definitions above).

It is clear PET can demonstrate profound changes in glucose uptake. The term “metabolic death” has come into usage to describe the situation where a cell mass that formerly actively accumulated FDG relative surrounding tissues subsequently becomes indistinguishable from surrounding tissue by FDG- PET. However without knowledge of other compensating metabolic adjustments that might have taken place, the implications in the term “metabolic death” may be overstated. Because of the large difference (theoretically about 15 fold) in energy yield from glycolysis compared to the complete aerobic oxidation of glucose, cells could switch to complete (aerobic) oxidation from previous exclusive reliance on glycolysis thereby reducing required uptake of glucose by up to 15 fold without compromising their net energy usage and the activities (e.g. proliferation) that might depend on it. Thus the so-called

"metabolic death" observed in PET could be nothing of the sort but could reflect merely a shift in emphasis between metabolic pathways.

The crucial question is whether the PET evidence of GIST "metabolic death" is actually linked to loss of tumour cells, and ultimately whether this translates into better outcomes such as survival and QoL. Limited evidence from instances where both PET imaging and biopsy examination have been done through time does indeed indicate that a loss of viable tumour cells is linked to a favourable PET response. This cell loss is coupled with appearance of histologically identified "myxoid degeneration" and macrophage (or other cell) infiltration within the tumour mass. These changes may occur in conjunction with CT evidence of tumour mass shrinkage. Evidence from studies with other tumours indicates that such changes monitored via PET are associated with improved survival.[92]

Appendix 5 Imatinib treatment for advanced GIST –single case studies.

<table>
<tr><th>Study, design, patients and treatment</th><th>Outcomes</th></tr>
<tr><td>ASCO abstract – Author Jankilevich G[36]. Argentina

- Title – Gastrointestinal stromal tumours (GISTs) in Argentina in the era of imatinib. Diagnostic problems and treatment results.
- Aim of trial: retrospective review of 38 pts with GIST currently in follow up in 5 institutions to determine diagnosis and treatment of imatinib.</td><td>Trial data: all 38 patients tested for KIT with 17 treated with imatinib. Response was evaluated in 13 patients. A complete response was in a 23-year-old woman with a para ovaric mass and peritoneal sarcomatosis. Seven pts had a partial response, 3 patients had stable disease and 2 patients had progressive disease. Responses were durable in all cases (6-8 months). Toxicity: oedema, nausea, asthenia, insomnia, and mild anaemia were common. Imatinib was discontinued in 1 pt due to severe rash.</td></tr>
<tr><td>Joensuu 2001[37]

- A single case study to evaluate the use of STI571 (imatinib) in a pt with metastatic GIST.
- No. pts: n = 1.
- Date of study: March 2000 to Feb 2001

- Diagnosis: Histologically confirmed GIST – CD117 immunostaining, the KIT mutation consisted of a deletion of 15bp from exon 11.

- Age & sex: 54yrs, female.
- Stage of disease: metastatic GIST.
- Previous treatment/s, disease history: presented in October 1996 with mild abdominal discomfort & a large mass in the upper abdomen. She underwent surgery at this time. Metastases – upper abdomen, excised February 1998 & September 1998. Chemo: 7 cycles with MESNA, doxorubicin, ifosfamide and dacarbazine, given November 1998 to March 1999 with no clinical response. March 1999 – surgery to remove metastases obstructing the large bowel. April 1999 to February 2000 – thalidomide 400mg and 900,000Ц of sc interferon alfa three times per day – still disease progression.

- Intervention: Imatinb 400mg orally per day.
- Length of time on treatment: 11months to publication.</td><td>No. pts confirmed CD117 positive: 1.

QoL/PM: WHO performance measure: improved from 1 (indicating the presence of cancer related symptoms) to 0 (normal) during imatinib therapy. Measurement times not stated.

Mortality: Patient still alive at publication. Note: In Demetri paper NEJM 347 pg 478 mention this pt “is still on therapy 22 months after its initiation”

Response:

MRI Scan
<table><tr><td>Baseline</td><td>112.5 cm2</td></tr><tr><td>Day 14</td><td>67 cm2</td></tr><tr><td>Month 1</td><td>54 cm2</td></tr><tr><td>Month 2</td><td>42 cm2</td></tr><tr><td>Month 4</td><td>36 cm2</td></tr><tr><td>Month 5.5</td><td>33 cm2</td></tr><tr><td>Month 8</td><td>28cm2</td></tr><tr><td>Diff from baseline to month 8</td><td>84.5cm2 (75% reduction)</td></tr></table>
PET
<table><tr><td>Baseline</td><td>Multiple liver metastases & increased accumulation of</td></tr></table></td></tr>
</table>

<table>
<tr>
<td>
- Adjuvant therapy: none
- Follow up intervals: every 2 to 4 wks.
- Length of follow up: 11 months (Started March 2000 to February 2001).
- Note: In Demetri paper NEJM 347 pg 478 mention this pt “is still on therapy 22 months after its initiation” How is she? Don’t say, partial response still?
- Adjuvant therapy: none described.

- QoL/PM: WHO performance status.
- Response: measured by tumour size.
- Evaluated by:
▪ MRI scan: liver metastases measured as the sum of the products of 2 perpendicular axes of each of eight large liver metastases.
▪ PET scan: observed 18f deoxyglucose uptake, eyeballed no. sites of uptake before imatinib and compared 1 month after treatment had started.
▪ Histological findings: biopsies taken 1 and 2 months from start of treatment examined for density of tumour cells and KIT and K-67 immunohistochemistry.
- Side effects: CTC version 2.0
</td>
<td>
<table>
<tr><td></td><td>18F in the right renal pelvis & ureter were seen.</td></tr>
<tr><td>Month 1</td><td>No abnormal intake of 18F was seen in the liver or right kidney. A finding consistent with the changed, hypo dense appearance of metastases on MRI.</td></tr>
<tr><td>Month 2</td><td>“cold” areas with less uptake of 18F than in the surrounding liver parenchyma were seen at the sites of liver metastases.</td></tr>
</table>
Imunohistochemical analysis.
At 1 and 2 months after the start of treatment, compared to pre treatment biopsies, there was a decrease in cell density, and tumour cells did not stain for Ki67 (a marker for cell division).

Adverse events:
Transient nausea when taking the tablets – improved with food.
Main subjective side effects: grade 1 on CTC 2.0 = increase in bowel movements (2-4 per day), occasional muscle cramps in the legs and slight transient ankle oedema.

Comments: This lady had severe disease at presentation and had severe metastastic disease 2 yrs prior to treatment with imatinib.
</td>
</tr>
<tr>
<td>
Högenauer 2003 [38]

- A single case study to evaluate the use of STI571 (imatinib) in a pt with metastatic GIST.
- No. pts: n = 1.

- Diagnosis: GIST – CD117 positive the KIT mutation at exon 11.
- Diagnosed 1998.
- Age & sex: 51yrs, male.
- Stage of disease: hepatic metastatic GIST & reoccurrence.
- Previous treatment/s, disease history: primary tumour removed 1998, no evidence of metastases at that time. November 2000 CT scan detected reoccurrence with hepatic and intra-abdominal spread. Subsequently the pt received 3 courses of chemotherapy between Jan and July 2001, with combined administration of doxorubicin & ifosfamide and with
</td>
<td>
No. pts confirmed CD117 positive: 1/1.

QoL/PM: State that QLQ-C30 test done – detailed results not reported just that the patient improved with imatinib

Mortality: Patient still alive at time of analysis.

Response:

MRI Scan
<table>
<tr><td>Baseline</td><td>454cm2 – multiple liver metastases, confluent tumour masses in the peritoneum as well as masses in the mesentery & pelvis.</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>docetaxel & gemcitabine. Despite this progression occurred

- Intervention: Imatinb 400mg orally per day.
- Length of time on treatment: 7months to analysis.
- Adjuvant therapy: none
- Follow up intervals: followed up at 1 and 5 months.
- Length of follow up: 7 months (Started treatment November 2001).
- Adjuvant therapy: none described.

- Outcomes measured.
- QoL: QLQ-C30 test.
- Response: measured by:
▪ MRI scan: evaluated by EORTIC RECIST criteria
▪ PET scan
▪ Histological findings: residual tumour examined for viable cells.
- Side effects: described</td>
<td>
<table>
<tr><td>Month 1</td><td>143cm2 – histology showed groups of apoptotic tumour cells as well as viable KIT positive tumour cells.</td></tr>
<tr><td>Month 5</td><td>99cm2 with remaining tumour masses appearing necrotic</td></tr>
<tr><td>Diff. from baseline to month 5</td><td>355cm2 (78% reduction)</td></tr>
</table>

PET
<table>
<tr><td>Baseline</td><td>Multiple large glucose-utilizing lesions in the abdomen.</td></tr>
<tr><td>Month 1</td><td>Uptake of FDG reduced to non-detectable levels.</td></tr>
<tr><td>Month 2</td><td>Uptake of FDG at non-detectable levels.</td></tr>
</table>

Imunohistochemical analysis:
At 1 month histology showed groups of apoptotic tumour cells as well as viable KIT (CD117) positive tumour cells. At 5 months histology demonstrated areas of myxoid degeneration with few macrophages and stromal elements but no viable tumour cells.

Adverse events:
Mild periorbital oedema, routine laboratory tests showed no evidence of haematological, hepatic or renal side effects.
</td>
</tr>
<tr>
<td>Brooks 2002[39]

- A single case study reporting the treatment of a man with an abdominal GIST and also a brain malignancy.
- No. Pts: = 1
- Date of study: July 2001.
-
- Diagnosis: Primary abdominal GIST positive for CD117.
- Ff
- Age & sex: 75yrs, male.
- Stage of disease: Metastatic, reoccurrence.
- Previous treatments: Surgery for primary disease.
-
- Intervention: 800mg imatinib daily (in 2 divided doses).
- Length of time on treatment: 4 months.
- Adjuvant therapy: none.</td>
<td>No pts confirmed CD117 positive: 1/1.

QoL/PM: Post treatment performance status = 0. Not given pre treatment.
Tumour response: authors state that there was a decrease in size of the intra-abdominal sarcomatosis as well as liver metastases.
MRI scan revealed complete resolution of all abnormalities, consistent with complete response in the CNS.</td>
</tr>
</table>

- Follow up intervals: not stated. - Length of follow up: 4 months. - Outcome measures. - QoL/PM: ECOG performance status. - Tumour response: CT scan, MRI.	
Miyagawa et al 2002 (letter)[40] - Case study of a man with inoperable metastatic GIST – aim of letter was to report that the mans longstanding psoriasis had cleared up since he commenced treatment with imatinib - No. Pts: n = 1. - Started imatinib: July 2001 (still on it at time of analysis July 2002) - Diagnosis: GIST – CD117 positive (exon 11). - Age & sex: 62yrs, male. - Stage of disease: inoperable metastatic. - Previous treatment, disease history: Surgery for primary tumour, which had metastatic nodules in the spleen and omentum that were resected. When the pt developed reoccurrence he under went surgery for these 9 times between 1997 and 2001. - Intervention: Imatinb 400mg orally per day. Dose reduced to 300mg per day, due to side effect of diarrhoea. - Length of time on treatment: ongoing up to July 2002. - Adjuvant therapy: none for GIST therapy. - Follow up intervals: not stated. - Length of follow up: 12 months, still ongoing? - Length of time on treatment: 12 months to analysis. - Adjuvant therapy: none - Follow up intervals: followed up at 1 and 5 months. - Length of follow up: 12 months (Started treatment July 2001). - Adjuvant therapy: none described. - Outcomes measured. - Response: MRI measurement. - Adverse events: described.	No. Pts confirmed CD117 positive: 1/1. Mortality: pt still alive at analysis. After contacting the authors, they kindly wrote back stating that the pt had continued with imatinib with good response but had recently died from cardiac arrest. This means the pt had been on imatinib for approx 2 years. Response: MRI scan, authors state that MRI scans showed a marked reduction in GIST. Morbidity: cleared up his psoriasis. Adverse events: Results of routine laboratory tests remained stable throughout the observation. Notes: This paper aimed to report the outcome of imatinib treatment on psoriasis therefore GIST outcomes are not reported in detail, in addition the publication is a letter.

Terashima et al 2002.[41] - Case study of a patient with GIST, treated with imatinib. - No. Pts: n = 1. - Study conducted: Started treatment September 2000 - - Diagnosis: GIST –KIT positive. - Age & sex: 32yrs, female. - Stage of disease: hepatic metastatic GIST. - Previous treatment, disease history: 1998 primary tumour treated with surgery. Peritoneal reoccurrence May 2000 & November 2000. Liver metastases August 2000. - Intervention: Imatinib 400mg orally per day. - Length of time on treatment: 28days. - Adjuvant therapy: none. - Follow up intervals: unclear. - Length of follow up: 7wks.	No. Pts confirmed KIT positive: 1/1. Mortality: pt still alive at analysis. Response: CT scan at 3 weeks showed rapid tumour shrinkage (reduction rate of 56%). Response continued at 7 wks – reduction rate of 71%, authors evaluated the response as 'partial response'. Adverse event: Leukocytopenia, oedema, diarrhoea and nausea – all toxicities mild and tolerable. **Note: paper written in Japanese, information from abstract only.**
Mukaide et al et al 2002.[42] - Case study of a patient with GIST, treated with imatinib. - No. Pts: n = 1. - - Diagnosis: GIST – KIT positive. - Age & sex: 45yrs, female. - Stage of disease: metastasis GIST. - Previous treatment, disease history: primary surgery that removed a GIST arising from the small intestine. 2 yrs later pt developed multiple peritoneal metastases and required 4 successive operations to remove these. Imatinib was started to try and treat diffuse metastases not amenable to surgery. - - Intervention: Imatinib 400mg orally per day. - Length of time on treatment: 9 months. - Adjuvant therapy: none. - Follow up intervals: unclear. - Length of follow up: 9 months to analysis.	No. Pts confirmed KIT positive: 1/1. Mortality: pt still alive at analysis. Response: The pt is free from peritoneal masses for 9 months of imatinib treatment. Adverse event: Not described in abstract. **Note: paper written in Japanese, information from abstract only.**

-	
Omori et al 2002.[43] - Case study of a patient with GIST, treated with imatinib. - No. Pts: n = 1. - - Diagnosis: GIST –KIT positive. - Age & sex: 64yrs, female. - Stage of disease: intraperitoneal metastatic GIST. - Previous treatment, disease history: 1998 primary tumour treated with surgery. 5 subsequent operations to remove intraperitoneal recurrences. Inoperable occurrence in January 2002 that caused obstruction of the right urinary tract. Double J tube catheter inserted and imatinib commenced. - Intervention: Imatinib 400mg orally per day. - Length of time on treatment: 2 months. - Adjuvant therapy: none. - Follow up intervals: - Length of follow up: possibly 2 months? Unclear from abstract. - Outcomes - QoL: described. - Tumour response – CT scan. - Morbidity: described - Adverse events: described	No. Pts confirmed KIT positive: 1/1. QoL: improved, no further details given in abstract. Mortality: pt still alive at analysis. Response: 2 lesions estimatable on CT, reduced to 62% and 70% in size, with no new lesions found. It was evaluable by the authors as a 'partial' response. Morbidity: Hypogastric pain and low back pain disappeared and both abdominal fullness and constipation improved symptomatically. Adverse event: Not described in abstract. **Note: paper written in Japanese, information from abstract only.**
Fujimoto H et al 2002.[44] - Case study of a patient with GIST, treated with imatinib. - No. Pts: n = 1. - Started treatment June 2001 - - Diagnosis: GIST – CD 117 tested, KIT positive. - Age & sex: 59yrs, male. - Stage of disease: metastatic GIST. - Previous treatment, disease history: 1996 primary tumour treated with	No. Pts confirmed KIT positive: 1/1. Mortality: pt still alive at analysis. Response: after 9 months of treatment CT showed that tumours had decreased to less than 10% and the metastatic liver tumour had disappeared. No new lesions had appeared. As of May 2002 tumours at all sites continued to respond positively to treatment. Morbidity: patient remains clinically well at 9 months. Adverse event: Not described in abstract.

surgery. June 2001 saw several new intraabdominal tumours and liver metastases in progression. - Intervention: Imatinib 400mg orally per day. - Length of time on treatment: 9 months. - Adjuvant therapy: none. - Follow up intervals: unclear. - Length of follow up: 9 months to analysis. - Outcomes measured. - Tumour response: CT scan - Morbidity: described.	Note: paper written in Japanese, information from abstract only. Quite a substantial tumour response.

Appendix 6 Adverse events

Of the trials only 10 report adverse events. Of these, both imatinib trials used CTC version 2.0, whilst 1 trial (Rajan[47]) used CTC version 3.0. Four trials used CTC without giving the version number (Judson,[45] Bramwell,[63] Patel,[52] Ryan[46]). The remaining trials (Eilber,[53] Mavligit[48] and Edmonson[51]) just describe adverse events. Because of this variability of reporting it is very difficult to cross compare studies. To add to this difficulty whilst both imatinib trials used the same CTC version, they both chose to report grades in combination i.e. Demetri chose to report grade 3 and 4 combined, whereas van Oosterom combined grades 2 and 3. With a grade 2 event described as a "moderate adverse event" a grade 3 described as "severe and undesirable" and grade 4 as "life threatening and disabling" it is very difficult to know what type of event occurred and to cross compare the two trials. In a statement to us the NCI who administer the CTC said that they "preferred that results be reported according to grade and not be combined".

General trends

Imatinib. Of the imatinib trials Demetri[26]reported that at a median of 288 days on treatment 98% of patients had an adverse event of some kind, with 21% of patients having a severe event of grade 3 or 4. The most common serious event appears to be an unspecified haemorrhage (7 patients) and neutropenia (7 patients). The number of adverse events at grade 3 and 4 appears to increase over time with the number of adverse events at grade 3 and 4 increasing to 52.4%.[61] Their nature also appears to change with more serious GI events being reported. Overall adverse events appear to be more common in the van Oosterom trial but with the grades inconsistently lumped together it is very difficult to make sense of the data.

Of the other treatment trials, event reporting is much less ambiguous in that most trials that used grades did not combine them. In the trial by Judson[45], doxorubicin gave the most serious haematological adverse events with 47% of patients suffering a grade 4 neutropenia. In Ryan[46] patients treated with ET 743, again patients tend to suffer from haematological problems in particular leukopenia, neutropenia and anaemia. Of the two trials in which patients were treated with chemoembolization, pain seems to have been significant in a number of patients. Adverse events in Bramwell[63] found that alopecia was the most common event, whilst Edmonson[51] described toxicity as being significant with 33% of patients experiencing grade 3 vomiting. Finally Patel[52] (Gemcitabin) again found that haematological symptoms were the most common events suffered by the patients treated.

Haematological adverse events therefore are the most common events occurring in these trials, however in the imatinib trials only a small number of patients (n=7) were reportedly experienced severe neutropenia in comparison to larger numbers of patients in the alternative treatment trials. This is an odd finding as patients treated with imatinib for CML[29] also suffered haematological adverse effects, but again in much greater numbers for example 58% had grades 3 or 4 leukopenia/neutropenia, 43% had grade 3 or 4 thrombocytopenia, and 37% had grade 3 or 4 anaemia.[29] Could an element of disease specificity be the cause here? More serious adverse events involving the GI tract appear to occur later on in patients treated with imatinib (although the numbers involved are relatively small). The monitoring of adverse events throughout the course of treatment with imatinib, and in patients who are taken off the

drug is important to determine whether the events are disease specific or of a more general nature.

Table 18 Adverse events recorded in published imatinib and alternative treatment trials.

Study n=8	Adverse events		
Demetri[26] CTC 2.0 GIST (n=147) [imatinib]	These were measured using CTC version 2.0. Adverse events of grades 3 and 4 were as follows:		
		n = 147 analysis Oct 15 2001 (median follow up 288 days)	n = 147 analysis Aug 27th 2002 (additional 316 days)
		CTC grades 3 & 4	CTC grades 3 & 4
	Any adverse event with suspected relation to study drug	21%	
	GI symptoms		
	Nausea	1.4%	4.1%
	Diarrhoea	2.0%	4.8%
	Abdominal pain	0.7%	4.1%
	Vomiting	0.7%	4.1%
	Haematological		
	Anaemia	2.0%	4.8%
	Neutropenia	4.8%	
	Leukopenia	1.4%	
	Cardiovascular		
	Haemorrhage	4.8%	2.0%
	Tumour haemorrhage	2.7%	2.7%
	Upper GI tract bleeding or perforation	2.7%	3.4%
	Cerebral haemorrhage		0.7%
	Oedema		
	Oedema or fluid retention	1.4%	2.0%
	Facial oedema or fluid retention	0.7%.	
	Dermatological		
	Dermatitis or rash	2.7%	2.0%
	Hepatic		
	Abnormal liver-function results	2.7%	
	Fatigue	34.7	1.4%
	Back pain		1.4%
	Insomnia		0.7%
	In the first interim analysis a total of 144 patients (98%) had an adverse event of some kind with 31 patients (21.1%) having a serious adverse event classed at grade 3 or 4. In the second interim analysis all the patients (100%) had an adverse event of some kind. Of these 37.4% were classed as grade 3 and 15% were classed as grade 4, giving a total of adverse events at grade 3 and 4 as 52.4%.		

<table>
<tr><td>Van Oosterom[31]
CTC 2.0

GIST
(40)
[imatinib]</td><td>These were measured using CTC version 2.0. Adverse events (at 8 months of therapy): n = 40.

GI symptoms
Nausea/vomiting (grade 2-3) 25%
Anorexia (grade 2) 15%
Diarrhoea (grade 2) 12.5%
Oedema
Peri-orbital oedema (all events) 40%
Peripheral oedema (grade 2-3) 37.5%
Dermatological
Skin rash (grade 2-3) 30%
Constitutional symptoms
Fatigue (grade 2-3) 30%</td></tr>
<tr><td>Judson[45]
CTC

Soft tissue sarcoma retrospectively tested for GIST (21/94 GIST) [CAELYX vs. doxorubicin]</td><td>CTC Grade 3 and 4 reported here but the paper does document grades 1 and 2. (n = 94).

<table>
<tr><td>Drug</td><td>CAELYX 3</td><td>CAELYX 4</td><td>DOX 3</td><td>DOX 4</td></tr>
<tr><td>Grade</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Haematological</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Leucopenia</td><td>2%</td><td>0%</td><td>47%</td><td>12%</td></tr>
<tr><td>Neutropenia</td><td>4%</td><td>2%</td><td>30%</td><td>47%</td></tr>
<tr><td>Thrombocytopenia</td><td>0%</td><td>0%</td><td>2%</td><td>0%</td></tr>
<tr><td>Haemoglobin</td><td>4%</td><td>6%</td><td>5%</td><td>0%</td></tr>
<tr><td>GI symptoms</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Nausea</td><td>0</td><td>0%</td><td>2%</td><td>0%</td></tr>
<tr><td>Vomiting</td><td>2%</td><td>0%</td><td>2%</td><td>0%</td></tr>
<tr><td>Diarrhoea</td><td>0%</td><td>0%</td><td>2%</td><td>0%</td></tr>
<tr><td>Stomatitis (oral)</td><td>4%</td><td>0%</td><td>5%</td><td>0%</td></tr>
<tr><td>Anorexia</td><td>2%</td><td>0%</td><td>5%</td><td>0%</td></tr>
<tr><td>Infection</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Any infection</td><td>4%</td><td>0%</td><td>7%</td><td>0%</td></tr>
<tr><td>Febrile neutropenia</td><td>2%</td><td>0%</td><td>165</td><td>0%</td></tr>
<tr><td>Dermatological</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Alopecia</td><td>2%</td><td>0%</td><td>21%</td><td>0%</td></tr>
<tr><td>Palmar-plantar erythrodysesthesia</td><td>18%</td><td>0%</td><td>2%</td><td>0%</td></tr>
<tr><td>Pulmonary</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Cough</td><td>4%</td><td>0%</td><td>0%</td><td>0%</td></tr>
<tr><td>Shortness of breath</td><td>2%</td><td>2%</td><td>2%</td><td>2%</td></tr>
<tr><td>Flu like symptoms</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Lethargy</td><td>6%</td><td>0%</td><td>2%</td><td>0%</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Eilber[53]</td><td>There were no deaths relating to the surgical procedure or the intraperitoneal mitoxantrone. All patient deaths were due to their disease. In addition there were no systemic toxicity from intraperitoneal mitoxantrone. Local complications – (patients not given IP therapy) include: 2 abdominal infections and 1 small bowel stricture. Of which 1 infection and 1 stricture required reoperation.
Local complications – (patients given IP therapy) include: two small bowel fistulas and two abdominal infections. Of which 1 fistula required operation.</td></tr>
<tr><td>Ryan[46]</td><td>Toxicity was classed as moderate by the authors, because there “were no grade 4 haematologic toxicities”, see below. One patient, however, withdrew from the study due to toxicity. (n=?)

<table>
<tr><td></td><td>Grade 2</td><td>Grade 3</td></tr>
<tr><td>Haematological</td><td></td><td></td></tr>
<tr><td>Leukopenia</td><td>37%</td><td>26%</td></tr>
<tr><td>Anaemia</td><td>16%</td><td>11%</td></tr>
<tr><td>Thrombocytopenia</td><td>0</td><td>0</td></tr>
<tr><td>Neutropenia</td><td>21%</td><td>47%</td></tr>
<tr><td>Hepatotoxicity</td><td></td><td></td></tr>
<tr><td>Bilirubin</td><td>5%</td><td>0</td></tr>
<tr><td>Alkaline phosphate</td><td>0</td><td>0</td></tr>
<tr><td>SGOT</td><td>16%</td><td>42%</td></tr>
<tr><td>SGPT</td><td>11%</td><td>53%</td></tr>
</table></td></tr>
<tr><td>Rajan [47]
CTC 3.0

Metastatic sarcomas (34 procedures) (% per procedure) [chemo-embolization)</td><td>
<table>
<tr><td>Grade</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>GI symptoms</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Nausea</td><td>35%</td><td>15%</td><td>12%</td><td>0</td></tr>
<tr><td>Vomiting</td><td>18%</td><td>26%</td><td>0</td><td>0</td></tr>
<tr><td>Haematological</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Blood</td><td></td><td></td><td></td><td></td></tr>
<tr><td>HB</td><td>56%</td><td>26%</td><td>0</td><td>0</td></tr>
<tr><td>WBC</td><td>3%</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Platelets</td><td>0</td><td>0</td><td>3%</td><td>0</td></tr>
<tr><td>Coagulation</td><td>9%</td><td>6%</td><td>0</td><td>3%</td></tr>
<tr><td>Hepatic</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bilirubin</td><td>0</td><td>3%</td><td>9%</td><td>3%</td></tr>
<tr><td>GGT/ALK</td><td>38%</td><td>18%</td><td>21%</td><td>3%</td></tr>
<tr><td>AST</td><td>15%</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>ALT</td><td>9%</td><td>3%</td><td>0</td><td>0</td></tr>
<tr><td>Other</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pain</td><td>3%</td><td>6%</td><td>9%</td><td>4</td></tr>
<tr><td>Fever</td><td>6%</td><td>4</td><td>3%</td><td>0</td></tr>
<tr><td>Fatigue</td><td>15%</td><td>6%</td><td>9%</td><td>6%</td></tr>
<tr><td>Weight loss</td><td>29%</td><td>3%</td><td>0</td><td>0</td></tr>
<tr><td>Infection</td><td>0</td><td>6%</td><td>6%</td><td>0</td></tr>
<tr><td>Metabolic</td><td>3%</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Neurologic</td><td>0</td><td>0</td><td>3%</td><td>0</td></tr>
</table></td></tr>
</table>

Mavligit[48] Events measured by hepatic enzymes and pain assessment Leiomyosarcoma (14) [chemo-embolization	All patients experienced severe right upper quadrant pain after the treatment procedure. It was uniformly associated with significant elevation of hepatic enzymes including serum amino transferase, alkaline phosphatase and lactic dehydrogenase which usually lasted up to 7 days. Transient, but mild hyperbilirubinemia (median 1.9mg/dL; range 0.8-3.9mg/dL) was observed in most patients.
Bramwell[63] CTC Soft tissue sarcoma, GIST (26) or leiomoysarcoma – non GI origin (18) (not CD117 tested) [VX-710 + doxorubicin]	n=37 Grade 1 2 3 4 GI symptoms Nausea 51% 16% Vomiting 27% 16% Stomatitis 28% 14% 3% Anorexia 14% 14% 3% Constipation 16% 16% Diarrhoea 22% 6% 3% 3% Cardiovascular Vasodilation 22% *Constitutional symptoms* Asthenia 32% 35% 5% Headache 32% 11% Alopecia 5% 14% 19% Fever 8% 19% 3% *Pulmonary* Cough 8% 19% 3%
Edmonson[51] Described Stromal tumours of GI tract (21) [DTIC with MAP]	Toxicity was significant, with 33% of patients experiencing grade 3 (severe) vomiting despite the use of anti-emetics and this was grade 4 in 1 pt. 87% developed anorexia, with 8% at grade 3 intensity. 1 pt had grade 4 pulmonary toxicity following the fourth cycle and this was thought to be a major factor in her death. Grade 3 leukopenia occurred at some time in 42% and grade 3 thrombocytopenia was observed in 68% of pts. Transient diabetes requiring insulin occurred in 1 patient. Patterns of toxicity were similar for GIST and LMS.
Patel[52] CTC described Soft tissue sarcoma (56) [Gemcitabine]	Grade (n=56) *GI symptoms* Anorexia Grade 3 (2%) Haematological Neutropenia Grade 3 & 4 (4%) Thrombocytopenia Grade 3 & 4 (9%) Anaemia Grade 3 & 4 (4%) ALT Grade 3 (4%) *Cardiovascular* Oedema Extremity oedema Grade 3 (4%) *Constitutional symptoms* Myalgias Grade 3 (4%) Fatigue Grade 1 & 2 (20%)

Appendix 7 Experimental studies of non-Imatinib treatments for advanced GIST.

<table>
<tr><th>Study, design, patients and treatment</th><th>Outcomes</th></tr>
<tr><td>
Judson 2001[45]

- An RCT of CAELYX and doxorubicin in pts with advanced or metastatic adult soft tissue sarcoma (STS) with the end points of response rate, response duration and toxicity.
- Study conducted: not stated published 2001.
- No. Pts: total in trial n = 94. Estimated GIST = 12 (24%) CAELYX and 9 (20%) doxorubicin.
-
- Diagnosis: Soft tissue sarcoma, GIST identified retrospectively from the analysis of disease site i.e. visceral abdominal.
- Age and sex (all pts in trial): median age 52 yrs (range 19-80).
- Percentage males: 48% (48/94).
-
- Stage of disease: advanced/ metastatic.
- Previous treatment/s: Surgery – no, 13%, yes (curative), 61%, palliative, 20%, biopsy, 6.3%. Previous radiotherapy – no, 71% yes, 29%.

- Intervention: CAELYX vs. doxorubicin (standard treatment).
- CAELYX = 1hr infusion of 50mg/m2 every 4 wks.
- Doxorubicin = 75mg/m2 as a 5 min IV bolus injection every 3 wks.
- Intended that all pts receive a total of 6 cycles in view of the possible cardio toxicity of doxorubicin.

- Outcomes sought
- Mortality: survival analysis.
- Response: CP, PR, SD and PD.
- Response measured from the start of treatment to the date of documented progression or if CR from the date of the 1st documentation of CR. Response had to be confirmed 4 weeks later
</td><td>
No. Pts confirmed KIT positive: not KIT tested.

Mortality:

Median estimate overall survival for STS pts = 320 days for CAELYX (95% CI 272-505days) and 246 days for doxorubicin (95% CI 193 – 316 days).

Response:

<table>
<tr><th>Response</th><th>CAELYX n (%)</th><th>Doxorubicin n (%)</th></tr>
<tr><td>CR</td><td>1 (2)</td><td>1 (2)</td></tr>
<tr><td>PR</td><td>4 (8)</td><td>3 (7)</td></tr>
<tr><td>SD</td><td>16 (32)</td><td>18 (40</td></tr>
<tr><td>PD</td><td>24 (48)</td><td>20 (44)</td></tr>
<tr><td>Died from malignancy</td><td>4 (8)</td><td>1 (2)</td></tr>
<tr><td>Not accessible</td><td>1 (2)</td><td>2 (4)</td></tr>
<tr><td>95% CI</td><td>3.33 – 21.8</td><td>2.47 – 21.2</td></tr>
</table>
If GIST cases were excluded for response rates these would increase from 10% (CAELYX) and 9% (doxorubicin) to 14% and 12% respectively. Therefore from this we can assume that there were no positive responses amongst the GIST patients.

Adverse events:
CTC Grade 3 and 4 reported here but the paper does document grades 1 and 2.

CAELYX
Grade 3: Leucopenia (2%), Neutropenia (4%) Thrombocytopenia (0%) Haemoglobin (4%), Nausea (0%), Vomiting (2%), Stomatitis (oral) (4%), Anorexia (2%), Any infection (4%), Febrile neutropenia (2%), Alopecia (2%),
</td></tr>
</table>

Study, design, patients and treatment	Outcomes
	Palmar-plantar erythrodysesthesia (18%), Other (6%), Cough (4%), Shortness of Breath (2%), Flu like symptoms – lethargy (6%) Grade 4: Leucopenia (0%), Neutropenia (2%) Thrombocytopenia (0%) Haemoglobin (6%), Palmar-plantar erythrodysesthesia (2%). Doxorubicin. Grade 3: Leucopenia (47%), Neutropenia (30%), Thrombocytopenia (2%), Haemoglobin (5%), Nausea (2%), Vomiting (0%), Diarrhoea (2%), Stomatitis (oral) (5%), Anorexia (5%), Any infection (7%), Febrile neutropenia (16%), Alopecia (21%), Palmar-plantar erythrodysesthesia (0%), Cough (4%), Shortness of breath (2%), Flu like symptoms – lethargy (2%). Grade 4: Leucopenia (12%), Neutropenia (47%), Thrombocytopenia (0%) Haemoglobin (0%), Palmar-plantar erythrodysesthesia (2%), Other (0%)
Eilber et al 2000[53] - A cohort study to determine the effectiveness of IP chemotherapy in pts with recurrent gastrointestinal stromal sarcomas (presume GIST). - Study conducted: 1988 - 1998. - No. Pts = 46 of which 13 treated as controls. - Patients with gastrointestinal stromal sarcoma. Age & sex: not stated. - Stage of disease: Stage of disease: all had recurrent disease but it is unclear as to the severity of disease and metastatic status of pts. - Previous treatment/s: assume all had had previous surgery as pts had "recurrent disease". - Intervention: Postoperative IP therapy delivered by intraperitoneal catheters. IP chemotherapy consisted of mitoxantrone 20mg/m2 diluted in 21 of Ringer's lactate. Beginning 1 to 2 weeks after surgery, an equal volume of the mitoxantrone were given bilaterally and once given it was not removed from the peritoneal cavity. Each pt received a total of 4 to 6 courses of IP chemo with 2-3 week intervals between treatments. - Notes: 13 pts did not receive IP chemotherapy, of these 5 pts had surgery prior to the IP chemotherapy trial, 4 refused and 4 were excluded due to	Mortality: KM survival (read of figures) 1 year = IP 75% survival, non IP 70% survival 2 years = IP 42% survival, non IP 30% survival 3 years = IP 20% survival, non IP 20% survival Recurrence free: KM curves (read of figures) 1 year = IP 68% recurrence free, non IP 11% recurrence free 2 years = IP 30% recurrence free, non IP 0% recurrence free 3 years = IP 25% recurrence free, non IP 0% recurrence free Adverse events: No deaths relating to neither the surgical procedure nor the intraperitoneal mitoxantrone. All pt deaths were due to their disease. In addition there were no systemic toxicity from intraperitoneal mitoxantrone. Local complications – (pts not given IP therapy) include: 2 abdominal infections and 1 small bowel stricture. Of which 1 infection and 1 stricture required reoperation. Local complications – (pts given IP therapy) include: two small bowel fistulas and two abdominal infections. Of which 1 fistula required operation.

Study, design, patients and treatment	Outcomes
prior abdominal irradiation (n=2) and/or peritonitis (n=2). - Adjuvant therapy: prior to IP chemotherapy each pt had surgical resection, which consisted of excision of all gross disease, omentectomy and lysis of adhesions. Liver metastases were treated by primary resection, chemo-embolization or cryoablation. - Length of follow up: mean 19 months, 34 months for surviving pts. - Outcomes. - Mortality: KM survival and recurrence curves - Response: tumour response NA - Side effects: described.	

<table>
<tr><th>Study, design, patients and treatment</th><th>Outcomes</th></tr>
<tr><td>Ryan 2002 [46]
- Multicentre clinical trial to evaluate the efficacy, tolerability and pharmacokinetics of ecteinascidin 743 (ET-743).
- Study conducted: started August 1999.
- No pts: n = 20 (1 dropped out at the beginning).
- Diagnosis: Pts had measurable GISTs. Retrospective analysis found 16 pts KIT positive, 1 negative and 3 untested due to samples not being available.
- Age & sex: 44yrs (range 22-77), 77% male.
- Stage of disease: “advanced”.
- Previous treatments: most of the patients had been previously treated, with 19 (95%) having had surgery (probably for primary disease), 45% having had previous chemotherapy of which 9 had had adriamycin, 5 received ifosfamide, 3 DTIC and 2 pyrimidine analogue. In addition 20% had had radiotherapy.
- Intervention: ET – 743 Ecteinascidin, 1.5mg/m2 (reduced to 1.2mg/m2 and 1mg/m2if grade 4 neutropenia) was given by 24hour continuous IV infusion. This represented 1 cycle. One cycle every 3 weeks was given until disease progression. In addition 10mg IV of Dexamethosone was given for nausea.
-
- Outcomes sought
- Mortality using KM analysis
- Tumour response using CT scan
- Adverse events: looks like CTC but not clearly stated.</td><td>No. pts confirmed KIT positive: 16.

Mortality: 11 months into the study, 11 patients started receiving imatinib; therefore the K-M survival curves are confusing. The authors attempt to analyse the patients that did not receive imatinib and found that of the 7 that did not receive imatinib, the median survival was 8.6 months and 17.9% survival at 1 year. NOTE: these patients are most likely to be different from those receiving imatinib.
Response:
CR = 0
PR = 0
SD = 2 patients (1 patient received 4 cycles and 1 received 10 cycles of treatment)
DP = 16 patients (median time to progression 1.25 months, most of these patients received 2 cycles of treatment)
Non-evaluable = 2 patients (1 removed for toxicity reasons and was unevaluable for absence of repeat scan, the second patient withdrew prior to treatment commencing).

Adverse events: Toxicity was classed as moderate by the authors as there “were no grade 4 haematological toxicities”, see below. One patient, however, withdrew from the study due to toxicity.
<table>
<tr><th>Haematological</th><th>Grade 2</th><th>Grade 3</th></tr>
<tr><td>Leukopenia</td><td>7(37%)</td><td>5 (26%)</td></tr>
<tr><td>Anaemia</td><td>3 (16%)</td><td>2(11%)</td></tr>
<tr><td>Thrombocytopenia</td><td>0</td><td>0</td></tr>
<tr><td>Neutropenia</td><td>4(21%)</td><td>9(47%)</td></tr>
<tr><td>Hepatotoxicity</td><td></td><td></td></tr>
<tr><td>Bilirubin</td><td>1(5%)</td><td>0</td></tr>
<tr><td>Alkaline phosphate</td><td>0</td><td>0</td></tr>
<tr><td>SGOT</td><td>3(16%)</td><td>8(42%)</td></tr>
<tr><td>SGPT</td><td>2(11%)</td><td>10(53%)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Study, design, patients and treatment</th><th>Outcomes</th></tr>
<tr><td>DePas 2003 [19]

- A retrospective analysis of outcome of patients with gastrointestinal sarcomas treated with the same systemic chemotherapy as other soft tissue sarcomas.
- Thirteen Italian centres responded, with data from patients treated between 1979 and 1999, with 98.5% treated since 1990.
- No. Pts: n=67

- Diagnosis: gastrointestinal sarcomas, no further data on histology or CD117 test No data on patients age or sex.
- Stage of disease: advanced (metastatic n=64 (95%) reoccurrence n=3 (4.5%).
- Intervention: Combination chemotherapy (n = 51pts –76%) or monochemotherapy (n = 16pts – 24%). Where combination regimes contained an anthracycline plus isofosfamide in 42 pts additionally
- combined with dacarbazine in 11pts (note these figures are stated in the publication, it is not possible to tell further where the error is). Dose of ifosamide was >9g/m2 in 32/42 patients. Dose of doxorubicine and epirubicin was >60 and 90 mg/m2 respectively in all pts but one. 5/16 monotherapy pts received antracycline (over 9g/m2. 10/16 monotherapy pts received ifosfamide (over 9g/m2)
- Follow up: response evaluated after 2 or 3 cycles. Survival (KM) calculated to 50 months.

- Outcomes sought: survival KM calculated at 50 months; Response: CR, PR, SD & DP.</td><td>Mortality – overall survival 1yr 61% 2yrs 24% 3yrs 15%

With a median follow up of 11 months (range 2-60), the median survival time calculated from the start of chemotherapy was 16 months (range 2-16 months). Median survival of patients who obtained a major response with chemo was 18.5 months with an overall survival at 1 year of 80% dropping to 40% at 2 years. Non-responders had a median overall survival of 15 months (range 2 – 49).

<table>
<tr><th>Response</th><th>Ifosfamide + antracycline n=42</th><th>Other CT n=25</th><th>Total n=67</th></tr>
<tr><td>CR</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>PR</td><td>5</td><td>1</td><td>6</td></tr>
<tr><td>SD</td><td>15</td><td>9</td><td>24</td></tr>
<tr><td>Non evaluable</td><td>2</td><td>1</td><td>3</td></tr>
</table>
</td></tr>
<tr><td>Rajan et al 2001[47]

- A case series study to evaluate response and survival to chemo-embolization in pts with sarcomas metastatic to the liver that are surgically unresectable.
- Study conducted from January 1993 to January 2000.
- No. pts = 16.</td><td>Mortality:
Overall survival from time of diagnosis:
- 1-year 81% [95% CI 53% - 94%] 13pts.
- 2 years 54% [95% CI 25% - 75%] 9pts.
- 3 years 40% [95% CI 13% - 67%] 7pts.
Overall survival from time of treatment:
- 1 year 67% [95% CI 37% - 85%] 11pts.</td></tr>
</table>

<table>
<tr><th>Study, design, patients and treatment</th><th>Outcomes</th></tr>
<tr><td>
- Histologically confirmed metastatic sarcomas. (n= 11 pts (69%) had metastatic gastrointestinal sarcomas: 2 (13%) had splenic angiosarcomas; remaining 3 (19%) patients had broad ligament, leiomyosarcoma of the inferior vena cava and malignant fibrous histiocytoma of the colon respectively.
- Age and sex: age not described. Percentage males: 50%.
- Stage of disease: All primary tumours were resected. Six patients (37.5%) had synchronous liver metastases: the remainder developed metachronous lesions 6 months to 8 years after resection of the primary
- Previous treatment/s: 7 (44%) received various combinations of systemic chemotherapy before chemo-embolization.

- Intervention: Chemo embolization via hepatic artery route. Dose and drugs used: cisplatin 100mg, doxorubicin 50mg, mitomycin-C 10mg} emulsified in 1:1 ratio with Ethiodol. This emulsion was mixed with 150-250µ polyvinyl alcohol particles and instilled into 1-4ml aliquots.
- Adjuvant therapy: anti-emetics and antibiotics plus IV hydration.
- Follow up: 1 month after completion then a CT scan every three months.
- Length of follow up: 7 to 78 months (mean 27)

- Mortality: KM analysis from time of diagnosis and time of treatment.
- Response: WHO criteria, determined from the time of the first chemo-embolization.
- Modified pain scores.
</td><td>
- 2 years 50% [95% CI 22% - 73%] 8pts.
- 3 years 40% [95% CI 14% - 65%] 7pts.
Response (at 30 days after treatment):
- PR = 13% (2pts).
- SD = 69% (11pts).
- DP = 19% (3pts).
Adverse events
<table>
<tr><th>Grade</th><th>1</th><th>2</th><th>3</th><th>4</th></tr>
<tr><td>Pain</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>Fever</td><td>2</td><td>4</td><td>1</td><td>0</td></tr>
<tr><td>Nausea</td><td>12</td><td>5</td><td>4</td><td>0</td></tr>
<tr><td>Vomiting</td><td>6</td><td>9</td><td>0</td><td>0</td></tr>
<tr><td>Blood</td><td></td><td></td><td></td><td></td></tr>
<tr><td>HB</td><td>19</td><td>9</td><td>0</td><td>0</td></tr>
<tr><td>WBC</td><td>1</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Platelets</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>Coagulation</td><td>3</td><td>2</td><td>0</td><td>1</td></tr>
<tr><td>Fatigue</td><td>5</td><td>2</td><td>3</td><td>2</td></tr>
<tr><td>Weight loss</td><td>10</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Hepatic</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bilirubin</td><td>0</td><td>1</td><td>3</td><td>1</td></tr>
<tr><td>GGT/ALK</td><td>13</td><td>6</td><td>7</td><td>1</td></tr>
<tr><td>AST</td><td>5</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>ALT</td><td>3</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Infection</td><td>0</td><td>2</td><td>2</td><td>0</td></tr>
<tr><td>Metabolic</td><td>1</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Neurologic</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
</table>
</td></tr>
<tr><td>Mavligit et al 1995 [48]

- A case series study to evaluate response and survival after hepatic chemo-embolization of the liver in patients with gastro intestinal leimyosarcoma, metastatic to the liver.
</td><td>Mortality:
Median survival 18months. 7 pts had died at the time of publication post treatment at 4, 10, 10, 12, 14, 15 & 35months. 7 alive at time of publication post treatment at 18, 19, 21, 22, 27, 31 & 36 months. (n=140
Therefore time to survival in years =</td></tr>
</table>

<table>
<tr><th>Study, design, patients and treatment</th><th>Outcomes</th></tr>
<tr><td>
- Study conducted 1991 – 1994 (inferred time period).
- No. Pts = 14.

- Patients with leiomyosarcoma metastatic to the liver.
- Age & sex: 30-75yrs, 86% males.
- Stage of disease: all metastatic to the liver. Median % liver involvement = 44% range 20 - 80%. Five patients had metastes on diagnosis, therefore mean time to liver metastes in those without metastes at diagnosis = 27months.
- Previous treatments: all pts had had primary tumour resection, 5 pts received systemic or regional intraperitoneal chemotherapy and 1 pt received radiotherapy.
- Intervention: hepatic chemo-embolization infusion with cisplatin & vinblastine. Dose: 150mg cisplatin + 15ml polyvinyl sponge suspension + 10mg/m2 vinblastine. Treatment repeated on second lobe after 4 weeks.
- Follow up: CT scan 1 month after second procedure.
- Response: measured via CT scans, unclear as to which criteria used – authors define response as a ≥ 50% reduction.
- Side effects: measured hepatic enzymes and pain.
</td><td>
1 year: 10pts (4 dead)
2 years: 4 pts (2 dead + 4 censored)
3 years: 0 patient (1 dead + 3 censored)

Response:
<table>
<tr><th>No. Of courses</th><th>1 (2pts)</th><th>2 (5pts)</th><th>3 (2pts)</th><th>4 (1pt)</th><th>5 (2pts)</th><th>Total (14pts)</th></tr>
<tr><td>No. pts with response > 50%</td><td>0</td><td>4</td><td>2</td><td>1</td><td>2</td><td>9</td></tr>
</table>
Adverse events: All patients experienced severe right upper quadrant pain after the treatment procedure. It was uniformly associated with significant elevation of hepatic enzymes including serum amino transferase, alkaline phosphatase and lactic dehyrogenase that usually lasted up to 7 days. Transient, but mild hyperbilirubinemia (median 1.9mg/dL; range 0.8-3.9mg/dL was observed in most patients.
</td></tr>
<tr><td>
Chen et al 1998 [49]

- A retrospective cohort to determine whether surgical resection of liver metastatic leiomyosarcoma resulted in prolonged survival.
- Study conducted: 1984-1995.
- No. pts = 11.

- Patients with leiomyosarcoma metastatic to the liver. Age & sex: mean 56 yrs (range 30-69), 2 males (18%).
- Stage of disease: all metastatic to the liver. Mean no. liver metasteses 2.6, range 1 to 6. Mean size of largest lesion 3.8cm, range 1.1 to 10 cm.
- Previous treatments: all pts had had primary tumour resection. All had surgery without adjuvant chemotherapy, or radiation after primary
</td><td>
Mortality:
Median survival: median survival was 24 months for incomplete resection and it was not reached for complete resection. Log rank test 0.03. Five out of the 6 patients who had had complete resection were alive at the time of analysis living to 23, 32, 37, 43, and 53 months. Two of these patients, (survival of 23 and 43 months) were disease free at analysis with the remaining 3 surviving patients alive with disease. Patients who had received adjuvant chemotherapy died at 22, 24 and 19 months, the latter case had had a complete resection. All 5 patients who had had incomplete resection died before analysis, surviving to 18, 22, 24, 29 and 39 months (data read off KM curve).

Adverse events: None of the pts died during surgery.
</td></tr>
</table>

<table>
<tr><th>Study, design, patients and treatment</th><th>Outcomes</th></tr>
<tr><td>tumour resection. Prior to liver resection 1 pt had radiation + chemotherapy (adriamycin, dacarbazine & etoposide).
- Intervention: Complete (6pts) or incomplete (5 pts) liver resection. Adjuvant therapy: 4 pts. 3 pts received adjuvant chemo after liver resection (1 pt received doxorubicin, dacarbazine, isfosfamide and mesna, 1 pt received doxorubicin, dacarbazine, etoposide & 1 pt received cytoxan and vincristine). 1 pt received radiotherapy. Comments: All pts pre operatively were thought to be resectable, however, of the five pts with incomplete resections 3 were thought to be complete but were found to have had positive margins and in the remaining 2 only a small volume of residual disease was left behind.
- Outcomes.
- Follow up: 39 months.
- Response: not measured.
- Side effects: not measured.</td><td></td></tr>
<tr><td>Bramwell et al 2002[50]
- A case series to evaluate the safety/tolerability pharmocokinetics and efficiency of VX-710 plus doxorubicin in pts with inoperable, locally advanced or metastatic anthracycline – resistant/refractory soft tissue sarcoma (including 11pts with GIST).
- Study conducted: no dates given as to when trial conducted.
- No. pts: n = 29 plus adverse events data from an additional 8 pts who took part in the MTD part of this study who met the study criteria and were treated with the same doxorubicin dose used in the phase II part of this study.
- Diagnosis: Inoperable, locally advanced or metastatic soft tissue sarcoma (STS): measurable disease, anthracycline resistant/refractory disease (documented progression on doxorubicin defined as appearance of new lesions or >25% increase within 8 wks or chemotherapy naïve GIST or leiomyosarcoma metastatic to the liver).</td><td>Comments: 26/29 pts evaluable. Of those not evaluable, 1 with extensive liver metastases, concurrent to the 1st treatment cycle developed deteriorating liver function, became septic and died. A second pt did not have a histological confirmed sarcoma and a third did not have confirmed disease progression prior to the start of the trial.

Mortality: Reported if occurred, not specifically an outcome measure. 1 death (see ‘other’ section for details).

Response:
Tumour response
<table>
<tr><th>Tumour histology</th><th>Partial response</th><th>Stable disease</th><th>Early progression</th><th>Total no. pts</th></tr>
<tr><td>Non GIST</td><td>2</td><td>7</td><td>6</td><td>15</td></tr>
<tr><td>GIST</td><td>0</td><td>1</td><td>10</td><td>11</td></tr>
<tr><td>Overall</td><td>2</td><td>8</td><td>16</td><td>26</td></tr>
</table>
Pts with GIST progressed after 2 treatment cycles.</td></tr>
</table>

<table>
<tr><th>Study, design, patients and treatment</th><th>Outcomes</th></tr>
<tr><td>
- Age & sex: 51.7yrs (range 23-75), 59% males (17/29).
- Stage of disease: no individual pt detail, see description of pts as above.
- Previous treatment/s: no details regarding surgery.

- Intervention: VX-710, 120mg/m2/h was administered by CIV infusion for 68-72 hrs with the Maximum Tolerated Dose (MTD) of doxorubicin identified in Phase I administered at least 4 and no more than 8 hrs after the start of the VX –710 infusion. MTD doxorubicin = 60mg/m2.

- Treatment was administered every 3 wks.
- Adjuvant therapy: none described.

- Adverse events: looks like CTC. (n= 37)

- The following efficacy outcomes involved n= 29pts.
- Tumour response: RECIST.
- Progression free interval: KM survival curves.
- Post hoc analysis of GIST vs. non-GIST tumours.
</td><td>
Disease progression: Median progression-free intervals for all 26 evaluable pts, the subgroup of pts with non-GIST sarcomas were 6.3 wks, 6.1 wks and 13.6wks respectively.

Adverse events: CTC
<table>
<tr><th>Adverse event</th><th>Total (%)</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th><th>Grade 4</th></tr>
<tr><td>Asthenia</td><td>27 (73)</td><td>12</td><td>13</td><td>2</td><td></td></tr>
<tr><td>Nausea</td><td>25 (68)</td><td>19</td><td>6</td><td></td><td></td></tr>
<tr><td>Vomiting</td><td>18 (49)</td><td>10</td><td>6</td><td></td><td>2</td></tr>
<tr><td>Stomatitis</td><td>18(49)</td><td>11</td><td>5</td><td>1</td><td>1</td></tr>
<tr><td>Headache</td><td>16(43)</td><td>12</td><td>4</td><td></td><td></td></tr>
<tr><td>Alopecia</td><td>14 (38)</td><td>2</td><td>5</td><td>7</td><td></td></tr>
<tr><td>Anorexia</td><td>12 (32)</td><td>5</td><td>5</td><td>1</td><td></td></tr>
<tr><td>Constipation</td><td>12 (32)</td><td>6</td><td>6</td><td></td><td></td></tr>
<tr><td>Diarrhoea</td><td>11 (30)</td><td>8</td><td>2</td><td>1</td><td>1</td></tr>
<tr><td>Cough</td><td>11 (30)</td><td>3</td><td>7</td><td>1</td><td></td></tr>
<tr><td>Fever</td><td>11 (30)</td><td>3</td><td>7</td><td>1</td><td></td></tr>
<tr><td>Vasodilatation</td><td>8 (22)</td><td>8</td><td></td><td></td><td></td></tr>
</table>
Interesting comment at the end of the paper re: imatinib.
“ the lack of activity observed with the combination of VX-710 with doxorubicin in this study suggests that either constitutive activation of c-KIT or alternative biochemical mechanisms of drug resistance render GIST nonresponsive to doxorubicin cytotoxicity. Nonetheless, it is important to continue to study these mechanisms because even STI571 has not yielded complete responses in any pts with GIST and identification of resistance mechanisms will remain an important and relevant area of research. Additionally, it is of note that STI571 itself appears to be a substrate for efflux pumps such as the product of MDR1”.
</td></tr>
<tr><td>
Edmonson 2002 [51]

- A case series comparing the effect of DTIC with MAP regime in order to develop a regime that might yield superior activity against leiomyosarcomas.
</td><td>
No. pts confirmed KIT positive: not KIT tested.

Mortality:
92% of pts progressed (36/39) 82% (32/39) have died.
</td></tr>
</table>

<table>
<tr><th>Study, design, patients and treatment</th><th>Outcomes</th></tr>
<tr><td>
- Study conducted: 1994-1998.
- No. pts: n = GIST = 21, LMS = 18.
- Diagnosis: Gastrointestinal stromal tumour (GIST) n = 21 – where GIST = “stromal tumours of the stomach, small bowel, colon and pancreas origin”. LMS n= 18 where LMS = leiomyosarcomas of non-gastrointestinal origin.
- Age and sex: GIST = 55 (range 39-69), LMS = 54.5 (range27-78). GIST = 13 (62%) male, LMS = 3 (17%) male.
- Stage of disease: not clear.
- Previous treatment/s: all previously untreated.

- Intervention: DTIC plus MAP} DTIC 740mg/m2, MITO 6mg/m2, ADR 40mg/m2, CCDP 60mg/m2, GM-CSF 250µ/m2. Median cycles per pt = 4 (range 1-6).

- Outcomes
- Mortality: KM survival. Measured overall survival and observed metastatic spread.
- Tumour response: described.
- Adverse effects: described.
- Time to disease progression: KM analysis.
</td><td>
<table>
<tr><th></th><th>GIST</th><th>LMS</th></tr>
<tr><td>Median survival (from fig 1)</td><td>16.7 months (95% CI = 8.8 – 27.5 months)</td><td>17.5months (95% CI = 4-8.5months)</td></tr>
<tr><td>KM survival</td><td></td><td></td></tr>
<tr><td>1 year</td><td>63%</td><td>58%</td></tr>
<tr><td>2 years</td><td>44%</td><td>24%</td></tr>
<tr><td>3 years</td><td>17%</td><td>24%</td></tr>
</table>
Response: Objective tumour regression in GIST pts: 1/21 pts ((1.8%) 95% CI = 0 – 14.5%), LMS 11/18 (61%) (95% CI = 38-84%) including regression in 8/10 uterine cases.

Adverse events: Toxicity: significant, with 33% of pts experiencing grade 3 (severe) vomiting despite the use of anti-emetics and this was grade 4 in 1 pt. 87% developed anorexia, with 8% at grade 3 intensity. 1 pt had grade 4 pulmonary toxicity following the fourth cycle and this was thought to be a major factor in her death. Grade 3 leukopenia occurred at some time in 42% and grade 3 thrombocytopenia was observed in 68% of pts. Transient diabetes requiring insulin occurred in 1 pt. Patterns of toxicity were similar for GIST and LMS.

Time to progression:
<table>
<tr><th></th><th>GIST</th><th>LMS</th></tr>
<tr><td>KM survival (from fig 2)</td><td></td><td></td></tr>
<tr><td>1 year</td><td>18%</td><td>16%</td></tr>
<tr><td>2 years</td><td>0% (all progressed)</td><td>3%</td></tr>
</table>
</td></tr>
<tr><td>
Patel 2001 [52]

- A case series comparing the efficacy, toxicity and optimal dose rate of gemcitabine in adult pts with advanced soft tissue sarcomas (STS) by comparing levels of gemcitabine triphosphate (GTP) in peripheral blood mononuclear cells (PBMCs).
- Study conducted: 1998-2000.
- No. pts: n = GI leiomyosarcoma = 17, other soft tissue sarcomas (STS) 39. Total in trial = 56.
</td><td>
No. pts confirmed KIT positive: not KIT tested.

Response: First stage: no patients with GI leiomyosarcoma responded, one pt achieved a mixed response with regression (52% reduction in size) of a pelvic peritoneal metastases while the liver metastases progressed.

Adverse events:
Six pts experienced grade 3 & 4 neutropenia and 5 pts experienced grade 3 to 4 thrombocytopenia. Two pts had grade 3 and 4 anaemia. Grade 3 elevation of ALT
</td></tr>
</table>

<table>
<tr><th>Study, design, patients and treatment</th><th>Outcomes</th></tr>
<tr><td>
- Diagnosis: by histology, Gastrointestinal (GI) leiomyosarcoma.
- Age and sex: all pts with STS in trial = 54 (28-76 yrs), percentage males = 48% (27/56).
- Stage of disease: advanced metastatic disease.
- Previous treatment/s: 5/17 GI leiomyosarcoma had prior chemotherapy.

- Intervention: Gemcitabine 1000mg/m2 – 30 minute infusion weekly for up to 7 wks – followed by 1 week of rest and re-evaluation. In pts with stable or responding disease therapy was continued on a weekly basis for 3 wks followed by 1 wk of rest and tumour response assessment were made every 8 wks.

- Outcomes sought:
- Response: CP, PR, SD and PD.
- Adverse effects: described graded according to CTC
- Also measured KM time to progression.
</td><td>
(self limiting) was seen in 2 pts in 2 cycles. Grade 3 myalagias were experienced by 2 pts, with 2 pts encountering bilateral lower-extremity oedema with an erythematous rash and 1 pt complained of grade 3 anorexia. Grade 1 to 2 fatigue was reported by 11 pts.

Survival data: Survival analysis has been undertaken using the KM method and is given as 13.9 months. However it is of limited use as this survival has been analysed using all the patients in this trial and is impossible to separate the data for GI leiomyosarcoma, therefore is of little use.
</td></tr>
<tr><td>
Carson 1994 [54]

- A case series characterizing the presentation, diagnosis, and surgical management of this malignancy, the results of chemotherapy, radiation and cytoreductive surgery were examined.
- Study conducted: 1970 - 1991.
- No. pts: n = 32
- Diagnosis: pathological diagnosis of gastric leiomyosarcoma (LMS) or malignant leiomyoblastoma (LMB) was identified by tumour registry search.
- Age and sex: median age 57 yrs (range 13-81).
- Percentage males: 75% (24/32).
- Stage of disease: primary and advanced metastatic disease.
- Previous treatment/s: N/A.
-
- Intervention: surgery – curative, palliative surgery, chemotherapy, radiation and debulking.
-
- Outcomes sought:
</td><td>
No. pts confirmed KIT positive: not KIT tested.

Mortality:

<table>
<tr><th>Therapy</th><th>n</th><th>Median survival (mo)</th><th>Estimated 5 yr survival (%)</th><th>p</th></tr>
<tr><td>Resection</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Curative</td><td>21</td><td>40</td><td>34</td><td>0.05</td></tr>
<tr><td>Palliative</td><td>11</td><td>8</td><td>0</td><td></td></tr>
<tr><td>Chemotherapy</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Yes</td><td></td><td></td><td></td><td></td></tr>
<tr><td>No</td><td>25</td><td>27</td><td>19</td><td>0.23</td></tr>
<tr><td></td><td>7</td><td>124</td><td>67</td><td></td></tr>
<tr><td>Radiation</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Yes</td><td>7</td><td>40</td><td>43</td><td>0.19</td></tr>
<tr><td>No</td><td>25</td><td>24</td><td>21</td><td></td></tr>
<tr><td>Debulking</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Yes</td><td>14</td><td>34</td><td>14</td><td>0.42</td></tr>
<tr><td>No</td><td>18</td><td>27</td><td>37</td><td></td></tr>
</table>
</td></tr>
</table>

Study, design, patients and treatment	Outcomes
- Mortality, tumour response.	Response: 25 pts received chemotherapy, all but 5 progressed, 4 had a partial response, which had duration of less than 4 months and 1 had a complete response. Comments: bit difficult to compare this study with the others as difficult to tell as to the case mix of the chemotherapy, radiation therapy and debulking patients.

Appendix 8 Case studies of non-imatinib treatments

Study, design, patients and treatment	Outcomes
Shioyama 2001[55] - A single case study of a pt with GIST (retrospectively confirmed) who was treated with radiotherapy, chemotherapy – carboplatin & epirubicin, and immunotherapy – OK432 (5KE). - No. pts: n = 1. - Diagnosis: GIST retrospectively confirmed positive for KIT and CD 34. - Age and Sex: 75yrs, female. Stage of disease: reoccurrence. - Previous treatment/s: surgery for primary disease – gastrectomy, distal pancratectomy and splenectomy for sarcoma of the stomach in 1990. - Intervention: Radiotherapy, then chemotherapy with carboplatin & epirubicin, concurrently. Then the pt was given 4 intratumoral injections of a biological response modifier, OK432 (5KE). - Response: measured by: ▪ CT scan – immediately post treatment and 6 years post treatment. ▪ PET scan – immediately post treatment.	No. pts confirmed CD117 positive: 1/1 (retrospectively). Response: CT scan 6 yrs post treatment revealed that the tumour markedly decreased in size to a small low-density structure 20 mm in diameter. CT scan immediately after completion of radiotherapy. No significant change in tumour size but there is a decrease in density inside. PET scan: immediately after the treatment showed a decrease in FDG uptake, (SUV = 1.66) in comparison to that before treatment.
Pollock 2001 [56] - A single case study of a pt with GIST who was treated with radiotherapy, for an unresectable tumour – the tumour was unresectable, as the pt had refused an AP resection. - No. pts: n = 1. - Diagnosis: GIST CD 34 positive. - Age and Sex: 77yrs, female. Stage of disease: unresectable. - Previous treatment/s: surgery for part of the tumour.	No. pts confirmed CD117 positive: 0/1 but CD34 positive. Response: 1-year colonoscopy – a rectal fullness without a discrete mass was found. 2 year CT scan revealed continued regression of the left anterior rectal wall fullness – no progression or lymphadenopathy was noted. Mortality: Patient alive at 2 years. Adverse events:

Study, design, patients and treatment	Outcomes
- Intervention: Radiotherapy, 5040 cGy - Follow up: at 1 and 2 years. - Response measured by CT scan. - Description of patient's health and side effects.	At 4 months following treatment the pt reported some mild increase in post surgical rectal urgency and an increased need for a pad. At 2 years she reported stabilization in her present urgency.
Kamoshita et al 2002 [57] - Case study of a patient with GIST, who's primary and liver metastases were treated with surgery, recurrent liver metastases treated by ethanol injection therapy. - No. pts: n = 1. - - Diagnosis: GIST – CD117 positive. - Age & sex: 56yrs, female. - Stage of disease: inoperable metastatic. - Previous treatment, disease history: at primary presentation the pt had liver metastases as well as a tumour arising from the jejunum. - - Intervention: Surgery plus ethanol injection therapy for reoccurrences in the liver 3 months post surgery. Ethanol dose not given. - Length of time on treatment: N/A. - Adjuvant therapy: none. - Follow up intervals: 3 months post op. - Length of follow up: 8 months, pt still alive at time of report. - Response: CT scan 2 months post surgery.	No. pts confirmed CD117 positive: 1/1. Mortality: pt still alive at analysis (8 months post surgery). Response: CT scan 3 months post surgery. Recurrent tumour in the remnant liver detected by CT scan post surgery. (At this point the pt was treated by ethanol injection therapy). No further CT scan results given. Morbidity: Pt described as being in good condition at home 8 months after surgery (still with a recurrent tumour in the remnant liver).

Study, design, patients and treatment	Outcomes
Miyauchi T et al 2002 [58] - Case study of a patient with GIST, presenting as an oesophageal hiatus hernia, treated with a self expandable metallic stent - No. pts: n = 1. - - Diagnosis: GIST – CD34 positive and KIT positive. - Age & sex: 85yrs, female. - Stage of disease: unresectable. - Previous treatment, disease history: at primary presentation pt presented with an unresectable tumour. - Intervention: Insertion of a self-expandable metallic stent (SEMS). - Length of time on treatment: N/A. - Adjuvant therapy: none. - Follow up intervals: 3 months post op. - Length of follow up: 12 months, pt died from disease in February 2002.	No. pts confirmed KIT positive: 1/1. Mortality: pt died of disease 12 months post insertion of SEM. Response: N/A palliative treatment only. Morbidity: Patient needed a jejunostomy for tube feeding on 13 August 2001, she then became markedly emaciated before her death.

Appendix 9 Ongoing studies

As this drug was recently developed it was felt that there would be ongoing trials. The following sources were searched:

• Trials registers: m*eta*Register of Controlled Trials (*m*RCT), National Research Register 2003 Issue 2, ClinicalTrials.gov (National Institutes of Health), International Cancer Research Portfolio, Current Trials (MRC Clinical Trials Unit), UKCCCR National Register of Cancer Trials, CancerBACUP, Cancer.gov (National Cancer Institute). Searches were carried out 8-9 July 2003. Unless otherwise stated the registers were searched using the drug terms Imatinib, Glivec, Gleevec, STI571, ST1571 and the results browsed for references to the relevant population.

Eight trials were identified as ongoing, the following is a list of data obtained from sources such as abstracts and register reports.

Trial Name
EORTC – STBSGH, ISG and AGITG trial

Data sources
Novartis submission, ASCO abstract no.s 3271 & 3272 (2003), 1650 (2002).

Aim of trial
Phase III trial which is a comparison of two doses (400mg daily and 400mg twice daily) of imatinib in the treatment of patients with advanced gastrointestinal stromal tumours. The trial is powered to detect a 10% difference of progression free survival with the final analysis requiring 340 failures.

Trial data.
(ASCO abstract 1650) The aim of this abstract was to report toxicity. As from February 2001 the trial had accrued 753 patients. Twenty one patients to date are off study (progressive disease 10, side effects 5). Toxicity data available for 352 patients, with the most frequent side effects being anaemia (88%) , oedema – particularly periorbital oedema (67%), fatigue (60%), nausea (44%), granulpenia (32%) and skin rash (24%). Most events were mild to moderate. One patient died of drug related neutropenic sepsis.
(ASCO abstract 3272[32]) Between Feb 2001 and Feb 2002, 946 patients with GIST have been randomised. This abstract reports the results of a planned interim analysis conducted at 172 events. Patients median age 59, number of males 61%, Toxicity profile reported in Abstract 1650. Median follow up 8.4 months. Complete response observed in 3 and 2% (400mg and 800mg doses). Median reduction of tumour load after 2,4, 6, and 9 months were respectively 24% vs 21%, 32% vs 30%, 34% vs 32% and 40% vs 35%. Progression free survival estimates at 6 and 12 months are 73% vs 78% and 64% vs 69%.

Trial Name
Intergroup S0033

Data sources
Novartis submission, ASCO abstract 3271 (2003), 1651 (2002), SWOG website.

Aim of trial
(ASCO 3271[33]). Randomised phase III study comparing 400mg daily to 400mg twice daily in patients with KIT positive, metastatic or unresectable GIST. Primary aim to assess the impact of imatinib dose on survival. Secondary aims to evaluate response rates and confirm the tolerability of imatinib therapy for GIST.

Trial data
(ASCO abstract 3271). Between 15.12.00 and 1.9.01 746 patients registered. With a median follow up of 14 months 556 patients are still living. No differences have appeared between the two doses. Response rate is 43% at 400mg and 41% at 800mg. Median time to response was 4 to 6 months. The response rate + stable disease is 75% at 400mg and 73% at 800mg. 18% have crossed over to a higher dose following progression. 4% have discontinued therapy due to toxicity.

Trial Name
Abstract ASCO 1609[35]. First author Judson I.

Title: Imatinib (Gleevec) an active agent for GIST but not for other soft tissue sarcoma subtypes not characterized for KIIT and PDGF-R expression, results of EORTC phase II studies.

Aim of trial
To treat 2 groups, GIST and other STS not characterized for KIT or PDGFR expression at 400mg twice daily.

Trial data
Fifty one patients recruited (28 GIST, 23 non GIST), median age 55.All but one non-GIST are off the study with most GIST patients still on treatment. Current responses are 7% CR, 25% PR, 24% PD, 30% SD. Adverse events were anaemia (90%), oedema (82%), skin rash (66%), fatigue (64%), nausea (52%), and granulocytopenia (40%). Still ongoing.

Trial Name
ASCO abstract 3312[34] – Author Ryu MH, South Korea

Title
Efficacy of imatinib mesylate in metastic or unresectable malignant gastrointestinal stromal tumour (GIST).

Aim of trial

To evaluate the efficacy and safety of imatinib in metastatic or unresectable GISTs and to identify the pattern of KIT mutations ands its influence on tumour response in Korean GIST patients.

Trial data
Between June 2001 and October 2002, 33 patients were treated with imatinib 400mg daily on days 1-28 every 4 weeks. The dose was escalated to 600mg daily in case of disease progression. Median age was 52 years. Tumour response was 48.4% PR, 32.3% SD and 19.4% DP. Median time to response was 10 weeks, range 4 to 26 weeks. Median follow up was 36 weeks, (range 4 to 79) with median time to progression for all patients not reached. Five patients had dose escalation and none showed a response. Side effects were anaemia, nausea, periorbital oedema, skin rash and asthenia and were generally mild to moderate. Two patients had bowel perforation due to rapid tumour shrinkage. Activating mutations were examined, no differences in response were found between patients with and without an exon 11 mutation. Unsure if still ongoing.

Trial name
ASCO abstract 1444[36] – Author Jankilevich G. Argentina

Title
Gastrointestinal stromal tumours (GISTs) in Argentina in the era of imatinib. Diagnostic problems and treatment results.

Aim of Trial
Retrospective review of 38 patients with GIST currently in follow up in 5 institutions to determine diagnosis and treatment with imatinib.

Trial data
All 38 patients tested for cKIT, with 17 treated with imatinib. Response was evaluated in 13 patients. A complete response was
in a 23 year old woman with a para ovaric mass and peritoneal sarcomatosis. Severn patient had a partial response, 3 patients had stable disease, and 2 patients had progressive disease. Responses durable in all cases (6-8 months). Toxicity: oedema, nausea, asthenia, insomnia and mild anaemia were common. Imatinib discontinued in 1 patient due to severe rash.

Trial name
Protocol IDs PCI-01-028, MB-NAVY-BO1-053, NCI-02-C0020, NCI-53331.
Found in cancer.gov. Lead investigator: Ramanathan R. Pittsburgh USA.

Title
Phase I study of imatinib meslylate in patients with advanced malignancies and varying degrees of liver dysfunction.

Aim of trial
Dose escalation, multicentre study, to find the MTD and dose limiting toxicities in patients with liver dysfunction.

Trial data
No results reported, still ongoing.

Trial name
Protocol IDs CWRU-1Y01, NCI-02-C0073, NCI-5340.
Found in cancer.gov. Lead investigator: Remick, SC. Ireland.

Title
Phase I study of imatinib mesylate in patients with advanced malignancies and varying degrees of renal dysfunction.

Aim of trial
Dose escalation, multicenter study to find the MTD and dose limiting toxicities in patients with renal dysfunction.

Trial data
No results reported, still ongoing.

Trial name
Found in Current Controlled Trials. Organisation that supplied the information: The Royal Marsden NHS Trust.

Title
Phase III, randomised, intergroup, international trial, assessing the clinical effectiveness at two dose levels in patients with unresectable or metastatic gastrointestinal tumours (GIST) expressing the KIT receptor (CD117).

Aim of trial
To compare the outcome of patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) expressing KIT(CD117) treated with low dose STI571 versus high dose STI571. Secondary objectives will be to assess response rates.

Trial data
Royal Marsden NHS Trust has recruited 300 patients overall the trial hopes to recruit 3000 in total. No further data given in Current Controlled Trials.

Appendix 10 Excluded studies

Table 19 Potential imatinib studies excluded after at stage two of inclusion process.

Study	Reason for exclusion
Bauer S, Hartung J, Gauler T, Gocke P, Trarbach T, Flasshove M, *et al*. Gemcitabine-containing chemotherapy in the treatment of patients with advanced soft tissue sarcoma. *Tumor Diagnostik und Therapie* 2002; **23**(6):219-224	Not GIST
Casper ES. Gastrointestinal stromal tumors. *Current Treatment Options in Oncology* 2000; **1**(3):267-273.	Review
Dagher R, Cohen M, Williams G, Rothmann M, Gobburu J, Robbie G, *et al*. Approval summary: Imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *Clinical Cancer Research* 2002; **8**(10):3034-3038.	Approval summary
Feussner H, Kauer W, Siewert JR. Laparoscopic surgery in the palliation of malignant gastrointestinal diseases. *Chirurgische Gastroenterologie* 1996; **12**(SUPPL.2):35-40.	Laproscopic vs open surgery
van Glabbeke, van Oosterom, Oosterhuis JW, Mouridsen H, Crowther D, Somers R, *et al*. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline-containing first-line regimens--a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. *J CLIN ONCOL* 1999; **17**(1):150-157.	Not GIST
Goss, G. A., Rubin, B. P.,Desai, J. Clinical features and lack of response to conventional therapies of metastatic and advanced gastrointestinal stromal tumours (GIST) defined by expression of the kit receptor tyrosine kinase (CD117) [Unpublished]	Treatment not related to outcome
Grann A, Paty PB, Guillem JG, Cohen AM, Minsky BD. Sphincter preservation of leiomyosarcoma of the rectum and anus with local excision and brachytherapy *Diseases of the Colon & Rectum* 1999; **42**(10):1296-1299.	Primary disease
Hemming AW, Langham MR, Reed AI, van der Werf WJ, Howard RJ. Resection of the inferior vena cava for hepatic malignancy. *American Surgeon* 2001; **67**(11):1081-1087.	Rare occurrence
Hill MA, Mera R, Levine EA. Leiomyosarcoma: a 45-year review at Charity Hospital, New Orleans. *American Surgeon* 1998; **64**(1):53-60	Prognostic study
Judson I, Leahy M, Whelan J, Lorigan P, Verrill M, Grimer R, *et al*. A guideline for the management of gastrointestinal stromal tumour (GIST). *Sarcoma* 2002; **6**(3):83-87.	Review/treatment guidelines
Klomp HJ, Zornig C. Sarcoma of the gastrointestinal tract. *Langenbecks Archiv fur Chirurgie* 1990; **375**(4):235-238.	Primary disease
Lev D, Kariv Y, Issakov J, Merhav H, Berger E, Merimsky O, *et al*. Gastrointestinal stromal sarcomas. *British Journal of Surgery* 1999; **86** (4):545-549.	Prognosis
Miquel PJ, Martin DA, Martinez ME, Gonzalez-Palacios J, Sanjuan BA, Boixeda DM. Atypical colonic stromal tumor. *Gastroenterologia y Hepatologia* 2001; **24**(7):339-342.	Atypical disease
Muler JH, Baker L, Zalupski MM. Gastrointestinal stromal tumors: chemotherapy and imatinib. *Current Oncology Reports* 2002; **4**(6):499-503.	Review
Nakamura M, Oonishi S, Yukimoto S, Nakamura Y, Tsuji E, Sugano M, *et al*. A case of huge gastrointestinal stromal tumor originating in the small intestine complicated by ileus *Japanese Journal of Medical Ultrasonics* 2002; **29**(3):J269-J278.	Primary disease
Nakayama T, Hirose H, Isobe K, Shiraishi K, Nishiumi T, Mori S, *et al*. Gastrointestinal stromal tumor of the rectal mesentery. *J GASTROENTEROL* 2003; **38**(2):186-189.	Primary disease
Patel SR, Benjamin RS. Management of peritoneal and hepatic metastases from gastrointestinal stromal tumors. *Surg Oncol* 2000; **9**(2):67-70.	Review
Takano M, Ono K, Miyamoto O, Akiyama H, Iida K. A case of gastrointestinal stromal tumor of the small intestine with peritoneal dissemination effectively treated with chemotherapy. *Japanese Journal of Gastroenterological Surgery* 2002; **35**(6):659-662.	Primary disease
Van den Abbeele AD, Badawi RD. Use of positron emission tomography in oncology and its potential role to assess response to imatinib mesylate therapy in gastrointestinal stromal tumors (GISTs). *European Journal of Cancer* 2002; **38 Suppl 5**:S60-S65.	PET analysis
Zornig C, Klomp HJ, THOMA G, WEH HJ, Schroder S. primary gastrointestinal	Prognosis

sarcomas - a report of 21 cases. *Onkologie* 1992; **15**(1):20-24.	

Table 20 Excluded alternative treatments at stage 2 (n= 64)

Paper	Reason for exclusion
Basso N, Rosato P, De Leo A, Picconi T, Trentino P, Fantini A, *et al*. Laparoscopic treatment of gastric stromal tumors. *Surgical Endoscopy-Ultrasound and Interventional Techniques* 2000; **14**(6):524-526.	Laproscopic vs open surgery
Bauer S, Hartung J, Gauler T, Gocke P, Trarbach T, Flasshove M, *et al*. Gemcitabine-containing chemotherapy in the treatment of patients with advanced soft tissue sarcoma. *Tumor Diagnostik und Therapie* 2002; **23**(6):219-224.	Not GIST
Casper ES. Gastrointestinal stromal tumors. *Current Treatment Options in Oncology* 2000; **1**(3):267-273. Casper	Review
Catena F, Pasqualini E, Campione O. Gastrointestinal stromal tumors: Experience of an emergency surgery department. *Digestive Surgery* 2000; **17**(5):503-507.	Not effectiveness
Chambonniere M-L, Mosnier-Damet M, Mosnier J-F. Expression of microtubule-associated protein tau by gastrointestinal stromal tumors. *Human Pathology* 2001; **32**(11):1166-1173.	Diagnosis
Clere F, Carola E, Halimi C, De Gramont A, Bonvalot S, Panis Y, *et al*. Current findings on gastrointestinal stromal tumors: from seven observations of malignant tumors. *Revue de Medecine Interne* 2002; **23**(6):499-507.	Pathological description
Correa P. Gastric neoplasia. *Curr Gastroenterol Rep* 2002; **4**(6):463-470.	Review
Dagher R, Cohen M, Williams G, Rothmann M, Gobburu J, Robbie G, *et al*. Approval summary: Imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *Clinical Cancer Research* 2002; **8**(10):3034-3038.	Approval summary
DeMatteo RP, Heinrich MC, El Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: Before and after STI-571. *Human Pathology* 2002; **33**(5):466-477.	Review*
Dougherty MJ, Compton C, Talbert M, Wood WC. Sarcomas of the gastrointestinal tract. Separation into favorable and unfavorable prognostic groups by mitotic count. *Annals of Surgery* 1991; **214**(5):569-574	Prognosis
Edmonson JH, Marks RS, Buckner JC, Mahoney MR. Contrast of response to dacarbazine, mitomycin, doxorubicin, and cisplatin (DMAP) plus GM-CSF between patients with advanced malignant gastrointestinal stromal tumors and patients with other advanced leiomyosarcomas. *Cancer Investigation* 2002; **20**(5-6):605-612	Prognosis
Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, *et al*. Diagnosis of gastrointestinal stromal tumors: A consensus approach. [Review] [38 refs]. *Human Pathology* 2002; **33**(5):459-465	Diagnosis
Gallegos-Castorena S, Martinez-Avalos A, Ortiz de la OE, Sadowinsky-Pine S, Del Valle PL, Guerrero A. Gastrointestinal stromal tumor in a patient surviving osteosarcoma .. *Medical and Pediatric Oncology, Vol 40(5) (pp 338-339), 2003*	Atypical case study
Goss, G. A., Rubin, B. P.,Desai, J. Clinical features and lack of response to conventional therapies of metastatic and advanced gastrointestinal stromal tumours (GIST) defined by expression of the kit receptor tyrosine kinase (CD117) [Unpublished]	Treatment not related to outcome
Grann A, Paty PB, Guillem JG, Cohen AM, Minsky BD. Sphincter preservation of leiomyosarcoma of the rectum and anus with local excision and brachytherapy 677. *Diseases of the Colon & Rectum* 1999; **42**(10):1296-1299.	Primary disease
Hatch KF, Blanchard DK, Hatch GF, Wertheimer-Hatch L, Davis GB, Foster RS, *et al*. Tumors of the appendix and colon. *World Journal of Surgery* 2000; **24**(4):430-436.	Review
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Hwang ES, Gerald W, Wollner N, Meyers P, LaQuaglia MP. Leiomyosarcoma in childhood and adolescence. . *Annals of Surgical Oncology* 1997; **4**(3):223-227.	Prognosis
Joensuu H, Fletcher C, Dimitrijevic S, Silberman S, Roberts P, Demetri G. Management of malignant gastrointestinal stromal tumours. *LANCET ONCOL* 2002; **3**(11):655-664.	Imatinib treatment
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2002; **13**(SUPPL. 4):287-289.	
Katai H, Sasako M, Sano T, Maruyama K. Surgical treatment for gastric leiomyosarcoma. *Annales Chirurgiae et Gynaecologiae* 1998; **87**(4):293-296.	Primary disease
Kimura H, Yonemura Y, Kadoya N, Kosaka T, Miwa K, Miyazaki I, *et al*. Prognostic factors in primary gastrointestinal leiomyosarcoma: a retrospective study. *World Journal of Surgery* 1991; **15**(6):771-776.	Primary disease
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Miettinen M, El Rifai W, Sobin HL, Lasota J. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. *Hum Pathol* 2002; **33**(5):478-483.	Review
Miettinen M, Majidi M, Lasota J. Pathology and diagnostic criteria of gastrointestinal stromal tumors (GISTs): *European Journal of Cancer* 2002; **38** :S39-S51	Review
Mihssin N, Moorthy K, Sengupta A, Houghton PWJ. Gastric stromal tumours: a practical approach. *Annals of the Royal College of Surgeons of England* 2000; **82**(6):378-382.	Primary disease
Montes JAR, Tellez LGS, Martinez JL, de Lis SF, Martin LGS. Malignant stromal tumors of the stomach. *Hepato-Gastroenterology* 1998; **45**(23):1918-1921.	Primary disease
Mudan SS, Conlon KC, Woodruff JM, Lewis JJ, Brennan MF. Salvage surgery for patients with recurrent gastrointestinal sarcoma. Prognostic factors to guide-patient selection. *Cancer* 2000; **88**(1):66-74.	Prognosis
Muler JH, Baker L, Zalupski MM. Gastrointestinal stromal tumors: chemotherapy and imatinib. *Current Oncology Reports* 2002; **4**(6):499-503.	Review
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Peiper M, Schroder S, Zornig C. Stromal sarcoma of the stomach - a report of 20 surgically treated patients. *Langenbecks Archives of Surgery* 1998; **383**(6):442-446.	Primary disease
Peitgen K, Walz MK, Schmidt U, Hoederath A, Wilke H, Eigler FW. Gastric leiomyosarcoma - Clinical, morphological and therapeutic results. *Medizinische Klinik* 1996; **91**(3):123-130.	Primary disease
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Plappert G, Heymer T, Schroeder P. Gastrointestinal stromal tumour: Individualized treatment for a special tumour class. *Deutsche Medizinische Wochenschrift* 2001; **126** (7):172-175.	Primary disease
Pross M, Manger T, Schulz HU, Lippert H, Roessner A, Gunther T. Gastrointestinal stromal tumors - problems in diagnosis and therapy. *Chirurg* 1999; **70**(7):807-812.	Primary disease
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Roberts PJ, Eisenberg B. Clinical presentation of gastrointestinal stromal tumors and treatment of operable disease. *European Journal of Cancer* 2002; **38 Suppl 5**:S37-S38.	Review
Rubin BP, Singer S, Tsao C, Duensing A, Lux ML, Ruiz R, *et al*. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. . *Cancer Research* 2001; **61**(22):8118-8121.	Diagnosis
Sanders L, Silverman M, Rossi R, Braasch J, Munson L. Gastric smooth muscle tumors:	Prognosis

Diagnostic dilemmas and factors affecting outcome. *World Journal of Surgery* 1996; **20**(8):992-995.	
Silberman S, Joensuu H. Overview of issues related to imatinib therapy of advanced gastrointestinal stromal tumors: a discussion among the experts. *European Journal of Cancer* 2002; **38 Suppl 5**:S66-S69.	Review
Spira AI, Ettinger DS. The use of chemotherapy in soft-tissue sarcomas 594. *Oncologist* 2002; **7**(4):348-359.	Review
Sturgeon C, Chejfec G, Espat NJ. Gastrointestinal stromal tumors: A spectrum of disease. *Surgical Oncology* 2003; **12**(1):21-26.	Review including ongoing trials
Van den Abbeele AD, Badawi RD. Use of positron emission tomography in oncology and its potential role to assess response to imatinib mesylate therapy in gastrointestinal stromal tumors (GISTs). *European Journal of Cancer* 2002; **38 Suppl 5**:S60-S65.	Diagnosis
Walsh RM, Ponsky J, Byody F, Matthews BD, Heniford BT. Combined endoscopic/laparoscopic intragastric resection of gastric stromal tumors.. *Journal of Gastrointestinal Surgery* 2003; **7**(3):386-392.	Primary disease
Zornig C, Klomp HJ, Thoma G, WEH HJ, Schroder S. Primary gastrointestinal sarcomas - a report of 21 cases. *Onkologie* 1992; **15**(1):20-24.	Prognosis

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Antonini C, Forgiarini O, Chiara A, Briani G, Sacchi G. Clinico-pathological study of eleven gastrointestinal stromal Tumors. *Gastroenterology International* 2001; **14**(1-2):14-19.
Bilimoria MM, Holtz DJ, Mirza NQ, Feig BW, Pisters PWT, Patel S, *et al*. Tumor volume as a prognostic factor for sarcomatosis. *Cancer* 2002; **94** (9):2441-2446.
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Knoop M, St Friedrichs K, Dierschke J. Surgical management of gastrointestinal stromal tumors of the stomach. *Langenbecks Archives of Surgery* 2000; **385**(3):194-198.
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Toquet C, Le Neel JC, Guillou L, Renaudin K, Hamy A, Heymann M-F, *et al*. Elevated (>=10%) MIB-1 proliferative index correlates with poor outcome in gastric stromal tumor patients: A study of 35 cases. *Digestive Diseases & Sciences* 2002; **47**(10):2247-2253.

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Appendix 11 York CRD Quality Criteria and Hierarchy of Evidence.

Check lists for quality assessment of included studies

From the York CRD handbook[16]
(http://www.york.ac.uk/inst/crd/crd4_ph5.pdf)

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?
Adequate approaches to sequence generation
- Computer-generated random numbers
- Random numbers tables
Inadequate approaches to sequence generation
- Use of alternation, case record numbers, birth dates or weekdays

2. Was the treatment allocation concealed?
Adequate approaches to concealment of randomisation
- Centralised or pharmacy-controlled randomisation
- Serially-numbered identical containers
- On-site computer based system with a randomisation sequence that is not readable until allocation
- Other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients
Inadequate approaches to concealment of randomisation
- Use of alternation, case record numbers, birth dates or weekdays
- Open random numbers lists
- Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were the point estimates and measure of variability presented for the primary outcome measure?
9. Did the analyses include an intention to treat analysis?

Quality criteria for assessment of observational studies

From the York CRD handbook
(http://www.york.ac.uk/inst/crd/crd4_ph5.pdf)

Cohort studies
- Is there a sufficient description of the groups and the distribution of prognostic factor
- Are the groups assembled at a similar point in their disease progression?
- Is the intervention/treatment reliably ascertained?
- Were the groups comparable on all-important confounding factors?
- Was there adequate adjustment for the effects of these confounding variables?
- Was a dose-response relationship between intervention and outcome demonstrated?
- Was outcome assessment blind to exposure status?
- Was follow-up long enough for the outcomes to occur?
- What proportion of the cohort was followed-up?
- Were dropout rates and reasons for dropout similar across intervention and unexposed groups?

Case-control studies
- Is the case definition explicit?
- Had the disease state of the cases been reliably assessed and validated?
- Were the controls randomly selected from the source of population of the cases?

- How comparable are the cases and controls with respect to potential confounding factors?
- Were interventions and other exposures assessed in the same way for cases and controls?
- How was the response rate defined?
- Were the non-response rates and reasons for non-response the same in both groups?
- Is it possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
- Was an appropriate statistical analysis used (matched or unmatched)?

Case series

- Is the study based on a representative sample selected from a relevant population?
- Are the criteria for inclusion explicit?
- Did all individuals enter the survey at a similar point in their disease progression?
- Was follow-up long enough for important events to occur?
- Were outcomes assessed using objective criteria or was blinding used?
- If comparisons of sub-series are being made, was there a sufficient description of the series and the distribution of prognostic factors?

Checklist for assessing economic evaluations

From the York CRD handbook
(http://www.york.ac.uk/inst/crd/crd4_ph5.pdf)

1. Is there a well-defined question?
2. Is there comprehensive description of alternatives?
3. Are all important and relevant costs and outcomes for each alternative identified?
4. Has clinical effectiveness been established?
5. Are costs and outcomes measured accurately?
6. Are costs and outcomes valued credibly?
7. Are costs and outcomes adjusted for differential timing?
8. Is there an incremental analysis of costs and consequences?
9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?
10. How far do study results include all issues of concern to users?
11. Are the results generalisable to the setting of interest in the review?

Based on Drummond's checklist

Topic Specific Quality Checks

- Was the method of GIST diagnosis reported? If so what was the method?
- Was the year of study reported?

Grading of Evidence http://www.york.ac.uk/inst/crd/crd4_ph8.pdf

Grade	Level of Evidence	Effectiveness
A	1	High quality experimental studies without heterogeneity and precise results
B	2/3	Low quality experimental studies, high quality controlled observational studies
C	4	Low quality controlled observational studies, case series
D	5	Expert opinion.

Appendix 12 Quality Assessment Trial Data

Study	1. Is the study based on a representative sample from a relevant population?	2.Are the criteria for inclusion explicit?	3. Did all individuals enter the survey at a similar point in disease progression?	4. Was follow up long enough for important events to occur?	5. Were outcomes assessed using objective criteria or was blinding used?	6. If comparisons of sub-series was there a sufficient description of the series and distribution of prognostic factors	Comments
Demetri[26]	Unsure	Yes	Yes	Yes for response and adverse events, no for survival	Yes RECIST and CTC, no blinding	N/A	
van Oosterom [31]	Unsure	Yes	Unsure Difficult to tell, but all pts had evidence of progression	Yes for response and adverse events, no for survival	Yes CTC and tumour response, no blinding.	N/A	
Judson[45]	Unsure	Yes	Unsure	Yes	Yes, WHO criteria used for response, unsure blinding.	N/A	Unsure as to the diagnosis of GIST, 21 retrospectively diagnosed as GIST from histological analysis.
Eilber[53]	Unsure	No	Yes, all had metastatic spread in the peritoneum.	Yes	Yes objective criteria used, unsure blinding	N/A	All described as having STS but description of patient characteristics limited.
Ryan[46]	Yes	Yes	Yes	Yes	Yes, unsure about blinding	No – insufficient comparison between patients on imatinib and those not.	
DePas[19]	Unsure	Unsure	Unsure	Yes	Yes (used WHO criteria for tumour response, but don't give reference)	N/A	Authors admit likely selection bias.
Rajan[47]	Unsure	Yes	Yes	Yes	Yes (used WHO criteria for tumour response, but do not mention any blinding)	N/A	11patients had gastrointestinal leiomyosarcoma metastatic to the liver.

Study	1. Is the study	2.Are the	3. Did all	4. Was follow up long	5. Were outcomes	6. If comparisons of sub-	Comments

	based on a representative sample from a relevant population?	criteria for inclusion explicit?	individuals enter the survey at a similar point in disease progression?	enough for important events to occur?	assessed using objective criteria or was blinding used?	series was there a sufficient description of the series and distribution of prognostic factors	
Mavligit[48]	Unsure	Yes	Unsure	Yes	Unsure (basis of measures not described clearly)	N/A	Patients diagnosed as gastrointestinal leiomyosarcoma metastatic to the liver. Individual patient information provided.
Chen[49]	Unsure	Yes	Yes	Yes	Yes (survival, mortality)	N/A	Patients diagnosed with leiomyosarcoma with metastatic liver disease (1984 – 1995).
Bramwell[63]	Unsure	Yes	No	Yes	Yes, CTC, tumour response measures described, no blinding.	N/A	Described as GIST and non-GIST, no details given.
Edmonson[51]	Unsure	Yes	Unsure little detail given.	Yes	Unsure, survival measured, other outcomes described, no blinding.	N/A	Unsure as to diagnosis, patients had "gastrointestinal stromal tumour".
Patel[52]	Unsure	Yes	Unsure	Yes	No response and adverse events described only, no blinding.	N/A	Unsure as to diagnosis, patients had gastrointestinal leiomyosarcoma.
Carson[54]	Unsure	Yes	No, both primary and advanced disease included.	Yes	Unsure, outcomes described only, no blinding.	N/A	Unsure as to diagnosis, patients had leiomyosarcoma or leiomyosarcoma.

Appendix 13 Illustration

In the baseline-case Novartis model, the proportion of patients in the state “progressive disease” in the imatinib arm is estimated indirectly by subtraction of the proportion of patients in imatinib treatment from the proportion of all surviving patients. This was done using exponential extrapolation to 10 years of trial data for all surviving patients to 23 months, and by exponential extrapolation of trial data for time to treatment failure up to 15 months. This generates curves shown in the diagram below. [Text and data related to the unpublished Goss study is commercial in confidence and has been removed].

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