Health Technology Assessment 2005; Vol. 9: No. 25

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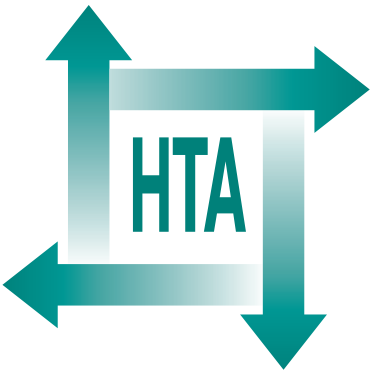
July 2005



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Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation

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Declared competing interests of authors: D 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. J Raftery is Director of the NCCHTA but he was not involved in the editorial process for this report.

Published July 2005

This report should be referenced as follows:

Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*. Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation. *Health Technol Assess* 2005;**9**(25).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

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The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 03/01/01. The protocol was agreed in April 2003. The assessment report began editorial review in March 2004 and was accepted for publication in November 2004. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

Abstract

Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation

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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.

Data sources: Electronic databases.

Review methods: As 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.

Results: Evidence from published uncontrolled trials involving 187 patients, and from abstracts reporting similar uncontrolled trials involving 1700 patients, indicates 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 patients may respond in this way. Fifteen studies where possible GIST patients had been treated with therapies other than imatinib or best supportive care were also identified. All imatinib-treated patients experienced adverse effects, although they were relatively mild. Overall, imatinib was reported to be well tolerated. The most common serious events included unspecified haemorrhage and neutropenia. Skin rash, oedema and periorbital oedema were the common adverse events observed. Patients on the highest dose regimen (1000 mg per day in one trial) may experience dose-limiting drug toxicity. A structured assessment was carried out of the Novartis economic evaluation of imatinib for unresectable and/or metastatic GIST. The model was clearly presented and well written, its 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 disproportion of survival and time-to-treatment failure in the imatinib arm, and the use of a possibly biased survival curve for patients in the control arm. The original Novartis model was modified to correct these two important shortcomings, which made it less sensitive to the choice of the survival curve for the control patients. According to the modified Novartis model, the estimated cost per quality-adjusted life-year (QALY) was £85,224 (range £51,515–98,889) after 2 years, £41,219 (£27,331–44,236) after 5 years and £29,789 (£21,404–33,976) 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. Further research is needed into quality of life within trials involving patients

with advanced malignancy, and long-term follow-up of adverse events is needed. Subgroup analysis of which, if any, patient types have a better or worse response to imatinib is also required. 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, drug resistance and the optimum time-point in the disease course at which to give the drug. Secondary research such as an update of this systematic review and a reassessment of the model is highly recommended when ongoing trials reach completion.

Contents

List of abbreviations

AIC	academic in confidence
ALK	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSC	best supportive care
CD117	KIT
CI	confidence interval
CML	chronic myeloid leukaemia
CPMP	Committee for Proprietary Medicinal Products
CR	complete response
CRD	Centre for Reviews and Dissemination
CT	computed tomography
CTC	common toxicity criteria
DP	disease progression
DTIC	Dacarbazine
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 Dimensions
ET-743	ecteinascidin 743
FDA	Food and Drug Administration
FDG	[^{18}F]2-fluoro-2-deoxyglucose
FDGP	2-fluorodeoxyglucose-6-phosphate
GANT	gastrointestinal autonomic nerve tumour
GGT	γ-glutamyl transferase
GI	gastrointestinal
GIST	gastrointestinal stromal tumour
HC	histologically confirmed
ICC	interstitial cells of Cajal
ICER	incremental cost-effectiveness ratio
IP	intraperitoneal
KIT	tyrosine kinase (CD117) protein express by the *kit* proto-oncogene
KM	Kaplan–Meier
LMS	leiomyosarcoma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	not applicable
NCI	National Cancer Institute
NE	non-evaluable
NICE	National Institute for Health and Clinical Excellence
PET	positron emission tomography
PM	performance measure
PR	partial response
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SCF	stem cell factor
SD	stable disease
STS	soft-tissue sarcoma
SUV	standard uptake value
SWOG	Southwestern Oncology Group
TTF	time to treatment failure

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objectives

The objectives of this study were 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 based mainly 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 eight 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 patients may respond in this way. Fifteen studies where possible GIST patients had been treated with therapies other than imatinib or best supportive care were also identified. Because of the problems of diagnosis, in particular, an indirect comparison using these studies was not possible, therefore the results of these studies were not 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 to be well tolerated. The most common serious events included unspecified haemorrhage and neutropenia. Skin rash, oedema and periorbital oedema were the common adverse events observed. Patients on the highest dose regimen (1000 mg per day in one trial) may experience dose-limiting drug toxicity.

A systematic review of prognostic studies confirmed that a large number of patients with advanced GIST 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 academic in confidence and has been removed.)

Cost-effectiveness

Novartis submitted an economic evaluation of imatinib for unresectable and/or metastatic GIST. After a structured assessment of the Novartis model, it was found to be 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 disproportion of survival and time-to-treatment failure in the imatinib arm, and 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 quality-adjusted life-year (QALY) was £85,224 (range £51,515–98,889) after 2 years, £41,219 (£27,331–44,236) after 5 years and £29,789 (£21,404–33,976) 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 very uncertain because they were based on 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.

Recommendations for research

- More emphasis should be placed on quality of life within trials involving patients with advanced malignancy. Adverse events should be reported so that intertrial comparisons can be made. As indicated by the increase in grade 3 adverse events with longer term use of imatinib reported in the industrial submission, long-term follow-up of adverse events is needed.
- Patients diagnosed with GIST are a heterogeneous group. Subgroup analysis of which, if any, patient types have a better or worse response to imatinib is needed. 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 for which patients should be on imatinib, the dose (i.e. is it better to step up or step down), drug resistance and the optimum time-point 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 be forthcoming and ongoing trials on adjuvant therapy in patients with primary disease may 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.

Chapter 1

Aims and background

Aims

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

Description of underlying health problem

Gastrointestinal stromal tumours: definition

The meaning of the term GIST has evolved since the 1970s 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 ultrastructure available with the use of the electron microscope
- profiling of tumours using immunohistochemical methods to determine the 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 complementary DNA (cDNA) arrays to determine messenger RNA (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 in 1984,[1] and gastric stromal tumour was introduced by Mazur and Clark in 1983.[2] GISTs then encompassed gastrointestinal tract tumours that were judged to have developed from gastrointestinal stroma cells of mesenchymal origin. GISTs were thus separated from epithelium-derived tumours. Soon the term came into wide usage, but its meaning has shifted in line with the knowledge and opinion that has accrued with the application of the newer techniques of investigation.[3]

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

- smooth-muscle cells and their progenitors
- autonomic neurons of the myenteric plexuses
- fibroblasts and fibroblast-like cells
- neuron sheath cells (Schwann cells)
- pacemaker cells [interstitial cells of Cajal (ICC)] and their progenitors
- adipocytes
- mast cells
- other mesenchymal cells.

Some of these are specific to the gastrointestinal tract, whereas others occur at other sites where they may also give rise to tumours that, in turn, may metastasise to new sites.

GISTs were first thought to derive from smooth-muscle cells in the gastrointestinal wall or to differentiate towards a muscle phenotype. However, it became evident that the appearance of GISTs (cellularity, nuclear shape, eosinophilia), as well as their propensity to metastasise and their 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 'myoneural' character.

The era of immunohistochemical 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, was characterised by expression of the surface antigen CD117, the product of the *kit* proto-oncogene. Positive immunochemical reaction for CD117, shared morphological features and a claimed common positive immunoreaction for the CD34 antigen led to the notion that these GISTs were derived from the ICC or, because KIT-positive tumours arise at sites where ICC are not

found (gastrointestinal mesentery and omentum), from multipotent cells that are precursors of ICC. These findings have driven reappraisals of the classification of gastrointestinal 'mesenchymal' tumours.[4–6]

A consensus view[5] and that expressed in the WHO classification of gastrointestinal tumours[7] (published in 2000) is that the term GIST should be reserved for KIT-positive tumours, while the rarer gastrointestinal-associated muscle-derived myosarcomas (immunopositive for actin and desmin) and Schwannomas are viewed as separate entities. Nevertheless, the current literature accepts the concept of the rare KIT-negative GIST, which resembles KIT-positive forms in all respects other than immunoreactivity for KIT. These tumours do not express KIT 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 gastrointestinal autonomic nerve tumours (GANTs) are now included as GISTs and the term GANTs may no longer warrant designation as a separate entity.

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

Symptoms

GISTs can cover a spectrum of disease. Patients may 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.

Diagnosis

The definite diagnosis is made from biopsy. Morphology of the tissue sample is examined by a pathologist. A raft of immunohistochemical tests is undertaken to characterise the cell type and aid elimination of certain other types of tumours. The recent immunohistochemical test for the KIT 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 as the diagnostic gold standard for GIST.[14] However, as discussed elsewhere (Appendix 1), the reproducibility and validity of the test are yet to be fully established. If treatment options partly depend on pathologists' interpretation of immunohistochemical test results for KIT and on surgeons' judgements regarding unresectability, then there may be considerable latitude for subjectivity.

Epidemiology and occurrence

Incidence estimates range from 4 to 40 cases per million.[15,16] In the UK it has been estimated that 10 per million (i.e. 500–1000) patients a year are affected;[17] however, this incidence estimate may eventually be found to be higher as more patients are tested for KIT. The majority of tumours occur in the stomach (60–70%), with the small bowel (25–35%), colon and rectum (5%) and oesophagus also 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[18] 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.

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.[14,19] Prognosis for unresectable and/or metastatic GIST is generally seen as poor. For example, Conlon and colleagues[20] 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.[21] In metastatic disease a median survival rate of only 19 months was reported in 94 patients with metastatic GIST.[22] 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 immunohistological testing. Prognosis estimates that date from before the introduction of immunological testing 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.

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 the benefits of these treatments remain uncertain.[17] Treatment of people with unresectable and/or metastatic GIST currently comprises symptom relief and best supportive care (BSC; more recently termed active symptom control). 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 and practitioners have been developed and published.[17] 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 400 mg 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.

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. As described previously, 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.[22,23] Imatinib was first used in patients with chronic myeloid leukaemia (CML).[24]

Dosage and administration

The Novartis website (http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf, accessed 17 September 2003) has detailed information regarding prescribing practice. 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 tumours. They recommend a dose of imatinib of 400 or 600 mg per 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 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 100 or 400-mg 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, as these drugs may increase imatinib plasma concentrations, or conversely drugs that are inducers of CYP2A4 activity may decrease imatinib plasma concentrations. 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 September 2003).

Licensing

The Food and Drug Administration (FDA) approved imatinib in the USA in February 2002 for the treatment of GIST[25] and it 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 24 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 (CSTI571-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 licensed for use in patients with CML.[24]

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.[29] 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 £1557–3115 per month per patient (depending on dose), this would result in a cost to the NHS (England and Wales) of between £5.6 and £11.2 million per year. Little additional service impact was envisaged because imatinib can be used on an outpatient basis.

*This study by Demetri[26] is a published trial report of CSTI571-B2222, which was supplied to the authors in an industry submission.[61] CSTIB2222[60] is an update of this trial report, also supplied to the authors by industry.

Chapter 2

Systematic review methods

Methods for reviewing effectiveness

Problems envisaged in determining imatinib effectiveness

The first major problem for this review was that the scoping search indicated early on that there would be no published randomised controlled trials (RCTs) or any controlled trials that directly compared imatinib with current standard treatment for unresectable and/or metastatic GIST. It was therefore decided, in the absence of comparative trials after systematic searching, that an indirect comparison of imatinib and standard treatment would be attempted. This would involve 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 second major problem specific to this review was the changing definition of GIST over the past 20 years or so. The advent of molecular analysis has recently clarified the definition of GIST, but before such techniques were available the term GIST encompassed many different pathologies, with the consequence that patients in studies undertaken before these techniques were available may or may not have had GIST as judged by current criteria. This will cause difficulties with the validity of any indirect comparisons used in the evidence synthesis. To try to flag this up throughout the report, when results tables are given, patient diagnoses are repeatedly described. This recent shift in the definition of GIST also had implications for development of a model for economic analysis, because one important component of the model was an understanding of the natural course of the disease in the absence of treatment. Studies that were undertaken before molecular/KIT-based diagnosis of GIST came on stream may have included patients who were not suffering from GIST (as currently defined), making the use of these natural histories of GIST extremely problematic. Conversely, because the diagnosis of GIST through molecular techniques is so recent (<4 years old), a full understanding of the progression of KIT-positive disease may not be possible.

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

Search strategy

The search strategy was divided into six parts and aimed to look for trials of imatinib (with or without standard treatment comparators), trials of alternative/experimental treatments, studies that observed patient prognosis without treatment (to enable a comparison of disease progression should trials without comparators be available) and diagnostic papers, to gain an insight into the uncertainty of GIST diagnosis and possible consequences of treating false positives. Ongoing trials were also sought, as imatinib is a very recently developed 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

- Bibliographic databases: Cochrane Library (CENTRAL) 2003 Issue 2, MEDLINE (Ovid) 1966 to week 3 April 2003, EMBASE (Ovid) 1980 to week 16 April 2003, SCI Search (Web of Science) 1981 to April 2003, CancerLit (PubMed) 1966 to May 2003, and CINAHL (Ovid) 1982 to 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

- Bibliographic databases: Cochrane Library (CENTRAL) 2003 Issue 2, MEDLINE (Ovid) 1966 to week 4 April 2003, EMBASE (Ovid)

1980 to week 19 May 2003, SCI Search (Web of Science) 1981 to May 2003, CancerLit (PubMed) 1966 to May 2003, and CINAHL (Ovid) 1982 to week 4 April 2003.

Where appropriate, searches were restricted to systematic reviews and clinical trials (see Appendix 2 for details).

Prognosis and natural history of GISTS

- Bibliographic databases: MEDLINE (Ovid) 1966 to week 3 April 2003, EMBASE (Ovid) 1980 to week 17 April 2003, CINAHL (Ovid) 1982 to week 3 April 2003.

Diagnosis of GISTs

- Bibliographic databases: MEDLINE (Ovid) 1966 to week 3 April 2003, EMBASE (Ovid) 1980 to week 17 April 2003, CINAHL (Ovid) 1982 to week 3 April 2003.

Ongoing trials

- Trials registers: *meta*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 and Cancer.gov (National Cancer Institute). Searches were carried out on 8–9 July 2003. Unless otherwise stated, the registers were searched using the drug terms Imatinib, Glivec, Gleevec and STI 571, and the results browsed for references to the relevant population.

Economic evaluation and 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 to July 2003, EMBASE (Ovid) 1980 to July 2003, Cochrane Library (NHS EED) 2003 Issue 2, Cochrane Library (DARE) 2003 Issue 2 and HEED June 2003.
- Internet sites of national economic units: University of York Centre for Health Economics, Health Economics Research Unit and 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 focused on specific searches for costs and quality of life of the condition (see Appendix 2 for details).

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 or exclusion using the title and, where available, the abstract. The following inclusion criteria were applied.

- 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 were included.
- Population: ideally, patients diagnosed with KIT-positive unresectable and/or metastatic GISTs (including primary or recurrent tumours) were included. 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 metastasise 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, and retroperitoneal leiomyosarcoma.
- Intervention: imatinib, in an oral dosage (any dose) (where imatinib = STI 571, Glivec, Gleevec or CGP57148).
- Comparators: the ideal comparator was the current standard treatment (symptom relief and BSC) 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 computed tomographic (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) scans].

Disagreements were resolved by discussion. Inclusion/exclusion decisions were made before

detailed scrutiny of the results and study quality assessment. Publications in languages other than English 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: include 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: include 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 with open surgery.
- Prognosis: include papers describing primary research that involved the prognosis of ten or more patients where clinical outcomes are described. Ignore reviews.
- Diagnosis: include papers describing primary research that involved ten or more patients where clinical outcomes are 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 four case studies included in the review, as it was not felt that a translation would add value to the review.

Data extraction strategy

Two reviewers independently extracted data using a predesigned data extraction form (see Appendix 3). 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.

Quality assessment strategy

Quality of studies was assessed using the York Centre for Reviews and Dissemination (CRD) criteria[30] for experimental and observational studies (see Appendix 4). 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 and length of time with GIST), and any possible sources of bias in patient selection, treatment provided and outcomes measured; where found, these were reported.

Methods of analysis and 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.

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' and 'academic in confidence' data have been removed from this report.

Chapter 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-positive GIST, the following assessment was based on data from uncontrolled trials, case series or single case studies.

Quantity and quality of research available

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 1* shows how many studies were identified from the systematic search.

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

At stage 2, 24 published full papers out of 34 potential imatinib studies were excluded after scrutiny of the full publications. These, together with the unpublished study, are listed and reasons for exclusion provided in *Table 24* (see Appendix 5). Of a total of 64+1 papers describing possible alternative treatments that were scrutinised using the full paper copy, 49 were excluded for the reasons given in *Table 25* (see Appendix 5). In total, 49 papers were scrutinised regarding prognosis data; of these, 35 papers were excluded because no survival data were available. These are listed in *Table 26* (Appendix 5).

Number and types of study included

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

Imatinib treatment

Two uncontrolled trials and eight single case studies that treated KIT-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 four trials and one case series published in abstract form only.

Alternative treatments

Eleven published trials and four 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 KIT as they commenced before the test was available. A retrospective analysis of patients for KIT was undertaken by Ryan and colleagues.[46]

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 plus five abstracts and one unpublished[a]	64 + 1[a]	48 plus one unpublished[a]	109
Stage 3: included	Ten (one trial = two publications) plus four ongoing trials with interim results published in abstract only, plus one retrospective case series published in abstract form only	15	14 including one unpublished[a]	Not sorted further systematically

[a] Unpublished study by Goss *et al*. included with the industrial submission.

TABLE 2 *Included studies reporting imatinib treatment of KIT-positive advanced GIST*

Study ID (Trial recruitment)	No. in study	Age, median (range) (years) Gender	Previous treatments	Stage of disease (Time to treatment of advanced disease)	Imatinib dose per day (follow-up)	Outcomes sought
Uncontrolled trials (published in full)						
Demetri *et al.*, 2002[26] (July 2000 to April 2001) Status: ongoing	147	54 (18–83) 57%, male	Surgery 98%, chemotherapy 51%, radiotherapy 15%	Unresectable 100%, metastatic 100%, recurrent 51%	400 or 600 mg (9 months)	Mortality: KM Tumour: response: MRI/CT QoL/PM: ECOG Adverse events: CTC 2.0
van Oosterom *et al.*, 2001,[31] 2002[32] (August 2000 to December 2000) Status: ongoing	40	53 (29–69) 62.5%, male	Chemotherapy 60%, radiotherapy 10%	Metastatic (liver) 75%	400, 600, 800 or 1000 mg (9–13 months)	Mortality: described Tumour: response: MRI/CT/PET (RECIST criteria) Adverse events: CTC 2.0
Uncontrolled trials (interim results published in abstract form only)						
Verweij *et al.*, 2003[33] (February 2001 to February 2002) Status: ongoing	946	59 (18–91) 61% male	Surgery 85%, chemotherapy 67%, radiotherapy 7%	Metastatic (liver) 71%	400 or 800 mg (median 8.4 months)	Progression-free survival Tumour: response: RECIST criteria Adverse events
Benjamin *et al.*, 2003[34] (December 2000 to September 2001) Status: ongoing	746	NR	NR	'Advanced'	400 or 800 mg (median 14 months)	Progression-free survival Tumour: response: RECIST criteria Adverse events
Ryu *et al.*, 2003[35] (June 2001 to October 2002) Status: ongoing	33	52 (33–73) NR	NR	Metastatic or unresected 100%	400 or 600 mg (median 19 months)	Tumour: response Side-effects
Judson *et al.*, 2003[36] (NR) Status: ongoing	28 GIST of 51	55	Chemotherapy 73%	NR	800 mg	Tumour: response: RECIST criteria Adverse events
Case series (published in abstract form only)						
Jankilevich *et al.*, 2003[37] Status: ongoing	17	NR	NR	NR	NR	Tumour: response Toxicity

continued

TABLE 2 *Included studies reporting imatinib treatment of KIT-positive advanced GIST (cont'd)*

Study ID (Trial recruitment)	No. in study	Age, median (range) (years) Gender	Previous treatments	Stage of disease (Time to treatment of advanced disease)	Imatinib dose per day (follow-up)	Outcomes sought
Case studies						
Joensuu *et al.*, 2001[38]	1	54 female	Surgery, chemotherapy (thalidomide)	Metastatic (4 years)	400 mg (11 months)	QoL/PM: WHO performance status Tumour: response: MRI/PET biopsy Adverse events: CTC 2.0
Hogenauer *et al.*, 2003[39]	1	51 male	Surgery, chemotherapy	Metastatic (1 year)	400 mg (7 months)	QoL/PM: QLQ-C30 test Tumour: response: MRI/PET biopsy (by immunohistology) Adverse events: described
Brooks *et al.*, 2002[40]	1	75 male	Surgery	Metastatic (many sites) (0)	800 mg (4 months)	QoL/PM: ECOG Tumour: response: CT/MRI
Miyagawa *et al.*, 2002[41] [a]	1	62 male	Surgery	Unresected, metastatic (4 years)	300 mg (12 months)	Tumour: response: MRI Adverse events: described
Terashima *et al.*, 2002[42] [a]	1	32 female	Surgery	Metastatic (4 months)	400 mg (7 weeks)	Tumour: response: CT Adverse events: described
Mukaide *et al.*, 2002[43] [a]	1	45 female	Surgery	Unresected, metastatic (0)	400 mg (9 months)	Tumour: response: described
Omori *et al.*, 2002[44] [a]	1	64 female	Surgery	Metastatic (0)	400 mg (2 months)	QoL/PM: described Tumour: response: CT Morbidity: described
Fujimoto *et al.*, 2002[45]	1	59 female	Surgery	Metastatic (0)	400 mg (9 months)	

[a] Published in Japanese: information from abstract only.

CTC, common toxicity criteria; ECOG, Eastern Cooperative Oncology Group; KM, Kaplan–Meier; NR, not reported; PM, performance measure; QLQ-C30, EORTC Quality of Life Questionnaire; QoL, quality of Life; RECIST, Response Evaluation Criteria in Solid Tumours.

TABLE 3 *Included studies reporting non-imatinib treatment of GIST*

Study ID	Diagnosis	No. in study (Dates of study)	Age, median (range) (years) Gender	Previous treatments	Stage of disease	Intervention (follow-up)	Outcomes sought
RCT							
Judson *et al*., 2001[47]	STS, some GIST by retrospective diagnosis	94; 21 GIST (NR)	52 (19–80) 48% male	Surgery 61%, radiotherapy 29%, chemotherapy 0%	Advanced metastatic	CAELYX vs doxorubicin (?)	Mortality Tumour: response Adverse events: CTC
Uncontrolled trials							
Ryan *et al*., 2002[46]	HC GIST 16/20 KIT positive by retrospective diagnosis	20 (August 1999–?)	44 (22–77) 77% male	Surgery 95%, radiotherapy 20%, chemotherapy 45%	Advanced	ET-743 (?)	Mortality: KM Tumour: response: CT Adverse events: CTC
De Pas *et al*., 2003[18]	'GI sarcomas'	67 (1979–1999)	NR	NA	Advanced mets 95%, recurrent 5%	STS therapy (?)	Mortality: KM Tumour: response
Rajan *et al*., 2001[48]	HC metastatic sarcomas	16 (1993–2000)	NR 50% male	Chemotherapy 44%	Metastatic	Chemoembolisation (3 years)	Mortality: KM Tumour: response: WHO criteria Adverse events
Mavligit *et al*., 1995[49]	HC LMS	14 (1991–1994)	(30–75) 86% male	Surgery 100%, radiotherapy 7%, chemotherapy 36%	Metastatic (liver)	Chemoembolisation (3 years)	Tumour: response: CT Adverse events
Chen *et al*., 1998[50]	HC LMS	11 (1984–1995)	56 (30–69) 18% male	Surgery 100%, radiotherapy plus chemotherapy 9%	Metastatic (liver)	Resection of liver metastases (39 months)	Mortality: KM
Bramwell *et al*., 2002[51]	HC GIST or LMS	26; 11 GIST (NR)	51.7 58% male	?	Locally advanced or metastatic	VX-710 plus doxorubicin (?)	Mortality: described, no median survival for GIST Tumour: response Adverse events: CTC
Edmonson *et al*., 2002[52]	Stromal tumours, 18 LMS[a]	39; 21 GIST (1994–1998)	55 (39–69) 62% male	None	Advanced	DTIC with mitomycin, doxorubicin, cisplatin	Mortality: KM Tumour: response Adverse events

continued

TABLE 3 *Included studies reporting non-imatinib treatment of GIST (cont'd)*

Study ID	Diagnosis	No. in study (Dates of study)	Age, median (range) (years) Gender	Previous treatments	Stage of disease	Intervention (follow-up)	Outcomes sought
Patel *et al.*, 2001[53]	HC STS	56 (1998–2000)	54 (28–76) 48% male	Chemotherapy 29%	Advanced metastatic	Gemcitabine (?)	Tumour: response Adverse events Time to progression: KM, but not all data given for GIST patients
Cohort study							
Eilber *et al.*, 2000[54]	GIST	46 (13 control) (1988–1998)	NR	NR	Recurrent and metastatic[b]	IP chemotherapy (mean 19 months)	Mortality Recurrence Adverse events
Case series							
Carson *et al.*, 1994[55]	Gastric LMS or leiomyoblastoma	32 (1970–1991)	57 (13–81) 75% male	NA	Primary or metastatic	Chemotherapy, radiotherapy, or surgery (?)	Mortality Tumour: response
Case studies							
Shioyama *et al.*, 2001[56]	Retrospective diagnosis cKIT-positive GIST	1 (1993)	75 female	Surgery	Recurrent	Chemotherapy, radiotherapy, immunotherapy (6 years)	Tumour: response: CT/PET
Pollock *et al.*, 2001[57]	CD34-positive GIST	1 (NR)	77 female	None	Unresectable	Radiotherapy (2 years)	Tumour: response Adverse events
Kamoshita *et al.*, 2002[58]	KIT-positive GIST	1 (NR)	56 female	None	Metastatic (liver)	Surgery plus ethanol injection therapy (8 months)	Tumour: response: CT
Miyauchi *et al.*, 2002[59]	CD34-positive GIST	1 (NR)	82 female	None	Unresectable	Self-expandable stent (12 months)	Mortality

[a] Of non-gastrointestinal origin.
[b] Not beyond liver or peritoneum.
DTIC, dacarbazine; ET-743, ecternascidin 743; GI, gastrointestinal; HC, histologically confirmed; IP, intraperitoneal; LMS, leiomyosarcoma; NR, not reported; STS, soft-tissue sarcoma.

Quality of included studies and evidence rating

Quality was assessed using the York CRD checklist[30] for case studies (see Appendix 4). This checklist helps to 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 are given below (for further details see Appendix 6).

Demetri and colleagues (2002)[26]

In this trial eligibility criteria were explicit, that is, all patients had to have KIT-positive GIST and all were in a similar state of 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 Southwestern Oncology Group (SWOG) criteria were used for tumour response measurement and CTC were used for adverse events. Unfortunately, in reporting of the CTC scale grades 3 and 4 were combined. In addition, two 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, but the fundamental problem of no control group means that it represents evidence of grade C according to the York CRD criteria.[30]

Van Oosterom and colleagues (2001, 2002)[31,32]

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 versus 36). For this reason data used in this review came from the later publication, which offered more mature data. Eligibility criteria were explicit (all patients KIT-positive GIST), but the representativeness of the sample is uncertain. It was unclear whether 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 intratrial and intertrial 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.[30]

Alternative treatments

In all the trials of alternative treatments, it was difficult to ascertain whether the sample was representative, as details of patient recruitment were not given and in all but four trials it was difficult to ascertain disease status. Most trials 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 two 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 tested for KIT. The cohort study used control patients who were ineligible for the trial, which may make these controls different from the cases. In summary, although 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.

Results reported in imatinib included studies

Two uncontrolled trials published in full, Demetri (2002)[26] and van Oosterom (2002),[32] 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 took place between July 2000 and April 2001; of these, 135/137 tested positive for KIT, with ten samples being unavailable for analysis. Two KIT-negative patients were judged ineligible. Patient characteristics are listed in *Table 2*; 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 a dose increase from 400 to 600 mg in nine patients. Patients whose disease progressed were withdrawn from treatment; these plus withdrawals for any other reason and those who 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, and every 6 months thereafter, according to the 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 nor disease progression); and DP, disease progression (≥ 50% increase **or** 10 cm increase in the 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 owing to disease progression). All responses were confirmed by repeated imaging within 1–4 months.

Results of survival analysis and tumour responses observed in the Demetri trial are summarised in *Tables 4* and *5*.

Approximately 65% of patients remained without treatment failure for 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]deoxyglucose uptake or new sites of uptake in those patients who experienced disease progression. More detailed results summarising PET observations obtained at one study centre (n = 25) at 21 months after the start of treatment were 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 7. 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

TABLE 4 *Survival of patients treated with imatinib in the Demetri trial*

		Survival from start of treatment			Survival from diagnosis[a]		
Study	**Diagnosis (*n*)**	**Median**	**1 year**	**2 years**	**Median**	**2.66 years**	**4 years**
Demetri *et al.*, 2002[26,61]	GIST 91% KIT-positive (147)	Not reached	88%	78%	Not reached	88%	77%

[a] For most of the time since diagnosis most patients were not receiving imatinib.

TABLE 5 *Tumour responses to imatinib observed in the Demetri trial*[a]

Study	**Unevaluable**	**CR**	**PR**	**SD**	**DP**
Demetri *et al.*, 2002[26 b] (n = 147) (at 21 months[61])	4.8%[c] (5%)	0%[c] (0%)	53.7%[c] (66%)	27.9%[c] (17%)	13.6%[c] (12.2%)

[a] SWOG criteria.
[b] All doses.
[c] Median follow-up 9 months; (supplied by Novartis).

TABLE 6 *ECOG performance status results in the Demetri trial*

	Month of visit						
Performance status[61]	**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

TABLE 7 *Survival in the van Oosterom trial*

Study	**Diagnosis (*n*)**	**Survival from start of treatment**			**Survival from diagnosis**		
Van Oosterom *et al*., 2002[32]	GIST 88% KIT-positive (40)	NR	90%[a]	NR	NR	NR	NR

[a] At 9–12 months.

TABLE 8 *Tumour response[a] to imatinib in the van Oosterom trial[b]*

Study	**Unevaluable**	**CR**	**PR**	**SD**	**DP**
Van Oosterom *et al*., 2002[32] ($n = 35$)[c]	8% no longer on treatment	0%	51%	31%	8.5%

[a] RECIST criteria.
[b] KIT-positive patients only.
[c] Five non-GIST patients had disease progression; results as of September 2001.

kind. Of these, 37.4% were classed as grade 3 and 15% 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 (seven patients) and neutropenia (seven patients). In the later analysis gastrointestinal symptoms such as nausea, vomiting, abdominal pain and diarrhoea become slightly more frequent, but the numbers are very small (seven or fewer). Overall, imatinib was reported to be well tolerated.

van Oosterom trial

The van Oosterom (2002) study[31,32] is an ongoing three-centre Phase I (dose-determining) study of imatinib that recruited 40 patients, 35 with KIT-positive GIST, between August and December 2000. Eligible patients were required to have evidence of disease progression less than 6 weeks before starting imatinib treatment. Daily doses ranged from 400 mg (in one dose, $n = 8$), through 600 mg (in two doses, $n = 8$) and 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 European Organisation for Research and Treatment of Cancer (EORTC) criteria (see Appendix 8) 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 *Tables 7* and *8*.

Tumour function determined by [^{18}F]deoxyglucose uptake observed by PET was evaluable in 14 out of 16 patients. Response was monitored on day 0, then on day 8, and again on day 28 for

TABLE 9 *Tumour functional status by PET in 14 patients treated with imatinib*

Response	CR day 28	PR day 28	SD day 28	DP day 28
CR day 8	8	–	–	–
PR day 8	2	–	–	–
SD day 8	1	–	–	–
DP day 8	–	–	–	3

confirmation of any functional change seen on day 8. EORTC criteria classify four categories of response (see Appendix 8): complete response, partial response, stable disease (no change) and disease progression. Results are summarised in *Table 9*. Survival data from this trial are shown in *Table 7*.

Adverse events observed in the van Oosterom study[32] are tabulated in Appendix 7. Five of the eight patients on the highest dose regimen experienced dose-limiting drug toxicity. Skin rash, oedema and periorbital oedema were the most common adverse events observed.

Single case studies

In addition to the two uncontrolled trials, eight case studies of imatinib for advanced GIST were included.[38–45] They describe patients treated between March 2000 and June 2002. Six patients received 400 mg per day, one 2 × 400 mg per day and another 300 mg per day. Time to treatment after metastases ranged from 0 months to 4 years. 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 9.

Interim results published in abstract format only

Interim results of four ongoing trials and a case series reported in abstract form only are incorporated into summary tables (*Tables 10* and *11*). For further details see Appendix 10.

Results reported in studies of alternative treatments

Fifteen studies[18,46–58] were included (of which nine were trials, one controlled) that reported on treatments other than imatinib for advanced GIST. In only one small study was cKIT status analysed (retrospectively, by Ryan and co-workers[46]). Studies date from 1970 to 1999. The median age was in the fifth decade and both genders were represented. All of the trials looked at patients with advanced disease. Diagnosis was described as leiomyosarcoma, gastrointestinal leiomyosarcoma, gastrointestinal sarcoma and GIST. Although some patients may have had GIST as defined today, others may have had leiomyosarcoma or other gastrointestinal sarcomas, and 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 four reporting prior chemotherapy in about one-third of patients and three reporting prior radiotherapy in a small proportion of patients. Interventions were heterogeneous: three trials describe novel strategies of chemotherapy,[46,47,53] whereas three trials examined standard sarcoma chemotherapy, either alone[18] or with enhancement of additional drugs.[51,52] A single study looked at intraperitoneal therapy,[54] while two tested the effect of hepatic chemoembolisation for liver metastases. Finally, two studies reported the effect of surgery on metastatic disease.[50, 55]

The results (*Tables 10* and *11*) observed in these intervention studies in general did not promise patient benefit. Seven studies reported median survival (range 8–24 months). Survival probability was about 72% at 1 year (range 18–100%), reducing at 2 years to about 40% (range 30–66%) and to 16% at 3 years (range 0–40%). Of the nine trials that measured tumour response, only one patient (unlikely to have a true GIST) had a complete response.[55] In terms of tumour response, 13 patients out of a total of 258 cases (5%) achieved a partial response, while 64 (24%) were described as having stable disease. Adverse events were only described in eight trials. In the trial by Judson and colleagues,[47] doxorubicin gave the most serious haematological adverse events, with 47% of patients suffering grade 4 neutropenia. In Ryan,[46] patients treated with ET-743 again tended to suffer from haematological problems, in particular leucopenia, neutropenia and anaemia. Of the two trials in which patients were treated

TABLE 10 *Summary of tumour response in studies of treatment for advanced GIST*

Study (in full or abstract)	Diagnosis (*n*) [treatment]	Subgroups	Tumour response (%)				
			CR	PR	SD	DP	NE
Uncontrolled trials (published in full)							
Demetri *et al*., 2002[26,61] (in full)	GIST (147)	Median 9 months' follow-up	0	54	28	14	5
	[imatinib]	At 21 months	0	66	17	12	5
van Oosterom *et al*., 2002[32] (in full)	GIST (40) [imatinib]		0	51	31	9	8
Uncontrolled trials (interim results published in abstract form only)							
Verweij *et al*., 2003[33] (abstract)	GIST (946)	Low-dose arm[a]	3	48	33	26	
	[imatinib]	High-dose arm	2	49	33	26	
Benjamin *et al*., 2003[34]	GIST (746)	Low-dose arm[b]	43		32	25	
(abstract)	[imatinib]	High-dose arm	41		32	25	
Ryu *et al*., 2003[35] (abstract)	GIST (33) [imatinib]		0	48	32	19	
Judson *et al*., 2003[36] (abstract)	28 GIST of 51	GIST[c]	4	64	?	?	4
Case series (published in abstract form only)							
Jankilevich *et al*., 2003[37] (abstract)	GIST (17) [imatinib]	13 of 17 evaluated	6	41	18	12	24
Included studies reporting non-imatinib treatment for GIST							
Judson *et al*., 2001[47] (in full)	STS	GIST patients only, CAELYX	0	0	0	?	?
	Retrospective GIST (21/94) [CAELYX/doxorubicin]	Doxorubicin	0	0	0	?	?
Ryan *et al*., 2002[46] (in full)	[ET-743] (18/20 patients 16/18 cKIT GIST)		0	0	11	89	0
De Pas *et al*., 2003[19] (in full)	GI sarcomas (67)	Ifosfamide plus anthracyclin	0	12	36	48	5
	[STS therapy]	Other	0	4	36	56	4
		All	0	9	36	51	5
Rajan *et al*., 2001[48] (in full)	Metastatic sarcomas (16) [chemoembolisation]	30 days after treatment	0	13	69	19	0
Mavligit *et al*., 1995[49] (in full)	LMS (14) [chemoembolisation]		–	–	–	–	–
Bramwell *et al*., 2002[51] (in full)	STS; GIST (26), LMS (18)	Non-GIST	0	13	47	40	0
	[VX-710 + doxorubicin]	GIST	0	0	9	91	0
Edmonson *et al*., 2002[52] (in full)	GI 'Stromal' (21)	GIST	0	2	NR	NR	NR
	[DTIC with MAP]	Leiomyosarcoma	0	61	NR	NR	NR
Patel *et al*., 2001[53] (in full)	STS (56)	GI leiomyosarcoma	0	0	0	100	0
	[Gemcitabine]	Non-GI, STS	0	18	0	82	0
Carson *et al*., 1994[55] (in full)	LMS or leiomyoblastoma (32) [chemotherapy (25)]	Chemotherapy Duration of PR <4 months	4	16	0	80	0

[a] 'Objective response' interpreted as CR + PR; data partly from Institute of Cancer Research submission to the National Institute for Health and Clinical Excellence (NICE); DP calculated by difference.
[b] 'Rate of response plus stable disease' interpreted as CR + PR + SD; SD by subtraction.
[c] Numbers calculated from Institute of Cancer Research submission to NICE assuming 27 patients evaluated.
NE, non-evaluable.

TABLE 11 *Summary of patient survival in studies of treatments for advanced GIST*

Study	Diagnosis (*n*) [treatment]	Survival from start of treatment			
		Median	1 year	2 years	3 years
Imatinib treated					
Demetri *et al*., 2002[26,61]	GIST (147) [imatinib]	Not reached at 24 months	88%	78%	Not reached
Van Oosterom *et al*., 2002[32]	GIST (40) [imatinib]	NR	90%	NR	Not reached
Other treatments					
Eilber *et al*., 2000[54]	GI stromal sarcomas [33 IP therapy, 13 controls no treatment (NT)]	[?]	75% IP 70% NT	42% 30%	20% 20%
Ryan *et al*., 2002[46] (only non-imatinib patients)	GIST (7) [ET-743]	8.6 months	18%	NR	NR
Ryan *et al*., 2002[46] (n = 18)	GIST (assume 18) [ET-743]	Median survival not yet observed	71%	NR	NR
De Pas *et al*., 2003[18]	GI sarcomas (67) [STS therapy]	16 months (range 2–60)	61%	24%	15%
Rajan *et al*., 2001[48] (from time of treatment)	Metastatic sarcomas (16) [chemoembolisation]	[?]	67%	50%	40%
Mavligit *et al*., 1995[49]	Leiomyosarcoma (14) [chemoembolisation]	18 months	71%	66%	0%
Chen *et al*., 1998[50]	Leiomyosarcoma (5) [surgery: incomplete resection]	24 months	100%	40%	20%
Edmonson *et al*., 2002[52]	GI stromal tumours (21) [DTIC with mitomycin, doxorubicin, cisplatin	16.7 months (95% CI 8.8 to 27.5)	63%	44%	17%
Carson *et al*., 1994[55]	Leiomyosarcoma or leiomyoblastoma (32) [chemotherapy, radiotherapy, surgery (total/partial)]	Surgery total (21/32) 40 months Surgery partial (11/32) 8 months	NR	NR	34% (at 5 years)

with chemoembolisation, pain seems to have been significant in a number of patients. Bramwell and colleagues[51] found that alopecia was the most common adverse event, while Edmonson and colleagues[52] described toxicity as being significant, with 33% of patients experiencing grade 3 vomiting. Finally, Patel and co-workers[53] 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, the considerable heterogeneity of hopeful treatments attempted, the small number of patients investigated and uncontrolled study design in nearly all studies it was difficult to draw firm conclusions from many 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 Appendix 11.

Summary of effectiveness assessment

Two published trials (still ongoing) and eight 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 that 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 diagnosis, in particular, an indirect comparison using these studies was not possible, and therefore the results of these studies will not be compared with the imatinib trials in the following section.

Two fully published uncontrolled trials (Demetri,[26] n = 147, and van Oosterom,[31] n = 40) provided information on the effects of imatinib treatment. A proportion of advanced GIST patients (8% in

van Oosterom and 14% in Demetri) experienced 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 a 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 (Demetri 54%, van Oosterom 51%) experienced 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, among these partial responders, the functional competence of remaining tumour mass may be severely compromised. Information on tumour response provided only in abstracts (two large trials, $n = 946$ and $n = 746$, two 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 the disease status of patients in these studies.

Survival is an objective clinical outcome measure and was recorded in the Demetri trial.[26] The estimation of any putative benefit of imatinib treatment on survival requires comparison with a suitable control group over an appreciable period. Unfortunately, to date, trial follow-up time was limited and control group data were only available indirectly from historical studies in which judgements of diagnosis and disease status may have been applied differently from the Demetri trial. The choice of comparator among those available may greatly influence estimates of the 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 to 100%, 24 to 66% and 0 to 40%, respectively. Survival was better in the Demetri trial (median > 24 months, at 1 year 88%, at 2 years 78%); however, it must be borne 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 worsen prognoses. 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 in Chapter 4. This was provided so that any choices made regarding suitable comparators can be placed in their proper context.

Both trials of imatinib monitored and reported the 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 and 4 by Demetri[26], and grades 2 and 3 by van Oosterom[32]). In a statement to the authors, the National Cancer Institute (NCI), which administers the CTC, said that it "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 any meaningful comparison between trials and the combination of data across trials problematic. The industrial submission provided further information on adverse events 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. The relatively good treatment retention in patients in the Demetri trial is consistent with this assertion.

Quality of life was not measured directly. Measures of functional status in everyday life tasks (ECOG), which relate to some dimensions of health-related quality of life, 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 quality of life, 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[26,32] indicates some effectiveness of imatinib for some patients, since large decreases in tumour mass with probable loss of functional integrity occur in about half of 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 was problematic; it required 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 regard to unresectability and metastases), together with consideration of quality of life experienced by compared groups of patients. These problems are addressed extensively in Chapter 5 and are not discussed further here.

Chapter 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 were no trials that directly compared imatinib with alternative treatments for patients with unresectable and/or metastatic GIST, the relative effectiveness of imatinib could 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.

Methods

Studies were included if they were primary studies that included more than ten patients with unresectable and/or metastatic GIST, and 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 evaluated imatinib are not the focus of this section of the review, although a few studies in which some patients subsequently received imatinib were considered within this section. The included studies were assessed concerning patient characteristics, KIT 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 a ruler was used to obtain the results of survival outcome.

Main results

Fourteen papers were identified (*Table 12*). Histological confirmation of CD117 was provided in only two studies: one by Ryan and colleagues[46] and an unpublished study by Goss and colleagues,[63] which was supplied on an academic 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,[46,63] some surviving patients finally received imatinib.

Median survival

Median survival was reported (or could be estimated) in 12 studies (with 983 patients in total) (*Table 13*). The reported median survival was different across studies and different patients groups (from 2 to 39 months). [Academic-in-confidence text removed.] Another two studies that included advanced or recurrent GIST[52,64] reported a median survival of about 16 months. The median survival of patients with incompletely resected GIST was about 12 months or less, except in a study by Crosby and co-workers[65] (median survival 20 months).

Survival curves

The survival curves from the included studies are presented in *Figure 1*. The survival rate was 37–80% at year 1, 6–45% at year 3, and 0–45% at year 5. It may not be a surprise to observe very different results, considering differences in patient diagnoses, start points of follow-up and interventions received.

The survival curves based on the most relevant study[63] [data removed; academic in confidence] (*Figure 1*). [Academic-in-confidence text removed.] However, 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.[61] Over the study period patients who died early had no opportunity, or much less opportunity to be treated with imatinib than patients who survived longer. [Academic-in-confidence text removed.] Thus, the survival curve of patients never treated with imatinib greatly underestimates the survival of patients with metastatic or recurrent GIST in the study by Goss and colleagues[63] (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.

TABLE 12 *Included prognostic studies: study characteristics and survival outcomes*

Study, design, patients and treatment	Survival outcomes				Other
Chen *et al.*, 1998[50] Patients with metastatic liver disease from leiomyosarcoma (between 1984 and 1995) Hepatic resection of metastases No KIT test	*Median survival* (months) (n = 11)	39			Patients with a complete resection (n = 6) had a significantly longer survival than those who had incomplete resections (n = 5)
Clary *et al.*, 2001[66] Patients with GIST from 1982 to 1999 Leiomyosarcoma arising within GI sites were classified as GIST; 8% with locally recurrent and 45% metastatic disease Surgery; some received adjuvant treatment and/or CT No KIT test	*Overall 5-year survival* (n = 239)	28%			Data for the first 200 patients used in DeMatteo *et al.*, 2000.[22] Novartis used a survival curve for patients with metastatic GIST and incomplete resection as the historical control in sensitivity analysis
	Median survival (months)				
	Complete resection (n = 136)	59			
	Incomplete resection (n = 100)	12			
	Disease-specific survival (%)	1 year	3 years	5 years	
	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	
	Metastases/incomplete resection (n = 74)	50	14	7 (4 year)	
Crosby *et al.*, 2001[65] A database created in 1989–1998 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 pathological standards 78% primary and 22% recurrence at the time of referral; 18% (n = 9) presented with distant metastatic disease Surgery; about 20% received adjuvant treatment No KIT test	*Disease-specific survival* (%)	1 year	3 years	5 years	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, range 2–91)
	Overall (n = 50)	84	51	41	
	Complete resection (n = 35)	97	66	42	
	Incomplete resection (n = 15)	73	8	8	
	Median (mean) survival (months)				
	Complete resection	50 (mean 60, range 4.5–176)			
	Incomplete resection	20 (mean 29, range 1–157)			
	Survival rate for stage III patients (%) (multiple primary lesions or distant metastases at diagnosis, n = 11; estimated from *Figure 4*)	1 year	2 years		
		73	27		

continued

TABLE 12 *Included prognostic studies: study characteristics and survival outcomes (cont'd)*

Study, design, patients and treatment	Survival outcomes	Other
DeMatteo *et al.*, 2000[22] Patients with malignant GIST from 1982 to 1998; histological diagnosis 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 NB. Patient data also used in Clary *et al.*, 2001[66]	*Disease-specific survival* (%) Overall (*n* = 200): 1 year 69; 3 years 44; 5 years 35 *Median survival* (months) Primary (*n* = 93): 60 Metastatic (*n* = 94): 19 Locally recurrent (*n* = 13): 12 *Survival outcomes after first recurrence in patients with primary disease and completed resection (%) (estimated according to data in Table 7)* All recurrent patients (*n* = 27): median 8 months (mean 17.5, range 1–125) 1 year 41; 2 years 14 Patients with metastases (*n* = 18): median 10.5 months (mean 11.7, range 1–40) 1 year 44; 2 years 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[18] 76 patients with advanced GIST (between 1979 and 1999) Systemic chemotherapy as adjuvant treatment (*n* = 15) or for metastatic disease (*n* = 67) No KIT test	*Median survival* (months) (*n* = 67): 16 (range 2–60) *Survival rate* (%) (*n* = 67, (From the start of chemotherapy): 1 year 62; 2 years 24; 3 years 15; 4 years 10	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
Edmonson *et al.*, 2002[52] Prospective Phase II study of 21 patients with advanced histologically confirmed GIST between 1994 and 1998; no standard curative therapy was known Patients received intravenous chemotherapy (dacarbazine, mitomycin, doxorubicin and cisplatin plus GM-CSF) No KIT test	*Median survival* (months) (*n* = 21): 16.7 (95% CI 8.8 to 27.5) *Survival rate* (%): 1 year 67; 2 years 39; 3 years 8	Objective tumour regression was observed in one of 21 (1.8%) GISTs. Time to disease progression was 7.3 months (95% CI 4 to 8.5)

continued

TABLE 12 *Included prognostic studies: study characteristics and survival outcomes (cont'd)*

Study, design, patients and treatment	Survival outcomes					Other
Howe *et al.*, 2001[67]	*Disease-specific survival* (%)		1 year	3 years	5 years	
	Overall (n = 590)		77.6	48.2	38.9	
Data from the National Cancer Data Base for patients with primary small bowel sarcoma between 1985 and 1995; majority (75%) with leiomyosarcoma	Leiomyosarcoma (n = 456)		81.8	51.0	40.3	
	Stage					
	Local (n = 214)		93.1	80.0	75.0	
Surgery, plus radiotherapy and/or chemotherapy	Regional (n = 172)		80.2	40.0	30.8	
	Distant (n = 146)		54.1	12.4	6.5	
No KIT test						
Pierie *et al.*, 2001[68]	*Survival* (%)		1 year	3 years	5 years	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 months (range 8–300)
	Overall (n = 69)			38	29	
Retrospective review of 70 GIST patients from 1973 to 1998. Metastatic disease at initial visit was present in 41% of patients. GIST defined as any sarcoma of the gut	Complete resection (n = 41)		88	54	42	
	Incomplete resection (n = 28)		42	13	9	
Surgery						
No KIT test						
McGrath *et al.*, 1987[69]	*Median survival* (months)					46% (12/26) recurrent after complete resection. Median interval from initial resection to detection of recurrence was 2 years (range 6–98 months)
	Distant metastases (n = 28)		10			
Patients with primary gastrointestinal sarcomas from 1952 to 1984; charts and histopathological slides were reviewed	Partial resection (n = 21)		9			
	Survival rate (%)	1 year	2 years	3 years	4 years	5 years
Surgery; some received radiation and/or chemotherapy	Partial resection (n = 21)	46	27	21	14	10
No KIT test	Adjacent spread (n = ?)	67	46	38	28	20
	Distant metastases (n = 28)	36.5	12	6		

continued

TABLE 12 *Included prognostic studies: study characteristics and survival outcomes (cont'd)*

Study, design, patients and treatment	Survival outcomes	Other
Ng *et al.*, 1992[64] Patients with gastrointestinal leiomyosarcomas from 1957 to 1987; diagnosis confirmed by a pathologist Surgery, plus chemotherapy in 76% and radiation therapy in 20% of patients No KIT test	*Median survival* (months) All patients (n = 191): 29 (range 1–284) Recurrence after complete resection: 14–19 Peritoneal recurrence with metastasis: 9–13 *Survival rate* (%): Recurrent (>18 months, n = 56): 1 year 73, 2 years 44, 3 years 31, 4 years 22, 5 years 11 Recurrent (<18 months, n = 54): 1 year 56, 2 years 23, 3 years 8, 4 years 3, 5 years –	Patients who had relapses 18 months after surgery had a better survival outcome than those who relapsed before 18 months
Rajan *et al.*, 2001[48] Patients (n = 16) with histologically proven metastatic (to liver) sarcoma from January 1993 to January 2000 Chemoembolisation No KIT test	Median survival (months) (n = 16): 20 *Survival rate* (%) (n = 16): 1 year 81, 2 years 54, 3 years 40, 4 years 26 (From time of diagnosis)	
Ryan *et al.*, 2002[46] Phase II trial of patients with unresectable advanced or metastatic GIST, which was proven histologically Cytotoxic agent: ET-743; 11 patients subsequently received imatinib (but no data about the time and duration of treatment with imatinib) KIT positive in 16/17 (three unknown)	*Overall 1-year survival rate* (%) (n = 18): 71.1 The 1-year survival rate for those who 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' to receive imatinib. The selection bias is therefore obvious. A further consideration is the toxicities from chemotherapy	
Yao *et al.*, 2000[70] Patients with primary gastrointestinal sarcomas from 1981 to 1996 Surgery No KIT test	*Median survival* (months) All patients (n = 55): 32 Complete resection (n = 35): 46 Incomplete resection (n = 17): 10 *Estimated 5-year survival* (%) Complete resection: 28 Incomplete resection: 0	

continued

TABLE 12 *Included prognostic studies: study characteristics and survival outcomes (cont'd)*

Study, design, patients and treatment	Survival outcomes	Other
Goss *et al.*, unpublished[63] [Academic in confidence] A retrospective review of 143 patients with histological confirmation GIST, between 1996 and 2001; 132 patients had recurrent or metastatic GIST Various chemotherapy regimens; some patients subsequently received imatinib CD117 (KIT) positive	[Academic in confidence text removed]	

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

Study	Patients	No. of patients	Median survival (months)
Chen *et al*., 1998[50]	Leiomyosarcoma liver metastasis	11	39
Clary *et al*., 2001[66]	Incomplete resection (all):	100	12
	Primary plus incomplete resection	18	34
	Local recurrence plus incomplete resection	8	2
	Metastases plus incomplete resection	74	12
	Local recurrence (all)	18	23.2
	Metastases (all)	109	17.6
Crosby *et al*., 2001[65]	Incomplete resection (small bowel)	15	20
De Pas *et al*., 2003[18]	Advanced GIST	67	16
Edmonson *et al*., 2002[52]	Advanced GIST	21	16.7
Goss *et al*., unpublished[63]	All recurrence/metastasis	[AIC]	[AIC]
	Recurrence/metastases, no imatinib		
Howe *et al*., 2001[67]	Small-bowel sarcomas:		
	Regional stage	172	28.6
	Distant stage	146	13.8
Pierie *et al*., 2001[68]	Incomplete resection	28	10.4
McGrath *et al*., 1987[69]	Incomplete resection	21	9
Ng *et al*., 1992[64]	Recurrent GIST	110	16.5
Rajan *et al*., 2001[48]	Sarcoma liver metastasis	16	20
Yao *et al*., 2000[70]	Incomplete resection	17	10
Total		983	

AIC, academic in confidence.

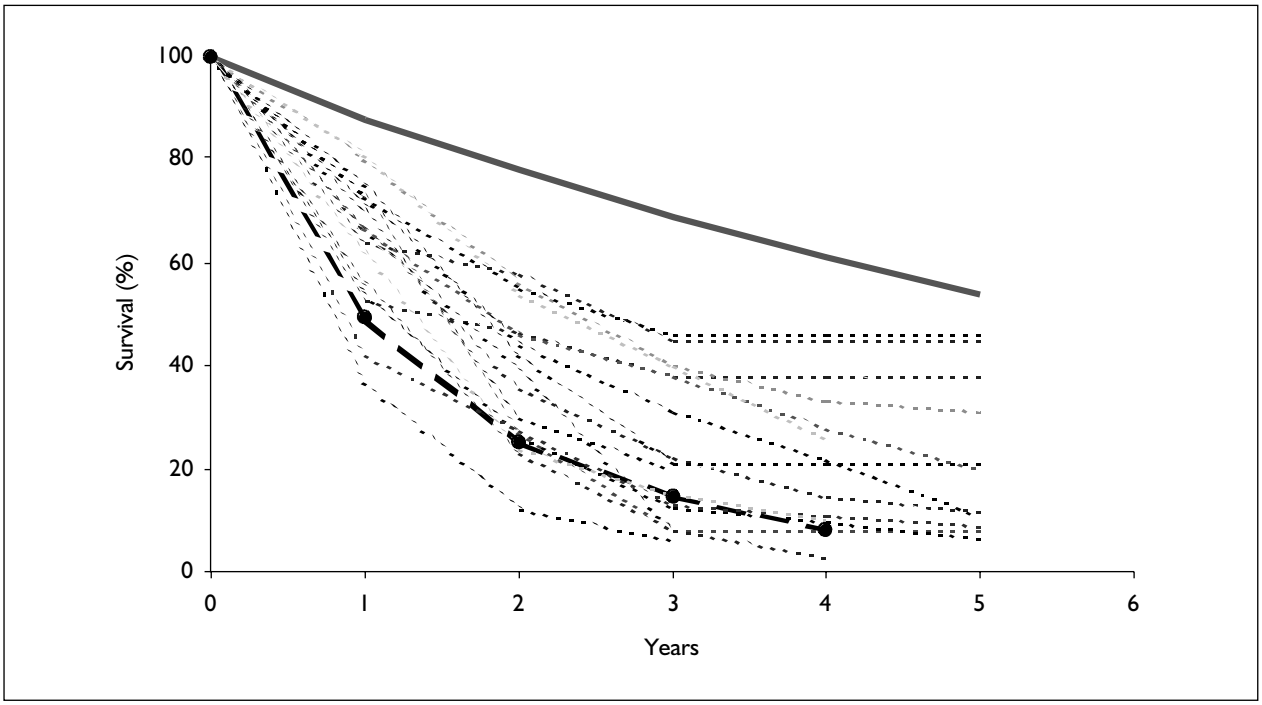

FIGURE 1 *Survival curves from included prognostic studies. Solid line: imatinib trial (CSTI571-B2222), 25 months' follow-up and extrapolated. [Academic in confidence, deleted.] [Academic in confidence, deleted.] Circles: Clary (metastatic and incompletely resected GIST).[66] Studies shown in* Table 13 *also represented as dashed lines.*

The industry submission stated that the Goss study[63] overestimated the survival of patients with advanced GIST. However, they only used a worse scenario for the sensitivity analysis, based on the result of patients with metastases plus incomplete resection in Clary,[66] which was inappropriate according to the empirical data presented in *Figure 1*. In Chapter 5, the Novartis submitted model has been modified, and it was confirmed that the patients included in the major imatinib trials (CSTI571-B2222) were relatively comparable to all patients with metastatic and/or recurrent GIST in the Goss study.[63]

[Academic-in-confidence data removed]

FIGURE 2 *Survival curves in metastatic or recurrent patients in the Goss study[63]*

Long surviving patients

Although a large number of patients with advanced GIST 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) of more than 241 weeks before the start of the study, and a recurrence history (from first recurrence) of 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 (*Figures 3* and *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.

Remarks

It has been widely quoted that patients with advanced unresectable GIST have a gloomy prognosis; most of them die soon after diagnosis, with a median survival about 12 months. The empirical evidence summarised in *Table 13* and *Figure 1* indicates 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 several 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[57] (explicitly or implicitly) about unresectability, and the availability of alternative interventions (including imatinib) may influence

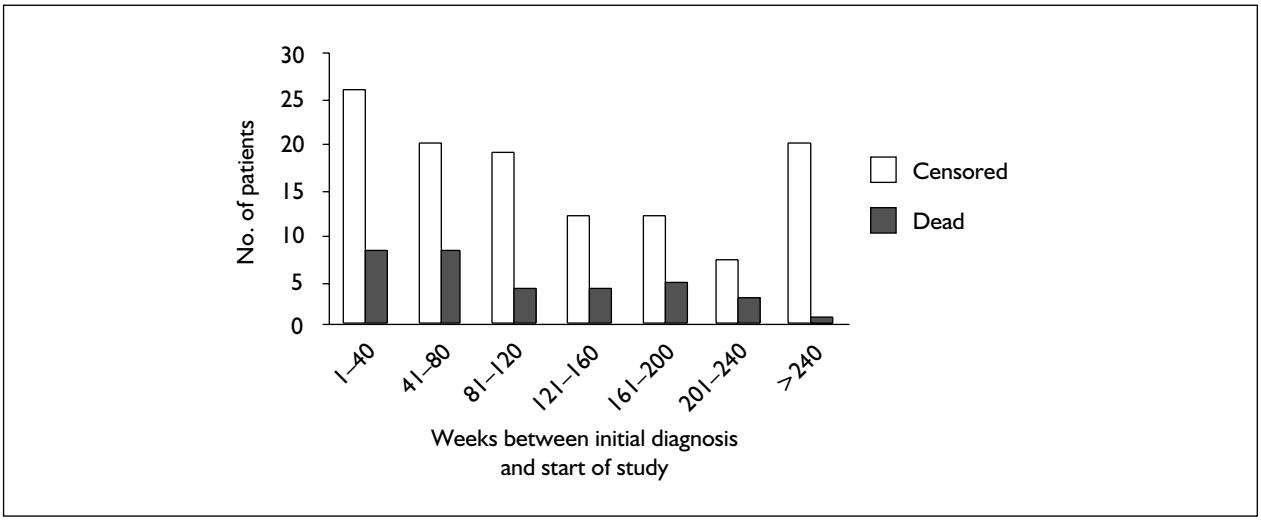

FIGURE 3 *Duration of disease (from initial diagnosis to the start of the study) and death. Patients in study CSTI571-B2222 (censored=114, dead=33) (data from Novartis).[60]*

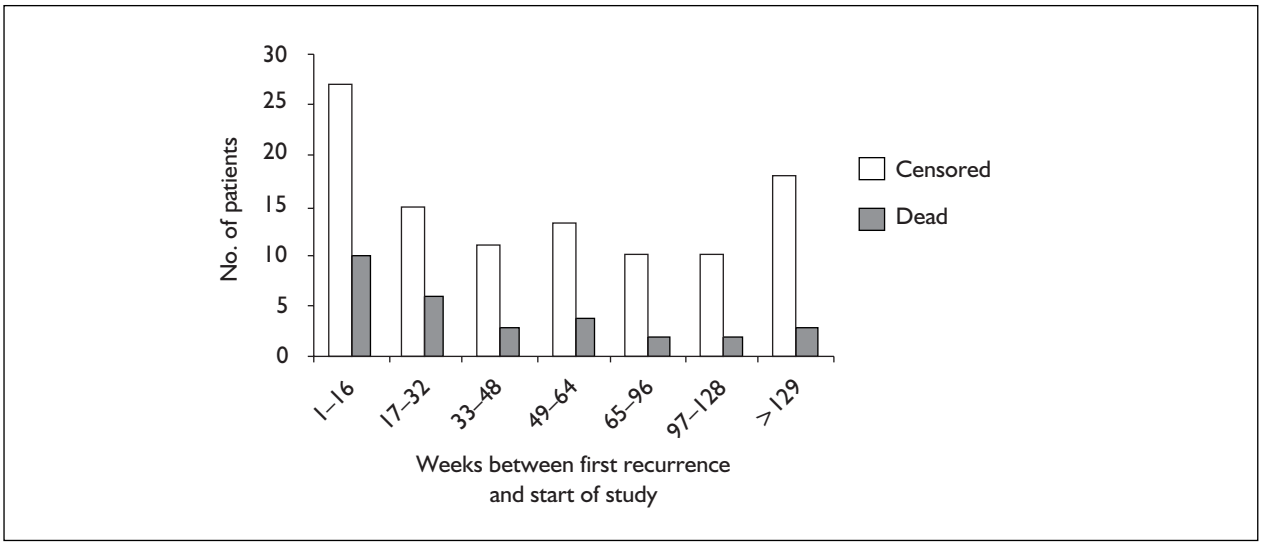

FIGURE 4 *Duration of recurrent disease and death. Patients in study CSTIB2222 (censored=104, dead=30) (data from Novartis).*[60]

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[46,63] 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[63] are available, the data should be reanalysed 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, regardless of whether they finally received imatinib. The impact of imatinib in the Goss study[63] was likely to be small because it became available very late on, and for only a 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 may be worse than those 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]) are also presented in *Figure 1* (thick solid line). There is little doubt that the treatment with imatinib has improved the survival of patients with advanced GIST, although 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) the validity of the long-term projection of survival beyond observed data.

Chapter 5

Economic evaluation

In this chapter, the model that Novartis submitted to NICE was assessed. The Novartis model was then modified 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.

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,[71] the model assessment focuses on three areas: the model structure, data used and model validation.

Objectives and perspectives

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

Model structure

States in the model

The Novartis model was a state-transition model, and had two arms: the control and the imatinib treatment arm (*Figure 5*). The patients in the control arm had 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 was added into the model. Patients in the state of imatinib treatment included those who had a stable disease or who achieved 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 were in the state of imatinib treatment. Patients in the imatinib group who failed to respond or whose disease progressed

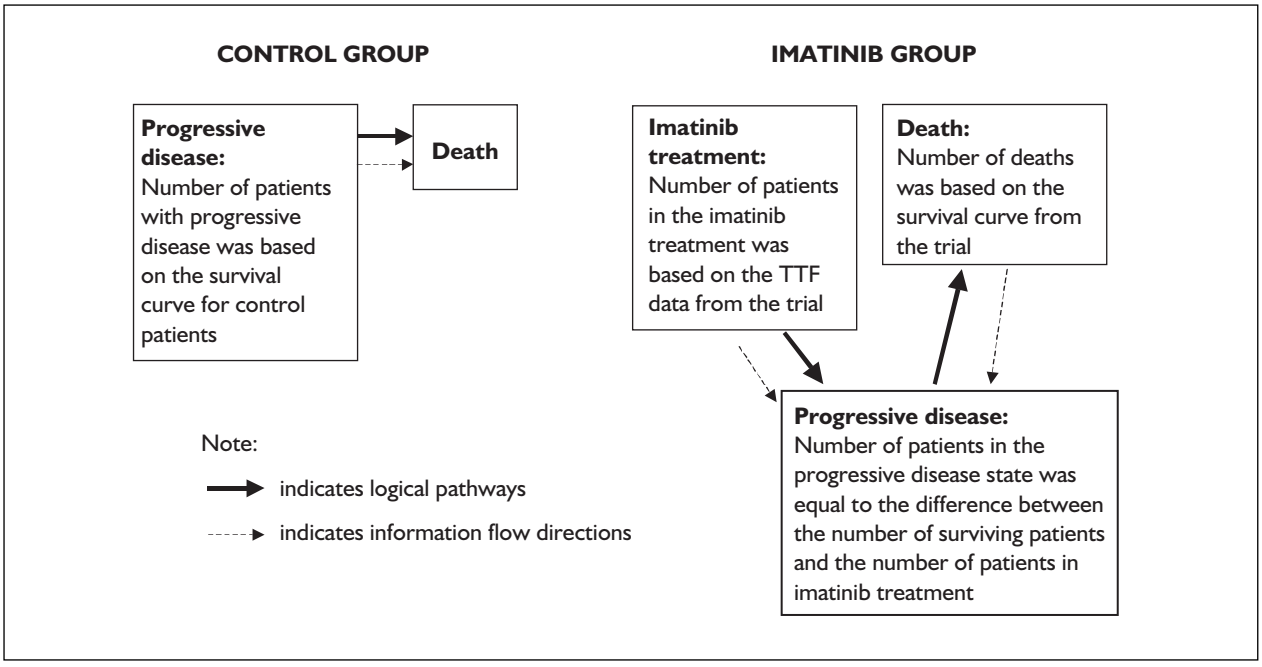

FIGURE 5 *States in the control and in the imatinib arm: the original Novartis model. TTF, time to treatment failure.*

were 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 should soon move to the state of death (*Figure 5*).

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

State transitions in the model

The number of patients in each state was calculated every 4 weeks. The reported outcomes were up to 10 years, although 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 was determined by the survival curve of historical patients who had not received imatinib treatment.

In the imatinib arm, surviving patients were 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 were not the same as the directions of information flow in the actual model. First, the Novartis model estimated the number of surviving patients according to the survival curve from a clinical trial. Then it estimated the number of patients in the state of imatinib treatment, according to the TTF curve from the same trial. Finally, the number of patients in the state of progressive disease equalled 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 was that the TTF and survival curves were independently calculated, and no efforts had been made to calibrate the outcomes of the two curves. As shown in *Figure 6*, the small proportion of patients in the state of imatinib treatment was proportionate 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 were 44% and 79%, respectively, after 2 years, 13% and 55% after 5 years, and 2% and 30% 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 die in 2 years (this point is further illustrated in Appendix 13).

[Academic-in-confidence data removed]

FIGURE 6 *Proportions in the state 'imatinib treatment' and overall survival (Novartis model)*

Data used in the model

Input data required

To estimate the relative effectiveness and utility of imatinib treatment for unresectable and/or metastatic GIST, the Novartis model required 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
- TTF for patients who receive imatinib.

The Novartis model required the following cost data:

- drug cost of imatinib treatment (about £20,000 per year)
- cost of outpatient visits including tests (£440 per year)
- cost of CT scans (£656 for imatinib patients and £82 for patients with progressive disease)
- cost of GP visit (£40 per year) and
- cost of management of adverse events (on average £159 per year, range £127.20–190.80).

Data on quality of life

The literature search identified no studies that had directly evaluated quality of life using EuroQoL 5 Dimensions (EQ-5D) for patients with advanced GIST.[61] In the Novartis model, utility values for patients in the imatinib arm were estimated by a mapping of ECOG performance status to EQ-5D scores. ECOG data were from the CST157I-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 the small number of clinicians involved.

Data on the survival of patients

The key input data for the effectiveness modelling

were the relative survival benefits 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 were 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 had 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 or 600 mg per day) in 147 patients with malignant unresectable and/or metastatic GISTs. The advantage of using this trial was that it provided 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 1 year and 78% after 2 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 TTF for patients treated with imatinib (*Figure 6*) 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 were considered unreliable. According to the Novartis submission sensitivity analyses suggested no difference if all data available were 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).

Survival data for control patients
It was more problematic to obtain good survival data for control patients because of the following difficulties. First, 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 immunotesting this made it generally impossible to separate KIT-positive GIST from other gastrointestinal sarcomas in the older studies. A second problem was that there is a lack of objective definition of unresectability for recurrent or metastatic GISTs.

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 was about 12 months, ranging from 2 to 20 months. An unpublished study by Goss and colleagues[63] used 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 Goss study (median survival [Academic-in-confidence data removed]) was used in the baseline scenario, and survival curves from Clary and colleagues[66] (median survival 12 months) were used for sensitivity analysis. The follow-up was over or close to [Academic-in-confidence data removed] in the Goss study and 5 years in the Clary study.[66] The fitted exponential curves were well matched with the observed survival curves for the control patients.

Text related to the study by Goss and colleagues[63] is academic in confidence and has been removed.

[Data related to the unpublished Goss study are academic in confidence and have been removed]

FIGURE 7 *Survival curves for patients in the control arm[63]*

Model validation

According to Weinstein and colleagues,[71] 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 were no directly controlled trials that compared imatinib with alternative interventions for patients with unresectable and/or metastatic GIST.

Summary

Because of a 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 was clearly presented. The model structure and input data were transparent. The model

structure and level of simplification seem reasonable in terms of the model's objectives and data availability. The cost estimates seemed reasonable.

The original Novartis model[61] had overestimated the cost-effectiveness of imatinib for patients with unresectable and/or metastatic GIST because of the disproportion of survival and TTF in the imatinib arm, and because the survival curve for patients in the control arm may have been biased against long-term survivors. Sensitivity analyses were carried out using different input values for patient survival. However, these sensitivity analyses were designed in such a way that the results tended to exacerbate further the overestimation of the cost-effectiveness for the imatinib treatment.

In response to the identified shortcomings, the Novartis model was modified as presented below.

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 a more appropriate survival curve for patients in the state of progressive disease (Modified-B).

Modified-A

To overcome the Novartis model's weakness that the state of imatinib treatment is independent from the survival, the following modifications were made. (It is called Modified-A, to distinguish between different versions.) First, the number of patients in the state of imatinib treatment was estimated according to the same TTF curves, as in the original Novartis model. It was assumed that all patients in the state of imatinib treatment were alive. Patients who fail to respond to imatinib were 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 was 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 was determined by both the TTF curves and the survival curve for patients with progressive disease. An important advantage with the Modified-A model is that both the imatinib arm and the control arm 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 to 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 overestimated the survival benefit of imatinib treatment given the same survival curve for the control patients and for the progressive disease 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 (ICERs) are similar between the Novartis model and the Modified-A model. After about 3 years, the estimated cost per quality-adjusted life-year (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.

Modified-B

Since the survival curve for patients who never received imatinib in the Goss study[63] underestimated the survival of control patients, the Novartis model was further modified (additional to the change in Modified-A) using the survival curve for all patients with metastatic or recurrent GIST in the Goss study.[63] In addition, the exponential TTF curve and the imatinib dose based on all available data from the trial CSTI571-B2222 were used. The results of this further modification are shown in *Table 14*. The cost per QALY gained is £85,224 after 2 years, £41,219

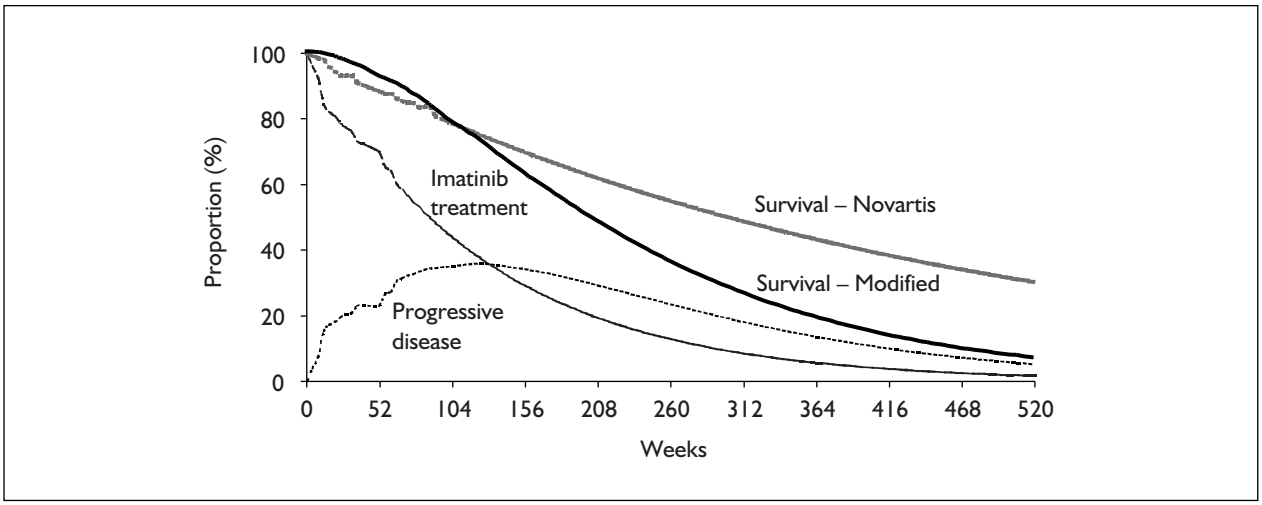

FIGURE 8 *The modified-A model: survival curves of the proportion of patients in the state of imatinib treatment. Also shown are the proportion of patients in the state of imatinib treatment and the proportion of patients in progressive disease (based on the Modified-A model, baseline scenario). In the Modified-B model the control survival curve used was different to, and more appropriate than, that used in the Novartis model.*

TABLE 14 *Results of the original Novartis model and the modified models*

Year	Imatinib		Control		Cost per 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

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;[63] (3) the exponential TTF curve based on all trial data (CSTI571-B2222); (4) cost of imatinib as in the imatinib trial.

after 5 years and £29,789 after 10 years. The results from the Modified-B model suggest a lower cost-effectiveness of imatinib than do the results of the original Novartis model (*Table 14*).

The use of the survival curve for all patients in the Goss study[63] resulted in 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 (CSTI571-B2222) and the curve estimated by

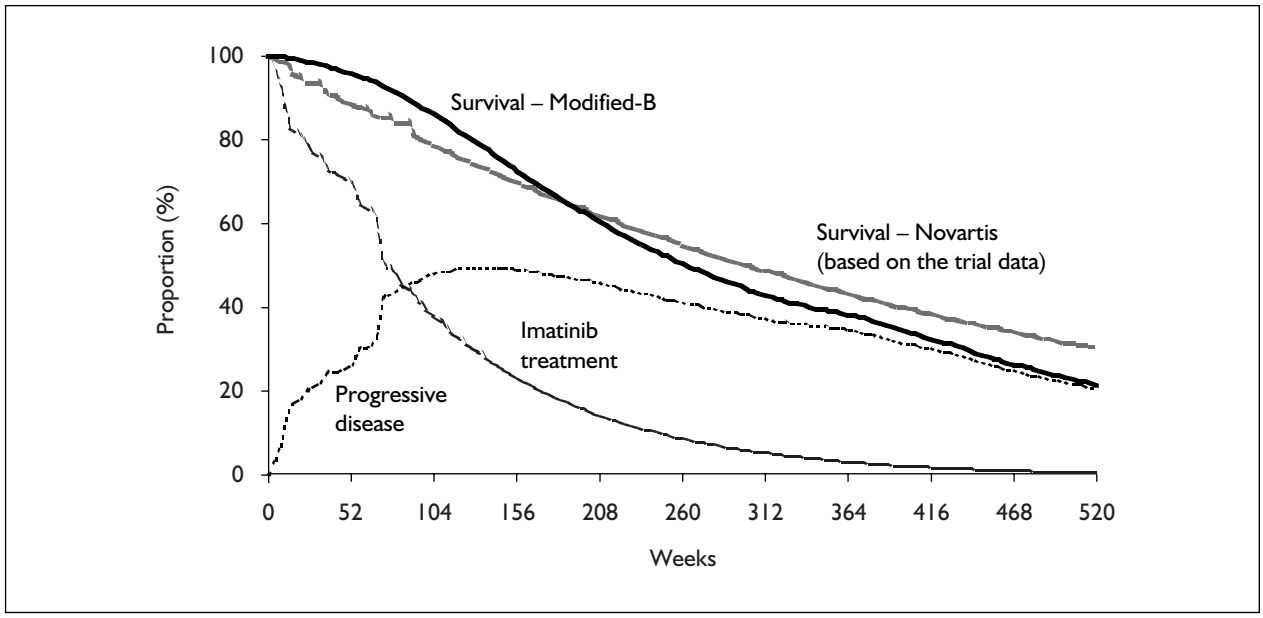

FIGURE 9 *Survival curves in the original Novartis model and Modified-B model. The two survival curves are similar, although the estimated survival is better than that observed before 190 weeks and then worse than that observed after 190 weeks. This evidence suggested that the survival curve for the control patients used in Modified-B model (i.e. 'all patients' data in the Goss study[63]) 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 study[63] will at least partially resolve the concern about the disproportion of patient survival and TTF in the original Novartis model.*

the Modified-B model. The two curves are similar, although the estimated survival was better than the observed survival before about 190 weeks, and worse than the observed survival 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 study.[63] Thus, the survival curve for the control patients used in Modified-B model (i.e. 'all patients' data in the Goss study[63]) 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 study[63] will at least partially resolve the concern about the disproportion of patient survival and TTF in the original Novartis model.

Sensitivity analyses using the modified Novartis model

The original Novartis model provided central, low and high estimates for relevant costs. In addition, the different curves had been fitted for the TTF for imatinib-treated patients. The central, low and high estimates of input values in the modified Novartis model were used 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.

Summary

The best evidence (results from the Modified-B model) 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.

The Birmingham model

A four-state probability Markov model was developed which differed from the Novartis model in four main ways: by a Monte Carlo simulation to allow for uncertainty in 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.

Model structure

The aim of the Birmingham model was to investigate the cost-effectiveness of imatinib in treatment of unresectable and/or metastatic GISTs compared with BSC. Four states apply to the imatinib treatment group: on imatinib treatment at a 400-mg dose, imatinib treatment at a 600-mg

TABLE 15 *Results of the 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 per day start dose: £370.38
Other costs per imatinib-treated patient	£1,136	£1,786	£570
Other costs per progressive disease 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-week data: –0.0079
Survival curve for patients in the state of progressive disease	All patients data from the Goss study	All patients data from the Goss study	Patients who never received imatinib in the Goss study
Utility value	Imatinib-treated: 0.935 Progressive: 0.875	Imatinib-treated: 0.900 Progressive: 0.875	Imatinib-treated: 0.935 Progressive: 0.875
Costs per 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

Data were from the original Novartis model,[61] except for the survival curve for all patients in the Goss study.[63]
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.

dose, progressive disease state and death. Two states apply to the BSC group: progressive disease and death. Transitions between states are defined over 4-week cycles. The simulation length was 10 years (130 × 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 states. It was assumed that all patients in the imatinib treatment group started at the imatinib treatment state (400 mg 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 the 400-mg dose. Patients whose disease progressed while being treated with imatinib at 400 mg per day, 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 600 mg 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. *Figure 10* summarises all the possible health state pathways at the end of each cycle in the imatinib treatment group.

In the 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, from where they could either remain in this state or die at the next cycle of the simulation.

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

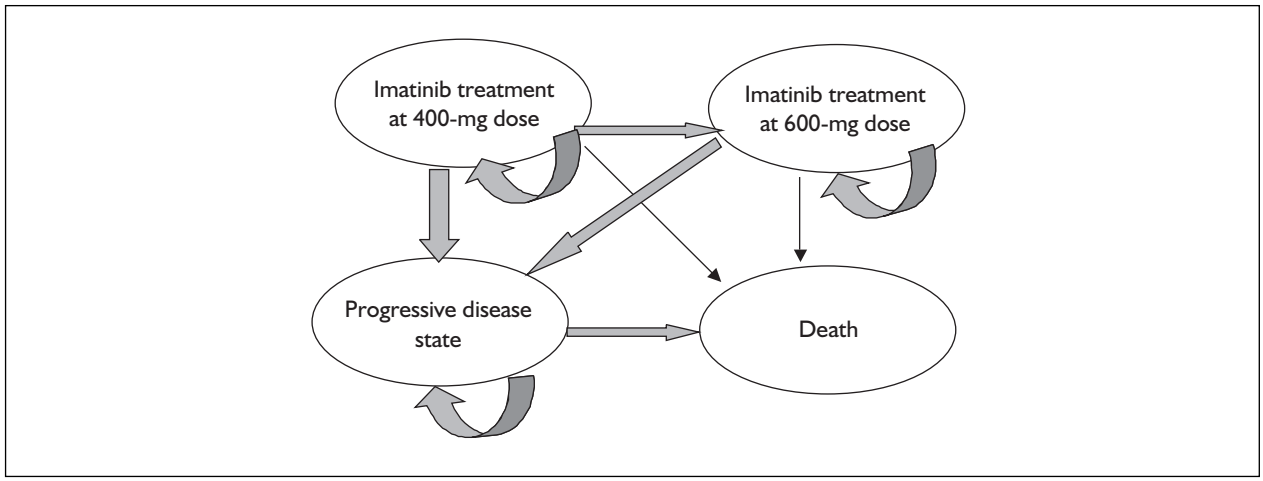

FIGURE 10 *Patient pathways in the imatinib arm: the new Birmingham model*

TABLE 16 *Input costs and quality of life 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 400 mg	£1,453.54	£18896
Cost of imatinib at dose of 600 mg	£1,874.49	£24,368
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 costs for imatinib-treated patient	£87.38	£1,136
Utility at imatinib treatment	0.935	0.935
Utility at progressive state	0.875	0.875

Assumptions used in modelling

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

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

If a patient failed to respond to imatinib at the 400-mg dose, they were moved to receive the 600-mg dose. A random number was generated to decide whether patients would be likely to be resistant to a higher dose if they failed at 400 mg. The probability that a patient would be resistant for 600 mg imatinib after failing at 400 mg per day was estimated from the Demetri report.[26] In this trial it was reported that, of the nine patients who received the higher dose after evidence of disease progression was observed, three had a sustained partial response or stable disease after cross-over. Patients who moved to the state of imatinib 600 mg were assumed to have the same probability of progressing as patients in the state of 400 mg imatinib treatment.

Deaths due to other causes 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 (CSTB2222) (data from industry submission, Appendix 6.2). All patients who entered into the progressive disease state, irrespective of whether they had previously received the 400- or 600-mg dose of imatinib or had not received imatinib (BSC arm), were assumed to have the same probability of staying in the progressive state or of proceeding to death.

Input data for cost and QALYs

The cost and utility input data used in the Birmingham model were the same as those in the model proposed in the industry submission by Novartis and are shown in *Table 16*. Costs and

QALYs are discounted annually at 6% and 1.5%, respectively.

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 the control and the imatinib arm in the same direction. As has been discussed in considering the modified Novartis model, the patients in the imatinib trial were relatively comparable to all patients with metastatic or recurrent GIST in the Goss study.[63] Therefore, the base-case scenario in the Birmingham model used the Goss 'all patients' survival for patients in the state of progressive disease in both control arm and the imatinib treatment arm.

For the Goss all-patient group, the wider confidence interval around the Kaplan–Meier estimate of survival after 40 months indicated that the data after that period were becoming less reliable. There was also a flat period in the curve after 40 months, possibly indicating that imatinib was introduced during that time. Therefore, it is more reasonable to use the first 40 months' data to project long-term survival for this group of patients in this model.

However, the use of the survival curve for all patients in the Goss study[63] is likely to overestimate the true survival for patients who are in the progressive state. The use of the survival curve for patients who were never treated with imatinib considerably underestimates the survival of patients with metastatic or recurrent GISTs in the Goss study.[63] Therefore Goss 'all patients' survival data were used in the baseline scenario and Goss 'selected patients' were used for sensitivity analysis.

Extrapolating beyond trial data

In the Goss study,[63] the follow-up was close to [Academic-in-confidence data removed] years with usable data up to [Academic-in-confidence data removed] 40 months. Extrapolating beyond the study was necessary to investigate the long-term effect (in this case, 10 years).

The two most commonly used parametric models to fit the survival time for severe diseases are the Weibull distribution and the exponential distribution. For the exponential distribution, the underlying assumption is that the hazard rate does not depend on time. Thus, as time progresses for a particular individual, the probability of death in successive time intervals remains unchanged. For the Weibull distribution, the hazard rate could increase or decrease with time. Whether it increases or decreases with time depends on the shape parameter in Weibull distribution. If the shape parameter is greater than 1, the hazard rate increases with time. If the shape parameter is less than 1, the hazard decreases with time. If the shape parameter equals to 1, then the Weibull reduces to the exponential distribution.

Assessing the assumption of a constant hazard rate

A graphical method to test the suitability of the Weibull or exponential distribution to describe the data can be derived by plotting the log (–log [$s(t)$]) against log t. If the plot is approximately a straight line with a slope not equal to unity, this indicates that a Weibull distribution may describe the data sufficiently well. If it is close to unity, the exponential distribution could be used as an approximation. The plot also provides a way to estimate the two parameters for the Weibull distribution.

[Data related to the unpublished Goss study are academic in confidence and have been removed]

FIGURE 11 *Log (–log[s(t)]) plot against log (t) for the Goss all-patient group based on the first 40 months of observation*

For the Goss 'all patients' group, the log (–log[$s(t)$]) plot against log (t) is shown in *Figure 11*. The shape parameter (the slope for the line in *Figure 11*) is [Academic-in-confidence data removed] indicates that there is [Academic-in-confidence text removed] (*Figure 13*). In the present model, exponential fitting was used as the baseline scenario and Weibull fitting was used in a sensitivity analysis.

[Data related to the unpublished Goss study are academic in confidence and have been removed]

FIGURE 12 *Hazard rate for Weibull and exponential distributions based on Goss all patients*[63]

For the Goss 'selected' patients' group, in the Novartis model, an exponential survival curve was used for the extrapolation after the first 162 weeks.

[Data related to the unpublished Goss study are academic in confidence and have been removed]

FIGURE 13 *Kaplan–Meier survival curve with fitted Weibull and exponential fitting based on 40 months for Goss, all patients*

However, use of an exponential survival function assumes that the hazard rate was constant over time. The same method as before was used to estimate the two parameters and examine the suitability of the assumption of constant hazard (exponential distribution) for this data. It was suggested that a Weibull distribution function to fit the survival curve for these group patients was more suitable.

The two parameter estimates in the Weibull survival function are $\lambda = 0.009063$ and $\gamma = 1.3293$. The shape parameter at 1.3292 (much greater than 1, as implied by the exponential curve) also confirmed that the Weibull survival fitted the data. *Figure 14* shows the different hazard rates for fitting the Weibull and exponential distribution.

Extrapolating survival curve for TTF in imatinib treatment

The same TTF data were used as in the Novartis model. The first 70 weeks for the Kaplan–Meier estimates for the survival function of study CSTI571-B2222 were used. The estimated shape parameter for the Weibull distribution was 0.9487. This indicated that the hazard rate decreases with time for the imatinib treatment group. However, it is close to unity, so exponential fitting would be quite suitable.

However, the authors are fully aware of the uncertainty around the survival curves by using 70 weeks' data to project 10-year survival function. Therefore, a sensitivity analysis is needed to assess the parameter uncertainty for the TTF curves. This could be done by fitting different survival curves around the observed data. The effects of fitting different TTF curves to the trial data were explored using Weibull and exponential fitted curves and also upper and lower values around the fitted exponential curve (*Table 12* and *Figure 15*).

Results from the Birmingham model

Simulated survival curves for the imatinib treatment patient group and BSC group for the four-state Markov model based on 10,000 patient simulations over 10 years are shown in *Figure 16*.

Table 17 shows the results for the base-case scenario. The estimated costs per QALY gained by the imatinib treatment are £70,206, £51,514, £36,479 and £25,859 at years 2, 3, 5 and 10, respectively. Sensitivity analyses using different fitted curves for TTF show only small differences in the estimated ICERs (*Table 18*).

However, the ICER will change depending upon whether the Weibull or exponential distribution is used. The ICER based on Weibull fitting is £26,427, but £21,707 for exponential fitting. The effect of a change in model structure on the ICER was also examined by not allowing movement to the higher dose if a patient progressed on the 400-mg dose. The result for this is shown in *Table 18*, with the ICER at £23,547.

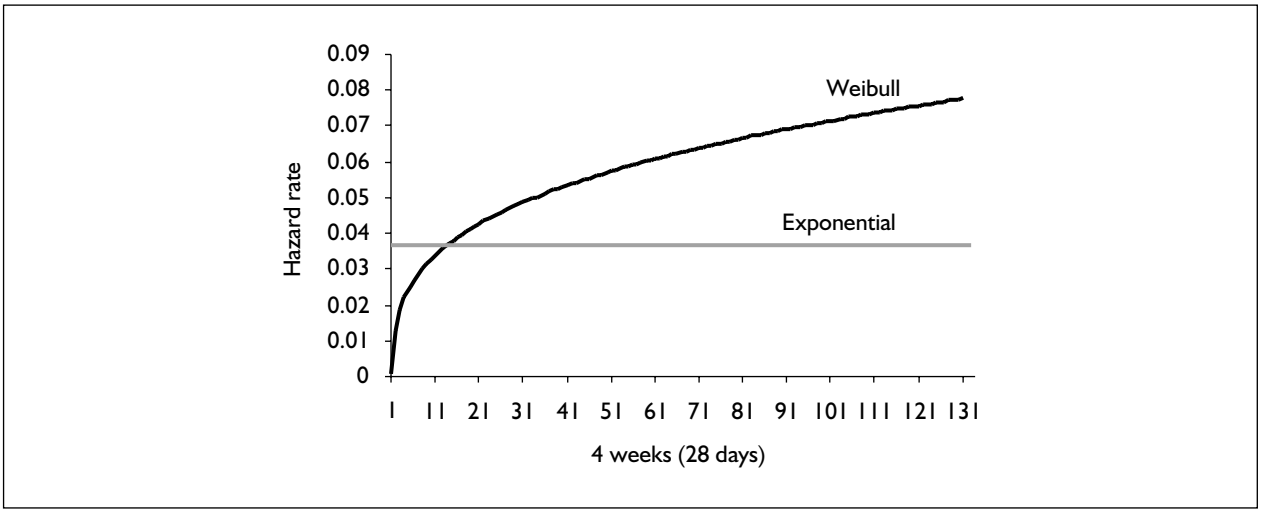

FIGURE 14 *Hazard rates for Weibull and exponential distributions*

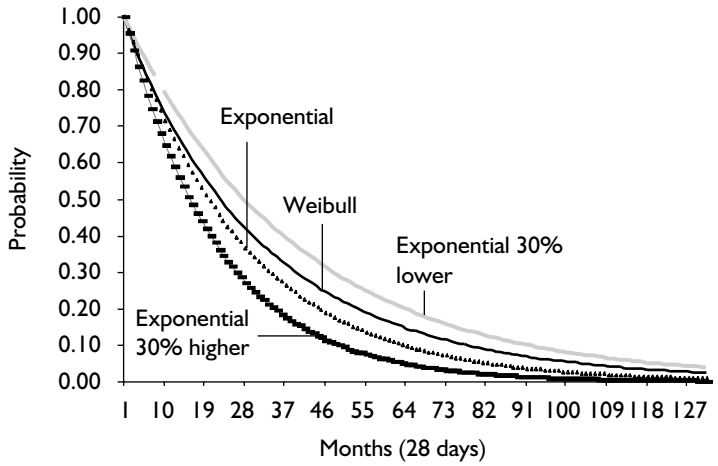

FIGURE 15 *Fitted curves for TTF*

[Data related to the unpublished Goss study are academic in confidence and have been removed]

FIGURE 16 *Survival curves for imatinib and BSC*

TABLE 17 *Results of the base-case scenario*

Year	Imatinib		BSC		Cost per QALY
	Cost (£)	QALYs	Cost (£)	QALYs	
2	31,160	1.82	1,998	1.40	70,206
3	39,482	2.54	2,630	1.82	51,514
5	49,466	3.65	3,446	2.38	36,479
10	56,146	4.98	4,230	2.98	25,859

The hazard for TTF used in the model was based on the exponential curve extrapolation from 70 weeks of data. Survival function for progressive disease state was based on the exponential survival function for Goss all patients using the first 40 months' data.

TABLE 18 *Results of the base-case scenario but with Weibull fitting for the BSC survival curve*

Different fitting for survival curves for BSC	Year	Imatinib		BSC		Cost per QALY
		Cost (£)	QALYs	Cost (£)	QALYs	
Exponential for BSC, Weibull for TTF	10	62,617	5.23	4,230	2.95	25,643
Weibull for BSC, exponential for TTF	10	56,094	4.88	4,276	2.94	26,732
Weibull for BSC, Weibull for TTF	10	62,974	5.15	4,271	2.92	26,315

TABLE 19 *Results of the base-case scenario but with different fitting for TTF curves*

Different fitting for survival curves for TTF	Year	Imatinib		BSC		Cost per QALY
		Cost (£)	QALYs	Cost (£)	QALYs	
Exponential for BSC (higher hazard at 0.0365 for TTF)	10	56,146	4.98	4,230	2.98	25,859
Exponential for BSC (higher hazard at 0.0475 for TTF)	10	46,150	4.57	4,222	2.94	25,710
Exponential for BSC (lower hazard at 0.02565 for TTF)	10	70,811	5.58	4,218	2.91	24,948

TABLE 20 *Results of the sensitivity analysis by fitting a Weibull survival curve for survival of Goss selected patient group*

Year	Imatinib		BSC		Cost per QALY
	Cost (£)	QALYs	Cost (£)	QALYs	
2	30,353	1.72	2,371	1.24	58,671
3	39,422	2.35	3,067	1.50	42,965
5	49,500	3.15	3,632	1.68	31,057
10	56,018	3.72	3,773	1.74	26,427

The hazard for TTF used in the model was based on the exponential curve extrapolation from 70 weeks of data. Survival function for progressive disease state was based on the Weibull survival function for Goss selected patients group.

TABLE 21 *Results of the sensitivity analysis by fitting an exponential survival curve for survival of Goss selected patient group*

Year	Imatinib		BSC		Cost per QALY
	Cost (£)	QALYs	Cost (£)	QALYs	
2	31,494	1.77	2,423	1.13	45,533
3	39,441	2.38	2,917	1.37	36,245
5	50,017	3.35	3,456	1.62	27,022
10	54,483	4.05	3,720	1.71	21,708

The hazard for TTF used in the model was based on the exponential curve extrapolation from 70 weeks of data. Survival function for progressive disease state was fitted using an exponential survival function based on Goss selected patients group.

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 TTF survival curve). When extrapolated, this generated a large proportion of patients in the progressive disease state who exhibited prolonged survival. This large number of long-term survivors contrasted with the control arm, where patients in the progressive disease state were associated with much poorer survival probability.

This incompatibility could result from at least three non-exclusive explanations:

1. The progressive disease state after treatment failure with imatinib differs from the

TABLE 22 *Results of the sensitivity analysis by fitting different parametric models for TTF*

		Imatinib		BSC		
Four-state model (Allowing for a switch to 600-mg dose)	**Year**	**Cost (£)**	**QALYs**	**Cost (£)**	**QALYs**	**Cost per QALY**
Based on Goss all patients (40 months) (hazard at 0.0204)	10	56,146	4.98	4,230	2.98	25,859
TTF Weibull fitting (hazard for progress varies with time)	10	63,830	5.28	4,240	2.98	25,909
TTF exponential fitting (hazard for progress at 0.0365)	10	56,266	4.98	4,225	2.96	25,724

TABLE 23 *Results of the sensitivity analysis by fitting different parametric models for TTF (no switching from 400 to 600 mg in the model)*

		Imatinib		BSC		
Three-state model (Not allowing for a switch to 600-mg dose)	**Year**	**Cost (£)**	**QALYs**	**Cost (£)**	**QALYs**	**Cost per QALY**
TTF Weibull fitting (hazard for progress varies with time)	10	46,513	4.72	4,214	2.92	23,500
TTF exponential fitting (hazard for progress at 0.0365)	10	41,345	4.50	4,213	2.92	23,547

progressive disease state in the patients never treated with imatinib (i.e. they have better survival probability).
2. The control arm patients had a worse survival probability than the imatinib arm patients at the start of treatment (i.e. the patients were not comparable between the two arms).
3. Erroneous extrapolation beyond the observed data occurred, especially in the TTF and overall survival curves in the imatinib arm.

Explanation (1) is unlikely since an increase in tumour load (from start of treatment) greater than 50% 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 who 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 using a more suitable historical control group) resulted in less attractive estimates of the ICER of imatinib relative to BSC. According to the Modified-B Novartis model, the estimated cost per QALY was £85,224 (range £51,515–98,889) after 2 years, £41,219 (£27,331–44,236) after 5 years, and £29,789 (£21,404–33,976) after 10 years. The results from the new Birmingham model were also within the range of estimates from the Modified-B Novartis model.

Chapter 6
Discussion

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 needed 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 have yet to mature and the trials that were available for assessment principally focused on dosage and safety. Thus, the relative effectiveness of imatinib in the treatment of unresectable and/or metastatic GIST has 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 by Goss and colleagues,[63] which included retrospective KIT 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 pre-dated 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 to arrive at an estimate of the cost-effectiveness of imatinib. This report assessed the model developed by Novartis and modifications were made in response to identified major shortcomings in the original Novartis model. In addition, an alternative model for cost-effectiveness was proposed.

Major results

Tumour response

Evidence from published uncontrolled trials involving 187 patients, and from abstracts reporting similar uncontrolled trials involving 1700 patients, indicates 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 may 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. In addition, 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.

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 whether and how 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 and

co-workers,[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 die soon after diagnosis, with a median survival of about 12 months. A review of prognostic studies confirmed this gloomy prognosis, but also showed that it was not homogeneous to all such patients. Although a large number of patients with advanced GIST die within a few years of diagnosis, 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,[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. DeMatteo[22]) that describe disease status variably as recurrent (local or otherwise), metastatic or unresectable (or resection incomplete), that are based on diagnoses that did not include the 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 historical cases. Since no direct evidence was available, we used a modelling approach, and concluded that patients in the imatinib trial (CSTIB2222[60]) 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 and colleagues.[63] [Academic in confidence data removed.] This group of patients in the Goss study had histologically confirmed GIST and were cKIT positive, and details of demography were similar to patients in the imatinib trial.

Quality of life

Anecdotal evidence[72–74] (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, quality of life measures have not been reported for patients with GIST and the impact of imatinib on patient quality of life is uncertain. The Demetri trial[26] provided data showing that after imatinib treatment patients recorded an improvement in ECOG score (a measure of functional capacity in everyday life tasks). In the absence of results for a control group, it must be assumed that these changes were imatinib rather than time dependent. The industry 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 quality of life (EQ-5D). This exercise provides what may be reasonable estimates of quality of life for imatinib-treated and control GIST patients; however, because it was rooted in a questionnaire addressed to clinicians (rather than patients), of whom only three out of nine responded, these estimates must be viewed with some caution and their uncertainty adds to the difficulty in determining the effectiveness of imatinib. It is possible that serious long-term adverse events may 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.

Cost-effectiveness

The structure of the industry 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 TTF data and the assumed disease prognosis for the progressive state (i.e. the same survival probability as a patient with progressive disease in the control arm), there was a disproportionate number of survivors in the imatinib arm; and (2) it used a

possibly biased survival curve for patients in the control arm.

The Novartis model was modified by using a more valid estimate of survival probability for patients in the 'progressive state' and using the TTF to determine the proportion of patients moving into the progressive state through time in the imatinib arm. The results of the 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 that 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 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.

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 data from a short follow-up period are 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 TTF 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 ongoing uncontrolled trials will only partially address these problems, and it seems that no data on the quality of life of 'control' patients will ever become available, as RCTs to determine the effectiveness of imatinib are unlikely to be undertaken.

The scope of this report was limited to the analysis of effectiveness and cost-effectiveness of imatinib for treatment of patients with unresectable and/or metastatic KIT-positive GISTs. However, other aspects may impact on treatment outcomes. 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 the latitude implicit both in the judgement of 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 the most effective time-point in disease progression for the 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 the relative effectiveness of 400 and 800 mg per 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 recurrence at 48 months.[75] If the data from this small study (n = 48) are found to be typical, this means that a large proportion of patients with GIST initially treated with complete surgical resection would 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 preoperatively or postoperatively 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-S0132, principal investigator B Eisenberg, Lebanon, 2002, and ACOSOG-Z9000, principal investigator R DeMatteo, New York, 2003).

Experimental evidence indicates that mutation of the *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 may be targeted for therapy. Currently, several drugs in various stages of development and clinical trials are being considered as alternatives and/or supplements of imatinib therapy. For example, an abstract (and a website 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 detected 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 both the well-being of the patient and survival are of paramount importance in patients with advanced malignant disease, estimates of patient-centred quality of life and adverse events should also be measured as a matter of course.

Conclusions

Evidence from uncontrolled studies indicates that 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 because 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 from longer follow-up periods.

Recommendations for future research

- More emphasis should be placed on quality of life[76] in trials involving patients with advanced malignancy. Adverse events should be reported so that intertrial comparisons could be made. As indicated by the increase in grade 3 adverse events with longer term use of imatinib reported in the industry submission, 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 disease. Most are KIT-positive GIST, but a small proportion are KIT negative. Patients may have undergone a number of surgical procedures and other treatments, may succumb to the disease quickly or may survive for many months. Added to this, GIST can affect all parts of the gastrointestinal tract; therefore, the symptoms and consequences of the disease can be many and varied depending on the disease site. Subgroup analysis of which, if any, patient types have a better or worse response to imatinib is needed. 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 for which patients should be on imatinib, the dose (i.e. whether it is 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 be forthcoming, and ongoing trials on adjuvant therapy in patients with primary disease may 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.

Acknowledgements

We would like to thank the four peer reviewers for commenting on the manuscript and Novartis for providing a copy of an unpublished paper. We also thank Dr DSA Sanders (Senior Lecturer in Pathology, Honorary Consultant Histopathologist) for initial advice regarding the pathology of GIST and Ann Setser, BSN (Medical Nurse Consultant, Office of the Associate Director, Cancer Therapy Evaluation Programme) for advice on CTC. Adrian Boulton and Rebecca Mason provided secretarial support. Dr Fujian Song, as the senior reviewer, takes the main responsibility for any errors.

Contribution of authors

Jayne Wilson (Systematic Reviewer) and Fujian Song (Reader in Research Synthesis) developed and commented on the review protocol.
Anne Fry-Smith (Information Specialist) designed the search strategies and searched the electronic databases. Jayne Wilson (Systematic Reviewer) and Martin Connock (Systematic Reviewer) reviewed effectiveness studies. Fujian Song and Martin Connock reviewed prognostic studies. Fujian Song and Martin Connock assessed and modified the Novartis model. Guiquing Yao (Research Fellow in Health Economics) and James Raftery (Director, Health Economics Facility) developed the new Birmingham model. Jayne Wilson, Martin Connock and Fujian Song wrote the report. David Peake (Consultant in Clinical Medicine) provided clinical advice. All authors commented on the draft manuscript.

Publication information

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.

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Appendix 1

Immunohistochemical demonstration of KIT

Method

Routine identification of KIT (CD117)-positive GISTS is made almost exclusively by using immunohistochemical test procedures. Test use probably exceeds that implied by the incidence of GIST 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 perform it, in which case samples would be likely to be sent to a large centre that holds the appropriate reagents and has more extensive experience.

It is unlikely that the test for KIT would be carried out in isolation; rather, a raft of immunological techniques would be used, including tests for CD34, S100 (neural crest antigen), desmin and smooth-muscle actin.

The KIT immunohistochemical 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 KIT in the tissue section (*Figure 17*). 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 KIT protein; then, biotinylated secondary antibody specific for the type of primary antibody used 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 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 KIT), blocking procedures are often used to eliminate these. Such sites may be considered unusual in alimentary tissue and blocking may be omitted. Sections tested are likely to contain KIT-positive mast cells and these act as an internal positive control; alternatively, an external positive control may be included in the tissue block.

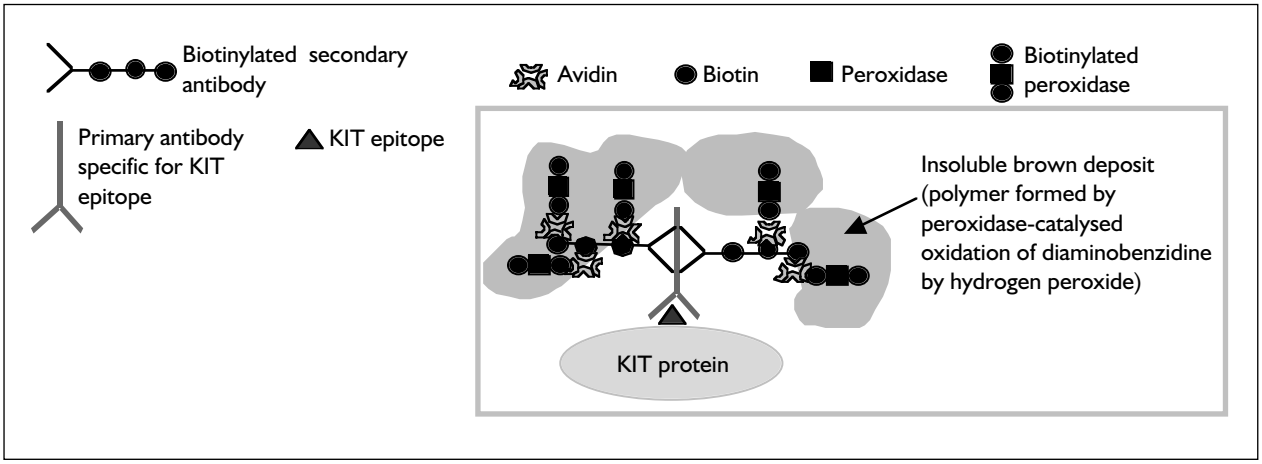

FIGURE 17 *Dye deposition at sites of KIT tissue section*

Because KIT epitopes may be masked and initially undetectable by the primary antibody, some workers use epitope retrieval procedures before the application of the immunohistochemical test. These may 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 KIT are commercially available. These have been used in research and have not generated wholly concordant results in the hands of different researchers.

Interpretation and quality assurance

A pathologist interprets sections submitted to an immunohistochemical test for KIT visually. The use of objective densitometry methods would be unlikely. A typical subjective three-point scale used to interpret a test for KIT positivity might be 'positive', 'problematic' or 'negative'. Problematic samples may 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.[77]

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 quality control, which determines the degree to which 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 immunohistochemical test for KIT, but this is unlikely.

Quality assurance for immunocytochemistry; approved guideline,[78] published by the National Committee for Clinical Laboratory Standards (NCCLS), provides general guidelines for performing immunocytochemical procedures.

Result of KIT test and subsequent implementation of imatinib treatment

The limited available evidence indicates that interlaboratory and interobserver reproducibility of immunohistochemical tests in general may be limited (e.g. research and immunohistochemical quality assessment data relevant to KIT testing indicates that test results may vary from laboratory to laboratory). False-negative test results (KIT 'activated cells not immunoreactive'[79])[17] may be obtained for many potential reasons. In view of the negligible cost of the immunohistochemical test for KIT relative to the high cost of imatinib treatment, the lack of alternative effective treatment options for non-resectable or metastatic KIT-positive GIST, and the significant possibility of error in the immunohistochemical test, it would be sensible for the immunohistochemical 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 immunohistochemical reaction for CD117 as the sole determinant of whether a patient may benefit from the putative effectiveness of imatinib. These include the following.

- 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 KIT driven CD117-positive tumours.[80,81]
- It is possible that some mutations in the *kit* oncogene that drive transformation may alter the CD117 protein sufficiently for it to be no longer recognised by the antibodies used for the immunohistochemical test, or other factors may be responsible for the lack of KIT immunoreactivity in KIT-'activated' cells.[17,79]
- The literature indicates that antigen retrieval of CD117, and therefore its demonstration by immunohistochemistry, may depend strongly on the particular procedure adopted. Further, opinion is divided as to whether or not epitope retrieval should be attempted.
- CD117 immunohistochemical responses of GISTs may vary according to the commercial polyclonal antibody preparation used.

- There is a lack of objective criteria for judgement of CD117-positivity. Although the presence of CD117-positive mast cells in gastrointestinal tissue affords a convenient and probably consistently staining positive control, the intensity of staining and its distribution (e.g. membrane-associated, diffuse cytoplasmic or punctate cytoplasmic) in tumour cells vary, making arbitrary demands on interpretation.

Interobserver and interlaboratory consistency and quality control of immunohistochemical tests for CD117[82] (and other tumour markers[83]) have not been widely practised or investigated.[84] One study,[85] carried out on the Ki67 marker (used as an index of proliferative activity), reported considerable variation between observers and laboratories, a result that points to the desirability that quality controls should be implemented in circumstances where the test result may determine eligibility for potentially effective but expensive therapy.

Appendix 2

Search strategy details

Effectiveness of imatinib for treating GISTs

MEDLINE (Ovid) 1966 to week 3 April 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)

EMBASE (Ovid) 1980 to week 16 2003

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)

CINAHL (Ovid) 1982 to week 3 April 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)

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

PubMed 1966 to 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$)

ISI SCI Search (Web of Science) 1981 to April 2003

The searches were undertaken in three 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

MEDLINE (Ovid) 1966 to Week 3 April 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)

EMBASE (Ovid) 1980 to week 17 2003

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)

CINAHL (Ovid) 1982 to week 3 April 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

MEDLINE 1966 to week 3 April 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)

EMBASE (Ovid) 1980 to week 17 2003

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)

CINAHL 1982 to week 3 April 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

MEDLINE 1966 to week 4 April 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:

42 randomized controlled trial.pt. (173090)
43 controlled clinical trial.pt. (62778)
44 randomized controlled trials/ (28135)
45 random allocation/ (47999)
46 double blind method/ (73226)
47 single blind method/ (7177)
48 or/42-47 (293764)
49 (animal not human).sh. (2662788)
50 48 not 49 (279480)
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)

EMBASE (Ovid) 1980 to week 19 2003

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)
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)

ISI SCI Search (Web of Science) 1981 to May 2003

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

PubMed 1966 to 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.

Cochrane Library (CENTRAL) 2003 Issue 2

Sets 1–41 of the MEDLINE strategy above were repeated.

Economic evaluation/model

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)
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)

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 3

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)

.....

How diagnosed .....

No. patients

intervention .....

control .....

Age

intervention .....

control .....

Percentage males

intervention .....

control .....

Stage of disease

Unresectable primary tumour .....

Metastatic .....

Recurrence .....

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 4

York CRD quality criteria and hierarchy of evidence

Checklists for quality assessment of included studies

From the York CRD handbook[30] (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

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 subseries are being made, was there a sufficient description of the series and the distribution of prognostic factors?

Checklist for assessing economic evaluations

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 5

Excluded studies

TABLE 24 *Potential imatinib studies excluded at stage 2 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):219–24.	Not GIST
Casper ES. Gastrointestinal stromal tumors. *Curr Treat Options Oncol* 2000;**1**:267–73.	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. *Clin Cancer Res* 2002;**8**:3034–8.	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 M, van Oosterom AT, 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**:150–7.	Not GIST
Goss GA, Rubin BP, 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. *Dis Colon Rectum* 1999;**42**:1296–9.	Primary disease
Hemming AW, Langham MR, Reed AI, van der Werf WJ, Howard RJ. Resection of the inferior vena cava for hepatic malignancy. *Am Surg* 2001;**67**:1081–7.	Rare occurrence
Hill MA, Mera R, Levine EA. Leiomyosarcoma: a 45-year review at Charity Hospital, New Orleans. *Am Surg* 1998;**64**: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**:83–7.	Review/treatment guidelines
Klomp HJ, Zornig C. Sarcoma of the gastrointestinal tract. *Langenbecks Arch Surg* 1990; **375**:235–8.	Primary disease
Lev D, Kariv Y, Issakov J, Merhav H, Berger E, Merimsky O, *et al*. Gastrointestinal stromal sarcomas. *Br J Surg* 1999;**86**:545–9.	Prognosis
Miquel PJ, Martin DA, Martinez ME, Gonzalez-Palacios J, Sanjuan BA, Boixeda DM. Atypical colonic stromal tumor. *Gastroenterol Hepatol* 2001;**24**:339–42.	Atypical disease
Muler JH, Baker L, Zalupski MM. Gastrointestinal stromal tumors: chemotherapy and imatinib. *Curr Oncol Rep* 2002;**4**: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**:J269–78.	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**:186–9.	Primary disease
Patel SR, Benjamin RS. Management of peritoneal and hepatic metastases from gastrointestinal stromal tumors. *Surg Oncol* 2000;**9**: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**:659–62.	Primary disease

continued

TABLE 24 *Potential imatinib studies excluded at stage 2 of inclusion process (cont'd)*

Study	Reason for exclusion
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). *Eur J Cancer* 2002;**38** Suppl 5:S60–5.	PET analysis
Zornig C, Klomp HJ, Thoma G, Weh HJ, Schroder S. Primary gastrointestinal sarcomas – a report of 21 cases. *Onkologie* 1992;**15**:20–4.	Prognosis

TABLE 25 *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. *Surg Endosc* 2000;**14**:524–6.	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**:219–24.	Not GIST
Casper ES. Gastrointestinal stromal tumors. *Curr Treat Options Oncol* 2000;**1**:267–73.	Review
Catena F, Pasqualini E, Campione O. Gastrointestinal stromal tumors: experience of an emergency surgery department. *Dig Surg* 2000;**17**:503–507.	Not effectiveness
Chambonniere M-L, Mosnier-Damet M, Mosnier J-F. Expression of microtubule-associated protein tau by gastrointestinal stromal tumors. *Hum Pathol* 2001;**32**:1166–73.	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. *Rev Med Interne* 2002;**23**:499–507.	Pathological description
Correa P. Gastric neoplasia. *Curr Gastroenterol Rep* 2002;**4**:463–70.	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. *Clin Cancer Res* 2002;**8**:3034–8.	Approval summary
DeMatteo RP, Heinrich MC, El Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: before and after STI-571. *Hum Pathol* 2002;**33**:466–77.	Review
Dougherty MJ, Compton C, Talbert M, Wood WC. Sarcomas of the gastrointestinal tract. Separation into favorable and unfavorable prognostic groups by mitotic count. *Ann Surg* 1991; **214**:569–74.	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 Invest* 2002;**20**:605–12.	Prognosis
Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, *et al*. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002;**33**:459–65.	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. *Med Pediatr Oncol* 2003;**40**:338–9.	Atypical case study
Goss GA, Rubin BP, 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. *Dis Colon Rectum* 1999; **42**:1296–9.	Primary disease

continued

TABLE 25 *Excluded alternative treatments at stage 2 (n = 64) (cont'd)*

Paper	Reason for exclusion
Hatch KF, Blanchard DK, Hatch GF, Wertheimer-Hatch L, Davis GB, Foster RS, *et al*. Tumors of the appendix and colon. *World J Surg* 2000;**24**:430–6.	Review
Howe JR, Karnell LH, Scott-Conner C. Small bowel sarcoma: analysis of survival from the National Cancer Data Base. *Ann Surg Oncol* 2001;**8**:496–508.	Prognosis
Hwang ES, Gerald W, Wollner N, Meyers P, LaQuaglia MP. Leiomyosarcoma in childhood and adolescence. *Ann Surg Oncol* 1997;**4**:223–7.	Prognosis
Joensuu H, Fletcher C, Dimitrijevic S, Silberman S, Roberts P, Demetri G. Management of malignant gastrointestinal stromal tumours. *Lancet Oncol* 2002;**3**:655–64.	Imatinib treatment
Judson I. Gastrointestinal stromal tumours (GIST): biology and treatment. *Ann Oncol* 2002; **13**(Suppl 4):287–9.	Review
Katai H, Sasako M, Sano T, Maruyama K. Surgical treatment for gastric leiomyosarcoma. *Ann Chir Gynaecol* 1998;**87**:293–6.	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 J Surg* 1991;**15**:771–6.	Primary disease
Kwon SJ. Surgery and prognostic factors for gastric stromal tumor. *World J Surg* 2001;**25**:290–5.	Primary disease
Le Cesne A. C-kit and GIST: rational use of Glivec in gastrointestinal stromal tumors. *Ann Pathol* 2002;**22**(Special Issue 1):S1–4.	Review
Levitzki A. Tyrosine kinases as targets for cancer therapy. *Eur J Cancer* 2002;**38** Suppl 5:S11–18.	Review
Miettinen M, El Rifai W, Sobin HL, Lasota J. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. *Hum Pathol* 2002;**33**:478–83.	Review
Miettinen M, Majidi M, Lasota J. Pathology and diagnostic criteria of gastrointestinal stromal tumors (GISTs). *Eur J Cancer* 2002;**38**:S39–51.	Review
Mihssin N, Moorthy K, Sengupta A, Houghton PWJ. Gastric stromal tumours: a practical approach. *Ann R Coll Surg England* 2000;**82**:378–82.	Primary disease
Montes JAR, Tellez LGS, Martinez JL, de Lis SF, Martin LGS. Malignant stromal tumors of the stomach. *Hepatogastroenterology* 1998;**45**:1918–21.	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**:66–74.	Prognosis
Muler JH, Baker L, Zalupski MM. Gastrointestinal stromal tumors: chemotherapy and imatinib. *Curr Oncol Rep* 2002;**4**:499–503.	Review
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**:186–9.	Primary disease
Papagrigoriadis S, Papadopoulou P, Kolias V, Panagiotidis H, Loizou M. Gastrointestinal leiomyosarcomas: experience of 14 cases and review of published reports. *Eur J Surg* 1998; **164**:693–6.	Primary disease
Peiper M, Schroder S, Zornig C. Stromal sarcoma of the stomach – a report of 20 surgically treated patients. *Langenbecks Arch Surg* 1998;**383**:442–6.	Primary disease
Peitgen K, Walz MK, Schmidt U, Hoederath A, Wilke H, Eigler FW. Gastric leiomyosarcoma – clinical, morphological and therapeutic results. *Med Klin* 1996;**91**:123–30.	Primary disease
Pidhorecky I, Cheney RT, Kraybill WG, Gibbs JF. Gastrointestinal stromal tumors: current diagnosis, biologic behavior, and management. *Ann Surg Oncol* 2000;**7**:705–12.	Review
Pierie J-P, Choudry U, Muzikansky A, Beow YY, Souba WW, Ott MJ, *et al*. The effect of surgery and grade on outcome of gastrointestinal stromal tumors. *Arch Surg* 2001;**136**:383–9.	Prognosis
Plaat BE, Hollema H, Molenaar WM, Torn Broers GH, Pijpe J, Mastik MF, *et al*. Soft tissue leiomyosarcomas and malignant gastrointestinal stromal tumors: differences in clinical outcome and expression of multidrug resistance proteins. *J Clin Oncol* 2000;**18**:3211–20.	Prognosis

continued

TABLE 25 *Excluded alternative treatments at stage 2 (n = 64) (cont'd)*

Paper	Reason for exclusion
Plappert G, Heymer T, Schroeder P. Gastrointestinal stromal tumour: individualized treatment for a special tumour class. *Deutsche Medizinische Wochenschrift* 2001;**126**:172–5.	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**:807–12.	Primary disease
Ray-Coquard I, Le Cesne A, Michallet V, Boukovinas I, Ranchere D, Thiesse P, *et al*. Gastro-intestinal stromal tumors: news and comments. *Bull Cancer* 2003;**90**:69–76.	Review incidence data – 2003
Roberts PJ, Eisenberg B. Clinical presentation of gastrointestinal stromal tumors and treatment of operable disease. *Eur J Cancer* 2002;**38** Suppl 5:S37–8.	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 Res* 2001;**61**(22):8118–8121.	Diagnosis
Sanders L, Silverman M, Rossi R, Braasch J, Munson L. Gastric smooth muscle tumors: diagnostic dilemmas and factors affecting outcome. *World J Surg* 1996;**20**:992–5.	Prognosis
Silberman S, Joensuu H. Overview of issues related to imatinib therapy of advanced gastrointestinal stromal tumors: a discussion among the experts. *Eur J Cancer* 2002; **38** Suppl 5:S66–9.	Review
Spira AI, Ettinger DS. The use of chemotherapy in soft-tissue sarcomas. *Oncologist* 2002;**7**:348–59.	Review
Sturgeon C, Chejfec G, Espat NJ. Gastrointestinal stromal tumors: a spectrum of disease. *Surg Oncol* 2003;**12**:21–6.	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). *Eur J Cancer* 2002;**38** Suppl 5:S60–5.	Diagnosis
Walsh RM, Ponsky J, Byody F, Matthews BD, Heniford BT. Combined endoscopic/laparoscopic intragastric resection of gastric stromal tumors. *J Gastrointest Surg* 2003;**7**:386–92.	Primary disease
Zornig C, Klomp HJ, Thoma G, WEH HJ, Schroder S. Primary gastrointestinal sarcomas – a report of 21 cases. *Onkologie* 1992;**15**:20–4.	Prognosis

TABLE 26 *List of excluded prognosis studies (no survival curves available)*

Adani GL, Marcello D, Sanna A, Mazzetti J, Anania G, Donini A. Gastrointestinal stromal tumours: evaluation of biological and clinical current opinions. *Chir Ital* 2002;**54**:127–31.

Antonini C, Forgiarini O, Chiara A, Briani G, Sacchi G. Clinico-pathological study of eleven gastrointestinal stromal tumors. *Gastroenterology International* 2001;**14**: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**:2441–6.

Carrillo R, Candia A, Rodriguez-Peralto JL, Caz V. Prognostic significance of DNA ploidy and proliferative index (MIB-1 index) in gastrointestinal stromal tumors. *Hum Pathol* 1997;**28**:160–5.

Dougherty MJ, Compton C, Talbert M, Wood WC. Sarcomas of the gastrointestinal tract. Separation into favorable and unfavorable prognostic groups by mitotic count. *Ann Surg* 1991;**214**:569–74.

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continued

TABLE 26 *List of excluded prognosis studies (no survival curves available) (cont'd)*

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Appendix 6

Quality assessment trial data

TABLE 27 *Quality assessment*

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 subseries was there a sufficient description of the series and distribution of prognostic factors?	Comments
Demetri *et al.*, 2002[26]	Unsure	Yes	Yes	Yes for response and adverse events, no for survival	Yes, RECIST and CTC, no blinding	NA	
van Oosterom *et al.*, 2002[31]	Unsure	Yes	Unsure; difficult to tell, but all patients had evidence of progression	Yes for response and adverse events, no for survival	Yes, CTC and tumour response, no blinding	NA	
Judson *et al.*, 2001[47]	Unsure	Yes	Unsure	Yes	Yes, WHO criteria used for response, unsure blinding	NA	Unsure as to the diagnosis of GIST; 21 retrospectively diagnosed as GIST from histological analysis
Eilber *et al.*, 2000[54]	Unsure	No	Yes, all had metastatic spread in the peritoneum	Yes	Yes, objective criteria used, unsure blinding	NA	All described as having STS, but description of patient characteristics limited
Ryan *et al*[46]	Yes	Yes	Yes	Yes	Yes, unsure about blinding	No, insufficient comparison between patients on imatinib and those not	
De Pas *et al.*, 2003[18]	Unsure	Unsure	Unsure	Yes	Yes, used WHO criteria for tumour response, but do not give reference	NA	Authors admit likely selection bias

continued

TABLE 27 *Quality assessment (cont'd)*

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 subseries was there a sufficient description of the series and distribution of prognostic factors?	Comments
Rajan *et al.*, 2001[48]	Unsure	Yes	Yes	Yes	Yes, used WHO criteria for tumour response, but do not mention any blinding	NA	11 patients had gastrointestinal leiomyosarcoma metastatic to the liver
Mavligit *et al.*, 1995[49]	Unsure	Yes	Unsure	Yes	Unsure (basis of measures not described clearly)	NA	Patients diagnosed as gastrointestinal leiomyosarcoma metastatic to the liver. Individual patient information provided
Chen *et al.*, 1998[50]	Unsure	Yes	Yes	Yes	Yes, survival, mortality	NA	Patients diagnosed with leiomyosarcoma with metastatic liver disease (1984–1995)
Bramwell *et al.*, 2002[51]	Unsure	Yes	No	Yes	Yes, CTC, tumour response measures described, no blinding	NA	Described as GIST and non-GIST, no details given
Edmonson *et al.*, 2002[52]	Unsure	Yes	Unsure; little detail given	Yes	Unsure, survival measured, other outcomes described, no blinding	NA	Unsure as to diagnosis, patients had "gastrointestinal stromal tumour"

continued

TABLE 27 *Quality assessment (cont'd)*

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 subseries was there a sufficient description of the series and distribution of prognostic factors?	Comments
Patel *et al.*, 2001[53]	Unsure	Yes	Unsure	Yes	No, response and adverse events described only, no blinding	NA	Unsure as to diagnosis, patients had gastrointestinal leiomyosarcoma
Carson *et al.*, 1994[55]	Unsure	Yes	No, both primary and advanced disease included	Yes	Unsure, outcomes described only, no blinding	NA	Unsure as to diagnosis, patients had leiomyosarcoma or leiomyoblastoma

Appendix 7

Adverse events

Only ten of the trials report adverse events (*Table 28*). Of these, both imatinib trials used CTC version 2.0, while one trial[48] used CTC version 3.0. Four trials used CTC without giving the version number.[46,47,51,53] The remaining trials[49,52,54] just describe adverse events. Because of this variability in reporting it is very difficult to cross-compare studies. To add to this difficulty, although both imatinib trials used the same CTC version, they both chose to report grades in combination: Demetri and colleagues[26] reported grades 3 and 4 combined, whereas van Oosterom and colleagues[32] combined grades 2 and 3. 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', it is very difficult to know what type of event occurred and to cross-compare the two trials. In a statement to the authors, the NCI, which administers 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 and colleagues[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 (seven patients) and neutropenia (seven patients). The number of adverse events at grades 3 and 4 appears to increase over time, with the number of adverse events at grades 3 and 4 increasing to 52.4%.[61] Their nature also appears to change, with more serious gastrointestinal events being reported. Overall adverse events appear to be more common in the van Oosterom trial,[32] but with the grades inconsistently lumped together it is very difficult to make sense of the data.

Other treatment

Event reporting is much less ambiguous, in that most trials that used grades did not combine them. In the trial by Judson and colleagues,[47] 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 tended to suffer from haematological problems, in particular leucopenia, neutropenia and anaemia. In the two trials in which patients were treated with chemoembolisation, pain seems to have been significant in a number of patients. Bramwell and colleagues[51] found that alopecia was the most common adverse event, whereas Edmonson and colleagues[52] described toxicity as being significant, with 33% of patients experiencing grade 3 vomiting. Finally, Patel and co-workers,[53] using Gemcitabin, 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 ($n = 7$) 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[24] also suffered haematological adverse effects, but again in much greater numbers; for example, 58% had grade 3 or 4 leucopenia/neutropenia, 43% had grade 3 or 4 thrombocytopenia and 37% had grade 3 or 4 anaemia.[24] Could an element of disease specificity be the cause here? More serious adverse events involving the gastrointestinal 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 28 *Adverse events recorded in published imatinib and alternative treatment trials*

Study	Adverse events		
Demetri *et al.*, 2002[26,61] 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 15 October 2001 (median follow-up 288 days)	(n = 147) Analysis 27 August 2002 (additional 316 days)
	CTC grade	3 and 4	3 and 4
	Any adverse event with suspected relation to study drug	21%	
	Gastrointestinal		
	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%	
	Leucopenia	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% as grade 4, giving a total of adverse events at grades 3 and 4 of 52.4%		
Van Oosterom *et al.*, 2002[32] CTC 2.0 GIST (n = 40) [imatinib]	These were measured using CTC version 2.0. Adverse events (at 8 months of therapy, n = 40):		
	Gastrointestinal		
	Nausea/vomiting (grade 2–3)	25%	
	Anorexia (grade 2)	15%	
	Diarrhoea (grade 2)	12.5%	
	Oedema		
	Periorbital 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%	

continued

TABLE 28 *Adverse events recorded in published imatinib and alternative treatment trials (cont'd)*

Study	Adverse events
Judson *et al*., 2001[47] CTC STS retrospectively tested for GIST (21/94 GIST) [CAELYX vs doxorubicin]	CTC grade 3 and 4 reported here, but the paper does document grades 1 and 2 (n = 94): Drug

Grade	CAELYX 3	CAELYX 4	Doxorubicin 3	Doxorubicin 4
Haematological				
Leucopenia	2%	0%	47%	12%
Neutropenia	4%	2%	30%	47%
Thrombocytopenia	0%	0%	2%	0%
Haemoglobin	4%	6%	5%	0%
Gastrointestinal				
Nausea	0	0%	2%	0%
Vomiting	2%	0%	2%	0%
Diarrhoea	0%	0%	2%	0%
Stomatitis (oral)	4%	0%	5%	0%
Anorexia	2%	0%	5%	0%
Infection				
Any infection	4%	0%	7%	0%
Febrile neutropenia	2%	0%	16%	0%
Dermatological				
Alopecia	2%	0%	21%	0%
Palmar–plantar erythrodysaesthesia	18%	0%	2%	0%
Pulmonary				
Cough	4%	0%	0%	0%
Shortness of breath	2%	2%	2%	2%
Flu-like symptoms				
Lethargy	6%	0%	2%	0%

Eilber *et al*., 2000[54]	There were no deaths relating to the surgical procedure or the intraperitoneal mitoxantrone. All patient deaths were due to their disease. In addition, there was no systemic toxicity from intraperitoneal mitoxantrone. Local complications (patients not given intraperitoneal therapy) include two abdominal infections and one small bowel stricture, of which one infection and one stricture required reoperation. Local complications (patients given intraperitoneal therapy) include two small bowel fistulas and two abdominal infections, of which one fistula required operation
Ryan *et al*., 2002[46]	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 owing to toxicity (n = ?)

Grade	2	3
Haematological		
Leucopenia	37%	26%
Anaemia	16%	11%
Thrombocytopenia	0	0
Neutropenia	21%	47%
Hepatic		
Bilirubin	5%	0
Alkaline phosphate	0	0
SGOT	16%	42%
SGPT	11%	53%

continued

TABLE 28 *Adverse events recorded in published imatinib and alternative treatment trials (cont'd)*

Study	Adverse events				
Rajan *et al*., 2001[48] CTC 3.0 Metastatic sarcomas (34 procedures) (% per procedure) [chemoembolisation)	Grade	1	2	3	4
	Gastrointestinal				
	Nausea	35%	15%	12%	0
	Vomiting	18%	26%	0	0
	Haematological				
	Haemoglobin	56%	26%	0	0
	White blood cells	3%	0	0	0
	Platelets	0	0	3%	0
	Coagulation	9%	6%	0	3%
	Hepatic				
	Bilirubin	0	3%	9%	3%
	GGT/ALK	38%	18%	21%	3%
	AST	15%	0	0	0
	ALT	9%	3%	0	0
	Other				
	Pain	3%	6%	9%	4
	Fever	6%	4	3%	0
	Fatigue	15%	6%	9%	6%
	Weight loss	29%	3%	0	0
	Infection	0	6%	6%	0
	Metabolic	3%	0	0	0
	Neurological	0	0	3%	0
Mavligit *et al*., 1995[49] Events measured by hepatic enzymes and pain assessment Leiomyosarcoma ($n = 14$) [chemoembolisation]	All patients experienced severe right upper quadrant pain after the treatment procedure. It was uniformly associated with significant elevation of hepatic enzymes, including serum aminotransferase, alkaline phosphatase and lactic dehydrogenase, which usually lasted for up to 7 days. Transient, but mild hyperbilirubinaemia (median 1.9 mg dL^{-1}, range 0.8–3.9 mg dL^{-1}) was observed in most patients				
Bramwell *et al*., 2002[51] CTC Soft-tissue sarcoma, GIST ($n = 26$) or leiomyosarcoma, non GI origin ($n = 18$) (not CD117 tested) [VX-710 + doxorubicin]	($n = 37$)				
	Grade	1	2	3	4
	Gastrointestinal				
	Nausea	51%	16%		
	Vomiting	27%	16%		
	Stomatitis	28%	14%	3%	
	Anorexia	14%	14%	3%	
	Constipation	16%	16%		
	Diarrhoea	22%	6%	3%	3%
	Cardiovascular				
	Vasodilatation	22%			
	Constitutional				
	Asthaenia	32%	35%	5%	
	Headache	32%	11%		
	Alopecia	5%	14%	19%	
	Fever	8%	19%	3%	
	Pulmonary				
	Cough	8%	19%	3%	

continued

TABLE 28 *Adverse events recorded in published imatinib and alternative treatment trials (cont'd)*

Study	Adverse events
Edmonson *et al*., 2002[52] Described Stromal tumours of GI tract (n = 21) [DTIC with mitomycin, doxorubicin, cisplatin]	Toxicity was significant, with 33% of patients experiencing grade 3 (severe) vomiting despite the use of antiemetics; this was grade 4 in one patient. 87% developed anorexia, with 8% at grade 3 intensity. One patient had grade 4 pulmonary toxicity following the fourth cycle and this was thought to be a major factor in her death. Grade 3 leucopenia occurred at some time in 42% and grade 3 thrombocytopenia was observed in 68% of patients. Transient diabetes requiring insulin occurred in one patient. Patterns of toxicity were similar for GIST and LMS
Patel *et al*., 2001[53] CTC described Soft-tissue sarcoma (n = 56) [gemcitabin]	

	Grade	(n = 56)
Gastrointestinal		
Anorexia	3	(2%)
Haematological		
Neutropenia	3 and 4	(4%)
Thrombocytopenia	3 and 4	(9%)
Anaemia	3 and 4	(4%)
ALT	3	(4%)
Cardiovascular		
Oedema		
Extremity oedema	3	(4%)
Constitutional		
Myalgias	3	(4%)
Fatigue	1 and 2	(20%)

ALK, alkaline phosphatase; ALT, alanine transaminase; AST, asparatate transaminase; GGT, γ-glutamyl transferase; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamate pyruvate transaminase.

Appendix 8

Imaging methods for monitoring disease

CT scan

The CT scan [or computed axial tomography (CAT) scan] uses X-rays and advanced computer technology to generate highly detailed cross-sectional (tomographic) images of the body. The technique can 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 it 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 to 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 the X-ray source only concentrically with a complete array of detectors that surround the patient (rotate/stationary geometry) (*Figure 18*). 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 (a photoelectrode plus a 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 in a solid, these detectors have a long path-length for collection of photons, and use a gas with a high atomic number (xenon) under pressure (8–20 atm) 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 the resolution of structures of interest. These are administered orally or intravenously.

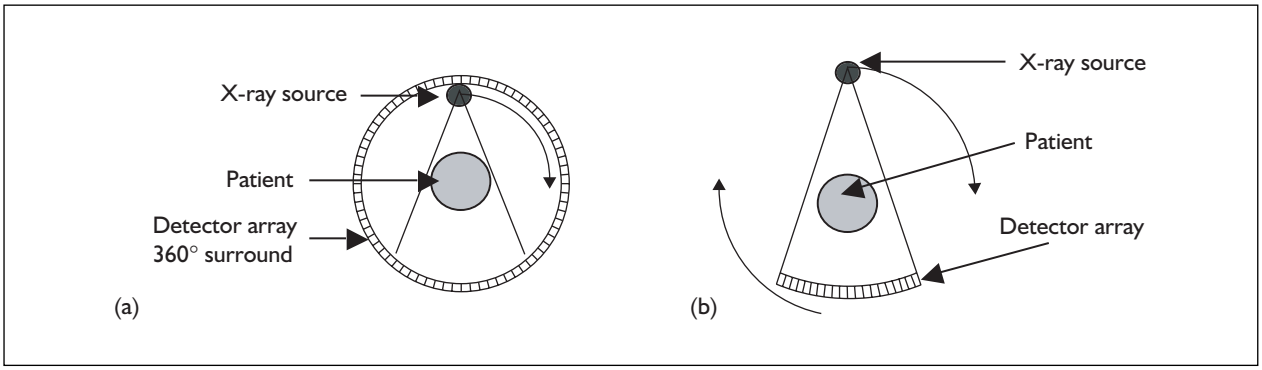

FIGURE 18 *(a) Rotate/stationary geometry, (b) rotate/rotate geometry. Adapted from URL: http://www.medcyclopaedia.com, Amersham Health (accessed July 2003)*

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.

PET scan

PET has been used to monitor the changes in tumour status that occur through time. Whereas CT and MRI provide purely morphological information, PET can indicate 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 can be compared and quantified. A recent meta-analysis[86] of non-invasive imaging methods used to screen for hepatic metastases from gastrointestinal cancers found 2-fluoro-2-deoxyglucose (FDG)-PET to be superior to contrast-enhanced CT, contrast-enhanced MRI and ultrasound methods. In contrast, a recent study of 30 consecutive patients,[87] comparing PET and dynamic enhanced MRI for the evaluation of liver metastases, found the latter to be slightly superior.

The PET technique depends on the use of the radioactive glucose analogue [^{18}F]2-fluoro-2-deoxyglucose (FDG) (*Figure 19a*), which is injected into the bloodstream. FDG is then taken up by those cells that transport and metabolise glucose. Like glucose, FDG undergoes the first reaction of glycolysis (becoming phosphorylated by action of the enzyme hexokinase), but unlike glucose the phosphorylated form of FDG [2-fluorodeoxyglucose-6-phosphate (FDGP)] (*Figure 19b*) cannot proceed through the remaining reaction steps of glycolysis. In addition, FDPG cannot be transported out of the cell and is resistant to dephosphorylation; 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 cells[7,88,89] and as a result they often take up and accumulate much more radioactive FDG than do surrounding tissues. (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.)

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) 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 for which 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 FDG is injected when the blood glucose level is stable and within a known and specified range.

The EORTC PET Study Group proposed a method of analysing PET scan results for the purposes of determining tumour status.[90] This proposal depends on several measures:

- standard uptake value (SUV)

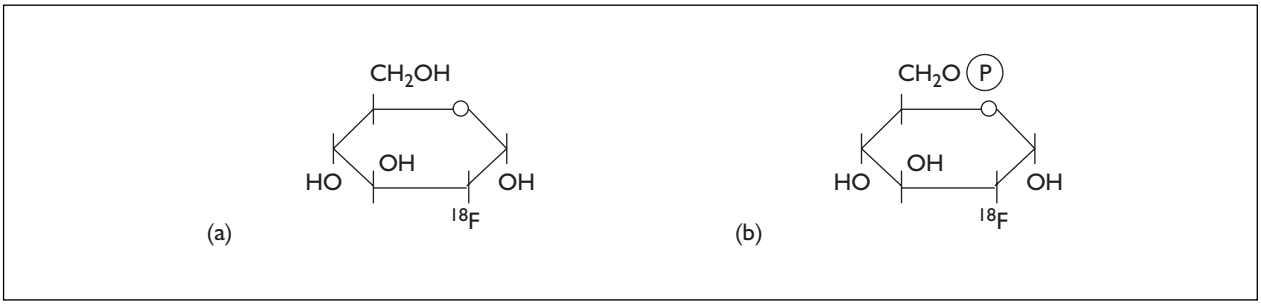

FIGURE 19 *^{18}F-labelled 2-fluoro-2-deoxyglucose, (b) ^{18}F-labelled-2-fluorodeoxyglucose-6-phosphate*

- the longest dimension of the uptake site
- the appearance of previously undetectable uptake sites.

The SUV is an estimate of FDGP accumulation at a site and is given by $(Q_t \times \text{BSA})/Q_i$, 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:

- progressive disease: ≥ 25% increase in SUV, **or** ≥ 20% increase in longest dimension, **or** appearance of at least one new lesion
- stable disease: ≤ 25% increase and ≤ 15% decrease in SUV, and ≤ 20% increase in longest dimension
- partial response: ≥ 15–25% decrease in SUV after one cycle of chemotherapy **and** >25% decrease in SUV after more than one 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 decrease in SUV of at least 25%. 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 that PET can demonstrate profound changes in glucose uptake. The term metabolic death has come into use to describe the situation where a cell mass that formerly actively accumulated FDG relative to surrounding tissues subsequently becomes indistinguishable from surrounding tissue by FDG-PET. However, without knowledge of other compensating metabolic adjustments that may 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 with the complete aerobic oxidation of glucose, cells could switch to complete (aerobic) oxidation from previous exclusive reliance on glycolysis, thereby reducing the required uptake of glucose by up to 15-fold without compromising their net energy usage and the activities (e.g. proliferation) that may depend on it. Thus, the 'metabolic death' observed in PET may be nothing of the sort, but may merely reflect 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 improved survival and quality of life. 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 the 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.[91]

Appendix 9

Imatinib treatment for advanced GIST: single case studies

TABLE 29 *Imatinib single case studies*

Study, design, patients and treatment	Outcomes
Joensuu *et al*., 2001[38] Single case study to evaluate the use of STI571 (imatinib) in a patient with metastatic GIST *No. of patients*: 1 *Date of study*: March 2000 to February 2001 *Diagnosis*: histologically confirmed GIST: CD117 immunostaining, the KIT mutation consisted of a deletion of 15 bp from exon 11 *Age and gender*: 54 years, female *Stage of disease*: metastatic GIST *Previous treatment and disease history*: presented in October 1996 with mild abdominal discomfort and a large mass in the upper abdomen. She underwent surgery at this time. Metastases: upper abdomen, excised February 1998 and September 1998. Chemotherapy: seven 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 400 mg and 900,000 u of s.c. interferon-α three times per day; still disease progression *Intervention*: imatinib 400 mg orally per day *Length of time on treatment*: 11 months to publication *Adjuvant therapy*: none *Follow-up intervals*: every 2–4 weeks *Length of follow-up*: 11 months (started March 2000 to February 2001) *Adjuvant therapy*: none described *Outcomes measured* *QoL/PM*: WHO performance status *Response*: measured by tumour size *Evaluated by*: MRI scan: liver metastases measured as the sum of the products of two perpendicular axes of each of eight large liver metastases PET scan: observed [^{18}F]FDG uptake, counted number of 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	*No. of patients 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,[26] p. 478, this patient "is still on therapy 22 months after its initiation" *Response*: *MRI* Baseline: 112.5 cm^2 Day 14: 67 cm^2 Month 1: 54 cm^2 Month 2: 42 cm^2 Month 4: 36 cm^2 Month 5.5: 33 cm^2 Month 8: 28 cm^2 Difference from baseline to month 8: 84.5 cm^2 (75% reduction) *PET* Baseline: Multiple liver metastases and increased accumulation of FDG in the right renal pelvis and ureter were seen Month 1: No abnormal intake of FDG was seen in the liver or right kidney. A finding consistent with the changed, hypodense appearance of metastases on MRI Month 2: 'Cold' areas with less uptake of FDG than in the surrounding liver parenchyma were seen at the sites of liver metastases *Immunohistochemical analysis*: at 1 and 2 months after the start of treatment, compared with pretreatment 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 patient had severe disease at presentation and severe metastastic disease 2 years before treatment with imatinib

continued

TABLE 29 *Imatinib single case studies (cont'd)*

Study, design, patients and treatment	Outcomes
Hogenauer *et al.*, 2003[39] Single case study to evaluate the use of STI571 (imatinib) in a patient with metastatic GIST *No. of patients*: 1 *Diagnosis*: GIST: CD117-positive KIT mutation at exon 11; diagnosed in 1998 *Age and gender*: 51 years, male *Stage of disease*: hepatic metastatic GIST and recurrence *Previous treatment and disease history*: primary tumour removed in 1998; no evidence of metastases at that time. November 2000: CT scan detected recurrence with hepatic and intra-abdominal spread. Subsequently, the patient received three courses of chemotherapy between January and July 2001, with combined administration of doxorubicin and ifosfamide and with docetaxel and gemcitabine. Despite this, progression occurred *Intervention*: imatinib 400 mg orally per day *Length of time on treatment*: 7 months 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	*No. of patients confirmed CD117 positive*: 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* Baseline: 454 cm^2: multiple liver metastases, confluent tumour masses in the peritoneum as well as masses in the mesentery and pelvis Month 1: 143 cm^2: histology showed groups of apoptotic tumour cells as well as viable KIT-positive tumour cells Month 5: 99 cm^2 with remaining tumour masses appearing necrotic Difference from baseline to month 5: 355 cm^2 (78% reduction) *PET* Baseline: Multiple, large, glucose-utilising lesions in the abdomen Month 1: Uptake of FDG reduced to undetectable levels Month 2: Uptake of FDG at undetectable levels *Immunohistochemical 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

continued

TABLE 29 *Imatinib single case studies (cont'd)*

Study, design, patients and treatment	Outcomes
Brooks *et al.*, 2002[40] Single case study reporting the treatment of a man with an abdominal GIST and also a brain malignancy *No. of patients*: = 1 *Date of study*: July 2001 *Diagnosis*: primary abdominal GIST: CD117 positive *Age and gender*: 75 years, male *Stage of disease*: metastatic, recurrence *Previous treatment*: surgery for primary disease *Intervention*: 800 mg imatinib per day (in two divided doses) *Length of time on treatment*: 4 months *Adjuvant therapy*: none *Follow-up intervals*: not stated *Length of follow-up*: 4 months *Outcomes measured* *QoL/PM*: ECOG performance status. *Tumour response*: CT scan, MRI	*No. of patients confirmed CD117 positive*: 1 *QoL/PM*: post-treatment performance status = 0. Not given pretreatment *Response*: authors state that there was a decrease in size of the intraabdominal sarcomatosis as well as liver metastases. MRI scan revealed complete resolution of all abnormalities, consistent with complete response in the CNS

continued

TABLE 29 *Imatinib single case studies (cont'd)*

Study, design, patients and treatment	Outcomes
Miyagawa *et al.*, 2002[41] (Letter) Case study of a man with inoperable metastatic GIST: aim of the letter was to report that the man's longstanding psoriasis had cleared up since he began treatment with imatinib *No. of patients*: 1 *Date of study*: started treatment in July 2001 *Diagnosis*: GIST: CD117 positive (exon 11) *Age and gender*: 62 years, male *Stage of disease*: inoperable metastatic *Previous treatment and disease history*: surgery for primary tumour, which had metastatic nodules in the spleen and omentum that were resected. When the patient developed recurrence he underwent surgery for these nine times between 1997 and 2001 *Intervention*: imatinib 400 mg orally per day. Dose reduced to 300 mg per day, owing 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 in July 2001) *Adjuvant therapy*: none described *Outcomes measured* *Response*: MRI scan *Adverse events*: described	*No. of patients confirmed CD117 positive*: 1 *Mortality*: patient still alive at analysis. After contacting the authors, they kindly wrote back stating that the patient had continued with imatinib with good response, but had recently died from cardiac arrest. This means that the patient had been on imatinib for approximately 2 years *Response*: MRI scan: authors state that MRI scans showed a marked reduction in GIST *Morbidity*: psoriasis cleared up *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

continued

TABLE 29 *Imatinib single case studies (cont'd)*

Study, design, patients and treatment	Outcomes
Terashima *et al.*, 2002[42] Case study of a patient with GIST, treated with imatinib *No. of patients*: 1 *Date of study*: started treatment in September 2000 *Diagnosis*: GIST: KIT positive *Age and gender*: 32 years, female *Stage of disease*: hepatic metastatic GIST *Previous treatment and disease history*: 1998 primary tumour treated with surgery. Peritoneal recurrence May 2000 and November 2000. Liver metastases August 2000 *Intervention*: imatinib 400 mg orally per day *Length of time on treatment*: 28 days *Adjuvant therapy*: none *Follow-up intervals*: unclear *Length of follow-up*: 7 weeks	*No. of patients confirmed KIT positive*: 1 *Mortality*: patient still alive at analysis *Response*: CT scan at 3 weeks showed rapid tumour shrinkage (reduction rate of 56%). Response continued at 7 weeks: reduction rate of 71%; authors evaluated the response as a 'partial response' *Adverse events*: Leucocytopenia, oedema, diarrhoea and nausea: all toxicities mild and tolerable *Note*: paper written in Japanese; information from abstract only

continued

TABLE 29 *Imatinib single case studies (cont'd)*

Study, design, patients and treatment	Outcomes
Omori *et al.*, 2002[44] Case study of a patient with GIST, treated with imatinib *No. of patients*: 1 *Diagnosis*: GIST: KIT positive *Age and gender*: 64 years, female *Stage of disease*: intraperitoneal metastatic GIST *Previous treatment and disease history*: 1998: primary tumour treated with surgery. Five 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 400 mg orally per day *Length of time on treatment*: 2 months *Adjuvant therapy*: none *Follow-up intervals*: unclear *Length of follow-up*: possibly 2 months? Unclear from abstract *Outcomes measured* *QoL*: described *Tumour response*: CT scan *Morbidity*: described *Adverse events*: described	*No. of patients confirmed KIT positive*: 1 *QoL*: improved, no further details given in abstract *Mortality*: patient still alive at analysis *Response*: two lesions estimatable on CT, reduced to 62% and 70% in size, with no new lesions found. It was evaluated by the authors as a 'partial' response *Morbidity*: hypogastric pain and low back pain disappeared, and both abdominal fullness and constipation improved symptomatically *Adverse events*: not described in abstract *Note*: paper written in Japanese; information from abstract only

continued

TABLE 29 *Imatinib single case studies (cont'd)*

Study, design, patients and treatment	Outcomes
Fujimoto *et al*., 2002[45] Case study of a patient with GIST, treated with imatinib *No. of patients*: 1 *Date of study*: started treatment in June 2001 *Diagnosis*: GIST: CD117 tested, KIT positive *Age and gender*: 59 years, male *Stage of disease*: metastatic GIST *Previous treatment and disease history*: 1996: primary tumour treated with surgery. June 2001: several new intra-abdominal tumours and liver metastases in progression *Intervention*: imatinib 400 mg 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	*No. of patients confirmed KIT positive*: 1 *Mortality*: patient still alive at analysis *Response*: after 9 months of treatment CT showed that tumours had decreased to <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 events*: not described in abstract *Notes*: paper written in Japanese, information from abstract only. Quite a substantial tumour response

Appendix 10

Ongoing studies

As imatinib was recently developed it was felt that there would be ongoing trials. The following sources were searched. Trials registers: *meta*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 on 8–9 July 2003. Unless otherwise stated, the registers were searched using the drug terms Imatinib, Glivec, Gleevec, STI571 and ST1571, and the results were 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 abstracts 3271 and 3272 (2003), 1650 (2002).

Aim of trial

Phase III trial, which is a comparison of two doses (400 mg daily and 400 mg twice daily) of imatinib in the treatment of patients with advanced gastrointestinal stromal tumours. The trial is powered to detect a 10% difference in 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 $n = 10$, side-effects $n = 5$). Toxicity data are available for 352 patients, with the most frequent side-effects being anaemia (88%), oedema, particularly periorbital oedema (67%), fatigue (60%), nausea (44%), granulopenia (32%) and skin rash (24%). Most events were mild to moderate. One patient died of drug-related neutropenic sepsis.

ASCO abstract 3272:[33] between February 2001 and February 2002, 946 patients with GIST were randomised. This abstract reports the results of a planned interim analysis conducted at 172 events. The patients' median age was 59 years, and the proportion of males was 61%. The toxicity profile is reported in abstract 1650. Median follow-up was 8.4 months. Complete response was observed in 3% and 2% with 400-mg and 800-mg doses, respectively. Median reduction in tumour load after 2, 4, 6 and 9 months was 24% versus 21%, 32% versus 30%, 34% versus 32% and 40% versus 35%, respectively. Progression-free survival estimates at 6 and 12 months are 73% versus 78% and 64% versus 69%.

Trial name

Intergroup S0033.

Data sources

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

Aim of trial

ASCO 3271:[34] randomised Phase III study comparing 400 mg daily to 400 mg 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:[34] 746 patients registered between 15 December 2000 and 1 September 2001. With a median follow-up of 14 months, 556 patients are still alive. No differences have appeared between the two doses. Response rate is 43% at 400 mg and 41% at 800 mg. Median time to response was 4–6 months. The response rate plus stable disease is 75% at 400 mg and 73% at 800 mg. Eighteen per cent have crossed over to a higher dose following progression and 4% have discontinued therapy owing to toxicity.

Trial name

ASCO Abstract 1609[36] (Judson).

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

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

Trial data
Fifty-one patients were recruited (28 GIST, 23 non-GIST), median age 55 years. All but one non-GIST patient are off the study, with most GIST patients still on treatment. Current responses are 7% CR, 25% PR, 24% DP and 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[35] (Ryu, South Korea).

Title
Efficacy of imatinib mesylate in metastatic 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 and its influence on tumour response in Korean GIST patients.

Trial data
Between June 2001 and October 2002, 33 patients were treated with imatinib 400 mg daily on days 1–28 every 4 weeks. The dose was escalated to 600 mg 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 4–26 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 owing to rapid tumour shrinkage. Activating mutations were examined; no differences in response were found between patients with and without an exon 11 mutation. Unsure whether still ongoing.

Trial name

ASCO Abstract 1444[37] (Jankilevich, 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 five institutions to determine diagnosis and treatment with imatinib.

Trial data
All 38 patients were tested for KIT, with 17 treated with imatinib. Response was evaluated in 13 patients. A complete response was reported in a 23-year-old woman with a paraovaric mass and peritoneal sarcomatosis. Seven patients had a PR, three had SD and two had DP. Responses were durable in all cases (6–8 months). Toxicity: oedema, nausea, asthenia, insomnia and mild anaemia were common. Imatinib was discontinued in one patient owing to a severe rash.

Trial name

Protocol IDs PCI-01-028, MB-NAVY-BO1-053, NCI-02-C0020 and NCI-53331, found in cancer.gov (lead investigator: Ramanathan, 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 and NCI-5340, found in cancer.gov (lead investigator: Remick, Ireland).

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

Aim of trial
Dose escalation, multicentre 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 11

Experimental studies of non-imatinib treatments for advanced GIST

TABLE 30 *Experimental studies of non-imatinib treatments*

Study, design, patients and treatment	Outcomes
Judson *et al.*, 2001[47] RCT of CAELYX and doxorubicin in patients with advanced or metastatic adult STS with the end-points of response rate, response duration and toxicity *No. of patients*: total in trial *n* = 94. Estimated GIST = 12 (24%) CAELYX and 9 (20%) doxorubicin *Date of study*: not stated; published 2001 *Diagnosis*: STS; GIST identified retrospectively from the analysis of disease site, i.e. visceral abdominal *Age and gender (all patients in trial)*: median age 52 years (range 19–80); percentage males: 48% (48/94) *Stage of disease*: advanced/metastatic *Previous treatment*: surgery: no 13%, yes (curative) 61%, palliative 20%, biopsy 6.3%; previous radiotherapy: no 71%, yes 29% *Intervention*: CAELYX vs doxorubicin (standard treatment) CAELYX: 1-hour infusion of 50 mg m^{-2} every 4 weeks Doxorubicin: 75 mg m^{-2} as a 5-minute i.v. bolus injection every 3 weeks Intended that all patients receive a total of six cycles in view of the possible cardiotoxicity of doxorubicin *Outcomes measured* *Mortality*: survival analysis *Response*: CR, PR, SD and DP. Response measured from the start of treatment to the date of documented progression, or if CR from the date of the first documentation of CR. Response had to be confirmed 4 weeks later	*No. of patients confirmed KIT positive*: not KIT tested *Mortality*: median estimate overall survival for STS patients = 320 days for CAELYX (95% CI 272 to 505 days) and 246 days for doxorubicin (95% CI 193 to 316 days) *Response*: Response / CAELYX / Doxorubicin CR: 1 (2%) / 1 (2%) PR: 4 (8%) / 3 (7%) SD: 16 (32%) / 18 (40%) DP: 24 (48%) / 20 (44%) Died from malignancy: 4 (8%) / 1 (2%) Not accessible: 1 (2%) / 2 (4%) 95% CI: 3.33 to 21.8 / 2.47 to 21.2 If GIST cases were excluded for response rates these would increase from 10% (CAELYX) and 9% (doxorubicin) to 14% and 12%, respectively. Therefore, it can be assumed that there were no positive responses among 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%), palmar–plantar erythrodysaesthesia (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 erythrodysaesthesia (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 erythrodysaesthesia (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%)

continued

TABLE 30 *Experimental studies of non-imatinib treatments (cont'd)*

Study, design, patients and treatment	Outcomes
Eilber *et al.*, 2000[54] Cohort study to determine the effectiveness of intraperitoneal (IP) chemotherapy in patients with recurrent GI stromal sarcomas (presume GIST) *No. of patients*: 46, of whom 13 treated as controls *Date of study*: 1988–1998 *Diagnosis*: GIST *Age and gender*: not stated *Stage of disease*: all had recurrent disease, but severity of disease and metastatic status of patients unclear *Previous treatment*: assume all had had previous surgery as patients had 'recurrent disease' *Intervention*: postoperative IP therapy delivered by intraperitoneal catheters. IP chemotherapy consisted of mitoxantrone 20 mg m^{-2} diluted in 2 l of Ringer's lactate. Beginning 1–2 weeks after surgery, an equal volume of mitoxantrone was given bilaterally and once given it was not removed from the peritoneal cavity. Each patient received a total of four to six courses of IP chemotherapy with 2–3-week intervals between treatments *Notes*: 13 patients did not receive IP chemotherapy; of these, five patients had surgery before the IP chemotherapy trial, four refused and four were excluded owing to prior abdominal irradiation ($n = 2$) and/or peritonitis ($n = 2$). *Adjuvant therapy*: before IP chemotherapy each patient had surgical resection, which consisted of excision of all gross disease, omentectomy and lysis of adhesions. Liver metastases were treated by primary resection, chemoembolisation or cryoablation *Length of follow-up*: mean 19 months, 34 months for surviving patients *Outcomes measured* *Mortality*: KM survival and recurrence curves *Response*: tumour response NA *Side-effects*: described	*Mortality*: KM survival (read off 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 off 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 either the surgical procedure or the IP mitoxantrone. All patient deaths were due to their disease. In addition, there was no systemic toxicity from IP mitoxantrone. Local complications (patients not given IP therapy) include two abdominal infections and one small bowel stricture, of which one infection and one stricture required reoperation; local complications (patients given IP therapy) include two small-bowel fistulae and two abdominal infections, of which one fistula required operation

continued

TABLE 30 *Experimental studies of non-imatinib treatments (cont'd)*

Study, design, patients and treatment	Outcomes
Ryan *et al.*, 2002[46] Multicentre clinical trial to evaluate the efficacy, tolerability and pharmacokinetics of ET-743 *No. of patients*: 20 (one dropped out at the beginning) *Date of Study*: started August 1999 *Diagnosis*: patients had measurable GISTs. Retrospective analysis found 16 patients to be KIT positive, one negative and three untested owing to samples not being available *Age and gender*: 44 years (range 22–77), 77% male *Stage of disease*: 'advanced' *Previous treatment*: most of the patients had been previously treated, with 19 (95%) having had surgery (probably for primary disease), 45% having had previous chemotherapy, of whom nine had had adriamycin, five ifosfamide, three DTIC and two pyrimidine analogue. In addition, 20% had had radiotherapy *Intervention*: ET-743 1.5 mg m^{-2} (reduced to 1.2 and 1 mg m^{-2} if grade 4 neutropenia) was given by 24-hour continuous i.v. infusion. This represented one cycle. One cycle every 3 weeks was given until disease progression. In addition, 10 mg i.v. of dexamethosone was given for nausea *Outcomes measured* *Mortality*: KM analysis *Tumour response*: CT scan *Adverse events*: looks like CTC but not clearly stated	*No. of patients confirmed KIT positive*: 16 *Mortality*: 11 months into the study, 11 patients started receiving imatinib; therefore, the KM survival curves are confusing. The authors attempted to analyse the patients who did not receive imatinib and found that of the seven who did not receive imatinib, the median survival was 8.6 months and 17.9% survival at 1 year. (NB. These patients are most likely to be different from those receiving imatinib) *Response*: CR: no patients; PR: no patients; SD: two patients (one patient received four cycles and one received ten cycles of treatment); DP: 16 patients (median time to progression 1.25 months; most of these patients received two cycles of treatment); non-evaluable: two patients (one removed for toxicity reasons and was unevaluable for absence of repeat scan, the second patient withdrew before treatment began) *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 owing to toxicity

Haematological	Grade 2	Grade 3
Leucopenia	7 (37%)	5 (26%)
Anaemia	3 (16%)	2 (11%)
Thrombocytopenia	0	0
Neutropenia	4 (21%)	9 (47%)
Hepatotoxicity		
Bilirubin	1 (5%)	0
Alkaline phosphate	0	0
SGOT	3 (16%)	8 (42%)
SGPT	2 (11%)	10 (53%)

continued

TABLE 30 *Experimental studies of non-imatinib treatments (cont'd)*

Study, design, patients and treatment	Outcomes
De Pas *et al.*, 2003[18] Retrospective analysis of outcome of patients with gastrointestinal sarcomas treated with the same systemic chemotherapy as other STS. Thirteen Italian centres responded, with data from patients treated between 1979 and 1999, with 98.5% treated since 1990 *No. of patients*: 67 *Diagnosis*: gastrointestinal sarcomas, no further data on histology or CD117 test *Age and gender*: no data *Stage of disease*: advanced [metastatic $n = 64$ (95%), recurrence $n = 3$ (4.5%)] *Intervention*: combination chemotherapy [$n = 51$ (76%)] or monochemotherapy [$n = 16$ (24%)]. Where combination regimens contained an anthracycline plus isofosfamide in 42 patients, additionally combined with dacarbazine in 11 patients. (NB. These figures are stated in the publication; it is not possible to tell further where the error is.) Dose of ifosamide >9 g m^{-2} in 32/42 patients. Dose of doxorubicine and epirubicin >60 and 90 mg m^{-2}, respectively, in all patients but one. 5/16 monotherapy patients received antracycline (>9 g/m^{-2}); 10/16 monotherapy patients received ifosfamide (>9 g m^{-2}) *Follow-up*: response evaluated after two or three cycles. Survival (KM) calculated to 50 months *Outcomes measured* *Survival*: KM calculated at 50 months *Response*: CR, PR, SD and DP	*Mortality*: overall survival 1 year: 61%; 2 years: 24%; 3 years: 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 chemotherapy 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) Response: Ifosfamide + anthracycline ($n = 42$); Other CT ($n = 25$); Total ($n = 67$) CR: 0; 0; 0 PR: 5; 1; 6 SD: 15; 9; 24 Non-evaluable: 2; 1; 3

continued

TABLE 30 *Experimental studies of non-imatinib treatments (cont'd)*

Study, design, patients and treatment	Outcomes
Rajan *et al.*, 2001[48] Case series study to evaluate response and survival to chemoembolisation in patients with sarcomas metastatic to the liver that are surgically unresectable *No. of patients*: 16 *Date of study*: January 1993 to January 2000 *Diagnosis*: histologically confirmed metastatic sarcomas: 11 patients (69%) had metastatic gastrointestinal sarcomas; two (13%) had splenic angiosarcomas, and the remaining three (19%) had broad ligament, leiomyosarcoma of the inferior vena cava and malignant fibrous histiocytoma of the colon, respectively *Age and gender*: 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*: seven (44%) received various combinations of systemic chemotherapy before chemoembolisation *Intervention*: chemoembolisation via hepatic artery. Dose and drugs used: cisplatin 100 mg, doxorubicin 50 mg, mitomycin-C 10 mg, emulsified in a 1:1 ratio with Ethiodol. This emulsion was mixed with 150–250 μm polyvinyl alcohol particles and instilled into 1–4 ml aliquots *Adjuvant therapy*: antiemetics and antibiotics plus intravenous hydration *Follow-up*: 1 month after completion then a CT scan every 3 months *Length of follow-up*: mean 27 months (range 7–78) *Outcomes measured* *Mortality*: KM analysis from time of diagnosis and time of treatment *Response*: WHO criteria, determined from the time of the first chemoembolisation Modified pain scores	*Mortality*: Overall survival from time of diagnosis: 1 year: 13 patients (81%) (95% CI 53 to 94%) 2 years: nine patients (54%) (95% CI 25 to 75%) 3 years: seven patients (40%) (95% CI 13 to 67%) *Overall survival from time of treatment*: 1 year: 11 patients (67%) (95% CI 37 to 85%) 2 years: eight patients (50%) (95% CI 22 to 73%) 3 years: seven patients (40%) (95% CI 14 to 65%) *Response (at 30 days after treatment)*: PR: two patients (13%); SD: 11 patients (69%); DP: three patients (19%) *Adverse events*:

Grade	1	2	3	4
Pain	1	2	3	4
Fever	2	4	1	0
Nausea	12	5	4	0
Vomiting	6	9	0	0
Blood				
Haemoglobin	19	9	0	0
White blood cells	1	0	0	0
Platelets	0	0	1	0
Coagulation	3	2	0	1
Fatigue	5	2	3	2
Weight loss	10	1	0	0
Hepatic				
Bilirubin	0	1	3	1
GGT/ALK	13	6	7	1
AST	5	0	0	0
ALT	3	1	0	0
Infection	0	2	2	0
Metabolic	1	0	0	0
Neurological	0	0	1	0

continued

TABLE 30 *Experimental studies of non-imatinib treatments (cont'd)*

Study, design, patients and treatment	Outcomes
Mavligit *et al.*, 1995[49] Case series study to evaluate response and survival after hepatic chemoembolisation of the liver in patients with GI leiomyosarcoma, metastatic to the liver *No. of patients*: 14 *Date of study*: 1991–1994 (inferred period) *Diagnosis*: leiomyosarcoma metastatic to the liver *Age and gender*: 30–75 years, 86% males *Stage of disease*: all metastatic to the liver. Median proportion of liver involvement: 44% (range 20–80%). Five patients had metastases on diagnosis, therefore mean time to liver metastases in those without metastases at diagnosis = 27 months *Previous treatments*: all patients had had primary tumour resection, five received systemic or regional intraperitoneal chemotherapy and one received radiotherapy *Intervention*: hepatic chemoembolisation infusion with cisplatin and vinblastine. Dose: 150 mg cisplatin + 15 ml polyvinyl sponge suspension + 10 mg m^{-2} vinblastine. Treatment repeated on second lobe after 4 weeks *Follow-up*: CT scan 1 month after second procedure *Outcomes measured* *Response*: measured via CT scans; unclear as to which criteria used: authors define response as at least a 50% reduction *Side-effects*: measured hepatic enzymes and pain	*Mortality*: median survival 18 months. Seven patients had died at the time of publication post-treatment at 4, 10, 10, 12, 14, 15 and 35 months. Seven were alive at the time of publication post-treatment at 18, 19, 21, 22, 27, 31 and 36 months (n = 140) Therefore, time to survival: 1 year: ten patients (four dead) 2 years: four patients (two dead, four censored) 3 years: no patients (one dead, three censored) Response: No. of courses: 1 (n = 2); 2 (n = 5); 3 (n = 2); 4 (n = 1); 5 (n = 2); Total (n = 14) No. of patients with response >50%: 0; 4; 2; 1; 2; 9 *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 aminotransferase, alkaline phosphatase and lactic dehydrogenase, that usually for lasted up to 7 days. Transient, but mild hyperbilirubinaemia (median 1.9 mg dL^{-1}, range 0.8–3.9 mg dL^{-1}) was observed in most patients

continued

TABLE 30 *Experimental studies of non-imatinib treatments (cont'd)*

Study, design, patients and treatment	Outcomes
Chen *et al.*, 1998[50] Retrospective cohort to determine whether surgical resection of liver metastatic leiomyosarcoma resulted in prolonged survival *No. of patients*: 11 *Date of study*: 1984–1995 *Diagnosis*: leiomyosarcoma metastatic to the liver *Age and gender*: mean 56 years (range 30–69), two males (18%) *Stage of disease*: all metastatic to the liver. Mean no. of liver metastases: 2.6 (range 1–6). Mean size of largest lesion: 3.8 cm (range 1.1–10 cm) *Previous treatment*: all patients had had primary tumour resection. All had surgery without adjuvant chemotherapy, or radiation after primary tumour resection. Before liver resection one patient had radiation plus chemotherapy (adriamycin, dacarbazine and etoposide) *Intervention*: Complete ($n = 6$) or incomplete ($n = 5$) liver resection. Adjuvant therapy: $n = 4$. Three patients received adjuvant chemotherapy after liver resection (one patient received doxorubicin, dacarbazine, isfosfamide and MESNA, one received doxorubicin, dacarbazine and etoposide, and one received cytoxan and vincristine). One patient received radiotherapy *Comments*: all patients preoperatively were thought to be resectable; however, of the five patients with incomplete resections three were thought to be complete but were found to have had positive margins, and in the remaining two only a small volume of residual disease was left behind *Follow-up*: 39 months *Outcomes measured* *Response*: not measured *Side-effects*: not measured	*Mortality*: median survival was 24 months for incomplete resection and was not reached for complete resection. Log rank test 0.03. Five out of the six 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 three 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 five 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 patients died during surgery

continued

TABLE 30 *Experimental studies of non-imatinib treatments (cont'd)*

Study, design, patients and treatment	Outcomes
Bramwell *et al*., 2002[51] Case series to evaluate the safety/tolerability pharmocokinetics and efficiency of VX-710 plus doxorubicin in patients with inoperable, locally advanced or metastatic anthracycline resistant/refractory STS (including 11 patients with GIST) *No. of patients*: 29 plus adverse events data from an additional eight patients who took part in the maximum tolerated dose (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 *Date of study*: not given *Diagnosis*: inoperable, locally advanced or metastatic STS: measurable disease, anthracycline-resistant/refractory disease (documented progression on doxorubicin defined as appearance of new lesions or >25% increase within 8 weeks or chemotherapy-naive GIST or leiomyosarcoma metastatic to the liver) *Age and gender*: 51.7 years (range 23–75), 59% males (17/29) *Stage of disease*: no individual patient detail; see description of patients above *Previous treatments*: no details regarding surgery *Intervention*: VX-710, 120 mg m^{-2} per hour was administered by continuous intravenous infusion for 68–72 hours with the MTD of doxorubicin identified in Phase I administered at least 4 and no more than 8 hours after the start of the VX-710 infusion. MTD doxorubicin: 60 mg m^{-2}. Treatment was administered every 3 weeks *Adjuvant therapy*: none described *Outcomes measured* *Adverse events*: looks like CTC (n = 37) The following efficacy outcomes involved 29 patients: *Tumour response*: RECIST *Progression-free interval*: KM survival curves Post hoc analysis of GIST vs non-GIST tumours	*Comments*: 26/29 patients evaluable. Of those not evaluable, one with extensive liver metastases, concurrent to the first treatment cycle, developed deteriorating liver function, became septic and died. A second patient did not have a histologically confirmed sarcoma and a third did not have confirmed disease progression before the start of the trial *Mortality*: reported if occurred, not specifically an outcome measure. One death *Response*: Tumour histology / PR / SD / Early progression / Total no. of patients Non-GIST: 2 / 7 / 6 / 15 GIST: 0 / 1 / 10 / 11 Overall: 2 / 8 / 16 / 26 Patients with GIST progressed after two treatment cycles *Disease progression*: median progression-free intervals for all 26 evaluable patients; in the subgroup with non-GIST sarcomas were 6.3 weeks, 6.1 weeks and 13.6 weeks respectively *Adverse events*: CTC Adverse event / Total / Grade 1 / Grade 2 / Grade 3 / Grade 4 Asthenia: 27 (73%) / 12 / 13 / 2 Nausea: 25 (68%) / 19 / 6 Vomiting: 18 (49%) / 10 / 6 / 2 Stomatitis: 18 (49%) / 11 / 5 / 1 / 1 Headache: 16 (43%) / 12 / 4 Alopecia: 14 (38%) / 2 / 5 / 7 Anorexia: 12 (32%) / 5 / 5 / 1 Constipation: 12 (32%) / 6 / 6 Diarrhoea: 11 (30%) / 8 / 2 / 1 / 1 Cough: 11 (30%) / 3 / 7 / 1 Fever: 11 (30%) / 3 / 7 / 1 Vasodilatation: 8 (22%) / 8 Comment at the end of the paper regarding imatinib: "the lack of activity observed with the combination of VX-710 with doxorubicin in this study suggests that either constitutive activation of KIT or alternative biochemical mechanisms of drug resistance render GIST non-responsive to doxorubicin cytotoxicity. Nonetheless, it is important to continue to study these mechanisms because even STI571 has not yielded complete responses in any patients 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"

continued

TABLE 30 *Experimental studies of non-imatinib treatments (cont'd)*

Study, design, patients and treatment	Outcomes
Edmonson *et al*., 2002[52] Case series comparing the effect of DTIC with mitomycin, doxorubicin, cisplatin regimen to develop a regimen that might yield superior activity against leiomyosarcomas *No. of patients*: GIST: 21; LMS: 18 *Date of Study*: 1994–1998 *Diagnosis*: GIST: 21, where GIST = "stromal tumours of the stomach, small bowel, colon and pancreas origin"; LMS: 18, where LMS = "leiomyosarcomas of non-gastrointestinal origin" *Age and gender*: GIST: 55 (range 39–69); LMS: 54.5 (range 27–78); GIST: 13 (62%) male; LMS: 3 (17%) male *Stage of disease*: not clear *Previous treatment*: all previously untreated *Intervention*: DTIC 740 mg m^{-2}, mitomycin (MITO) 6 mg m^{-2}, doxorubicin (DOX) 40 mg m^{-2}, mitomycin + doxorubicin + cisplatin (CCDP) 60 mg m^{-2}, granulocyte macrophage colony stimulating factor (GM-CSF) 250 μ m^{-2}. Median cycles per patients: 4 (range 1–6) *Outcomes measured* *Mortality*: KM survival. Measured overall survival and observed metastatic spread *Tumour response*: described *Adverse effects*: described *Time to disease progression*: KM analysis	*No. of patients confirmed KIT positive*: not KIT tested *Mortality*: 92% of patients progressed (36/39); 82% (32/39) have died GIST: Median survival (from *Figure 1*) 16.7 months (95% CI 8.8 to 27.5 months); KM survival 1 year 63%, 2 years 44%, 3 years 17% LMS: Median survival (from *Figure 1*) 17.5 months (95% CI 4 to 8.5 months); KM survival 1 year 58%, 2 years 24%, 3 years 24% *Response*: objective tumour regression in GIST patients: 1/21 patients ((1.8%) (95% CI 0 to 14.5%), LMS 11/18 (61%) (95% CI 38 to 84%) including regression in 8/10 uterine cases *Adverse events*: toxicity: significant, with 33% of patients experiencing grade 3 (severe) vomiting despite the use of antiemetics; this was grade 4 in one patient. 87% developed anorexia, with 8% at grade 3 intensity. One patient had grade 4 pulmonary toxicity following the fourth cycle and this was thought to be a major factor in her death. Grade 3 leucopenia occurred at some time in 42% and grade 3 thrombocytopenia was observed in 68% of patients. Transient diabetes requiring insulin occurred in one patient. Patterns of toxicity were similar for GIST and LMS *Time to progression*: KM survival (from *Figure 2*): 1 year GIST 18%, LMS 16%; 2 years GIST 0% (all progressed), LMS 3%

continued

TABLE 30 *Experimental studies of non-imatinib treatments (cont'd)*

Study, design, patients and treatment	Outcomes
Patel *et al.*, 2001[53] Case series comparing the efficacy, toxicity and optimal dose rate of gemcitabine in adult patients with advanced STS by comparing levels of gemcitabine triphosphate in peripheral blood mononuclear cells *No. of patients*: GI leiomyosarcoma: 17; other STS: 39; total in trial: 56 *Date of study*: 1998–2000 *Diagnosis*: GI leiomyosarcoma, by histology *Age and gender*: all patients with STS in trial: 54 (28–76 years); percentage males: 48% (27/56) *Stage of disease*: advanced metastatic disease *Previous treatment*: 5/17 with GI leiomyosarcoma had prior chemotherapy *Intervention*: gemcitabine 1000 mg m^{-2}, 30-minute infusion weekly for up to 7 weeks, followed by 1 week of rest and re-evaluation. In patients with stable or responding disease therapy was continued on a weekly basis for 3 weeks, followed by 1 week of rest, and tumour response assessments were made every 8 weeks *Outcomes measured* *Response*: CR, PR, SD and DP *Adverse effects*: described graded according to CTC Also measured KM time to progression	*No. of patients confirmed KIT positive*: not KIT tested *Response*: first stage: no patients with GI leiomyosarcoma responded; one patient achieved a mixed response, with regression (52% reduction in size) of a pelvic peritoneal metastases while the liver metastases progressed *Adverse events*: six patients experienced grade 3 and 4 neutropenia and five patients experienced grade 3 and 4 thrombocytopenia. Two patients had grade 3 and 4 anaemia. Grade 3 elevation of ALT (self-limiting) was seen in two patients in two cycles. Grade 3 myalagias were experienced by two patients, with two patients having bilateral lower extremity oedema with an erythematous rash, and one patient complained of grade 3 anorexia. Grade 1–2 fatigue was reported by 11 patients *Survival data*: survival analysis was undertaken using the KM method and is given as 13.9 months. However, it is of limited use as this survival was analysed using all the patients in this trial and is impossible to separate the data for GI leiomyosarcoma

continued

TABLE 30 *Experimental studies of non-imatinib treatments (cont'd)*

Study, design, patients and treatment	**Outcomes**
Carson *et al.*, 1994[55] Case series characterising the presentation, diagnosis and surgical management of this malignancy; the results of chemotherapy, radiation and cytoreductive surgery were examined *No. of patients*: 32 *Date of study*: 1970–1991 *Diagnosis*: pathological diagnosis of gastric leiomyosarcoma (LMS) or malignant leiomyoblastoma, identified by tumour registry search *Age and gender*: median 57 years (range 13–81); percentage males: 75% (24/32) *Stage of disease*: primary and advanced metastatic disease *Previous treatment*: NA *Intervention*: surgery: curative, palliative surgery, chemotherapy, radiation and debulking *Outcomes measured* Mortality and tumour response	*No. of patients confirmed KIT positive*: not KIT tested *Mortality*: *Response*: 25 patients received chemotherapy; all but five progressed, four had a partial response, which had a duration of <4 months, and one had a complete response *Comments*: difficult to compare this study with the others as difficult to determine the case-mix of patients undergoing chemotherapy, radiation therapy and debulking

Therapy	*n*	Median survival (months)	Estimated 5-year survival (%)	*p*
Resection				
Curative	21	40	34	0.05
Palliative	11	8	0	
Chemotherapy				
Yes	25	27	19	0.23
No	7	124	67	
Radiation				
Yes	7	40	43	0.19
No	25	24	21	
Debulking				
Yes	14	34	14	0.42
No	18	27	37	

Appendix 12

Case studies of non-imatinib treatments

TABLE 31 *Non-imatinib treatments: single case studies*

Study, design, patients and treatment	Outcomes
Shioyama *et al.*, 2001[56] Single case study of a patient with GIST (retrospectively confirmed) who was treated with radiotherapy, chemotherapy (carboplatin and epirubicin) and immunotherapy [OK432 (5KE)] *No. of patients*: 1 *Diagnosis*: GIST: retrospectively confirmed positive for KIT and CD34 *Age and gender*: 75 years, female *Stage of disease*: recurrence *Previous treatment*: surgery for primary disease: gastrectomy, distal pancreatectomy and splenectomy for sarcoma of the stomach in 1990 *Intervention*: radiotherapy, then chemotherapy with carboplatin and epirubicin, concurrently. Then the patient was given four 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. of patients confirmed CD117 positive*: 1 (retrospectively) *Response*: CT scan 6 years 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 was a decrease in density inside. PET scan immediately after treatment: decrease in FDG uptake (SUV = 1.66) compared with before treatment
Pollock *et al.*, 2001[57] Single case study of a patient with GIST who was treated with radiotherapy, for an unresectable tumour: the tumour was unresectable, as the patient had refused an abdominoperineal resection *No. of patients*: 1 *Diagnosis*: GIST: CD34 positive *Age and gender*: 77 years, female *Stage of disease*: unresectable *Previous treatment*: surgery for part of the tumour *Intervention*: radiotherapy, 5040 cGy *Follow-up*: at 1 and 2 years *Response*: CT scan Description of patient's health and side-effects	*No. of patients confirmed CD117 positive*: 0, 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*: at 4 months following treatment the patient reported some mild increase in postsurgical rectal urgency and an increased need for a pad. At 2 years she reported stabilisation in her present urgency

continued

TABLE 31 *Non-imatinib treatments: single case studies*

Study, design, patients and treatment	Outcomes
Kamoshita *et al.*, 2002[58] Case study of a patient with GIST, whose primary and liver metastases were treated with surgery; recurrent liver metastases treated by ethanol injection therapy *No. of patients*: 1 *Diagnosis*: GIST: CD117 positive *Age and gender*: 56 years, female *Stage of disease*: inoperable metastatic *Previous treatment and disease history*: at primary presentation the patient had liver metastases as well as a tumour arising from the jejunum *Intervention*: surgery plus ethanol injection therapy for recurrences in the liver 3 months postsurgery. Ethanol dose not given *Length of time on treatment*: NA *Adjuvant therapy*: none *Follow-up intervals*: 3 months postsurgery *Length of follow-up*: 8 months, patient still alive at time of report *Response*: CT scan 2 months postsurgery	*No. of patients confirmed CD117 positive*: 1 *Mortality*: patient still alive at analysis (8 months postsurgery) *Response*: CT scan 3 months postsurgery: recurrent tumour in the remnant liver detected (at this point the patient was treated by ethanol injection therapy). No further CT scan results given *Morbidity*: patient described as being in good condition at home 8 months after surgery (still with a recurrent tumour in the remnant liver)

continued

TABLE 31 *Non-imatinib treatments: single case studies*

Study, design, patients and treatment	Outcomes
Miyauchi *et al*., 2002[59] Case study of a patient with GIST, presenting as an oesophageal hiatus hernia, treated with a self-expandable metallic stent *No. of patients*: 1 *Diagnosis*: GIST: CD34 positive and KIT positive *Age and gender*: 85 years, female *Stage of disease*: unresectable *Previous treatment and disease history*: at primary presentation patient presented with an unresectable tumour *Intervention*: insertion of a self-expandable metallic stent *Length of time on treatment*: NA *Adjuvant therapy*: none *Follow-up intervals*: 3 months postsurgery *Length of follow-up*: 12 months, patient died from disease in February 2002	*No. of patients confirmed KIT positive*: 1 *Mortality*: patient died of disease 12 months after insertion of the self-expandable metal stent *Response*: NA (palliative treatment only) *Morbidity*: patient needed a jejunostomy for tube feeding on 13 August 2001; she then became markedly emaciated before her death

Appendix 13

Illustration

In the baseline-case Novartis model, the proportion of patients in the state 'disease progression' (DP) in the imatinib arm was 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 TTF up to 15 months. This generates curves shown in *Figure 20*.

For the control arm the baseline-case Novartis model estimated the proportion of patients in the DP state by exponential fitting to the data of [academic-in-confidence] (i.e. patients not in receipt of imatinib). [This survival curve is academic in confidence.] If one assumes the same survival probability for the DP state in both arms then the proportion in the DP state at [academic-in-confidence] in the imatinib arm [academic-in-confidence].

One explanation for the discrepancy noted above is that the prognosis of the historical control patients [academic-in-confidence] is worse than that of patients in the Demetri trial.[61] If one assumes that patients in the Demetri trial were to have similar survival probability (prognosis) as [academic-in-confidence], a modified Novartis survival curve can be approximated for patients treated with imatinib, which may allow a more equitable comparison of the two treatments. The proportion of patients moving each month from treatment to DP is calculated from the Novartis exponential TTF. By the end of the month the proportion of these surviving is calculated using the data in *Table 32*.

The total proportion in DP state predicted over the first 48 months is also shown in *Table 32*.

The total proportion of patients surviving (imatinib arm) is given by adding those in treatment to those in DP. The survival curve generated is shown in *Figure 21* and is

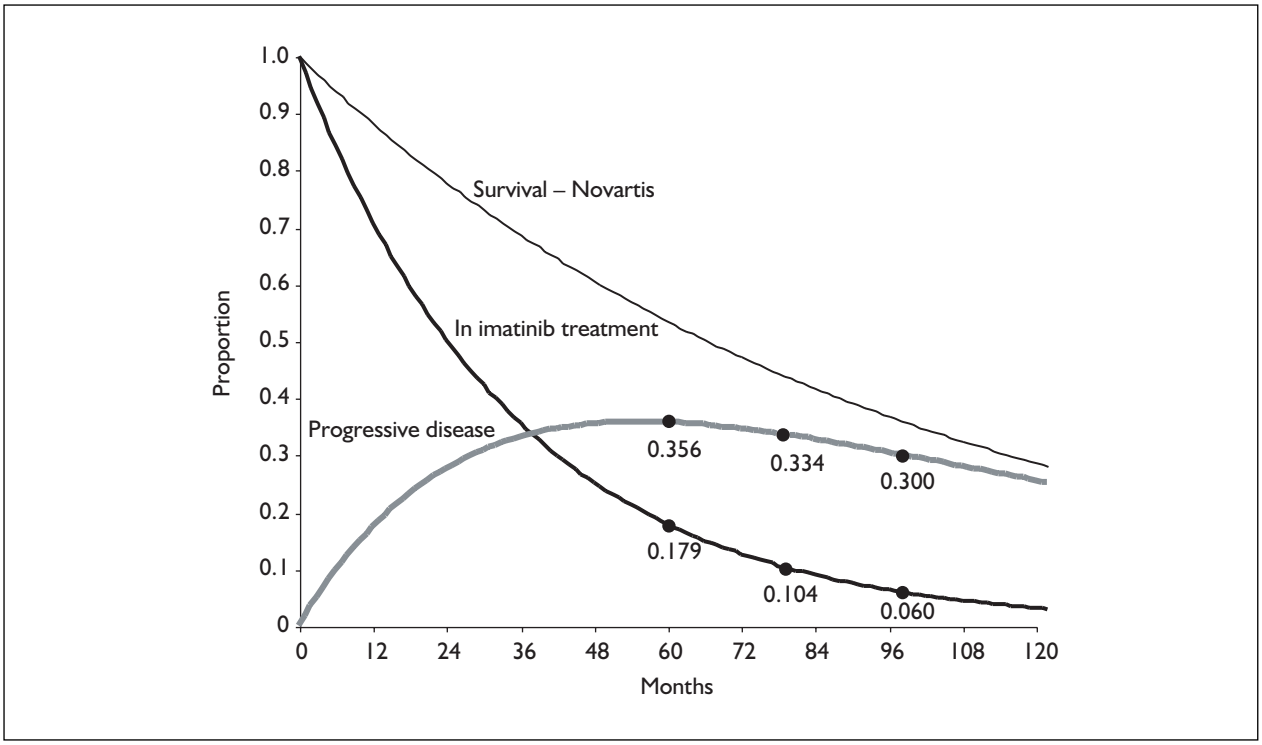

FIGURE 20 *Proportion in progressive disease state calculated by difference*

TABLE 32 *Survivors calculated from the proportion in treatment and those in progressive disease state using survival probability proposed by Novartis for those in control arm*

Month	Proportion in treatment	Proportion lost from treatment to DP in month	Proportion in DP at risk of death at start of month	Total proportion in DP	New surviving proportion
0	1	0	0		
1	0.9688941	0.0311059	0.0311059		
2	0.9387557	0.0301384	0.0602033		
3	0.9095548	0.0292009	0.0873893		
4	0.8812623	0.0282926	0.1127572		
5	0.8538498	0.0274125	0.136396		
6	0.82729	0.0265598	0.158391		
7	0.8015564	0.0257336	0.1788238		
8	0.7766232	0.0249332	0.1977722		
9	0.7524656	0.0241576	0.2153109		
10	0.7290595	0.0234061	0.2315112		
11	0.7063814	0.0226781	0.2464413		
12	0.6844087	0.0219727	0.2601663		
13	0.6631195	0.0212892	0.2727484		
14	0.6424926	0.020627	0.2842472		
15	0.6225073	0.0199853	0.2947196		
16	0.6031436	0.0193637	0.3042199		
17	0.5843822	0.0187613	0.3127998		
18	0.5662045	0.0181778	0.3205091		
19	0.5485922	0.0176123	0.3273949		
20	0.5315277	0.0170645	0.3335024		
21	0.514994	0.0165337	0.3388747		
22	0.4989746	0.0160194	0.3435529		
23	0.4834536	0.0155211	0.3475762		
24	0.4684153	0.0150383	0.350982l		
25	0.4538448	0.0145705	0.3538062		
26	0.4397275	0.0141173	0.3560826		
27	0.4260494	0.0136781	0.3578437		
28	0.4127967	0.0132527	0.3591203		
29	0.3999563	0.0128404	0.359942		
30	0.3875153	0.012441	0.3603368		
31	0.3754613	0.012054	0.3603314		
32	0.3637822	0.0116791	0.3599512		
33	0.3524664	0.0113158	0.3592204		
34	0.3415026	0.0109638	0.3581621		
35	0.3308798	0.0106228	0.3567982		
36	0.3205875	0.0102923	0.3551495		
37	0.3106153	0.0099722	0.3532359		
38	0.3009534	0.009662	0.351076		
39	0.2915919	0.0093614	0.348688		
40	0.2825217	0.0090702	0.3460886		
41	0.2737336	0.0087881	0.3432941		
42	0.2652188	0.0085147	0.3403198		
43	0.256969	0.0082499	0.3371801		
44	0.2489757	0.0079933	0.3338889		
45	0.2412311	0.0077446	0.3304592		
46	0.2337274	0.0075037	0.3269034		
47	0.226457	0.0072703	0.3232332		
48	0.2194129	0.0070442	0.3194596		

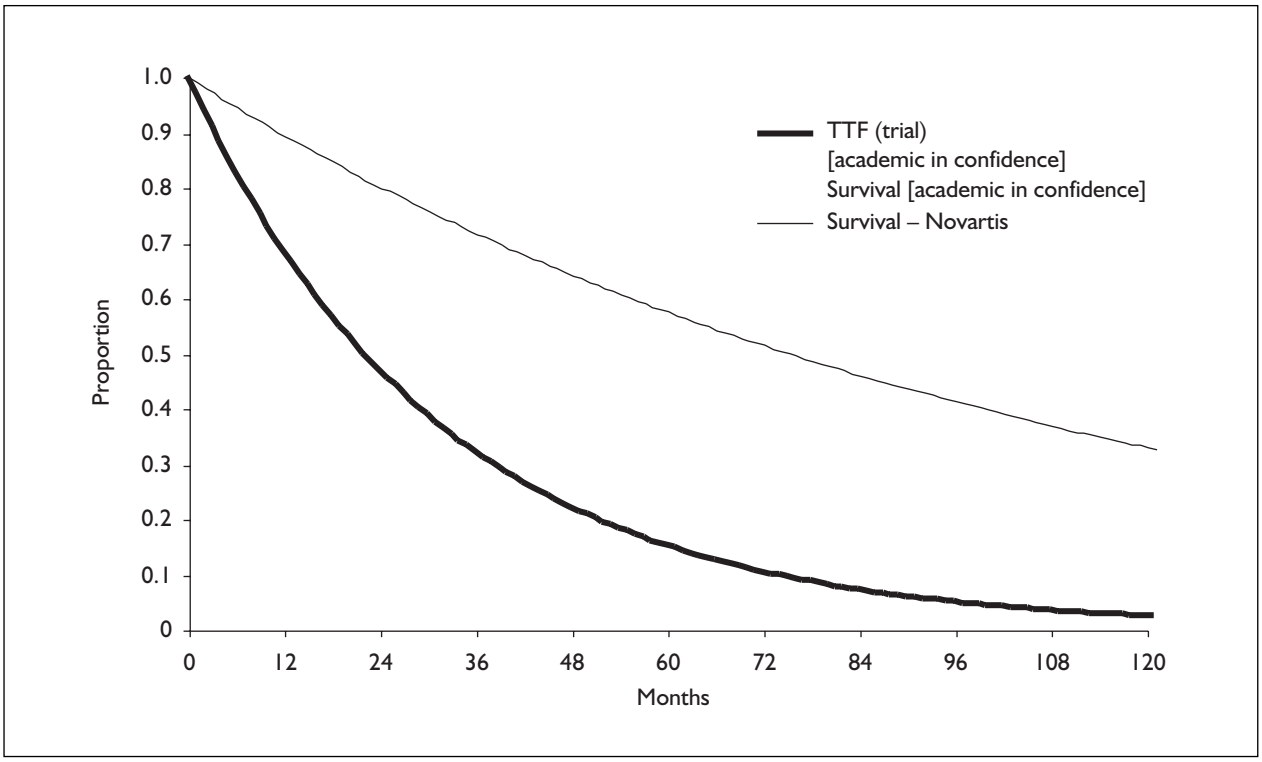

FIGURE 21 *Uses extrapolated exponential curves of Novartis model (for TTF and control arm)*

considerably more pessimistic than that presented in the unmodified Novartis model.

The above modification is calculated in the same manner as that described in the text (see Chapter 5) except that extrapolated exponential curves were used (as in the Novartis model) rather than patient numbers from Demetri[26] and Goss.[63] The influence that different choices of control (DP state) survival curves have on the estimated overall survival in the imatinib arm is illustrated in *Figure 22*.

As part of the sensitivity analysis the Novartis model introduced an alternative exponential for TTF that was fitted to all data from the Demetri trial[61] (rather than data to 15 months). When this exponent is used to calculate modified survival curves (based on various selections of DP survival in the control arm), the survival curves for the imatinib arm become slightly more pessimistic than with the original TTF curve, as shown in *Figure 23* (compare with set of curves in *Figure 22*).

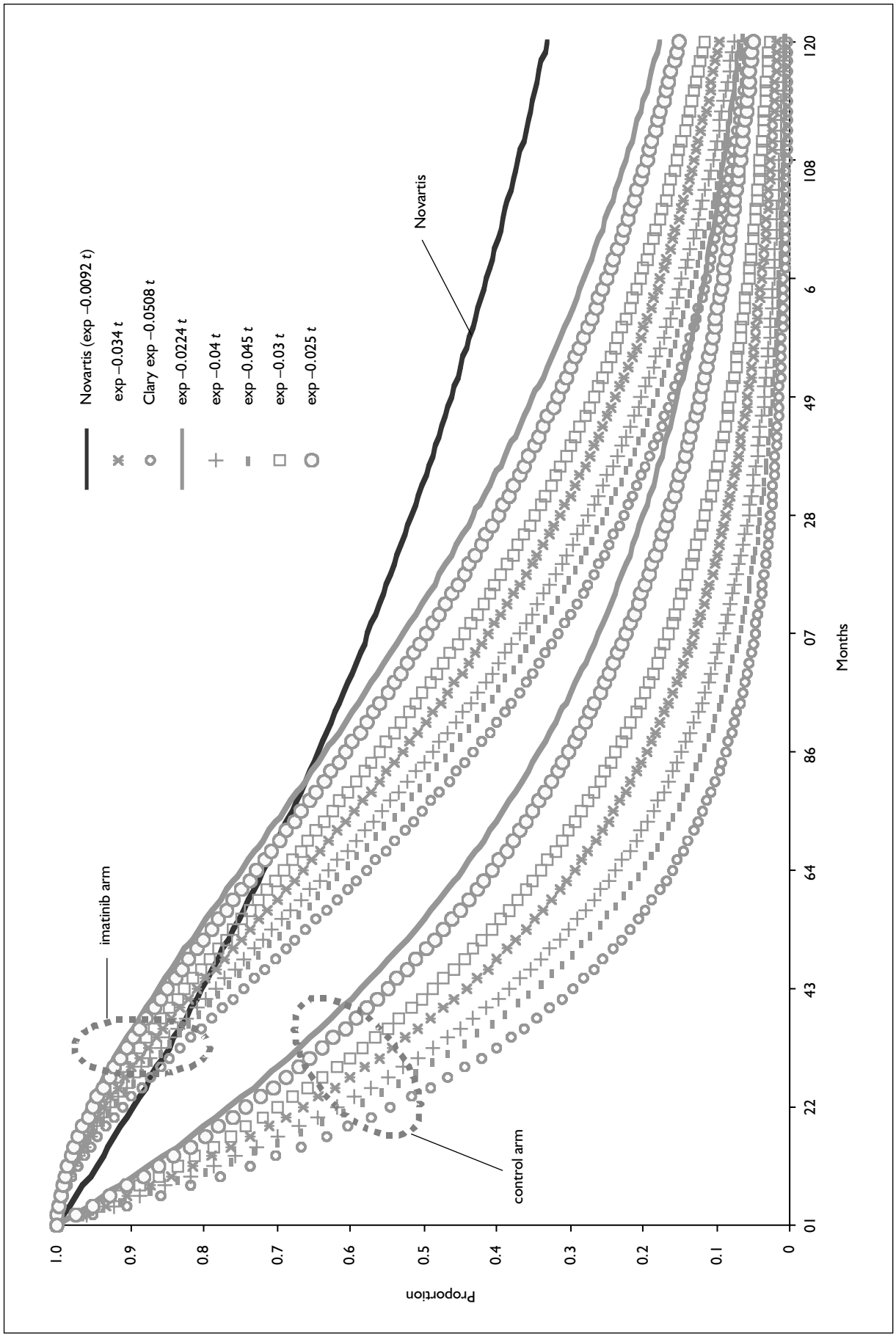

FIGURE 22 *Effect on surviving population (imatinib arm) by applying various exponential survival curves for those not in treatment (control arm)*

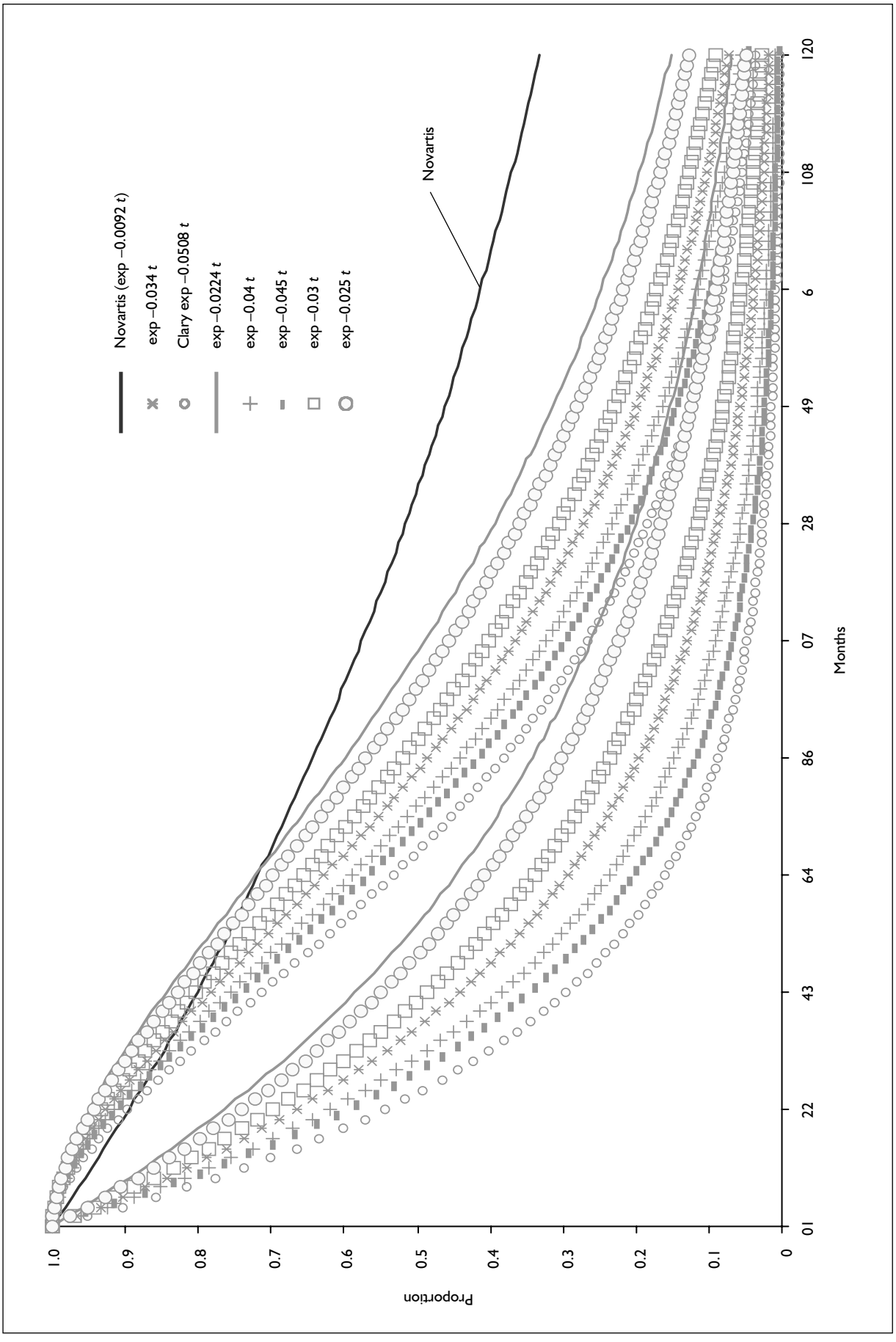

FIGURE 23 *Uses all Novartis TTF data (exp –0.0372 t)*

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The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

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ISSN 1366-5278