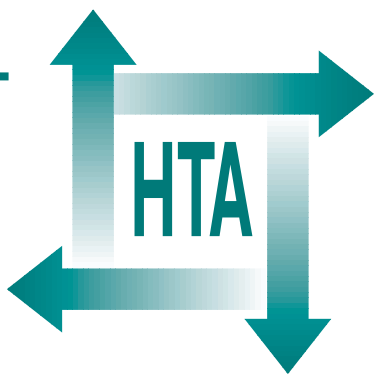
Health Technology Assessment 2002; Vol. 6: No. 33

The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review

R Garside
A Round
K Dalziel
K Stein
P Royle

Health Technology Assessment
NHS R&D HTA Programme



How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review

R Garside[1*]
A Round[1]
K Dalziel[1]
K Stein[1]
P Royle[2]

[1] Peninsula Technology Assessment Group, Exeter, UK
[2] Southampton Health Technology Assessments Centre, Wessex Institute for Health Research and Development, Southampton, UK

[*] Corresponding author

Declared competing interests of the authors: none

Published March 2003

This report should be referenced as follows:

Garside R, Round A, Dalziel K, Stein K, Royle P. The effectiveness and cost-effectiveness of imatinib for chronic myeloid leukaemia: a systematic review. *Health Technol Assess* 2002;**6**(33).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA website (see opposite).

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Technology assessment reports are completed in a limited time to inform the appraisal and guidance development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidance produced by NICE are informed by a wide range of sources.

The research reported in this monograph was funded as project number 01/26/01.

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. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report.

ISSN 1366-5278

Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

T

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Abelson oncogene An oncogene is a cancer-causing gene. The Abelson oncogene is located on that part of chromosome 9 that translocates to chromosome 22 in chronic myeloid leukaemia.

Autogenic transplant A bone marrow or stem cell transplant using marrow from another person. If the marrow is from an identical twin, it is termed syngeneic.

Allopurinol A drug used to control excessive white blood cells and to minimise the build-up of blood uric acid.

Autologous transplant A bone marrow or stem cell transplantation using the patient's own marrow, which was removed, treated and stored before treatment.

Basophilia An excess number of basophils, a rare type of white cell, found in the peripheral blood.

Blast cells Immature cells found in and produced by the bone marrow.

Bone marrow The soft substance that fills bone cavities. It is composed of mature and immature blood cells and fat. Red and white blood cells and platelets are formed in the bone marrow.

Bone marrow transplant A procedure where a patient's bone marrow is replaced by healthy bone marrow. The bone marrow to be replaced may be deliberately destroyed by high doses of chemotherapy and/or radiation therapy. The replacement marrow may come from another person, or it may be previously harvested from the patient's own marrow.

Breakpoint cluster region The region on a chromosome where breaks cluster. In the case of CML, the narrow part of chromosome 22 where the translocation to chromosome 9 occurs, which includes the Abelson oncogene (BCR-ABL). The BCR-ABL protein product results in the excessive proliferation of a tyrosine kinase.

Chemotherapy The treatment of a disease by chemicals to destroy cancer cells. Chemotherapy can affect the whole body.

Cytogenetic response (CR) A response to treatment at a level of chromosomal abnormalities. In the case of CML, assessed by counting the number of Ph+ cells in metaphase (usually 20 metaphases are analysed). A complete response reveals no Ph+ cells, a partial response leaves up to 35% Ph+ cells evident and with a minor response from 35% to 95% Ph+ cells are still evident.

Cytopenia A reduction in the number of cells circulating in the blood.

CRKL An adapter protein that becomes tyrosine phosphorylated by BCR-ABL.

EQ-5D A European quality of life questionnaire containing five physical and psychological dimensions.

Erythrocytes Red blood cells that carry oxygen around the body and carbon dioxide back to the lungs.

Extramedullary disease Disease occurring outside the bone marrow.

Gompertz function A function used to estimate survival curves.

Haematological response (HR) Refers to the normalisation of blood cell counts. CML causes over-proliferation of WBCs and treatments aim to lower these. Typically, the response is classified as complete

continued

Glossary *contd*

(WBC < 10×10^9/l, platelets < 450×10^9/l, no immature cells in the peripheral blood with normal differential count, and disappearance of symptoms and signs.

Hydroxyurea A drug used in the treatment of CML that inhibits DNA synthesis.

Interferon-α (IFN-α) Interferon is a protein derived from human cells. It has a role in fighting viral infections by preventing virus multiplication in cells. IFN-α is made by leucocytes. It is often used as first-line therapy in CML.

Karyotypic abnormality Abnormality in the number, form or structure of chromosomes.

Landmark analysis A form of survival analysis where only subjects who have survived a specified period are included in the analysis.

Leucocyte alkaline phosphatase score A histochemical stain for a neutrophil enzyme.

Leucocytes White blood cells responsible for fighting infections.

Leukapheresis A process of removing excess white blood cells from the peripheral blood.

Leukopenia A reduced number of white cells in the blood – it may affect a single cell type or all white cells.

Matched unrelated donor (Also **Unrelated autogenic transplant**) The person donating marrow is unrelated to the patient. The chances of finding an unrelated compatible donor from the general population depends on the rarity of the individual's tissue type. Genetic and ethnic background can also affect the likelihood of finding a donor.

Metamyelocyte A transitional form of myelocyte.

Metaphase The second phase of mitosis (cell division). Cells in this phase of division are used for cytogenetic analysis in CML to identify the proportion of Ph+ chromosomes.

Mitosis A division of cells consisting of four phases – prophase, metaphase, anaphase and telophase.

Myelocytes Committed progenitor cells produced by, and found in, the bone marrow that develop into mature leucocytes.

Neutropenia A decrease in neutrophils (white blood cells) circulating in the blood.

Neurotoxicity Poisonous to the nervous system.

Peripheral blood In this report, peripheral blood refers to blood in the circulatory system.

Promyelocytes Committed progenitor cells produced by and found in the bone marrow that develop into myelocytes.

Radiation therapy Treatment using high-energy radiation from X- or other rays intended to damage cancer cells and stop them multiplying.

Splenomegaly Enlargement of the spleen.

Stem cells Very early progenitor cells that divide and mature to become all the types of cells that make up the blood and immune system.

Thrombocytes Platelets (fragments of bone marrow cells) found in the blood that help to form clots and control bleeding.

Thrombocytopenia A reduced number of thrombocytes (platelets) in the blood.

Toxicity The quality of being poisonous. The National Cancer Institute grade toxicity levels of treatments as 1 – mild, 2 – moderate, 3 – severe and 4 – life-threatening.

Tyrosine kinase An enzymatic protein that adds phosphate residues to other proteins in the cell. In CML the abnormal tyrosine kinase, BCR-ABL, phosphorylates proteins that cause cellular proliferation.

Weibull curve A mathematical function that is often used in modelling to describe survival times, and in which the chance of survival varies with time.

List of abbreviations

ABL	Abelson oncogene
ara-C	cytarabine (cytosine arabinoside)
ASH	American Society of Hematology
BCR	breakpoint cluster region
BMT	bone marrow transplant
BNF	*British National Formulary*
BU	busulphan
CI	confidence interval
CML	chronic myeloid leukaemia
CNS	central nervous system
CR	cytogenetic response
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for the Evaluation of Medicinal Products
EQ-5D	EuroQoL-5 dimensions
FCE	finished consultant episode
FDA	Food and Drug Administration (USA)
FISH	fluorescence *in situ* hybridisation
HHT	homoharringtonine
HU	hydroxyurea
HR	haematological response
ICER	incremental cost-effectiveness ratio
IFN-α	interferon-alpha
ITT	intention-to-treat
MI	myocardial infarction
6-MP	6-mercaptopurine
mRNA	messenger RNA
MU	mega-units
NCI	National Cancer Institute
NICE	National Institute for Clinical Excellence
NR	not reported
NS	not stated
OR	odds ratio
PB	peripheral blood
Ph+	Philadelphia positive cell
Ph–	Philadelphia negative cell
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RT-PCR	reverse transcriptase polymerase chain reaction
SD	standard deviation
VCR	vincristine
WBC	white blood cell
WHO	World Health Organization

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

Background

Chronic myeloid leukaemia (CML) is a rare blood cancer with an incidence of 1.0 per 100,000 in men and 0.8 per 100,000 in women. In CML, an excessive number of leukaemic white blood cells are produced that suppress the production of normal white blood cells. In 95% of cases of CML, patients have a specific chromosomal abnormality, the Philadelphia chromosome. This is a reciprocal translocation between part of the long arm of chromosome 22 and chromosome 9. The consequent molecular abnormality is a fusion protein, BCR-ABL, which is a tyrosine kinase.

CML is not currently curable with conventional chemotherapy or immunotherapy. Patients diagnosed in the chronic phase may expect a median survival of 3–5 years. Bone marrow transplant offers a cure but is only available to a minority of people.

Current drug treatments include interferon-alpha (IFN-α) and hydroxyurea. Imatinib mesylate is a new, rationally designed competitive inhibitor of the BCR-ABL protein tyrosine kinase.

Objectives

To systematically review the efficacy and cost-effectiveness of imatinib for the treatment of CML in the chronic, accelerated and blast phases, and compare it to existing drug regimes.

Methods

Nineteen electronic databases were searched from inception to August 2001.

Randomised controlled trials (RCTs), cohort studies and case series of existing first- and second-line drug treatments were included, subject to a minimum of 20 participants, as well as economic analyses and quality of life studies. Novartis provided pre-publication reports of three Phase II studies as commercial in confidence material (this status was later lifted). Main outcomes are survival at 1 year, haematological response (HR), cytogenetic response (CR) and adverse effects.

The report represents a narrative summary – no formal statistical synthesis of results was undertaken.

Results

Included studies

Three Phase II studies of imatinib, one in each phase of CML, were included. Eleven RCTs, ten in chronic phase CML and one in the accelerated/blast phase, were included, none of which included imatinib. In addition, 40 case series studies, 27 in the chronic phase and 13 in the accelerated and blast phases, were included. No published economic analyses of imatinib were found. No published studies reviewing quality of life with imatinib were found.

Study quality

The imatinib studies had not been peer reviewed at the time this report was written. There were important differences in patient characteristics, treatment and doses between trials. The RCTs were of moderate quality. The case series studies were often small and of widely varying quality. Comparisons between case series are particularly susceptible to confounding and should be interpreted with great caution.

Evidence of clinical effectiveness

The RCTs compared various IFN-α, hydroxyurea, busulphan and chemotherapy regimens. In the chronic phase, imatinib shows similar 1-year survival to other treatments, but higher complete HR and CR rates. No information on survival beyond 1 year was available.

In the accelerated phase, survival with imatinib appears to be longer than reports for other drugs, but this relies on comparisons of case series. In the blast phase, imatinib appears to show limited longer survival compared to other reports in the literature and complete CR and HR rates for imatinib are within the range of other studies. However, the characteristics of the patients enrolled in these other studies are not well described. There are few studies published and study populations are small. Absence of control groups limits the reliability of the analysis.

Cost-effectiveness

Novartis has funded an unpublished economic analysis of imatinib. The industry submission concludes that imatinib is a cost-effective treatment for CML in the chronic phase after IFN-α failure, in the accelerated phase and in blast crisis.

An extensive evaluation of the model's assumptions was carried out, and additional sensitivity analyses were undertaken. The cost per quality-adjusted life-year (QALY) estimates generated by the industry models may be underestimates. The model is sensitive to the (cumulative) assumptions made and when changed to reflect what we consider to be more realistic values, incremental cost-effectiveness ratios were: for the chronic phase, £45,592–£301,446; for the accelerated phase, £35,633–£56,052; and for the blast phase, £52,354–£64,724.

The cost per QALY of imatinib is high in all phases, but with a large potential range in the chronic phase. This reflects great sensitivity to long-term survival assumptions.

Conclusions

Based on the limited evidence available, imatinib appears to offer an alternative treatment for CML in the accelerated and blast phases.

As yet there is not enough information about imatinib in the chronic phase to draw firm conclusions. Cost–utility estimates for imatinib are particularly sensitive to assumptions about long-term survival, and may be extremely high.

Recommendations for further research

More research into imatinib for CML is needed. Key areas include:

- the efficacy of imatinib in chronic phase CML in the long term;
- RCTs to establish the effectiveness of imatinib in all phases of CML compared to IFN-α, hydroxyurea and other chemotherapy;
- further elucidation of the relationship between response rates (HR and CR) and long-term survival with different treatments in all phases of CML.

Chapter 1
Introduction

Aims of the review

To provide an assessment of the efficacy and cost-effectiveness of imatinib (STI 571) in the treatment of chronic myeloid leukaemia (CML) compared to existing CML treatments.

Background

Nature of CML

Leukaemia is a rare type of cancer that affects the blood; CML is the third most common type of the disease. In CML the bone marrow produces an excessive number of abnormal stem cells (the precursor cells of white cells, red cells and platelets). The abnormal cells eventually suppress the production of normal white blood cells (WBCs), which act to protect the body against infection.

Molecular mechanisms

In 95% of cases of CML, patients have a specific chromosomal abnormality caused by a reciprocal translocation between part of the long arm of chromosome 22 and chromosome 9 (the Philadelphia chromosome).[1] This is not an inherited abnormality but is acquired by individual stem cells. As a result, proliferation of both mature and immature WBCs, to potentially life-threatening levels, occurs in the bone marrow and the blood.

The Abelson oncogene (ABL) is located on chromosome 9. In CML this translocates to the breakpoint cluster region (BCR) gene on chromosome 22 and an abnormal protein, a tyrosine kinase, is formed. Patients with CML who do not have the Philadelphia chromosome have complex or different translocations that still result in the formation of the BCR-ABL gene and its product. The most recent World Health Organization (WHO) classification of lympho-haematopoietec neoplasms proposes that BCR-ABL-negative CML should be reclassified into a new group.[2]

Tyrosine kinases function as part of the internal communication network of cell-regulating processes such as proliferation, differentiation and survival.[3] In CML, the BCR-ABL protein product results in the production of a tyrosine kinase that is not controlled by normal cellular mechanisms. The cells containing the abnormal gene and protein replicate quickly, and may be protected from programmed cell death (apoptosis). They therefore come to predominate initially in the bone marrow and subsequently in the bloodstream. By the time these cells are detected in the bloodstream, the disease process is well under way. Patients with CML at presentation or relapse usually have a total burden of more than 10^{12} malignant cells.[4] Several additional complex genetic abnormalities are acquired during progression of CML and are implicated in progression of disease. However, molecular mechanisms underlying the development of CML and the inevitable transformation to blast crisis are not completely understood.[5] For example, the BCR-ABL abnormality can be detected in people who have not developed CML.[6]

Diagnostic procedures

CML is diagnosed by the presence of a characteristic blood and bone marrow cellular picture, together with cytogenetic and molecular diagnostic techniques.

- **Cytogenetic techniques** detect the Philadelphia chromosome, and were originally considered the gold standard. Cytogenetic analysis requires the examination of at least 20–30 bone marrow cells in mitosis, so that the metaphases can be examined. There are considerable sampling errors because of the relatively small numbers of cells examined and the infrequency of measurement (bone marrow examination is invasive, which precludes frequent testing). The limit of detection is between 1% and 5%. The definition of minimal residual disease may therefore vary in the literature.
- **Fluorescence *in situ* hybridisation (FISH)** tests for the presence of the BCR-ABL gene, and can be positive in the absence of the Philadelphia chromosome. It uses a fluorescent-labelled DNA probe to determine the presence or absence of a particular segment of DNA. In the case of CML it looks for the BCR-ABL fusion gene in bone marrow or peripheral blood cells. It combines both molecular and cytogenetic examination in that it has the ability to

identify a specific gene or gene region with direct visualisation of the cells and/or chromosomes under the microscope. In the FISH test, approximately 200 cells are examined, making it more sensitive than the traditional cytogenetic count of 20–30 metaphases. It is susceptible to false-positive results, and the limit of detection is considered to be between 1% and 5% abnormal cells.[7] The advantage of this technique is that cells do not need to be cultured or analysed in metaphase.[8]

- **Southern and Western blotting techniques** have a similar sensitivity to FISH, but can be performed on peripheral blood.
- **Reverse transcriptase polymerase chain reaction (RT-PCR)** is a very sensitive assay that tests for the presence of messenger RNA (mRNA), the intracellular product that enables proteins to be produced from the DNA gene. Each mRNA is specific for the particular protein that it encodes. RT-PCR can detect a single leukaemia cell in 10^5–10^6 normal cells.[9]
- **CRKL phosphorylation assay**. Functional tests have been developed for the intracellular activity of the BCR-ABL tyrosine kinase. The CRKL phosphorylation assay is raised in people with CML, drops back to normal levels when the patient has a cytogenetic response, and then becomes elevated again with relapse. The sensitivity and specificity of this test is not yet clear.[10]

Natural history and clinical presentation

Three phases of CML are usually identifiable – the chronic phase, accelerated phase and blast phase. The accelerated phase is seen in about two-thirds of patients, while others progress directly to the blast phase. Transition between the phases may be gradual or rapid. Typically, the annual progression from chronic to blast phase is 5–10% in the first 2 years and 20% in subsequent years.[11]

The chronic phase

Typically of 3–5 years' duration from diagnosis, the chronic phase is the initial, usually relatively stable and benign phase of CML. During this period malignant progenitor cells proliferate rapidly but retain their ability to differentiate. Progression of CML is a result of the gradual loss of differentiation potential of malignant cells.

Clinically, in the chronic phase there are less than 10% blasts and promyelocytes in the bone marrow. There is an elevated WBC count, including basophilia, and often an elevated platelet count as well.

Because the disease progresses slowly, it is difficult to detect in its early stages. In 40% of people CML is only discovered when a routine blood test or examination for an unrelated disorder is performed.[11]

The majority of patients are in the chronic phase at presentation. The main clinical symptoms are:

- Fatigue or looking pale because of anaemia. This is often the first symptom that patients recognise and that leads them to seek medical advice.
- A feeling of 'fullness' or a tender lump on the left side of their abdomen, caused by enlargement of the spleen. (Half of all patients have splenomegaly.) Sometimes the liver is also enlarged.
- A temperature and night sweats.
- Weight loss may also be apparent.

The accelerated phase

The accelerated phase marks the transition to the blast phase, lasting up to 18 months[12] but generally leading to a rapidly fatal blast crisis within 6 months. Cells develop genetic and karyotypic abnormalities and there is an increased number of poorly differentiated cells in peripheral bone and marrow, together with splenomegaly.

As the accelerated phase is associated with numerous haematological, cytogenetic and clinical signs and symptoms, no single set of criteria for its onset is accepted.[13] However, in some cases the accelerated phase is defined as > 5% blasts in the peripheral blood and bone marrow but < 30% blasts in both peripheral blood and bone marrow. Other authors use > 15% blasts as a cut-off.[13] The presence of cytogenetic abnormalities in addition to the Philadelphia chromosome is also regarded as a sign of disease progression.

Symptoms in the accelerated phase may include fatigue (because of anaemia), infections, bruising or bleeding.

The blast phase

The blast phase is usually fatal within 3–6 months of onset; it is clinically defined as the presence of 30% or more blast cells in the bone marrow or the presence of blast cells within the peripheral blood. The blast phase is also marked by karyotypic evolution, and the accumulation of multiple characteristic genetic abnormalities.[14] In a third of patients, the blast phase is characterised by a lymphoid structure and expresses lymphoid markers, while two-thirds of patients have an

acute myeloblastic or undifferentiated leukaemia-like phenotype.[15]

The blast phase is characterised by signs and symptoms such as fever, sweats, pain, weight loss, hepato-splenomegaly, enlarged lymph nodes and extramedullary disease.

Cytogenetic and haematological response

Cytogenetic and haematological response as intermediate outcomes

The achievement of a haematological response (HR) and/or cytogenetic response (CR) has been suggested as an intermediate outcome in CML, that is as a proxy for long-term survival. It has been postulated that these responses indicate a reduction in the tumour burden, and therefore a reduction in the number of clonal, genetically unstable cells. This may, in turn, reduce the rate of secondary genetic change and postpone progression of the disease to blast crisis.[16] However, the effects of interferon-α (IFN-α) in increasing cytogenetic abnormalities while prolonging survival suggest this is not a straightforward relationship.[17] An alternative theory is that the cells destined to produce blast crisis are already present at the time of diagnosis, and time to progression depends on host factors and the doubling time of the blast cells.[18] Classification of CRs by bone marrow metaphase analysis is shown in *Table 1*.

HR to treatment refers to the normalisation of blood counts, typically to those levels shown below. In most trials, HR is reported as the best response achieved over the length of the trial follow-up.

Complete HR is defined as:

- WBC ≤ 10×10^9/l, platelets ≤ 450×10^9/l
- no immature cells in peripheral blood
- absence of all signs of disease including splenomegaly
- resolution of symptoms.

If one therapy delivers prolonged survival compared to the alternative and is associated with higher rates of HR and CR, it is tempting to assume that HR and CR are on the causal pathway by which therapy influences outcome. However, it remains possible that HR and/or CR are an epiphenomenon, seen more commonly with a particular therapy, but which may not be produced by an alternative effective therapy. Conversely, the appearance of CR and/or HR may not be associated with prolonged survival with an alternative therapy such as imatinib. Responses to therapy may simply represent the identification of subsets of patients with better prognosis.

Observational studies do not provide good evidence to distinguish between these scenarios. Randomised controlled trials (RCTs) may provide stronger evidence, although difficulties remain.

The evidence that complete HR and/or complete CR are intermediate outcomes for long-term survival is described in detail on page 44.

Risk scores

Several risk scoring systems have been developed that allow patients in chronic phase CML to be categorised into risk groups that reflect their survival prognosis. The most commonly used is the Sokal score, although other prognostic scores have also been developed (appendix 1). In clinical practice, knowledge of individual risk scores may inform treatment decisions. The three Sokal categories represent those with good prognosis (low risk), those with intermediate prognosis (intermediate risk) and those with poor prognosis (high risk). Expected median survival for CML patients treated with chemotherapy at high, intermediate and low risk has been estimated at 2.5, 3.5 and 5 years, respectively.[21]

The Sokal score has been shown to perform less well as a prognostic indicator among people receiving IFN-α treatment compared to those treated with hydroxyurea or busulphan chemotherapy. In response to this, a new prognostic

TABLE 1 *Degree of CR*

		Talpaz *et al.*, 1987[19]	Cortes *et al.*, 1996[20]
None		> 95%	> 99% bone marrow metaphases remain Ph+
Minimal		35–95%	35–99% bone marrow metaphases remain Ph+
Partial	Major	5–34%	1–34% bone marrow metaphases remain Ph+
Complete	Major	No Ph+ metaphases detectable	No bone marrow metaphases remain Ph+

Ph+, Philadelphia positive cell

score (the Hasford or IFN-α score) has been developed (see appendix 1).[22]

Both Sokal and Hasford scores have been shown to be strong predictors of survival, and a number of studies have found that apparent differences in survival seen with different drug regimens disappear when the patients are stratified according to risk group. One group found that "risk profile…overrides therapy effects on survival by a factor of about two".[23] This suggests that risk profile is an extremely important potential confounder in comparisons of treatment and should always be taken into account, preferably through the use of randomisation in the context of direct comparisons.

Both risk score systems have shown a significant association with HR and CR. Risk category and HR in particular are strongly associated ($p = 0.002$ for the Hasford score and $p = 0.005$ for Sokal). For both, the association is less strong for CR, and the new score has a weaker association than the Sokal score ($p = 0.061$ for the Hasford score and $p = 0.01$ for Sokal).[24]

Epidemiology

Incidence and prevalence

All types of leukaemia account for 2.1% of all cancers in England and Wales[25] and the sex ratio for men:women is 1.7:1. In 1997, 531 new cases of CML were diagnosed in England; an annual rate of 1.0 per 100,000 for men and 0.8 per 100,000 for women.[25]

While CML is rare below the age of 20, it does occur in all age groups. National cancer registers may not be notified of all disease. A local registry of patients in north-east England may be more accurate and gives a median age at onset of between 60 and 69 years.[26] A population-based survey of CML patients in Norway found a median age at onset of 62 years.[27] Academic publications tend to report much younger populations, with median onset of 50–55 years.[11,28] This may well reflect positive selection practices in clinical trials, bias arising from studies being carried out mainly in secondary care and inconsistencies in mortality coding in the elderly, where other conditions predominate as causes of death.

Prevalence is difficult to estimate given varying estimates of survival (see below). Based on median survival times of 3–5 years, there are probably about 3000–3500 people with CML in England, or approximately 90–105 people per Strategic Health Authority area of 1.5 million people.

Survival

A population-based survey in Norway described a median survival of 3 years, with only 16% of those over 55 alive at 5 years.[27] Survival is also dependent on other medical conditions that are prevalent in the elderly population, such as heart and respiratory disease. A significant proportion (30%) of people with chronic phase CML die from an unrelated condition.[27] However, in the literature, median survival is reported as 3–5 years, with a range of less than 1 year to more than 10 years. This is likely to refer to a younger and more selected population than is seen in routine clinical practice, and it is likely that all clinical trials overestimate survival.

Changes in the availability of blood testing and, possibly, earlier presentation and diagnosis over time, suggest that length of survival is not comparable between cohorts established at different times. This may be a result of lead time bias[29] and developments in adjunctive treatment, such as more effective anti-infective agents.

Quality of life and CML

No studies were identified that evaluated quality of life (QoL) and the use of imatinib in CML. Novartis is currently collecting data on QoL in its randomised trial of imatinib compared to IFN-α. When available, this should provide useful comparative data about QoL with CML under these two regimens. Little published evidence was found about the QoL for patients with CML or undertaking various treatments for CML. Two published studies that were reviewed are described below.

One study was identified that assessed QoL for patients in Sweden undergoing chemotherapy for CML.[30] This study was based on a young group of patients (< 57 years of age) who underwent allogenic or autogenic bone marrow transplantation at 23 Swedish hospitals. Patients received a variety of chemotherapy treatments aimed at inducing a CR before transplantation, and QoL was assessed in relation to these chemotherapy courses.

QoL instruments were developed specifically for use in patients with leukaemia and are reported as having been validated. Comparing QoL scores in the week after IFN-α therapy with scores in a week following no IFN-α therapy, the study failed to find significant differences in the QoL scores after the first and second course of chemotherapy.

However, the authors found it difficult to achieve their objectives and only managed to obtain results for 44% (n = 48) of the CML patients that were in contact with the Swedish CML group over the recruitment period. The sample may not be representative of those receiving treatment and there is no way of knowing how or why particular patients were included in the study. Thus the results may over- or under-represent patients who react badly to intensive chemotherapy courses. In addition, the study looked at the effects of intensive chemotherapy courses before bone marrow transplantation and may not reflect the experience of people with CML who have no prospect of a bone marrow transplant and who may receive long-term chemotherapy treatment. The study looked at younger patients with CML and the median age of those interviewed was 43 (range 19–53). This may not be comparable with an older age group receiving chemotherapy for CML.

Other evidence that may be relevant comes from the second study, a randomised trial using IFN-α in multiple myeloma, another type of haematological cancer.[31] The doses were comparable to those used in CML, a validated cancer-specific questionnaire was used, and high response rates were achieved (83%). Data on both symptoms and QoL were collected. An intention-to-treat analysis was used, which provides a conservative estimate of results. Overall, despite a slightly worse symptom profile, the influence of IFN-α on QoL was small and statistically not significant except in the first month of therapy. It was postulated in this report that the psychological benefits of taking a drug in a trial situation with the possibility of long-term gain was sufficient to outweigh the effect of the symptoms on QoL.

Clinician consensus is that the adverse effects of IFN-α have a major impact on QoL and performance status. Adverse effects limit the dose that can be given, and some patients cease therapy completely.[32] The published evidence is very limited, but this clinician view is not well supported.

QoL is not solely determined by the adverse effects of therapy – the physical consequences of the disease itself and the psychological effects of knowing the poor prognosis with CML may be important determinants.[33] It has also been suggested that a strong determinant of QoL in CML is reaction to the uncertainty of living with this disease.[33] In these circumstances, the adverse effects of treatment may play a relatively small part for some patients, although individuals' experiences will differ. Taking all these factors into account means that it is extremely difficult to predict the impact of imatinib on QoL.

Current service provision

CML is not currently curable with conventional chemotherapy or immunotherapy, and most such treatments aim to return the patient to the chronic phase of the disease. There is no single standard treatment for patients with CML, especially in the blast phase. Treatment depends on the overall health and age of the patient and, for bone marrow transplantation, the availability of a suitable matched bone marrow donor. *Figure 1* shows a possible treatment pattern, prior to the development of imatinib, for CML for patients aged under 55 in the UK. Clinicians suggest that older, frailer patients are offered much more limited treatment alternatives and may, in practice, be restricted to hydroxyurea.

Current treatment in the chronic phase

Listed below are the main alternative treatments for CML; IFN-α and hydroxyurea are considered in more detail later.

- **Allogenic bone marrow transplantation** is the favoured treatment for young patients with chronic phase CML. At 10 years, 50–55% of patients under 40 may remain disease-free.[36] The most favourable timing of the transplant is controversial, but is generally thought to be more successful if offered relatively early in the disease process.[11,37]
- **IFN-α therapy** was introduced in the 1980s and is regarded as improving survival over other chemotherapeutic options.[38] However, daily injections are needed, relatively high doses have to be given to induce a CR and most people experience adverse effects, at least initially. These factors reduce treatment adherence. Given the perceived unpleasantness of IFN-α in first-line treatment, it is worth noting that it is also possible that imatinib will be considered as an alternative to IFN-α, despite a lack of licence for this use. Comparison to IFN-α has therefore been made in this assessment.
- **Hydroxyurea** relieves symptoms with few adverse effects, and is generally held to be superior to busulphan, which gives poorer survival as well as having an adverse effect profile.[29,39] Hydroxyurea is often used when IFN-α fails or is not tolerated.
- **Busulphan** can control the signs and symptoms of CML through controlling the blood count but has little or no effect on progression of the disease. Busulphan is not usually used regularly for CML, because it has less favourable survival

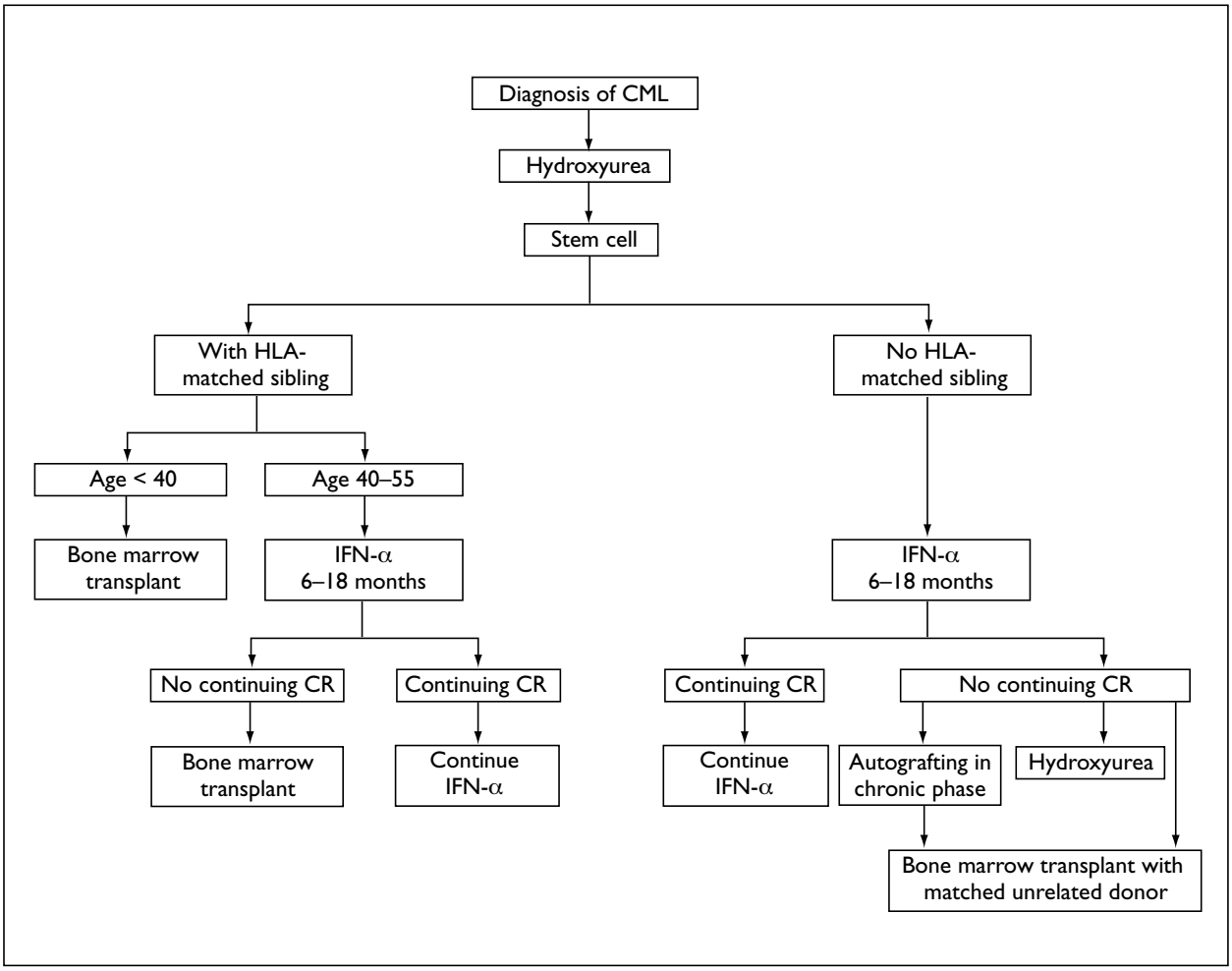


FIGURE 1 *Possible treatment pathways prior to imatinib for a CML patient aged under 55 in the UK. HLA, human leucocyte antigen. Adapted from Leadingham and colleagues, 2001*[34] *and Brunstein and McGlave, 2001*[35]

than hydroxyurea, as well as a less favourable adverse effects profile.

Detailed results for treatment in chronic phase CML can be found on page 33.

Current treatment in the accelerated and blast phases

Accelerated and blast phase CML respond poorly to treatment. No standard therapy exists. Most patients will have received prolonged treatment for the chronic phase of the disease – usually hydroxyurea or IFN-α. If a suitable donor is available, bone marrow or stem cell transplant is an option, although long-term survival is much poorer than in the chronic phase (approximately 40% in the accelerated phase and 15% in the blast phase).[35]

For patients in blast crisis, treatment with high-dose combination chemotherapy regimens commonly used for acute leukaemia is the only effective therapeutic option, inducing responses in 20–40% of patients. Cytotoxic agents used include 6-mercaptopurine, dexamethasone, prednisone, idarubicin, etoposide, azacytidine, vincristine sulphate, daunorubicin and decitabine. The response to such treatment is generally sustained for < 6 months.[40] Although such responses are usually short-lived, this may provide the necessary window to allow for a transplant if this is appropriate and available. Those with lymphoid blast crisis respond better to such chemotherapy regimens than those in myeloid blast crisis.[15]

Detailed results for treatments in the accelerated and blast phases are given on page 39.

Description of comparator treatments

Bone marrow or stem cell transplantation is the only potentially curative treatment for CML. However, it should be noted that the empirical evidence for cure is not unequivocal, and relies on observational studies, with very small cohorts followed up for long periods of time. No RCTs comparing bone marrow transplant with IFN-α

have been performed. Clinician consensus relies predominantly on analyses suggesting that the survival curves of IFN-α and bone marrow transplantation cross at about 7–8 years, with an advantage for bone marrow transplantation after this.[28] Weighed against this is a substantial transplant-related mortality of between 20% and 40%.[28] Currently only about one-fifth of patients are both suitable for a bone marrow transplant (are in good general condition and aged under 55) and have access to a donor.[11]

Bone marrow transplantation has been excluded as a comparison treatment in this report, because:

- Patients with CML who undergo transplantation in the chronic phase have a better survival than those who undergo transplantation later.[11] Therefore bone marrow treatment is considered as the first option in those in whom it is suitable, and imatinib would not be considered.
- The relatively short-term survival data available for imatinib are not comparable to bone marrow transplantation survival data because of the considerable early transplant-related mortality.
- CRs are substantially more common after bone marrow transplantation because of the nature of the treatment, and are not directly comparable to those gained with chemotherapy. Likewise HRs are not comparable.
- Adverse effects of bone marrow transplantation are not directly comparable.

Interferon-α

Interferons are a complex group of naturally occurring proteins with potent multiple effects on immunity and cell function. IFN-α regulates cytokine expression and inhibits haematological growth factors. It is also an immunomodulator (alters T cell reactivity), and is directly cytotoxic for some tumour cells.[17,32] However, the exact basis of its effects in CML is not known, and may vary from person to person.[41]

IFN-α induces an HR in a significant proportion (up to 80%) of patients, and for up to a quarter, a major CR.[32] There is evidence that even those who fail to achieve a CR with IFN-α have prolonged survival compared to those treated with traditional chemotherapy.[42] A meta-analysis of seven randomised trials of IFN-α showed an overall reduction in annual death rate of 26% ($p = 0.001$) when IFN-α was compared with hydroxyurea, and of 36% ($p = 0.00007$) when compared with busulphan.[38]

The evidence relating to the relationship of HR and/or CR to survival is discussed on page 44.

IFN-α has a toxic profile producing both acute and chronic adverse effects. It is currently impossible to predict which patients will encounter intolerable adverse effects. IFN-α often causes adverse effects similar to the symptoms of 'flu, especially chills, fever, headache and aching in the back, joints and muscles. Flu-like symptoms may self-resolve or respond to paracetamol within a few weeks. Neurological toxicity, in particular fatigue, is also common. Thrombocytopenia and anaemia may also develop but are rare.[43] Because of this toxic profile, clinician consensus is that many older or frailer patients should never be offered IFN-α. Such patients may make up a large proportion of the CML population.

Details of adverse effects reported by trials are shown on page 46.

The effect of combining IFN-α with other agents such as cytarabine (ara-C) is being studied, with some results showing improved CR and survival compared with IFN-α alone.[44–46] However this combination is not currently licensed in the UK.

Detailed results are shown on page 30.

Hydroxyurea

Until the advent of IFN-α therapy, hydroxyurea was considered the standard treatment for newly diagnosed patients. Hydroxyurea suppresses the excessive multiplication of the myeloid peripheral cells by inhibiting one of the enzymes involved in DNA replication. It produces HR in over 90% of patients but has little or no effect on CR. It is generally accepted that hydroxyurea can modestly prolong survival compared to busulphan.[39] Adverse effects including neutropenia, anaemia, bruising or bleeding, and fever are relatively common, while gastrointestinal symptoms (such as weight loss and nausea), hair loss and skin rash are less common. Adverse effects are reversible on stopping therapy and hydroxyurea is therefore sometimes used as first-line treatment in very elderly or frail people. It is also commonly used as second-line treatment in people who have failed to respond to, or cannot tolerate, IFN-α.

CML treatment in the NHS

There were 7366 finished consultant episodes (FCEs) for CML (4322 men) in England in 1999–2000. FCEs count each episode of care delivered under a single consultant during each period of

hospital stay (as a day-case or inpatient). This means that each patient may be counted a number of times. The mean age of onset was 51 from this data source; age distribution is shown in *Table 2*. This discrepancy compared to the age at onset described on page 4 may be a result of more intensive hospital-based therapy, such as bone marrow transplantation, among younger CML patients, which accounts for greater numbers of FCEs among this age group. These FCEs represent 7133 hospital admissions, 5317 of which were day-cases. A total of 18,206 bed-days were accounted for by CML.

TABLE 2 *Number of FCEs for CML in England, 1999–2000*

Age	Number
0–14	189
15–59	4541
60–74	1798
75+	838

Imatinib – description of the technology

Imatinib mesylate (STI 571, also Gleevec® or Glivec®, Novartis Pharmaceuticals) is a rationally designed competitive inhibitor of the BCR-ABL protein tyrosine kinase.

Mechanism of action

Imatinib acts by blocking the adenosine triphosphate binding site on the BCR-ABL tyrosine kinase. This inhibition prevents the phosphorylation of the tyrosine residue on the attached substrate, reducing cellular proliferation. BCR-ABL has a long half-life and requires the continuous presence of inhibitors to substantially reduce its function.[5]

Licensing and product information

Imatinib (UK tradename Glivec®) received marketing authorisation from the European Agency for the Evaluation of Medicinal Products (EMEA) in November 2001. The EMEA granted the licence "under exceptional circumstances", stating that "the indications for which the medicinal product in question [imatinib] 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."[47] Novartis have agreed to an identified programme of studies, including those considered in this review, which will form the basis of an annual reassessment of the risk–benefit profile of imatinib. The licence is based on HR and CR rates and recognises that there are no controlled trials demonstrating a clinical benefit or increased survival.

The EMEA marketing licence has been granted for adult CML patients with Ph+ CML in the chronic phase for failed IFN-α patients, and for those in accelerated or blast phase CML. *Box 1* gives two definitions of IFN-α treatment failure.

In the USA, the early findings of studies also led to imatinib being given fast track approval from the Food and Drugs Administration (FDA), despite no long-term or RCT evidence. It was licensed in May 2001 for use in CML in blast crisis, the accelerated phase or in the chronic phase when IFN-α treatment had failed. The FDA approved imatinib (US tradename Gleevec®) under its 'orphan drug program', which provides financial incentives for drugs developed to treat rare diseases.

Other countries that had given a licence to Novartis for imatinib as at January 2002 include Argentina, Australia, Bulgaria, Canada, Chile, Columbia, Dominican Republic, Ecuador, El Salvador, Guatemala, Israel, Indonesia, Jordan, Kuwait, Malta, Mexico, Nicaragua, Palestine, Peru, Romania, Russia, South Korea, Switzerland, Syria, the USA, Uruguay and Venezuela.

There are no randomised trials published (one is still in progress; interim results of 1-year follow-up are due to be published early in 2003), and the Phase II studies are only published in abstract form, or as part of the licensing agreement details published by the EMEA. The data assessed in this report have been provided by Novartis, and have not undergone peer review, other than as part of this report's production. Caution should, therefore, be used in interpreting the results.

Special populations

- There are no pharmacokinetic data in paediatric patients.
- No clinical studies have been conducted in patients with impaired hepatic function.
- No clinical studies have been conducted in patients with moderate to severe impairment of renal function (studies excluded patients with serum creatinine concentration more than twice the upper limit of the normal range). Imatinib and its metabolites are not significantly excreted via the kidney.
- No clinical studies have been conducted in patients with overt cardiac disease.

Adverse effects of imatinib

The adverse effects of imatinib are reported in detail on page 46. Those frequently reported in

BOX 1 Treatment failure with IFN-α

Definition 1

1. Haematological resistance (at 5 MU/m^2 daily or maximum tolerated dose), one of:
   - failure to achieve at least a partial HR after at least 3 months of therapy;
   - failure to achieve a complete HR after at least 6 months of therapy;
   - loss of HR after achieving complete HR with an increasing WBC count > 12 × 10^9/l on optimal IFN-α therapy documented for at least 4 weeks.
2. Cytogenetic resistance (at 5 MU/m^2 daily or maximum tolerated dose), one of:
   - failure to obtain a CR (Ph+ > 89%) after at least 1 year of therapy;
   - loss of CR with a return to Ph+ cells to > 90%.
3. IFN-α intolerance (no dose specified)
   - Grade 3 or 4 unacceptable toxicity[48]

Definition 2

1. Haematological failures: patients who were resistant to or relapsed during IFN-α treatment (no dose specified)
   - failure to achieve a complete HR of at least 1 month duration following at least 6 months of IFN-α treatment (concomitant hydroxyurea permitted for up to 50% of the treatment);
   - WBC increasing to > 19 × 10^9/l (confirmed by two samples taken at least 2 weeks apart) while receiving IFN-α (concomitant hydroxyurea allowed for up to 50% of treatment duration).
2. Cytogenetic failures: patients who were resistant or who relapsed during IFN-α-based therapy (no dose specified)
   - 64% Ph+ in bone marrow after 1 year of IFN-α-based treatment;
   - in patients who had previously achieved a CR, Ph+ metaphases increased by at least 30% (confirmed by two samples 1 year apart) or to > 64%.
3. IFN-α intolerance (at 25 MU/week or more, CML diagnosed at least 6 months)
   - any non-haematological toxicity of grade 3 persisting for more than 1 month.[13]

trials include nausea, vomiting, oedema (fluid retention), muscle cramps, skin rash, diarrhoea, heartburn and headache. Severe fluid retention occurred in up to 2% of patients. Cytopenia, particularly neutropenia and thrombocytopenia, were found in all studies (pack data). Incidence is higher in the blast and accelerated phases compared to the chronic phase. Severe elevation of transaminases or bilirubin occurred in 1.1–3.5%[49] of cases.

The majority of patients experience adverse reactions at some time and the drug has been discontinued for adverse events in 1% of patients in the chronic phase, 2% in the accelerated phase and 5% in blast crisis.[49]

Dose of imatinib

Recommended dosage is 400 mg/day for those in chronic phase CML and 600 mg/day for those in the accelerated and blast phases. The dose is administered orally and given once daily with a meal and a large glass of water.

Dose escalation from 400 to 600 mg/day for patients with chronic phase disease, or from 600 to 800 mg/day (given as 400 mg twice daily), is advised in patients in the accelerated phase or blast crisis, providing there is no severe adverse drug reaction or severe non-leukaemia-related neutropenia or thrombocytopenia.

Dose escalation may also be considered where there is:

- disease progression (at any time)
- failure to achieve HR after at least 3 months of treatment
- loss of a previously attained HR.

Cost

Imatinib costs £12.98/100 mg. The approximate annual cost for 400 mg/day in the chronic phase is £18,951, and for 600 mg/day in the accelerated or blast phase is £28,426. Doses of 800 mg/day will cost £37,902 per year.

Duration of response and resistance to imatinib

The duration of response to imatinib remains a crucial unanswered question. Because its mechanism of action suggests that continual exposure to the drug is required, it is not known whether imatinib can ever be safely stopped. In contrast to this, longstanding unmaintained remission has been documented in a small number of people treated with IFN-α and some IFN-α-treated patients remain in remission for 10 years.[32] It has been suggested that IFN-α can produce an

'operational cure' even though pathology is still detectable.[7]

Resistance to chemotherapy is a common feature of many cancers, and has been documented with imatinib. Disease progression is at least partly associated with the failure to maintain effective inhibition of BCR-ABL kinase activity[50] as measured by the CRKL assay. Secondary oncogenic changes that permit malignant proliferation independent of BCR-ABL are also possible, but appear to be less likely as an explanation.[51] It is probable that resistance will be an important determinant of long-term survival with imatinib and details of mechanism of resistance are shown in appendix 2.

Many aspects of imatinib therapy are still not understood. Dose escalation of imatinib in relapsing blast crisis patients has not produced remission, as might be expected.[52] Blast crisis cells show similar intrinsic resistance as chronic phase cells to imatinib *in vitro*, despite differing clinical responses.[53] It has been noted that *in vitro* cell lines can regain sensitivity to imatinib after drug withdrawal for 2–3 months, but the clinical implications of these findings have not yet been studied.[14]

It is also unclear why some patients fail to achieve a response. Possibilities are:

- There is poorer inhibition of BCR-ABL by imatinib in less mature cells, that is a high proportion of immature cells are less sensitive to imatinib.
- Relatively resistant stem cells have a proliferation advantage and eventually predominate.
- The percentage of BCR-ABL-positive stem cells may vary considerably between people.[46]

Potential long-term toxicity and adverse effects

With follow-up of only 12 months reported, it is not possible to comment on possible long-term toxicity or adverse effects.

Theoretically, it is possible that imatinib may inhibit other tyrosine kinases within the cell. This may lead to myelosuppression, abnormal lymphocyte function or impaired wound healing.[5]

Chapter 2

Review methods

Research questions

The following questions were addressed in this assessment:

1. What is the efficacy of imatinib in the treatment of CML compared to existing treatments?
2. What is the cost-effectiveness of imatinib in the treatment of CML compared to existing treatments?

Review team and advisory group

The review was carried out by a team comprising Dr Ken Stein, Dr Ali Round, Ruth Garside and Kim Dalziel.

Additionally, an external advisory group of clinical, health economic and statistical experts provided advice during the assessment. Details of this group appear in the 'Acknowledgements' on page 73.

General methods

The review methods generally adhered to the guidelines published by the York Centre for Reviews and Dissemination. The *a priori* methods used for the review are outlined in the review protocol (appendix 3), although some changes were made. After an initial review of the literature, bone marrow transplantation was dropped from the list of comparator treatments, as justified on page 6.

Hydroxyurea and IFN-α are the comparators considered in the chronic phase. In the accelerated and blast phases, other chemotherapies are considered as comparators.

There is no direct comparative data between imatinib and any other therapy yet available. Because of this, comparisons have been made with data from both RCTs and case series.

Search strategy

Sources of information

Electronic databases were searched for published studies, as well as recently completed and ongoing research. Appendix 4 lists the databases and the search strategies used.

During the initial literature review it became clear that a range of chemotherapies have been used in the accelerated and blast phases of the disease, and so an additional search for articles relating to these phases was undertaken.

Bibliographies of articles reviewed were searched for further relevant articles and the manufacturers of imatinib were approached for unpublished studies, including a cost-effectiveness model.

Inclusion criteria

Method of application

Using the criteria described below, two reviewers independently made the inclusion or exclusion decisions. Disagreement was resolved by consensus. Decisions were made independently of the data extraction and prior to detailed scrutiny of results.

For imatinib

Study design: Given the paucity of published data about imatinib, all Phase I and Phase II studies were included. Details of three major studies were provided by Novartis as commercial in confidence information at the time of the review. The results of these studies were available in the public domain only as conference abstracts, and as part of the licence information. Two Phase I studies reviewing safety and efficacy were published.[54,55] Commercial in confidence status has since been removed.

Intervention: Imatinib orally.

Population: Adults with chronic phase CML who had failed IFN-α, accelerated or blast phase.

Outcomes:

- overall survival
- progression-free survival

- HR, complete and partial
- CR, complete and partial
- adverse effects
- cost.

For hydroxyurea, IFN-α and other chemotherapies

Study design: All RCTs and cohort studies or case series involving more than 20 patients, with a minimum follow-up period of 1 year, were included.

Intervention: Hydroxyurea and/or IFN-α and/or other chemotherapy.

Population: Adults with CML in chronic, accelerated or blast phase.

Outcomes:
- overall survival
- progression-free survival
- HR, complete and partial
- CR, complete and partial
- adverse effects
- cost
- QoL.

Data extraction

Data were extracted by one researcher and checked by another. Response rates and survival were calculated, where possible, from original data presented in the report and not from percentages given, because these are often adjusted for a variable number of drop-outs. In some cases, 1-year survival was estimated from survival curves presented in the results.

Quality assessment strategy

Using a structured form, two reviewers independently assessed the internal and external validity of included trials for the aspects outlined below.[56]

IFN-α and hydroxyurea RCT studies

Internal validity
- sample size
- selection bias (allocation strategies, eligibility criteria, similarity of groups compared)
- performance bias (similar concurrent therapies for both groups)
- detection bias (blinding procedures)
- attrition bias (intention-to-treat analysis, drop-outs, loss to follow-up).

External validity
- representativeness of sample used
- usual care setting
- standard treatment regimen
- standard treatment outcomes measured
- length of follow-up.

For non-randomised studies of all treatments – imatinib, IFN-α, hydroxyurea and other chemotherapy studies

Internal validity
- selection criteria
- explicit inclusion and exclusion criteria
- stage of disease at entry
- concurrent treatments explicit and similar for all patients
- extent of blinding (where appropriate)
- intention-to-treat analysis.

External validity
- patient characteristics
- treatment regime followed.

Methods of analysis

Clinical effectiveness

This assessment considered all outcome measures reported in included trials.

There are no direct comparisons between imatinib and alternative therapies. We have therefore calculated the outcome measures directly from trial reports and tabulated the data to enable an approximate assessment of the efficacy of imatinib seen in relationship to other published evidence. It cannot be emphasised too strongly that this kind of comparison is subject to bias, particularly in terms of potential differences in the populations studied, the variable completeness of follow-up, publication bias, and lack of blinding throughout the literature.

A further difficulty arises from the short-term follow-up in the imatinib trials and consequent reliance upon HR and CR as proxy outcome measures for longer-term survival. RCT evidence alone was considered to assess the validity of this, as observational data can describe associations only.

Survival has been used as a primary outcome measure in studies in the blast and accelerated phases as expected survival in these phases is short.

Where 95% confidence intervals (CIs) were not described in the imatinib trials, these have been calculated using STATA™.

Economic evaluation

An independent economic analysis was not performed, because of the high degree of uncertainty about overall survival and effectiveness of imatinib compared to other therapies, and time constraints on the assessment.

Economic evaluations were sought of any treatment in CML. A brief summary of economic analyses of IFN-α treatments is provided, to give some background information prior to a detailed critique of the industry analysis and model. Using the Drummond criteria,[57] this reviews the model structure and assumptions, and performs a number of sensitivity analyses to explore in more detail some of the key model parameters and the effect of altering these on cost-effectiveness.

Impact on the NHS

A brief critique of the industry submission to the National Institute for Clinical Excellence (NICE) is provided for completeness.

Chapter 3
Results

Studies identified

Searching yielded a total of 567 separate references. These references included trial results as well as background information about CML, imatinib, the biochemistry of CML treatments, QoL issues, cost-effectiveness studies and overviews of this clinical area. Appendix 5 includes a diagram showing which trials were included. Studies were included if they fitted the inclusion criteria described on page 11.

Included studies

No published full accounts of Phase II studies of imatinib were identified from this search, although some details have been reported in abstract form and results only presented in other papers. Two publications relate to Phase I studies of imatinib. Novartis provided details of three Phase II studies being prepared for publication.

Ten RCTs (described in appendix 6) and 27 case series for CML treatments in the chronic phase were included. For accelerated and blast phase CML, one RCT was available and information from 13 case series studies included. No studies directly compare imatinib with other treatments and the review therefore had to rely on comparisons between different studies.

Excluded studies

These are listed, with reasons for exclusion, in appendix 6.

Quality assessment

Overview of quality

This section outlines aspects of quality in the included studies that may give rise to bias in the study results. For both imatinib and the comparators, bias is discussed with reference to internal and external validity. Internal validity is a measure of the extent to which the study is likely to give unbiased results. It is discussed under four headings:

- **Selection bias** (was patient entry to the trial biased towards those more likely to have favourable results?).
- **Performance bias** (did the treatment given, including concomitant treatments, allow an unbiased estimate of the effect of the therapy under investigation?).
- **Detection bias** (was assessment of outcomes performed in a way that minimised bias?).
- **Attrition bias** (was patient follow-up adequate to prevent bias?).

External validity is a measure of the extent to which the results found in the trial can be generalised to the overall population of patients with CML.

This section also reviews the analytic methods used and their appropriateness.

Case series present significant methodological problems in their interpretation. The absence of control groups means that, except where natural history is well understood and the effects are dramatic, it is difficult to attribute effects to the treatment being considered. Case series studies are more open to selection bias than well-designed RCTs, as participants may be selected by the investigators if they are thought to be potentially more responsive to treatment or are more motivated. Case series may be defined retrospectively, in some cases by factors associated with outcome. Missing records are not generally included but may report a poorer outcome. All these factors may lead to an overestimate of treatment effect.

The comparisons we present here, regardless of study design, are fraught with potential problems. In particular, differences in study populations, as indicated by baseline risk assessment, and care received other than the treatment of interest, may produce significant confounding.

RCTs are generally less susceptible to bias. The randomisation process in RCTs, where appropriately conducted, will control for known and unknown confounders of treatment effect. However, small study size and poor technique within RCTs may result in residual confounding and other forms of bias, which may or may not be detectable.

In this case, the RCTs we describe do not directly compare imatinib with other therapies, so it is

important to review the design and conduct of these trials for susceptibility to bias, as with imatinib. It is difficult to detect residual confounding and to determine the direction or magnitude of its effect on the results.

Imatinib

The main body of information on the efficacy of imatinib comes from three large case series studies undertaken by Novartis. These studies are not currently fully published, although the results are available as abstracts from the American Society of Hematology (ASH) meeting in December 2000. In addition, the trial results have been included in articles describing imatinib.[3] The more detailed information on these studies was provided to the review team as commercial in confidence material. Each study looks at the effects of imatinib on patients in a different phase of CML:

- Study 110: Chronic phase Glivec™ (imatinib mesylate) induces hematologic and cytogenetic responses in the majority of patients with chronic myeloid leukemia in chronic phase: Results of a Phase II study.[58]
- Study 109: Accelerated phase Glivec™ (imatinib mesylate) induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: Results of a Phase II study.[13]
- Study 102: Blast phase Glivec™ (imatinib mesylate) induces hematologic and cytogenetic responses in patients with chronic myeloid leukemia in myeloid blast crisis: Results of a Phase II study.[59]

Details of these studies are further discussed on page 23.

Internal validity

Selection bias

Details of recruitment procedures to the studies are not given. It is not clear, for example, whether all potentially eligible patients were invited to participate or if investigators' discretion affected those included.

Although there are no figures for numbers of people considered for inclusion in the study, full details are given for the number of patients enrolled in the study and those who were actually eligible to participate (*Table 3*).

In all studies, those who were not eligible to participate did not have a confirmed diagnosis of the relevant phase of the disease. The numbers not eligible – 78 in the chronic phase, 54 in the accelerated phase and 31 in the blast phase – seem relatively high, although the CML phase was strictly defined in each study protocol. Results from Novartis presented in this report are on an intention-to-treat population.

Specific inclusion and exclusion criteria are described in all three studies. While a full list of inclusion and exclusion criteria are provided in the study reports supplied to us in advance of the industry submission (appendix 7), these are not included in the final industry submission from Novartis. One exclusion criterion, which is listed in all three studies, allowed for patients to be excluded "if they were considered by the investigator to be potentially unreliable". This clearly allows considerable potential for investigators to influence which patients were included. In the chronic phase study, the main inclusion criteria was IFN-α failure, defined as no HR within 3 months, no CR within 1 year, or IFN-α intolerance. This allows entry to the study at a number of different points in disease progression. In total, 63% of patients had been diagnosed for 2 years or more, with a median time from diagnosis of 32 months. Bias, in terms of quoted survival rates, is likely to be against imatinib in comparison to other chronic phase studies, where patients are generally recruited much earlier in the disease process.

Specific time periods for the use of other drugs for CML, prior to the accelerated and blast phase imatinib studies, are stated and listed as exclusion criteria. For example, patients should have been excluded from taking imatinib if they had been treated with IFN-α within 48 hours or ara-C within

TABLE 3 *Patients recruited to imatinib trials*

Study (phase)	Number recruited	Number eligible	Reason for ineligibility
110 (chronic)*[58]	532	454 (85%)	Chronic phase not confirmed
109 (accelerated)[13]	235	181 (77%)	Accelerated phase not confirmed
102 (blast)[59]	260	229 (88%)	Blast phase not confirmed

* *Failed IFN-α patients*

28 days. However, it is not clear whether these criteria were strictly applied. It could be that a patient using these drugs at the time of recruitment would be excluded, or that current prescription was stopped for the required period and then entered the study – 66% of those in the accelerated phase study had received prior treatment, as had 35% of those in the blast phase study. This latter group includes only those who had received treatment other than IFN-α, hydroxyurea or ara-C. Prior treatment with these drugs was permitted in the protocol and the numbers who had received them are not stated. It is not clear what effect this may have on outcomes.

Performance bias

Drug dosage: In all studies, the protocol for drug escalation, reduction and interruption is described. In the chronic phase study, details are not given about the number of patients who required dose adjustment. In the accelerated phase study, dose reductions because of adverse effects are reported in 49% of patients in the 400 mg group, and 52% of patients in the 600 mg group. In the blast phase study, drug reductions were reported in similar numbers of people: 43% of the 400 mg group and 47% of the 600 mg group. No details are given on drug escalation, which might be required to achieve or sustain a response.

Concomitant drugs: In the chronic phase study, all patients had "failed IFN-α" treatment previously and no concomitant cancer drugs were permitted. Allopurinol was permitted to counteract the effects of a rapid reduction in the number of WBCs and discontinued at the investigators' discretion. Any effects seen are likely to be a true reflection of the drug's effect.

In the accelerated and blast phase studies, it is stated that hydroxyurea use within 24 hours was an exclusion criteria although hydroxyurea (up to a maximum of 5 g/day) was also permitted concurrently within the trial period, including in the first 28 days. Anagrelide (to treat essential thrombocythemia), leukapheresis and allopurinol were also permitted within the first 28 days of the trial, as were colony-stimulating factors to treat febrile neutropenia or infection. It is assumed that other drug regimens may have been permitted outside this initial 28-day period, although this is not clearly stated. No details of concomitant drug use are provided in the reports.

No data were collected on patient compliance with treatment regimens but this was assumed by the study authors to be good.

Detection bias

No blinding was reported in these Phase II studies, that is those assessing clinical outcomes (including adverse effects), the care providers, and those assessing HR and CR, were all aware that the patient was taking imatinib. The patients themselves were aware that they were taking imatinib. This gives potential for bias, particularly around the reporting of adverse effects. This bias could be in either direction, but is more likely to result in under-reporting of symptoms, reflecting the understandable desire for the new therapy to be effective. However, the main outcome measures are moderately objective and not likely to be subject to substantial bias.

Attrition bias

All three studies in the industry submission state that intention-to-treat analyses are used for HR and CR rates.

Few details are reported on the number of people lost to follow-up. However, there were a large number of withdrawals, particularly from the accelerated and blast phase studies. In the chronic phase, 8% of patients were reported as having withdrawn from therapy (*Table 4*).

In the accelerated and blast phase studies, survival was censored at the time treatment was discontinued to allow bone marrow transplantation, or at the last recorded contact when patients were alive. In total, 43% of patients were reported as withdrawn from treatment.

External validity

Co-morbidity

Patients were excluded from the studies if they had liver disease, an ECOG Performance Status (see appendix 8) of 3 or higher, or severe cardiac disease. Other co-morbidity in the study sample is not reported.

Patient characteristics

Relatively little detail is given about patient characteristics to inform comparisons with other treatments. The patients are older than in most studies of CML therapies. A predominance of men are entered, as would be expected, with the exception of the accelerated study, when the male to female ratio is equal. No patients in Study 110 had extramedullary or lymph node involvement, and few (2%) had moderate splenomegaly. Haematological parameters seemed moderately well controlled. In Study 110, all patients had failed IFN-α treatment and 63% had been diagnosed for more than 2 years,

TABLE 4 *Reasons for withdrawal from protocol in imatinib studies*

Study (phase)	Sample	Withdrawals	Reasons for withdrawal*
110 (chronic)[58]	532	42 (8%)	Disease progression: 28 (5%) Adverse events: 8 (2%) Protocol violations: 2 (0.4%) Death during therapy: 2 (0.4%) Consent withdrawn: 1 (0.2%) Administrative reasons: 1 (0.2%)
109 (accelerated)[13]	235	100 (43%)	Disease progression/unsatisfactory therapeutic effect: 73 (31%) Adverse events: 14 (6%) Death during treatment: 7 (3%) Bone marrow therapy: 4 (2%) Withdrawal of consent: 2 (1%)
102 (blast)[59]	260	197 (76%)	Disease progression/unsatisfactory therapeutic effect: 134 (52%) Adverse events or laboratory test results: 25 (10%) Death during therapy: 20 (8%) Bone marrow therapy: 13 (5%) Protocol violations: 3 (1%) Withdrawal of consent: 2 (0.8%)

* *Percentages sum to more than total because of rounding*

longer than most studies. In Study 109, around a quarter had moderate splenomegaly, and the median WBC count was well above the normal range. In Study 102, extramedullary involvement was present in 70%, lymph node involvement in 10%, moderate splenomegaly in 27%. Haematological parameters were much poorer, with a median value for red cells, white cells and platelets all outside the normal range.

Risk factors

In assessing patient prognosis in the chronic phase of CML, two main scores, the Sokal score and the Hasford score (shown in appendix 1), have been used in pharmacological research. As discussed on page 3, some studies have shown a much bigger difference between risk groups than between treatment groups. In these studies, apparent differences in survival between treatments have disappeared when stratified for risk score.

The imatinib trials do not describe a risk score for patients enrolled. The rationale for this is that risk scores are only appropriate for newly diagnosed disease. However, Sokal's score was developed based on 813 non-blastic chronic granulocyte leukaemia patients who were treated between 1962 and 1981.[24] These patients were not all newly diagnosed. Indeed, early diagnosis was less frequent during that time than is currently the case. Later diagnosis, likely to be accompanied by gradually worsening factors that make up the risk score, such as higher WBC counts and blast cell counts, would simply translate into a higher proportion of patients found to be in higher-risk groups.[21] For the Hasford score, the time since diagnosis was at a median of 24 days (range 0–136),[22] which may make it unsuitable for use with this different patient group. However, there is considerable overlap between these two scores.

Lack of knowledge of risk scores makes comparison with other studies difficult. No risk scores exist for accelerated and blast phase patients. The industry submission comments that the definition of accelerated phase used in this study is more stringent than other authors have used, defining the accelerated phase as at least 15% blasts and less than 30% in the peripheral blood and bone marrow, rather than the less stringent definition of more than 5% but less than 30% blasts. A patient group with less favourable prognosis has therefore been selected. In addition, those patients in the chronic phase study have failed IFN-α treatment, and most have been diagnosed with CML for more than 2 years.

Statistical analyses

Power calculations were performed at the design stage of each study, and the numbers recruited

were sufficient to detect the outcomes specified. Appropriate statistical tests were carried out.

Subgroup analyses were not specified in the study protocol. This is a concern because a number of subgroup analyses were presented but it is not known how many overall were carried out and whether results were selectively reported.

Survival analysis is a loosely defined term encompassing a variety of statistical techniques for analysing variables such as time to death or time to failure of a component or system. The distinguishing feature from other analytic methods is that many of the observed data include only partial information, that is they are censored. For example, people participating in a study may drop out before the end-point is reached, or the study may finish before all participants have reached an end-point. In addition, some people may be lost to follow-up. In order to perform an analysis, an assumption must be made that the censoring is independent of the time at which it occurred, and of relevant covariates. Novartis have stated that all patients are followed up for survival even if they have withdrawn from treatment, which should minimise bias.

Landmark analysis, a type of survival analysis, is performed in the accelerated and blast phase studies. This takes all patients alive at a certain time point after entry to the trial and compares survival in two subgroups. This overestimates survival of the whole group, but is not biased in favour of one group. If the time at which the landmark analysis is carried out varies between studies, it is not possible to compare survival from this kind of analysis.

Duration of response
The length of follow-up in all the studies is short. It is not possible to draw conclusions about long-term duration of response.

Quality of evidence for effectiveness of other treatments for CML: chronic phase, RCTs

Descriptive comparison between CML treatments has been used in this review. In this section the included studies, both RCTs and case series studies, are considered against the quality criteria as specified above. Details of aspects of study quality are shown in appendices 7 and 9.

RCTs carried out in the chronic phase compare IFN-α with hydroxyurea or busulphan,[39,42,60–62] hydroxyurea with busulphan,[63] IFN-α alone with IFN-α combined with ara-C or hydroxyurea[45,64,65] or busulphan with lomustine with ara-C[18] (*Table 5*).

Internal validity

Selection bias
It is not clear whether all potentially eligible patients were invited to participate. In some studies, investigators had discretion about inclusion. No data are reported for numbers of people considered for inclusion in the study. The studies had different inclusion and exclusion criteria (see *Table 5*), but these are similar to those applied in the imatinib study, with the exception of time from diagnosis, which was generally much shorter. A review by the ASH reported that, "selective exclusion of patients from treatment post-randomisation (due to poor response, eligibility for bone marrow transplantation, or other factors) is a common methodological problem" in leukaemia studies, and clearly biases the results.[28]

Performance bias
The degree of discretion available to physicians to move patients between study arms and use additional drugs varied in the trials, as did the dosage of IFN-α. Again, the ASH review[28] comments there is often:

- failure to completely adhere to a standardised protocol
- variability in treatment regimens, which are not documented and in which clinicians are given latitude to alter the dosage or add other agents based on concerns around HR or toxicity
- crossover: patients allocated to received IFN-α are sometimes given chemotherapy when clinicians consider IFN-α ineffective or too toxic.

However this is not likely to substantially bias the comparison with imatinib made here.

Detection bias
None of the RCTs report that blinding was applied to patients or physicians. As chemotherapy is usually given orally while IFN-α is delivered subcutaneously, and there is a characteristic range of adverse effects often experienced with IFN-α, blinding is problematical for patients. However, blinded outcome assessment would be possible. A similar range of outcomes to the imatinib trial has generally been used.

Attrition bias
Six studies report complete follow-up.[18,39,60–62,65] However, the length of follow-up is not stated in two of these. The other studies do not document

TABLE 5 *Characteristics of RCTs of treatments for CML in the chronic phase*

Study	Intervention	Comparator	Median age (years)	Inclusion criteria	Exclusion criteria
Baccarani *et al.*, 1998[62]	IFN-α	BU or HU	41	NS	NS
The Benelux CML Study Group, 1998[64]	IFN-α	IFN-α plus HU	IFN-α 55.7 HU 56.4	Newly diagnosed, untreated, aged over 18, adequate hepatic and renal function	Abnormalities other than Ph+, not Ph+/BCR-ABL
Broustet *et al.*, 1991[60]	IFN-α	HU	55.6	Ph+ CML, absence of previous treatment, diagnosis < 3 months, aged over 18, absence of karyotypic abnormalities	*A priori* exclusion of those who would benefit from allograft
Giles *et al.*, 2000[65]	IFN-α	IFN-α plus ara-C	IFN-α 40 IFN-α + ara-C 42	ECOG score ≥ 2, baseline bilirubin ≤ 1.5 upper limit of normal range, not pregnant or lactating	Impaired cardiac status, MI within 3 months, angina needing medication, serious medical or psychiatric condition, hypersensitivity to IFN-α, autoimmune diseases, thyroid function abnormalities; history of another malignant disease within 5 years
Guilhot *et al.*, 1997[45]	IFN-α	IFN-α plus ara-C	IFN-α 51 IFN-α + ara-C 50	Under 70 years, Ph+ CML, chronic phase, diagnosis within preceding 6 months, previously treated only with HU	Accelerated or blast phases, history of depressive illness or psychiatric disorder, severe hepatic, renal or cardiovascular disorders
Hehlmann *et al.*, 1993[63]	HU	BU	49.7	One of: feeling ill/fatigue; weight loss > 10% in 6 months; fever > 38.5°C on 5+ days; organomegaly; leucocytes > 50 x 10^9/l; thrombocytosis > 1 x 10^{12}/l	Not in chronic phase; no treatment required; pretreatment with cytostatics, IFN-α or splenic irradiation; no informed consent; other neoplasia; "other reasons that made therapy according to protocol unlikely"
Hehlmann *et al.*, 1994[39]	IFN-α	BU or HU	IFN-α 47.4 BU 48.5 HU 46.9	Newly diagnosed, not pretreated, chronic phase; also six of: unexplained fatigue, weight loss > 10% in 6 months; fever of > 38.5°C on 5+ consecutive days; organomegaly-related symptoms, leucocytes > 50 x 10^9/l and/or thrombocytosis > 1 x 10^{12}/l	Living overseas/psychiatric problems/language barriers – too difficult to keep to protocol

continued

***TABLE 5* contd** *Characteristics of RCTs of treatments for CML in the chronic phase*

Study	Intervention	Comparator	Median age (years)	Inclusion criteria	Exclusion criteria
Ohnishi *et al.*, 1998[61]	IFN-α	BU	IFN-α 48% aged 50+ BU 47% aged 50+	Ph+ CML, chronic phase, no serious heart, liver or kidney disease, no severe infectious or psychiatric disorders, no other neoplasm, ECOG score of 0–2, aged 20–70, no hypersensitivity reaction	Accelerated or blast phase (defined)
Shepherd *et al.*, 1996[42]	IFN-α	BU or HU	IFN-α 56% aged 50+ Chemo 53% aged 50+	Under 75 years, chronic phase CML with no contra-indications to IFN-α therapy	NS
Silver *et al.*, 1992[18]	Lomustine	BU	< 50 53% > 50 47%	Demonstrated Ph+, leucocyte count ≥ 40,000/μl on two occasions not less than 24 hours or more than 96 hours apart, at least 80% of cells in PB of the granulocytic series, < 30% myeloblasts and promyelocytes in PB or bone marrow by 100 cell differential count on two occasions; hypercellular bone marrow aspirate or biopsy specimen, leucocyte alkaline phosphatase or biopsy specimen below 25	Previous treatment

how many withdrawals there were from the trial, and one reports a large number of post-randomisation exclusions.[65] Similar caveats to those applied to the imatinib studies therefore apply.

External validity

The trials vary enormously in the amount of detail reported on patient characteristics. The majority include a risk score, enabling some of the differences between trials to be explained in terms of patient selection. In general, the trials included people with a younger median age than those in the imatinib trials (median age range 40–60), but a similar male to female ratio. Performance status, haematological characteristics, splenomegaly and hepatomegaly are variably reported, making comparison difficult. No trials explicitly discuss co-morbidity.

Statistical analysis

An intention-to-treat analysis is reported in only two trials.[39,62] Five out of the ten RCTs report a power calculation,[39,45,61,63,64] but subgroup analyses are rarely reported as having been pre-specified. Analytic tests are generally appropriately used. However, the censoring rules in the survival analysis are not clearly explained.

Quality of evidence for effectiveness of other treatments for CML: chronic phase, case series studies

In addition to the randomised studies of IFN-α and chemotherapy for the chronic phase, 25 non-randomised observational studies of IFN-α and two of other therapies were identified. Some similar methodological problems to those identified in the randomised trials are evident.

Internal validity

See appendix 7 for further details.

Selection bias

The majority of case series reviewed do not give any details about their recruitment process. Even those reporting that consecutive patients were included do not state whether this was retrospectively or prospectively defined. If the former, there is potential for considerable bias in excluding patients with poor outcomes.

A range of inclusion and exclusion criteria are used. No inclusion criteria are stated in seven studies.[19,66–71] In addition, some of those that describe inclusion criteria are very broad, for example describing only a defined phase of CML,[72–76] while others are lengthy and include restrictions such as age and co-morbidity.

Performance bias

Drug dosage: For a full list of treatment regimens see appendix 10. In many cases, drug dose varied depending on WBC counts, disease progression or adverse effects.

- Busulphan. Drug doses varied and could be changed at the physician's discretion, depending on WBC counts. Initial doses could be between 4 and 6 mg or between 0.1 and 40 mg/kg a day.
- Hydroxyurea. Doses were often varied at the physician's discretion, depending on WBC counts. Initial oral doses of 1.5–50 mg/day were described.
- IFN-α regimens. The trials had various drug dose regimens, and IFN-α could be combined with hydroxyurea or ara-C. Interferons could be recombinant or human and either IFN-α or, occasionally, IFN-γ.

Daily subcutaneous IFN-α doses ranged from 3 to 9 MU. Those studies that combined IFN-α with ara-C also used various doses from 10 to 20 mg, in some cases varying at the physician's discretion, depending on patients' WBC counts. These ara-C regimens might be daily for 2 weeks initially, followed by 7 days every 4 weeks or for 5 days a week. In addition, many trials allowed the investigators discretion to dictate crossover to other regimens or alteration in the drug doses.

Concomitant drugs: In 14 case series studies in the chronic phase, no description of concomitant drug use was provided.[20,48,67–70,74,77–83] In the rest, co-treatment with hydroxyurea, busulphan or ara-C was permitted. No information about drugs supplied for other conditions was given. Some inclusion and exclusion criteria specify that no pretreatment for the studied phase of CML was permitted (see appendix 7 for details).

No information about patient compliance with prescribed regimens was reported.

Detection bias

Blinding of patients, care providers, assessors and outcomes were not reported in any study. Nine studies only included Ph+ CML patients,[40,46,73,75,76,78,79,82,84] but others did not specify this, so the denominator for calculating CR rates is not known.

Attrition bias

Ten studies do not report complete follow-up.[40,66–68,72,73,82,84–86] However, it is generally not clear whether the case series was retrospectively defined – in which follow-up is, almost by definition, complete – or prospectively defined. Six studies do not report on length of follow-up[68,72,76,79,82] and, while the majority of studies (24) do report some measure of length of follow-up, this varies considerably. Around half of the studies report on withdrawals, but in only a small proportion are figures for the number of withdrawals given. The way in which withdrawal from treatment is reported varies considerably between studies. Withdrawal may be for disease progression, bone marrow transplantation, death during treatment, or for intolerable adverse effects. Patients may also have withdrawn consent for treatment. In some cases reasons for withdrawal are not reported at all, while others report only death or only withdrawal from adverse effects. Withdrawal for adverse effects alone is discussed on page 46. Details of attrition can be seen in appendix 9.

External validity

Details of patient characteristics are presented in appendix 11. As would be expected from the epidemiology of CML, studies of CML treatments included a slightly higher proportion of male patients than female patients. Median age in chronic phase CML studies ranged from 41 to 60. Note that all intervention studies tended to recruit younger patients with CML, when compared to epidemiological studies. Performance status, haematological characteristics, hepatomegaly and splenomegaly are not reported in all studies.

There were also differences in the numbers of CML patients who had low prognostic risk scores.

Differences in the numbers of high- and low-risk patients have been used to explain some of the differences in survival and response that have been observed.[28] In ten[19,48,66,73,74,78,81,83,87,88] of the 27 case series in the chronic phase the distribution of Sokal scores for their study population is reported while the rest do not report a score. For those that report a score, the percentage of low-risk patients varies between 15% and 43% of study participants (appendix 11). The distribution of Sokal scores in the general population of people with CML is not known.

None of the studies describes or discusses co-morbidity in the sample of patients studied.

Statistical analysis

No studies report whether an intention-to-treat analysis was undertaken. None of the case series report a power calculation, and subgroup analysis is frequently performed but rarely reported as pre-specified (four studies). Analytic tests are generally appropriately used, although occasionally *p*-values (significance testing) are reported without commenting on which test was performed, and statements about strong associations made without any supporting statistical analysis.

The rules relating to withdrawals and censoring in the analyses are, in general, not clearly explained. This can have a considerable effect on the calculation of HR or CR rates, or on survival. The usual direction of bias is to increase the apparent response rates.

Efficacy – imatinib

Imatinib: published Phase I studies

Information on the efficacy of imatinib is sparse. Two Phase I studies have been published, one in patients with chronic phase CML[54] and one with those in the blast phase.[55]

In 2001, 83 patients in chronic phase CML who had failed IFN-α therapy were recruited by Druker and co-workers.[54] Fourteen successive dose cohorts from 25 to 1000 mg/day were used. A dose of 300 mg was found to be the threshold for a maximally effective dose. Of the patients treated at or above 300 mg/day, 98% showed a complete HR and 13% a complete CR.

No dose-limiting toxicity was reported. Most commonly reported adverse effects were nausea (43%), myalgia (41%), oedema (39%) and diarrhoea (25%).[54] Doses of 600–1000 mg/day increased the number of patients in the chronic phase experiencing grade 3 or 4 adverse effects.

Fifty-eight patients in blast crisis were treated with imatinib in oral doses ranging from 300 to 1000 mg/day.[55] Patients had Ph+ CML (n = 38) or Ph+ acute lymphoid leukaemia (n = 20). Four patients with CML (11%) had a complete HR and 17 (45%) had a decrease in blasts in the marrow to 15% or less.[55]

Over half (n = 32) of the patients suffered from nausea and 41% developed oedema. Oedema was grade 3 or 4 in 7% of patients. Two-thirds (n = 38) of patients also suffered from grade 3 or 4 neutropenia and two-thirds from thrombocytopenia.[55]

These studies were small and primarily designed to consider safety and dosage. Insufficient detail is given about patient population or follow-up to draw any conclusions about efficacy.

Imatinib: unpublished Phase II studies

This section considers the three Novartis trials described on page 16 more fully. Details of these trials compared to the others in this review are presented in tabular form in appendices 7–11.

All three trials were open-label non-randomised Phase II studies. They recruited patients with CML from between 18 and 27 centres in the USA and Europe, including two UK centres. No indication is given of how many patients were recruited at each centre. It is likely that aspects of standard care for patients with CML vary between countries, although these are not described. Other aspects of quality are discussed on page 16.

Inclusion and exclusion criteria

Specific inclusion and exclusion criteria are described in all three studies. A main inclusion criteria for Study 110 in the chronic phase was IFN-α failure, defined as no HR achieved within 3 months, no CR achieved within 1 year or IFN-α intolerance. For Studies 109 and 102, the main requirements were for the patients to be in the accelerated or blast phase respectively. Full details of the inclusion and exclusion criteria are given in appendix 7.

Drug dosage

Study 110 had an initial oral imatinib dose of 400 mg/day. This could be increased to 400 mg twice daily in the event of failure to achieve a complete HR, HR relapse or failure to achieve a CR.

Studies 102 and 109 both had an initial daily imatinib dose of 400 mg/day. However, this was increased by protocol to 600 mg when the results of the Phase I study became clear. About two-thirds of patients in Study 109 and 86% of those in Study 102 received a starting dose of 600 mg/day. Analyses are provided separately for those who started with 400 and 600 mg/day.

For patients who relapsed, dose escalation was permitted at the discretion of the investigator and if no response was achieved after a month of therapy. In the blast phase study, escalation of dosage occurred in 56% of patients who started on 400 mg/day and 35% of those who started on 600 mg/day.

Patient characteristics

Chronic phase – Study 110 (*n* = 532)

The patient group recruited was in mid to late chronic phase, with a median time from diagnosis of 34 months and a total of 63% of patients 2 years or more from diagnosis. The median age was 57 (range 18–90), and 40% of the patients were aged over 60. The male to female ratio was 1.5:1, and most patients (93%) had an ECOG score of 0 or 1 (see appendix 8). No patients had lymph node or extramedullary involvement, and only splenomegaly > 10 cm or hepatomegaly > 5 cm was reported (2% for each). Median haemoglobin was normal. No other details on co-morbidity were given. A risk score was not calculated.

Accelerated phase – Study 109 (*n* = 235)

In Study 109 the median age of the patients was 57 (range 22–86) and 66% had received prior therapy for accelerated phase disease. No information is given on the time since original diagnosis or since diagnosis of the accelerated phase. The male to female ratio was 1:1, and 79% were ECOG score 0 or 1; 58% had splenomegaly.

Blast phase – Study 102 (*n* = 260)

In Study 102, median age was 56 (range 19–81) and participants had been diagnosed with CML for a median of 3.4 years (range 1.5–5.8). They had been in blast phase CML for a median of 0.6 months (interquartile range 0.3–2.5) and were described as typical for patients with CML in blast crisis. Male to female ratio was 1.3:1, 70% had extramedullary involvement and 59% an ECOG score of 0 or 1. Median haemoglobin level was 9.3 g/l (mild anaemia).

Primary outcome measures

Objective outcome measures were used in all studies – survival, CR and HR. However, because the follow-up time for the studies is limited (see *Table 6*), the rates of CR and HR are used as proxy measures of efficacy in the chronic phase study in particular. The median duration of treatment times is given in *Table 6*.

Withdrawals

In total, 8% of patients in the chronic phase study, 34% in the accelerated phase study and 76% in the blast phase study were withdrawn, predominantly for disease progression. These patients were included in the overall survival analysis. An intention-to-treat analysis is reported for response rates.

Results

The results have been grouped by outcome, with a breakdown by stage within each outcome. *Figures 2* to *10* in this section have been reproduced from the industry submission.

Haematological response

Chronic phase: Complete HR was achieved in 89% of patients (95% CI not quoted, calculated for this report as 85–91% by a one-sample test of proportion, STATA). It should be noted that the criteria for a complete HR are a little less stringent than those used in some other chronic phase studies of CML (see page 3), in that up

TABLE 6 *Outcome measures used and length of treatment in imatinib studies*

Study (phase)	Stated primary outcome measure	Median length of treatment (range)
110 (chronic)[58]	Rate of major CR	11.4 months (0.5–13.7)
109 (accelerated)[13]	Rate of HR lasting ≥ 4 weeks*	400 mg group, 9.9 months (0.2–17) 600 mg group, 11.0 months (0.2–15)
102 (blast)[59]	Rate of HR lasting ≥ 4 weeks	400 mg group, 3.7 months (1.5–7.6†) 600 mg group, 4.0 months (1.9–7.4†)

* *Assessed as complete HR, marrow response, return to chronic phase or no response*
† *25th–75th quartiles*

to 5% of immature cells were allowed in the peripheral blood and relief from symptoms was not essential (see *Box 2*).

BOX 2 Haematological response

For chronic phase CML
WBC < 10×10^9/l, platelets < 450×10^9/l, myelocytes and metamyelocytes < 5% in peripheral blood, no blasts or promyelocytes in peripheral blood, < 20% basophils and no extramedullary involvement.

For accelerated/blast phase CML
Myeloblast count < 5% in marrow, no circulating peripheral blood blasts, neutrophil count ≥ 1.5×10^9/l, platelet count ≥ 100×10^9/l and no extramedullary involvement.

The difference in definition of HR in different phases of CML is explained as a reflection of the different aims of treatment – a return to the chronic phase for those in advanced stages, and a return to normal blood counts in the chronic phase.

Median time to achieve an HR was < 1 month, and 89% of patients responded within 3 months.

Duration of HR was not reported, but time to progression is reported in *Figure 2*.

Accelerated and blast phases: The primary end-point in the accelerated and blast phase studies was sustained HR (at least 4 weeks). In the accelerated phase, 69% of patients met this end-point. In total, 34% showed complete HR, and 22% had a return to the chronic phase (no CI quoted). The definition of complete HR in this study is shown in *Box 2*. Duration of HR, in those with sustained response, was estimated to exceed 1 year in 70% (95% CI, 61 to 80%) (*Figure 3*). There were, however, a large number of withdrawals and censored observations in the analysis (43%), which may give an unduly optimistic indication of duration of response.

In the blast phase study an overall HR of 29% (95% CI, 23 to 35%) was reported, of which 7% was complete and 20% a return to the chronic phase. Duration of HR is also reported for the blast phase in *Figure 4*.

Cytogenetic response
Chronic phase: This is used as the primary outcome measure in Study 110 and was defined as the best response measured at any stage over

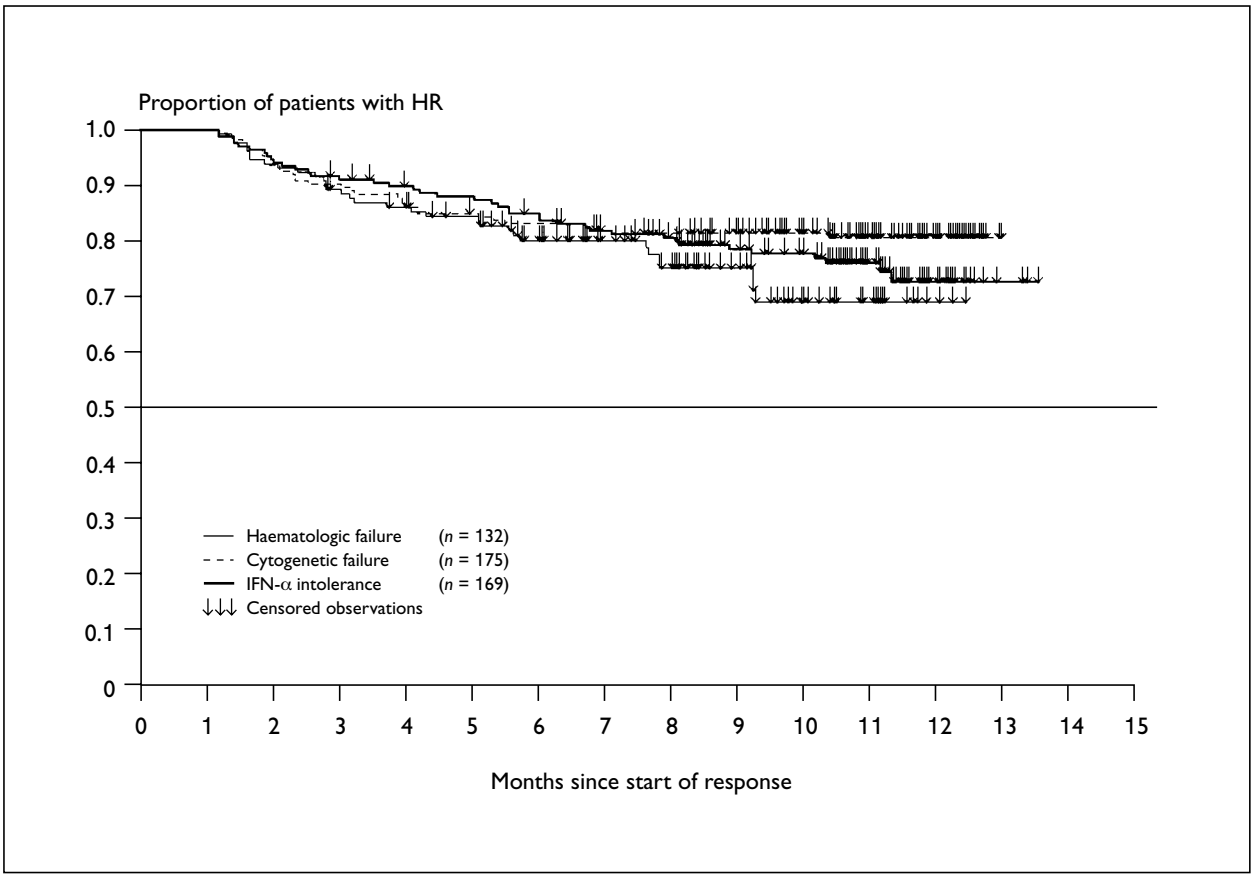


FIGURE 2 *Chronic phase: duration of complete HR (n = 476)*

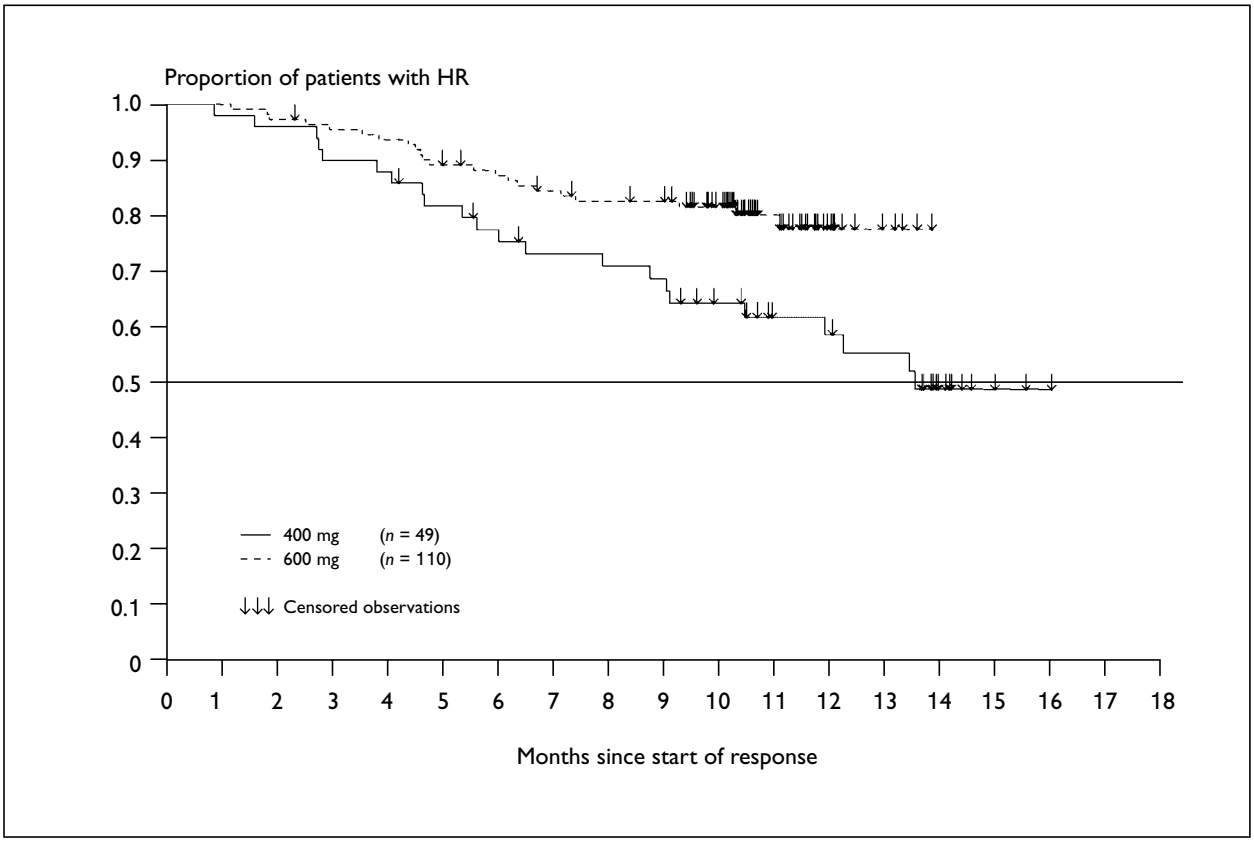


FIGURE 3 *Accelerated phase: duration of HR (*n *= 159)*

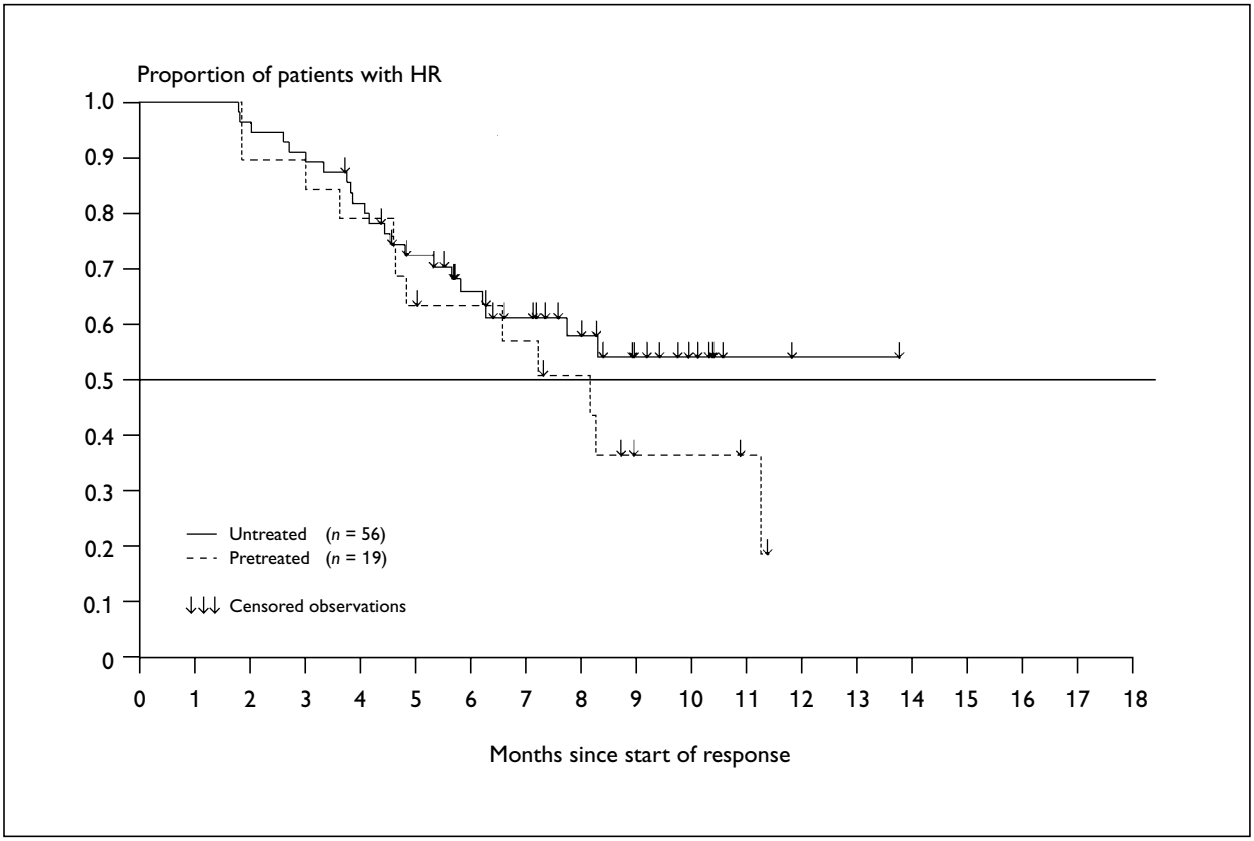


FIGURE 4 *Blast phase: duration of HR (*n *= 75)*

the follow-up and measured every 3 months. Major CR was reported in 55% and complete CR in 37% of patients and this is defined as the best response at any stage during the trial. Although 95% CIs were not reported, they were calculated by us to be 50 to 60% for major CR, and 33 to 41% for complete CR.

This study found that prior response to IFN-α (those who had cytogenetic relapse with IFN-α) was strongly predictive of a response with imatinib (odds ratio (OR) 4.3 compared to patients who were intolerant to IFN-α). A shorter time since diagnosis was also strongly predictive of a response to imatinib (OR 4.1 for diagnosis within a year compared to diagnosis over 3 years ago). Normal platelet count, normal haemoglobin and < 5% blasts in the marrow were also predictive of a CR, that is patients who traditionally would be in the lower risk categories are more likely to develop a CR with imatinib. Around half the people who achieved a major CR did so within the first 3 months. However, CRs were still being produced at a year (*Figure 5*).

Accelerated phase: In Study 109, a major CR was reported in 23% (95% CI, 18 to 31%) of patients and a complete CR in 17% (95% CI not quoted, calculated by us as 12 to 22%). Study 109 shows a difference in response between the dose groups. Among those receiving a starting dose of 600 mg/day a major CR was achieved by 27% (complete CR 19%) compared to 16% (complete CR 12%) for those on a 400 mg/day initial dose. Statistical significance was not reported, but was calculated by us (STATA™, comparison of two proportions) as just failing to reach statistical significance for major CR ($p = 0.07$) and not significant for complete CR ($p = 0.16$).

Blast phase: In Study 102 a major CR was reported in 16% (95% CI, 11 to 21%) of patients, and complete CR in 7% (95% CI not quoted, calculated as 3 to 10%). There was no difference in response rates between previously untreated and pretreated patients. However, it is stated in the text that there is a strong relationship with dose for major CR. In total, 17% of patients given 600 mg and only 6% of patients taking 400 mg of imatinib a day achieved a major CR. Our calculation suggests this difference is not statistically significant ($p = 0.09$).

Disease progression

Chronic phase: In total, 9% (95% CI, 6 to 11%) of the cohort are estimated to have progressed

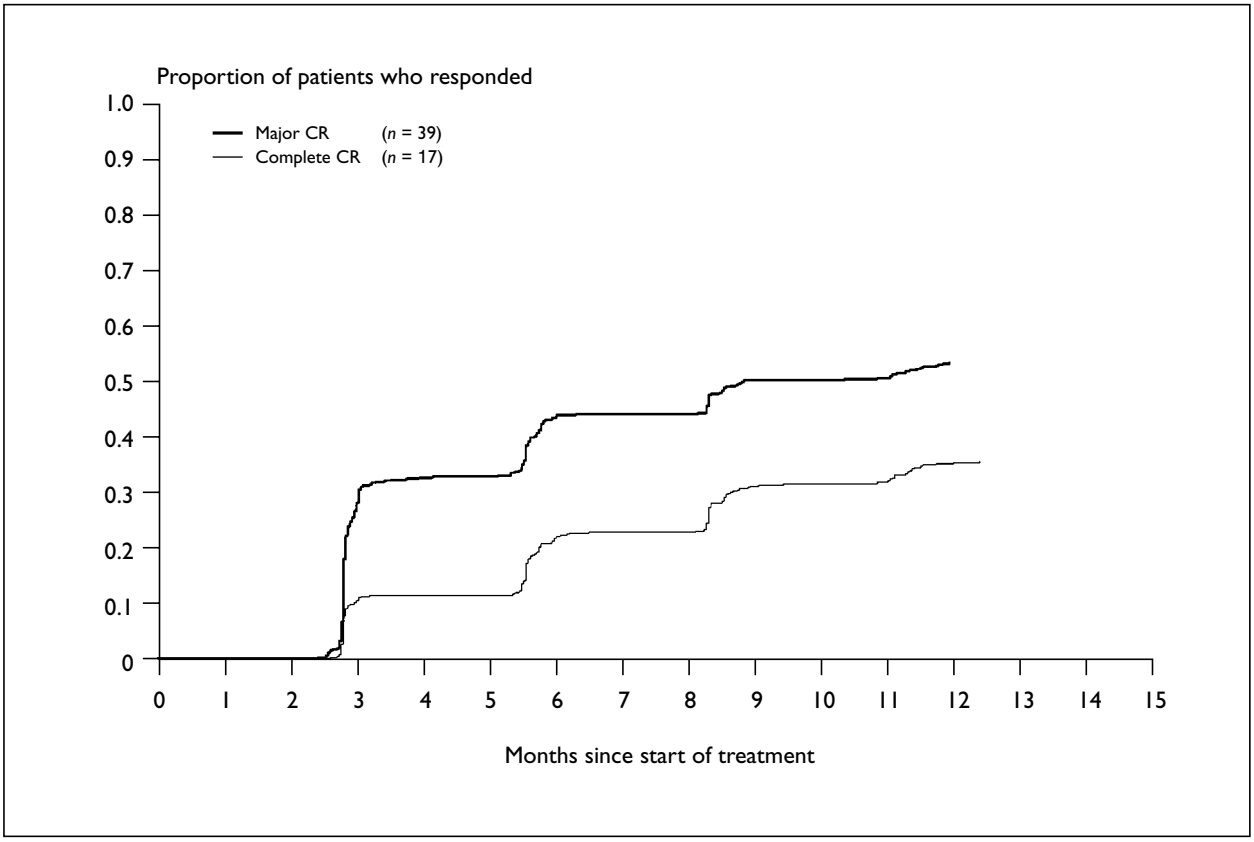


FIGURE 5 *Chronic phase: time to major and complete CR*

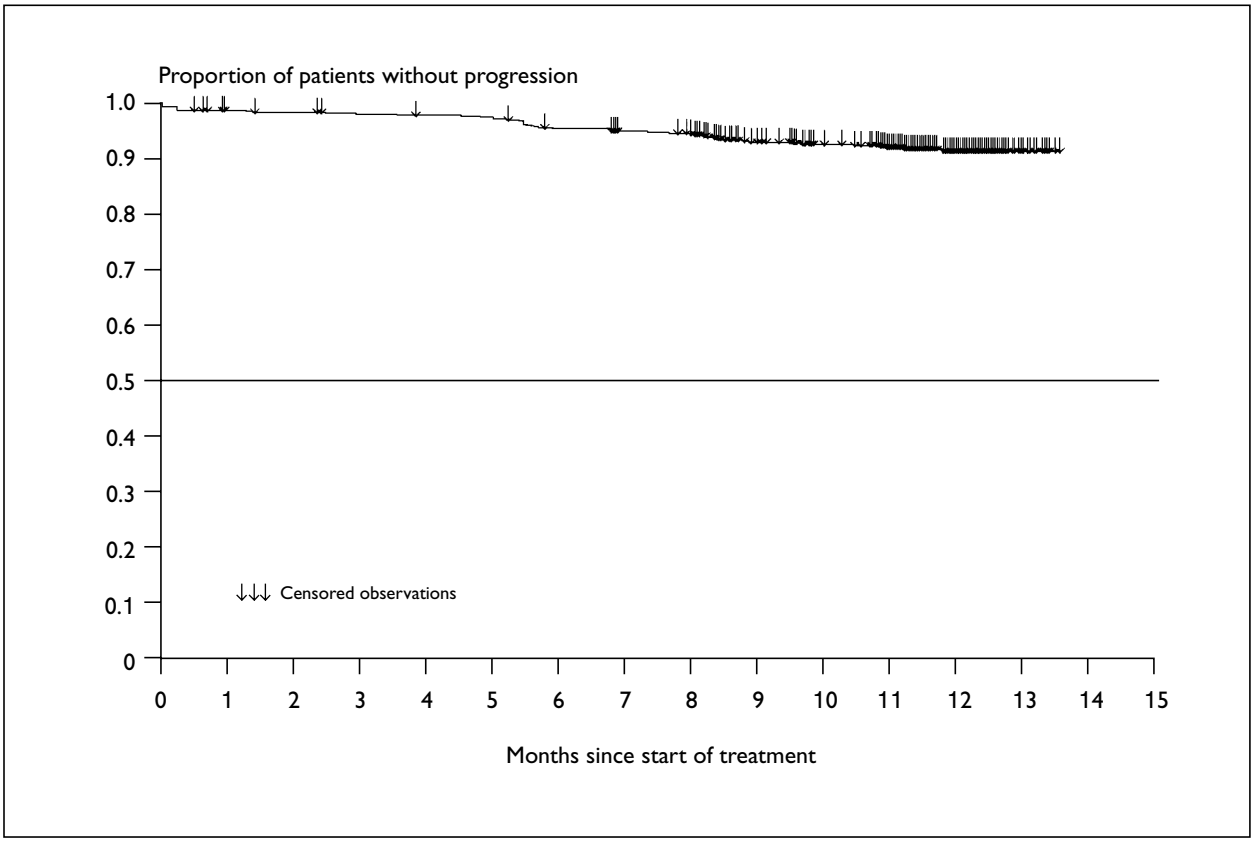


FIGURE 6 *Chronic phase: time to accelerated or blast phase (n = 454)*

to the accelerated or blast phase at 1 year (*Figure 6*). Study follow-up has been too short so far to give a reliable estimate of response duration. However, it should be noted that 62% of patients in this study had been diagnosed with CML for 2 or more years, in contrast to other treatment studies in CML where patients were recruited shortly after diagnosis. Disease progression on imatinib may therefore be better than would be expected given time since diagnosis, although this is speculative.

Accelerated phase: The median duration of CR was reported as 7.4 months for the 400 mg group and 10.2 months for the 600 mg group. A haemoglobin level > 10 g/l at the beginning of the study was the best predictor of prolonged remission. Being female, and starting on an initial dose of 600 mg imatinib, were also predictive. *Figure 7* shows time to disease progression.

Blast phase: Median duration of HR was 8.3 months (95% CI, lower limit 6.3, upper limit not definable) for those achieving a sustained response. Progression-free survival is not reported. Duration of CR is not reported.

Survival at 1 year

Chronic phase: Study 110 estimates progression-free survival of 90% (95% CI, 89 to 94%) at 1 year of follow-up. Overall survival at 1 year for the 454 patients with confirmed chronic phase CML is reported as 97%. It should be noted, however, that this survival time is at 1 year from starting imatinib treatment, rather than from time of diagnosis, and 62% had been diagnosed with CML for 2 or more years. The survival may be affected in two different ways – on the one hand, those with a longer time since diagnosis would be expected to have a lower survival rate than newly diagnosed patients but it may also mean that the patients with the poorest prognosis have already died, leaving a population with better prognosis in the imatinib group.

Accelerated phase: Study 109 reports 74% survival at 1 year (95% CI, 68 to 81%), and progression-free survival of 59% (95% CI, 52 to 66%) (*Figure 8*). Multivariate analysis suggests that a starting dose of 600 mg was significantly associated with survival and disease-free progression. Survival and progression-free survival were 78% (95% CI, 70 to 87%) and 67% (95% CI, 58 to 76%) respectively in the 600 mg group.

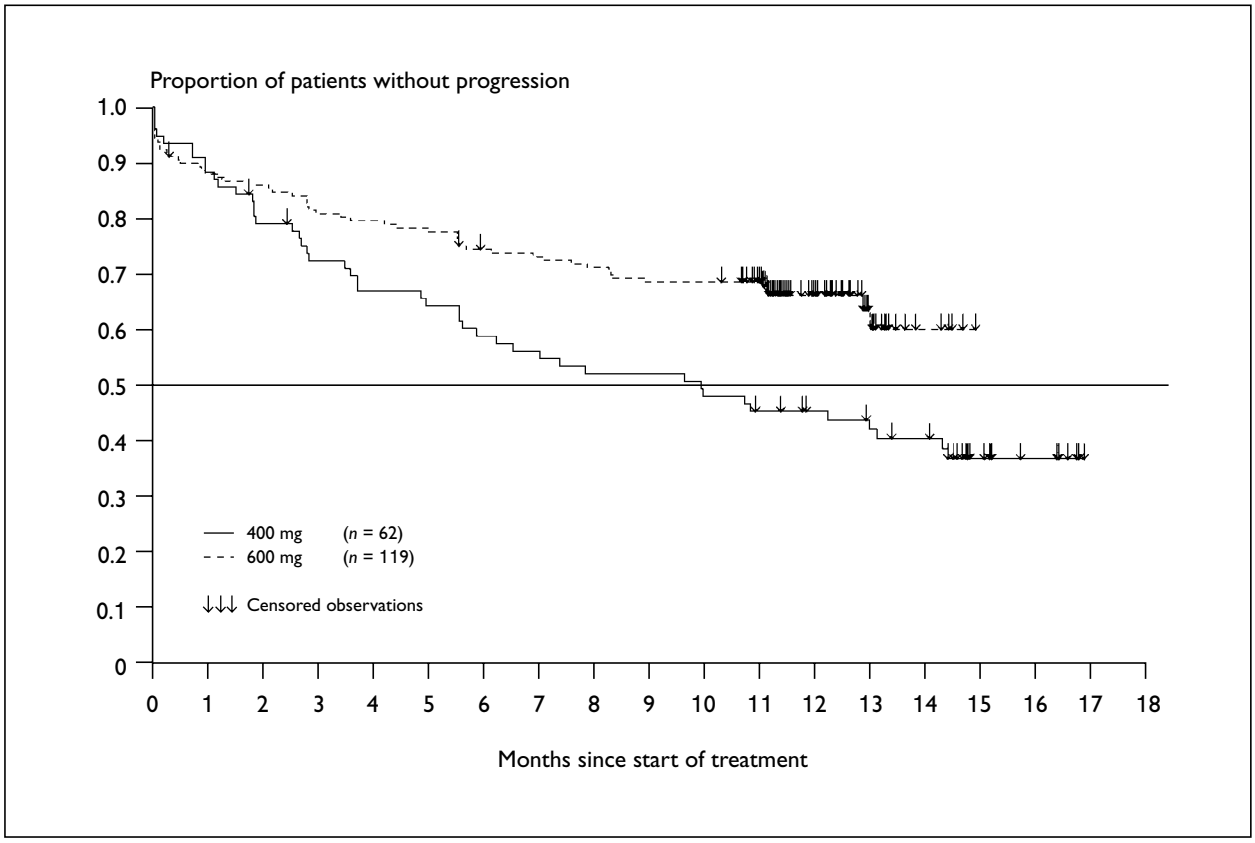


FIGURE 7 *Accelerated phase: time to disease progression*

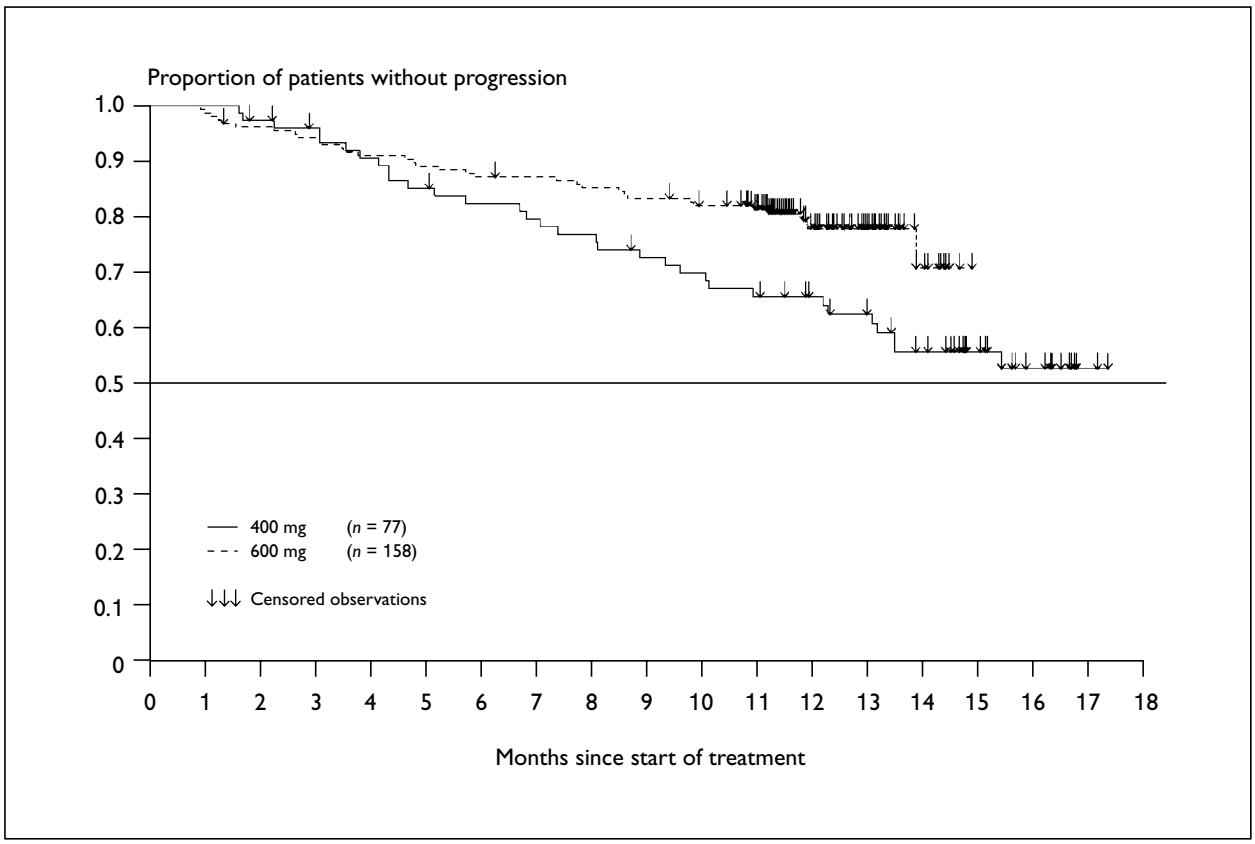


FIGURE 8 *Accelerated phase: overall survival*

There were, however, a large number of withdrawals and censored observations in the survival analysis, which may lead to overestimation of survival during the study period and give an unduly optimistic indication of long-term survival.

Blast phase: Median survival was reported as 6.9 months (95% CI, 5.7 to 8.7). In previously untreated patients median survival was 7.5 months, compared to 5.6 months for those pretreated (*Figure 9*). Estimated 1-year survival rates are 30.4% overall, and 27.9% for the 600 mg dose group (i.e. a higher initial dose was not associated with prolonged survival, despite higher HR and CR). Predictive factors of prolonged survival were platelet count < 100×10^9/l and < 50% blasts in the peripheral blood.

The landmark analysis curves in the blast phase of predicted 1-year survival show an initial survival advantage for those obtaining a CR at 3 months. However, this advantage is short-lived and does not extend beyond about 11 months, where the survival curves converge (*Figure 10*). Conversely, patients with an HR show a marked survival advantage. Of those alive at 3 months, 77% of haematological responders were still alive at 1 year compared to 21% of non-responders ($p < 0.001$, log-rank test) (*Figure 11*). The numbers in each group of patients is unclear from the reports.

Table 7 summarises the major outcomes for imatinib in chronic, accelerated and blast phase CML.

Imatinib in context – key haematological, cytogenetic and survival results for CML treatments

Key results for all the studies included in the assessment are summarised in *Tables 8* and *9* (further details are provided in appendix 12). Where necessary, results have been recalculated on an intention-to-treat basis. The different arms in the RCTs have been reported separately, according to the treatment given. As no RCT data for imatinib exists, comparisons with other treatments have had to be made, despite the considerable limitations inherent in this approach. Comparisons with other studies and treatments are difficult because of the differences, both known and unknown, in the characteristics of the patients recruited, the uncertain times since

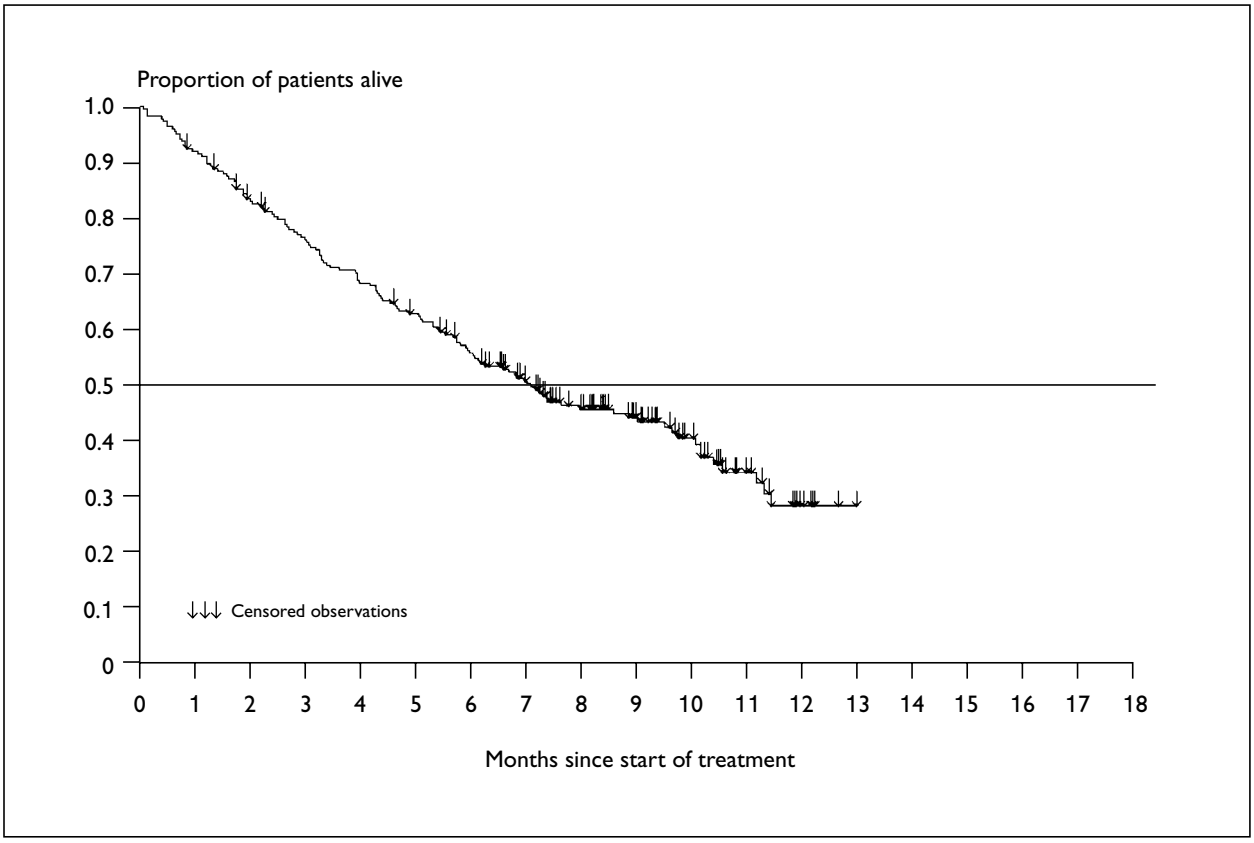


FIGURE 9 *Blast phase: overall survival for 600 mg dose* (n = *223)*

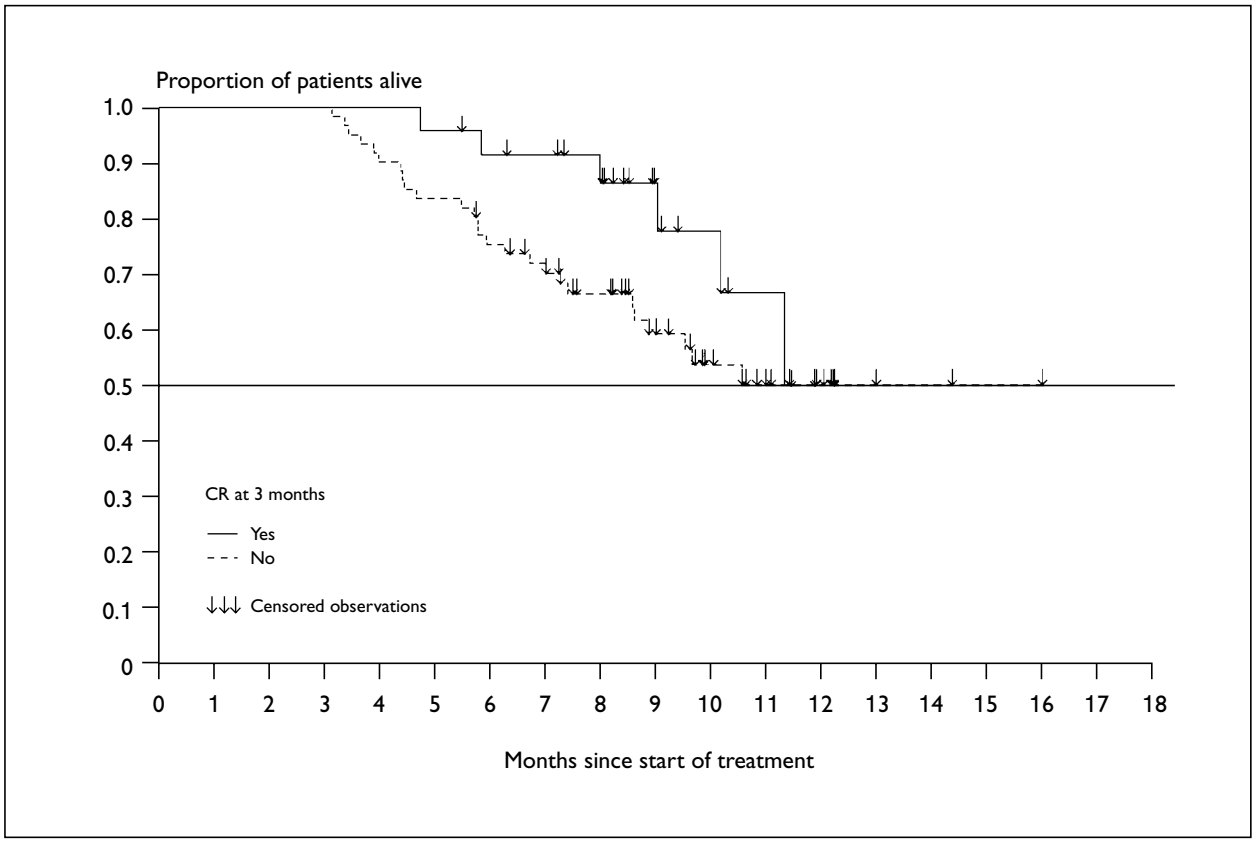


FIGURE 10 *Blast phase: landmark analysis of survival by CR at 3 months*

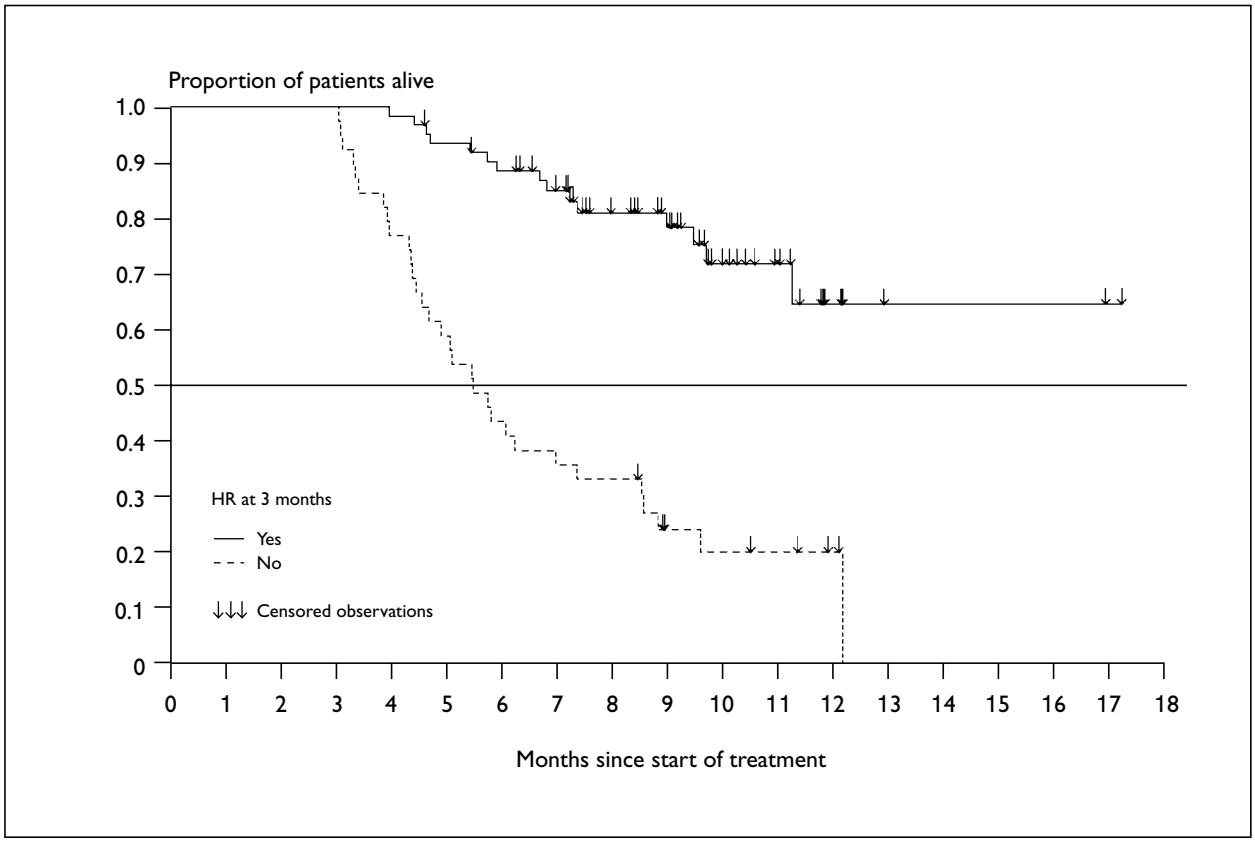


FIGURE 11 *Blast phase: landmark analysis of survival by HR at 3 months*

TABLE 7 *Summary of major outcomes for the imatinib studies*

Study (phase)	Complete HR (95% CI)	Complete CR (95% CI)	Survival at 1 year (95% CI)
110 (chronic)[58]	89% (86.2 to 91.6)	36% (31.7 to 40.5)	97% (95.1 to 98.1)
109 (accelerated)[13]	35% (28.8 to 41.0)	17% (12.2 to 21.8)	74% (68.4 to 76.9)
102 (blast)[59]	7% (4.16 to 10.7)	7% (4.16 to 10.7)	30% (24.4 to 35.6)

TABLE 8 *Key results reported in chronic phase studies*

Study	RCT	Sample size	Treatment	Survival at 1 year (%)	Complete HR (%)	Complete CR (%)
Kantarjian *et al.*, 2001[58]	No	523	Imatinib	97 (95–98)	89 (86–92)	36 (32–40)
Baccarani *et al.*, 1998[62]	Yes	218	IFN-α	95	–	4
Broustet *et al.*, 1991[60]	Yes	30	IFN-α	–	–	7
Guilhot *et al.*, 1997[45]	Yes	361	IFN-α	97	55	9
Hehlmann *et al.*, 1994[39]	Yes	133	IFN-α	96	31	5
Ohnishi *et al.*, 1998[61]	Yes	85	IFN-α	98	–	8
Shepherd *et al.*, 1996[42]	Yes	293	IFN-α	94	–	–
Alimena *et al.*, 1990[66]	No	114	IFN-α	–	54	2
Beck *et al.*, 2001[89]	No	721	IFN-α	–	64	–
Cortes *et al.*, 1996[20]	No	35	IFN-α	97	69	20
Fernandez-Ranada *et al.*, 1993[85]	No	51	IFN-α	–	53	6
Freund *et al.*, 1989[67]	No	27	IFN-α	–	37	0
Giles *et al.*, 1992[72]	No	23	IFN-α	100	–	–
Guilhot *et al.*, 1991[73]	No	24	IFN-α	92	75	46
Kloke *et al.*, 2000[69]	No	71	IFN-α	97	–	13
Mahon *et al.*, 1996[78]	No	81	IFN-α	97	82	38
Mahon *et al.*, 1998[74]	No	116	IFN-α	98	84	33
Ozer *et al.*, 1993[79]	No	128	IFN-α	–	19	11
Russo *et al.*, 1995[84]	No	272	IFN-α	98.5	–	3
Sanchez *et al.*, 1992[75]	No	29	IFN-α	–	24	10
Schofield *et al.*, 1994[71]	No	41	IFN-α	–	61	7
Shtalrid *et al.*, 1993[76]	No	30	IFN-α	–	57	–
Talpaz *et al.*, 1987[19]	No	51	IFN-α	–	71	10
Thaler *et al.*, 1996[81]	No	80	IFN-α	–	36	8
The Benelux CML Study Group, 1998[64]	Yes	95	HU	97	38	0
Broustet *et al.*, 1991[60]	Yes	26	HU	–	–	0
Hehlmann *et al.*, 1993[63]	Yes	232	HU	96	–	0.4
Hehlmann *et al.*, 1994[39]	Yes	194	HU	96	39	1
Baccarani *et al.*, 1998[62]	Yes	104	HU, BU	96	–	0
Shepherd *et al.*, 1996[42]	Yes	294	HU, BU	93	–	–
Hehlmann *et al.*, 1993[63]	Yes	226	BU	96	–	0
Hehlmann *et al.*, 1994[39]	Yes	186	BU	96	23	0
Ohnishi *et al.*, 1998[61]	Yes	85	BU	94	–	–
Silver *et al.*, 1992[18]	Yes	32	BU	91	–	–
The Benelux CML Study Group, 1998[64]	Yes	100	IFN-α + HU	98	62	9

continued

***TABLE 8* contd** *Key results reported in chronic phase studies*

Study	RCT	Sample size	Treatment	Survival at 1 year (%)	Complete HR (%)	Complete CR (%)
Giles *et al.*, 2000[65]	Yes	79	IFN-α + HU	97	79	6
Tothova *et al.*, 2000[82]	Yes	22	IFN-α + HU	–	62	0
Freund *et al.*, 1993[90]	Yes	46	IFN-α + BU	–	59	13
Freund *et al.*, 1993[90]	Yes	48	IFN-α + ara-C	–	50	0
Giles *et al.*, 2000[65]	Yes	64	IFN-α + ara-C	100	74	5
Guilhot *et al.*, 1997[45]	Yes	360	IFN-α + ara-C	97	66	15
Tothova *et al.*, 2000[82]	Yes	21	IFN-α + ara-C	–	79	5
Arthur and Ma, 1993[87]	No	30	IFN-α + ara-C	–	93	30
Beck *et al.*, 2001[89]	No	721	IFN-α + ara-C	–	73	–
Thaler *et al.*, 1997[46]	No	91	IFN-α + ara-C	–	49	16
Giles *et al.*, 2001[88]	No	74	IFN-α + ara-C + HU	100	82	31
Sacchi *et al.*, 1997[70]	No	137	IFN-α + ara-C + HU	87	51	2
Hochhaus *et al.*, 1996[68]	No	133	IFN-α + HU + BU + ara-C	–	–	18
Kantarjian *et al.*, 1991[40]	No	96	IFN-α + combination	–	–	41
Silver *et al.*, 1992[18]	Yes	54	ara-C	89	69	–
Kantarjian *et al.*, 2000[48]	No	105	Other chemo	94	71	5
O'Brien *et al.*, 1995[83]	No	71	HHT	85	59	6

Note that these results are not necessarily comparable, hence numerical superiority does not necessarily indicate greater clinical effectiveness and difference between survival and response rates cannot be used to indicate the size of that effect

diagnosis in many studies, and the large numbers of withdrawals or losses to follow-up in many studies. Furthermore, publication bias is likely to operate in favour of positive results. Considerable caution must therefore be used in interpreting these study results.

Patient characteristics

Chronic phase: In general, other therapies have been studied in younger populations than those included in the imatinib trial. A similar male to female ratio is seen. *Table 10* shows the range of patient characteristics reported in the RCTs and those reported in Study 110 for imatinib in the chronic phase. As far as can be judged, patients appear to be of similar, or less severe, disease in the imatinib study. The main difference is the length of time from diagnosis, with 62% of imatinib patients having been diagnosed for 2 or more years compared to other trials that include recently diagnosed patients.

Accelerated and blast phases: The median age range for imatinib trials is 56, for both accelerated and blast phases, whereas trials of other therapies tend to be on younger populations. Male to female ratio is similar to the imatinib trials. *Table 11* shows the range of patient characteristics reported in case series studies of treatments for accelerated and blast phase CML.

Length of follow-up

In the chronic phase, median length of follow-up also varies substantially between studies, from 14 to 145 months (range 1–155). However, length of follow-up is not always clear from study reports. Accelerated or blast phase studies are even less clear, with only two studies clearly reporting follow-up times.[48,95]

Where long-term follow-up is described in included studies, reports of survival data at 1 year have often been estimated from survival curves and may be inaccurate.

Chronic phase results

It should be noted that the case series tend to report better complete HR and CR than the RCTs; a comparison of mean CR between RCTs and case series was significant at $p < 0.05$ (t-test). *Table 12* shows key outcomes for imatinib and comparators. Values for imatinib are included, shown separately for ease of comparison. Imatinib trials only provide survival data at 1 year, and this may not be wholly comparable, as previously discussed. However, as can be seen, during chronic phase treatment, survival at 1 year is usually high and varies little between treatments.

In the chronic phase, the results for imatinib are equivalent for survival and considerably better for

TABLE 9 *Key results reported in accelerated and blast phase studies*

Study	Sample size	Treatment	Survival at 1 year (%)	Complete HR (%)	Complete CR (%)	Myeloid crisis (%)
Accelerated phase						
Talpaz *et al.*, 2001[13]	235	Imatinib	74 (68–77)	35 (29–41)	17 (12–22)	
Kantarjian *et al.*, 1992[44]	20	IFN-α + ara-C		50	20	
Carella *et al.*, 1994 A[91]	22	Other chemo	–	–	23	
Kantarjian *et al.*, 1992 A[12]	24	Other chemo	37	25	4	
Kantarjian *et al.*, 1997 A[92]	20	Other chemo	28	35	0	
Accelerated/blast phase						
Dutcher *et al.*, 1992[93]	40	Other chemo	37	–	13	
Blast phase						
Sawyers *et al.*, 2001[59]	260	Imatinib	30 (24–36)	7 (4.2–10.7)	7 (4.2–10.7)	100
Coleman *et al.*, 1980 RCT[94]	Arm I 83 Arm II 140	Other chemo	–	Arm I 13 Arm II 11	–	–
Alimena *et al.*, 1996[95]	71	IFN-α				72
Canellos *et al.*, 1971[96]	30	Other chemo	–	20	–	–
Carella *et al.*, 1994 B[91]	38	Other chemo	–	–	21	–
Hernandez-Boluda *et al.*, 2001[97]	60	Other chemo	–	5	–	86
Iacoboni *et al.*, 1986[98]	21	Other chemo	–	23	–	71
Kantarjian *et al.*, 1988[99]	27	Other chemo	–	26	–	–
Kantarjian *et al.*, 1992 B[12]	24	Other chemo	18	33	8	87
Kantarjian *et al.*, 1997 B[92]	17	Other chemo	10	10	0	75
Pedersen-Bjergaard *et al.*, 1977[100]	24	Other chemo	0	25	–	–
Vallejos *et al.*, 1974[101]	39	Other chemo	–	10	–	–
Winton *et al.*, 1981[102]	30	Other chemo	–	0	–	–

Note that these results are not necessarily comparable, hence numerical superiority does not necessarily indicate greater clinical effectiveness and difference between survival and response rates cannot be used to indicate the size of that effect

A = accelerated phase; B = blast phase

TABLE 10 *Range of patient characteristics in RCTs for chronic phase CML*

	RCTs	Imatinib Study 110
Performance status	78–94% in ECOG stage 0 or 1	91% in ECOG stage 0 or 1
Median haemoglobin level reported	10–12 g/dl	12.4 g/dl
Splenomegaly	61–78% (any enlargement)	2% ≥ 10 cm below costal margin
Hepatomegaly	44–49% (any enlargement)	2% ≥ 5 cm below costal margin
Extramedullary involvement	6%	6%
Median age range	47–59	57

TABLE 11 *Range of patient characteristics in case series studies for accelerated and blast phase CML*

	Case series	Imatinib Studies 109, 102
Performance status	60–81% in ECOG stage 0 or 1	58–77% in ECOG stage 0 or 1
Haemoglobin level reported	63–76% < 10 g/dl	Median 92 g/l*
Splenomegaly (any)	28–55% (any enlargement)	25–67% ≥ 10 cm below costal margin
Median platelets	50–135 x 10^9/l	75–263 x 10^9/l
Median age range	41–60	56–56

* *Haemoglobin levels only reported for Study 109*

TABLE 12 *Summary of RCTs and case studies: survival and complete response rates, chronic phase*

	RCTs	Case series	Imatinib
Survival % at 1 year			
Median	96	97.5	97
Range	93–98	87–100	
Complete HR (%)			
Median	55	63	89
Range	23–79	22–93	
Complete CR (%)			
Median	4	12	36
Range	0–15	0–46	

Note that means and CIs are not calculated because these studies are extremely heterogeneous in nature and of greatly varying size

HR and CR. The comparison of 1-year survival is not ideal as nearly two-thirds of the imatinib trial patients had been diagnosed with CML for more than 2 years and most of the study populations for the other treatments are enrolled as newly diagnosed with CML, or have received the diagnosis within 1 year of starting the study. This may underestimate the survival advantage with imatinib. In contrast, 8% of patients withdrew from the study because of disease progression, which may lead to the survival rate being overestimated.

We cannot estimate the likely effects of bias arising from different study designs, but some exploration of potential confounders has been carried out. The following figures are scatter plots of results from all reported studies of treatments for CML, including imatinib, according to factors that might be expected to affect the level of complete HR and major CR found among different study populations. For each figure, one point represents one treatment arm of a study and the points are coded by treatment. The trend line on each scatter plot is based on patients who have received IFN-α in combination with another drug such as hydroxyurea or ara-C, as the IFN-α combination seems to offer the best results among existing drug treatments. The number of points on each graph differs, according to the number of studies providing the information required.

Figures 12–14 show scatter plots of the percentage of study patients in the chronic phase of CML achieving a complete HR against various factors –

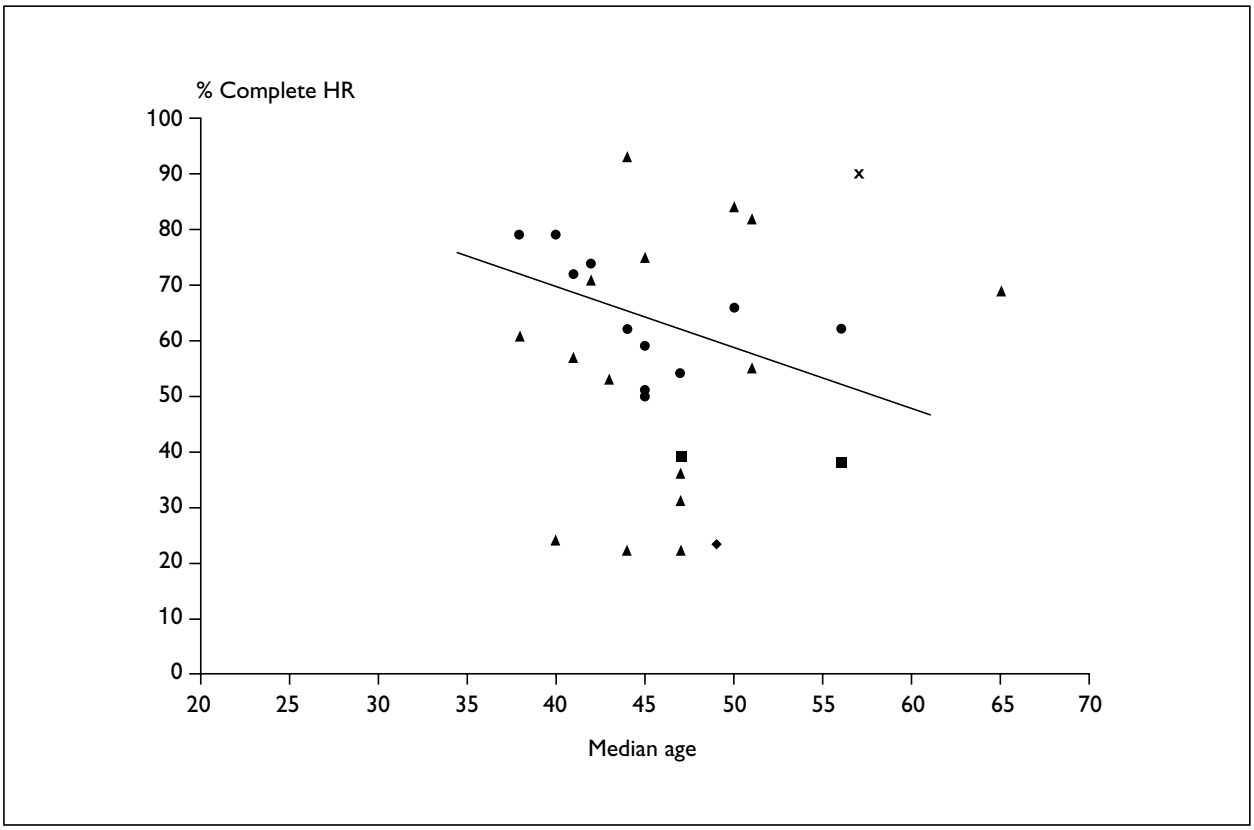


FIGURE 12 *Complete HR in the chronic phase by median age (◆, busulphan; ■, hydroxyurea; ▲, IFN alone; ●, IFN plus; ✕, imatinib; ——, linear trend (IFN plus))*

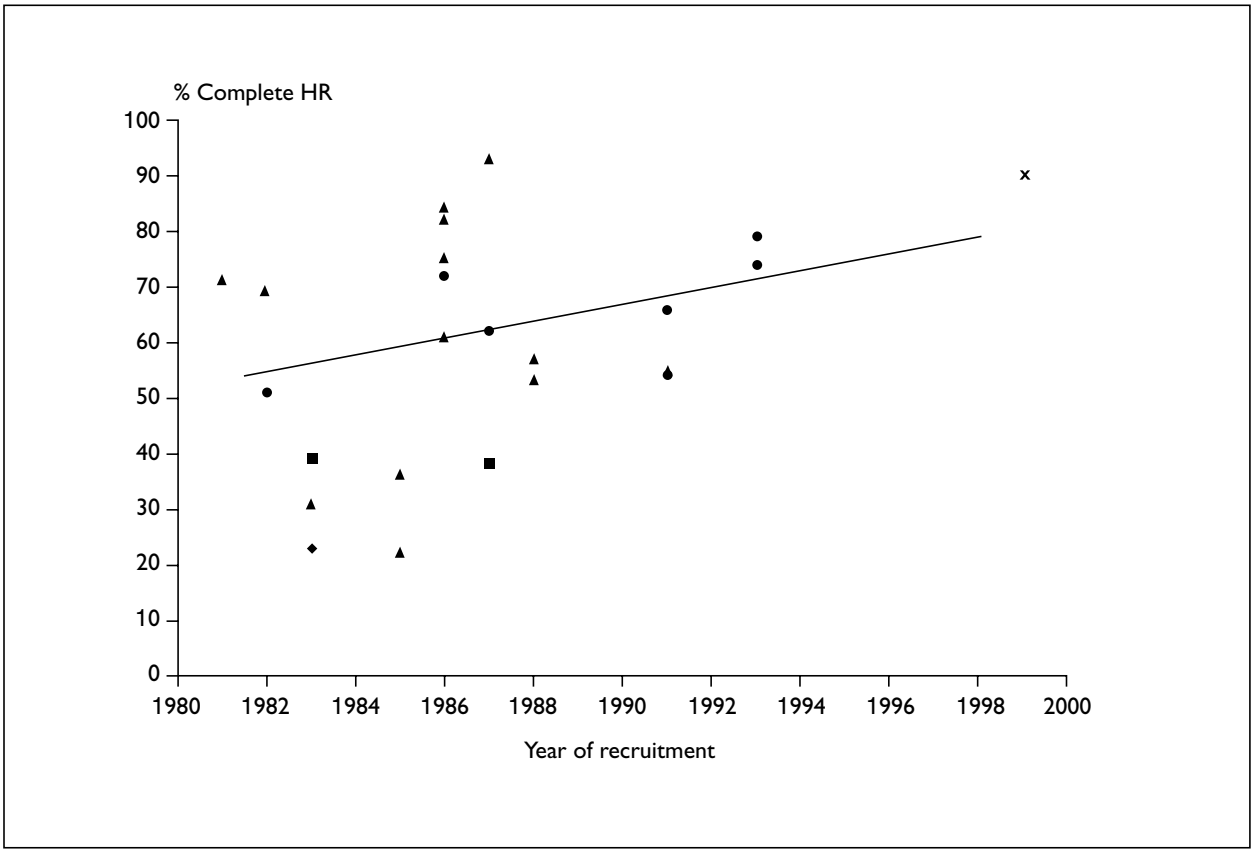


FIGURE 13 *Complete HR in the chronic phase by year of recruitment (◆, busulphan; ■, hydroxyurea; ▲, IFN alone; ●, IFN plus;* **X**, *imatinib; ——, linear trend (IFN plus))*

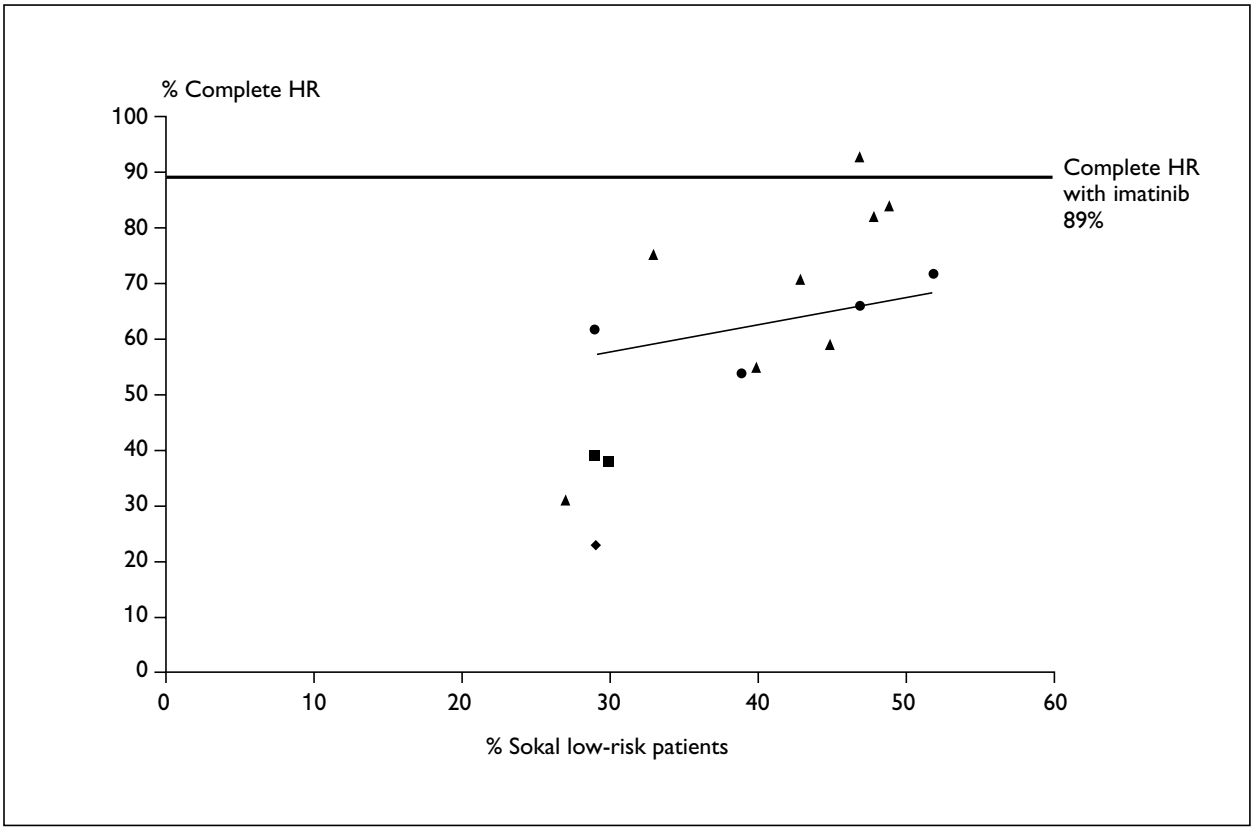


FIGURE 14 *Complete HR in the chronic phase by percentage of low-risk patients (◆, busulphan; ■, hydroxyurea; ▲, IFN alone; ●, IFN plus;* **X**, *imatinib; ——, linear trend (IFN plus))*

median age of the study patients, the percentage of patients categorised as low risk by Sokal or Hasford score, and the date of recruitment to the studies (as a proxy for earlier diagnosis and improved concurrent treatment). IFN-α treatments combined with ara-C or hydroxyurea are coded as 'IFN plus' in the key.

Figure 12 shows complete HRs plotted against the median age of study patients. The trend line indicates a decline in complete HR with increasing age. However, the imatinib plot is well above the trend line. A high proportion of patients taking imatinib achieve a complete HR despite the relatively older median age of the patients in the trial compared to other studies.

Figure 13 shows complete HRs plotted against the year of recruitment into a trial. The trend line indicates a slight increase in complete HR with later date of recruitment. Imatinib is slightly above this line. The one IFN-α study point that has a higher complete HR is based on results from a small sample of 30 patients.

Figure 14 shows complete HR against the percentage of patients in the sample who were classified as being at low risk using Sokal score or Hasford score. Imatinib patients were not so classified but a line has been inserted to show the complete HR of this study. This suggests that even if the imatinib had contained a high proportion of low-risk patients, the level of complete HR achieved with imatinib remains high compared to other trials included.

Overall, *Figures 12–14* show imatinib produces high levels of HR in patients, above that which might be expected from other therapies, taking into account some possible confounders.

Figures 15–17 show scatter plots of the percentage of study patients in the chronic phase of CML achieving a major CR (complete plus partial CR) against various factors – median age of the study patients, the percentage of patients categorised as low risk by Sokal or Hasford score and the date of recruitment. These factors may be confounders for major CR achieved and treatment details. Major CR was used here as we wanted to use as much comparative data as possible, and some studies did not report a complete CR. In addition, these categories represent a continuum of response given the level of accuracy of cytogenetic tests used to measure such a response (see page 1). This presentation allows a graphic illustration of the

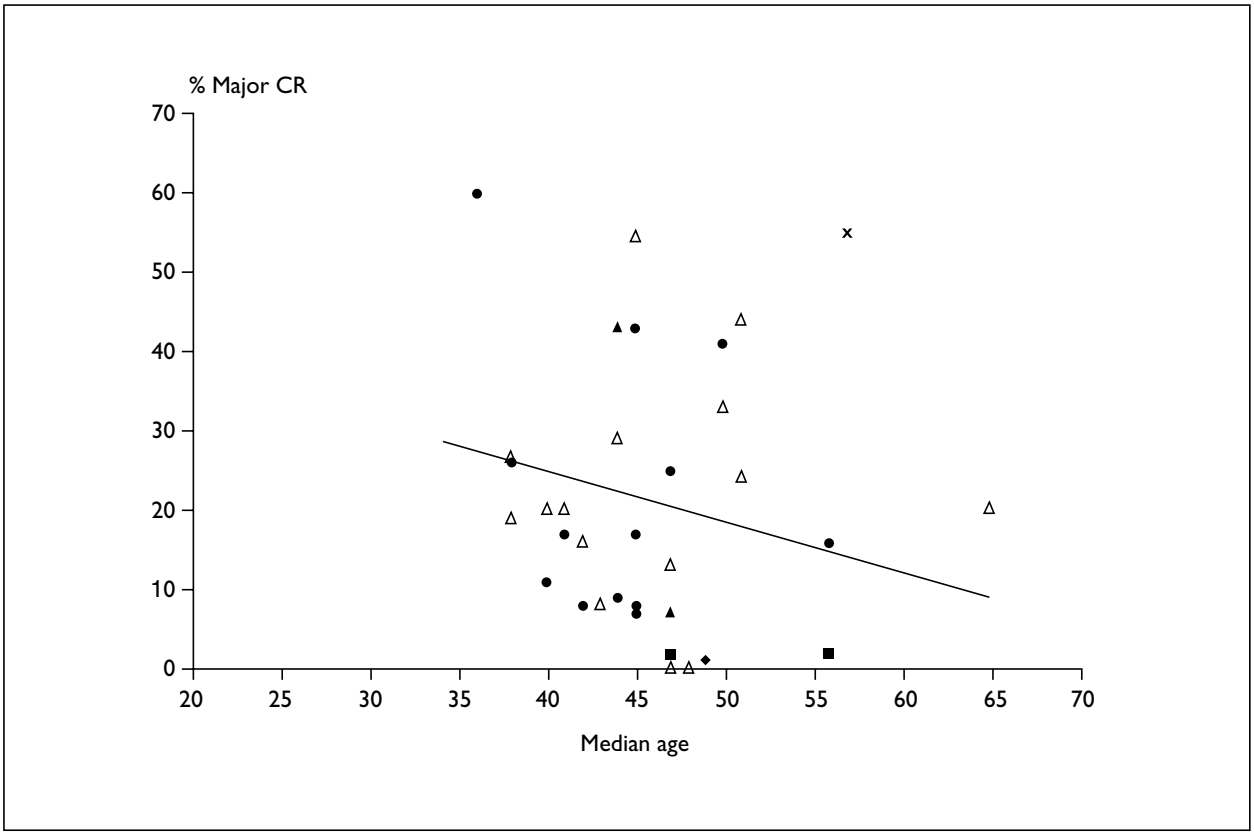


FIGURE 15 *Major CR and median age in chronic phase CML (◆, busulphan; ■, hydroxyurea; ▲, IFN alone; ●, IFN plus;* ***X****, imatinib; ——, linear trend (IFN plus))*

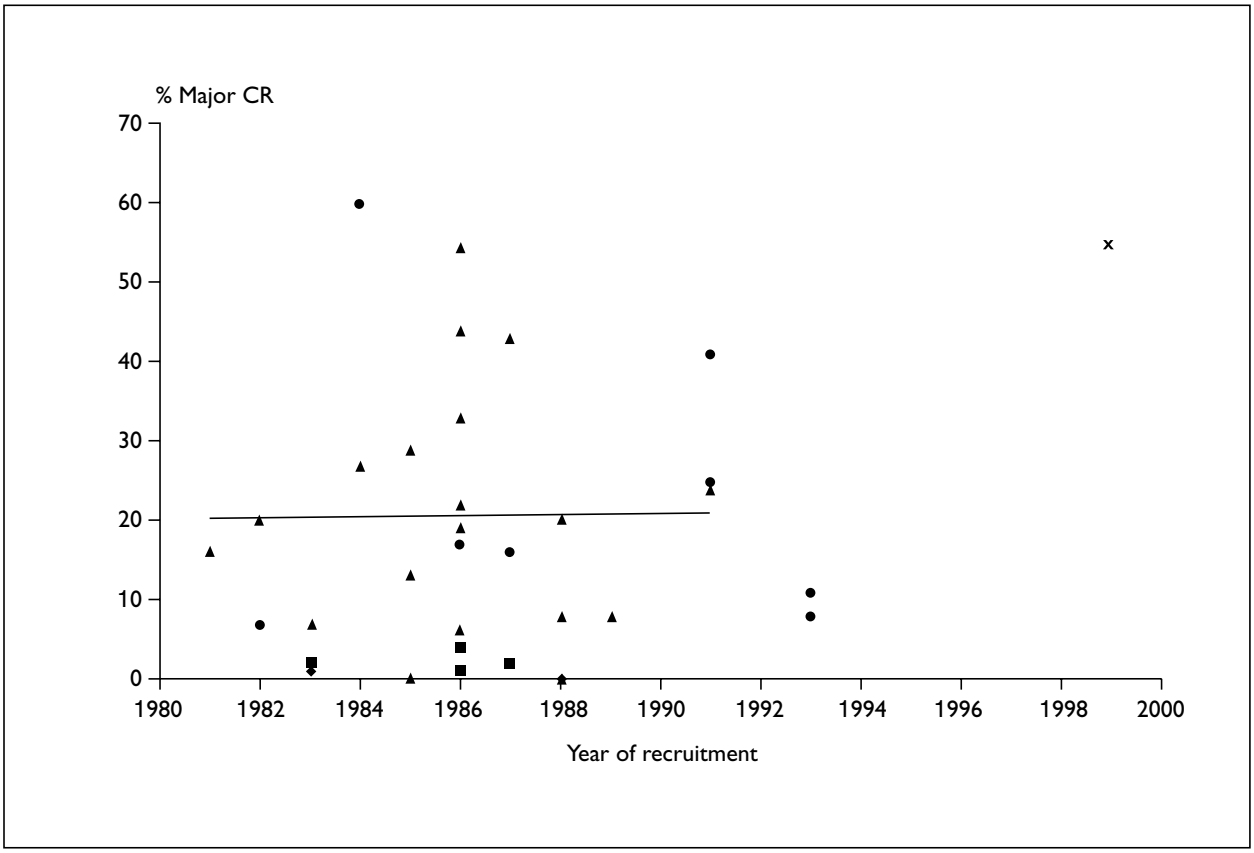


FIGURE 16 *Major CR and year of recruitment in chronic phase CML (◆, busulphan; ■, hydroxyurea; ▲, IFN alone; ●, IFN plus;* **X**, *imatinib; ——, linear trend (IFN plus))*

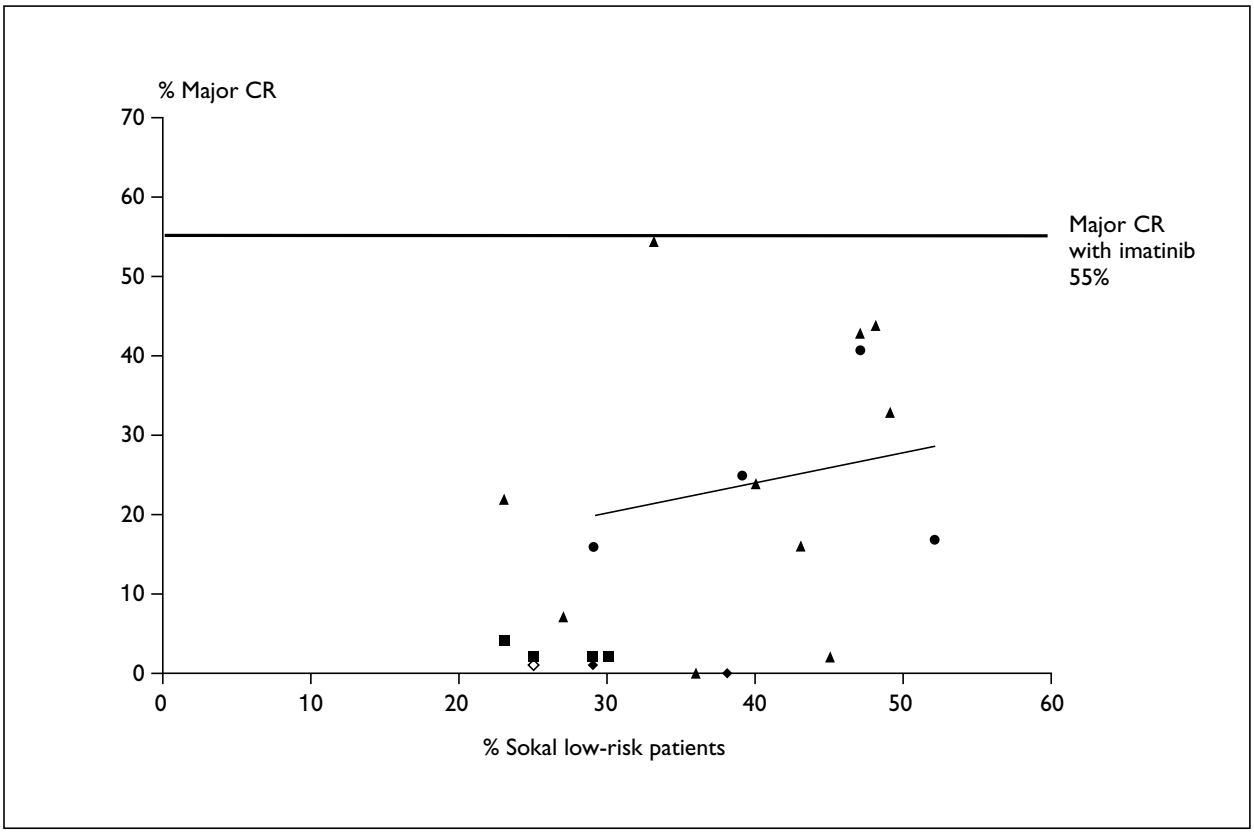


FIGURE 17 *Major CR and percentage of low-risk patients in chronic phase CML (◆, busulphan; ■, hydroxyurea; ▲, IFN alone; ●, IFN plus;* **X**, *imatinib; ——, linear trend (IFN plus))*

performance of imatinib and other treatments in the context of these factors.

Figure 15 shows major CR by median age of study population. The highest rate of major CR is in a pilot study of 32 patients with IFN-α combination therapy. As might be expected, the trend line shows a reduction in the percentage of patients achieving a major CR with age. However, the rate of major CR for patients taking imatinib is high, particularly given the relatively old population studied.

Figure 16 shows major CR by year of recruitment. The trend line is essentially flat, showing no increase with later recruitment date. Imatinib has been studied considerably more recently than other treatments but this factor does not seem to be important.

Figure 17 shows major CR and the percentage of low-risk patients in the sample. As the imatinib trial did not report a Sokal score, the overall major CR rate for imatinib has been drawn in. It is well above the trend line, again showing that even if the trial included an unusually high proportion of low-risk patients, CR rate was high.

Overall, these scatter plots show that the level of HR and CR with imatinib is high even considering study characteristics that might affect this result. Whether this will ultimately translate into longer survival is not yet known.

Accelerated and blast phase results

This section examines the key results of survival, HR and CR for imatinib in advanced phases of CML in the context of other published results. Again, there is no direct comparator for imatinib and most of the results for other agents come from small observational studies. *Table 9* shows survival, CR and HR results reported in each included study, together with a sample size for reference. Full details of the chemotherapy regimens used are shown in appendix 10.

For the blast phase, few studies report 1-year survival, median survival in months being a more appropriate measure for the generally short duration of this phase of CML. In addition, few studies report CR.

Table 13 summarises survival and response rates for studies of patients in accelerated phase CML. *Table 14* shows the survival and response rates for studies in blast phase CML. Note that CIs are not calculated as these studies are extremely heterogeneous in nature, and of greatly varying size.

TABLE 13 *Summary of RCTs and case studies: survival and complete response rates, accelerated phase*

	Case series (*n* = 4)	Imatinib (*n* = 1)
Survival % at 1 year		
Median	32.5	74
Range	28–37	
HR		
Median	35	35
Range	25–50	
CR		
Median	13	17
Range	0–23	

TABLE 14 *Summary of RCTs and case studies: survival and complete response rates, blast phase*

	RCT (*n* = 1)	Case series (*n* = 12)	Imatinib (*n* = 1)
Survival (weeks)			
Median	–	13	28
Range	–	6–17	
HR			
Median	12	20	7
Range	11–13	0–33	
CR			
Median	–	8	7
Range	–	0–21	

In the accelerated phase, survival rate is high despite an HR within the range of the other studies and a lower than average CR. There are, however, few studies in the accelerated phase and they are of small size.

In the blast phase, median survival is longer than has been reported with other treatments, and an absolute difference of around 11 weeks is seen. The complete HR is lower than other studies report on average, although within their range. Only two other studies report complete CR in patients treated at this stage of the disease, one of zero[92] and one of 21%.[91] This compares to 7% reported in the imatinib blast phase trial. Not all of the blast phase studies report the proportion of patients in lymphoid or myeloid crisis – the latter tend to respond less well to treatments. Of those that do report, a median of 75% (range 71–87%) of patients are in myeloid

crisis. All of those in the imatinib study are in myeloid crisis, which might be expected to decrease the rate of response.

Figures 18 and *19* show scatter plots of complete HR in accelerated and blast phase CML and various factors, as before. No prognostic scores are calculated for the accelerated or blast phase, so an exploration of this is not possible. In these plots, points are coded according to both the type of treatment and the phase of disease. Four included studies contain patients in both accelerated and blast phase CML. In two of these, data were not presented in such a way as to allow accelerated and blast phase patients to be described separately. In two cases this was possible, so the blast and accelerated phase patients in the same study are represented by separate points. There is, however, a paucity of suitable comparison data, with all but one of the studies considered here being small case series.

Figure 18 shows complete HR by year of recruitment. In addition to the point for the imatinib study, there is only one other plotted point for CML in the accelerated phase. Despite a later recruitment date, imatinib shows a lower level of complete HR. More points are plotted for CML in the blast phase and again fewer patients in the imatinib study showed a complete HR, despite a much more recent recruitment date.

Figure 19 shows complete HR in accelerated and blast phase CML by median age. For both phases the median age of the samples in the imatinib studies is the eldest. There is one comparison point for imatinib in the accelerated phase and imatinib induced the same number of patients with complete HR as this study. In the blast phase, imatinib levels of complete HR are within the range of those produced by other treatments.

Figures 20 and *21* show scatter plots of major CR against various factors. Generally, only a few points are plotted on each graph as many studies, particularly earlier trials, have not included information about CR.

Figure 20 shows major CR and median age of the study samples. The imatinib studies have the oldest median age of all samples. There is only one study to compare to the imatinib study in the accelerated phase and two for the blast phase. The other two studies contain patients in both accelerated and blast phase CML. The imatinib

FIGURE 18 *Complete HR by year of recruitment in the accelerated and blast phases (**x**, imatinib – accelerated; □, other chemo – blast; ●, IFN + ara-C – accelerated; +, imatinib – blast)*

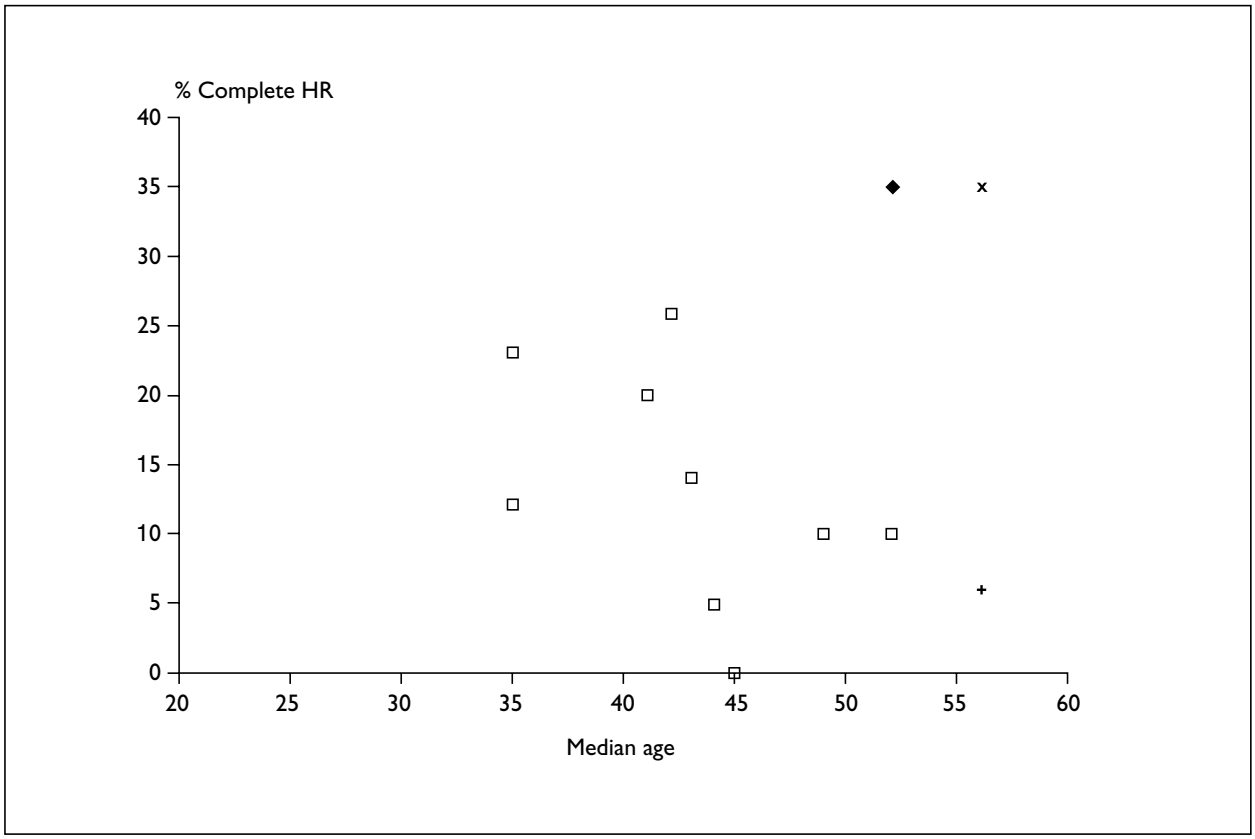


FIGURE 19 *Complete HR by median age in the accelerated and blast phases (**x**, imatinib – accelerated; □, other chemo – blast; **+**, imatinib – blast; ◆, other chemo – accelerated)*

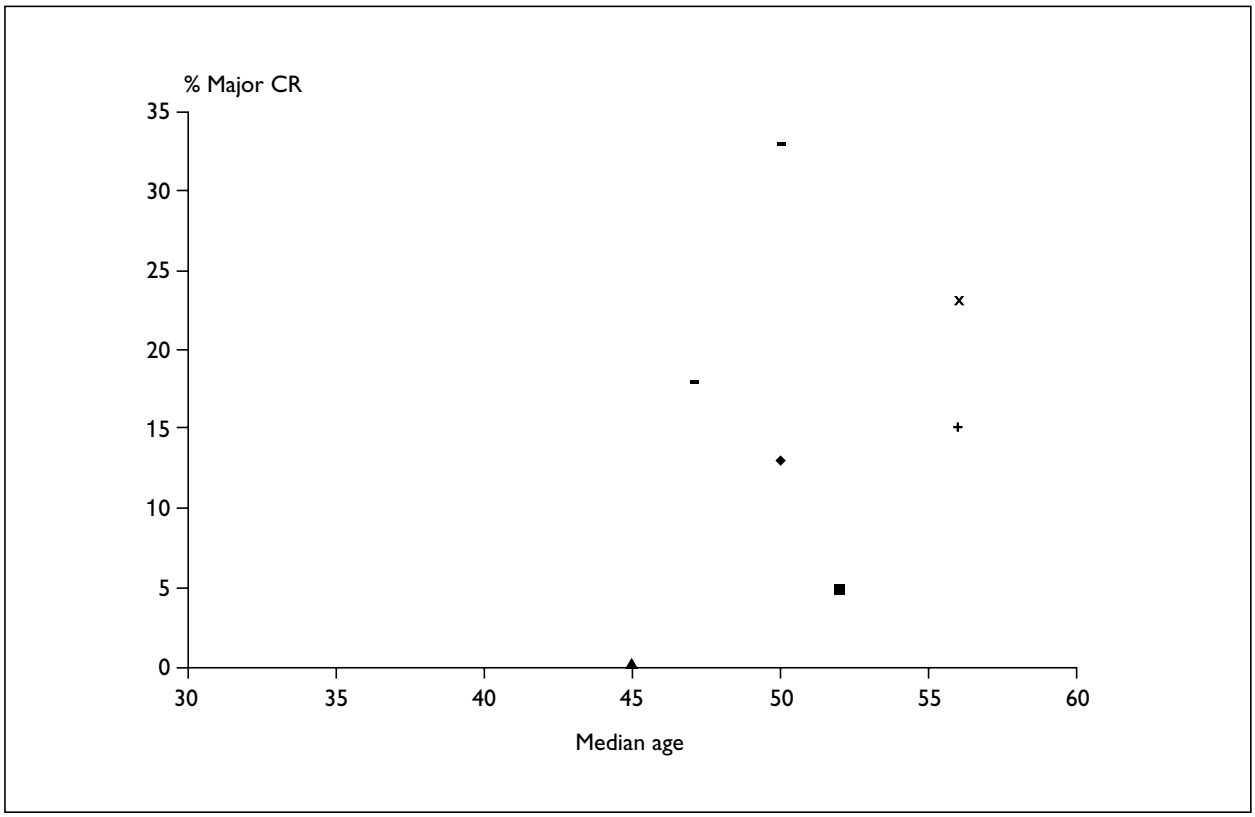


FIGURE 20 *Major CR by median age in the accelerated and blast phases (▲, IFN – blast; **X**, imatinib – accelerated; **+**, imatinib – blast; **-**, other chemo – accelerated + blast; ◆, other chemo – accelerated; ■, other chemo – blast)*

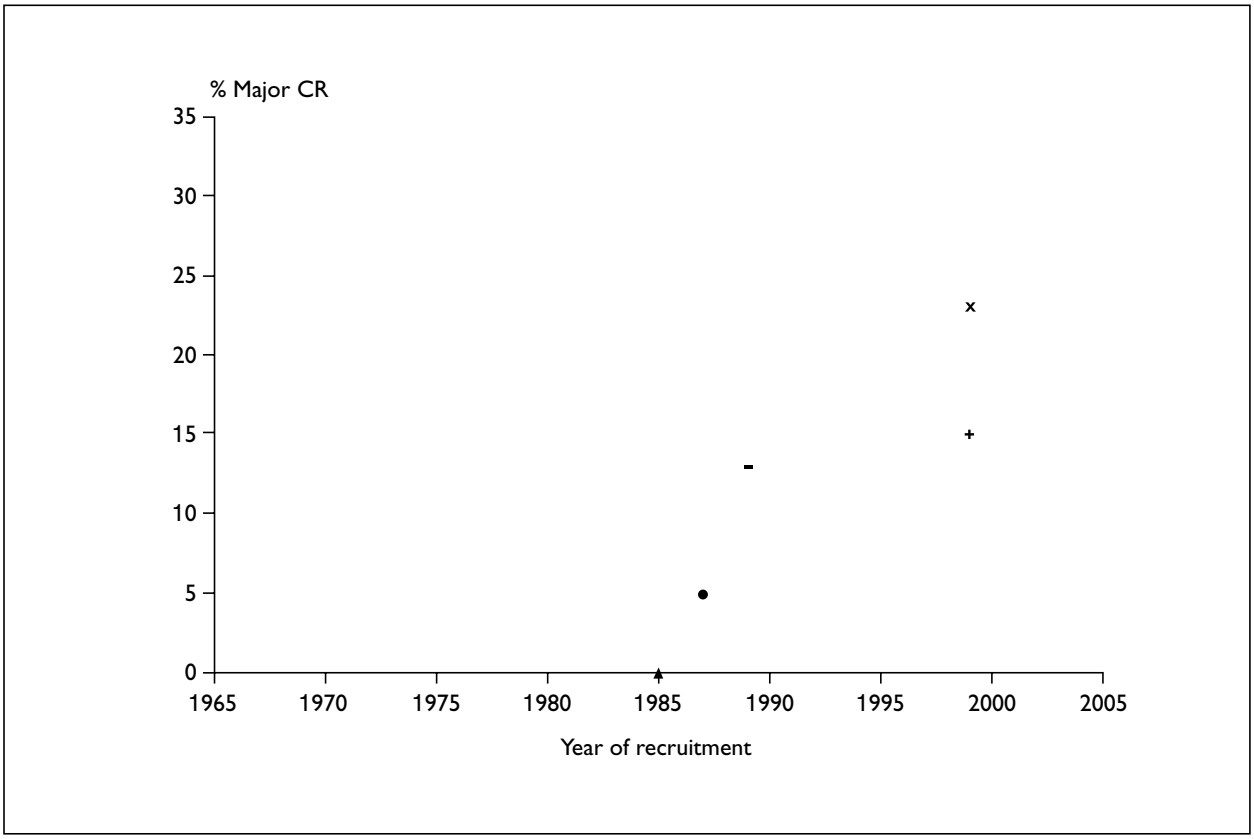


FIGURE 21 *Major CR by year of recruitment in the accelerated and blast phases (▲, IFN – blast; ●, IFN plus – accelerated;* **X**, *imatinib – accelerated;* **+**, *imatinib – blast;* **-**, *other chemo – accelerated)*

trials seem to show a good level of major CR despite the older median age of their sample.

It might be expected that a higher age would result in less likelihood of CR. However, the graph does not show such a trend, possibly as a result of imprecision because of the small number of observations.

Figure 21 shows major CR and date of recruitment. Again there are few points. The imatinib studies in both accelerated and blast phases reported high major CR compared to other treatments. They are much more recent studies, recruiting more than 10 years later than the other, although this did not appear to be a confounding factor for chronic studies.

Overall, these figures provide sparse information about CR with various regimes for CML in the accelerated and blast phases. Few studies report on the CR, making it difficult to draw conclusions or establish trends.

Survival in accelerated and blast phase CML

Table 15 shows the survival rates for accelerated and blast phase CML patients treated with various drug regimes. All data comes from small case series studies, with the problems of selection and publication bias. Aspects of the quality of these trials are detailed further in appendices 7 and 9. As before, CIs have not been calculated because of the heterogeneous nature of the studies.

Information is limited, making comparisons with imatinib difficult. As the median survival had not been reached at the time of analysis in the accelerated phase imatinib study, only 1-year survival is known. Of the studies in accelerated phase patients included in this report, only two also report this measure. One-year survival with imatinib appears to be considerably higher than with other chemotherapy regimes but this should be interpreted with caution given the amount and quality of evidence available.

For the trial involving imatinib in the blast phase, a median survival time is reported. Again, an apparent advantage for imatinib patients can be seen but again this should be interpreted with caution. Blast phase CML is resistant to treatment and survival is very limited, with a median of 3–6 months being usual.[97] A variety of chemotherapy regimes may be used in the blast phase to

TABLE 15 *Median and 1-year survival for accelerated and blast phase CML*

Study	Treatment	Phase	Median survival (weeks)	1-year survival (%)
Talpaz *et al.*, 2001[13]	Imatinib	Accelerated	–	74
Kantarjian *et al.*, 1992[44]	IFN-α + ara-C	Accelerated	–	–
Carella *et al.*, 1994 A[91]	Other chemo	Accelerated	–	23
Kantarjian *et al.*, 1992 A[12]	Other chemo	Accelerated	32	37
Kantarjian *et al.*, 1997 A[92]	Other chemo	Accelerated	39	28
Dutcher *et al.*, 1992[93]	Other chemo	Accelerated/blast	16.4	37
Sawyers *et al.*, 2001[59]	Imatinib	Blast	27.6	–
Coleman *et al.*, 1980 I[94]	Other chemo	Blast	13.8	–
Coleman *et al.*, 1980 II[94]	Other chemo	Blast	10.8	–
Alimena *et al.*, 1996[95]	IFN-α	Blast	–	–
Canellos *et al.*, 1971[96]	Other chemo	Blast	–	–
Carella *et al.*, 1994 B[91]	Other chemo	Blast	–	21
Hernandez-Boluda *et al.*, 2000[97]	Other chemo	Blast	17	–
Iacoboni *et al.*, 1986[98]	Other chemo	Blast	12	0
Kantarjian *et al.*, 1988[99]	Other chemo	Blast	14	–
Kantarjian *et al.*, 1992 B[12]	Other chemo	Blast	16	18
Kantarjian *et al.*, 1997 B[92]	Other chemo	Blast	17	10
Pedersen-Bjergaard *et al.*, 1977[100]	Other chemo	Blast	8	–
Vallejos *et al.*, 1974[101]	Other chemo	Blast	–	–
Winton *et al.*, 1981[102]	Other chemo	Blast	5.6	–

A = accelerated phase; B = blast phase; I = arm I; II = arm II

try and return the patients to chronic phase CML. However, these may be very toxic and their effect appears to be limited. *Figure 22* shows the survival of patients in the blast phase treated with three different chemotherapy regimens in an RCT[94] and with intravenous chemotherapy and an oral 6-mercaptopurine regime from a small case series study.[97] The survival curve for imatinib treatment in the blast phase is also represented. The data from these studies were extracted from survival curves and re-plotted on the same axes for ease of reference.

Figure 22 shows an apparent survival advantage for patients treated with imatinib, who have a median survival of 7 months compared to 3–4 months with various chemotherapy regimens. However, we should be cautious about concluding that this treatment effect would be shown in a direct comparison.

Summary of imatinib in context

Chronic phase

- Survival data are only available for 1 year, limiting comparisons with other treatments.
- Compared to existing treatments, imatinib does not show a difference in survival at 1 year, however, most patients in the imatinib study have been diagnosed with CML for 2 or more years so are not strictly comparable with a newly diagnosed population.
- Imatinib produces better complete HR and CR than other treatments.

Comparisons between treatments for CR and HR are difficult, but differences appear to remain when examined in the context of some potential confounders.

Accelerated and blast phases

- There appears to be a survival advantage for imatinib over existing treatments in accelerated disease and a small advantage in the blast phase.
- Without direct comparator evidence, a selection bias effect cannot be ruled out.

Given the importance of HR and CR in assessing the effectiveness of imatinib in the chronic phase, the next section looks at the evidence for using these as proxy measures of survival.

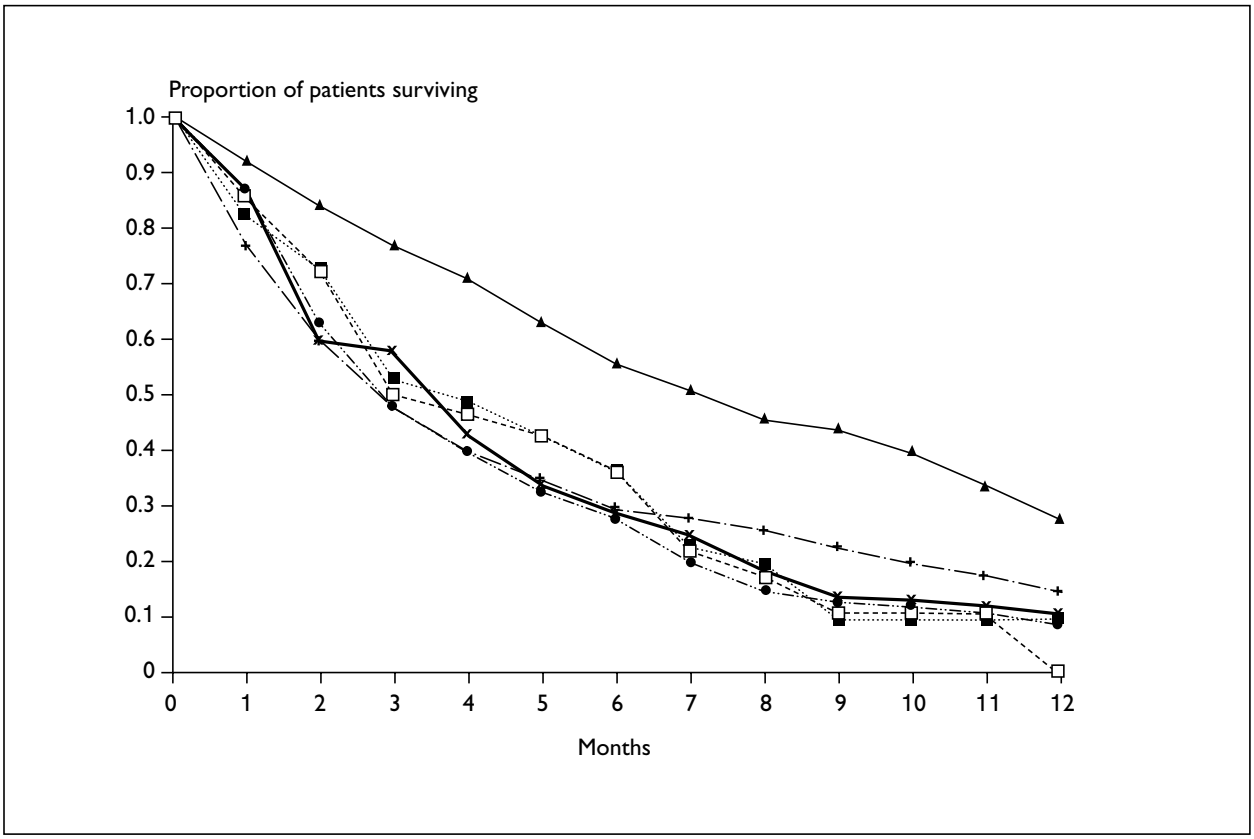


FIGURE 22 *Overall survival in blast phase CML (□, Hermandez chemotherapy; ▲, imatinib; ■, Hermandez – MP-6; ✕, Coleman 1; ●, Coleman 2; +, Coleman 3)*

Using HR and CR as proxy outcomes

Given the short follow-up for the imatinib studies, particularly in the chronic phase, information about survival is limited and so proxy indicators of survival, HR and CR, are important measures. This section looks at information available from trials of a range of treatments for CML. Two questions are important:

- For individuals receiving a treatment, does achieving HR or CR predict survival?
- For groups of individuals on different treatments, does a difference in HR or CR predict a difference in survival between treatments?

CR or HR is a measure of the suppression of the rapidly proliferating abnormal cell line, which means that it decreases or becomes no longer detectable. However, with the possible exception of bone marrow transplantation, where the whole bone marrow is ablated to try to ensure removal of the abnormal cell line, treatment does not reverse the initial oncogenic effect. As the sensitivity of conventional techniques for measuring CR is between 1% and 5%, a patient with 'negative' results may indeed harbour no malignant cells or may have as many as 10^{10} residual leukaemic cells. Although the patient may be described as having an HR or CR, this term refers only to an arbitrary point on the continuum of residual leukaemia cell numbers.

'Complete CR' may not be truly 'complete', being a function of the sensitivity of the test used for definition. It has been demonstrated with both imatinib and IFN-α that BCR-ABL is still detectable in patients with complete CR, if RT-PCR is used (*Table 16*). (See page 1 for a description of RT-PCR, FISH and other diagnostic procedures.) The frequency of PCR negativity is higher if the RT-PCR strategy used is of lower sensitivity.[105,106] It has also been reported that demonstrating complete CR by cytogenetic analysis does not necessarily correlate with FISH analysis.[107]

Only RCTs are considered in this section, to assess the relationship between HR and CR and survival in the chronic phase, as they provide stronger evidence than observational data on causal association. Observational data are

TABLE 16 *Variation in test sensitivity with imatinib or IFN-α therapy*

Reference	Drug	No. of people with complete CR	No. (%) of those people who are PCR-negative
Sawyers, 2001[14]	Imatinib	18	9 (50%)
Quackenbush *et al.*, 2000[103]		5	0 (0%)
Paschka *et al.*, 2000[104]		9	0 (0%)
Hochhaus *et al.*, 2000[105]	IFN-α	54	0 (0%)
Kurzock *et al.*, 1998[106]		18	10 (55%)

presented for the blast phase as no evidence is available based on experimental designs.

Haematological response

HR is defined differently in different trials, which makes it difficult to interpret the validity of HR as a proxy outcome. Nine trials in the chronic phase report both on some kind of HR and survival (appendix 6).

In two of the six positive trials (i.e. those trials showing a survival benefit for one therapy over another) a higher rate of HR was seen in the treatment arm with prolonged survival[45,63] but in two others,[39,42] HR rates were no different between the treatments. One of these trials showed survival benefit for IFN-α-treated patients[39] and noted that those who discontinued IFN-α early had poorer survival than those who continued, regardless of haematological control. This suggests that IFN-α treatment per se produces improved survival, not the achievement of an HR. Two trials did not report these HR rates.[61,62]

In two out of three negative trials (i.e. those trials where no difference was shown in survival), a similar HR was seen in both arms.[18,65] However, in the other negative trial, a higher rate of HR was seen in one arm.[64]

One of the negative trials[18] reported a highly significant difference in duration of HR (35 months versus 12 months) but showed no difference in overall survival, mainly because one-third of the long response group died while in apparent remission.

Within treatment arms, patients who develop an HR have (generally) significantly improved survival compared to those who do not. This is most commonly reported with IFN-α, but seen with all therapies.

In the accelerated and blast phases, there is only one RCT to review the association between HR and survival.[94] No significant difference in HR or in survival was observed by treatment, while responders in both treatment arms lived significantly longer than non-responders.

A comparative case series[97] from one centre reviewed intensive intravenous chemotherapy compared to oral treatment for the blast phase. The two cohorts were separated in time – there had been a change in clinical practice so that all patients between 1979 and 1989 received intensive therapy and all patients between 1990 and 2000 received oral therapy. Despite a 20% HR in the intensive group, no difference in survival was noted between the two groups.

Taken together, this evidence suggests that when comparing treatments, the rate of HR is not a good proxy outcome for long-term survival. On an individual basis, achievement of HR is a good prognostic indicator.

Cytogenetic response

IFN-α therapy is notable for producing higher percentages of patients achieving a CR in all of the trials compared to hydroxyurea or busulphan. This, together with the general acceptance that IFN-α produces prolonged survival, has led to the supposition that CR is a good proxy outcome for survival. However, detailed examination of the trial evidence provides only partial support for this theory.

In four of the six IFN-α trials reporting survival and CR, higher rates of CR were seen in the treatment arm with prolonged survival.[39,42,62] However, one trial showed higher rates of CR in the IFN-α arm but no improved survival,[64] and one trial showed a lower rate of CR with non-significantly improved survival.[65] Furthermore, in one trial,[42] non-responders to IFN-α had better survival than the comparator chemotherapy group, again suggesting that IFN-α produces a survival benefit regardless of CR.

The production of CR is rare with other therapies. Significant differences in outcome between therapies have been reported,[63] despite minimal CR rates.

Achieving CR does not appear to be an essential requirement for improved survival according to treatment, although on an individual basis, the achievement of a major CR does translate to improved survival. It is likely with these therapies that production of a CR is recognition of a favourable prognosis. It has been suggested that differences in the risk group profile (see page 3) of the study populations may account for these differences in CR and survival. Two randomised trials reported an association between CR and risk score with higher CR in patients with a lower risk score.[42,45]

There is some evidence in the blast phase that cytotoxic chemotherapy can produce transient CR, but has no appreciable effect on survival (*Figure 23*).[12]

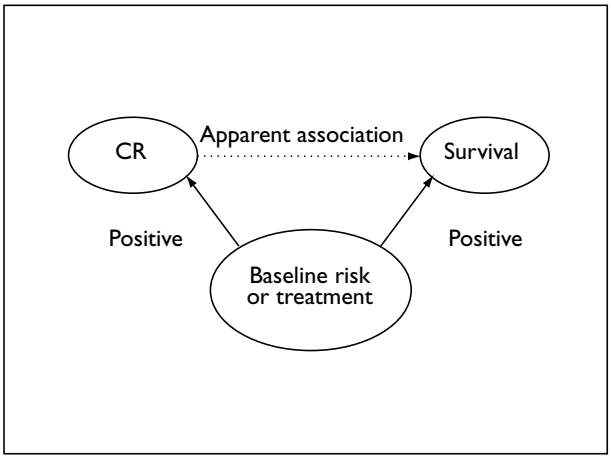


FIGURE 23 *Possible confounding influence of CR on predicted survival*

In summary, the evidence does not clearly distinguish between the possibilities that HR and/or CR allows recognition of a prognostically favourable subgroup, or that achieving an HR or CR is a therapeutic success that will lead to prolonged survival. For IFN-α treatment in the chronic phase, the weight of evidence is probably that CR is useful as a proxy measure. However, in other phases, and for other treatments, there is little reliable evidence that rates of CR and HR recorded in a study are useful measures of efficacy. The use of HR and CR as proxy outcomes that will translate into improved survival for a particular treatment must therefore be viewed with caution.

Adverse effects

Adverse effects – imatinib

The three Phase II studies report that imatinib is well tolerated by patients. However, almost all patients experienced both haematological and non-haematological adverse events that were attributed to imatinib. Treatment interruptions were required for 25–40% of patients because of adverse effects. In addition, it is reported that less than half of patients required dose reduction at some time, although actual figures are not given. Only adverse effects occurring in more than 5% of patients were reported, with the exception of very severe effects. Note that the percentages quoted include all patients enrolled in the trials, some of whom may have received treatment for very short periods of time before study closure or withdrawal. The rates may therefore underestimate side-effect rates that would be experienced in practice.

Serious adverse effects and deaths on imatinib

Two deaths were reported in the chronic phase study, one due to myocardial arrest, attributed to pre-existing cardiovascular disease, and one due to cerebral haemorrhage, attribution not stated.

One death due to liver failure in the accelerated phase study was attributed to treatment with imatinib, although the patient had been taking large doses of paracetamol (liver toxic in overdose) in the month before commencing imatinib therapy. One death in the blast phase study was due to renal and cardiac failure, and attributed to drug toxicity.

If these four deaths were all caused by imatinib toxicity, this gives a fatality proportion of 0.4% (95% CI, 0.1 to 1%) for all people who use imatinib. A true rate cannot be calculated because there is insufficient information on length of time on treatment.

Other adverse effects on imatinib

The most frequently reported adverse effects were nausea, vomiting and oedema. It is suggested that the high incidence of nausea and vomiting was a result of trial design, which initially prohibited participants from taking imatinib with food. Although it is now recommended in the drug pack notes that imatinib is taken with food and a large glass of water, no empirical evidence was presented to show what effect the change of advice has had on the incidence of nausea and vomiting. Mild oedema was more

frequently reported among those taking higher doses of imatinib.

Grade 3 and 4 events (those that are severe or life-threatening; see appendix 13 for a description of the National Cancer Institute (NCI) toxicity grades) that led to drug interruption or discontinuation included fluid retention (pleural or pericardial effusions, ascites, pulmonary oedema), skin rash, liver toxicity and gastrointestinal haemorrhage. Serious adverse effects were noted in 5% of participants in the chronic phase study (of whom 1.7% had therapy discontinued), 23% of participants in the accelerated phase study (of whom 5% had therapy discontinued) and 14% of participants in the blast phase study (of whom 3% had therapy discontinued).

Although outcome measures have been reported in dose groups for accelerated and blast phase patients, little information about adverse effects was reported by these dose groups. Grade 1 or 2 (mild or moderate) oedema was reported more frequently in the 600 mg dose group, but other reactions were comparable in the accelerated phase study. In the blast phase study, oedema, dermatitis, vomiting, muscle cramps, myalgia, arthralgia and weight increase (grade 1 or 2) were all reported more frequently on the higher dose. In addition, all terminations of therapy for drug toxicity were seen at the higher dose. It is likely, therefore, that higher doses of imatinib are associated with more clinically significant toxicity.

For comparative purposes *Tables 17* and *18* show the percentage of adverse effects at grade 3 and 4 (NCI Common Toxicity Criteria) and at all grades reported in trials of other therapies for CML. It should be noted that not all studies reported adverse effects.

Compared to IFN-α regimes, the levels of serious grades (3 and 4) reported in imatinib trials are higher for haematological adverse effects such as anaemia, thrombocytopenia, and leukopenia or neutropenia. With older therapies it may be that experience in clinical usage allows more accurate titration of dose; that adverse haematological effects are not reported or that they are genuinely less frequent. The range of symptoms reported in IFN-α trials are somewhat different from those reported with imatinib. Pain was quite commonly reported with imatinib, particularly abdominal, limb and joint pain, whereas neurotoxicity and flu-like symptoms are more common with IFN-α. Hydroxyurea use appears to be associated with few reports of adverse effects.

Imatinib studies reported higher rates of anaemia, thrombocytopenia, leukopenia/neutropenia, nausea/vomiting and diarrhoea and dermatological problems for all grades of adverse effects. Over half also reported oedema. IFN-α studies reported higher levels of fatigue and myalgia as

TABLE 17 *NCI grades 3 and 4 of adverse effects for IFN-α, imatinib and other chemotherapy*

Adverse effects	Imatinib		IFN-α		Other chemotherapy	
	No. of studies reporting	Median % (range)	No. of studies reporting	Median % (range)	No. of studies reporting	Median % (range)
Anaemia	3	37% (6–51)	5	4% (0–18)	0	
Thrombocytopenia	3	43% (18–60)	9	13% (0–26)	0	
Leukopenia/neutropenia	3	58% (34–63)	7	5% (0–12)	3	61.5% (23–100)
Nausea/vomiting	3	2% (1–3)	3	1% (0–2)	2	2% (0–4)
Diarrhoea	3	0.6% (0.5–0.8)	3	3% (2–5)	2	4% (4–4)
Myalgia/flu symptoms	2	0.6% (0.2–1.0)	6	4% (0–8)	0	
Oedema	3	3% (1–3)	1	0%	0	
Neurological/neurotoxic	0		6	4.5% (0–17)	1	3.5% (2–9)
Dermatological	3	2% (1–3)	3	1% (0–8)	1	0
Depression/psychological	0		4	0% (0–2)	0	
Liver	0		2	1% (0–2)	2	21% (19–23)
Weight loss	0		6	6.5% (2–11)	0	
Fatigue/lethargy	2	0.7% (0.2–1.2)	6	2.5% (0–21)	0	

TABLE 18 *All NCI grades of adverse effects for IFN-α, imatinib and other chemotherapy*

Adverse effects	Imatinib		IFN-α		Other chemotherapy	
	No. of studies reporting	Median % (range)	No. of studies reporting	Median % (range)	No. of studies reporting	Median % (range)
Anaemia	3	37% (6–51)	7	27% (2–32)	1	91%
Thrombocytopenia	3	43% (18–60)	14	26% (2–83)	1	54%
Leukopenia/neutropenia	3	58% (34–63)	9	35% (7–53)	2	61.5% (23–100)
Nausea/vomiting	3	62% (53–65)	6	16.5% (4–56)	8	63% (5–100)
Diarrhoea	3	29% (23–37)	6	10.5% (5–20)	6	34% (3–50)
Myalgia/flu symptoms	3	14% (6–16)	12	32.5% (2–100)	3	68% (46–96)
Oedema	3	54% (51–64)	1	3%	0	
Neurological/neurotoxic	0		12	14% (1–42)	5	5% (2–19)
Dermatological	3	22% (15–29)	8	4.5% (0–20)	3	7% (3–8)
Depression/psychological	0		7	12% (4–20)	0	
Liver	0		6	3.5% (1–17)	6	46% (21–52)
Weight loss	0		10	10.5% (1–41)	1	21%
Fatigue/lethargy	2	9.5% (7–12)	9	30% (10–69)	2	48.5% (5–92)

well as a number of adverse effects not reported at all with imatinib, for example weight loss and neurotoxicity.

Clinician consensus is that IFN-α is a difficult drug to tolerate and that early experience with imatinib is of a much improved adverse effects profile. Many people may not tolerate IFN-α and withdraw from therapy because of adverse effects. Imatinib appears to be better tolerated, despite a high level of grade 1 and 2 adverse effects. *Table 19* shows the number and percentage of patients reported as withdrawing from studies because of adverse effects. In particular, imatinib caused lower drop-out in all phases than other treatments, especially IFN-α and chemotherapy used in advanced phases.

Summary of effectiveness

Imatinib

- The evidence base is limited to three industry-funded case series, provided as commercial in confidence material only at the time of the review.
- The case series studies appear to be well conducted, although they did not report how patients were selected.
- There is an absence of direct control groups.
- The importance of baseline risk is not addressed.
- Although confounding is likely, as far as can be ascertained imatinib performs relatively well against comparators.
- Chronic phase:
  - imatinib shows better HR and CR
  - survival is equivalent, although the effects of lead time are important and may mask a survival advantage for imatinib.
- Accelerated and blast phase:
  - imatinib shows equivalent HR and CR
  - survival appears to be improved.
- The results are difficult to quantify as this kind of comparison is very open to bias.

Other agents for CML

- The largest body of literature is on IFN-α.
- There is good evidence from RCTs for the effectiveness of IFN-α, although there is considerable clinical heterogeneity.
- Case series data are less robust than RCTs.

TABLE 19 *Withdrawal because of adverse effects on treatments for CML*

Study	No. (%) of patients withdrawing because of adverse effects
Chronic phase – imatinib	
Kantarjian *et al.*, 2001[58]	9/532 (1.7)
Chronic phase – RCTs	
Baccarani *et al.*, 1998[62]	IFN-α 39/218 (18)
The Benelux CML Study Group, 1998[64]	IFN-α 24/100 (24) Control 4/95 (4)
Broustet *et al.*, 1991[60]	HU 1/26 (4) IFN-α 6/24 (25)
Giles *et al.*, 2000[65]	NR
Guilhot *et al.*, 1997[45]	IFN-α + ara-C 94/360 (26) IFN-α 97/361 (27)
Hehlmann *et al.*, 1993[63]	NR
Hehlmann *et al.*, 1994[39]	IFN-α 24/133 (24) BU 19/186 (10)
Ohnishi *et al.*, 1998[61]	NR
Shepherd *et al.*, 1996[42]	NR
Silver *et al.*, 1992[18]	NR
Chronic phase – IFN-α	
Alimena *et al.*, 1990[66]	3/114 (3)
Arthur and Ma, 1993[87]	1/30 (3)
Cortes *et al.*, 1996[20]	NR
Fernandez-Ranada *et al.*, 1993[85]	6/51 (12)
Freund *et al.*, 1989[67]	2/27 (7)
Freund *et al.*, 1993[90]	NR
Giles *et al.*, 1992[72]	3/23 (13)
Giles *et al.*, 2001[88]	16%
Guilhot *et al.*, 1991[73]	NR
Hochhaus *et al.*, 1996[68]	NR
Kantarjian *et al.*, 1991[40]	3/32 (9)
Kantarjian *et al.*, 2000[48]	NR
Kloke *et al.*, 2000[69]	NR
Mahon *et al.*, 1996[78]	5/81 (6)
Mahon *et al.*, 1998[74]	12/116 (10)
O'Brien *et al.*, 1995[83]	7/71 (10)
Ozer *et al.*, 1993[79]	NR
Russo *et al.*, 1995[84]	NR
Sacchi *et al.*, 1997[70]	NR
Sanchez *et al.*, 1992[75]	0/29
Schofield *et al.*, 1994[71]	0/41
Shtalrid *et al.*, 1993[76]	NR
Talpaz *et al.*, 1987[19]	6/51 (12)
Thaler *et al.*, 1996[81]	NR
Thaler *et al.*, 1997[46]	16/91 (18)
Tothova *et al.*, 2000[82]	NR

continued

***TABLE 19* contd** *Withdrawal because of adverse effects on treatments for CML*

Study	No. (%) of patients withdrawing because of adverse effects
Accelerated/blast phase – imatinib	
Sawyers *et al.*, 2001[59]	13/260 (5)
Talpaz *et al.*, 2001[13]	6/235 (3)
Accelerated/blast phase – IFN-α	
Alimena *et al.*, 1996[95]	NR
Kantarjian *et al.*, 2000[48]	Accelerated 4/20 (20)
Accelerated/blast phase – other chemotherapies	
Canellos *et al.*, 1971[96]	NR
Carella *et al.*, 1994[91]	NR
Coleman *et al.*, 1980[94]	NR
Dutcher *et al.*, 1992[93]	NR
Hernandez-Boluda *et al.*, 2001[97]	NR
Iacoboni *et al.*, 1986[98]	Unclear, 3/21 (14%) deaths relating to toxicity
Kantarjian *et al.*, 1988[99]	Not clear, one possible death relating to toxicity
Kantarjian *et al.*, 1992[44]	NR
Kantarjian *et al.*, 1997[92]	NR
Pedersen-Bjergaard *et al.*, 1977[100]	NR
Vallejos *et al.*, 1974[101]	18 deaths (50%) related to infection
Winton *et al.*, 1981[102]	Not clear, possible 7/30 (23%) deaths related to toxicity

Chapter 4
Economic analysis

The aim of this chapter is to outline published economic evaluations of treatments for CML and report in detail on the economic analyses submitted to NICE on imatinib. We highlight the applicability of evaluations to patients and the health system in England and Wales and discuss the likely economic impact on the NHS.

No published economic evaluations of imatinib or second-line therapy for CML were identified, nor were evaluations for drugs other than IFN-α. We have briefly evaluated economic studies of IFN-α in the treatment of CML for comparative purposes, in order to assist judgements about the validity and robustness of the Novartis-sponsored economic evaluation for imatinib.

Economic evaluations of IFN-α

Four economic articles were identified by the search strategy described in appendix 4. One is an editorial discussing the other three economic studies and has been excluded from further discussion.[108] Two published studies present decision analyses and Markov models comparing the cost-effectiveness of IFN-α to hydroxyurea.[109] One study performed an economic analysis of IFN-α usage in CML using a Gompertz model.[110]

A cost–utility analysis of imatinib for second-line treatment based on comparison with hydroxyurea, using a Markov model, was included in the Novartis submission to NICE. Although peer review is no guarantee of quality, it should be noted that this has not been published and has not, therefore, been reviewed other than by the authors of this assessment.

Markov models

A Markov model is "a type of mathematical model containing a finite number of mutually exclusive and exhaustive health states, having time periods of uniform length, and in which the probability of movement from one state to another depends on the current state and remains constant over time".[111] The transition probabilities are applied to each 'cycle' of the model, the cycle being of fixed duration.

A Markov model consists of a number of potential health states and corresponding transition probabilities between these states.[57] Markov models allow for the synthesis of data on costs, effects and health-related QoL, of alternative clinical strategies through the calculation of life expectancy, quality-adjusted life expectancy and lifetime costs, by tracking a simulated hypothetical cohort through the model.[112]

One of the main limitations of Markov models is the underlying assumption often referred to as 'zero memory'. Transition probabilities depend only on current health state and not on past health states.[100] Another limitation is the assumption that all people in a particular health state are identical. Any degree of heterogeneity within a state may introduce bias.[112] It is difficult to determine whether these assumptions are met in practice.

Models of IFN-α in CML

Kattan and co-workers, 1996[77]

The aim of this evaluation was to compare the cost-effectiveness of IFN-α and hydroxyurea as first-line therapy for patients with CML. A Markov model was developed containing eight health states (HR + CR, complete HR without CR, partial HR, chronic phase, accelerated phase, blast phase, bone marrow transplantation and death). In this model it is possible to progress to death from all other health states (*Figure 24*).

Clinical data on survival, HR and CR were obtained from studies by Hehlmann,[113] the Italian Cooperative Study Group on Chronic ML,[114] Ozer[79] and Kantarjian.[115] Utilities were assessed by a clinical panel, and were 0.9 for patients receiving IFN-α therapy, 1.0 for patients receiving hydroxyurea therapy and 0.5 for patients in the blast or accelerated phases.

The marginal cost-effectiveness of IFN-α over hydroxyurea was US$26,500 per life year saved. When adjusted for quality of health states the estimated cost-effectiveness increased to US$34,800 per quality-adjusted life-year (QALY). Year of costs was not stated but the paper was published in 1996.

The cost-effectiveness of IFN-α was dependent on the age of the patient and the monthly cost

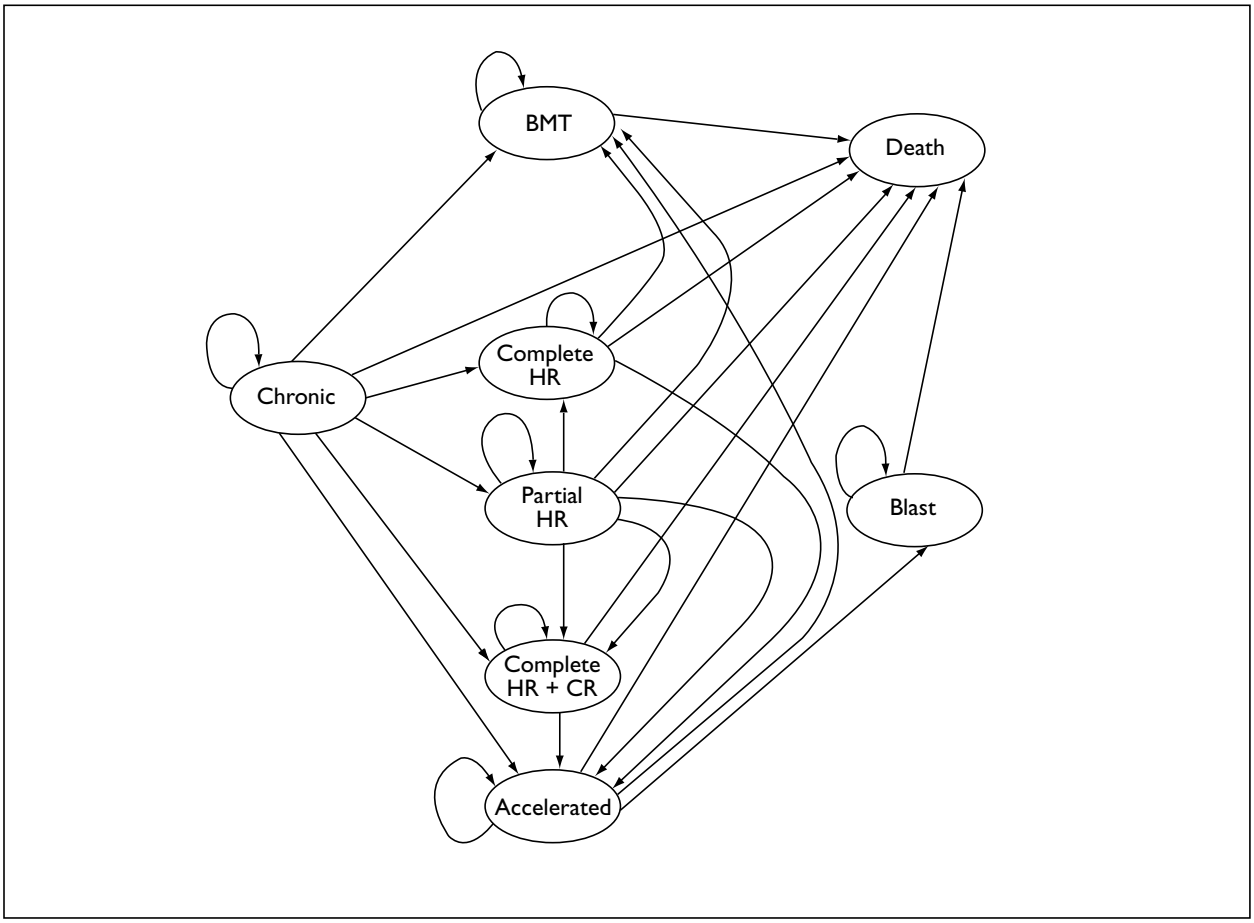


FIGURE 24 *Influence diagram showing transition between health states in Markov model used by Kattan and co-workers*[70]

of IFN-α, with the cost-effectiveness ratio being most favourable in younger patients. The authors concluded that compared with hydroxyurea, IFN-α is, in most clinical scenarios, a cost-effective initial therapy for patients with chronic phase CML who can tolerate the drug.

Liberato and co-workers, 1997[109]

The purpose of this study was to evaluate the cost-effectiveness of IFN-α compared to conventional chemotherapy in patients with CML. A decision analysis was designed that incorporated a Markov model to estimate the cost–utility of IFN-α (*Figure 25*).

It is unclear from the study report whether patients can progress to death from all other health states. Two scenarios were modelled:

1. Prolonged treatment for patients who achieved an HR.
2. Prolonged treatment only for patients who achieved a CR within 2 years.

Effectiveness data were taken from nine studies, including five RCTs. IFN-α treatment increased the quality-adjusted life expectancy by 15.5 months (scenario 1) and 12.5 months (scenario 2) relative to conventional chemotherapy. Utilities were estimated by ten physicians and were 0.875 for patients receiving IFN-α therapy, 0.98 for patients on hydroxyurea, 0.94 for patients receiving busulphan and 0.5 for patients in the blast phase. The study reports a marginal cost-effectiveness ratio of US$89,500 (scenario 1) and US$63,500 (scenario 2) per QALY gained. The year on which these costs were based is not stated but the paper was published in 1997.

The results were sensitive to the cost of IFN-α therapy and the probability of CR. The authors conclude that IFN-α is substantially superior to conventional chemotherapy in terms of quality-adjusted survival, but at current doses the marginal cost-effectiveness ranges from US$50,000 to US$100,000 per QALY gained.

Messori, 1998[110]

The aim of this evaluation was to assess the cost-effectiveness of IFN-α treatment for CML. The total area under the survival curve for each drug

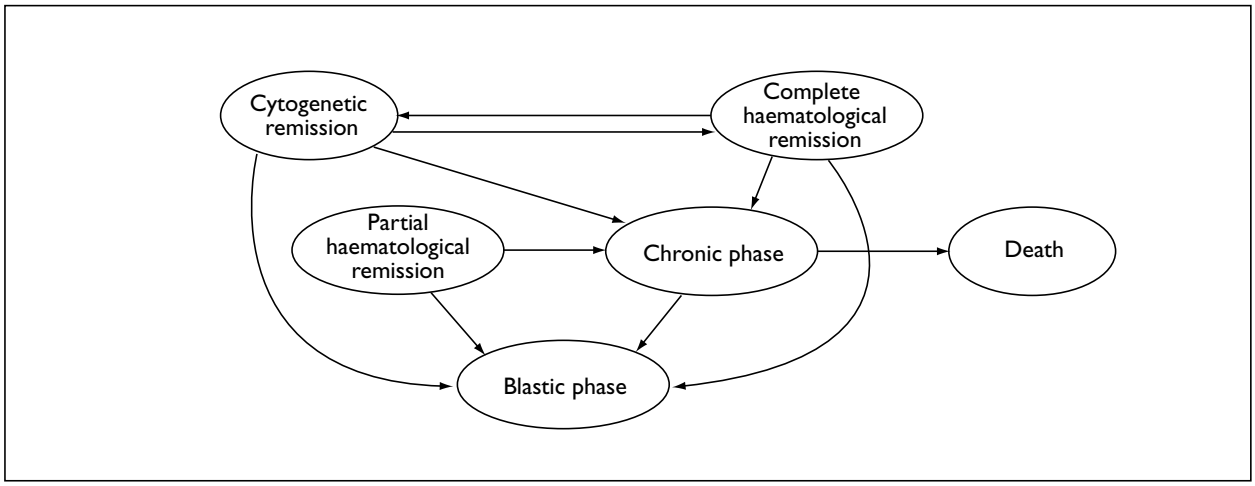


FIGURE 25 *Influence diagram showing transition between health states in Markov model used by Liberato and co-workers*[109]

was calculated, using a Gompertz function to extend the observed 1-year survival curve (the Gompertz function is frequently used to estimate survival curves). No adjustment for the quality of life-years gained was included.

Four RCTs formed the basis of the effectiveness data. The incremental cost-effectiveness ratio (ICER) of IFN-α versus cytotoxic therapy ranged from US$93,000 to US$226,000 per discounted life-year gained (with the study published in 1998 – no cost year is given).

Conclusions were sensitive to the dose of IFN-α used. When adding in a non-randomised trial with particularly favourable results for IFN-α the cost-effectiveness ratio ranged from US$56,022 for a dose of 10 MU per patient per week to US$204,680 for an IFN-α dose of 60 MU.

The authors of this evaluation conclude that long-term treatment with IFN-α without careful selection of patients may not be cost-effective.

Summary of existing evidence and external validity

Table 20 summarises the results of the three cost-effectiveness studies comparing IFN-α to chemotherapy for CML.

There is a wide range of estimates for the cost-effectiveness of IFN-α for CML. There are several reasons for this variation. Firstly, there are obvious differences in methodology, with the Liberato[109] and Kattan[77] studies using Markov models to calculate cost per QALY, and the Messori study[110] using a Gompertz model without quality adjustment of life-years gained.

The estimates from the Liberato study[109] are similar to the lower estimates of the Messori study.[110] The combination of higher survival values and lower costs of IFN-α therapy account for the Kattan study's significantly lower ICERs than Liberato[109] or Messori.[110] Kattan and colleagues[77] also used slightly higher values of estimated survival gains from IFN-α than the other two studies.[109,110] The Kattan study also used lower estimates of cost per patient of IFN-α therapy than the other two studies, as IFN-α therapy is more expensive in Italy than in the USA. The study also excluded costs such as drug administration, laboratory processing and physician time, whereas the Messori study[110] included estimates and values for these resources.

Economic evaluation of imatinib – Novartis submission overview

The aim of the unpublished submission from Novartis was to compare the cost–utility of imatinib against hydroxyurea for all phases of CML second-line use, as per the licensed indication. This

TABLE 20 *Summary of cost-effectiveness studies comparing IFN-α and chemotherapy*

Study	ICER
Kattan *et al.*, 1996[77]	US$34,800 per QALY gained
Liberato *et al.*, 1997[109]	US$89,500 and US$63,500 per QALY gained
Messori, 1998[110]	US$93,000 to US$226,000 per life-year gained

evaluation is based on three spreadsheet Markov models of chronic, accelerated and blast phases of CML (*Figure 26*).

Each model begins with a cohort of 1000 people, uses a monthly cycle, and continues until all patients in the hypothetical cohort die. The effectiveness data for imatinib are from the three unpublished case series studies[13,58,59] described earlier in this report. As the follow-up in these studies is short, assumptions have been made about response rates and survival after the first year. Many assumptions are also made about treatment after imatinib has failed. Effectiveness of hydroxyurea is based on data from the Italian RCT, which had a 10-year follow-up.[116]

The ICERs generated by the models are shown in *Table 21*.

The following sections review the model in more detail, and explore the effect of altering the key assumptions. The underlying structure of the model has not been altered, although a critique of the structure is presented.

Evaluation of model presented by Novartis

This section sets out the salient features of each model, makes comments on critical assumptions about model parameters and provides an appraisal of the evaluation according to the schema of Drummond.[57] It is concluded that the effect of many of the assumptions favour imatinib, that is we believe it is likely that the true cost–utility will be higher than that suggested in the Novartis submission.

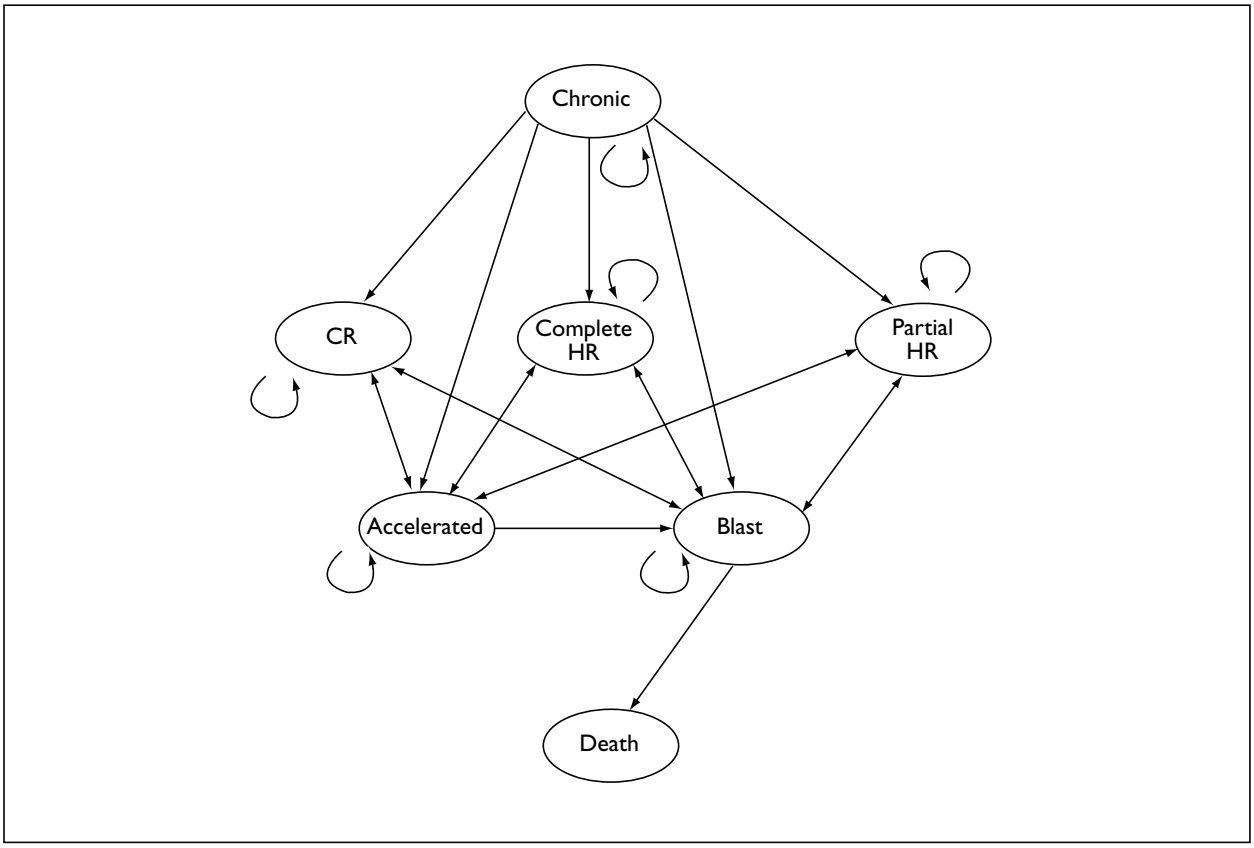


FIGURE 26 *Influence diagram showing transition between health states in Markov model used by Novartis*

TABLE 21 *Industry submission ICERs for imatinib versus hydroxyurea*

Phase	Original ICER in submission (cost per QALY, £)
Chronic	33,224–35,002
Accelerated	21,826–30,389
Blast	33,272–43,467

1. **Was a well-defined question posed in answerable form?**
   Yes. The study examined both costs and effects of imatinib compared to hydroxyurea in chronic phase patients who have failed IFN-α, and 'conventional chemotherapy' in advanced phases. There is no ideal comparator for imatinib as second-line treatment to IFN-α. While hydroxyurea is used in practice, it is not an ideal comparator as the aims of treatment and action of the drugs are different. The question posed in this analysis will only provide answers about the incremental cost–utility of imatinib over hydroxyurea. It would be useful to obtain incremental analyses of imatinib compared to IFN-α in the chronic phase as it is likely that imatinib will to some extent replace IFN-α in practice. In addition, it is unclear what 'conventional chemotherapy' refers to for advanced phase disease. There is currently no standard treatment, and this may be taken to mean hydroxyurea, or a range of chemotherapies that may be used. The viewpoint of the analyses is the health system and this is appropriate.

2. **Was a comprehensive description of the competing alternatives given (i.e. can we tell who did what to whom, where, and how often?)**
   A full description is provided, although the description relies heavily on assumptions, many of which may not be justified (see following comments).

3. **Was the effectiveness of the programmes or services established?**
   The effectiveness of imatinib is based on three case series, one for each of the three phases of CML. The case series design is highly susceptible to bias. Effectiveness data beyond 1 year were not available. This necessitated the assumptions that imatinib would assume the same survival curve as IFN-α beyond 1 year in order to evaluate cost-effectiveness over the potential duration of treatment.

   It is not clear that effectiveness data for imatinib and hydroxyurea are comparable. *Table 22* outlines the main assumptions in the evaluation regarding survival, disease progression and background mortality. Comments have been made for each assumption.

   There is no validation of the model against empirical trial data. A survival curve was not presented in the chronic phase trial, therefore the survival curves used in estimating the ICER have been extrapolated from the model (*Figure 27*). The flattening of the imatinib curve after year 10 is unrealistic and almost certainly overestimates the number of life-years gained; this reflects the small numbers, low death rate and progression rates for IFN-α in year 10 of the Italian trial.[62]

   For the accelerated and blast phases, the survival curves obtained with 1 year of imatinib treatment in the model are compared to that obtained in the actual study (*Figures 28* and *29*). Both suggest that the model overestimates survival, in the accelerated phase more than in the blast phase.

4. **Were all important and relevant costs and consequences for each alternative identified?**
   Yes. Costs were identified from the health system perspective. Resources considered were drugs, inpatient bed-days, home/hospital palliative care, bone marrow examinations, outpatient visits, X-rays and CT scans, blood transfusions and home nursing/GP visits. Cost savings from avoided future healthcare were also identified and included. *Table 23* outlines the key resource assumptions and includes comments on each.

   The following costs were omitted and may be important:

   - overhead/capital costs (included but not in a clear way)
   - the costs of materials and processing the haematological and cytogenetic tests
   - the costs associated with adverse drug reactions/events.

   The main outcome is the QALY based on physicians' evaluations, which is consistent with the adoption of a health system perspective and a cost–utility analysis. The consequences were reasonable, although the only way to progress to death was through the blast phase, which is not reasonable.

5. **Were all costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life-years)?**
   Costs and consequences were measured in appropriate units.

TABLE 22 *Key model assumptions and comments on survival, disease progression and mortality*

Survival data and disease progression	**Comments**
Rate of progression for year 2 onwards is assumed to be the same as IFN-α in the imatinib arm (chronic model only)	The survival data for IFN-α and HU are taken from the Italian trial,[62] which is the most favourable for IFN-α and shows the biggest difference between IFN-α and HU of the IFN-α trials. Median age of entry in this trial was 39. No allowance is made for the older age and late stage of entry (late chronic phase) of patients into the imatinib trial, which is likely to have the effect of reducing overall survival[27]
Rate of progression is fixed in the accelerated and blast models	Reasonable assumption
Disease progression after year 10 is the same as year 10	Overestimates imatinib and underestimates HU due to small numbers and occurrence of low death and progression rates in year 10 in Italian trial for IFN-α, and high death and progression rates for HU.[62] Leads to bias in favour of imatinib
Patients cannot die from CML in the model unless they are in the blast phase	Underestimates death rates in both arms. Up to a third of patients have been reported to die in the chronic phase, depending on age at diagnosis.[18] Direction of bias unknown
Transition probabilities for years 2 onwards for HR and CR are assumed to be the same as for year 1	Not evidence-based. CR tends to vary between first and subsequent years; there may be very few CRs observed after year 2[19]
Imatinib patients who experience HR within 3 months continue treatment, whereas others stop	In Study 110, 22% of patients who have a complete HR have not done so by month 3. In practice, patients who do not have a response within 3 months have their dose escalated to 400 mg twice daily.[58] May not realistically reflect clinical practice and may bias the results in favour of imatinib
For chronic progressing patients, 70% progress to accelerated phase and 30% to blast phase	Model bases this figure on clinician estimates. There is no evidence to support this. Unknown direction of bias, if any
22.5% of patients per year in the accelerated phase lose their HR per year, and 2.1% progress per month	According to Study 102 (accelerated phase)[13] the median duration of CR is 10.2 months (for 600 mg dose), therefore 50% loss of response and a monthly progression of 6.6%
Once a patient is a non-responder they automatically assume the progression rates and utilities of the HU group	Not evidence-based. Direction of bias uncertain. For example, some non-responders to IFN-α have a better prognosis than those not on IFN-α[39]
Neither chemo nor palliative care induce HR, CR or delay disease progression (accelerated and blast phases)	Chemo is known to produce a complete HR response ranging from 23%[39] to 59%[83] and a CR in some trials (albeit short-lived) (*Table 8*)
Background mortality	**Comments**
The death rate from causes other than CML is fixed at a simple rate	Fixed death rate used in model is too low compared to UK life expectancy tables, and does not increase with time. This results in the chronic model running for over 60 years before the whole cohort is dead in the imatinib arm – this is unreasonable when the median age of entry is 56 years. Overestimates life-years and QALYs gained in the imatinib arm compared to the HU arm (also see comments on validation)

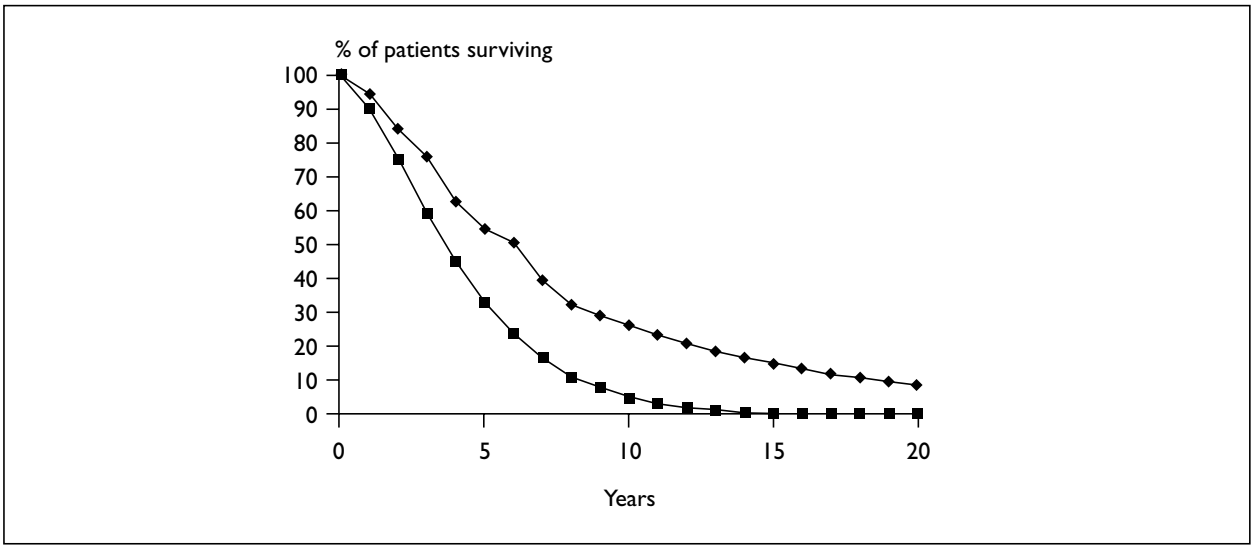


FIGURE 27 *Survival curves resulting from chronic phase model for imatinib (◆) and hydroxyurea (■)*

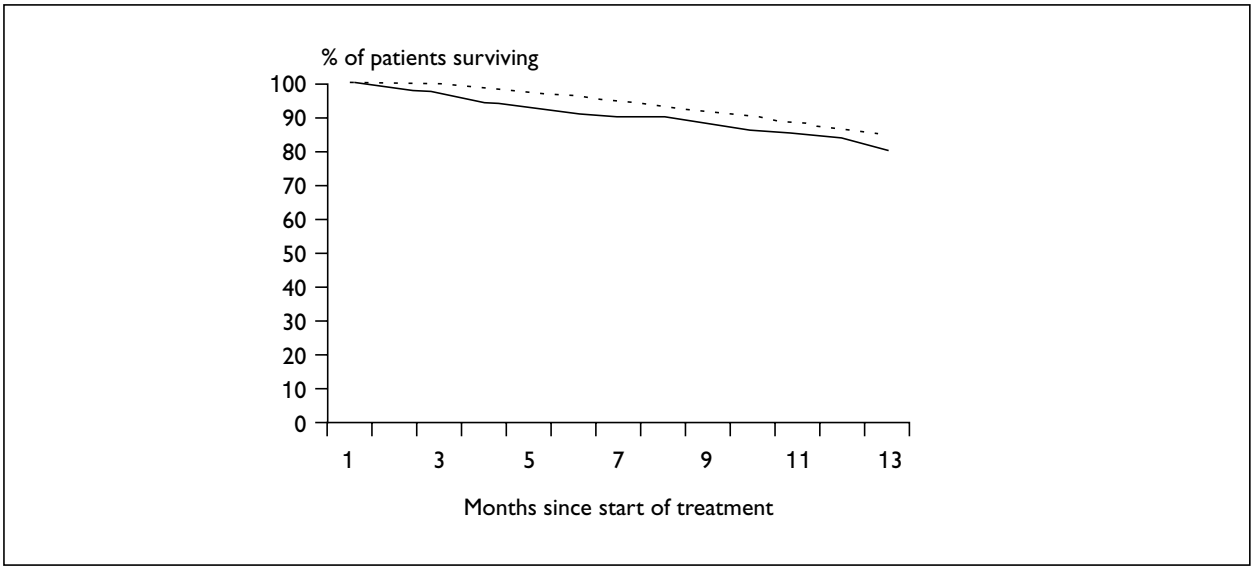


FIGURE 28 *Accelerated phase year 1 survival from model compared to original trial (– – –, imatinib modelled submission; ——, imatinib trial)*

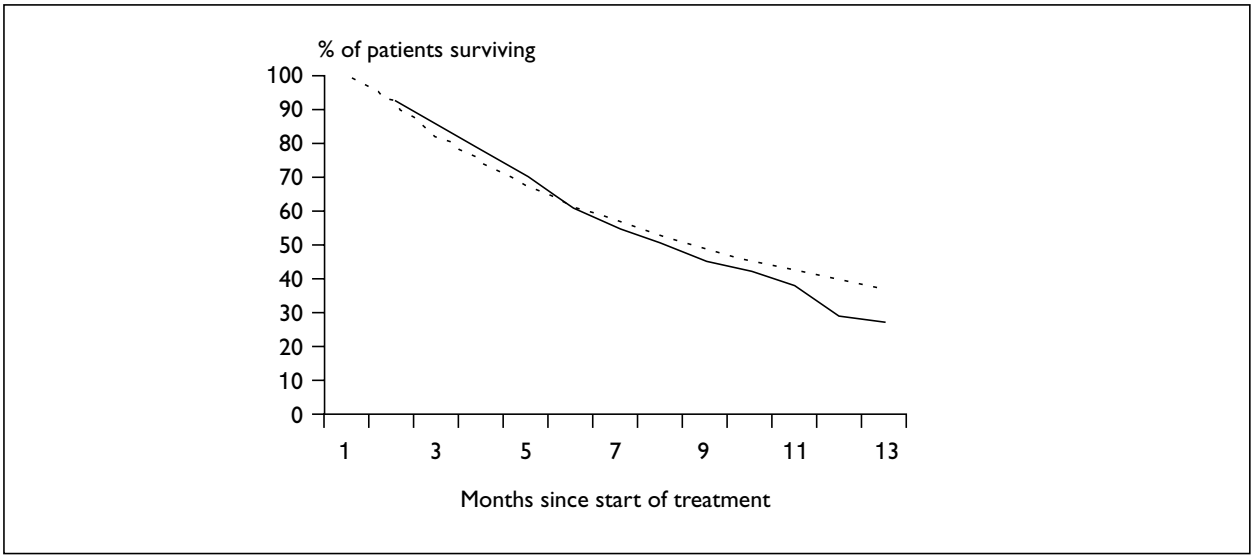


FIGURE 29 *Blast phase year 1 survival from model compared to original trial (– – –, imatinib modelled submission; ——, imatinib trial)*

TABLE 23 *Key model assumptions for resource use and valuation*

Key assumptions	Comments
The dose of imatinib is 400 mg/day in the chronic phase and 600 mg/day in the accelerated/blast phase	The dose in the chronic phase was escalated to 800 mg/day.[58] Dose escalation in the accelerated phase to 800 mg/day according to physician discretion.[13] Imatinib is licensed up to 600 mg/day in the chronic phase and 800 mg/day in the accelerated or blast phases. Underestimates the cost of imatinib
Once patients experience disease progression treatment stops and they receive chemo or palliation	Unlikely to mirror actual practice, where some patients will continue to receive treatment regardless of progression[61]
Dose remains constant regardless of response	Patients frequently have their doses adjusted (usually increased).[13,58] Underestimates the cost of imatinib
No supplementary treatment	Allopurinol, HU, anagrelide, leukapheresis and anticancer drugs were also administered after 28 days.[13,58] May underestimate cost of imatinib
Imatinib has the same or fewer adverse effects than the comparator	The evidence suggests that imatinib has more adverse effects than HU. This would increase the cost of imatinib treatment if modelled and may reduce the relative utility, although the effects are likely to be small
Cost of bone marrow examination is the same as an outpatient visit (£60)	Omits cost of processing and materials. Underestimates the cost of imatinib

6. Were all costs and consequences valued credibly?

Costs – the costs of resources used in the model in general were estimated credibly. Sources included the *British National Formulary* (*BNF*), NHS reference costs, Health Services Financial Database and Comparative Tool (CIPFA), NHS Trusts, the National Blood Donor Registry, and the Personal and Social Services Research Unit (PSSRU). No cost data were available for bone marrow examination so it was assumed to be the same as an outpatient visit. This is a questionable assumption but is unlikely to significantly affect the model. The costs of physical examination were reasonably assumed to be absorbed within the cost of an outpatient visit. Blood chemistry tests were also assumed to be included in outpatient visits, which is likely to lead to slight underestimation of imatinib costs.

Consequences – a panel of clinicians estimated the proportion of patients who, on progressing to the accelerated phase from the chronic phase, would receive combination chemotherapy and palliative care. There are some concerns over these estimates. Chronic phase patients progressing to the accelerated phase receive the following treatments: 10% chemotherapy in hospital and 90% palliative care at home. In contrast, chronic phase patients progressing to the blast phase receive the following treatments: 50% chemotherapy in hospital, 10% palliative care in hospital and 40% palliative care at home. These differences in treatment according to stage are not justified and seem unlikely *a priori*. The estimates vary widely within and between phases and treatments, were not tested in sensitivity analysis and it is questionable that they reflect what would be expected in practice. No justification is presented.

Utility values were estimated using a panel of clinicians who mapped CML health states onto those of the EQ-5D, a generic measure of QoL. Utilities for EQ-5D health states have been estimated from a UK general population sample. The average values for utilities of health states on the EQ-5D identified by clinicians as being equivalent to CML states were used in the model. The clinicians valued receiving combination chemotherapy as 0.01 in the accelerated phase and as –0.09 in the blast phase. Patients receiving hospital and home palliative care respectively in the accelerated phase were assigned utilities of 0.07 and 0.34, which are lower than expected. In the blast phase, patients were assigned utilities of –0.18 and 0.04 respectively. These utilities are constant throughout the accelerated and blast

phases. It is assumed that chemotherapy and palliative care offer no treatment benefits and it is therefore questionable why patients would agree to such treatments if they are also associated with low (and even negative) utilities (*Table 24*).

The literature varies considerably in the allocation of utilities to specific health states. The range of utilities estimated for EQ-5D health states is relatively large. There is therefore scope for small differences in health states to be associated with relatively large differences in utility. On the other hand, the values for EQ-5D health states have the advantage of being estimated from a general population sample.

In order to place the utilities of CML health states in context, *Table 25* illustrates some values reported in the literature. They suggest that some of the utilities assigned in this model may be too low.

7. **Were costs and consequences adjusted for differential timing?**
Future costs were discounted at 6% per year and future benefits were discounted at 1.5%, which is in accordance with NICE guidelines.

8. **Was an incremental analysis of costs and consequences of alternatives performed?**
Yes. Model outputs are ICERs.

9. **Was allowance made for uncertainty in the estimates of costs and consequences?**
Allowance for uncertainty was made by adjusting the cost of palliative care. Each ICER is presented twice, once assuming that the cost of home palliative care is the same as hospital palliative care (£181), and secondly assuming that the cost of home palliative care is zero. This seems reasonable. The sensitivity analyses shown in *Tables 26–28* were calculated and include each of the three CML phases. Two further sensitivity analyses were per-

TABLE 24 *Key model assumptions for utility*

Key assumptions	Comments
The utility weight is 0.01 for people in the accelerated phase receiving chemo	Questionable. Utilities of comparators seem low Baseline utility of 0.5 for accelerated phase[77] Bias in favour of imatinib
The utility weight is –0.09 for people in the blast phase receiving chemo	Possibly too low. Baseline blast utility of 0.5[77,109] Bias in favour of imatinib

TABLE 25 *Examples of utilities assigned to various health states from the literature*

Health state – CML	Utility	Source
Chronic lymphocytic leukaemia, life-threatening bacterial infection*	0.46	Weeks *et al.*, 1991[117]
Accelerated phase of CML	0.50	Kattan *et al.*, 1996[77]
Blast crisis of CML (either months 1–4 or after month 4)	0.50	Kattan *et al.*, 1996[77]
Blast phase of CML	0.50	Liberato *et al.*, 1997[109]
Cancer, CML, on IFN-α therapy	0.90	Kattan *et al.*, 1996[77]
Health state – other diseases for comparison	**Utility**	**Source**
Influenza, haemophilus type B, meningitis, associated with severe childhood disability	–0.12	McIntyre *et al.*, 1994[118]
Non-malignant disease, child, allogenic bone marrow transplant, grade I–IV graft vs host disease	0.00	Quaglini *et al.*, 1994[119]
Stroke, severe, motor deficit	0.03	Solomon *et al.*, 1994[120]
Stroke, severe, cognitive deficit	0.08	Solomon *et al.*, 1994[120]
Cerebrovascular disease, intracranial aneurysm, persistent vegetative state, unresponsive and speechless until death after acute brain damage	0.08	Aoki *et al.*, 1998[121]

* *For illustration, a severe state related to leukaemia*

formed only for the chronic phase (*Tables 29* and *30*). Rate of progression after year 1 is predicted using a fitted Weibull curve to the first 1 year's data for imatinib patients.

The chronic phase estimates were sensitive to the discount rate used for costs and consequences and the rate of progression values used. Blast phase estimates were sensitive to the utility assigned.

Uncertainty, or variability, in estimates used for critical model parameters is not extensively explored. It would have been useful to explore the following areas:

- increasing the dose of imatinib
- increasing the fixed constant death rate per month to a more realistic figure
- increasing the utilities assigned to chemotherapy and palliative care
- increasing the death rate after year 10
- varying the proportion of patients who progress to accelerated and blast phases
- varying the transition probabilities to chemotherapy and palliative care
- altering survival and progression rates after the first year for hydroxyurea and IFN-α.

We have extended the analysis by exploring reasonable variation in estimates of these

TABLE 26 *Sensitivity analysis: costs and QALYs are both discounted at 6%*

Phase	Original ICER in submission (cost per QALY, £)	Results of sensitivity analyses (cost per QALY, £)
Chronic	33,224–35,002	53,123–53,271
Accelerated	21,826–30,389	25,564–35,594
Blast	33,272–43,467	34,825–45,496

TABLE 27 *Sensitivity analysis: costs are discounted at 6% and QALYs are not discounted*

Phase	Original ICER in submission (cost per QALY, £)	Results of sensitivity analyses (cost per QALY, £)
Chronic	33,224–35,002	27,586–29,063
Accelerated	21,826–30,389	20,589–28,667
Blast	33,272–43,467	32,755–42,792

TABLE 28 *Sensitivity analysis: utility scores for the hydroxyurea group are the same as for the imatinib group*

Phase	Original ICER in submission (cost per QALY, £)	Results of sensitivity analyses (cost per QALY, £)
Chronic	33,224–35,002	34,115–35,941
Accelerated	21,826–30,389	23,703–33,002
Blast	33,272–43,467	40,992–53,553

TABLE 29 *Sensitivity analysis: non-responders continued to received imatinib until disease progression*

Phase	Original ICER in submission (cost per QALY, £)	Results of sensitivity analyses (cost per QALY, £)
Chronic	33,224–35,002	34,702–36,437

TABLE 30 *Sensitivity analysis: rate of progression using Weibull curve after 1 year*

Phase	Original ICER in submission (cost per QALY, £)	Results of sensitivity analyses (cost per QALY, £)
Chronic	33,224–35,002	43,730–45,584

variables through one-way and multi-way analyses (see below).

10. **Did the presentation and discussion of study results include all issues of concern to users?** The costs to the patient and/or carers were not included in the analysis or discussed.

In summary, the submission states that the cost per QALY figures generated are likely to have been overestimated for the following reasons:

- Adverse events have not been addressed in the modelling.
- Long-term data for imatinib will be more favourable (CR, HR and survival) than the currently modelled transition probabilities of IFN-α.

In contrast, we believe that the cost per QALY figures generated may have been underestimated for the following reasons:

- Doses higher than those modelled are common and dose escalation constitutes 'standard practice'.
- There is no evidence that long-term data for imatinib will actually be more favourable than IFN-α.
- The model has underestimated death rates due to CML and non-CML causes, and does not reflect the older age and later stage of disease of people enrolled in the trial.
- The utilities assigned to comparators and blast/accelerated phases may be too low.
- The adverse events associated with imatinib are, on current evidence, greater than with hydroxyurea.
- Disease progression after year 10 is underestimated.
- Patients are only able to die from CML once they are in the blast phase, which underestimates overall death rates from the disease.

Review of assumptions and further sensitivity analyses

We have varied some of the key assumptions of the Novartis model in order to present what we believe are more realistic estimates of the likely cost-effectiveness of imatinib. Note that in each case the first ratio reflects a maximum home nursing cost (£181) whereas the second reflects a home nursing cost of zero.

Cost of imatinib/dose

Increasing the dose of imatinib increases the ICERs. In the Novartis model, doses of 400 mg/day (chronic phase) and 600 mg/day (accelerated and blast phases) were used and no sensitivity analyses were performed. We have been told by Novartis (personal communication) that these doses approximately reflected the actual doses used so far in the trials. However, in order to assess what the effect of dose escalation is in practice we have performed a sensitivity analysis.

Table 31 shows the ICERs when an average dose of 500 mg/day in the chronic phase, and 700 mg/day in the accelerated/blast phase, is used (i.e. 50% of people are on 400 mg and 50% on 600 mg in the chronic phase).

If the average dose is increased to the maximum licensed level of 600 mg/day in the chronic phase and 800 mg/day in the accelerated and blast phases then the ICERs for imatinib would increase as shown in *Table 32* (this represents an extreme value on this parameter).

If the dose in the chronic phase were also increased to 800 mg, as was permitted in the trial, then the ICER for imatinib would further increase, as shown in *Table 33* (this represents an extreme value on this parameter).

It should also be noted that increasing imatinib drug costs to include the concurrent therapies allopurinol, anagrelide and leukapheresis would also increase the ICERs. Furthermore, the cost of the materials and processing of the cytogenetic tests have not been included, which would also increase the cost per QALY of imatinib, although by a small amount.

Mortality data from non-CML causes

The chronic model assumes a constant death rate from causes unrelated to CML of 0.4% for every year of the model. This partly accounts for the

TABLE 31 *Varied dose assumption: 500 mg chronic and 700 mg accelerated/blast*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – dose (cost per QALY, £)
Chronic	33,224–35,002	42,198–43,977
Accelerated	21,826–30,389	21,826–30,389
Blast	33,272–43,467	40,939–51,135

TABLE 32 *Varied dose assumption: 600 mg chronic and 800 mg accelerated/blast*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – dose (cost per QALY, £)
Chronic	33,224–35,002	51,173–52,951
Accelerated	21,826–30,389	31,643–40,206
Blast	33,272–43,467	48,607–58,892

TABLE 33 *Varied dose assumption: 800 mg chronic*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – dose (cost per QALY, £)
Chronic	33,224–35,002	69,121–70,900

fact that the Novartis model runs for 60 years, until all participants have died.

We ran the model with death rates taken from life tables for Great Britain.[122] The average age in the chronic phase of the industry trial was 57, so we started at age 57 on the tables, and averaged the death rates for men and women. We used increasing death rates for 20 years, using the life-table estimates of mortality, and then continued at the same rate. The annual death rate used was 0.5% in year 1, rising to 5% in year 20. We converted the annual death rates in the life tables to monthly transition probabilities. [$p = 1 - e(-rt)$, where p = monthly transition probability, r = death rate, at time t in months.) We also assumed the death rate in the accelerated phase from causes unrelated to CML was the same as the age 62 death rate from the life table (assuming 5 years on average to progress from the chronic phase to the accelerated phase). This rate is fixed in all the models, and the existing structure did not allow variation. In our analysis the chronic phase model runs for 28 years, until all the cohort are dead, as compared to 60 years in the original model. The resulting ICERs are shown in *Table 34*.

We performed another calculation with the same assumptions as in *Table 33,* except that we assumed the probability of progressing from the accelerated phase to death was double the age 62 death rate from the life table. This is likely to approximate more accurately the death rate in this chronically ill population. The resulting ICERs are shown in *Table 35*. This assumption makes very little difference to the resulting ICERs reported in *Table 34*.

Rate of progression and survival from year 2 onwards – chronic model

Survival after the first year of imatinib therapy is taken from the IFN-α arm of the Italian RCT

TABLE 34 *Varied mortality assumption*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – constant death rate (cost per QALY, £)
Chronic	33,224–35,002	35,145–37,225
Accelerated	21,826–30,389	21,762–30,428
Blast	33,272–43,467	33,110–43,441

TABLE 35 *Varied mortality assumption: doubling age 62 death rate*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – constant death rate + rate of progression from accelerated phase to death (cost per QALY, £)
Chronic	33,224–35,002	35,164–37,229
Accelerated	21,826–30,389	21,891–30,457
Blast	33,272–43,467	32,930–43,398

trial.[62] This shows the most favourable survival, the largest difference between IFN-α and hydroxyurea, and was performed on a younger group of patients at lower risk than some of the other trials (median age 39 compared to median age of 50 in the IFN-α meta-analysis[38]) (see appendices 11 and 12). We have therefore modelled the survival from a trial at the other end of the spectrum[64] for which long-term survival data were available, in order to assess the sensitivity of the model to this parameter. Data are available in the trial report to 7 years, and years 8 to 10 were estimated by taking the same proportionate decrease in survival as the Italian trial. The Benelux trial[64] showed a non-significant survival difference between IFN-α and hydroxyurea, and recruited an older population, with more high-risk patients (i.e. this population is likely to be more similar to the imatinib patients than the Italian trial) (*Table 36*).

The model is very sensitive to assumptions about long-term survival, the parameter for which there is no empirical evidence at all. Although using the Benelux trial[64] data may underestimate the survival benefit of treatment, it demonstrates the cost–utility that would be produced, were imatinib to have a small effect on survival over a comparator, such as hydroxyurea or IFN-α.

As the model is heavily reliant on the long-term survival assumptions, we attempted to validate the survival curves produced. We compared the modelled survival for the first 5 years for the industry model, and for our analysis using the Benelux trial data,[64] with the survival curve taken from the IFN-α meta-analysis (*Figure 30*).[38] Neither model is a particularly good fit, both overestimating survival in the first few years. *Figure 31* shows the modelled 20-year survival, again from the industry model and our adjusted values. It is seen that there is a considerable gap between the survival curves, and it is this that accounts for the large difference in cost–utility. It is clear that little reliance can be placed on the model in the absence of empirical data on survival.

TABLE 36 *Varied assumption: patient characteristics – age and risk group*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – survival from Benelux trial (cost per QALY, £)
Chronic	33,224–35,002	267,900–270,106

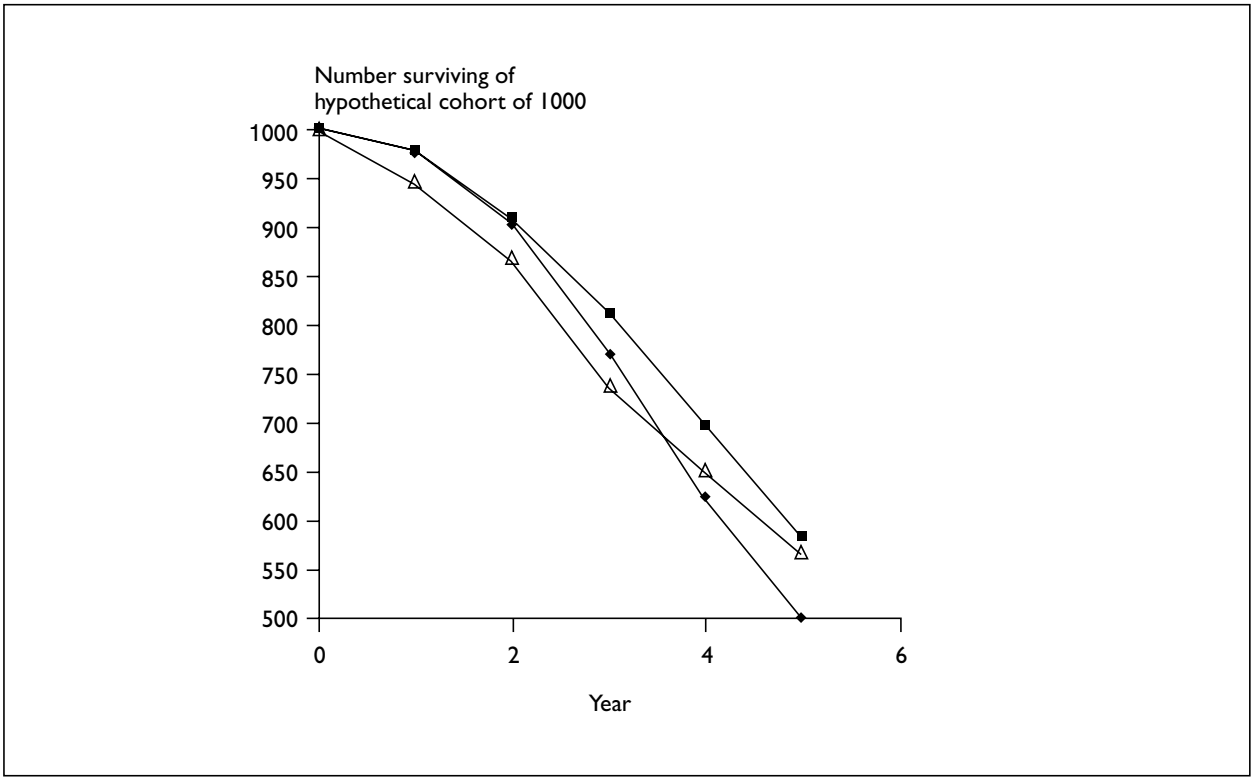


FIGURE 30 *Modelled survival compared to meta-analysis of survival with IFN-α (◆, adjusted model; ■, industry model; △, meta-analysis)*

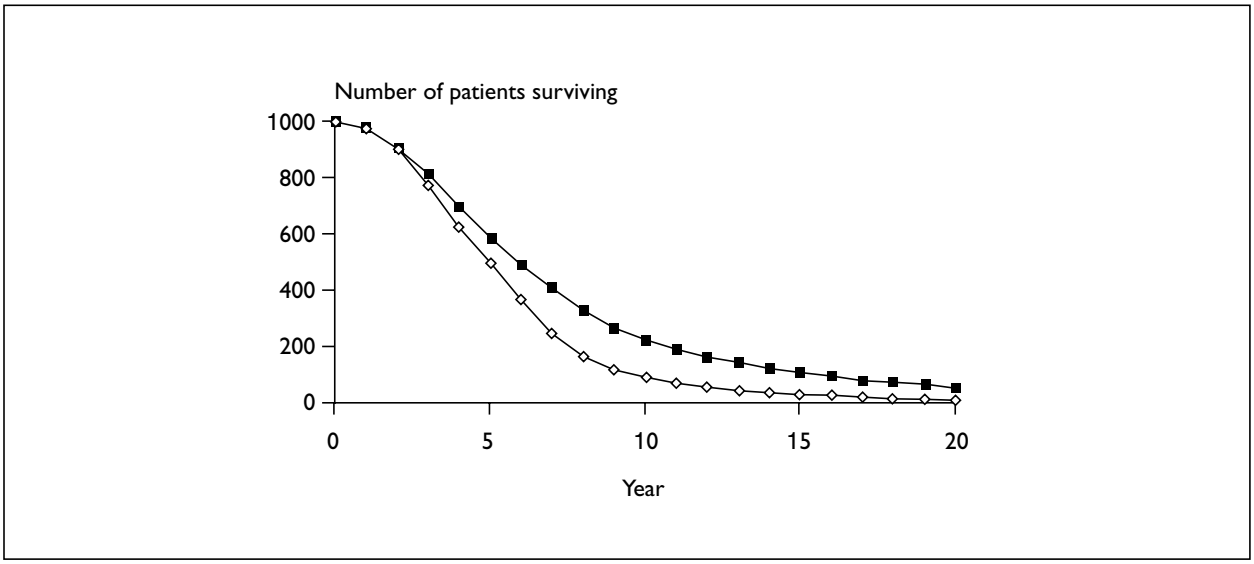


FIGURE 31 *Modelled survival for a hypothetical cohort of 1000 patients with CML (◇, adjusted model; ■, industry model)*

Duration of response in the accelerated phase

We have altered the model to use the median length of CR as a measure of disease-free progression in the accelerated phase of the model, rather than the HR.[13] Median duration of response was 7.4 months for patients receiving a 400 mg dose of imatinib and resulted in the ICERs shown in *Table 37*.

The median duration of response was 10.2 months for patients receiving a 600 mg dose of imatinib in the accelerated phase[13] and resulted in the ICER shown in *Table 38*.

Treatment following loss of response in the chronic phase

In the model the transition probabilities from the chronic phase to further treatment in the accelerated/blast phase (chemotherapy and palliative care) are based on clinician estimates. We have applied extreme case scenarios in order to determine the extent to which these probabilities affect the model. The model was adjusted so that all patients progressing from the chronic phase would receive palliative care at home; the results are shown in *Table 39*.

The model was adjusted so that all patients progressing from the chronic phase would receive palliative care in hospital; the results are shown in *Table 40*.

Finally, the model was adjusted so that all patients progressing from the chronic phase would receive chemotherapy in hospital; the results are shown in *Table 41*.

In all cases the blast phase was the most sensitive. The chronic phase is relatively unaffected by the changes in assigned treatments following progression. When patients are all assigned to palliative care in hospital with no home nursing costs, the blast phase is especially sensitive. When all patients are assigned to chemotherapy in hospital, blast phase ICERs are lower when home

TABLE 37 *Varied assumption: duration of response 7.4 months*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – duration of CR (cost per QALY, £)
Accelerated	21,826–30,389	21,344–40,494

TABLE 38 *Varied assumption: duration of response 10.2 months*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – duration of CR (cost per QALY, £)
Accelerated	21,826–30,389	21,850–38,257

TABLE 39 *Varied assumption: all patients progressing from chronic phase receive palliative care at home*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – treatment following loss of response (cost per QALY, £)
Chronic	33,224–35,002	32,529–35,364
Accelerated	21,826–30,389	21,932–31,447
Blast	33,271–43,467	41,153–39,368

TABLE 40 *Varied assumption: all patients progressing from chronic phase receive palliative care in hospital*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – treatment following loss of response (cost per QALY, £)
Chronic	33,224–35,002	32,616–32,616
Accelerated	21,826–30,389	21,796–35,450
Blast	33,272–43,467	40,163–70,535

TABLE 41 *Varied assumption: all patients progressing from the chronic phase receive chemotherapy in hospital*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – constant death rate + rate of progression from accelerated phase to death (cost per QALY, £)
Chronic	33,224–35,002	35,001–35,001
Accelerated	21,826–30,389	18,158–31,812
Blast	33,272–43,467	13,109–43,481

nursing is assigned the maximum cost. It is difficult to estimate the exact proportion of patients who will progress to these treatment states; it is also likely that not all relevant treatments have been included. What has been demonstrated is that varying the proportion of patients receiving these treatments once they progress will affect the ICER, mainly in the blast phase.

Hospital costs and percentage reduction in bed-days

A comparison of intensive versus palliative chemotherapy has been reported in a recent paper by Hernandez-Boluda and colleagues,[97] showing no difference in survival for the two regimes. Using the palliative regime, a cost of £20 per month for chemotherapy is obtained (figures taken for the average dose of 6-mercaptopurine from the *BNF*) in comparison to £575 per month that was used in the Novartis model. Hernandez-Boluda and colleagues[97] also report that chemotherapy treatment reduced hospital bed-day use by 64% for patients with CML. We varied the model by incorporating a cost of £20 per month for chemotherapy and assumed a conservative reduction in hospital bed-days of 50% in the accelerated and blast phases. The resulting ICERs are shown in *Table 42*. The blast phase model shows moderate sensitivity.

Utilities

A panel of clinicians estimated the utilities used in the Novartis model. If the most conservative position is taken then it could be assumed that the utilities are the same for imatinib, chemotherapy and palliative care. The effect of varying the utilities as such is shown in *Table 43*.

TABLE 42 *Varied assumption: hospital costs and percentage reduction in bed-days*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – hospital costs and % reduction in bed-days (cost per QALY, £)
Chronic	33,224–35,002	33,364–35,143
Accelerated	21,826–30,389	22,369–30,932
Blast	33,272–43,467	36,199–46,394

TABLE 43 *Varied assumption: utilities provided by clinicians*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – utilities (cost per QALY, £)
Chronic	33,224–35,002	33,635–35,436
Accelerated	21,826–30,389	23,703–33,002
Blast	33,272–43,467	40,992–53,553

TABLE 44 *Varied assumption: utilities provided in literature*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – utilities (cost per QALY, £)
Chronic	33,224– 35,002	33,654–35,456
Accelerated	21,826–30,389	23,477–32,689
Blast	33,272–43,467	47,469–62,015

TABLE 45 *Varied assumption: utility of 0.5 for accelerated and blast phases*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – utilities (cost per QALY, £)
Chronic	33,224–35,002	33,654–35,456
Accelerated	21,826–30,389	24,060–33,500
Blast	33,272–43,467	39,744–51,922

TABLE 46 *Varied assumption: transition probabilities 70% accelerated and 30% blast phases*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – transition probabilities (cost per QALY, £)
Chronic	33,224–35,002	34,074–35,145
Accelerated	21,826–30,389	18,243–29,802
Blast	33,272–43,467	24,121–41,981

Alternatively we could assign the utilities estimated in the papers by Kattan[77] and Liberato[109] to patients in chronic and blast phase (utility = 0.5) assigned to chemotherapy or palliative care. The ICERs are shown in *Table 44*.

This is an unlikely scenario because it is improbable that imatinib will have a lower utility than chemotherapy or palliative care in the blast phase. We therefore assigned patients in the accelerated and blast phases (imatinib, chemotherapy and palliative care) utilities of 0.5, as estimated in the studies by Kattan[77] and Liberato[109] and the results are shown in *Table 45*. The results show moderate sensitivity to the utilities in the blast phase.

Disease progression probabilities

The original model assumes that when CML progresses from the chronic phase, or from a treatment-induced response, 70% of patients proceed to the accelerated phase and 30% proceed to the blast phase. This is based on estimates from the clinician panel. If an extreme case scenario is modelled by reversing the estimates so that 70% of patients proceed to blast phase and 30% to accelerated phase then the effect on the ICERs is shown in *Table 46*. If the probabilities are varied so that 90% of patients proceed to accelerated phase and 10% to blast phase the results are as shown in *Table 47*. It can be seen above that the blast model, and to a lesser extent the accelerated model, is moderately sensitive to these parameters.

Cumulative effect of our key variations

From these analyses it has been demonstrated that we are uncertain of the exact ICER for

TABLE 47 *Varied assumption: transition probabilities 90% accelerated and 10% blast phases*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumption – constant death rate + rate of progression from accelerated phase to death (cost per QALY, £)
Chronic	33,224–35,002	32,799–34,931
Accelerated	21,826–30,389	23,615–30,683
Blast	33,272–43,467	37,835–44,208

imatinib in the treatment of CML, especially when considering the cumulative effect of several underestimates. In order to estimate this cumulative effect we have performed a multi-way sensitivity analysis incorporating all of the following assumptions in order to produce the most extreme possible case (*Table 48*):

- Average dose of 500 mg in the chronic phase, and 700 mg in the accelerated/blast phase.
- Median duration of response was 10.2 months for patients in the accelerated phase.
- Death rates not due to CML are age-specific death rates from UK life expectancy tables.
- The death rate from the accelerated phase is increased (as per age 62 in life tables).
- Using utilities of 0.5 for all treatments in the accelerated and blast phases.
- Hospital costs of chemotherapy are £20 and there is a 50% reduction in bed-days.
- Long-term survival data taken from Benelux trial.

In addition, to explore the impact of uncertain estimates of survival beyond the existing empirical data, we performed sensitivity analysis in the chronic phase using all of the above parameters, excluding survival changes. This gave the ICER estimates shown in *Table 49*.

Setting aside uncertainty regarding survival, the Novartis model is still moderately to highly sensitive to cumulative likely changes in key variables.

Other factors

The cost of adverse events is also likely to influence the ICERs. While we have not attempted to cost and model them it is likely that imatinib has more adverse events than hydroxyurea and therefore incurs a higher treatment cost. The result would be to further increase the ICER for imatinib although the magnitude of impact is unknown.

The cost-effectiveness of imatinib is likely to depend on the age of the individual patient. In the imatinib studies the median age of patients was 56–57 years. Studies of IFN-α and hydroxyurea have demonstrated similar median ages. It was, however, highlighted in a cost-effectiveness study by Kattan and co-workers[77] that IFN-α was more cost-effective in younger patients. For example, patients aged 30 achieved benefits at US$30,830 per QALY whereas in patients aged 70, cost-effectiveness was estimated as US$61,200. It is likely that imatinib will also be more cost-effective in younger patients, although we do not have the necessary data to explore this.

Using IFN-α as the comparator is another factor that would influence the results. This comparison would be interesting, as it is likely that imatinib will diffuse into the first-line setting, perhaps substitut-

TABLE 48 *ICERs from industry submission and our cumulative key variations*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumptions (cost per QALY, £)
Chronic	33,224–35,002	299,379–301,446
Accelerated	21,826–30,389	35,633–56,052
Blast	33,272–43,467	52,354–64,724

TABLE 49 *ICERs from industry submission and our cumulative key variations excluding survival*

Phase	Original ICER in submission (cost per QALY, £)	ICER with varied assumptions (cost per QALY, £)
Chronic	33,224–35,002	45,592–47,712

ing for IFN-α to some degree. If the two drugs were modelled in comparison to each other it would eliminate much of the survival advantage that imatinib has in the current model, as it is modelled on IFN-α data. The model is clearly most sensitive to assumptions about survival. The cost of imatinib is considerably greater than IFN-α, and therefore the ICER is likely to be high.

Conclusions

The Novartis model structure is reasonable in the context of other models of CML. A simple Markov model is used with progression to death only allowed through the blast phase. This is likely to underestimate mortality within the model, an important finding given that length of survival is a key determinant of cost–utility (demonstrated also in the existing economic literature on CML).

The Novartis results suggest moderate cost–utility for imatinib. Inevitably many assumptions are made, and insufficient review of assumptions and sensitivity analysis were included in the submission. The effect of changing these assumptions is predominantly to increase the cost–utility. The relative paucity of data for the chronic phase model means that the submitted estimate for cost–utility should be viewed with particular caution.

Impact on the NHS budget

The impact on the NHS budget will depend on the following:

- the proportion of CML patients failing first-line IFN-α therapy
- imatinib uptake rates as second-line treatment
- the cost of imatinib (dependent on the dose)
- the extent of adoption of imatinib as a first-line treatment.

The prevalence of CML in England and Wales is estimated to be 2660 patients. The annual incidence of CML in England and Wales is approximately 700 new patients.

The likely impact of a positive NICE recommendation will be an increase in the number of CML patients who are considered for continuing treatment. There is a possibility that imatinib will be used in the first-line setting and replace IFN-α to some extent. There may also be increases in administration of concurrent therapies along with the materials and processing of cytogenetic tests.

The Novartis submission presents a predicted impact of imatinib on the NHS budget as follows:

Year	Cost (£ million)
Year 1	7.9
Year 2	13.5
Year 3	18.0
Year 4	21.7
Year 5	24.8

The submission presents sensitivity analyses around these estimates, varying the percentage of CML patients who receive IFN-α treatment, the uptake rates of imatinib, the non-responders continuing imatinib therapy past month 3 and progression-free survival varying from 37% to 57%. The estimated impact on the NHS budget in these scenarios is between £5.8 million and £9.4 million in year 1, rising to between £19.2 million and £31.4 million in year 5.

There are a number of reasons why these predictions may be underestimates. The submission predicts that 18.6% of patients are intolerant of IFN-α and that 5.6% of patients are resistant. IFN-α resistance, according to Kantarjian and colleagues,[58] is composed of either haematological failure or cytogenetic resistance (see *Box 1*, page 1). The literature suggests that in reality between 18% and 30% withdraw from IFN-α treatment because of adverse effects[39,45,58,62,64] and between 25% and 30% are IFN-α-resistant.[58] It can be argued that all patients fail IFN-α eventually.

If we were to take the lower ranges of IFN-α failure from the literature then the estimated impact on the NHS drugs budget would rise to £11.8 million in the first year. If we were to assume the upper ranges of IFN-α failure from the literature then the estimated impact would rise to £15.8 million in the first year.

In addition the number of patients considered eligible for imatinib therapy may increase as a result of its use as first-line treatment. The upper limit of cost is bound under the assumption that all patients would receive imatinib, in all phases of CML. Based on a prevalence of 2660, and assuming doses of 500 mg in the chronic phase and 700 mg in the blast phase, the cost to the NHS would be £61.4 million per year.

Chapter 5
Discussion

Main results

Imatinib is a new technology and to date little research has been published about its effectiveness in treating CML. There is no RCT evidence available at present. Only three case series studies have been undertaken, one in each phase of CML. This would not generally be considered as strong evidence of effectiveness, although it is considered sufficient evidence for efficacy to permit marketing in many countries. In addition, details of these trials were not in the public domain at the time of this report and were provided as commercial in confidence material. The normal peer review process had not been undertaken.

Chronic phase

Given the available survival data (at only 1 year in the chronic phase), proxy measures of effectiveness have been used. As yet there is not enough evidence to establish whether high levels of HR and CR with imatinib will ultimately translate into improved survival for patients with CML. Compared to existing evidence, imatinib offers an HR and CR that is within the range of reported responses to existing treatments (albeit at the upper end). Extrapolation from responses with other treatments is speculative, as the mechanism of action is different, and the molecular mechanisms of disease for progression to accelerated and blast phase are not well understood. Other studies report significant proportions of deaths during disease remission, and this may prove to be the case with imatinib.

The finding that CR rates with imatinib are higher in people who had an initial response to IFN-α, and then relapsed, as opposed to those who were IFN-α-resistant, may suggest that individual factors and individual disease characteristics are more important in determining response than therapy. It is generally accepted that prognosis of individual patients can be estimated by calculation of risk scores based on patient and disease characteristics, and that baseline risk can outweigh treatment effect. In other words, a low-risk patient treated with hydroxyurea will, on average, do better than a high-risk patient treated with IFN-α. No information on risk scores was presented for the imatinib case series, making it extremely difficult to judge whether the high survival rates can be attributed to therapy or case selection.

Accelerated and blast phases

Comparison with existing treatments in accelerated and blast phase CML is insecure as it is based predominantly on small case series. Such studies are likely to report results in a favourable group of patients. As the imatinib studies recruited small numbers of patients from many centres, a similar problem applies, as a favourable subgroup of patients may have been selected for inclusion.

One-year survival appears to be greater with imatinib for CML patients in the accelerated phase than with other treatments reported in the literature. No risk score is available in the literature, hampering comparison between studies. Hydroxyurea was allowed as an adjunctive treatment in the first 28 days but it is unlikely that this therapy would have a sustained effect on the outcomes measured in the trial.

Median survival for patients with CML in the blast phase appears to be improved with imatinib, but the results are not as striking as those seen in the accelerated phase. Similar caveats to those in the accelerated phase apply. It is also noteworthy that patients with a CR had initially improved survival but this was not long-lasting. In the blast phase, CR does not appear to be a good proxy outcome, and this must cast some doubt over its use as such in the chronic phase.

Adverse effects

In all phases of the illness, patients taking imatinib report relatively high levels of haematological adverse effects compared to patients using other regimens. These may require additional medication, which would have implications for adverse effects and patient experience as well as overall cost and resource use.

In addition, over half developed oedema and a considerable number experienced pain at various sites. Because of the short follow-up of trials, the longer-term effects of taking imatinib are not known. However, a median of only 3% were withdrawn from the study because of adverse

effects (range 1.7–5%), less than the IFN-α studies as well as those taking hydroxyurea.

In total, 5% of people were reported as having serious adverse effects, and less than 1% died, potentially as a direct result of imatinib therapy. This may be thought acceptable in the context of such a serious disease as CML, particularly in the accelerated and blast phases. Nevertheless, continued close monitoring of adverse effects may be considered wise by policy-makers.

Economic analysis

The economic model provided by industry was sensitive to cumulative assumptions and when changed to reflect more realistic values the ICERs shown in *Table 50* were demonstrated.

Cost per QALY of imatinib may be higher than is generally considered, on this criteria alone, to represent good value to the NHS. There is potentially a very wide range in the chronic phase, predominately because of uncertainty about long-term survival.

Assumptions, limitations and uncertainties applicable to all phases

The trials of CML, both RCTs and case series, are, in general, susceptible to bias as used in this report to compare with imatinib. Selection of patients clearly occurs, but insufficient detail is reported in order to understand the differences between cohorts. Blinding is not reported, and levels of attrition are often not explicitly stated. This precludes drawing firm conclusions. The published case series studies tend to show more favourable results than published RCT evidence, supporting evidence from other fields that case series overestimate treatment effects.

Evidence of resistance to imatinib has been discovered. A number of different mechanisms are postulated, some of which may severely limit the effect of imatinib. Longer-term follow-up is required in order to establish the full impact of resistance on the survival of imatinib-treated patients. Published reports of some of the patients included in the blast phase series indicate that resistance has occurred, and has not responded to increased dosage of imatinib. There must be caution, therefore, in assuming that high levels of CR and HR will translate into prolonged survival.

There is little QoL information about CML in general and effects of treatments on QoL. QoL while taking imatinib has not been assessed. Given the somewhat different spectrum of adverse effects reported with imatinib compared to hydroxyurea and IFN-α, this is an important consideration. QoL, however, is not solely determined by the adverse effects of therapy – the physical consequences of the disease itself and the psychological effects of knowing the poor prognosis with CML must be important determinants. It is extremely difficult to predict the impact of imatinib on QoL, which introduces further significant uncertainty into the assessment of cost–utility.

Conclusion

Initial results for studies on imatinib for CML suggest that this is a potential alternative treatment, particularly for the accelerated and blast phases. However, the amount of evidence available is very limited and is based on three commercial in confidence case series. In the authors' opinion, until further research is undertaken or published it is difficult to make secure recommendations for its use or to predict the cost of the treatment.

Need for further research

More research into imatinib for CML is needed. Key areas include:

- Efficacy of imatinib in chronic phase CML in the long term.
- RCTs to establish effectiveness of imatinib in all phases of CML compared to IFN-α, hydroxyurea and other chemotherapy.
- Further elucidation of the relationship between response rates (HR and CR) and long-term

TABLE 50 *ICERs from industry submission and our cumulative key variations*

Phase	ICER with varied assumptions (cost per QALY, £)
Chronic	Range between 45,592 and 47,712 and 299,379 and 301,446
Accelerated	35,633–56,052
Blast	52,354–64,724

survival with a range of treatments in all phases of CML.
- Adverse effects and long-term imatinib use.

In addition, the following areas should be explored:

- The establishment of prognostic indicators for survival in the accelerated and blast phases.
- QoL studies for patients with CML using various drug regimens.
- Cost of illness studies for CML.
- More detailed empirical estimates for resource use in CML to enable accurate cost analyses.
- Better estimates of utility for specific health states.

Acknowledgements

The authors want to thank the peer reviewers of this report and the members of the Expert Advisory Group for their help and advice during the writing of this report:

Dr Stephen G O'Brien, Senior Lecturer, Honorary Consultant, Department of Haematology, Royal Victoria Infirmary, Newcastle.

Professor P W M Johnson, Consultant in Oncology, Southampton General Hospital, Southampton.

Professor O B Eden, Consultant in Paediatrics, Christie Hospital, Manchester.

Dr Andrew Walker, Health Economist, Robertson Centre for Biostatistics, University of Glasgow, Glasgow.

Mr Keith Pratt, Management Committee Member Leukaemia Care, Worcester.

Contributions of the authors

Ruth Garside assessed studies for their eligibility and validity and independently extracted data from them. She drafted the report.

Ali Round designed the protocol and the criteria used for assessment of eligibility, validity and data extraction. She supervised the overall process. She assessed studies for their eligibility and validity and independently extracted data from them.

Kim Dalziel assessed studies for their eligibility and validity and independently extracted data from them. She also provided a critique of the health economics model and conducted sensitivity analyses.

Pam Royle undertook searches for studies.

Ken Stein helped to design the protocol, assessed studies for their eligibility and validity and independently extracted data from them. He also read and commented on the draft review.

This report was commissioned by the NHS R&D HTA Programme on behalf of NICE.

The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. The authors are responsible for any errors.

References

1. Perkins D, Brennan S, Carstairs K, Bailey D, Pantalony D, Poon A, *et al.* Regional cancer statistics: a report on 1143 diagnostic cases. *Cancer Genet Cytogenet* 1997;**96**:64–80.

2. Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. WHO classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyons: IARC; 2001. p. 45–60.

3. Mauro MJ, Druker BJ. STI571: targeting BCR-ABL as therapy for CML. *Oncologist* 2001;**6**:233–8.

4. Clarkson B, Strife A. Linkage of proliferative and maturational abnormalities in chronic myelogenous leukaemia and relevance to treatment. *Leukemia* 1993;**7**:1683–721.

5. Jahagirdar BN, Miller JS, Shet A, Verfaillie CM. Novel therapies for chronic myelogenous leukemia. *Exp Hematol* 2001;**29**:543–56.

6. Bose S, Deninger M, Gora-Tybor J, Goldman JM, Melo JV. The presence of typical and atypical BCR-ABL fusion genes in leukocytes of normal individuals: biological significance and implications for the assessment of minimal residual disease. *Blood* 1998;**92**:3362.

7. Hochhaus A, Reiter A, Saussele S, Reichert A, Emig M, Kaeda J, *et al.* Molecular heterogeneity in complete cytogenetic responders after interferon-alpha therapy for chronic myelogenous leukemia: low levels of minimal residual disease are associated with continuing remission. German CML Study Group and the UK MRC CML Study Group. *Blood* 2000;**95**:62–6.

8. Tcachuk DC, Westbrook CA, Andreeff M, Donlon TA, Cleary ML, Suryanarayan K, *et al.* Detection of bcr-abl fusion in chronic myelogenous leukaemia by in situ hybridization. *Science* 1990;**250**:559–62.

9. Cross NC, Feng L, Chase A, Bungey J, Hughes TP, Goldman JM. Competitive polymerase chain reaction to estimate the number of BCR-ABL transcripts in chronic myeloid leukemia patients after bone marrow transplantation. *Blood* 1993;**82**:1929–36.

10. Baron F, Frere P, Fillet G, Beguin Y. Treatment of leukemia relapse after allogeneic hematopoietic stem cell transplantation by donor lymphocyte infusion and STI-571. *Haematologica* 2001;**86**:993–4.

11. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med* 1999;**340**:1330–40.

12. Kantarjian HM, Talpaz M, Kontoyiannis D, Gutterman J, Keating MJ, Estey EH, *et al.* Treatment of chronic myelogenous leukemia in accelerated and blastic phases with daunorubicin, high-dose cytarabine, and granulocyte-macrophage colony-stimulating factor. *J Clin Oncol* 1992;**10**:398–405.

13. Talpaz M, Silver RT, Druker B, Goleman JM, Gambacorti-Passerini MD, Guilhof MD, *et al.* Glivec TM (imatinib mesylate) induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a Phase II study. 2001. Basel, Switzerland, Novartis Pharma AG. 11-9-0001 (unpublished).

14. Sawyers CL. Molecular studies in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors. *Semin Hematol* 2001;**38**:15–21.

15. Faderl S, Talpaz M, Estrov Z, Kantarjian HM. Chronic myelogenous leukemia: biology and therapy. *Ann Intern Med* 1999;**131**:207–19.

16. Hehlmann R, Willer A, Heimpel H, Hasford J, Kolb HJ, Pralle H, *et al.* Randomized studies with interferon in chronic myelogenous leukemia (CML) and comparative molecular aspects. *Leukemia* 1997;**11**:506–11.

17. Maloisel F, Uettwiller F, Laplace A, Lioure B, Herbrecht R, Mark M, *et al.* Emergence of unusual cytogenetic abnormalities under interferon-alpha therapy in patients with chronic myelogenous leukemia. *Cancer Genet Cytogenet* 1999;**113**:172–6.

18. Silver RT, Karanas A, Dear KB, Weil M, Brunner K, Haurani F, *et al.* Attempted prevention of blast crisis in chronic myeloid leukemia by the use of pulsed doses of cytarabine and lomustine. A Cancer and Leukemia Group B study. *Leuk Lymphoma* 1992;**7**:63–8.

19. Talpaz M, Kantarjian HM, McCredie KB, Keating MJ, Trujillo J, Gutterman J. Clinical investigation of human alpha interferon in chronic myelogenous leukemia. *Blood* 1987;**69**:1280–8.

20. Cortes J, Kantarjian H, O'Brien S, Robertson LE, Pierce S, Talpaz M. Result of interferon-alpha therapy in patients with chronic myelogenous leukemia 60 years of age and older. *Am J Med* 1996;**100**:452–5.

21. Giralt S, Kantarjian H, Talpaz M. The natural history of chronic myelogenous leukemia in the interferon era. *Semin Hematol* 1995;**32**:152–8.

22. Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Nelemans JC, *et al.* A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. *J Natl Cancer Inst* 1998;**90**:850–8.

23. Hehlmann R, Ansari H, Hasford J, Heimpel H, Hossfeld DK, Kolb HJ, *et al.* Comparative analysis of the impact of risk profile and of drug therapy on survival in CML using Sokal's index and a new score. German Chronic Myeloid Leukaemia (CML) Study Group. *Br J Haematol* 1997;**97**:76–85.

24. Bonifazi F, De Vivo A, Rosti G, Tiribelli M, Russo D, Trabacchi E, *et al.* Testing Sokal's and the new prognostic score for chronic myeloid leukaemia treated with alpha-interferon. *Br J Haematol* 2000;**111**:587–95.

25. Kumar P, Clark M, editors. Clinical medicine. 4th ed. London: WB Saunders, 2001. p. 425–32.

26. Taylor P, Proctor SJ. Northern Leukaemia Register. Newcastle: University Department of Haematology, Royal Victoria Infirmary; 2000.

27. Lamvik J, Brinich L, Dahl I, Sjo M, Nesthus I, Tangen J, *et al.* Chronic myeloid leukemia in health regions 1, 3, 4 and 5 during the period 1990–96. *Tidsskr Nor Laegeforen* 1999;**119**:1733–6.

28. Silver RT, Wolf SH, Hehlmann R, Appelbaum F, Anderson JE, Bennet C. An evidence based analysis of the effects of busulfan, hydroxyurea, interferon and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukaemia: developed for the American Society of Hematology. *Blood* 1999;**94**:1517–36.

29. Hehlmann R, Heimpel H, Hasford J, Allan N, Burnett A, Shepherd P, *et al.* Hydroxyurea versus busulphan for chronic myeloid leukaemia: an individual patient data meta-analysis of three randomized trials. *Br J Haematol* 2000;**110**:573–6.

30. Stalfelt AM, Zettervall O. Quality of life in young patients with chronic myelocytic leukaemia during intensive treatment including interferon. *Leuk Res* 1997;**21**:775–83.

31. Wisloff F, Hjorth M, Kaasa S, Westin J. Effect of interferon on the health related quality of life of multiple myeloma patients: results of a Nordic randomised trial comparing melphalan-prednisone to melphalan-prednisone plus alpha interferon. *Br J Haematol* 1996;**94**:324–32.

32. Talpaz M. Interferon-alfa-based treatment of chronic myeloid leukemia and implications of signal transduction inhibition. *Semin Hematol* 2001;**38**:22–7.

33. Bertero C, Eriksson BE, Ek AC. Explaining different profiles in quality of life experiences in acute and chronic leukemia. *Cancer Nurs* 1997;**20**:100–4.

34. Leadingham JGG, Warrell DA. Concise Oxford textbook of medicine. Oxford: OUP, 2001. p. 192–5.

35. Brunstein CG, McGlave PB. The biology and treatment of chronic myelogenous leukemia. *Oncology* 2001;**15**:23–31.

36. Kalidas M, Kantarjian H, Talpaz M. Chronic myelogenous leukemia. *JAMA* 2001;**286**:895–8.

37. Mughal TI, Goldman JM. Chronic myeloid leukaemia. STI 571 magnifies the therapeutic dilemma. *Eur J Cancer* 2001;**37**:561–8.

38. Chronic Myeloid Leukemia Trialists' Collaborative Group. Interferon alfa versus chemotherapy for chronic myeloid leukemia: a meta-analysis of seven randomized trials. *J Natl Cancer Inst* 1997;**89**:1616–20.

39. Hehlmann R, Heimpel H, Hasford J, Kolb HJ, Pralle H, Hossfeld DK, *et al.* Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. The German CML Study Group. *Blood* 1994;**84**:4064–77.

40. Kantarjian HM, Talpaz M, Keating MJ, Estey EH, O'Brien S, Beran M, *et al.* Intensive chemotherapy induction followed by interferon-alpha maintenance in patients with Philadelphia chromosome-positive chronic myelogenous leukemia. *Cancer* 1991;**68**:1201–7.

41. Bonifazi F, De Vivo A, Rosti G, Guilhot F, Guilhot J, Trabacchi E, *et al.* Chronic myeloid leukemia and interferon-alpha: a study of complete cytogenetic responders. *Blood* 2001;**98**:3074–81.

42. Shepherd PCA, Richards SM, Allan NC. Progress with interferon in CML – results of the MRC UK CML III Study. *Bone Marrow Transplant* 1996;**17**:S15–18.

43. Wetzler M, Kantarjian H, Kurzrock R, Talpaz M. Interferon-alpha therapy for chronic myelogenous leukemia: a review. *Am J Med* 1995;**99**:402–11.

44. Kantarjian HM, Keating MJ, Estey EH, O'Brien S, Pierce S, Beran M, *et al.* Treatment of advanced stages of Philadelphia chromosome-positive chronic myelogenous leukemia with interferon-alpha and low-dose cytarabine. *J Clin Oncol* 1992;**10**:772–8.

45. Guilhot F, Chastang C, Michallet M, Guerci A, Harousseau JL, Maloisel F, *et al.* Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. *N Engl J Med* 1997;**337**:223–9.

46. Thaler J, Hilbe W, Apfelbeck U, Linkesch W, Sill H, Seewann H, *et al.* Interferon-alpha-2C and LD ara-C for the treatment of patients with CML: preliminary results of the Austrian multicenter phase II study. *Leuk Res* 1997;**21**:75–80.

47. European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products European Public Assessment Report: Glivec CPMP/2418/01. 2001.

48. Kantarjian HM, Talpaz M, Smith TL, Cortes J, Giles FJ, Rios MB, *et al.* Homoharringtonine and low-dose cytarabine in the management of late chronic-phase chronic myelogenous leukemia. *J Clin Oncol* 2000;**18**:3513–21.

49. GLEEVEC (TM) (imatinib mesylate) capsules NDA 21-335 Package insert. 2001. New Jersey, New York, Novartis Pharma AG.

50. Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Nagesh RP, *et al.* Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science* 2001;**293**:876–80.

51. Sawyers CL, editor. Implications of signal transduction inhibition for the treatment of chronic myeloid leukemia. *Semin Hematol* 2001;**38**:S1–42.

52. Barthe C, Cony-Makhoul P, Melo JV, Mahon JR. Roots of clinical resistance to STI-571 cancer therapy. *Science* 2001;**293**:2163.

53. Gambacorti-Passerini C, Barni R, Marchesi E, Verga M, Rossi F, Rossi F, *et al.* Sensitivity to the abl inhibitor STI571 in fresh leukaemic cells obtained from chronic myelogenous leukaemia patients in different stages of disease. *Br J Haematol* 2001;**112**:972–4.

54. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, *et al.* Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001;**344**:1031–7.

55. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, *et al.* Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 2001;**344**:1038–42.

56. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001;**323**:42–6.

57. Drummond M, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: OUP; 1999.

58. Kantarjian H, Sawyers CL, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, *et al.* Glivec™ (imatinib mesylate) induces hematologic and cytogenic responses in the majority of patients with chronic myeloid leukemia: results of a phase II study. 2001 (unpublished).

59. Sawyers CL, Hochhaus A, Feldman E. Glivec™ (imatinib mesylate) induces hematologic and cytogenetic responses in patients with chronic myeloid leukemia in myeloid blast crisis: results of a Phase II study. 2001 (unpublished).

60. Broustet A, Reiffers J, Marit G, Fiere D, Jaubert J, Reynaud J, *et al.* Hydroxyurea versus interferon alfa-2b in chronic myelogenous leukaemia: preliminary results of an open French multicentre randomized study. *Eur J Cancer* 1991;**27**:S18–21.

61. Ohnishi K, Tomonaga M, Kamada N, Onozawa K, Kuramoto A, Dohy H, *et al.* A long term follow-up of a randomized trial comparing interferon-alpha with busulfan for chronic myelogenous leukemia. *Leuk Res* 1998;**22**:779–86.

62. Baccarani M, Tara S, De Vivo A, Bonifazi F, Fiachini M, Russo D, *et al.* Long-term follow-up of the Italian trial of interferon-alpha versus conventional chemotherapy in chronic myeloid leukemia. *Blood* 1998;**92**:1541–8.

63. Hehlmann R, Heimpel H, Hasford J, Kolb HJ, Pralle H, Hossfeld DK, *et al.* Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: prolongation of survival by hydroxyurea. The German CML Study Group. *Blood* 1993;**82**:398–407.

64. The Benelux CML Study Group. Randomized study on hydroxyurea alone versus hydroxyurea combined with low-dose interferon-alpha 2b for chronic myeloid leukemia. *Blood* 1998;**91**:2713–21.

65. Giles FJ, Shan J, Chen S, Advani SH, Supandiman I, Aziz Z, *et al.* A prospective randomized study of alpha-2b interferon plus hydroxyurea or cytarabine for patients with early chronic phase chronic myelogenous leukemia: the International Oncology Study Group CML1 study. *Leuk Lymphoma* 2000;**37**:367–77.

66. Alimena G, Morra E, Lazzarino M, Liberati AM, Montefusco E, Inverardi D, *et al.* Interferon alpha-2b as therapy for patients with Ph-positive chronic myelogenous leukemia. *Eur J Haematol Suppl* 1990;**52**:25–8.

67. Freund M, Von Wussow P, Diedrich H, Eisert R, Link H, Wilke H, *et al.* Recombinant human interferon (IFN) alpha-2b in chronic myelogenous leukaemia: dose dependency of response and frequency of neutralizing anti-interferon antibodies. *Br J Haematol* 1989;**72**:350–6.

68. Hochhaus A, Lin F, Reiter A, Skladny H, Mason PJ, van Rhee F, *et al.* Quantification of residual disease in chronic myelogenous leukemia patients on interferon-alpha therapy by competitive polymerase chain reaction. *Blood* 1996;**87**:1549–55.

69. Kloke O, Opalka B, Niederle N. Interferon alfa as primary treatment of chronic myeloid leukemia: long-term follow-up of 71 patients observed in a single center. *Leukemia* 2000;**14**:389–92.

70. Sacchi S, Kantarjian HM, O'Brien S, Beran M, Koller C, Pierce S, *et al.* Long-term follow-up results of alpha-interferon-based regimens in patients with late chronic phase chronic myelogenous leukemia. *Leukemia* 1997;**11**:1610–16.

71. Schofield JR, Robinson WA, Murphy JR, Rovira DK. Low doses of interferon-alpha are as effective as higher doses in inducing remissions and prolonging survival in chronic myeloid leukemia. *Ann Intern Med* 1994;**121**:736–44.

72. Giles FJ, Aitchison R, Syndercombe C, Schey S, Newland AC. Recombinant alpha 2B interferon in combination with oral chemotherapy in late chronic phase chronic myeloid leukaemia. *Leuk Lymphoma* 1992;**7**:99–102.

73. Guilhot F, Dreyfus B, Brizard A. Cytogenetic remissions in chronic myelogenous leukemia using interferon alpha-2a and hydroxyurea with or without low dose cytosine arabinoside. *Leuk Lymphoma* 1991;**4**:49–55.

74. Mahon FX, Faberes C, Pueyo S, Cony MP, Salmi R, Boiron JM, *et al.* Response at three months is a good predictive factor for newly diagnosed chronic myeloid leukemia patients treated by recombinant interferon-alpha. *Blood* 1998;**92**:4059–65.

75. Sanchez A, Robinson WA, Cohn A, Gonzalez R, Adlakha A. Low-dose alpha-interferon treatment of chronic myeloid leukemia. *Am J Hematol* 1992;**39**:61–2.

76. Shtalrid M, Lugassy G, Rosensaft J, Berrebi A. Treatment of chronic myeloid leukemia with interferon alpha (Roferon): results of the Israeli Study Group on CML. *Leuk Lymphoma* 1993; **11** Suppl 11;193–7.

77. Kattan MW, Inoue Y, Giles FJ, Talpaz M, Ozer H, Guilhot F, *et al.* Cost-effectiveness of interferon-alpha and conventional chemotherapy in chronic myelogenous leukemia. *Ann Intern Med* 1996;**125**:541–8.

78. Mahon FX, Faberes C, Montastruc M, Si MS, Boiron JM, Marit G, *et al.* High response rate using recombinant interferon-alpha in patients with newly diagnosed chronic myeloid leukemia. *Bone Marrow Transplant* 1996;**17** Suppl 3:33–7.

79. Ozer H, George SL, Schiffer CA, Rao K, Rao PN, Wurster-Hill DH, *et al.* Prolonged subcutaneous administration of recombinant alpha 2b interferon in patients with previously untreated Philadelphia chromosome-positive chronic-phase chronic myelogenous leukemia: effect on remission duration and survival: Cancer and Leukemia Group B study 8583. *Blood* 1993;**82**:2975–84.

80. Thaler J, Gastl G, Fluckinger T, Niederwieser D, Huber H, Seewann H, *et al.* Treatment of chronic myelogenous leukemia with interferon alfa-2c: response rate and toxicity in a phase II multicenter study. *Semin Hematol* 1995;**30**:17–19.

81. Thaler J, Gastl G, Fluckinger T, Niederwieser D, Huber H, Seewann H, *et al.* Interferon alpha-2c therapy of patients with chronic myelogenous leukemia: long-term results of a multicenter phase II study. *Ann Hematol* 1996;**72**:349–55.

82. Tothova E, Fricova M, Kafkova A, Stecova N, Guman T, Raffac S, *et al.* Hematological and cytogenetic response of interferon alpha 2b alone and combined interferon alpha plus cytarabine as a first-line treatment in chronic myeloid leukemia. *Neoplasma* 2000;**47**:125–8.

83. O'Brien S, Kantarjian H, Keating M, Beran M, Koller C, Robertson LE, *et al.* Homoharringtonine therapy induces responses in patients with chronic myelogenous leukemia in late chronic phase. *Blood* 1995;**86**:3322–6.

84. Russo D, Baccarani M, Zaccaria A, Saglio G, Guerrasio A, Martinelli G, *et al.* Chronic myeloid leukemia, BCR/ABL transcript, response to alpha-interferon and survival. *Leukemia* 1995; **9/10**:1648–52.

85. Fernandez-Ranada JM, Lavilla E, Odriozola J, Garcia-Larana J, Lozano M, Parody R, *et al.* Interferon alpha 2A in the treatment of chronic myelogenous leukemia in chronic phase. Results of the Spanish Group. *Leuk Lymphoma* 1993; **11** Suppl 1:175–9.

86. Bourantas KL, Syrou M, Tsiara S, Danella M, Konstantinides P. Combination therapy with interferon alfa-2b and hydroxyurea during the accelerated phase of chronic myelogenous leukemia. *Acta Haematol* 1996;**95**:117–21.

87. Arthur CK, Ma DD. Combined interferon alfa-2a and cytosine arabinoside as first-line treatment for chronic myeloid leukemia. *Acta Haematol* 1993;**89** Suppl 1:15–21.

88. Giles FJ, Kantarjian H, O'Brien S, Rios MB, Cortes J, Beran M, *et al.* Results of therapy with interferon alpha and cyclic combination chemotherapy in patients with Philadelphia chromosome positive chronic myelogenous leukemia in early chronic phase. *Leuk Lymphoma* 2001;**41**:309–19.

89. Beck JR, Guilhot J, Giles FJ, Aoki N, Wirt DP, Guilhot F. Cytarabine added to interferon improves the cost-effectiveness of initial therapy for patients with early chronic phase chronic myelogenous leukemia. *Leuk Lymphoma* 2001;**41**:117–24.

90. Freund M, Grote-Metke AF, Nowak RF, Otremba BF, Wormann BF, Koch OF, *et al.* Combination of chemotherapy and interferon alfa-2b in the treatment of chronic myelogenous leukemia. *Semin Hematol* 1993;**30**:11–13.

91. Carella AM, Frassoni F, Podesta M, Pungolino E, Pollicardo N, Ferrero R, *et al.* Idarubicin, intermediate-dose cytarabine, etoposide, and granulocyte-colony-stimulating factor are able to recruit CD34+/HLA-DR-cells during early hematopoietic recovery in accelerated and chronic phases of chronic myeloid leukemia. *J Hematother* 1994;**3**:199–202.

92. Kantarjian HM, O'Brien SM, Keating M, Beran M, Estey E, Giralt S, *et al.* Results of decitabine therapy in the accelerated and blastic phases of chronic myelogenous leukemia. *Leukemia* 1997;**11**:1617–20.

93. Dutcher JP, Eudey L, Wiernik PH, Paietta E, Bennett JM, Arlin Z, *et al.* Phase II study of mitoxantrone and 5-azacytidine for accelerated and blast crisis of chronic myelogenous leukemia: a study of the Eastern Cooperative Oncology Group. *Leukemia* 1992;**6**:770–5.

94. Coleman M, Silver RT, Pajak TF, Cavalli F, Rai KR, Kostinas JE, *et al.* Combination chemotherapy for terminal-phase chronic granulocytic leukemia: cancer and leukemia group B studies. *Blood* 1980;**55**:29–36.

95. Alimena G, Lazzarino M, Morra E, Mancini M, Cedrone M, Montefusco E, *et al.* Clinical and cytologic characteristics of blastic phase in Ph-positive chronic myeloid leukemia treated with alpha-interferon. *Leukemia* 1996;**10**:615–18.

96. Canellos GP, DeVita VT, Whang-Peng J, Carbone PP. Hematologic and cytogenetic remission of blastic transformation in chronic granulocytic leukemia. *Blood* 1971;**38**:671–9.

97. Hernandez-Boluda JC, Cervantes F, Alvarez A, Costa D, Montserrat E. Single-agent therapy with oral mercaptopurine for nonlymphoid blast crisis of chronic myeloid leukemia. *Ann Hematol* 2001;**80**:516–20.

98. Iacoboni SJ, Plunkett W, Kantarjian HM, Estey E, Keating MJ, McCredie KB, *et al.* High-dose cytosine arabinoside: treatment and cellular pharmacology of chronic myelogenous leukemia blast crisis. *J Clin Oncol* 1986;**4**:1079–88.

99. Kantarjian HM, Walters RS, Keating MJ, Talpaz M, Andersson B, Beran M, *et al.* Treatment of the blastic phase of chronic myelogenous leukemia with mitoxantrone and high-dose cytosine arabinoside. *Cancer* 1988;**62**:672–6.

100. Pedersen-Bjergaard J, Worm AM, Hainau B. Blastic transformation of chronic myelocytic leukaemia. Clinical manifestations, prognostic factors and results of therapy. *Scand J Haematol* 1977;**18**:292–300.

101. Vallejos CS, Trujillo JM, Cork A, Bodey GP, McCredie KB, Freireich EJ. Blastic crisis in chronic granulocytic leukemia: experience in 39 patients. *Cancer* 1974;**34**:1806–12.

102. Winton EF, Miller D, Vogler WR. Intensive chemotherapy with daunorubicin, 5-azacytidine, 6-thioguanine, and cytarabine (DATA) for the blastic transformation of chronic granulocytic leukemia. *Cancer Treat Rep* 1981;**65**:389–92.

103. Quackenbush RC, Talpaz M, Guo JQ, Arlinghaus RB, Resta D, Capdeville R, *et al.* Monitoring minimal residual disease by BCR-ABL western and quantitative competitive RT PCR in Philadelphia chromosome (Ph) positive chronic myelogenous leukemia (CML) on STI571 therapy. *Blood* 2000;**96**:736a.

104. Paschka P, Schoch C, Lahaye T, Weisser A, Kuhn C, La Rosee P, *et al.* Monitoring the response of CML patients treated with STI571 by molecular cytogenetics and quantitative RT-PCR. *Blood* 2000;**96**:3174.

105. Hochhaus A, Weisser A, La Rosee P, Emig M, Muller M, Saubele S, *et al.* Detection and quantification of residual disease in chronic myelogenous leukemia. *Leukemia* 2000;**14**:998–1005.

106. Kurzock R, Estrov Z, Kantarjian H, Talpaz M. Conversion of interferon induced long term cytogenetic remissions in chronic myelogenous leukaemia to polymerase chain reaction negativity. *J Clin Oncol* 1998;**16**:1526–31.

107. Kantarjian H, O'Brien S, Hayes KL, *et al.* Value of interphase fluorescent in-situ hybridisation (iFISH) studies in monitoring response to STI 571 therapy in patients with Philadelphia chromosome positive chronic myeloid leukaemia. *Blood* 2000; **96**(11 Pt 2):255b (abstract 4833).

108. Goldman JM. Cost-effectiveness of interferon-alpha for chronic myeloid leukemia. *Ann Oncol* 1998;**9**:351–2.

109. Liberato NL, Quaglini S, Barosi G. Cost-effectiveness of interferon alfa in chronic myelogenous leukemia. *J Clin Oncol* 1997;**15**:2673–82.

110. Messori A. Cost-effectiveness of interferon in chronic myeloid leukaemia: analysis of four clinical studies. *Ann Oncol* 1998;**9**:389–96.

111. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.

112. Drummond M, McGuire A. Economic evaluation in health care. Oxford: Oxford University Press; 2001.

113. Hehlmann R, Heimpel H, Kolb HJ, Heinze B, Hochhaus A, Griesshammer M, *et al.* The German CML study, comparison of busulfan vs. hydroxyurea vs. interferon alpha and establishment of prognostic score 1. *Leuk Lymphoma* 1993; **11** Suppl 1:159–68.

114. Italian Cooperative Study Group on Chronic ML. A prospective comparison of alpha-IFN and conventional chemotherapy in Ph+ chronic myeloid leukemia. Clinical and cytogenetic results at 2 years in 322 patients. *Haematologica* 1992;**77**:204–14.

115. Kantarjian HM, Smith BD, O'Brien S, Beran M, Pierce S, Talpaz M. Prolonged survival in CML after cytogenetic response to interferon-alpha therapy. *Ann Intern Med* 1995;**122**:261.

116. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. *N Engl J Med* 1994;**330**:820–5.

117. Weeks JC, Tierney MR, Weinstein MC. Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia. *N Engl J Med* 1991;**325**:81–6.

118. McIntyre P, Hall J, Leeder S. An economic analysis of alternatives for childhood immunisation against Haemophilus influenza type b disease. *Aust J Public Health* 1994;**18**:394–400.

119. Quaglini S, Bellazzi R, Locatelli F, Stefanelli M, Salvaneschi C. An influence diagram for assessing GVHD prophylaxis after bone marrow transplantation in children. *Med Decis Making* 1994;**14**:223–35.

120. Solomon NA, Glick HA, Russo CJ, Lee J, Schulman KA. Patient preferences for stroke outcomes. *Stroke* 1994;**25**:1721–5.

121. Aoki N, Kitahara T, Fukui T, Beck JR, Soma K, Yamamoto W, *et al.* Management of unruptured intracranial aneurysm in Japan: a Markovian decision analysis with utility measurements based on the Glasgow outcome scale. *Med Decis Making* 1998;**18**:357–64.

122. The Governments Actuary Department. Interim life tables – expectation of life for Great Britain years 1997–1999. 2002.

123. Mahon FX, Deininger MW, Schuktheis B, Chabrol J, Reiffers J, Goldman JM, *et al.* Selection and characterisation of BCR ABL+ cell lines with differential sensitivity to the tyrosine kinase inhibitor STI571: diverse mechanisms of resistance. *Blood* 2000;**96**:1070–9.

124. Gambacorti-Passerini C, Barni R, le Coutre P, Zucchetti M, Cabrita G, Cleris L, *et al.* Role of alpha1 acid glycoprotein in the in vivo resistance of human BCR-ABL+ leukemic cells to the Abl inhibitor STI571. *J Natl Cancer Inst* 2000;**92**:1641–50.

125. Kloke O, Niederle N, Opalka B, Hawig I, Seeber S, Becher R. Prognostic impact of interferon alpha-induced cytogenetic remission in chronic myelogenous leukaemia: long-term follow-up. *Eur J Haematol* 1996;**56**:78–81.

126. Guilhot F, Guerci A, Fiere D, Harousseau JL, Maloisel F, Bouabdallah R, *et al.* The treatment of chronic myelogenous leukemia by interferon and cytosine-arabinoside: rationale and design of the French trials. *Bone Marrow Transplant* 1996; **17** Suppl 3:29–31.

127. Allan NC, Richards SM, Shepherd PC. UK Medical Research Council randomised, multicentre trial of interferon-alpha n1 for chronic myeloid leukaemia: improved survival irrespective of cytogenetic response. The UK Medical Research Council's Working Parties for Therapeutic Trials in Adult Leukaemia. *Lancet* 1995;**345**:1392–7.

128. Feldman E, Arlin Z, Ahmed T, Mittelman A, Puccio C, Chun H, *et al.* Homoharringtonine is safe and effective for patients with acute myelogenous leukemia. *Leukemia* 1992;**6**:1185–8.

129. Kreis W, Budman DR, Chan K, Allen SL, Schulman P, Lichtman S, *et al.* Therapy of refractory/relapsed acute leukemia with cytosine arabinoside plus tetrahydrouridine (an inhibitor of cytidine deaminase) – a pilot study. *Leukemia* 1991;**5**:991–8.

130. Tricot G, Weber G. Biochemically targeted therapy of refractory leukemia and myeloid blast crisis of chronic granulocytic leukemia with Tiazofurin, a selective blocker of inosine 5′-phosphate dehydrogenase activity. *Anticancer Res* 1996;**16**:3341–7.

Appendix 1

Prognostic scores

The Sokal score

Score	= Exp[0.0116 (age – 43.4) + 0.0345 (spleen size – 7.51) + 0.188 ([platelets/700]^2 – 0.563) + 0.0887 (blasts – 2.1)]
Low risk	< 0.8
Intermediate risk	= 0.8–1.2
High risk	> 1.2

New prognostic score (interferon score)[22]

New score	= 0.6666 x age [0 when age < 50; otherwise 1] + 0.042 x spleen size (cm below costal margin) + 0.0584 x blasts [%] + 0.0413 x eosinophils [%] + 0.2039 x basophils [0 when basophils < 3%; otherwise 1] + 1.0956 x platelet count [1 when platelets < 1500 otherwise 1]) x 1000
Low risk	≤ 780
Intermediate risk	= 780–1480
High risk	> 1480

Appendix 2

Resistance to imatinib

Possible mechanisms for resistance to imatinib are described below.

Cell intrinsic mechanisms

These are changes within the cell that reduce the sensitivity of BCR-ABL to imatinib. There is experimental evidence to support the existence of these changes:[50] cells from patients collected at various stages in the CML disease process showed a 10-fold reduction in sensitivity to imatinib *in vitro*. Various mechanisms could account for this:

- **Gene amplification**. This has been demonstrated in several patients who have relapsed following treatment with imatinib. The drug may select for proliferation of clones with multiple copies of BCR-ABL in some patients.[50]
- **Point mutations** within the gene BCR-ABL that confer resistance to imatinib. This has been demonstrated empirically,[50] and again, selection pressure conferred by the drug may play a part.
- **Over-expression of the multi-drug resistance gene**, which increases levels of P-glycoprotein, a cell membrane protein that pumps drugs out of the cell and lowers net intracellular drug concentration. This has been reported *in vitro*.[123]
- **Secondary genetic changes** could provide signals that replace BCR-ABL as the determinant of cell proliferation.[50,51] These could be mutations in other genes or other chromosomal changes. This has not yet been demonstrated empirically as a mechanism of resistance to imatinib.

Mechanisms extrinsic to the cell

Imatinib is 95% bound in plasma.

- **Functional sequestration of the drug**. Preclinical studies in mice have demonstrated that alpha 1 acid glycoprotein can bind imatinib in serum and inhibit activity against BCR-ABL.[124] Co-administration of other drugs can reduce this.
- **Functional inactivation of the drug** through enzyme modification. This is a theoretical possibility but has not been demonstrated.

Appendix 3

Review protocol

Rapid reviews for the HTA Programme

Protocol: The effectiveness and cost-effectiveness of imatinib (STI 571) in chronic myeloid leukaemia

A. This protocol is provisional and subject to change

B. Details of review team

Dr Ali Round, Senior Lecturer in Public Health (LEAD), Peninsula Technology Assessment Group

Dr Ken Stein, Senior Lecturer in Public Health, Peninsula Technology Assessment Group

Ms Ruth Garside, Research Fellow, Peninsula Technology Assessment Group

Ms Sandra Hollinghurst, Health Economist, RDSU, Bath

Dr Pam Royle, Senior Information Specialist, Southampton Health Technology Assessment Centre

C. Full title of research question

What is the effectiveness and cost-effectiveness of imatinib (STI 571) in the treatment of chronic myeloid leukaemia?

D. Clarification of research question and scope

Chronic myeloid leukaemia (CML) is a clonal disorder in which haemopoietic stem cells proliferate and eventually replace all normal bone marrow function. Median age at diagnosis is 67 years. The disease generally passes through three phases – a chronic stage in which patients usually present, and which lasts typically between 2 and 6 years; an accelerated stage where the number of blast cells in the blood increases and symptoms become more prominent; and a blastic stage when there is little remaining normal marrow function. Median survival is between 4 and 5 years from diagnosis.

Bone marrow transplantation is the only potential cure. It is possible in those patients for whom a suitable donor is available, preferably a tissue-type identical sibling, but matched unrelated donors can be used. Survival is between 60 and 70% at 5 years for sibling donors, less for unmatched donors. Bone marrow transplantation is not usually offered to patients older than 60 because of the increased risks of the procedure in older patients.

Drug treatments ameliorate symptoms and prolong overall survival. Hydroxyurea is the usual initial treatment and has relatively few adverse effects. Busulphan is now rarely used because of its unfavourable adverse effects and apparent lower efficacy. IFN-α has become increasingly used in the last few years as it prolongs survival by between 1 and 2 years.[1] However, it also has significant toxic effects, which requires a reduction in dose or cessation of therapy in a substantial proportion of patients. Cytosine therapy in combination with IFN-α increases the likelihood of remission at the expense of increased toxicity.

CML has a characteristic genetic abnormality of chromosomes 9 and 22 (known as Philadelphia chromosome). A protein known as BCR-ABL is produced as a result of this, and the enzyme activity of the protein (tyrosine kinase) appears to be implicated in the development of CML. Imatinib has been synthesised specifically to be an antagonist of this tyrosine kinase. It has a limited effect on other, normal, kinases. Antileukaemic activity has been demonstrated in a number of preclinical and animal models.

Preliminary review of the literature reveals that two Phase I studies have been published in peer reviewed journals,[2,3] reporting on 121 patients with CML. Three Phase II studies have been conducted, one in the chronic stage for patients who are resistant or refractory to IFN-α, one in the accelerated stage, and one in the blast stage of CML. These studies have been published in abstract only.[4–6] Effectiveness was evaluated on the basis of haematological or cytogenetic response. Duration of response has not been estimated because of short follow-up, however, these studies are ongoing. A randomised controlled trial comparing imatinib with IFN-α and cytosine arabinoside has closed recruitment. The primary outcome measure is time to progression of one of a number of end-points including loss of haematological remission, loss of cytogenetic

remission, progression to accelerated or blast phase, or death from CML. The first year report will not be available until the first quarter of 2002, with the final report not expected until 2005.

Adverse effects have been reported in the literature but no information on quality of life appears to be available. No published cost data has been identified so far.

There is little data on children, at least partly because CML is very rare in this age group.

Scope: This review will encompass the efficacy of imatinib in all stages of CML.

Population: All adults enrolled in trials with CML, in chronic, accelerated or blast stage.

Interventions to be considered:
As there is a paucity of published information, rigorous assessment of effectiveness and cost-effectiveness is deemed unlikely to be achievable. Inferences derived from Phase I and II studies do not provide good evidence of effectiveness.[6] Therefore the interventions to be considered are:

1. The efficacy of imatinib in CML that is resistant, intolerant of or refractory to INF-α.
2. The efficacy of imatinib in CML in accelerated phase.
3. The efficacy of imatinib in CML in blast crisis.
4. The safety of imatinib in CML of all stages.
5. The cost of imatinib in CML.

It is possible that the industry submission will include unpublished information from randomised controlled trials. Depending on the extensiveness of the information contained in the submission, if possible, we will assess effectiveness and cost-effectiveness, against comparators of standard treatment (hydroxyurea, INF-α and bone marrow transplantation).

Outcomes to be considered:
1. Progression-free survival (if available).
2. Overall survival (if available).
3. Haematological response, complete and partial.
4. Cytogenetic response, complete and partial.
5. Adverse effects including nausea, diarrhoea, myalgia, periorbital oedema, skin rash, peripheral oedema, liver toxicity, withdrawal from treatment, myelosuppression and cytopenia.
6. Cost.

It will not be possible to rigorously assess the optimal duration of treatment, or quality of life. However, if information on these factors is identified during the searching process, a summary and critique of the evidence will be provided.

E. Report methods

Search strategy
- Computerised databases including MEDLINE, EMBASE, the Cochrane Library Science Citation Index, Web of Science Proceedings, BIOSIS, Cancerlit, Conference Proceedings Index and AIDS and Cancer Research Abstracts, conference abstracts from the ASH and the American Society of Clinical Oncology
- ONS (Office of National Statistics) website, the FDA website, the NCI's CancerNet website, the Novartis website, http://www.gleevec.com/, and data from the National Cancer Intelligence Centre
- Bibliographies
- Contacting research groups and industry
- Trial registers in the UK (National Research Register), USA and Canada.

Inclusion
- RCTs: imatinib versus other interventions for the treatment of any stage of CML.
- Phase 1 and Phase 2 studies: imatinib used for the treatment of any stage of CML.
- Cost-effectiveness, cost–utility and cost–benefit studies – full economic evaluations.

The focus of the review will be on randomised comparisons, if these are available.

Exclusions
- Animal models
- Preclinical and biological studies

Data extraction strategy
Data will be extracted by one researcher and checked by a second researcher.

Quality assessment strategy and methods of analysis/synthesis
Studies identified will be assessed for quality using individual components of methodological quality, for observational or randomised studies, taken from the CRD report on systematic reviews No. 4.[7] Assessment will be made by one researcher and checked by a second.

Assessment of internal validity: Because of the potential for bias in observational studies, emphasis in this review will be placed on quality assessment, and identification and assessment of possible sources of bias.

Assessment of external validity: The selection of patients who have been entered into the trials will be a key issue, as patients receiving treatment may differ in several relevant aspects from the (intrinsic) comparison with historical outcomes. This will require more detailed information than is available in abstract form and adequate assessment of external validity will be dependent on the availability of this information.

If several Phase II trials are identified, a thorough consideration of possible sources of heterogeneity will be performed, and a summary and critique of the evidence provided. Sensitivity analyses will be performed.

Absolute risk and relative risk estimates, with confidence intervals, will be presented for adverse events, if data is available from a randomised controlled trial. Number needed to treat and number need to harm for outcomes and adverse events respectively will be presented if appropriate. Alternatively, point estimates of percentages suffering adverse effects, with confidence intervals, will be presented.

Economic data will be appraised using the criteria suggested by Drummond,[8] and presented as a summary and critique of the evidence.

Methods for estimating quality of life, costs and cost-effectiveness and/or cost/QALY

Costs for treatment and savings will be taken from published work and industry submission. If insufficient detail is available, estimates for cost will be derived from individual Trusts or groups of Trusts. Costs will be discounted at 6% p.a. and benefits at 1.5% (sensitivity analyses 0% to 6%). Cost-effectiveness and cost–utility will only be calculated if results from a randomised controlled trial are available. Alternatively, a presentation of a range of cost implications estimated under likely scenarios will be made, with sensitivity analyses performed.

Utility

If data is available from a randomised controlled trial, and time permits, utilities will be estimated from a panel of lay people, being established over the next few months by the Peninsula Technology Assessment Group as part of a methodology project grant by the NHS Executive (South West). This 'utility panel' will value the health states in the different stages of CML as described by experts. Alternatively, expert assessment of the utility of health states will be made. Further details of the Utility Panel are available on request.

1. Cost-effectiveness will be estimated as cost per year of life gained, compared to standard treatment.
2. Cost–utility will be estimated as £/QALY by aggregating appropriately discounted streams of benefits and net costs for people treated with imatinib compared to standard treatment.

F. Handling the company submission

As little published data is available, the industry submission is likely to contain a substantial amount of new information. It is essential to make early contact with the industry. Comparison of data assessment procedures will be performed and the reason for any differences explored.

G. Project management

a. Timetable

Draft protocol	04-08-01
Progress report	12-11-01
Draft final report	20-02-02

b. Competing interests

None.

c. External reviewers

A group is currently being formed. This group will act as an expert resource to guide the progress of the review. Separate experts will be identified as external reviewers of the completed draft review.

d. References

1. Chronic Myeloid Leukemia Trialists' Collaborative Group. Interferon alfa versus chemotherapy for chronic myeloid leukemia: a meta-analysis of seven randomized trials. *J Natl Cancer Inst* 1997;**89**:1616–20.

2. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, *et al.* Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001;**344**:1031–7.

3. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, *et al.* Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 2001;**344**:1038–42.

4. Kantarjian H, Sawyers CL, Hochhaus A, Guilhot F, Schiffer C, Resta D, *et al.* Phase II study of STI571, a tyrosine kinase inhibitor in patients with resistant, refractory Philadelphia

chromosome positive chronic myeloid leukemia (Ph+ CML). *Blood* 2000;**96**:470a.

5. Talpaz M, Silver RT, Druker B, Paquette R, Goldman JM, Reese SF, *et al.* Phase II study of STI571, in adult patients with Philadelphia chromosome positive chronic myeloid leukemia in accelerated phase. *Blood* 2000;**96**:470a.

6. Sawyers C, Hochhaus A, Feldman E, Goldman JM, Miller C, Ben Am R, *et al.* Phase II study to determine the safety and anti-leukemic effects of STI571, in patients with Philadelphia chromosome positive chronic myeloid leukemia in myeloid blast crisis. *Blood* 2000;**96**:470a.

7. NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness. CRD's guidance for those carrying out or commissioning reviews. CRD Report No 4 (second edition). York: University of York; 2001.

8. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 2nd ed. 1997, Oxford: Oxford Medical Publications; 1997.

Appendix 4

Search strategy

Sources of information, including databases searched and search terms used

Searches were made to identify published studies, and recently completed and ongoing research. The strategies shown below are those used to search MEDLINE. They were adapted as appropriate for other databases. The table on the next page lists all the databases searched. The complete details of all search strategies used are available on request.

Clinical effectiveness searches

1. STI-571

gleevec or glivec or imatinib or sti 571 or sti-571 or sti571 or st1 571 or st1-571 or st1571 or stl571 or stl-571 or stl 571

2. CML and bone marrow transplantation

(((‘Leukemia-Myeloid-Chronic’ / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml)) and ((‘Bone-Marrow-Transplantation’ / all subheadings in MIME,MJME) or (bone near marrow near transplant*) or (bmt))) and (((CLINICAL-TRIAL in PT:MEDS) or (CLINICAL-TRIAL-PHASE-II in PT:MEDS) or (CLINICAL-TRIAL-PHASE-III in PT:MEDS) or (CLINICAL-TRIAL-PHASE-IV in PT:MEDS) or (RANDOMIZED-CONTROLLED-TRIAL in PT:MEDS) or (CONTROLLED-CLINICAL-TRIAL in PT:MEDS)) or (CLINICAL-TRIAL-PHASE-I in PT:MEDS))

3. CML and hydroxyurea

((‘Leukemia-Myeloid-Chronic’ / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml)) and ((‘Hydroxyurea-’ / all subheadings in MIME, MJME) or (hydroxyurea)) and (((CLINICAL-TRIAL in PT:MEDS) or (CLINICAL-TRIAL-PHASE-II in PT:MEDS) or (CLINICAL-TRIAL-PHASE-III in PT:MEDS) or (CLINICAL-TRIAL-PHASE-IV in PT:MEDS) or (RANDOMIZED-CONTROLLED-TRIAL in PT:MEDS) or (CONTROLLED-CLINICAL-TRIAL in PT:MEDS)) or (CLINICAL-TRIAL-PHASE-I in PT:MEDS))

4. CML and IFN-α

((‘Leukemia-Myeloid-Chronic’ / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml)) and (((CLINICAL-TRIAL in PT:MEDS) or (CLINICAL-TRIAL-PHASE-II in PT:MEDS) or (CLINICAL-TRIAL-PHASE-III in PT:MEDS) or (CLINICAL-TRIAL-PHASE-IV in PT:MEDS) or (RANDOMIZED-CONTROLLED-TRIAL in PT:MEDS) or (CONTROLLED-CLINICAL-TRIAL in PT:MEDS)) or (CLINICAL-TRIAL-PHASE-I in PT:MEDS)) and ((interferon*) or (explode ‘Interferon-alpha’ / all subheadings in MIME,MJME))

Cost-effectiveness searches

5. STI-571

(gleevec or glivec or imatinib or sti 571 or sti-571 or sti571 or st1 571 or st1-571 or st1571 or stl571 or stl-571 or stl 571) and ((cost* or economic*) or (explode ‘Economics-’ / all subheadings in MIME,MJME) or (explode ‘Costs-and-Cost-Analysis’ / all subheadings in MIME,MJME))

6. CML and IFN-α

((((‘Leukemia-Myeloid-Chronic’ / all subheadings in MIME,MJME) or (chronic near myel* near (leukemia or leukaemia)) or (cml)) and ((interferon*) or (explode ‘Interferon-alpha’ / all subheadings in MIME,MJME))) and ((cost* or economic*) or (explode ‘Economics-’ / all subheadings in MIME,MJME) or (explode ‘Costs-and-Cost-Analysis’ / all subheadings in MIME,MJME))) and (English in la)

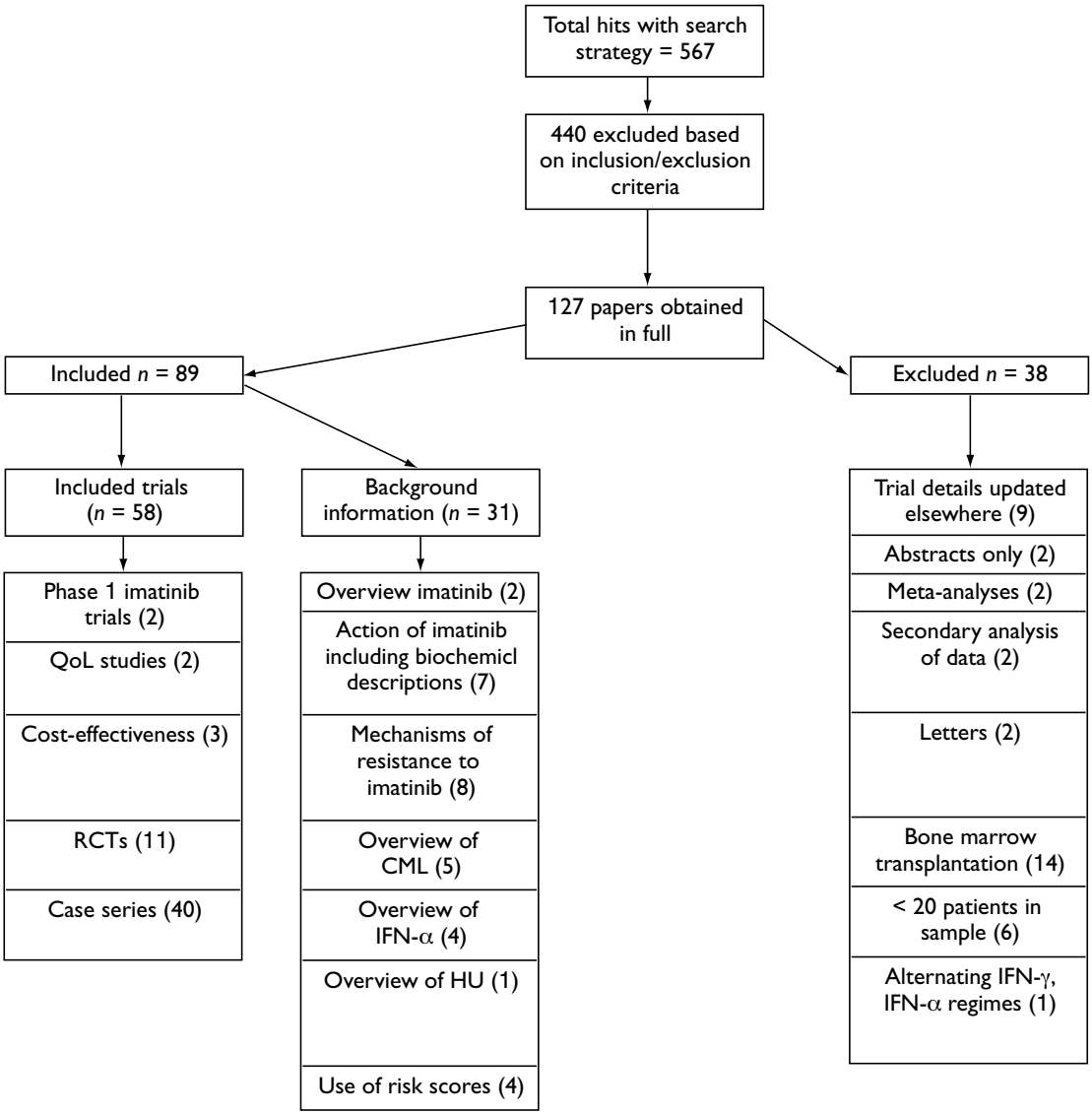
Additional searching

- Most recent version of the PDQ database at http://www.nci.nih.gov
- FDA website – Center for Drug Evaluation and Research, http://www.fda.gov/cder/- downloaded report by Novartis on Gleevec
- Novartis website, http://www.gleevec.com/
- EMEA website, http://www.emea.eu.int/home.htm
- Searched ONS website, http://www.statistics.gov.uk/ for mortality data, Cancer Registrations
- Personal communication with Dr Penny Babb, Senior Cancer Epidemiologist, National Cancer Intelligence Centre, ONS, for statistics on incidence of CML in England 1985–97.

Databases searched	Dates and issues of databases searched		
	Clinical effectiveness		Cost-effectiveness
	1. STI-571	**2. CML and bone marrow transplantation** **3. CML and hydroxyurea** **4. CML and IFN-α**	**5. STI-571** **6. CML and IFN-α**
Cochrane Library (all sections)	2002 issue 1	2001 issue 3	2002 issue 1
CancerLit	1966 to 12 November 2001		
MEDLINE (WebSPIRS)	1966 to August 2001	1990 to July 2001	1990 to November 2001
EMBASE (WebSPIRS)	1981 to September 2001	1991 to June 2001	1991 to January 2002
PubMed	Ran on 12 December 2001 – limited to records added in the last 90 days	Ran on 11 September 2001 – limited to records added in last 180 days	Ran on 8 February 2002 – limited to records added in last 180 days
Science Citation Index via Web of Science	1981 to 12 November 2001		
Web of Science Proceedings	1990 to 12 November 2001		
BIOSIS	1985 to 12 November 2001		
NRR (National Research Register)	2001 issue 4		
EWS (Early Warning System)	9 August 2001		
NLM Gateway	9 August 2001		
Current Controlled Trials	9 August 2001		
Clinical Trials.gov	9 August 2001		
CancerNet trials	9 August 2001		
Most recent version of conference abstracts reports at http://www.ash.org	9 August 2001		
CancerNET website http://www.nci.nih.gov/cancerinfo	12 November 2001		
Most recent version of conference abstracts reports at http://www.asco.org	9 August 2001		
Conference Proceedings Index	1982 to 13 August 2001		
AIDS and Cancer Research Abstracts	1982 to 13 August 2001		

Appendix 5

Path of included and excluded studies



Reasons for excluding studies

Chronic phase studies

The study by the Italian Cooperative Study Group on Chronic Myeloid Leukemia (1994)[116] was excluded because it duplicated more recent information on the same patients reported in the Baccarani study (1998).[62] However, patient details were reported more fully in the earlier paper and these were used.

Kloke and colleagues (1996)[125] was excluded because it duplicated more recent information on the same patients reported in a previous study by the same authors in 2000.[69]

Thaler and co-workers (1995)[80] was excluded because it duplicated more recent information on the same patients reported in a 1996 study by the same authors.[81]

Mahon and colleagues (1996)[78] was excluded because it duplicated more recent information on the same patients reported in Mahon (1998).[74]

The 1996 Guilhot study[126] was excluded because it reported solely on the study design and rationale for that design while Guilhot and colleagues (1997)[45] reported on the actual results of this trial.

Allan and co-workers (1995)[127] was excluded because more recent data on this MRC trial was reported in Shepherd and co-workers (1996).[42] However, patient characteristics were reported more fully in the Allan study, and these were utilised.

Accelerated and blast phase studies

Feldman and co-workers (1992)[128] was excluded because it reported on only two patients with CML, the remaining 64 had acute myelogenous leukaemia.

Kreis and colleagues (1991)[129] was excluded because only 7 of the sample of 32 had CML, the rest had refractory or recurrent acute leukaemia.

Tricot and Weber (1996)[130] was excluded because only 12 of the 27 patients had CML and the remaining patients suffered from acute myelogenous leukaemia.

Appendix 6

Description of RCTs

The UK trial[42] showed that IFN-α treatment produced significantly longer survival than conventional chemotherapy. Co-treatment with hydroxyurea or busulphan was allowed for haematological control in the IFN-α group.

HR was defined purely on the level of WBCs in the peripheral blood. Patients with an HR (69%) survived significantly longer than those without an HR, but the results were not split according to therapy, and the text states that HR was nearly identical for those treated with IFN-α and hydroxyurea.

The definition of no CR was more stringent than in other trials. In total, 11% of IFN-α-treated patients developed a major CR, compared to 2% of those on chemotherapy, and in both groups were only seen in those with the best HR. Cyto-genetic responders had better survival than non-responders. Time to CR was considerable, being a median of 84 weeks for a major response. However, non-responders to IFN-α had better survival than the chemotherapy-treated group (not stated if this was statistically significant or not). CR was also associated with Sokal score.

This trial suggests that the improved survival with IFN-α is not necessarily allied to HR or CR, and that treatment with IFN-α should not be abandoned because of lack of CR.

The Italian trial[62] also showed significantly improved survival for patients treated with IFN-α. Major CR was seen in 20% of patients on IFN-α and none of those on chemotherapy. Co-treatment with hydroxy-urea or busulphan was allowed for haematological control in the IFN-α group. This trial recruited more low-risk patients than other studies.

HR was defined as commonly used. For the IFN-α group, complete HR was significantly associated with a substantial prolongation of survival, around 50% at 10 years compared to 20% for those with less than a complete HR (for those still alive at 1 year). Results were not presented for the chemotherapy group.

CR results are likewise only presented for the IFN-α arm (no responses were seen in the chemotherapy arm). Median time to achieve best response was 2 years, and those with a major response survived significantly longer than those without. Sokal score was associated with CR.

A multivariate analysis was performed (Cox Proportional Hazards) and showed that Sokal score, percentage blast cells, HR and CR were significantly associated with survival in the IFN-α patients. However, when all patients were included, HR and CR were not entered into the model (the latter because there were no responses, the former not stated). Sokal score, age, spleen size and treatment arm were significant.

This trial shows an association between HR, CR and survival on IFN-α treatment, but does not provide evidence for this relationship with other chemotherapy.

The Japanese trial[61] compared IFN-α to busulphan. Patients with serious co-morbidity were excluded and also those that were hyper-sensitive to IFN-α. A significant survival benefit for IFN-α was demonstrated. A number of drop-outs appear to have occurred but were not noted in the text.

The common definition of HR was used. No results were presented reviewing the association between HR and survival.

The number of people achieving a CR was not stated. For the IFN-α group, the achievement of any CR was significantly associated with prolonged survival, but the degree of CR was not important (i.e. the patient with only a minor CR had a better survival than those with a partial CR, and similar to those with a complete CR). In the busulphan group, CR was also associated with better survival, those with a complete CR doing better (assumed to be non-significant although not stated). CR was not significantly associated with Sokal score in IFN-α patients.

In this trial, a high proportion of people discontinued IFN-α therapy (51%). Nevertheless, the achievement of any CR was associated with survival for patients treated with IFN-α.

The French trial[60] was small and compared IFN-α to hydroxyurea. Patients who might benefit from a bone marrow transplant were excluded. Fourteen per cent of patients were not initially analysed, further withdrawals occurred, follow-up was short and survival was not recorded. However, disease progression was noted.

HR was defined solely according to the WBC count; 67% of the IFN-α arm and 89% of the hydroxyurea arm achieved an HR (not significant). For those with an HR, three patients in the hydroxyurea group progressed within the first year (three withdrew), and no patients in the IFN-α group progressed (two withdrew).

CR was defined as minimal (1 to 25% Ph– in metaphases), incomplete (25% to 99%) or complete (100% Ph–). Eight per cent of the hydroxyurea group had incomplete or complete responses compared to 46% of the IFN-α group. Progression was not reported for these subgroups separately.

The small size, methodological limitations and limited reporting of this trial do not allow many conclusions to be drawn, although initial achievement of HR with hydroxyurea did not appear to be associated with delayed progression.

A German trial[39] compared IFN-α treatment to either hydroxyurea or busulphan. No concurrent therapy was allowed, patients could cross between arms but an intention-to-treat analysis was used. In total, 622 patients were randomised, but only 513 analysed, as early deaths or people who were Ph– were not included. A significant improvement in survival was shown for IFN-α patients over busulphan-treated patients, but not over hydroxyurea-treated patients.

HR was defined according to the usual criteria. Rates of HR were similar in all three groups, but analysis of survival and HR was only reported for IFN-α. This showed a significant survival advantage for IFN-α-treated patients who achieved a complete HR compared to those with partial or non-response. In addition, patients with WBC counts in the normal range at 6 months had a significantly prolonged survival in both the hydroxyurea and IFN-α groups, but not the busulphan group.

CR was defined according to the usual criteria. Less than 70% of recruited patients had an evaluation of CR. Seven per cent of the IFN-α group achieved a complete CR, with 11% showing a lesser response. The results for busulphan were 0% and 4%, and for hydroxyurea 1% and 4% respectively. There was no survival advantage for the IFN-α patients with CR over those without CR (results not reported for the other therapies).

In this study, patients who discontinued IFN-α early had poorer survival than those who continued, despite apparent subsequent disease control by hydroxyurea or busulphan. The results of this trial suggest, therefore, that continuation of IFN-α, despite apparent lack of response, may be relevant to prolonged survival.

The Benelux trial[64] compared IFN-α + hydroxyurea to hydroxyurea alone in 195 patients. Patients with significant co-morbidity were excluded. Hydroxyurea was used as an induction therapy in all patients. No survival difference was seen in the two groups. The Sokal score was predictive of survival.

HR was defined according to the usual criteria. The IFN-α group had a higher rate of HR, about 55% at 1 year, compared to about 42% in the hydroxyurea group. Both groups showed an association between achievement of complete HR and survival, strongly significant in the IFN-α group and marginally so in the hydroxyurea group.

CR was defined according to the usual criteria. The IFN-α group showed a higher rate of CR than the hydroxyurea group (9% complete versus 0% complete; 41% any response versus 11%). Within each group, those people achieving a CR demonstrated significantly improved survival.

This trial does not suggest a causative relationship between achievement of HR or CR, and survival, as the improved HR and CR rates in the IFN-α group were not translated into prolonged survival.

Guilhot and co-workers[45] performed an RCT of IFN-α alone versus IFN-α and ara-C. Hydroxyurea was given to all patients as part of induction, and if IFN-α and/or ara-C failed to produce or maintain an HR. The ara-C group had a better overall survival at 3 years. However, causes of death other than from CML, and those undergoing bone marrow transplantation, were censored.

HR was defined in the usual way. The ara-C group had a higher rate of complete HR than the IFN-α alone group (66% versus 55%) but survival results according to HR were not presented.

Forty-one per cent of patients in the IFN-α + ara-C group had a major CR, and 24% in the

IFN-α alone group. In both arms of the trial, patients with a major CR had significantly prolonged survival.

This trial shows a positive association between CR and survival, again with IFN-α therapy.

Giles and colleagues[65] studied IFN-α and hydroxyurea versus IFN-α and ara-C. Induction for 1 week with hydroxyurea or leukapheresis was allowed for all participants. Patients with significant co-morbidities were excluded. More than 25% of recruited patients were not analysed, mostly because of inadequate follow-up. No significant survival difference between the groups was reported, 95% for the ara-C arm and 85% for the hydroxyurea arm.

The usual definition of HR was reported. HR was achieved in 79% of the hydroxyurea and IFN-α patients, and 74% of the IFN-α and ara-C group (no significant difference).

CR was achieved in 23% of the hydroxyurea and IFN-α patients, and 16% of the IFN-α and ara-C group (no significant difference).

This trial does not show a positive association between CR and survival, as the IFN-α/hydroxyurea group with higher HR and CR had a lower overall survival. However, the large number of drop-outs in this trial means that less reliance should be placed on it.

A further German trial compared hydroxyurea to busulphan.[63] In total, 458 patients were recruited, and 63 (14%) were lost to follow-up. Survival advantage of a median of 13 months for hydroxyurea was demonstrated.

HR, as such, was not reported in this study. However, it was noted that 43% of the hydroxyurea group had a normal WBC count at 18 months compared to only 11% of the busulphan group. Patients in the hydroxyurea arm who had normal WBC counts were described as having a survival advantage, which just failed to reach statistical significance. No results for the busulphan arm were given.

CR, of any sort, was reported in six patients in total, four in the hydroxyurea arm and two in the busulphan arm. The survival advantage for hydroxyurea was clearly not associated with an increased CR.

The authors of this trial postulated that there was a causal association between reduction in WBC count, as a marker of reduced tumour burden, and survival. However, in the absence of results for the busulphan arm, it is difficult to agree this generalisation.

An American trial[18] compared busulphan to intensive treatment with ara-C and lomustine. Eight-six patients were randomised, with a median age of less than 50, and 13 (15%) lost to follow-up, a similar proportion in each group. No survival difference between the groups was noted. The busulphan group had complete HR in 84% and the cyt/lo group 69% (not significant), although the definition of HR was somewhat less stringent than often used. There was a highly significant difference in duration of HR, 35.2 months for busulphan and 12.4 months for cyt/lo. However, 32% of the busulphan group died while in remission, compared to only 4% of the cyt/lo group. CR was not reported. This trial suggests that factors other than HR are related to survival.

Appendix 7

Quality markers of included studies – selection, performance and detection bias

Chronic phase: imatinib

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	How treated	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Kantarjian *et al.*, 2001[58]	Not clear	Age 18+, Ph+ chronic phase CML, failed IFN-α at 25 MU/week or higher or did not tolerate IFN-α, adequate liver function, negative pregnancy test, use barrier methods of contraception, minimum period since cessation of other CML therapies (HU 1 week, IFN-α or ara-C 2 weeks)	ECOG score of 3+, grade 3–4 cardiac disease, previous BMT History of non-compliance or considered 'unreliable'	Chronic	400 mg imatinib with escalation, reduction and stopping rules		No	No	No	Yes	CR, HR, time to progression, overall survival

Chronic phase: RCTs

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	How treated	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Baccarani *et al.*, 1998[62]	Randomisation process not defined Allocated 2:1 IFN-α: chemo	Ph+ CML in first chronic phase, minimal pre-treatment (< 100 mg BU or < 50 g HU) or none Oral or written informed consent	> 70 years of age, accelerated or blast phase, any associated disorder that could influence treatment or its toxicity	Chronic			No	No	No	Yes	Survival, CR, adverse effects
The Benelux CML Study Group, 1998[64]	Randomisation process not described	Newly diagnosed, untreated, aged 18+, adequate hepatic and renal function, informed consent	Abnormalities other than Ph+, not Ph+/BCR-ABL	Chronic	All pretreated HU, additional HU "if necessary" after randomisation, monitoring under-taken at same intervals, those off protocol still followed up		No	No	No	Yes	HR, CR, survival, WBC
Broustet *et al.*, 1991[60]	Patients randomised according to a centralised randomisation list, equili-brated every 4 patients	Ph+ CML, no previous treatment (except leukapheresis), < 3 months after diagnosis, age > 18 years	Karyotypic abnormalities other than Ph+, patients who may benefit from an allograft	Chronic	Dose of HU varied to maintain WBC, IFN-α dose reduced if adverse effects		No	No	No	Yes	HR, CR, adverse effects
Giles *et al.*, 2000[65]	Unclear	ECOG score ≥ 2, baseline bilirubin ≤ 1.5 upper limit of normal range, not pregnant or lactating, advised not to plan on conceiving	Impaired cardiac status, MI within 3 months, angina needing medication, serious medical or psychiatric condition, hypersensitivity to IFN-α, autoimmune diseases, thyroid function abnormalities History of another malignant disease within 5 years	Chronic	Protocol between study arms differs depending on individual's WBC		No	No	No	Yes	HR, CR, survival, adverse effects/ toxicity

continued

Chronic phase: RCTs *contd*

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	How treated	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Guilhot *et al.*, 1997[45]	Consecutive with exclusion criteria	< 70 years old, Ph+, chronic phase, diagnosis within preceding 6 months, previously treated only with HU	Accelerated or blast phase, history of depressive illness or psychiatric disorder, severe hepatic, renal or cardiovascular disorders	Chronic	Rules for dose adjustment applied, duration of treatment and crossover at 6 months depended on response		No	No	No	Yes	Survival, HR, CR, adverse effects
Hehlmann *et al.*, 1993[63]	Consecutive patients randomised using hospital lists stratified for hospital, randomised centrally by phone	One of: feeling ill/ fatigue; weight loss > 10% in 6 months; fever > 38.5°C for 5+ days; organomegaly; leucocytes > 50 x 10^9/l; thrombocytosis > 1 x 10^{12}/l	Not in chronic phase; no treatment required; pre-treatment with cytostatics, IFN-α or splenic irradiation; no informed consent; 2nd neoplasia; "other reasons that made therapy according to protocol unlikely"	Chronic	Crossover to other drug if resistant to therapy at first check, to free therapy if resistant at second check		No	No	No	Yes	Survival, duration of chronic phase, CR, adverse events, 'normal' WBC counts
Hehlmann *et al.*, 1994[39]	Consecutive patients randomised using Efron lists, stratified for hospitals and randomised centrally by phone	Newly diagnosed, not pretreated, chronic phase Also 6 of: unexplained fatigue, weight loss > 10% in 6 months, fever > 38.5°C for 5+ days, organomegaly-related symptoms, leucocytes > 50 x 10^9/l and/or thrombocytosis > 1 x 10^{12}/l	Lack of consent; living overseas; psychiatric problems; language barriers as too difficult to keep to protocol	Chronic	3 arms – IFN-α, BU, HU IFN-α-2b and 2a as centre prefers Same check up schedule Crossover for drug resistance at 2nd checkpoint to treatment of investigators' discretion		No	No	No	Yes	Survival, HR, CR, adverse effects

continued

Chronic phase: RCTs *contd*

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	How treated	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Ohnishi *et al.*, 1998[61]	Randomisation process not described	Chronic Ph+ CML, ECOG score 0–2, age 20–70	Serious disorders of heart, lung, kidney and liver Serious infections or psychiatric disorders Further neoplasm Hypersensitivity reaction against IFN-α, accelerated or blast phase	Chronic	IFN-α dose escalated according to rules, BU dose adjusted according to rules and in order to maintain WBC		No	No	No	Yes	CR, survival, duration of response
Shepherd *et al.*, 1996[42]	Randomisation process not described	< 75 years, chronic CML with no contraindications to IFN-α therapy Informed consent given	NS	Chronic	Some patients received BU at start of trial whereas others received HU according to physician preference Dose of IFN-α was increased according to patient's response and BU or HU were added as deemed necessary		No	No	No	Yes	HR, CR, survival

continued

Chronic phase: RCTs *contd*

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	How treated	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Silver *et al.*, 1992[18]	Randomisation process not described	Demonstrated Ph+, leucocyte count ≥ 40,000/μl on two occasions not less than 24 hours or more than 96 hours apart, at least 80% of cells in PB of the granulocytic series, < 30% myeloblasts and promyelocytes in PB or bone marrow by 100 cell differential count on two occasions Hypercellular bone marrow aspirate or biopsy specimen, leucocyte alkaline phosphatase or biopsy specimen below 25	Previous treatment	Chronic	Randomised to receive experi-mental cycle of ara-C and lomustine or standard BU treatment		No	No	No	Yes	HR, survival

Chronic phase: IFN-α treatment

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	How treated	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Alimena *et al.*, 1990[66]	Unclear	NS	NS	Chronic	IFN-α at various doses and frequencies, with HU initially in at least 17 patients HU + 6-MP in 11, 7 BU, 2 BU and HU Protocol changed over time	Groups analysed together for some outcomes (including accelerated phase patients)	No	No	No	Yes	HR, cytogenic improvement (NS)
Arthur and Ma, 1993[87]	NS	Ph+ CML, age < 65 years, CML in chronic phase, diagnosis of < 1 year	Karnofsky score < 80, pregnant or lactating women, previous IFN-α or cytotoxic therapy, significant renal, hepatic, cardiac or respiratory disease, leucocytes < 2.0 x 10^9/l, platelets < 100 x 10^9/l, surgery or radiotherapy	Chronic	Doses and commencement of therapies depended on how individuals responded		No	No	No	Yes	HR, CR, median time to first CR, adverse effects
Beck *et al.*, 2001[89]	NS	NS	NS	Chronic			NS		NS	Yes	CR, HR, survival, toxicity necessitating discontinuation
Cortes *et al.*, 1996[20]	Consecutive	Age 60+, < 1 year since diagnosis, IFN-α primary therapy	NS	Chronic phase	Human leucocyte IFN-α, R-human IFN-α alone or with R-IFN-γ; R-IFN-α + HU	All treatment groups analysed together	No	No	No	Yes	HR, CR, survival, adverse effects
Fernandez-Ranada *et al.*, 1993[85]	Open trial, all patients eligible if they met inclusion criteria	CML chronic phase < 2 years from diagnosis, Karnofsky index > 80%	NS	Chronic	Drug dosage varied between patients and according to response		No	No	No	Yes	CR, HR, adverse effects, survival

continued

Chronic phase: IFN-α treatment *contd*

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	How treated	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Freund *et al.*, 1989[67]	Unclear	Chronic phase (defined) Treatment inclusion criteria: leucocytosis > 30 x 10^9/l or thrombocytosis > 1000 x 10^9/l	Severe organ-specific conditions (e.g. liver or renal insufficiency, cardiac failure, cerebral disease), pregnancy	Chronic	Doses were escalated or reduced depending on response and tolerance Range achieved was 2 MU to 56 MU/week	Dose-ranging study of low dose IFN-α-2B	No	No	No	Yes	Complete or partial response
Freund *et al.*, 1993[90]	Unclear	NS except in chronic phase	NS	Chronic	IFN-α according to protocol in separate studies	Groups analysed separately	No	No	No	Yes	HR, CR
Giles *et al.*, 1992[72]	Consecutive plus a historical cohort from previous 10 years at participating institutions	Established chronic phase CML	Over 70 years, presence of non-CML related major physical or mental illness, prior history of major cardio-vascular or CNS disease, or impaired liver function	Late chronic phase		Exclusion criteria were not the same for the historical control group	No	No	No	Yes	Adverse effects, disease progression, survival
Giles *et al.*, 2001[88]	Consecutive	Confirmed CML, adequate performance status, adequate renal and hepatic functioning, no known neurologic or psychological disorders, no life-threatening conditions Not in accelerated or blast phase	Not clear – full inclusion criteria	Chronic	Those with "suboptimal response" given cyclical chemo	Treatment groups analysed together	No	No	No	Yes	HR, CR, survival, duration or CR and HR
Guilhot *et al.*, 1991[73]	NS	Ph+ CML	NS	Chronic	Some patients had doses altered, some stopped treatment and some had ara-C Dose and administration of HU also varied		No	No	No	Yes	HR, CR, bone marrow cellularity, leucocyte alkaline phosphatase score

continued

Chronic phase: IFN-α treatment *contd*

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	How treated	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Hochhaus *et al.*, 1996[68]	Unclear	NS	NS	Chronic	Not standardised – IFN-α n1 or α 2a, b or c, some with a variety of additional chemo, one each splenectomy and splenic irradication		No	No	No	Yes	CR
Kantarjian *et al.*, 1991[40]	Unclear	Chronic phase < 30% blasts, Ph+, < 60 years old	Abnormal hepatic or renal function	Chronic	IFN-α		No	No	No	Yes	HR, CR, survival
Kloke *et al.*, 2000[69]	Unclear – consecutive?	NS	NS	Chronic	Combined results of 2 trials: untreated group IFN-α reduced in parallel to decrease in WBC, others assigned to receive IFN-α or IFN-α + IFN-γ	Reported together as IFN-α primary treatment group	No	No	No	Yes	CR and survival
Mahon *et al.*, 1996[78]	NS	Ph+ CML in chronic phase without clinical or biological signs of acceleration or blast crisis	NS	Chronic	IFN-α dose adjusted according to results, stopping rule		No	No	No	Yes	CR, HR, adverse effects, survival
Mahon *et al.*, 1998[74]	Unclear	Chronic phase	NS	Chronic	Most IFN-α, but some ASCT or BMT, over 70s HU, or combined IFN-α		No	No	No	Yes	HR, CR, survival, event-free survival
Ozer *et al.*, 1993[79]	Not clear	Ph+ CML in chronic phase ECOG score 0–3 (not bed-bound) Age > 15 Life expectancy > 12 months	NS	Chronic	First 16 patients had lower dose (2 MU)	These 16 patients were excluded from the survival analysis but not toxicity	No	No	No	Yes	Clinical response, CR, survival, toxicity

continued

Chronic phase: IFN-α treatment *contd*

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	How treated	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Russo *et al.*, 1995[84]	Unclear	Ph+ CML, first chronic phase, untreated or minimally pretreated and < 56 years	NS	Chronic	Protocol included allogeneic BMT in year 1 but at no set time, treatment at investigator's discretion after first year		No	No	No	Yes	Survival, disease progression, CR
Sacchi *et al.*, 1997[70]	Consecutive	NS	NS	Late chronic phase	Human IFN-α; R-IFN-α plus IFN-γ; R-IFN-α; R-IFN-α + HU; R-IFN-α + ara-C	Human IFN-α and R-IFN-α + IFN-γ analysed together	No	No	No	Yes	HR, CR, survival
Sanchez *et al.*, 1992[75]	NS	Ph+ CML	NS	Chronic (*n* = 27), accelerated (*n* = 2)	HU used as needed to control WBC, follow-up varied according to the time at which haematologic values were normal		No	No	No	Yes	HR, CR, survival
Schofield *et al.*, 1994[71]	Consecutive	NS	NS	Chronic	Patients who did not achieve a full HR were given HU in addition to IFN-α		No	No	No	Yes	HR and CR
Shtalrid *et al.*, 1993[76]	NS	Ph+ CML	NS	Chronic	Stopping rules and rules for adjusting dose		No	No	No	Yes	HR, CR, adverse effects, survival
Talpaz *et al.*, 1987[19]	Unclear	NS	NS	Chronic	Doses varied between 3 and 9 MU daily Reduction rules based on response and toxicity		No	No	No	Yes	HR, CR, survival, disease control

continued

Chronic phase: IFN-α treatment *contd*

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	How treated	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Thaler *et al.*, 1996[81]	NS	Ph+ CML in chronic phase, newly diagnosed or only pre-treated with conventional chemo	Disease acceleration or blast crisis, age > 70 years, Karnofsky performance < 50, pregnancy, active infection, and severe recurrent disease	Chronic	Dose was doubled after 3 months in non-responders, and patients were switched to chemo after a further 4 weeks if they did not respond Therapy continued beyond 12 months only in patients with complete CR		No	No	No	Yes	HR, CR, risk factors for survival, blastic transformation
Thaler *et al.*, 1997[46]	91 enrolled, all cases of newly diagnosed CML	Newly diagnosed cases of CML in chronic phase	Disease acceleration or blast crisis, Ph–, age > 70 years, Karnofsky performance status < 50, pregnancy, active infection, and severe concurrent disease	Chronic	With rules for dose adjustment, duration of therapy dependent on dose		No	No	No	Yes	HR, CR, survival, adverse effects
Tothova *et al.*, 2000[82]	Unclear	< 65, Ph+ chronic phase CML, not previously treated with chemo or IFN-α	Accelerated or blast phase History of depressive illness other than psychiatric disorder, severe hepatic, renal or cardiovascular disorders	Chronic	Scant detail provided		No	No	No	Yes	HR at 6 months, CR at 12 months

Chronic phase: other chemotherapy

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	How treated	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Kantarjian *et al.*, 2000[48]	Not clear	Age 15+; chronic or accelerated phase; Zubrod status 0–2; IFN-α treatment failure; normal renal and hepatic functions; no evidence of severe cardiac disease (IFN-α failure defined)	Blast phase	Chronic or accelerated			No	No	No	Yes	HR, CR, survival, adverse effects
O'Brien *et al.*, 1995[83]	Unclear	Diagnosis > 1 year; Zubrod score ≤ 2, normal renal and hepatic functions	Severe heart disease excluded	Late chronic phase			No	No	No	Yes	HR, CR, survival, adverse effects

Accelerated/blast phase: imatinib

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Sawyers *et al.*, 2001[59]	Not clear	Over 18, blast crisis, Ph+ (blast defined as 30% blasts in PB or marrow or extramedullary disease evidence), no significant liver or kidney disease, not pregnant, use of barrier contraceptives	ECOG score 3+, Grade 3–4 cardiac disease or serious concomitant disease, must have stopped any prior treatment by specified times before trial Excluded if non-compliant or thought unreliable by investigator	Blast		No	No	No	Yes	HR, CR, survival, adverse effects, duration of response
Talpaz *et al.*, 2001[13]	Not clear	Age 18+, confirmed Ph+ CML in accelerated phase, liver function criteria, negative pregnancy tests, use barrier contraceptives	Grade 3–4 cardiac disease, leukaemic CNS involvement, "or any serious concomitant medical condition" Treatment with other CML drugs within various time-frames prior to treatment with imatinib BMT within 6 weeks Excluded if had a history of non-compliance or considered to be unreliable by investigator	Accelerated	Rules for drug escalation, reduction and interruption	No	No	No	Yes	HR, CR, survival and adverse effects Duration of HR, time to progression

Accelerated/blast phase: RCTs

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Coleman *et al.*, 1980[94]	Those eligible from "participating centres"	Peripheral blasts and promyelocytes 30% at any time and either: completion of 2 courses of conventional treatment or survival of at least 12 months since diagnosis PLUS one of: peripheral blood blasts and promyelocytes 20%/haemoglobin value 9 g/100 ml/platelet count decreased from above 100,000/mm^3 to below 100,000/mm^3 during a conventional course of treatment/an increase of WBC after a conventional course of treatment to either 50,000 cells/mm^3 or more than twice the count at the start of the course of treatment No chemo for 2 weeks preceding study, and no exposure to drugs used within 3 weeks of study	NS	Terminal phase		No	No	No	Yes	Response defined, survival

Accelerated/blast phase: IFN-α treatment

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Alimena *et al.*, 1996[95]	Unclear – retrospective analysis of all those in blast phase from 238 treated in chronic phase	Blast phase as defined by Cervantes and Rozman	NS	Blast	Analysis done on those who progressed to blast phase	No	No	No	Yes	Progression to blast phase
Kantarjian *et al.*, 1992[12]	Unclear	Confirmation of CML; normal cardiac, hepatic and renal functions; no previous or existing serious neurological abnormalities CML diagnosis advanced – accelerated or blast	NS	Advanced – late chronic, accelerated		No	No	No	Yes	HR, CR, survival, adverse effects

Accelerated/blast phase: other chemotherapy

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Canellos *et al.*, 1971[96]	NS	NS	NS	Blast		No	No	No	Yes	Complete HR, survival
Carella *et al.*, 1994[91]	NS	NS	NS	Accelerated or blast	Same treatment protocol	No	No	No	Yes	CR
Dutcher *et al.*, 1992[93]	Unclear	CML diagnosis, accelerated or blast status, no previous treatment for that phase or only with single agent chemo, adequate renal, hepatic function, ECOG score of 0–2, normal left ventricular ejection fraction (other poor cardiac history OK)	One withdrawn by physician, one incorrectly diagnosed, one unevaluable for response	Accelerated or blast		No	No	No	Yes	Overall survival, response (= combined HR and CR), toxicity
Hernandez-Boluda *et al.*, 2001[97]	Retrospective reporting on 60/152 cases in blast selected because relevant data available on 30 ara-C treated patients Comparison group of 6-MP treated patients constructed by matching patients main characteristics plus available data for analysis	NS	NS	Blast	Those in ara-C groups received a variety of additional drug regimes depending on the current protocol for treatment at the centre over time	No	No	No	Yes	Survival
Iacoboni *et al.*, 1986[98]	NS	Informed consent	"No exclusion was made on the basis of age, prior therapy or performance status"	Blast	Different times between courses, different number of courses taken	No	No	No	Yes	Remission, treatment failures (categories defined)

continued

Accelerated/blast phase: other chemotherapy *contd*

Author/date	Selection/ randomisation	Inclusion criteria	Exclusion criteria	Disease point	Performance bias notes	Assessors blind?	Providers blind?	Patient blind?	Outcomes objective	What outcomes?
Kantarjian *et al.*, 1988[99]	NS	30% or more blasts in PB or marrow, informed consent	Patients with lymphoid blast crisis unless failed VCR, doxorubicin and decadron treatment	Blast	Previous treatment in blast phase varied	NS		NS	Yes	Remission (defined), survival
Kantarjian *et al.*, 1992[12]	Not clear	Ph+, accelerated or blast phase CML Those in blast were failed adriamycin or decadron	NS	Accelerated or blast		No	No	No	Yes	Complete HR, CR, survival, adverse effects
Kantarjian *et al.*, 1997[92]	NS	Documentation of disease, in blast phase as defined, Zubrod performance status ≤ 3, adequate renal and hepatic functions, informed consent	Those defined as in accelerated phase only by colonal evolution	Blast	Same treatment course and tests	No	No	No	Yes	HR, early death, aplastic death, resistant disease
Pedersen-Bjergaard *et al.*, 1977[100]	NS	NS	NS	Blast		No	No	No	Yes	Remission, survival
Vallejos *et al.*, 1974[101]	NS – all in study centre?	NS	NS	Blast		No	No	No	Yes	Remission, survival
Winton *et al.*, 1981[102]	NS	NS	NS	Blast		No	No	No	Yes	HR, marrow effects

Appendix 8

Eastern Cooperative Oncology Group (ECOG) Performance Status

These scales and criteria* are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for healthcare professionals to access.

Grade	ECOG criteria
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in *Am J Clin Oncol* (Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;**5**:649–55).

Appendix 9

Quality indicators of included trials – analysis and attrition

Chronic phase: imatinib

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Kantarjian *et al.*, 2001[58]	Sample size, Fleming curves with Kaplan–Meier, univariate and multivariate analysis for prognostic factors, chi-squared	Yes	Rate 20%, 30% haem. fail, cyto. fail	IFN-α haem. and cyto. failures, major CR Complete CR	Yes		Yes	Those with- response counted as non-responders	Median drawing before 11.4 months (0.5–13.7)	Yes	treatment

Chronic phase: RCTs

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Baccarani *et al.*, 1998[62]	Kaplan–Meier, chi-squared and Student's *t*-test, log-rank method, logistic regression, Cox proportional hazards model, two-sided *p*-values ITT analysis	NS	–	NS	Treatment, CR and non-CR		Yes	BMTs censored, 70% IFN-α and 82% chemo died, 18% IFN-α arms discontinued due to adverse effects	Living patients 95–129 median 112 months	No	18% of IFN-α arm withdrew because of adverse effects, 52% IFN-α and 35% chemo went off protocol before disease progression 12% underwent BMT
The Benelux CML Study Group, 1998[64]	Chi-squared Mann–Whitney point comparison, Kaplan–Meier survival curves and log-rank test Time to event analysis for both date of diagnosis and date of randomisation Landmark analysis for prognostic effects of HR, CR, WBC	Yes	To detect 20% improvement in freedom from progression	Yes	Sokal		Yes		Median 51 months, for living patients 66 months	Yes	
Broustet *et al.*, 1991[60]	NS, although appear descriptive	No	Uncertain that study had sufficient power	No			Yes	8 non-evaluable patients	NS	Yes	
Giles *et al.*, 2000[65]	Comparison between groups by Student test and Fisher's exact test Fisher's exact also used to compare CR in 2 arms and toxicity *P*-values two-sided Kaplan–Meier survival curves, log-rank method	NS		NS	By treatment groups and toxicity	Data on alive patients only censored	No	57 excluded after randomisation leaving 143	NS	No	Grade 3–4 toxicity listed but not clear if withdrawn

continued

Chronic phase: RCTs *contd*

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Guilhot *et al.*, 1997[45]	Wilcoxon test, Fisher's exact, Kaplan–Meier, log-rank test, Cox model	Yes	Study a sequential trial using triangular test	Major vs minor or no response	Yes	Analyses performed on ITT basis	No	Any follow-up figures after 6 months may be biased by the crossover of IFN-α non-responders to IFN-α + ara-C	NS	Yes	Adverse effects are all listed as leading to the discontinuation of treatment
Hehlmann *et al.*, 1993[63]	Adjustments to safeguard error described Kaplan–Meier curves and log-rank test for survival Prognostic factors using Cox proportional hazards Risk using Sokal	Yes	0.05 two-sided, power to detect 1.42 in median survival	Yes	Sokal risk group, and primary treatment crossover		No	192 (43%) died, censored events listed	NS Ongoing? Graphs to 8 years	Yes	
Hehlmann *et al.*, 1994[39]	Prob. for type 1 error adj. O'Brien and Fleming, ITT, Kaplan–Meier survival curves, differences log-rank test Cox's proportional hazards regression model for prognostic factors Correction for time-dependent variable Simon and Makuch Mantel–Byar test to compare survival or responders and non Conditional power analysis according to Anderson	Yes	George and Desu, 0.05 two-sided, ratio ≥ 1.42	Yes	Five interim analyses		Yes	BMT counted as lost to follow-up	Not clear "3 years after last patient randomised"	No	Withdrawal for BMT, death, adverse effects listed

continued

Chronic phase: RCTs *contd*

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Ohnishi *et al.*, 1998[61]	Kaplan–Meier, log-rank tests, Mann–Whitney *U*-test, Kruskal–Wallis rank test, Cox's proportional hazards regression	Yes	Overall HR rate of at least 15%	Previously untreated and pretreated patients, adverse effects by dosage, survival by HR at 3 months	Yes	Analyses based on ITT	Yes	Those withdrawing before response counted as non-responders	NS	No	
Shepherd *et al.*, 1996[42]	Differences in survival analyses by log-rank method Responders vs non-responders: Mantel–Byar method	No		Responders vs non-responders	Yes		No	Unable to assess as not enough details provided Some patients die during 5-year follow-up period	5 years	No	Analysis is performed on ITT basis
Silver *et al.*, 1992[18]	Two-sided exact and Wilcoxon test to compare patients, Cox's regression analysis to investigate factors affecting remission rates	NS		No	Only by treatment group		Yes	99 enrolled, 13 excluded by protocol, all 86 randomised reported on	NS	Yes	BU: Refractory to therapy 10% Died in remission 32% Lost or refused therapy 6% Blast crisis 52% ara-C: Refractory to therapy 31% Died in remission 4% Lost or refused therapy 34% Blast crisis 31%

Chronic phase: IFN-α treatment

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Alimena *et al.*, 1990[66]	NS	NS		NS	New cases by Sokal score	Mixture of case series and patient combinations, no rationale for combining them	No	9 off study for toxicity/late resistance	Median 32 months	Yes	Deaths and survival not reported
Arthur and Ma, 1993[87]	NS (although on inspection only descriptive statistics were used)	No	Uncertain that study had sufficient power		No		Yes	All patients followed up, two patients died	Median follow-up 14 months (10–53)	Yes	
Beck *et al.*, 2001[89]	None	NS		None		Paper primarily uses data to inform a cost-effectiveness study	Uncertain		Median 43 months	No	Data given for those withdrawn due to adverse effects, death and BMT Not all patients accounted for
Cortes *et al.*, 1996[20]	Chi-squared comparisons; Kaplan–Meier survival and compared using log-rank	NS		None	None – compared with < 60-year-old group		Yes		Median 57 months	No	Not clear, none reported
Fernandez-Ranada *et al.*, 1993[85]	Mann–Whitney *U*-test, Spearman's rank correlation, chi-squared, Yates correlation	No		Responders and non-responders	Yes		No	Four patients unevaluable because of acute toxicity, only patients with complete HR has CR reported	Initial, 6, 9 and last response Median 217 days (21–1150 days)	Yes	

continued

Chronic phase: IFN-α treatment *contd*

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Freund *et al.*, 1989[67]		No			Yes – according to pretreatment	No differences in complete or partial HR depending on pretreatment	Yes	Duration of follow-up not clear All responses were within 12 months	Median (for surviving patients) 30.4 (range 16.7–37.9)	No	
Freund *et al.*, 1993[90]	NS	NS		NS	Pretreated vs new	Descriptive	No	Discrepancy between numbers and calculated %	Median 20 (IFN-α + BU); median 8 (IFN-α + ara-C)	No	
Giles *et al.*, 1992[72]	Comparison of survival curves using Cox proportional hazards model, risk reduction and relative risk	No		No	No		No	Three patients discontinued treatment for adverse effects, and four patients died	NS	Yes	
Giles *et al.*, 2001[88]	Comparisons Wilcoxon or chi-squared; survival Kaplan–Meier and differences log-rank test Cox proportional hazards regression model Univariate analysis of significant variable ($p < 0.1$) in multivariate model	NS		NS	Sokal, historic comparator IFN-α alone		Yes		Median 145 months (103–155)	Yes	Resistance $n = 27$, toxicity $n = 10$, resistance and toxicity $n = 2$, no CR $n = 1$, death in remission $n = 1$, patient request $n = 8$
Guilhot *et al.*, 1991[73]	NS, although appear to be descriptive only	No	The study was designed as a pilot study	Untreated and pretreated	Yes		No	Three patients died, 1 BMT, 7 patients stopped treatment and 1 patient was lost to follow-up at 9 months	Median follow-up 33 months (10–42)	Yes	

continued

Chronic phase: IFN-α treatment *contd*

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Hochhaus *et al.*, 1996[68]	None	NS		NS	CR response status	Primarily methodo-logical paper	No	Only 83 evaluated for CR	NS	No	
Kantarjian *et al.*, 1991[40]	Chi-squared and log-rank	NS		NS	Initial CR	Subgroup was NS in methods	No		Median 67	No	Resistance and disease evolution
Kloke *et al.*, 2000[69]	Product limit survival (Kaplan–Meier) BMT and lost to follow-up censored Log-rank for comparison Landmark method at 2 years – alive and uncensored inclusive	NS		NS	By CR and Hasford score		Yes		Median 11.4 years	No	Lost to follow-up treated as censored cases in survival analysis
Mahon *et al.*, 1996[78]	Comparisons: log-rank and chi-squared, survival: Kaplan–Meier (compared using log-rank), prognostic factors: Cox model	No		No			Yes	Patients were excluded when they died or received transplant	Median 30 months (3–96)	Yes	

continued

Chronic phase: IFN-α treatment *contd*

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Mahon *et al.*, 1998[74]	Log-rank and chi-squared comparisons Kaplan–Meier survival curves and cumulative complete HR, complete CR Cox's multivariate analysis Landmark analysis (1 year) CR included as a time-dependent covariate, baseline variables where $p = 0.05$ included in proportional hazards model using step-wise procedure and tested with threshold or continuous variables	NS		NS	Variables associated with CR, survival by CR, effect of Sokal and CR on survival, effect of complete HR in 3 months on survival		Yes		Median 42 (3–114)	Yes	Withdrawal for adverse effects stated Deaths?
Ozer *et al.*, 1993[79]	Kaplan–Meier Log-rank Landmark analyses	No			Investigation of survival by CR and other prognostic factors	Landmark analysis suggested as the only appropriate analysis of the role of CR as prognostic factor given the lead time required to produce a CR	Yes			No	Not clear whether and why patients stopped treatment

continued

Chronic phase: IFN-α treatment *contd*

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Russo *et al.*, 1995[84]	Survival: Kaplan–Meier product limits methods, survival duration: log-rank method, comparison of clinical features: chi-squared and Student's *t*-tests	No		Yes	For a2b2 and a2b3		No	272 enrolled, 146 patients analysed 122 excluded as transcript was not identified, 2 because sample was unsuitable for analysis, and 2 because of an alternative BCR/ABL Baseline characteristics are provided for the excluded patients	Minimum of 1 year, up to 5–6 years	Yes	
Sacchi *et al.*, 1997[70]	Chi-squared; Kaplan–Meier; log-rank test	NS		NS	By IFN-α alone, α and γ or plus HU vs IFN-α plus ara-C; by time from diagnosis to therapy by CR and by pre-treatment characteristics (clinical state)		Yes		Median 49 months (1–149)	No	
Sanchez *et al.*, 1992[75]	NS, although on inspection all results are descriptive	No	Possibility of insufficient power	For disease progressed and stable	Yes		Yes		Median 48 months (range 11–100)	No	

continued

Chronic phase: IFN-α treatment *contd*

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Schofield *et al.*, 1994[71]	Kaplan–Meier curves Log-rank test	No		Yes	By time from diagnosis to treatment	18-year survival for group treated within 1 year of diagnosis 73% (95% CI, 51 to 95) 5-year survival for group treated at > 1 year since diagnosis 37% (95% CI, 9 to 65)	Yes		Median 52 months (9–141)	Yes	18 patients were censored from survival data 4 had BMT, 2 died of unrelated causes while in complete remission
Shtalrid *et al.*, 1993[76]	NS, although all appear descriptive	No	Possible that study had insufficient power	No	No		Yes	Follow-up appears complete	NS	No	
Talpaz *et al.*, 1987[19]	Kaplan–Meier, Wilcoxon test for comparing survival; chi-squared	NS		NS	HR, CR, risk score		Yes		Median 37 months	Yes	Criteria for removal from study stated
Thaler *et al.*, 1996[81]	Probabilities, Kaplan–Meier product limit method Comparisons between curves log-rank test Prognostic factors relationship – Cox proportional hazards model	No		Yes for pre-treated and untreated prior to study	Yes		No	3 excluded because of major protocol violation, and 3 underwent BMT in first 3 months	Median 42 months (1–108)	Yes	All analyses have been recalculated to include all patients enrolled in study

continued

Chronic phase: IFN-α treatment *contd*

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Thaler *et al.*, 1997[46]	Kaplan–Meier product limit method	No		None	No	Patients receiving BMT were censored	No	91 enrolled, 84 eligible Reasons for cessation of therapy are provided 6 patients taken off study for death (*n* = 2), compliance not associated with adverse effects (*n* = 3), lost to follow-up (*n* = 1)	Median observation period 28 months (5–59)	No	
Tothova *et al.*, 2000[82]	NS	NS	Power calculation NS and does not appear to have been undertaken	By treatment group, HR, CR			No	2 in ara-C not evaluated	Not clear – at least 12 months	No	

Chronic phase: other chemotherapy

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Kantarjian *et al.*, 2000[48]	Chi-squared for associations Kaplan–Meier survival, curves compared with log-rank test	No		NS	By response, by treatment		Yes		25 months median	No	18 deaths but not clear if any other reasons to go off study
O'Brien *et al.*, 1995[83]	NS	No		None	By cases and courses of treatment		Yes		NS	Yes	70% off study

Accelerated/blast phase: imatinib

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Sawyers *et al.*, 2001[59]	Sample size calculated on Fleming's single stage procedure Landmark analysis Kaplan–Meier curves compared with the log-rank test Multivariate Cox's regression model	Yes	Overall HR rate of at least 15%	Yes	Previously untreated and pretreated patients, adverse effects by dosage, survival by HR at 3 months		Yes	Those withdrawing before response counted as non-responders	Not clear	No	
Talpaz *et al.*, 2001[13]	Curves using Kaplan–Meier, univariate and multivariate analysis of prognostic factors, chi-squared or log-rank tests, Cox's regression	Yes			By starting dose and by complete HR		Yes	Those withdrawing before response counted as non-responders	Not clear – median treatment at time of analysis = 9.9 months (0.2–15)	No	

Accelerated/blast phase: RCTs

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Coleman *et al.*, 1980[94]	Corrected chi-squared test and Kruskal–Wallis test for differences in quantitative variables, differences in survival by Breslow's modification of Kruskal–Wallis tests, and survival curves plotted by life-table method	NS		Yes	By treatment arm and response		Yes		Not clear, to 80 weeks?	Not complete	Study I 96% died by study end Study II A 97% died by end of study B 97% died by end of study

Accelerated/blast phase: IFN-α treatment

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Alimena *et al.*, 1996[95]	Chi-squared	NS		NS	By treatment group, Sokal and HR, CR	Retrospective analysis of those progressing to blast phase	No	Those proceeding to blast phase reported on here	Median 51 months (7–96) Different for different treatment groups	No	No mention of attrition rates
Kantarjian *et al.*, 1992[12]	Chi-squared; survival Kaplan–Meier and compared with log-rank test	No		NS	Late chronic vs accelerated; by definition criteria for accelerated phase, compared to historical control IFN-α only, by CR		Yes		Not clear	Yes	Follow-up time unclear – graphs to 60 months

Accelerated/blast phase: other chemotherapy

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Canellos *et al.*, 1971[96]	NS	No		NS	By remission status		Yes		Not clear	No	NS
Carella *et al.*, 1994[91]	None	No		Yes	By disease phase		Not clear	Blast patients not discussed but shown in results table	Not clear	No	Only in those proceeding to BMT (n = 16) are deaths recorded
Dutcher *et al.*, 1992[93]	Association using Fisher's exact test Significance for predicting response using logistic regression, for predicting survival Cox regression/ Kaplan–Meier curves and differences by log-rank test Adverse effects Greenwood's formula Landmark analysis for difference in curves	No		NS	Responders vs non, type of blast crisis (myeloid or lymphoid), by CR	Historical comparators for survival curves presented	Yes	Initial 3 withdrawn	Not clear – graph to 33 months	Yes	
Hernandez-Boluda *et al.*, 2001[97]	Mann–Whitney rank sum test and chi-squared test with Yates correction for comparisons Kaplan–Meier survival curves compared using log-rank test	No		No	By treatment		Yes		Not clear	No	97% had died by time of analysis, remaining 2 patients censored as alive at 18 and 60 days
Iacoboni *et al.*, 1986[98]	Survival curves by Kaplan–Meier method, differences analysed by generalised Wilcoxon test	No			By patient response		Yes		Not clear	No	Deaths not clearly reported

continued

Accelerated/blast phase: other chemotherapy *contd*

Author/date	Statistical tests used	Power calc. at design?	Power notes	Subgroups	Subgroups reported?	Analysis notes	All followed up?	Notes on follow-up	Time of follow-up	Withdrawal reasons given?	Attrition notes
Kantarjian *et al.*, 1988[99]	Chi-squared for differences among subgroups, Kaplan–Meier for survival and remission duration curves, differences of these by modified Wilcoxon test	NS		Yes	By remission status		Yes		Not clear – longest survival reported at 104 weeks	No	8 died (30%) 2 BMT (7%) 6 to other treatments after induction (21%)
Kantarjian *et al.*, 1992[12]	Chi-squared for differences Survival and remission curves Kaplan–Meier and difference in curves log-rank test	NS		NS	By CML phase; patient characteristics		Yes		Not clear – median treatment duration 3.7 months (25th to 75th quartiles, 1.5–7.6 months)	No	Deaths and withdrawals unclear
Kantarjian *et al.*, 1997[92]	None	No			Blast and accelerated phase		Yes		Not clear	No	
Pedersen-Bjergaard *et al.*, 1977[100]	NS	NS		NS	By remission status		Yes		Not clear	No	
Vallejos *et al.*, 1974[101]	NS	NS		Yes	By remission status		Yes		Not clear – to 19 months?	No	Not complete – 20 died (51%) within 6 weeks, 18 died of infection (50%)
Winton *et al.*, 1981[102]	NS	NS		No			Yes		Not clear	No	Not clear 7 (23%) died in first 3 weeks, 1 (3%) died of haemorrhage

Appendix 10

Treatment details in included trials

Chronic phase: imatinib

Author/date	Severity of disease	Previous treatment	Drug type	Drug dosage	Rules for dose escalation	Drug timing	Drug route	Concomitant drugs
Kantarjian *et al.*, 2001[58]	Chronic	Oral allopurinol 48 hours prior to imatinib initiated IFN-α	Imatinib	400 mg	Increased to 400 mg twice daily after 3 months if no response or relapse	Daily	Oral	Agrylin, leukapheresis

Chronic phase: RCTs

Author/date	Severity of disease	Previous treatment	Drug type	Drug dosage	Rules for dose escalation	Drug timing	Drug route	Concomitant drugs
Baccarani *et al.*, 1998[62]	Chronic	None	IFN-α HU/BU	9 MU	NS	Daily	Subcutaneous Oral	HU, BU
The Benelux CML Study Group, 1998[64]	Chronic	None	IFN-α-2b HU	3 MU	HU adjusted to keep WBC 5–15 x 10^9/l	IFN-α 5 days/week HU NS	IFN-α subcutaneous HU oral	HU
Broustet *et al.*, 1991[60]	Chronic	Leukapheresis	HU IFN-α-2b	HU according to WBC IFN-α 4 MU	HU adjusted to maintain WBC	IFN-α daily	IFN-α subcutaneous HU oral	NS
Giles *et al.*, 2000[65]	Chronic	NS	IFN-α ara-C	4 MU 0–15 mg	Yes, according to WBC	5 days/week 4–5 days/week	Subcutaneous	HU
Guilhot *et al.*, 1997[45]	Chronic	None or HU	IFN-α ara-C	6 MU 20 mg/m^2	Dose reduced by half and then discontinued according to response	Daily 10 days/month	Subcutaneous	HU
Hehlmann *et al.*, 1993[63]	Chronic	None	BU HU	BU 0.1 mg/kg HU 40 mg/kg	Dose reduced, increased and discontinued	Daily	Oral	NS
Hehlmann *et al.*, 1994[39]	Chronic	None	IFN-α 2a or 2b BU HU	IFN-α 5 MU BU 0.1 mg/kg HU 40 mg/kg	Rules for dosage change/stop	Daily	IFN-α subcutaneous BU oral HU oral	NS
Ohnishi *et al.*, 1998[61]	Chronic	None	IFN-α BU	2 MU 6 mg	Dose escalated to 9 MU after 3 days, and then adjusted according to response	Daily	Subcutaneous Oral	BU
Shepherd *et al.*, 1996[42]	Chronic	NS	IFN-α HU/BU	2 MU	Increased incrementally to 6, 9 or 12 MU	Daily	NS	BU, HU
Silver *et al.*, 1992[18]	Chronic	None	Lomustine ara-C	35 mg/m^2 15 mg/m^2	NS	Day 1 Days 1–5 Repeated every 6 weeks	Oral Subcutaneous	BU

Chronic phase: INFα treatment

Author/date	Severity of disease	Previous treatment	Drug type	Drug dosage	Rules for dose escalation	Drug timing	Drug route	Concomitant drugs
Alimena *et al.*, 1990[66]	Chronic	Yes, NS	IFN-α-2b	2 or 5 MU	Dose increased to daily if no response	3 times/week	NS	HU
Arthur and Ma, 1993[87]	Chronic	None	IFN-α-2a	3 MU	Escalating by 3 MU every 3 days up to 9 MU	Daily	Subcutaneous	HU, ara-C
Beck *et al.*, 2001[89]	Chronic	NS	IFN-α ara-C	NS	NS	NS	NS	NS
Cortes *et al.*, 1996[20]	Chronic	None	IFN-α	5 MU	NS	Daily	Subcutaneous	NS
Fernandez-Ranada *et al.*, 1993[85]	Chronic	NS	IFN-α-2a	NS	Increased gradually to 5 MU	Daily	Subcutaneous	HU
Freund *et al.*, 1989[67]	Chronic	BU, HU, IFN-γ	IFN-α-2b	5 MU	Doses were escalated or reduced depending on response	3 times/week	Subcutaneous	NS
Freund *et al.*, 1993[90]	Chronic	Yes, NS	IFN-α, IFN-α-2b	BU 3 MU ara-C 3 MU	Escalated in both groups	BU weekly ara-C daily	Subcutaneous	ara-C
Giles *et al.*, 1992[72]	Late chronic	HU, BU, 6-MP + thioguanine	IFN-α-2b	3 MU	NS	3 times/week	Subcutaneous	HU, BU
Giles *et al.*, 2001[88]	Chronic	HU	IFN-α + ara-C	IFN-α 5 MU ara-C 100 mg/m^2	NS	Daily	IFN-α subcutaneous ara-C continuous infusion	HU, chemo
Guilhot *et al.*, 1991[73]	Chronic	HU, BU	IFN-α-2a	5 MU	NS	Daily	Subcutaneous	HU, ara-C
Hochhaus *et al.*, 1996[68]	Chronic	NS	IFN-α-2a, b or c, or IFN-α n1	NS	NS	NS	NS	NS
Kantarjian *et al.*, 1991[40]	Chronic	HU, BU	Daunorubicin, ara-C, VCR, prednisolone + IFN-α	3–5 MU	Adjusted to keep WBC normal	Daily	Subcutaneous	NS
Kloke *et al.*, 2000[69]	Chronic	None	IFN-α-2b or IFN-α plus IFN-γ	4 MU	Dose reduced to parallel the decrease of WBC	Daily	Subcutaneous	NS

continued

Chronic phase: INFα treatment *contd*

Author/date	Severity of disease	Previous treatment	Drug type	Drug dosage	Rules for dose escalation	Drug timing	Drug route	Concomitant drugs
Mahon *et al.*, 1996[78]	Chronic	NS	IFN-α	5 MU	Dose adjusted according to response	Daily	Subcutaneous	NS
Mahon *et al.*, 1998[74]	Chronic	None	IFN-α	5 MU	NS	Daily	Subcutaneous	NS
Ozer *et al.*, 1993[79]	Chronic	None	IFN-α-2b	5 MU	NS	5 times/week	Subcutaneous	NS
Russo *et al.*, 1995[84]	Chronic	Yes, NS	IFN-α-2a	5 MU	NS	Daily	NS	HU, BU, melphalan
Sacchi *et al.*, 1997[70]	Late chronic phase	NS	IFN-α, IFN-γ	IFN-α 5 MU IFN-γ 0.025 mg/m^2 HU 0.5–2.0 g ara-C 15 mg/m^2	Reduction for toxicity and bloods	Daily ara-C 7 days/month	IFN-α subcutaneous HU oral ara-C subcutaneous	NS
Sanchez *et al.*, 1992[75]	Chronic/ accelerated	HU, BU, IFN-a	IFN-α-2a	2 MU	NS	Daily for first 30 days and then 3 times/week	Subcutaneous	HU
Schofield *et al.*, 1994[71]	Chronic	NS	IFN-α	2 MU	NS	Daily for 28 days and then 3 times/week	Subcutaneous	Chemo
Shtalrid *et al.*, 1993[76]	Chronic	HU, BU	IFN-α	9 MU	NS	Daily	Subcutaneous	HU, BU
Talpaz *et al.*, 1987[19]	Chronic	BU, HU	IFN-α	3–9 MU	NS	Daily	Intramuscular	None
Thaler *et al.*, 1996[81]	Chronic	Chemo	IFN-α-2c	3.5 MU	Increased to 7.0 MU if no response after 3 months	Daily	Subcutaneous	NS
Thaler *et al.*, 1997[46]	Chronic	HU	IFN-α-2c ara-C	3 MU 10 mg/m^2	NS	Daily Daily for 10 days/month	Subcutaneous	NS
Tothova *et al.*, 2000[82]	Chronic	None	IFN-α HU ara-C	3 MU 50 mg/kg 20 mg/m^2	NS	Daily Daily Daily for 7 days/month	Subcutaneous Oral NS	NS

Chronic phase: other chemotherapy

Author/date	Severity of disease	Previous treatment	Drug type	Drug dosage	Rules for dose escalation	Drug timing	Drug route	Concomitant drugs
Kantarjian *et al.*, 2000[48]	Chronic or accelerated	IFN-α	HHT ara-C	HHT 2.5 mg/m^2 ara-C 15 mg/m^2	Criteria for dosage change/discontinuation	HHT daily for 5 days ara-C in 2 daily doses for 5 days	HHT continuous infusion ara-C subcutaneous	NS
O'Brien *et al.*, 1995[83]	Late chronic	IFN-α	HHT	2.5 mg/m^2	Maintenance period HHT 7 days/month	Daily over 14 days	Intravenous infusion	NS

Accelerated/blast phase: imatinib

Author/date	Severity of disease	Previous treatment	Drug type	Drug dosage	Rules for dose escalation	Drug timing	Drug route	Concomitant drugs
Sawyers *et al.*, 2001[59]	Blast	IFN-α, HU, ara-C, other chemo	Imatinib	400 or 600 mg	Increased to 600 mg daily or 400 mg twice daily if no response	Daily	Oral	NS
Talpaz *et al.*, 2001[13]	Accelerated	Yes, NS	Imatinib	400 mg	Increased by protocol to 600 mg and further if no response	Daily	Oral	NS

Accelerated/blast phase: RCTs

Author/date	Severity of disease	Previous treatment	Drug type	Drug dosage	Rules for dose escalation	Drug timing	Drug route	Concomitant drugs
Coleman *et al.*, 1980[94]	Blast	NS	Study I		HU and 6-MP doubled			Not clear – allopurinol
			HU	15 mg/kg	after 2 weeks if no	Daily	Oral	
			6-MP	1.5 mg/kg	response, and again	Daily	Oral	
			Dexamethasone	0.05 mg/kg	subsequent 2 weeks	Daily	Oral	
			Study II – A		If no response at day 56,			
			HU	30 mg/kg	removed from study	Daily	Oral	
			6-MP	3 mg/kg	6-MP reduced by 2/3	Daily	Oral	
			Prednisone	0.75 mg/kg	if allopurinol also used	Daily	Oral	
			Study II – B		Maintenance dose after			
			As A plus VCR	2.0 mg weekly for 4 doses	4 weeks	Weekly for 4 doses	Intravenously	

Accelerated/blast phase: IFN-α treatment

Author/date	Severity of disease	Previous treatment	Drug type	Drug dosage	Rules for dose escalation	Drug timing	Drug route	Concomitant drugs
Alimena *et al.*, 1996[95]	Blast	IFN-α, autologous stem cell transplantation	IFN-α-2b or IFN-α-2a	0.5–5 MU		Daily	Subcutaneous	Autologous stem cell transplantation
Kantarjian *et al.*, 1992[12]	Advanced	NS	IFN-α, ara-C	IFN-α 5 MU ara-C 15 mg/m^2	ara-C 7 days/4 weeks once in remission Rules for dose change	IFN-α daily ara-C daily for 2 weeks	IFN-α subcutaneous, ara-C intravenous infusion	NS

Accelerated/blast phase: other chemotherapy

Author/date	Severity of disease	Previous treatment	Drug type	Drug dosage	Rules for dose escalation	Drug timing	Drug route	Concomitant drugs
Canellos *et al.*, 1971[96]	Blast	NS – all other chemo stopped 1 week before entering protocol	VCR Prednisone	2 mg/m^2 60 mg/m^2	Treatment ceased in patients with disease progression, continued if HR	Weekly for at least 3 weeks Daily for at least 2 weeks then dose gradually tapered	Intravenous Oral	NS
Carella *et al.*, 1994[91]	Accelerated/ blast	IFN-α for median of 18 months, most also HU, 2 also BU	Idarubicin ara-C Etoposide Granulocyte-colony stimulating factor	6–8 mg/m^2 600–800 mg/m^2 150 mg/m^2 5 µg/kg	NS	Days 1–5 Days 1–5 Days 1–3 Until WBC satisfactory	NS NS NS NS	NS although leukapheresis also used daily until WBC > 3 x 10^9/l
Dutcher *et al.*, 1992[93]	Accelerated or blast	Single agents (not those in study) or combination of VCR + prednisone	Mitoxantrone, 5-Azacytidine, Allopurinol	12 mg/m^2 150 mg/m^2 300 mg/day	NS	Allo pretreated daily Mito daily days 1–2 5-aza daily in 3 doses days 1–5	Allo NS Mito intravenous bolus infusion 5-aza NS	Anti-emetic, broad spectrum antibiotics, platelet transfusion
Hernandez-Boluda *et al.*, 2001[97]	Blast	NS	ara-C plus chemo 6-MP	100 mg/m^2 50–200 mg/day	NS	For 5 days Daily	Intravenous Oral	NS
Iacoboni *et al.*, 1986[98]	Blast	38% splenectomy, 24% prior ara-C in chronic phase	ara-C	3 g/m^2	NS	Over 2 hours, 9–12 doses 12, 6 or 10 hour intervals	Intravenous	NS
Kantarjian *et al.*, 1988[99]	Blast	NS	Mitoxantrone ara-C	5 mg/m^2 3 g/m^2	Maintenance for those in remission 50–66% of ara-C induction dose	1 hour daily for 5 days 2 hours every 12 hours for 6 doses	Intravenous Intravenous	NS
Kantarjian *et al.*, 1992[12]	Accelerated/ blast	79% none	Daunorubicin Solu-Medrol GM-CSF	120 mg/m^2 then 1.5 g/m^2 100 mg 125 µg/m^2	NS	Over 2 days Continuous over 24 hours for 4 days Daily for 5 days Daily – 24 hours after chemo until recovery of granulocyte count	Intravenous infusion NS NS	NS

continued

Accelerated/blast phase: other chemotherapy *contd*

Author/date	Severity of disease	Previous treatment	Drug type	Drug dosage	Rules for dose escalation	Drug timing	Drug route	Concomitant drugs
Kantarjian *et al.*, 1997[92]	Blast	NS	Decitabine	100 mg/m^2	Subsequently reduced to 75 mg/m^2 over 6 hours for 12 hours for 5 days due to prolonged myelo-suppression No other dose changes described	Over 6 hours every 12 hours for 5 days	NS	NS
Pedersen-Bjergaard *et al.*, 1977[100]	Blast	NS	Cyclophosphamide. VCR, ara-C, prednisone, 1,3-bis-(2-chloroethyl)-1-nitrosurea, 6-MP, dibromomannitol, various regimes	NS	NS	NS	NS	Antibiotics for infections, prophy-lactic allopurinol and blood transfusions, electrolytes and parenteral fluid and nutrition as required
Vallejos *et al.*, 1974[101]	Blast	NS	17 different chemo combinations	Listed	Treatment stopped after 6 weeks if no response Schedules altered based on toxicity and response	At least 3 courses over 6 weeks		As needed – antibiotics, transfusions
Winton *et al.*, 1981[102]	Blast	40% pretreated with VCR and prednisone	Daunorubicin ara-C 6-thioguanine 5-azacytidine	10 mg/m^2 75 mg/m^2 75 mg/m^2 150 mg/m^2	NS	Daily for 5 days Every 12 hours for 10 doses Every 12 hours for 10 doses Daily for 5 days	NS Intravenous Oral Constant intravenous infusion	NS

Appendix 11

Patient characteristics in included trials

Chronic phase: imatinib

Author	Date of publication	Date of recruitment	No. recruited	CML phase	Age (median)	Sex (M:F)	Time since diagnosis	Sokal score
Kantarjian *et al.*[58]	2001	1999	454	Chronic	57 (18–90)	311:221	< 12 months 9% 12–< 24 months 27% 2–< 5 years 42% 5+ years 21%	NS

Chronic phase: RCTs

Author	Date of publication	Date of recruitment	No. recruited	CML phase	Age (median)	Sex (M:F)	Time since diagnosis	Sokal score
Baccarani *et al.*[62]	1998	1986	322 IFN-α 218 Chemo 104	Chronic	NS	NS	NS	NS
The Benelux CML Study Group[64]	1998	1987	195	Chronic	IFN-α 55.7 (20–83) HU 56.4 (27–84)	IFN-α 58:42 HU 53:42	Newly diagnosed	IFN-α Low 29% Int. 43% High 28% HU Low 30% Int. 33% High 37%
Broustet *et al.*[60]	1991	1990	58	Chronic	IFN-α 55.6 ± 10.6 HU 58.6 ± 7.1	IFN-α 15:9 HU 16:10	< 3 months	IFN-α Low 29.2% Int. 50% High 20.8% HU Low 26.9% Int. 46.2% High 26.9%
Giles *et al.*[65]	2000	1993	143	Chronic	IFN-α 40 (12–72) IFN-α + ara-C 42 (16–77)	IFN-α 59:42 IFN-α + ara-C 37:27	Newly diagnosed	NS
Guilhot *et al.*[45]	1997	1991	721	Chronic	IFN-α + ara-C 50 (7–71) IFN-α 51 (2–71)	IFN-α + ara-C 195:165 IFN-α 203:158	≤ 6 months	IFN-α + ara-C Low 47% Int. 39% High 14% IFN-α Low 40% Int. 42% High 18%
Hehlmann *et al.*[63]	1993	1983	458	Chronic	49.7	248:193	Newly diagnosed	Low 26% Int. 35% High 39%
Hehlmann *et al.*[39]	1994	1983	513	Chronic	IFN-α 47.4 (18–85) BU 48.5 (17–84) HU 46.9 (15–84)	IFN-α 88:45 BU 114:72 HU 98:96	Newly diagnosed	IFN-α Low 27.1% Int. 35.3% High 37.6% BU Low 28.5% Int. 38.7% High 32.8% HU Low 29.4% Int. 33.5% High 37.1%
Ohnishi *et al.*[61]	1998	1988	159	Chronic	BU ≤ 24 10% 25–49 43% 50+ 47% IFN-α ≤ 24 12% 25–49 48% 50+ 40%	BU 46:33 IFN-α 50:30	Newly diagnosed	BU Low 38% Int. 34% High 24% IFN-α Low 36% Int. 33% High 29%

continued

Chronic phase: RCTs *contd*

Author	Date of publication	Date of recruitment	No. recruited	CML phase	Age (median)	Sex (M:F)	Time since diagnosis	Sokal score
Shepherd *et al.*[42]	1996	1986	587	Chronic	NS	NS	Newly diagnosed	Low 23% Int. 35% High 42%
Silver *et al.*[18]	1992		86	Chronic	< 50 53% > 50 47%	50:36	NS	NS

Chronic phase: IFN-α treatment

Author	Date of publication	Date of recruitment	No. recruited	CML phase	Age (median)	Sex (M:F)	Time since diagnosis	Sokal score
Alimena *et al.*[66]	1990	NS	109	Chronic	NS	NS	Variable	For untreated patients Low 45% Int. 35% High 20%
Arthur and Ma[87]	1993	1987	30	Chronic	44 (6–63)	2.75:1	NS	High 13% Int. 40% Low 47%
Beck *et al.*[89]	2001	NS	721 IFN-α 361 IFN-α + ara-C 360	Chronic	NS	NS	NS	NS
Cortes *et al.*[20]	1996	1982	35	Chronic	65 (60–76)	NS	NS	NS
Fernandez-Ranada *et al.*[85]	1993	1988	51	Chronic	43 (13–70)	28:23	Median 55 days (0–681)	NS
Freund *et al.*[67]	1989	1985	27	Chronic	46.8	5:4	0–81.1 months	NS
Freund *et al.*[90]	1993	NS	46 48	Chronic	Mean 45 Mean 44	26:20 25:23	NS	NS
Giles *et al.*[72]	1992	NS	23	Late chronic	48 (18–66)	14:9	Median 19 months (1–56)	NS
Giles *et al.*[88]	2001	1986	IFN-α + chemo 74 IFN-α 208	Chronic	41 (17–67)	IFN-α + chemo 41:33 IFN-α 77:131	IFN-α for 12 months if no CR, 6 if no HR otherwise, while affective Overall median follow-up 145 months (103–155)	IFN-α + chemo Low 15% Int. 33% High 52% IFN-α Low 18% Int. 37% High 46%
Guilhot *et al.*[73]	1991	1986	24	Chronic	45 (5–74)	14:10	NS	Low 33% Int. 50% High 17%
Hochhaus *et al.*[68]	1996	NS	133	Chronic	45 (10–83)	83:50	NS	NS
Kantarjian *et al.*[40]	1991	1984	Study 32 Controls 64	Chronic	36 (14–58) 36 (17–60)	9:23 20:44	Newly diagnosed (< 2 weeks)	NS
Kloke *et al.*[69]	2000	1984	71	Chronic	38	40:31	Newly diagnosed	NS
Mahon *et al.*[78]	1996	1986	81	Chronic	50.5 (17–70)	45:36	Median 45.5 days	Low 48% Int. 40% High 12%
Mahon *et al.*[74]	1998	1986	116	Chronic	50.2 (9–70)	66:50	Median 36 days	Low 49% Int. 36% High 14%
Ozer *et al.*[79]	1993	1985	112	Chronic	44 (17–79)	61:54	2.6 weeks	NS

continued

Chronic phase: IFN-α treatment *contd*

Author	Date of publication	Date of recruitment	No. recruited	CML phase	Age (median)	Sex (M:F)	Time since diagnosis	Sokal score
Russo *et al.*, 1995[84]	1995	1989	272	Chronic	a2b2 mean (SD) 39.4 (10.9) a2b3 37.3 (11.2) Unidentified 38.7 (11.3)	165:105	NS	a2b2 1.02 (SD 0.972) a2b3 0.929 (0.813) Unidentified 1.1 (0.996)
Sacchi *et al.*[70]	1997	1982	123	Late chronic	45 (16–70)	81:56	> 36 months 39% < 36 months 61%	NS
Sanchez *et al.*[75]	1992	NS	29	Chronic/ accelerated	40 (24–67)	18:11	Median 22 months (1–72)	NS
Schofield *et al.*[71]	1994	1986	41	Chronic	38 (12–70)	21:20	7 months (0–81)	NS
Shtalrid *et al.*[76]	1993	1988	30	Chronic	41 (16–65)	21:9	Median 4 (1–16)	NS
Talpaz *et al.*[19]	1987	1981	51	Chronic	42 (20–70)	34:17	Within 6 months (90%)	Low 43% Int. 31% High 22%
Thaler *et al.*[81]	1996	1985	80	Chronic	47 (13–70)	44:33	1 (0–393) months	Risk stages (after Kantarjian, 1990) Total 1: 58% 2: 24% 3: 9% 4: 9%
Thaler *et al.*[46]	1997	1991	84	Chronic	47 (2–73)	52:32	NS	Low 39% Int. 36% High 25%
Tothova *et al.*[82]	2000	NS	IFN-α 22 IFN-α + ara-C 21	Chronic	IFN-α mean 43.7 (21–59) IFN-α + ara-C mean 38.4 (23–60)	IFN-α 10:12 IFN-α + ara-C 16:5	Newly diagnosed	NS

Chronic phase: other chemotherapy

Author	Date of publication	Date of recruitment	No. recruited	CML phase	Age (median)	Sex (M:F)	Time since diagnosis	Sokal score
Kantarjian *et al.*[48]	2000	NS	32	Late chronic/ accelerated	31% ≥ 60	54:51	< 12 months 6% 12–24 months 38% > 24 months 56%	NS
O'Brien *et al.*[83]	1995	NS	71	Late chronic	46 (23–71)	37:34	Median 37 months (4–188)	NS

Accelerated/blast phase: imatinib

Author	Date of publication	Date of recruitment	No. recruited	CML phase	Age (median)	Sex (M:F)	Time since diagnosis	Sokal score
Sawyers *et al.*[59]	2001	1999	229	Blast	56 (19–81)	136:124	7 years (25/75th percentiles 1.5–5.8)	NS
Talpaz *et al.*[13]	2001	1999	181	Accelerated	56 (22–86)	118:117	Newly diagnosed 34%	NS
Sawyers *et al.*[59]	2001	1999	260	Blast	56 (19–81)	136:124	3.4 years (25/75th percentiles 1.5–5.8)	NS
Talpaz *et al.*[13]	2001	1999	235	Accelerated	56 (22–86)	118:117	NS	NS

Accelerated/blast phase: RCTs

Author	Date of publication	Date of recruitment	No. recruited	CML phase	Age (median)	Sex (M:F)	Time since diagnosis	Sokal score
Coleman *et al.*[94]	1980	NS	83 Study I 140 Study II	Blast chronic granulocytic leukaemia	Study I 43 Study II 45	Study I 48:35 Study II 101:39	Blast	NS

Accelerated/blast phase: IFN-α treatment

Author	Date of publication	Date of recruitment	No. recruited	CML phase	Age (median)	Sex (M:F)	Time since diagnosis	Sokal score
Alimena *et al.*[95]	1996	1985	71	Blast	45 (18–75)	NS	81 (8–196)	Low 63% Int. 28.6% High 8.4%
Kantarjian *et al.*[12]	1992	NS	48	Accelerated/ blast	< 40 31% 40–49 40% > 50 29%	NS	< 12 months 15% 12–36 months 27% > 36 months 58%	NS

Accelerated/blast phase: other chemotherapy

Author	Date of publication	Date of recruitment	No. recruited	CML phase	Age (median)	Sex (M:F)	Time since diagnosis	Sokal score
Canellos *et al.*[96]	1971	1968–70	30	Blast chronic granulocytic leukaemia	Mean 41 (13–70)	17:13	"Entering" blast phase	NS
Carella *et al.*[91]	1994	NS	22 accelerated, 38 blast	Accelerated/ blast (chronic not reported here)	50	NS	Median 40 months (4–112)	NS
Dutcher *et al.*[93]	1992	NS	40	Accelerated or blast	47 (19–71)	22:18	By results, time in chronic = CR + partial response 37 (6–90) minor response 69 (7–144) no response 38 (0–138)	NS
Hernandez-Boluda *et al.*[97]	2001	1979–99	60	Blast	Study I 40 (13–73) Study II 43 (18–76)	36:24	NS (but length in chronic phase 3–180 months)	NS
Iacoboni *et al.*[98]	1986	1982–84	21	Blast	35 (20–62)	12:9	Blast	NS
Kantarjian *et al.*[99]	1988	NS	27	Blast	42 (19–61)	13:14	Not clear	NS
Kantarjian *et al.*[12]	1992	1987	60	Late chronic/ accelerated	≥ 50 years 40%	NS	Late chronic phase 1–3 years 52% > 3 years 48% Accelerated phase < 3 years 30% > 3 years 70%	NS
Kantarjian *et al.*[92]	1997	NS	20 (17)	Blast/ accelerated	52 (23–78)	22:15	Blast (accelerated)	NS
Pedersen-Bjergaard *et al.*[100]	1977	1967–74	24	Blast	NS	NS	NS	NS
Vallejos *et al.*[101]	1974	1967–72	39	Blast	48.5 (19–82)	24:15	Newly in blast phase	NS
Winton *et al.*[102]	1981	1977–78	30	Blast	45 mean (18–72)	17:13	Blast	NS

Appendix 12

Key outcome measures for included trials

Study	Prescription	1-year survival (%)	Complete HR	Partial HR	Major HR	Complete CR	Partial CR	Major CR
Chronic phase								
Kantarjian *et al.*, 2001[58]	Imatinib	97	89		89	36	19	55
Hehlmann *et al.*, 1993[63] (RCT)	BU	96			0	0		0
Hehlmann *et al.*, 1994[39] (RCT)	BU	96	23	69	92	0	1	1
Ohnishi *et al.*, 1998[61] (RCT)	BU	94			0			0
Silver *et al.*, 1992[18] (RCT)	BU	91	84					
Shepherd *et al.*, 1996[42] (RCT)	HU, BU	93			0		4	4
The Benelux CML Study Group, 1998[64] (RCT)	HU	97	42			0	2	2
Baccarani *et al.*, 1998[62] (RCT)	HU, BU	96			0	0	1	1
Broustet *et al.*, 1991[60] (RCT)	HU			88		0	31	
Hehlmann *et al.*, 1993[63] (RCT)	HU	96			0	< 1		
Hehlmann *et al.*, 1994[39] (RCT)	HU	96	39	51	90	1	1	2
Broustet *et al.*, 1991[60] (RCT)	IFN-α			67		7	46	53
Guilhot *et al.*, 1997[45] (RCT)	IFN-α	97	55		55	9	15	24
Hehlmann *et al.*, 1994[39] (RCT)	IFN-α	96	31	52	83	5	2	7
Baccarani *et al.*, 1998[62] (RCT)	IFN-α	95			0	4	2	6
Ohnishi *et al.*, 1998[61] (RCT)	IFN-α	98			0			0
Shepherd *et al.*, 1996[42] (RCT)	IFN-α	94			0		22	22
Alimena *et al.*, 1990[66]	IFN-α		54	20	74	2		
Arthur and Ma, 1993[87]	IFN-α		93	7	100	30	13	43
Beck *et al.*, 2001[89]	IFN-α		64		64		26	26
Cortes *et al.*, 1996[20]	IFN-α	97	69		69	20		20
Fernandez-Ranada *et al.*, 1993[85]	IFN-α		53	22	75	6	2	8
Freund *et al.*, 1989[67]	IFN-α		37	22	59	0	0	0
Giles *et al.*, 1992[72]	IFN-α	100			0			0
Guilhot *et al.*, 1991[73]	IFN-α	92	75		75	46	8.5	54.5
Kloke *et al.*, 2000[69]	IFN-α	97			0	13	16	29
Mahon *et al.*, 1996[78]	IFN-α	97	82		82	38	6	44
Mahon *et al.*, 1998[74]	IFN-α	98	84		84	33		33
Ozer *et al.*, 1993[79]	IFN-α		19	17	36	11	14	27
Russo *et al.*, 1995[84]	IFN-α	98.5			0	3	5	8
Sanchez *et al.*, 1992[75]	IFN-α		24	17	41	10	10	20
Schofield *et al.*, 1994[71]	IFN-α	100	61	20	81	7	12	19
Shtalrid *et al.*, 1993[76]	IFN-α		57	20	77		20	20
Talpaz *et al.*, 1987[19]	IFN-α		71	10	81	10	16	26
Thaler *et al.*, 1996[81]	IFN-α		36	33	69	8	5	13

continued

continued

Study	Prescription	1-year survival (%)	Complete HR	Partial HR	Major HR	Complete CR	Partial CR	Major CR
The Benelux CML Study Group, 1998[64] (RCT)	IFN-α + HU	98	62			9	7	16
Giles *et al.*, 2000[65] (RCT)	IFN-α + HU	97	79		79	6	5	11
Tothova *et al.*, 2000[82]	IFN-α + HU		62		62	0	9	9
Freund *et al.*, 1989[67] (RCT)	IFN-α + BU		59	30	89	13	4	17
Freund *et al.*, 1993[90] (RCT)	IFN-α + ara-C		50	31	81	0	8	8
Giles *et al.*, 2000[65] (RCT)	IFN-α + ara-C		74		74	5	3	8
Guilhot *et al.*, 1997[45] (RCT)	IFN-α + ara-C	97	66		66	15	26	41
Beck *et al.*, 2001[89]	IFN-α + ara-C		73		73		56	56
Giles *et al.*, 2001[88]	IFN-α + ara-C	100	82			31	11	42
Sacchi *et al.*, 1997[70]	IFN-α + ara-C	87	51		51	2	5	7
Thaler *et al.*, 1997[46]	IFN-α + ara-C		49	21	70	16	6	22
Tothova *et al.*, 2000[82]	IFN-α + ara-C		79		79	5	21	26
Hochhaus *et al.*, 1996[68]	IFN-α + HU + BU + ara-C				0	18	16	34
Silver *et al.*, 1992[18] (RCT)	ara-C + lomustine	89	69					
Kantarjian *et al.*, 1991[40]	IFN-α + combination	96	100		100	41	19	60
O'Brien *et al.*, 1995[83]	HHT	85	59			7	13	20
Kantarjian *et al.*, 2000[48]	Other chemo	94			0			0
Accelerated phase								
Talpaz *et al.*, 2001[13]	Imatinib	74	35		35	17	7	23
Kantarjian *et al.*, 1992[12]	IFN-α + ara-C		50			20	5	25
Carella *et al.*, 1994[91] (A)	Other chemo					23	14	37
Kantarjian *et al.*, 1997[92]	Other chemo	28	35	28	63	0	12	12
Kantarjian *et al.*, 1992[12] (A)	Other chemo	37	25			4	5	9
Accelerated/blast phase								
Dutcher *et al.*, 1992[93]	Other chemo	37			0	13	5	18
Blast phase								
Sawyers *et al.*, 2001[59]	Imatinib	30	6	19	25	7	9	15
Coleman *et al.*, 1980[94] (RCT)	Other chemo	–	Arm I 13 Arm II 11	22 17	35 28	–	–	–
Alimena *et al.*, 1996[95]	IFN-α				0			0
Canellos *et al.*, 1971[96]	Other chemo	–	20	–	20	–	–	–
Carella *et al.*, 1994[91] (B)	Other chemo	–	–	–	–	21	10	31
Hernandez-Boluda *et al.*, 2001[97]	Other chemo	–	5	5	10	–	–	–
Iacoboni *et al.*, 1986[98]	Other chemo	–	23	10	33	–	–	–
Kantarjian *et al.*, 1988[99]	Other chemo	–	26	4	30	–	–	–
Kantarjian *et al.*, 1992[12] (B)	Other chemo	18	33			8		
Kantarjian *et al.*, 1997[92] (B)	Other chemo	17	10	3	13	0	5	5
Pedersen-Bjergaard *et al.*, 1977[92]	Other chemo	–	25	–	25	–	–	–
Vallejos *et al.*, 1974[101]	Other chemo	–	10	26	36	–	–	–
Winton *et al.*, 1981[102]	Other chemo	–	0	13	13	–	–	–

Appendix 13

NCI toxicity grades for reported adverse effects

Adverse events	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anaemia	None	Mild	Moderate	Severe	Life-threatening
Thrombocytopenia	WNL	< LLN to 75.0 x 10^9/l	≥ 50.0 to < 75.0 x 10^9/l	≥ 10.0 to < 50.0 x 10^9/l	< 10.0 x 10^9/l
Leukopenia/ neutropenia	WNL WNL	< 3.0 x 10^9/l ≥ 1.5 to 2.0 x 10^9/l	≥ 2 to < 3.0 x 10^9/l ≥ 1.0 to < 1.5 x 10^9/l	≥ 1.0 to < 2.0 x 10^9/l ≥ 0.5 to < 1.0 x 10^9/l	< 1.0 x 10^9/l < 0.5 x 10^9/l
Nausea/	None	Able to eat	Oral intake significantly decreased	So significant intake, requiring intravenous fluids	–
vomiting	None	1 episode in 24 hours	2–5 episodes in 24 hours over pretreatment	≥ 6 episodes in 24 hours over pretreatment or need for intravenous fluids	Requiring parenteral nutrition or other life-threatening complication requiring surgical intervention (e.g. colostomy)
Diarrhoea	None	Increase of < 4 stools/day over treatment	Increase of 4–6 stools/day, or nocturnal stools	Increase of ≥ 7 stools/day or incontinence; or need for parenteral support for dehydration	Physiological consequences requiring intensive care or haemodynamic collapse
Myalgia/ flu symptoms	None	Mild pain not interfering with function	Moderate pain, pain or analgesics interfering with function, but not interfering with activities of daily living	Severe pain; pain or analgesics interfering with activities of daily living	Disabling
Oedema	None	Asymptomatic not requiring therapy	Symptomatic, requiring therapy	Symptomatic oedema limiting function and unresponsive to therapy or requiring drug discontinuation	Anasarca (severe generalised oedema)
Neurological/ neurotoxic	None	Mild	Moderate	Severe	Life-threatening or disabling
Dermatological	None	Mild	Moderate	Severe	Life-threatening or disabling
Depression/ psychological	Normal	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function but not interfering with activities of daily living	Severe mood alteration interfering with activities of daily living	Danger to self
Liver	None	Mild	Moderate	Severe	Life-threatening or disabling
Weight loss	< 5%	5 to < 10%	10 to < 20%	≥ 20%	
Fatigue/lethargy	None	Increased fatigue over baseline, but not altering normal activities	Moderate (e.g. decrease in ECOG score of 1 or more or 20% Karnofsky or Lansky) or causing difficulty performing some activities	Severe (e.g. decrease in ECOG score of ≥ 2 or 40% Karnofsky or Lansky) or loss of ability to perform some activities	Bedridden or disabling

LLN, lower limit of normality; WNL, within normal limits

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Kent Woods,
Director,
NHS HTA Programme, &
Professor of Therapeutics
University of Leicester

Professor Bruce Campbell,
Consultant Vascular
& General Surgeon,
Royal Devon & Exeter Hospital

Professor Shah Ebrahim,
Professor in Epidemiology
of Ageing,
University of Bristol

Dr John Reynolds,
Clinical Director,
Acute General Medicine SDU,
Oxford Radcliffe Hospital

Dr Ron Zimmern,
Director, Public Health
Genetics Unit,
Strangeways Research
Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Kent Woods,
Director,
NHS HTA Programme, &
Professor of Therapeutics
University of Leicester

Chair,
Professor Shah Ebrahim,
Professor in Epidemiology
of Ageing,
University of Bristol

Deputy Chair,
Professor Jon Nicholl,
Director, Medical Care
Research Unit,
University of Sheffield

Professor Douglas Altman,
Director, ICRF Medical
Statistics Group,
University of Oxford

Professor John Bond,
Director, Centre for Health
Services Research, University
of Newcastle-upon-Tyne

Professor John Brazier,
Director of Health Economics,
University of Sheffield

Dr Andrew Briggs,
Research Fellow,
Institute of Health Sciences,
University of Oxford

Ms Christine Clark,
Freelance Medical Writer,
Bury, Lancs

Professor Martin Eccles,
Professor of
Clinical Effectiveness,
University of Newcastle-
upon-Tyne

Dr Andrew Farmer,
General Practitioner &
NHS R&D Clinical Scientist,
Institute of Health Sciences,
University of Oxford

Professor Adrian Grant,
Director, Health Services
Research Unit,
University of Aberdeen

Dr Alastair Gray,
Director, Health Economics
Research Centre,
Institute of Health Sciences,
University of Oxford

Professor Mark Haggard,
Director, MRC Institute
of Hearing Research,
University of Nottingham

Professor Jenny Hewison,
Academic Unit of Psychiatry
& Behavioural Sciences,
University of Leeds

Professor Peter Jones,
University Department
of Psychiatry,
University of Cambridge

Professor Alison Kitson,
Director, Royal College of
Nursing Institute, London

Professor Sarah Lamb,
Research Professor
in Physiotherapy,
University of Coventry

Dr Donna Lamping,
Head, Health Services
Research Unit,
London School of Hygiene
& Tropical Medicine

Professor David Neal,
Department of Surgery,
University of Newcastle-
upon-Tyne

Professor Tim Peters,
Social Medicine,
University of Bristol

Professor Martin Severs,
Professor in Elderly
Health Care,
University of Portsmouth

Dr Jonathan Shapiro,
Senior Fellow, Health Services
Management Centre,
Birmingham

Dr Sarah Stewart-Brown,
Director, Health Services
Research Unit,
University of Oxford

Dr Gillian Vivian, Consultant
in Nuclear Medicine &
Radiology, Royal Cornwall
Hospitals Trust, Truro

continued

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern,
Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Mrs Stella Burnside,
Chief Executive,
Altnagelvin Hospitals Health & Social Services Trust,
Londonderry

Dr Paul O Collinson,
Consultant Chemical Pathologist &
Senior Lecturer,
St George's Hospital,
London

Dr Barry Cookson,
Director, Laboratory of Hospital Infection, Public Health Laboratory Service,
London

Professor Howard Cuckle,
Professor of Reproductive Epidemiology,
University of Leeds

Professor Adrian K Dixon,
Professor of Radiology,
Addenbrooke's Hospital,
Cambridge

Dr David Elliman,
Consultant in Community Child Health,
St. George's Hospital, London

Dr Tom Fahey,
Senior Lecturer in General Practice,
University of Bristol

Dr Andrew Farmer,
General Practitioner & NHS R&D Clinical Scientist,
Institute of Health Sciences,
University of Oxford

Professor Jane Franklyn,
Professor of Medicine,
University of Birmingham

Dr Antony J Franks,
Deputy Medical Director,
The Leeds Teaching Hospitals NHS Trust

Dr J A Muir Gray,
Programmes Director,
National Screening Committee,
NHS Executive, Oxford

Dr Peter Howlett,
Executive Director – Planning,
Portsmouth Hospitals NHS Trust

Dr S M Ludgate,
Medical Director,
Medical Devices Agency,
London

Professor Jennie Popay,
Professor of Sociology & Public Health,
Institute for Health Research,
University of Lancaster

Dr Susan Schonfield,
CPHM Specialist Commissioning,
Public Health Directorate,
Croydon Primary Care Trust

Mrs Kathlyn Slack,
Professional Support,
Diagnostic Imaging & Radiation Protection Team,
Department of Health,
London

Mr Tony Tester,
Chief Officer,
South Bedfordshire Community Health Council,
Luton

Dr Andrew Walker,
Senior Lecturer in Health Economics,
University of Glasgow

Professor Martin J Whittle,
Head of Division of Reproductive & Child Health,
University of Birmingham

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds,
Clinical Director,
Acute General Medicine SDU,
Oxford Radcliffe Hospital

Professor Tony Avery,
Professor of Primary Health Care,
University of Nottingham

Professor Iain T Cameron,
Professor of Obstetrics & Gynaecology,
University of Southampton

Mr Peter Cardy,
Chief Executive,
Macmillan Cancer Relief,
London

Dr Christopher Cates,
GP & Cochrane Editor,
Bushey Health Centre,
Bushey, Herts

Dr Karen A Fitzgerald,
Pharmaceutical Adviser,
Bro Taf Health Authority,
Cardiff

Dr Felicity J Gabbay,
Managing Director,
Transcrip Ltd,
Milford-on-Sea, Hants

Mr Peter Golightly,
Director, Trent Medicines Information Services,
Leicester Royal Infirmary

Dr Alastair Gray,
Director, Health Economics Research Centre,
Institute of Health Sciences,
University of Oxford

Mrs Sharon Hart,
Managing Editor, *Drug & Therapeutics Bulletin*,
London

Dr Christine Hine,
Consultant in Public Health Medicine,
Bristol South & West Primary Care Trust

Mrs Jeannette Howe,
Deputy Chief Pharmacist,
Department of Health,
London

Professor Robert Peveler,
Professor of Liaison Psychiatry,
Royal South Hants Hospital,
Southampton

Dr Frances Rotblat,
CPMP Delegate,
Medicines Control Agency,
London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, St James's University Hospital, Leeds

Mrs Katrina Simister,
New Products Manager,
National Prescribing Centre,
Liverpool

Professor Terence Stephenson,
Professor of Child Health,
University of Nottingham

Dr Richard Tiner,
Medical Director,
Association of the British Pharmaceutical Industry,
London

Professor Jenifer Wilson-Barnett, Head of Florence Nightingale School of Nursing & Midwifery, King's College,
London

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor John Bond,
Professor of Health Services Research, Centre for Health Services Research, University of Newcastle-upon-Tyne

Ms Judith Brodie,
Head of Cancer Support Service, Cancer BACUP, London

Ms Tracy Bury,
Head of Research & Development, Chartered Society of Physiotherapy, London

Mr Michael Clancy,
Consultant in A & E Medicine, Southampton General Hospital

Professor Collette Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham

Dr Carl E Counsell,
Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd,
Consultant Paediatrician, Derbyshire Children's Hospital, Derby

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Gene Feder,
Professor of Primary Care R&D, St Bartholomew's & the London, Queen Mary's School of Medicine & Dentistry, University of London

Professor Richard Johanson,
Consultant & Senior Lecturer, North Staffordshire Infirmary NHS Trust, Stoke-on-Trent (deceased Feb 2002)

Dr Duncan Keeley,
General Practitioner, Thame, Oxon

Dr Phillip Leech,
Principal Medical Officer for Primary Care, Department of Health, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester

Professor Rajan Madhok,
Medical Director & Director of Public Health, North & East Yorkshire & Northern Lincolnshire Strategic Health Authority, York

Dr Mike McGovern,
Senior Medical Officer, Heart Team, Department of Health, London

Dr John C Pounsford,
Consultant Physician, Frenchay Healthcare Trust, Bristol

Professor Mark Sculpher,
Professor of Health Economics, Institute for Research in the Social Services, University of York

Dr Ken Stein,
Senior Lecturer in Public Health, Peninsular Technology Assessment Group, University of Exeter

continued

Expert Advisory Network

Members

Mr Gordon Aylward,
Chief Executive,
Association of British
Health-Care Industries,
London

Mr Shaun Brogan,
Chief Executive,
Ridgeway Primary Care Group,
Aylesbury, Bucks

Mr John A Cairns,
Reader in Health Economics,
Health Economics
Research Unit,
University of Aberdeen

Professor Nicky Cullum,
Director of Centre for
Evidence-Based Nursing,
University of York

Dr Katherine Darton,
Information Unit,
MIND – The Mental
Health Charity, London

Professor Carol Dezateux,
Professor of
Paediatric Epidemiology,
Institute of Child Health,
London

Professor Pam Enderby,
Dean of Faculty of Medicine
Institute of General Practice
& Primary Care,
University of Sheffield

Mr Leonard R Fenwick,
Chief Executive,
Freeman Hospital,
Newcastle-upon-Tyne

Professor David Field,
Professor of
Neonatal Medicine,
The Leicester Royal
Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher &
Tutor & President,
National Childbirth
Trust, Henfield,
West Sussex

Ms Grace Gibbs,
Deputy Chief Executive
Director for Nursing,
Midwifery & Clinical
Support Services,
West Middlesex
University Hospital,
Isleworth, Middlesex

Dr Neville Goodman,
Consultant Anaesthetist,
Southmead Hospital, Bristol

Professor Robert E Hawkins,
CRC Professor & Director
of Medical Oncology,
Christie Hospital NHS Trust,
Manchester

Professor F D Richard Hobbs,
Professor of Primary Care
& General Practice,
University of Birmingham

Professor Allen Hutchinson,
Director of Public Health &
Deputy Dean of ScHARR,
University of Sheffield

Professor David Mant,
Professor of General Practice,
Institute of Health Sciences,
University of Oxford

Professor Alexander Markham,
Director,
Molecular Medicine Unit,
St James's University Hospital,
Leeds

Dr Chris McCall,
General Practitioner,
The Hadleigh Practice,
Corfe Mullen, Dorset

Professor Alistair McGuire,
Professor of Health Economics,
London School of Economics,
University of London

Dr Peter Moore,
Freelance Science Writer,
Ashtead, Surrey

Dr Andrew Mortimore,
Consultant in Public
Health Medicine,
Southampton City Primary
Care Trust

Dr Sue Moss,
Associate Director,
Cancer Screening
Evaluation Unit,
Institute of Cancer Research,
Sutton, Surrey

Mrs Julietta Patnick,
National Coordinator,
NHS Cancer
Screening Programmes,
Sheffield

Professor Chris Price,
Director of Clinical Research,
Bayer Diagnostics Europe,
Stoke Poges, Berks

Ms Marianne Rigge,
Director, College of Health,
London

Dr William Rosenberg,
Senior Lecturer &
Consultant in Medicine,
University of Southampton

Professor Ala Szczepura,
Director, Centre for
Health Services Studies,
University of Warwick

Dr Ross Taylor,
Senior Lecturer,
Department of General
Practice & Primary Care,
University of Aberdeen

Mrs Joan Webster,
Consumer member,
HTA – Expert
Advisory Network

Feedback

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

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278