Technology Assessment

Technology Assessment Program

REPORT ON THE RELATIVE EFFICACY OF ORAL CANCER THERAPY FOR MEDICARE BENEFICIARIES VERSUS CURRENTLY COVERED THERAPY: PART 3, IMATINIB FOR CHRONIC MYELOID LEUKEMIA (CML)

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Executive Summary

Chronic myeloid leukemia (CML) is a malignant clonal disorder of blood cells resulting from the cancerous transformation of a very primitive hematopoietic stem cell. CML's hallmark is the chromosome 9;22 translocation that produces the *BCR-ABL* gene, which is present in more than 95 percent of all cases of CML. Imatinib (Gleevec®) is an orally administered drug that competitively inhibits the BCR-ABL tyrosine kinase, a cellular enzyme that is encoded in the *BCR-ABL* gene. Imatinib works by blocking, or turning off, the signal from the tyrosine kinase protein, so that cancerous cells stop growing. Imatinib is approved by the Food and Drug Administration (FDA) for patients in the first-line and relapsed settings of all phases of CML.

There are three clinical phases of CML–chronic phase (CP), accelerated phase (AP), and blastic phase/blast crisis (BP)–distinguished by their prognoses and clinical presentation. Therapeutic options include imatinib, interferon-alpha with or without cytarabine, hydroxyurea, busulfan, other conventional chemotherapies, and stem cell transplantation (bone marrow transplantation, SCT). Allogeneic SCT is the only curative treatment for CML, however it is only available for 20-25 percent of patients predominantly due to lack of a suitable donor; 15 -30 percent treatment-related mortality can be expected with SCT.

This assessment of imatinib for treatment of CML was performed at the request of the Centers for Medicare and Medicaid Services (CMS) and is designed to inform the likely health outcomes associated with a current demonstration project which provides for payment for certain oral medications, including imatinib for CML, that are prescribed as replacements for other drugs currently covered under Medicare Part B.

Scope and Key Questions

The key questions for this review were developed with experts in the field of oncology, health economics, and health policy. The key questions are as follows:

1. In patients with chronic myeloid leukemia, what is the effect of imatinib compared to interferon alpha or best supportive care on overall survival, disease free survival, remission rates (PR, CHR, cytogenetic remission), and quality of life (QOL)?

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2. In patients with chronic myeloid leukemia, what is the effect of imatinib compared to interferon alpha or best supportive care on adverse effects, tolerability, and compliance with treatment?

3. What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy? In addressing this question, we will focus on the following: (1) predictive patient or tumor characteristics that are related to the mechanism of action of the drug (i.e., molecular target; performance status, while a powerful predictor of outcome, is not related to mechanism of action); (2) candidates for diagnostic testing (even if not commercially or clinically available currently (e.g., PCR)); and, (3) patient or tumor characteristics that are associated with clinically important differences in treatment response.

Methods

Search Strategy

Primary studies were sought in a computerized bibliographic search of MEDLINE (1966 through September 2004, updated July 2005) and limited to articles published in the English language. Additional strategies included searching ancillary bibliographic databases, searching abstracts presented at the ASCO and ASH professional meetings since 2004, querying experts, and checking references of included studies and review articles.

Selection Criteria

Each citation identified from the search strategies was evaluated according to the following selection criteria. Evaluations were performed by the authors.

Inclusion criteria were as follows:

Patients	Patients with CML–any phase
Interventions	Imatinib (Gleevec™ or Glivec™ or [STI571])
Comparators	Any

Study designs:

- *For **efficacy** questions*: Prospective clinical trials; may be phase II uncontrolled, or phase III randomized controlled trials.

- *For studies of **adverse effects:*** May be retrospective or prospective case series, cohort studies, or clinical trials provided the number of patients treated (at risk for adverse effects) as well as the number with adverse effects can be ascertained.

- *For studies of **predictors** of response:* May be retrospective or prospective case series, cohort studies, case-control studies, or clinical trials provided the response can be ascertained for patients with and without the predictor.

Outcomes:

*For **efficacy** questions*: Survival, disease-free survival, and quality of life (QOL). In addition to these clinical outcomes, the following intermediate outcomes are assessed.

- ***Complete hematologic remission*—**Normal complete blood count and normal physical examination
- ***Complete cytogenetic remission*—**Normal chromosome examination with no Ph-positive cells detectable on metaphase cytogenetic of bone marrow with 20-25 cells analyzed
- ***Molecular remission*—**Negative RT-PCR evidence of the *BCR-ABL* mRNA

Use of these outcomes can be justified based on their correlation with survival. Cytogenetic response is an independent prognostic factor for improved survival, and has been the therapeutic goal of many trials. An understanding of the relationship between molecular response and survival is developing, but in general molecular response—and specifically early molecular response—correlates with survival

- *For studies of **adverse effects**:* Adverse effects, tolerability, and compliance with treatment.

- *For studies of **predictors** of response:* Predictive value of patient or tumor characteristics that are associated with clinically important differences in treatment response that are:
  1) related to the mechanism of action of the drug (i.e., molecular target); and
  2) candidates for diagnostic testing (even if not commercially or clinically available currently [e.g., RT-PCR]).

The Evidence

Question 1: In patients with chronic myeloid leukemia, what is the effect of imatinib compared to interferon alpha or best supportive care on overall survival, disease free survival, remission rates (PR, CHR, cytogenetic remission (CR)), and quality of life (QOL).

The most compelling evidence for the efficacy of imatinib is the IRIS trial, an international multi-center phase III trial of imatinib vs. interferon plus cytarabine as initial therapy for newly diagnosed chronic phase CML. In the IRIS study, imatinib was clearly superior to interferon plus cytarabine in terms of cytogenetic response (CR; 74 percent vs. 9 percent), molecular response (42 percent vs. 13 percent of those with Complete CR at 6 months), progression free survival (PFS; 92 percent vs. 74 percent at 18 months), and QOL (TOI 84.4 vs. 67.7). Estimates of overall survival (OS) were not significantly different between imatinib and interferon plus cytarabine in the original IRIS publication. Since 58 percent of participants on the interferon plus cytarabine arm crossed over to imatinib in this trial, estimates of OS for the individual groups were difficult. In a followup report on the IRIS trial, the 30-month OS for imatinib was 95 percent. This compares favorably to the previously reported 36-month OS rates for interferon plus cytarabine of 86 percent in the Guilhot study. QOL was studied as part of the IRIS trial, and patients receiving imatinib had significantly better total QOL, social/family well-being, and emotional well-being. Pasquini el al. reported similar findings in a phase II trial conducted in Brazil.

There were some criticisms of the IRIS trial. Most notably, the overall mean dose intensity on the interferon plus cytarabine arm was only 58 percent of the target dose, with the dose intensity of the imatinib arm 97 percent of target. This compares similarly to the Guilhot et al. trial of interferon vs. interferon plus cytarabine where only 57 percent achieved the target dose intensity with interferon. The Baccarini study reported higher rates of achieving target dose intensity with interferon (70 percent), but did not report different survival rates than those seen with the Guilhot et al. trial. The other main criticism of the IRIS trial is that PFS was calculated using loss of CHR, loss of Major CR, or increases in WBC as criteria for progression. This criticism is

reflective of the variability in definition of disease progression in CML. For this reason, comparison of more uniform endpoints across trials such as Complete CR or OS may be a more objective measure of relative efficacy.

Efficacy is clearly different by phase of disease and timing within the treatment algorithm, as reflected in Figure 6. Earlier phases and patients treated in the first-line setting had the highest response rates. CP patients treated earlier in the course (i.e., <1 year from diagnosis) had better response rates with imatinib than those treated later in the CP period. In the post-interferon setting, the reason that the interferon was discontinued influenced response rates. Regardless, significant Complete CR rates are seen with imatinib in all treatment settings, including patients who are heavily pre-treated with myelotoxic chemotherapy with or without SCT. The response rates for the heavily pre-treated CP patients are similar to those of the interferon-refractory or intolerant CP patients. The historic control group for the interferon-refractory or intolerant CP patients likely reflects the same or better response rates than would an appropriate control group for the heavily pre-treated CP patients; this group has been used for the comparator group in the heavily-pretreated CP setting.

The AP and BP studies do not report comparator groups, however previous studies suggest that fewer than 5 percent of AP patients achieve a Major CR with interferon. The Complete CR rate for AP treated with interferon can therefore be expected to be lower than 5 percent, and BP lower yet. Studies identified in this review reported Complete CR rates with imatinib of 11-19 percent for AP and 0-10 percent for BP (Figure 6). One year survival rates of 74 percent (95 percent CI 68-81 percent) for AP patients treated with imatinib compare favorably to the historic 6-18 month median life expectancy described in Figure 2. Similarly, the median OS of 6.5-7 months for BP patients treated with imatinib is longer than the historic prognosis of 3-6 months.

Question 2: In patients with chronic myeloid leukemia, what is the effect of imatinib compared to interferon alpha or best supportive care on adverse effects, tolerability, and compliance with treatment?

Imatinib has far fewer adverse effects (any grade and grade 3/4) compared with interferon. The most reliable data on common adverse effects comes from the IRIS trial in which imatinib most commonly caused neutropenia (61 percent), thrombocytopenia (57 percent), superficial edema (56 percent), nausea (44 percent), and abnormal liver function results (43 percent). Interferon plus cytarabine most commonly caused thrombocytopenia (79 percent), abnormal liver function results (74 percent), neutropenia (67 percent), fatigue (66 percent), nausea (61 percent), anemia (55 percent), and headache (43 percent). The incidence of grade 3/4 side effects was primarily hematological with imatinib (neutropenia 14 percent and thrombocytopenia 8 percent) whereas interferon plus cytarabine included fatigue (24 percent) and hematological (neutropenia 25 percent and thrombocytopenia 17 percent). The incidence of side effects increased with imatinib dose and phase of illness, with hematologic side effects particularly increasing with advancing phases of illness.

Compliance with imatinib was not formally presented in the studies reviewed. Discussions with authors revealed that there is a forthcoming report investigating adherence to imatinib therapy using prescription data for a total of 4043 imatinib-treated patients tracked over 14 months.

Overall, the compliance rate was approximately 75 percent, and persistent continuation on therapy averaged 256 days of therapy over 12 months. Suboptimal adherence to imatinib therapy may be an under-recognized problem that requires active monitoring by healthcare professionals.

Question 3: What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy? In addressing this question, we will focus on the following: (1) predictive patient or tumor characteristics that are related to the mechanism of action of the drug (i.e., molecular target; performance status, while a powerful predictor of outcome, is not related to mechanism of action); (2) candidates for diagnostic testing (even if not commercially or clinically available currently (e.g., PCR)); and, (3) patient or tumor characteristics that are associated with clinically important differences in treatment response.

Molecular predictors: Group 1A--DNA factors at the start of imatinib therapy

DNA factors at the start of imatinib therapy that predict poorer tumor response and/or survival include the following:

- 90-100% of metaphases are Ph+ at the start of imatinib;

There were significantly more patients with a Major CR when <90 percent of metaphases were Ph+ at the start of therapy;[1, 2] a similar trend for survival was seen, but not statistically significant.

- Clonal evolution in AP or BP;

Cytogenetic abnormalities have been investigated both at the time of initial diagnosis and with clinical disease progression (e.g., from chronic to accelerated phase). The language that various authors use to describe this process is imprecise, including descriptions of "other chromosomal abnormalities," "complex cytogenetics," and "cytogenetic clonal evolution." Overall, the most common terminology in "clonal evolution" and therefore this grouping will be used to represent this category of predictive markers. Clonal evolution at the time of initial diagnosis may be a marker for more advanced or aggressive disease. Indeed, larger studies of patients in AP and BP supported that clonal evolution at baseline predicted poorer survival ($p<0.005$)[3, 4] and likely predicted disease progression ($p=0.086$)

- Clonal evolution in CP (predicts risk of relapse and poorer survival);

Ten studies including patients in CP and CP-IFN-r considered cytogenetic clonal evolution as a predictor of tumor response, although it was likely that these studies reflected multiple presentations of the same patient populations. Taken together these studies suggested that cytogenetic clonal evolution inconsistently predicted disease response but was a major predictor of the risk of disease relapse (relative risks (RR) reported 4.34, 4.912, and 14.8) and survival.

- Higher percentage of CD34+ cells in the bone marrow; two abstracts that indicated that the percent of CD34+ cells in the bone marrow in CML correlated with tumor response
- Chromosome 9 deletions

Deletions of the resultant DNA on chromosome 9 can be seen in up to 15 percent of cases of CML. Chromosome 9 deletions are known to negatively affect prognosis, decreasing survival by up to 20% at 5 years. These studies were conducted predominantly in patients on interferon-based therapies. In the setting of imatinib, chromosome 9 deletions lead to poorer PFS in CP,

AP and BP settings (p=0.02). Overall survival is not significantly different with a median follow up of 48 months.

- Genetic profiles

A number of genes are known to be related to drug resistance and programmed cell death (apoptosis) in leukemic cells. Evaluation of gene expression suggested that MRP-1 was overexpressed in blast crisis CML, and that MRP-1 overexpression was significantly correlated with poor tumor response to imatinib. Using gene microarray techniques, McLean and colleagues identified a genomic profile and microarray pattern characteristic of tumor response in CP CML. Patients whose CML met this ideal microarray profile had a substantially greater likelihood of Complete CR (odd ratio (OR) 200, 95 percent CI 19-3096) and Major CR (OR 19.9, 95 percent CI 6-67).

Molecular predictors: Group 1B-DNA factors monitored during imatinib therapy

DNA factors monitored during therapy that predict better tumor response and/or survival include the following:

- Cytogenetic response; and,

Cytogenetic response (CR) is the most commonly used surrogate marker of tumor response for CML. Its relationship to PFS and OS in the setting of imatinib therapy has been confirmed by at least 7 studies involving all phases of CML. Timing of the CR is also important. Across the analyses that evaluated the time course of the CR, CR by 3 or 6 months strongly predicted PFS and OS. In the only study that compared timepoints, partial CR by 6 months was most predictive of survival

- Degree of reduction of CD34+ cells in the bone marrow.

The degree of reduction in CD34+ cells in the bone marrow can be considered another surrogate marker of tumor response. Marin demonstrated that the degree of reduction of CD34+ cells in CML in the setting of imatinib treatment correlated with progression free survival (RR 0.88, 95 percent CI 0.53-0.93). This is consistent with imatinib decreasing the percentage of blasts and normalization to a CHR.

Molecular predictors: Group 2–Production of the RNA message

Response to imatinib is independent of BCR-ABL mRNA transcript number at the start of treatment; however, molecular monitoring during imatinib therapy is predictive of overall tumor response.
Factors related to production of the RNA message that are monitored during therapy and predict better tumor response include the following:

- Molecular response;

Nine studies support the association between MR and overall tumor response.[5-12] An individual patient's best MR predicts survival and those with very low levels of residual disease (median ratio <0.1 percent) have the more durable Complete CRs. Among all patients in the IRIS study who achieved a Complete CR, those who received imatinib had a greater MR than those who received interferon plus cytarabine (p=0.036).

- > 2 log reduction in BCR-ABL mRNA transcripts at 3 or 6 months;
- ≥ 3 log reduction in BCR-ABL mRNA transcripts at 12 months; and,
- BCR-ABL/ABL ratio <50 percent at 4 weeks.

Molecular predictors: Group 3–Interaction between the tyrosine kinase protein and imatinib

There is substantial current research effort focusing on mutations in tyrosine kinase that correspond to imatinib resistance. Of particular interest are mutations in the p-loop of the protein where ATP binds and the protein pocket where imatinib binds. These data are in development; clear evidence of the clinical utility of such information for predicting tumor response and overall survival with imatinib is not available yet.

Molecular predictors: Group 4-Other factors

Several other molecular studies point to other factors monitored during therapy that predict poorer tumor response.

- Myelosuppression due to imatinib of greater than Grade 2,
- Myelosuppression persisting for more than two weeks.

Discussion

Imatinib has been shown to have activity in all phases of CML, including interferon-refractory CML and CML which has recurred after a stem cell transplant. However, no long-term data exist as yet in regard to the durability of response, and there only emerging data about the efficacy of salvage strategies using interferon alfa or allogeneic stem cell transplantation after disease progression on imatinib.

Current State of Clinical Use

According to the National Comprehensive Cancer Network (NCCN) guidelines, imatinib is the standard of care as first-line therapy for CP CML when patients are not eligible for SCT. This recommendation of imatinib as first-line therapy is stronger than the previous NCCN guideline which presented imatinib and interferon-based therapy as more equal options. When patients are eligible for SCT, the choice of first-line therapy with imatinib or transplant is still under debate.

The recommended starting dose is 400 mg. The NCCN guideline recommends that therapy is modified if a CHR is not obtained by 3 months. Modification options include reconsideration of SCT, clinical trials, increasing the imatinib to 600-800 mg, or interferon with or without cytarabine. For patients who obtained a CHR at 3 months, 6 month evaluation should include cytogenetic analysis. Patients who achieve at least a Minor CR at 6 months should continue at their current dose or increase to 600-800 mg as tolerated. Potential therapy modifications for patients who do not achieve at least a Minor CR by 6 months again include reconsideration of SCT, clinical trials, increasing the imatinib to 600-800 mg, or interferon with or without cytarabine. For patients who achieve at least a Minor CR at 6 months, 12 month evaluation

should again include cytogenetic analysis. Those in Complete CR should continue imatinib at the current dose. Those in Major CR should be increased to 600-800 mg as tolerated, and those in Minor or no CR should proceed with therapy modification or continue imatinib with the goal of maintaining hematologic remission only. The option to start patients out at higher doses of imatinib is presented.

The NCCN guideline recommends bone marrow cytogenetic analysis even if FISH or Q-RT-PCR are available, because cytogenetic findings including clonal evolution may indicate the need to consider other treatment strategies (e.g., clinical trial, increased imatinib dose). Management strategies in the setting of chromosome 9 deletions are not discussed nor is the role of molecular monitoring.

According to the National Cancer Institute (NCI) clinical guide at www.cancer.gov, the timing and role of imatinib for newly diagnosed CP CML are not as clear. This review was most recently updated in February 2005. Particular questions raised by the NCI reviewers include the following:

- What is the best dose of imatinib and should it be combined with other agents (such as interferon alfa and/or cytarabine)?
- What is the role of allogeneic stem cell transplantation for younger, eligible patients, and should it be offered before or after initiation of imatinib?
- Will transplantation be more or equally efficacious before or after failure on imatinib?
- Will responses on imatinib be durable for many years, or will responses be short-lived and the relapsing disease be more difficult to control?

Both the NCCN and NCI guidelines are less clear about the optimal management of newly diagnosed AP or BP. Patients with newly diagnosed AP may be enrolled in a clinical trial, undergo SCT, be treated with imatinib, or receive interferon-based therapies (interferon-based treatment is not recommended for AP in the NCCN document). Patients with newly diagnosed BP may be enrolled in a clinical trial, undergo SCT, be treated with imatinib, or receive acute leukemia induction chemotherapy regimens (neither guideline recommends interferon). Imatinib is also a consideration in the relapsed or refractory disease settings when it has not previously been used.

When other treatment strategies have not been successful, chemotherapy with hydroxyurea or busulfan, transfusion support, or palliative care remain options for patients.

Implications for Future Research

Future directions of research on imatinib for CML fall into two main domains:

1. CLINICAL SCIENCES:
    - efficacy of imatinib therapy alone or in combination with other agents
    - better predictors of patients most likely to respond or at risk of poor response
    - better understanding of the relative efficacy across segments of the population including different racial, ethnic and age groups
    - long-term longitudinal follow up of imatinib in the various clinical settings

- understanding of the ideal timing of SCT
- meaning of surrogate markers such as molecular response at specific intervals after the initiation of therapy
- impact of minimal residual disease when patients are in Complete CR
- treatment algorithms subjected to objective evaluation
- safe discontinuation of imatinib when there is a good clinical response
- multiple drug regimens that include imatinib

2. BASIC SCIENCES:
   - refined understanding of imatinib's mechanism of action (e.g., anti-angiogenic properties)
   - molecular understanding of mechanisms of drug resistance for imatinib and other targeted therapies
   - better ability to predict individuals likely to be resistant to imatinib
   - development of new technologies so that knowledge of genetic profiles and molecular predictors of resistance can be translated into practical clinical tests
   - development of new targeted therapies that incorporate these molecular insights

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Introduction

Policy Context of the Current Technology Assessment

Section 641 of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) calls for a demonstration that would pay for drugs and biologicals that are prescribed as replacements for drugs currently covered under Medicare Part B. The demonstration project will be national in scope and will be limited to 50,000 beneficiaries or $500,000,000 in funding, whichever comes first. Forty percent of the funding for this demonstration will be reserved for oral anti-neoplastic drugs.

The Center for Medicare and Medicaid Services (CMS) has requested an assessment of the efficacy of selected oral cancer therapies included in the demonstration relative to drugs currently covered under Medicare Part B. This assessment will provide information that will be used to evaluate the likely effects of the demonstration on patient outcomes and may also provide underlying information to be used for cost-effectiveness analyses that will be completed by CMS.

The scope of the assessment will be limited to the following demonstration drugs and conditions:

- Imatinib for treatment of chronic myeloid leukemia;
- Imatinib for treatment of gastrointestinal stromal cancer;
- Gefitinib for treatment of non-small cell lung cancer;
- Thalidomide for treatment of multiple myeloma.

This report is responsive to the first item: an assessment of imatinib for the treatment of chronic myeloid leukemia (CML).

Clinical Context of the Current Technology Assessment

Chronic myeloid leukemia (CML, a.k.a. chronic myelogenous leukemia) is a malignant clonal disorder resulting from the cancerous transformation of a very primitive hematopoietic stem cell.[13, 14] CML's hallmark is the 9;22 translocation that produces the BCR-ABL gene, ultimately leading to an abnormal tyrosine kinase protein that renders the malignant activity. Imatinib is a competitive inhibitor of this tyrosine kinase that works by blocking the signal from the BCR-ABL protein, so that the cancerous cells stop growing. Imatinib was the first targeted cancer drug to be approved by the Food and Drug Administration (FDA) in 2001.

As a sign of imatinib's potential, more than 110 relevant phase II-III and predictor studies have been published in a short interval. This "clinical context" section is provided as both a scientific primer to review the emerging science behind imatinib, and as a structural framework that will ultimately be used to organize the studies reviewed.

This section is organized in according to the following:

- Burden of illness
- Diagnosis
- Staging
    - Chronic phase
    - Accelerated phase
    - Blastic phase/blast crisis
- Treatment
    - Approach to treatment
        - Newly diagnosed
        - Relapsed
    - Goals of treatment
    - Efficacy and tolerability of treatment options other than imatinib
- Prognosis and prognostic factors
    - Clinical prognostic factors
    - Medical prognostic factors

Incidence and Prevalence

Incidence and Prevalence. There are approximately 4,600 new cases of CML diagnosed in the United States (U.S.) annually, accounting for 13-15 percent of all cases of adult leukemia, with about 850 deaths annually.[15, 16] The incidence is 1-2 cases per 100,000 population, and incidence increases with age.[16] CML occurs predominantly in middle-aged adults, with a median age variably reported between 45 and 67 years.[14, 16, 17] Up to 76 percent of patients are older than 50 years at the time of diagnosis and 64 percent are over 60 years.[17] CML rarely occurs in children, with an incidence rate less than 1/20th that seen in adults over age 45.[18]

Diagnosis

Presentation and diagnosis. In developed countries, most patients are diagnosed when asymptomatic based on laboratory abnormalities. Typical laboratory findings include a markedly elevated white blood cell count (leukocytosis), anemia, and elevated platelets (thrombocytosis). Diagnosis and staging require a peripheral complete blood count with a white blood cell differential analysis, bone marrow examination with quantification of the percentage of blasts and basophils, and cytogenetic studies for the Philadelphia chromosome or its variants (see below). Histopathologic examination the bone marrow aspirate demonstrates excessive numbers of cells (hypercelluar marrow) with a shift in the myeloid series to immature forms; the number of immature cells increases as patients progress from chronic to blastic phases of the disease.[19] White blood cell differential counts of both peripheral blood and bone marrow demonstrate a spectrum of mature and immature granulocytes similar to that found in normal marrow. Increased numbers of eosinophils, basophils or monocytes may be present, and a megakaryocytosis may be noted in the marrow. Lymphocyte counts are usually suppressed, and the myeloid/erythroid ratio in the marrow is usually markedly elevated.

When symptomatic at diagnosis, most patients present with fatigue, weight loss, abdominal fullness, bleeding and/or night sweats.[20] Bruising and an enlarged spleen are common.

Role of the Philadelphia chromosome. The "Philadelphia chromosome" (Ph) is seen in >90 percent of cases of CML.[21] Ph is a balanced reciprocal translocation between chromosomes 9 and 22 (figure 1a); the cytogenetic designation is t(9;22)(q34;q11).[13] ABL is transferred from chromosome 9 to 22. DNA from chromosome 22 is shifted to 9 to take ABL's place. This translocation leads to the fusion of two parts of normal genes, the ABL gene on a portion chromosome 9 with a section on chromosome 22 called BCR. ABL is hooked with a breakpoint promoter region (BCR); this promoter area provides a continuous signal to the cell to transcribe the gene for the tyrosine kinase protein coded in ABL. The BCR-ABL gene is transcribed into messenger RNA (mRNA) and the mRNA is subsequently translated into the tyrosine kinase protein (figure 1b). The tyrosine kinase fusion protein that is produced is continuously active irrespective of regulatory influences within the cell (i.e., constitutively active). This uncontrolled enzymatic activity then usurps the normal physiologic processes of the cell.

Figure 1a: Development of the Philadelphia chromosome

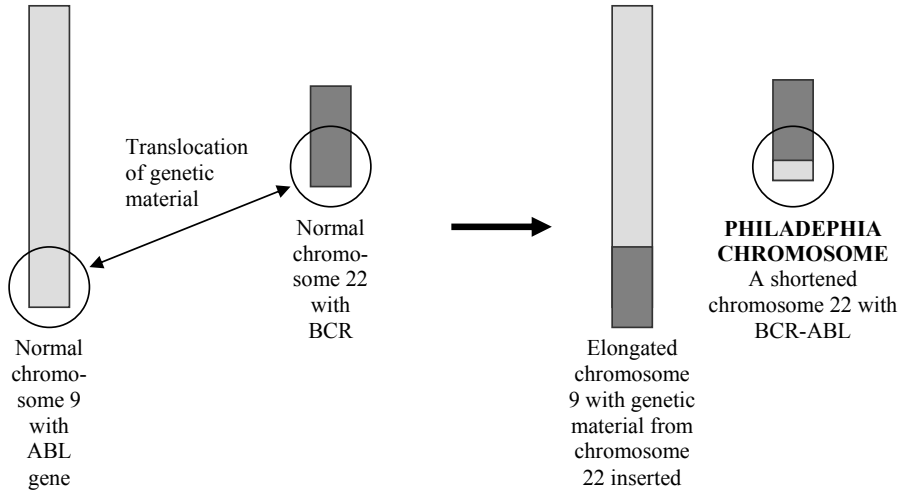
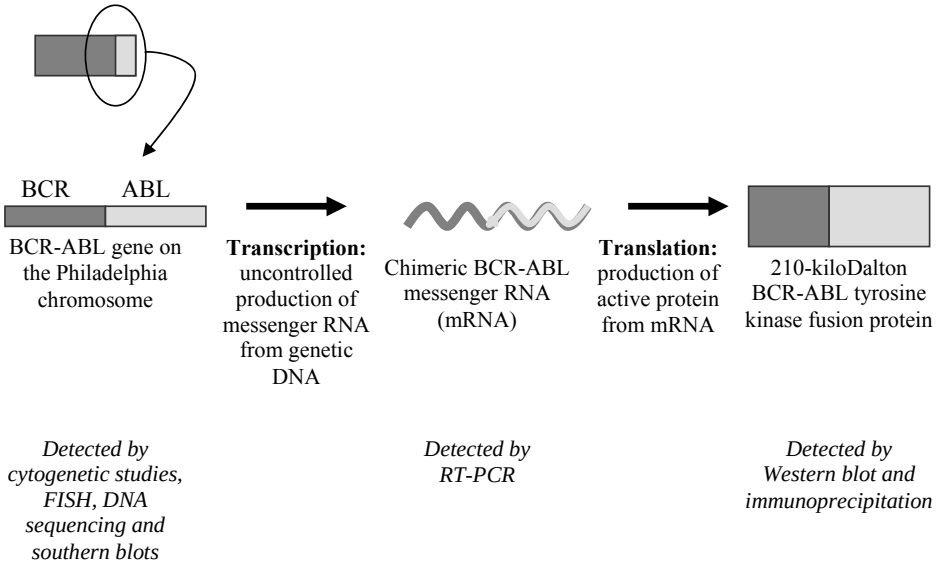


Figure 1b: Production of the BCR-ABL tyrosine kinase fusion protein



The formation of the BCR-ABL fusion gene within a pluripotential hematopoetic stem cell is the first step in developing CML.[13] The exact mechanism prompting formation of BCR-ABL is unknown. Daughter cells of the mutated stem cell all have BCR-ABL; all of the mutated cells more readily survive and produce progeny as compared to normal hematopoetic cells. The mutated CML cells with their constitutively active ABL tyrosine kinase protein gradually displace the normal cells within the bone marrow and other hematopoetic areas. The exact reason that cells with BCR-ABL more easily divide and take over is not known; however, growth-stimulating hormones and defective mechanisms of cell death are likely involved.[13] Importantly, the mutated CML cells only displace normal hematopoetic cells and do not destroy

residual normal stem cells. Therefore return to a normal or nearly normal hematopoetic state after eliminating the CML cells is presumed possible.

Detection of BCR-ABL and the tyrosine kinase fusion protein. Bone marrow cytogenetic analysis (Figure 1b) has long been considered the gold standard for evaluating CML and the presence of Ph.[16] Only cells going through the cell cycle are measured, so quiescent cells with Ph may be missed. Cytogenetic analysis is described in terms of the percent of metaphase cells with the cytogenetic abnormality.

Currently, reverse transcriptase polymerase chain reaction (RT-PCR) analysis is the most sensitive way of detecting BCR-ABL mRNA transcripts; it can be performed on peripheral blood (Figure 1b).[11, 22] RT-PCR can be used to pick up evidence of the mRNA, even when low copy numbers are present. Despite being an excellent tool, RT-PCR does have problems. The threshold of detection is such that the test may be negative and a patient could still harbor a million or more residual CML cells.[13] Alternatively, patients who appear to be disease-free by other parameters may continue to have evidence of BCR-ABL mRNA by RT-PCR for years after disease regression.[11] Low levels of BCR-ABL mRNA can also be detected by RT-PCR in the blood of healthy individuals, and this risk must always be considered when evaluating results.[23] Another limitation is that RT-PCR is dependent upon active transcription in order to detect an abnormality; quiet non-dividing interphase CML cells may be missed.[22] Recently, RT-PCR has also indicated "real-time" or quantitative PCR, indicating the ability to measure the number of mRNA copies present, extrapolating back to the amount of DNA and the number of cells with BCR-ABL genes in them. To avoid confusion between traditional RT-PCR and newer methods, the original PCR technique will be termed RT-PCR and the newer technique quantitative RT-PCR (Q-RT-PCR). Q-RT-PCR is most commonly expressed in terms of the ratio of BCR-ABL to ABL transcripts.

Other methods of detecting Ph include fluorescence in situ hybridization (FISH) which will detect dividing (metaphase) and interphase CML cells (Figure 1b). FISH uses two-color labeling to identify pieces of different chromosomes that shouldn't be near each other. Some authors report a high false positive rate that may decrease the utility of this test when the proportion of CML cells to normal cells drops less than 10 percent.[16] DNA sequencing and Southern blot analysis (Figure 1b) provide information on the exact genetic mutation, but are not practical for widespread clinical application. Western blots and immunoprecipitation (Figure 1b) can be used to evaluate the tyrosine kinase fusion protein product.

Ph-negative CML. There are a small group of patients with Ph-negative CML.[24] True Ph-negative CML has a poorer prognosis than Ph positive CML, however the majority of "CML Ph-negative" patients actually have Ph detectable by RT-PCR or Southern blot. Prognosis for those patients whose Ph is only detectable by very sensitive methods is the same as it is for those patients with readily detectable Ph.[25] Patients with true Ph-negative CML by RT-PCR have a course more consistent with chronic myelomonocytic leukemia, which is a different illness; some authors argue that no patients with CML are truly Ph-negative.[26]

Staging

Stage and course. The information provided in the physical exam, peripheral white blood count, bone marrow examination, and cytogenetic studies, FISH or RT-PCR are used to determine the patient's stage of illness and predict their course. The staging in CML is usually described in terms of "phases".

CML historically has had a triphasic course, presenting in an initial chronic phase (CP) with a median duration of 3-5 years, invariably progressing over time to an accelerated phase (AP) with a median duration of 6-18 months and finally to blastic phase (BP) lasting 3-6 months.[14, 27] Blast crisis (BC) is a period within BP that resembles acute leukemia, with two-thirds of patients having an acute myeloblastic or undifferentiated type of leukemia and the other one-third having an acute lymphoblastic leukemia.[16] In BC, patients have fever, malaise and an enlarging spleen in addition to the increasing number of blasts in their blood or bone marrow. In up to one-fourth of patients, blast crisis develops without an intervening accelerated phase.[28] The terms BP and BC are often used interchangeably (reviewers comments) and may not be as distinct as the literature suggests; for this reason, we have grouped BP and BC in the review of studies cited in this document and described this stage of disease in the same way as the authors of each individual study had in the original manuscript. The basic characteristics of the stages are provided in figure 2.

Figure 2: Phases of CML[19]		
Phase	***Clinical characteristics***	***Median duration***
Chronic phase	≤ 15% blasts and promyelocytes in the peripheral blood and bone marrow	3-5 years
Accelerated phase	> 15% to ≤ 30% blasts in either the peripheral blood or bone marrow	6-18 months
Blastic phase	> 30% blasts in the peripheral blood or bone marrow (some authors use this term interchangeably with "blast crisis")	3-6 months
Blast crisis	> 30% blasts are present in the face of fever, malaise, and progressive splenomegaly; blast crisis is a subset of blast phase (some authors use this term interchangeably with "blastic phase")	
Relapse	Any evidence of progression of disease from a stable remission, which may include increased myeloid or blast cells in the peripheral blood or bone marrow, cytogenetic positivity for BCR-ABL when previously cytogenetic negative, or FISH positivity for BCR-ABL when previously FISH negative (note that detection of BCR-ABL by RT-PCR during prolonged remissions does not constitute relapse on its own)	

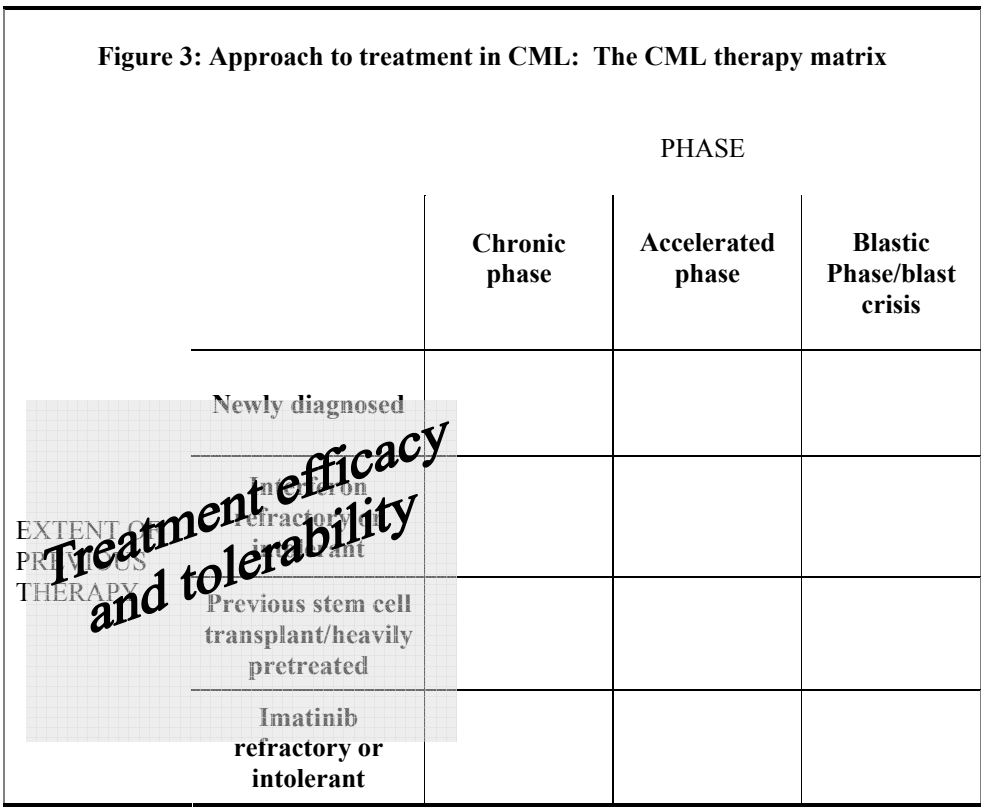
Varying phase assignments. The definitions of the three phases or "stages" of CML have fluctuated through the years. The definitions presented in Figure 2 reflect that reported on the NIH website, www.cancer.gov. Staging criteria have been proposed from MD Anderson[29], Sokal and colleagues[30], the International Bone Marrow Transplant Registry[31], and others. The

discrepancies among the stages are most important for "accelerated phase" where some patients with chronic phase CML by MD Anderson or other criteria would be reclassified as "accelerated phase" by the International Bone Marrow Transplant Registry (IBMTR). Since stage is such an important prognostic factor, "stage migration" due to varying use of definitions may make comparison of efficacy outcomes difficult outside of the randomized controlled trial setting. This is especially true for bone marrow transplant analyses that use the IBMTR criteria and compare results to historical controls using other criteria.[31]

Treatment

Approach to treatment. Treatment planning requires matching the likely most effective therapy with the patient in terms of diagnosis, phase of illness, previous therapies, and patient preference. Assuming that the diagnosis of Ph+ CML has been verified and the patient wishes to proceed with therapy, treatment planning can be considered within the following matrix (Figure 3):

Figure 3: Approach to treatment in CML: The CML therapy matrix



Treatment goals and assessment. Treatment in CML is aimed at reduction in the leukemic cell burden, and hopefully "cure." Reduction in the total white blood cell count is termed the "hematologic response." Reduction in the number of Ph cells is the "cytogenetic response". Since Ph+ cells produce mRNA that leads to the BCR-ABL tyrosine kinase protein, reduction in

the amount of mRNA produced is an indicator of reduction in the number of active Ph+ cells. This is called "molecular response."

The goals of treatment for CML are to achieve a hematologic remission (normal complete blood count and physical examination), to achieve cytogenetic remission (normal chromosome returns with 0 percent Ph-positive cells), and, most recently, to achieve molecular remission (negative RT-PCR result for the mutational BCR-AB*L* mRNA; figure 4). Major cytogenetic and molecular responses predict survival;[11] although minor or minimal cytogenetic responses are of little prognostic significance.

Cytogenetic and molecular responses are divided into major, minor and minimal responses. Molecular responses are measured by Q-RT-PCR and are most commonly expressed as log reductions from median pre-therapeutic value.[32, 33] Importantly, the vocabulary for the description of molecular responses has been evolving, and have included descriptions in "change in median ratios," longitudinal graphs, and transcript velocity. The measure of log reduction is becoming more standard.

The need for a complete molecular remission is hard to determine, as is the exact definition of "cure" in CML. CML patients who are alive and disease-free 5 years after an allogeneic stem cell transplant are generally considered to be cured.[13, 34] Even when patients are in CCR, evidence of CML can be found. Bhatia and colleagues showed that all of the 15 patients in Complete CR studied had evidence of BCR-ABL in their CD34+ cells as identified by FISH or RT-PCR up to 61 months after starting imatinib.[27] O'Dwyer reported similar findings for seven patients in Major CR.[35] Using sensitive RT-PCR techniques Paschka et al. found evidence of BCR-ABL in all samples of CCR patients on imatinib.[10] Taken together, these data support the notion that complete remission in CML may be conversion to a low grade chronic disease with continuous potential for relapse over the long term. Using the previous definition from the transplantation literature that "cure" is continued Complete CR at 5 years,[13, 34] "cure" may be a relative state of disease control rather than complete eradication. Whether "cure" indicates complete eradication of all CML clones or a minimal residual disease burden that can be kept in check by the patient's immune surveillance system is unknown. The "graft-versus-leukemia" effect described for allogeneic stem cell transplants is an example of this presumed immune surveillance.[36]

Disease progression can be defined in several ways. Older studies predominantly present disease progression in terms of loss of hematological or cytogenetic response.[28, 37] Newer studies describe recurrence of Ph positive cells. More recently, disease progression has been defined as > 10-fold increase in BCR-ABL/ABL percent as determined by Q-RT-PCR.[33]

Figure 4: Definition of tumor response criteria relevant to CML

Complete hematologic remission	Normal complete blood count and normal physical examination
Reported as Complete Hematologic Response (CHR)	
Complete HR	Normal complete blood count and exam
Partial HR	Improved but not normal complete blood count and exam
Hematologic improvement	Complete plus partial hematologic response
Complete cytogenetic remission	Normal chromosome examination with no Ph-positive cells detectable on metaphase cytogenetic of bone marrow with 20-25 cells analyzed
Reported as Complete Cytogenetic Response (CCR)[2]	
Complete CR	0% Ph positive cells detectable
Partial CR	1-34% Ph positive cells detectable
Major CR	<35% Ph positive cells detectable
Minor CR	35-65% Ph positive cells detected*
Minimal CR	66-95% Ph positive cells detected
No CR	>95% Ph positive cells detected
Note: Major CR = Complete CR plus Partial CR	*Some authors define Minor CR as 35-95% Ph positive cells[38]
Molecular remission	Negative RT-PCR evidence of the *BCR-ABL* mRNA
Variably reported as Complete Molecular Response (CMR)	
Complete MR	No detectable BCR-ABL mRNA
Major MR	≥ 3 log reduction in detectable BCR-ABL mRNA[33]
Overall survival (OS)	The percentage of CML subjects in a study who

Figure 4: Definition of tumor response criteria relevant to CML

	have survived for a defined period of time. Usually reported as time since diagnosis or treatment.
Time to progression (TTP)	A measure of time after CML is diagnosed (or treated) until it starts to get worse.
Progression-free survival (PFS)	The probability that a CML patient will remain alive, without the disease getting worse.
Disease-free survival (DFS)	Length of time after treatment during which no CML is found. Can be reported for an individual patient or for a study population.
Event-free survival (EFS)	Length of time after treatment that a CML participant in a clinical study remains free of pre-defined events. Events are defined by the study and can include adverse treatment effects, CML relapse/progression, or survival.
Survival rate	The percentage of people in a study or treatment group who are alive for a given period of time after diagnosis. Commonly expressed as 1-year, 2-year, 5-year, and 10-year survival.

Treatment options. Treatment of CML is usually initiated when the diagnosis is established;[14] however, the optimal front-line treatment for chronic-phase CML is controversial. Some argue that the only consistently successful curative treatment of CML for more than half of eligible patients has been allogeneic bone marrow or stem cell transplantation.[Goldman, 2003 #666;] Ideally the patient is transplanted in chronic phase.[16] However, many patients are not eligible for this approach because of age, comorbid conditions, or lack of a suitable donor. Currently, for patients able to undergo transplant the 5-year survival rates are quoted as 50-80 percent for overall survival and 30-70 percent for disease-free survival.[16] In a 2003 phase II study of 131 CML patients in newly diagnosed chronic phase (median age 43 years, range 14-66), 1-year survival was estimated at 91 percent and 3-year survival at 86 percent.[39] The 15-30 percent who are going to relapse do so within the first 5 years. In addition, there is substantial morbidity and

mortality from allogeneic bone marrow or stem cell transplantation; a 15-30 percent treatment-related mortality can be expected.[17] In the 2003 study of 131 transplanted CML patients, 65 percent developed acute graft vs. host disease (GVHD), 7 percent had Grade 3 or 4 GVHD, and 60 percent developed clinically extensive chronic GVHD at 1 year after transplant.[39] The estimated rate of non-relapse-related death was 10 percent (95 percent CI, 5-15 percent) at 1 year and 14 percent (95 percent CI, 7-21 percent) at 3 years. Pulmonary toxicity, infection, and GVHD were the main causes of death.

Prior to the approval of imatinib, the therapy of choice for those patients not eligible for transplant was interferon alfa. Long-term data demonstrate that approximately 10-30 percent of patients treated with interferon alpha have a complete cytogenetic response (CCR) with no evidence of the BCR-ABL translocation by any available test and the majority of these patients are disease-free beyond 10 years.[13] In a single-institution review of 512 early CP patients treated with interferon-based therapies between 1981 and 1995, 27 percent achieved a CCR and those patients who achieved a CCR had a 10-year survival was estimated at 78 percent.[40] In a systematic review and meta-analysis of seven randomized trials comparing interferon with traditional myelosuppressive chemotherapy such as hydroxyurea or busulfan, interferon was more efficacious with statistically better survival ($p<0.00001$ overall).[41] The annual death rate was reduced by 30 percent (standard deviation (SD) 6 percent) with the use of interferon; 5-year survival rates were 57 percent with interferon alpha and 42 percent with chemotherapy (absolute difference 15 percent (SD 3 percent), $p<0.00001$). Doses ranged from 2-9 million units/day. Maintenance of therapy with interferon is required. Some patients experience side effects that preclude continued treatment.

Interferon combined with cytarabine is more efficacious than interferon alone. In a randomized control trial (RCT) of interferon-alpha 2b (5 million units/m^2/day) with hydroxyurea (50 mg/kg/day) induction, interferon plus cytarabine (monthly 10-day courses of 20 mg/m2/day) with hydroxyurea induction, or hydroxyurea induction alone involving 810 participants with newly diagnosed CP CML, interferon plus cytarabine was superior with 41 percent achieving Major cytogenetic response (CR) vs. 24 percent for interferon alone ($p=0.001$).[42] The estimated 3-year survival was 86 percent for interferon plus cytarabine and 79 percent for interferon alone ($p=0.02$). Cytarabine was discontinued for evidence of CCR on two occasions; interferon was continued indefinitely unless intolerable. Major side effects leading to discontinuation of interferon plus cytarabine therapy and affecting $\geq$15 percent of participants included weight loss/asthenia (48 percent), nausea/vomiting/diarrhea (45 percent), hematologic toxicity other than low platelets (31 percent), mucositis (21 percent), low platelets (20 percent), rash (19 percent) and depression (15 percent). Major side effects leading to discontinuation of interferon therapy and affecting $\geq$15 percent of participants included weight loss/asthenia (20 percent), nausea/vomiting/ diarrhea (14 percent), and depression (21 percent). Overall, 26 percent of interferon plus cytarabine and 27 percent of interferon only participants discontinued therapy due to adverse effects.

Myelosuppressive therapy has also been a mainstay of treatment with the goal to convert a patient with CML from an uncontrolled phase to one with hematologic remission and normalization of the physical examination and laboratory findings.[16] Hydroxyurea, an inhibitor of deoxynucleotide synthesis, is the most common agent used. Most patients achieve hematologic remission within 1-2 months however the duration is limited and rarely is a

cytogenetic or molecular remission obtained. Other agents include busulfan, an alkylating agent. In a RCT comparing hydroxyurea to busulfan for chronic phase CML, the median survival was 45.4 months for busulfan and 58.2 months for hydroxyurea (p=0.008).[43] Less than 3 percent of patients across the study had a cytogenetic response. Side effects were predominantly described for busulfan, consisting of pulmonary fibrosis and prolonged marrow suppression lasting for months. Adverse events were virtually unseen with hydroxyurea.

Since tyrosine kinase activity is required for the transforming function of the BCR-ABL fusion protein, a specific inhibitor of the kinase could be an effective treatment for patients with CML.[13] Imatinib mesylate is a compound that inhibits the BCR-ABL protein. Imatinib has been shown to have activity in all phases of CML, including interferon-refractory CML and CML which has recurred after a stem cell transplant. The efficacy and tolerability profile of imatinib for CML is the major focus of this review. However, no long-term data exist as yet in regard to the durability of response, and there only emerging data about the efficacy of salvage strategies using interferon alfa or allogeneic stem cell transplantation after disease progression on imatinib. New agents for imatinib-refractory CML are in development or being tested.

Considerations when evaluating treatment efficacy. Differences in characteristics at presentation and response to therapy may depend on the particular population under investigation and referral patterns, as CML patients referred for clinical trials and to tertiary care centers tend to be younger and more commonly in good-risk categories.[16] Other challenges to interpreting this literature include the following:

- Participant population characteristics;
- Well established prognostic factors exist that may be variably represented in the participant population;
- Stage migration;
- Moving baseline for survival;
- Contribution from supportive care;
- Ph only detected in 90-95% of CMLs and Ph-negative CML may not be CML at all;
- Not all Ph positive diseases are CML; and,
- RT-PCR is best test for detection but is not entirely sensitive and may be abnormal in healthy individuals.

Prognosis and Prognostic Factors

Prognosis. Exact figures for median survival are difficult to determine. Historically, median survival for CML was 3 years from the time of diagnosis with less than 20 percent of patients alive at 5 years.[16, 29] Most current documents quote median survival of untreated CML as 4-6 years, with initial improvements due to earlier diagnosis, better supportive care, and improved anti-CML therapy.[29] In the pre-imatinib era of 1993, median survival was 5-6 years; 75-85 percent were alive at 3 years, 50-60 percent at 5 years, and more than 30 percent alive at 10 years.[29]

Historically, chronic phase patients with HLA-identical sibling donors can expect approximately 50 percent chance of cure with an allogeneic stem cell transplant.

The MD Anderson single-institution experience prior to imatinib was reported by Kantarjian et al. in 2004.[44] Among a historical cohort of 204 patients with early chronic-phase CML (i.e., diagnosed within 12 months) treated at their institution from 1982 to 1992 with interferon-based therapies, 37 (18 percent) had undergone allogeneic transplant as first line therapy, 27 (13 percent) homoharringtonine-based therapy, 86 (42 percent) hydroxyurea and/or busulfan, 24 (12 percent) cytarabine-based regimens, and 30 (15 percent) on other regimens. Among the 37 patients who underwent allogeneic transplant as initial treatment, the estimated 5-year survival was approximately 55 percent and 10-year survival was 42 percent. Sixty additional patients underwent allogeneic transplant after failure of a previous treatment, and 17 percent were still alive after a median followup of 109+ months after the transplant. Among the patients who received homoharringtonine-based therapy as initial treatment, the estimated 5-year survival was approximately 40 percent and 10-year survival was approximately 32 percent. Among the patients who received some other therapy as initial treatment, the estimated 5-year survival was approximately 22 percent and 10-year survival was approximately 20 percent.

Clinical prognostic factors. Certain patient and disease factors denote poorer survival; these include:

- Increased spleen size (splenomegaly);
- Older age;
- Male gender;
- Elevated serum lactate dehydrogenase (LDH);
- Cytogenetic abnormalities in addition to the Ph;
- A higher proportion of marrow or peripheral blood blasts (higher phase/stage);
- Elevated basophil count;
- Elevated eosinophil count;
- Elevated platelet count; and,
- Anemia (low hemoglobin).

These prognostic factors have been variably combined in several different scoring systems. The most commonly reported of these is the Sokal score, as originally described by Sokal and colleagues in the 1980s.[30, 45] The Sokal score was developed in the pre-interferon chemotherapy era, and may be less useful in the current era.[45] The Hasford score[46] was developed later and is better validated, especially for patients receiving interferon or bone marrow transplant.[47]

Cytogenetic response is an independent prognostic factor for improved survival, and has been the therapeutic goal of many trials.[16] An understanding of the relationship between molecular response and survival is developing, but in general molecular response–and specifically early molecular response–correlates with survival.[48]

Molecular prognostic factors. There are a number of variations of Ph and the tyrosine kinase fusion protein that still lead to CML, most notably variant genetic rearrangements and variant protein products (Figure 1). First, in up to 10 percent of cases, the BCR-ABL is produced by variant genetic rearrangements whereby DNA from other regions in the genome is contributing to the BCR-ABL product.[49] Despite their genetically complex nature, historically these variant rearrangements have not conferred any specific phenotypic or prognostic impact as compared to CML with a standard Ph chromosome, except perhaps abnormalities involving chromosome 17. These variant rearrangements accumulate with time, a process called "cytogenetic evolution" (sometimes called "karyotypic evolution" or "complex cytogenetics"). In most instances, standard Ph is the sole chromosomal anomaly during chronic phase, whereas additional genetic changes are demonstrable in 60-80 percent of cases in blastic phase/blast crisis. Example secondary chromosomal changes include +8, +Ph, i(17q), +19, -Y, +21, +17, and monosomy 7. Molecular genetic abnormalities preceding or occurring during blastic phase/blast crisis include overexpression of the BCR-ABL transcript, upregulation of the EVI1 gene, increased telomerase activity, and mutations of the tumor suppressor genes RB1, TP53, and CDKN2A. The cytogenetic evolution patterns vary significantly in relation to treatment given during chronic phase. Overall, the data on genetic rearrangements suggest that a variety of molecular mechanisms rather than a single genetic defect drives the progression from chronic to blastic phases.[13]

Second, 10-15 percent of CML patients have deletions of the resultant DNA on chromosome 9.[50] Essentially the residual chromosome 9 that is left over after formation of Ph on chromosome 22 is also susceptible to variations, predominantly through how much DNA is deleted. These residual chromosome 9 deletions are also influential in CML's aggressiveness. Such deletions negatively affect prognosis, decreasing survival by up to 20 percent at 5 years.[50-54]

Third, there are different versions of the resultant fusion protein. Depending on the site of the breakpoint in the BCR gene, the fusion protein can vary in size from 185 - 230 kiloDalton; each fusion gene encodes the same portion of the ABL gene but differs in the length of BCR sequence. The most common in adult CML is a 210-kiloDalton protein called $p210^{BCR\text{-}ABL}$.[16] The mRNAs for this protein are designated e13a2 (formerly b2a2) and e14a2 (formerly b3a2), and the specific mRNA does not appear to have prognostic significance.[13]

Fourth, there can be genetic mutations and problems with production of the BCR-ABL protein that lead to specific protein abnormalities. These are of particular interest for this discussion as they can produce resistance to targeted drugs like imatinib. In particular, aberrations that lead to changes in the ATP binding loop ("P loop") of the protein and the imatinib binding pocket are being studied.[55]

The Technology

The BCR-ABL tyrosine kinase protein is a cytoplasmic protein.[13] In the normal state, ABL, sends a signal inside the cell telling it to grow only as needed. ABL is protective against toxic stress such as DNA damage. When Ph forms, the mutant BCR-ABL gene is continuously being transcribed into mRNA and subsequently the abnormal BCR-ABL protein. The mutant BCR-ABL promotes continuous cell division, even in the face of toxic stress. This constant signal tells the cancerous cells to keep growing and leads to the malignant state.

Imatinib (STI-571, trade name Gleevec™ (U.S.) or Glivec™ (non-U.S.)) is a derivative of 2-phenylaminopyrimidine. Imatinib is a competitive tyrosine kinase inhibitor that targets several different tumor proteins, including the one that causes >95 percent of cases of CML which is encoded in the BCR-ABL gene. Imatinib works by blocking, or turning off, the signal from the BCR-ABL protein, so the cancerous cells stop growing.

Imatinib is available as an oral medication and is usually taken once a day at a recommended dose of either 400 mg/day or 600 mg/day. Imatinib should be administered with a meal and a large glass of water. Doses over 600 mg/day should be administered in divided doses, e.g., 400 mg twice daily. Tablets are available in 100 mg and 400 mg forms. Treatment can be continued as long as there is no evidence of disease progression or unacceptable toxicity.

Imatinib was originally approved for patients with newly diagnosed advanced CML and interferon-refractory CP CML by the Food and Drug Administration (FDA) in May 2001 under the accelerated approval program.[56] It was the first FDA-approved drug to target an intracellular signaling molecule for cancer therapy. Subsequently it was approved for first-line and relapsed settings of all phases of CML on December 20, 2002.

Scope and Key Questions

The key questions for this review were developed with experts in the field of oncology, health economics, and health policy. The key questions are as follows:

4. In patients with chronic myeloid leukemia, what is the effect of imatinib compared to interferon alpha or best supportive care on overall survival, disease free survival, remission rates (PR, CHR, cytogenetic remission), and quality of life (QOL)?

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5. In patients with chronic myeloid leukemia, what is the effect of imatinib compared to interferon alpha or best supportive care on adverse effects, tolerability, and compliance with treatment?

6. What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy? In addressing this question, we will focus on the following: (1) predictive patient or tumor characteristics that are related to the mechanism of action of the drug (i.e., molecular target; performance status, while a powerful predictor of outcome, is not related to mechanism of action); (2) candidates for diagnostic testing (even if not commercially or clinically available currently (e.g., PCR)); and, (3) patient or tumor characteristics that are associated with clinically important differences in treatment response.

Methods

Search Strategy

The search strategy was constructed by combining three concepts: (1) the intervention imatinib; (2) the disease chronic myeloid leukemia; and (3) prospective clinical trials. To identify the intervention concept, since these new drugs lack a specific term in the MeSH lexicon, we used text word searching for the following text strings: *imatinib* or *gleevec* or *glivec* or *STI571*. The disease concept was implemented using the MeSH headings *Leukemia, Chronic, Myeloid* and *Leukemia, Chronic, Philadelphia-Positive* as well as text word searching for *CML* or adjacent text strings for *chronic* within two words of *myeol$* adjacent to (*leukemia$* or *leukaemia*). This is designed to detect various spellings such as *chronic myelogenous leukemia* or *chronic myeloid leukemia* or *chronic myeloid leukaemia*, etc. A published strategy, validated for finding randomized controlled trials (RCTs), was used to identify prospective clinical trials.[57] This strategy is designed to find all prospective clinical trials (maximize sensitivity), rather than to eliminate non-randomized trials (maximize specificity), and so is appropriate for this study's goal of finding phase II and III prospective clinical trials. Finally, the three concepts were combined (Boolean "or"). The strategy was executed in MEDLINE (1966 through September 2004, updated July 2005) and limited to articles published in the English language. The exact text of the OVID MEDLINE versions of the search strategy is provided in Appendix A.

Supplemental searches were conducted in International Pharmaceutical Abstracts, *The Cochrane Library* (Central Register of Controlled Trials [CENTRAL] and Health Technology Assessment [HTA] database), American Society of Hematology 2004 annual meeting abstracts database, the American Society of Clinical Oncology 2004 and 2005 annual meeting abstracts databases. References lists of identified studies and relevant systematic reviews and meta-analyses were hand-checked. Additional articles not indexed in the major bibliographies by July 2005 were identified through ongoing searches and discussions with field experts and monitoring new sources.

Comment [dcm1]: And 2005?

Selection Criteria

Each citation identified from the search strategies was evaluated according to the following selection criteria. Evaluations were performed by the authors.

Inclusion criteria were as follows:

Patients	Patients with CML–any phase
Interventions	Imatinib (Gleevec™ or Glivec™ or [STI571])
Comparators	Any

Study designs:

- *For **efficacy** questions*: Prospective clinical trials; may be phase II uncontrolled, or phase III randomized controlled trials.

- *For studies of **adverse effects:*** May be retrospective or prospective case series, cohort studies, or clinical trials provided the number of patients treated (at risk for adverse effects) as well as the number with adverse effects can be ascertained.

- *For studies of **predictors** of response:* May be retrospective or prospective case series, cohort studies, case-control studies, or clinical trials provided the response can be ascertained for patients with and without the predictor.

Outcomes:

- *For **efficacy** questions*: Survival, disease-free survival, tumor response, and quality of life (QOL). Tumor response was defined according to Figure 4.

- *For studies of **adverse effects:*** Adverse effects, tolerability, and compliance with treatment.

- *For studies of **predictors** of response:* Predictive value of patient or tumor characteristics that are associated with clinically important differences in treatment response that are:
  1) related to the mechanism of action of the drug (i.e., molecular target); and
  2) candidates for diagnostic testing (even if not commercially or clinically available currently [e.g., RT-PCR]).

Data Abstraction

The following data were abstracted from included studies: study design, population characteristics (including sex, age, and diagnosis), eligibility and exclusion criteria, interventions (dose and duration), outcomes assessed and results for each outcome.

We developed data collection forms in Excel (Microsoft; Redmond, WA) and summarized the data in evidence tables. Predictors of disease response to imatinib were usually presented as results from univariate or mulitvariate stastitics. When multivariate results were available these were presented, delineated by the presentation of an odd ratio (OR), relative risk (RR) or hazard ratio (HR). Otherwise results reflect univariate analyses.

Quality Assessment

We assessed the quality of included studies by evaluating elements of internal validity (e.g., randomization and allocation concealment; similarity of compared groups at baseline; specification of eligibility criteria; blinding of assessors, care providers, and patients) and external validity (e.g., description of the patient population, similarity to the target population of the report, use of highly selective criteria). Importantly, quality assessment reflected the quality of reporting of the study in a clinical research context (internal and external validity); quality of the the basic science research or its reporting were not assessed as they were outside of the scope of this review.

We used as a framework the quality assessment criteria from the National Institute for Clinical Excellence (NICE).[58] These are displayed in Appendix B. They provide specific criteria for the range of study designs used in this report including experimental studies, cohort studies, case-control studies, and case series.

Point scores were allocated by assigning one point for each quality category. There were a total of six possible categories. Quality ratings of "yes" to a quality criteria were assigned one point; no and unknown were both assigned zero points. The last category, adequate description of subseries, was not applicable to all studies. Hence, the total possible quality points were five or six depending upon the applicability of the subseries category. We defined high quality studies as those with $\geq 3/5$ or 4/6 points. Abstract quality was not scored.

Data Synthesis

In addition to the data abstraction and quality analysis, a narrative description of study findings was prepared. Further quantitative analyses were considered, but the available data were not adequate to support these.

Results

The search strategy yielded 418 articles. The selection process is described below:

Identified by search strategy
(N=417)
|------ Excluded based on review of abstract
| (N=162)
|
Included based on review of abstract
(N=255)
|
|------ Unable to locate
| (N=8)
|------ Excluded based on full-text review
| (N=89)
| 23 not phase II–III for efficacy
| 11 case series not selected on response
| 2 case series selected on adverse events
| 25 no quantification of association
| 5 wrong drug
| 9 wrong outcomes
| 2 wrong disease
| 5 review articles
| 3 no data reported
| 4 abstracts superseded by published article
|
Included in full-text review and evidence tables
(N=158)

The 158 included reports comprised 69 full reports and abstract-only publications cited in Tables 1a–1d, as well as 36 full reports cited in the text of this report. Study designs included one published phase III controlled clinical trial with five sub-studies. The exact number of unique phase II uncontrolled clinical trials is difficult to establish, as many authors presented data from the same groups of subjects in multiple reports. By best assessment there are approximately 30 individual phase II trials presented here. All of the adverse events data were derived from the phase II and III clinical trials that were published in full reports, with the exception of four additional individual adverse event reports (two full-text articles and two abstracts).

Quality of the studies varied by outcome category (Tables 1a-1d, and Appendix B). The main imatinib efficacy studies published in full were of high quality. Quality, in general, was lower for predictor studies, consistent with these more commonly being written as basic science reports with minor clinical correlations. The other group of lower quality reports was emerging reports, especially those evaluating imatinib after stem cell transplant and in the heavily treated setting.

Table 1a. Details of included studies–Part 1 Imatinib efficacy studies

Study #	First Author, Year	Trial Phase	Imatinib dose per day (mg)	Comparator	Quality	Comments
Chronic phase–newly diagnosed						
1	O'Brien, Guilhot, et al,, 2003 [59]	III	400	IFN + Ara-C	5/5	Main results from the IRIS phase III trial
1	Branford, 2003[33]				5/6	IRIS sub-study–molecular responses
1	Hughes, 2003[11]				6/6	IRIS sub-study–molecular responses
1	Hahn, 2003[60, 61]				5/5	IRIS sub-study–QOL (on a separate efficacy–QOL table)
1	*Guilhot, 2004[62]				*	Follow up data
1	*Branford, 2004[32]				*	Follow up data
2	Karntarjian, Cortes, et al., 2003[63]	II	400	Historical controls	6/6	Main results of phase II trial
3	Karntarjian, Talpaz, et al., 2004[12]	II	800	Historical controls	5/5	Main results of phase II trial
2&3	Kantarjian, O'Brien, 2004[44]	II	400-800	Historical controls	3/6	Includes patients from another both studies above
2&3	*Cortes, Talpaz, OBrien, Giles, et al., 2004[64]	II	400-800		*	Compares 400 & 800 mg doses
4	*Hughes, 2004[65]	II	600-800	Compared to IRIS experience	*	
Chronic phase–interferon resistant or refractory						
5	Druker, Talpaz, et al., 2001[66]	I/II	25-1000		4/5	Main results of initial STI571 phase I/II
5	Braziel, 2002[67]				3/6	Druker sub-study - response predictors
6	Kantarjian, Sawyers, 2002[2]	II	400-800		6/6	Main results of phase II trial
6	Marin, Marktel, Szydlo, et al., 2003[68]			Historical controls	5/5	Survival follow up
7	Cortes, Giles, et al, 2003[69]	II	800		3/5	
6&8	Karntarjian, Talpaz, et al., 2002[70]	II	400-800		5/5	Some patients from the phase II trial plus expanded access
6,8,&9	Karntarjian, Talpaz, et al., 2003[71]	II	400-800		3/6	Some patients from the phase II trial plus expanded access–evaluation of higher dose I for pts resistant to 400 mg
6,8,&9	Kantarjian, O'Brien, 2004[44]	II	400-800	Historical controls	5/6	Includes patients presented in two studies
6&8	Karntarjian, Cortes, et al., 2004[72]	II	400-800	Historical controls	5/6	Includes patients presented in two studies; survival follow up
10	Le Coutre, 2003[73]	II	400		4/5	Part of expanded access program population
11	Marin, Goldman, et al., 2003[74]	II	600-1000		1/5	Evaluation of higher dose I for pts resistant to 400 mg
12	Marin, Marktel, Bua, et al., 2003[75]	II	200-800		2/5	
13	Rosti, 2004[8]	II	400		4/5	
14	*Pasquini, 2004[76]	Unclear	400-600		*	QOL on I (see QOL table)

Chronic phase –previous stem cell transplant/heavily pretreated						
15	Cervantes, 2003[37]	II	400	Prior auto SCT vs. IFN resistant/ intolerant	3/6	Autologous SCT
16	Fischer, 2002[77]	II	400		1/6	Autologous SCT
17	Kantarjian, O'Brien, et al., 2002[78]	II	400-1000		3/6	Allogeneic SCT
18	O'Brien, Giles, et al., 2003[79]	II	Not stated		3/5	Prior IFN, Ara C, and homoharringtonine +/- allogeneic SCT
19	*Hess, 2004[80]	II	400		*	Allogeneic SCT
20	*Corsetti, 2004[81]	II	400-400		*	Autologous SCT
Mixed phases						
FDA Approval	Cohen, 2002[82]	I II	25-1000 400-600		5/6	FDA Approval summary
21	*Silver, 2004[83]	II	400-600		*	4 yr follow up on three studies
22	Olavarria, 2003[84]	II	400-600		4/6	All relapsed after allogeneic SCT; all phases
23	Lahaye, 2005[85]	II	400-600		5/6	4.5 yr follow up
24	*Deshmukh, 2004[86]	II	Not stated		*	All phases, conducted in India
Accelerated phase						
25	Talpaz, 2002[87]	II	400-800		5/6	
25	* Cortes, Talpaz, OBrien, Gracia-Manero, et al., 2004[88]				*	Followup abstract
Blastic phase/blast crisis						
26	Druker, Sawyers, et al., 2001[89]	I/II	300-1000		5/6	
27	Kantarjian, Cortes, 2002[90]	I/II	300-1000		5/6	
28	Sawyers, 2002[3]	II	400-800		5/6	
29	Sureda, 2003[4]	II	600		4/5	
Imatinib efficacy/other						
30	Gardembas, 2003[38]	II	400 (w/ Ara-C SQ 20 mg/m^2/d on d15-28)		5/5	Combination=safe
31	Baccarani, 2004[91]	II	400 (w/ Peg-IFN at 50-150 mcg/wk)		4/5	Combination=safe

*Presented as peer-reviewed abstract only.
Abbreviations: Ara-C=cytarabine; I=imatinib; IFN=interferon; pts=patients; QOL=quality of life; Retro=retrospective; SCT=stem cell transplant

Table 1b. Details of included studies–Part 2 Studies with additional adverse event/harm data not already presented in the efficacy studies

First Author, Year	Trial Phase	Imatinib dose per day (mg)	Quality	Comments
Adverse events/harm only data presented				
Drummond, 2003[92]		CP=400 AP= 600 BC=600	2/5	Skin rash
Steegman, 2003[93]	II	100-400	4/5	Hypogammaglobulinemaia
Valeyrie, 2003[94]	II	100–800	3/5	Cutaneous reactions
*Al-Ali, 2004[95]	II	Not stated	*	Creatinine kinase levels

*Presented as peer-reviewed abstract only.

Table 1c. Details of included studies–Part 3 Studies with information about molecular predictors

First Author, Year	Trial Phase	Imatinib dose per day (mg)	Comparator	Quality	Comments
Molecular predictors: Group 1A—DNA factors at the start of imatinib therapy					
Cortes, Talpaz, et al., 2003[1]	II	400-600		6/6	% Ph+ metaphases @ start of therapy
Kantarjian, Sawyers, et al., 2002[2]	II	400		6/6	% Ph+ metaphases @ start of therapy
Marin, Goldman, et al., 2003[74]	II	600-1000		1/5	% Ph+ metaphases @ start of therapy
Marin, Marktel, Bua, et al., 2003[75]	II	200-800		2/5	% Ph+ metaphases @ start of therapy
O'Dwyer, 2004[96]	II	>300		2/5	% Ph+ metaphases @ start of therapy
Braziel, 2002[67]		300-600		3/6	Complex cytogenetics
Kantarjian, Cortes, 2002[90]	I/II	300-1000		5/6	Complex cytogenetics
Sawyers, 2002[3]	II	400-800		5/6	Complex cytogenetics
Sureda, 2003[4]	II	600		4/5	Complex cytogenetics
Talpaz, 2002[87]	II	400-800		5/6	Complex cytogenetics
Cortes, Talpaz, et al., 2003[1]	II	400-600		6/6	Cytogenetic clonal evolution
El-Zimaity, 2004[97]	Retro	Unclear		3/6	Cytogenetic clonal evolution
Kantarjian, Sawyers, et al., 2002[2]	II	400		6/6	Cytogenetic clonal evolution
Karntarjian, Talpaz, et al., 2002[70]	II	400-800		5/5	Cytogenetic clonal evolution
Kantarjian, O'Brien, et al., 2004[44]	II	400-800	Historical controls	5/6	Cytogenetic clonal evolution
Kantarjian, O'Brien, et al., 2003[98]	II	400-800	Historical controls	3/6	Cytogenetic clonal evolution
Karntarjian, Cortes, et al., 2004[72]	II	400-800	Historical controls	5/6	Cytogenetic clonal evolution
Marin, Marktel, Bua, et al., 2003[75]	II	200-800		2/5	Cytogenetic clonal evolution
Marktel, 2003[99]	II	400-800		5/6	Cytogenetic clonal evolution

Table 1c. Details of included studies–Part 3 Studies with information about molecular predictors

First Author, Year	Trial Phase	Imatinib dose per day (mg)	Comparator	Quality	Comments
O'Dwyer, 2004[96]	II	>300		2/5	Cytogenetic clonal evolution
*Marin, 2004[100]	Unclear	400			CD34+ cells in the bone marrow
*Elliott, 2004[101]	Unclear	400		*	CD34+ cells in the bone marrow
El-Zimaity, 2004[97]	Retro	Unclear		3/6	Variant Ph translocations
Huntly, 2003[51]	II	Not stated		2/6	Chromosome 9 deletions
Lange, 2003[102]	Retro	600		4/6	Genes related to apoptosis and drug resistance in leukemia cells
McLean[103]	III	400	IFN+Ara-C	5/6	Genomic microarrays
Molecular predictors: Group 1B—DNA factors monitored during imatinib therapy					
Marin, Marktel, Szydlo, et al., 2003[68]	II	400-800	Historical controls	5/5	Cytogenetic response to imatinib
O'Dwyer, 2004[96]	II	>300		2/5	Cytogenetic response to imatinib
Rosti, 2004[8]	II	400		4/5	Cytogenetic response to imatinib
*Silver, 2004[83]	II	400-600		*	Cytogenetic response to imatinib
Karntarjian, Cortes, et al., 2004[72]	II	400-800	Historical controls	5/6	Cytogenetic response to imatinib
*Guilhot, 2004[62]	III	400	IFN+Ara-C	*	Cytogenetic response to imatinib
Marin, Marktel, Bua, et al., 2003[75]	II	200-800		2/5	Cytogenetic response to imatinib
*Marin, 2004[100]	Unclear	400			Change in CD34+ cells in the bone marrow
Marin, Marktel, Szydlo, et al., 2003[68]	II	400-800	Historical controls	5/5	Cytogenetic response to imatinib
Molecular predictors: Group 2–Production of the RNA message					
Paschka, 2003[10]	II	400-800		4/6	Molecular response as a marker of tumor response
Müller, 2003[104]	III	400	IFN+Ara-C	5/6	Molecular response as a marker of tumor response
Hughes 2003[11]	III	400	IFN+Ara-C	6/6	Molecular response as a marker of tumor response
Merx, 2002[105]	II	400-800		5/5	Molecular response as a marker of tumor response
Rosti, 2004[8]	II	400		4/5	Molecular response as a marker of tumor response
Stentoft, 2001[7]	II	400-600		4/5	Molecular response as a marker of tumor response
Wu, 2002[6]	II	400-600		3/5	Molecular response as a marker of tumor response
*Cortes, Talpaz, OBrien, Giles, et al., 2004[5]	II	Not stated		*	Molecular response as a marker of tumor response
Moravcova, 2004[9]	II	400-600		3/6	Molecular response as a marker of tumor response
Karntarjian, Talpaz, et al., 2004[12]	II	800	Historical controls	5/5	Molecular response as a marker of tumor response
Müller, 2003[104]	III	400	IFN+Ara-C	5/6	Prognostic value of baseline transcript levels
Hochhaus, 2002[55]	II	400-600		5/6	Prognostic value of baseline transcript levels
Wu, 2002[6]	II	400-600		3/5	Prognostic value of baseline transcript levels

Table 1c. Details of included studies–Part 3 Studies with information about molecular predictors

First Author, Year	Trial Phase	Imatinib dose per day (mg)	Comparator	Quality	Comments
Branford, 2003[33]	III	400	IFN+Ara-C	5/6	Prognostic value of transcript trends while on imatinib
Hughes 2003[11]	III	400	IFN+Ara-C	6/6	Prognostic value of transcript trends while on imatinib
Rosti, 2004[8]	II	400		4/5	Prognostic value of transcript trends while on imatinib
Müller, 2003[104]	III	400	IFN+Ara-C	5/6	Prognostic value of transcript trends while on imatinib
*Müller, 2004[106]	III	400		*	Prognostic value of transcript trends while on imatinib
*Branford, 2004[32]	III	400		*	Prognostic value of transcript trends while on imatinib
*Cortes, Talpaz, OBrien, Giles, et al., 2004[5]	II	Not stated		*	Prognostic value of transcript trends while on imatinib
*Press, 2004[107]	II	Not stated		*	Prognostic value of transcript trends while on imatinib
Wang, 2003[48]	II	Not stated		2/5	Prognostic value of transcript trends while on imatinib
Wu, 2002[6]	II	400-600		3/5	Prognostic value of transcript trends while on imatinib
Merx, 2002[105]	II	400-800		5/5	Prognostic value of transcript trends while on imatinib
Molecular predictors: Group 3–Interaction between the tyrosine kinase protein and imatinib					
Hochhaus, 2002[55]	II	400-600		5/6	Mutations in tyrosine kinase domain that may lead to imatinib resistance
Shah, 2002[108]	Retro	Not stated		1/6	Mutations in tyrosine kinase domain that may lead to imatinib resistance
Molecular predictors: Group 4—Other factors					
Frater, 2003[109]	II	400		1/5	Bone marrow cellularity
Sneed, 2003[110]	II	300-400		5/6	Myelosuppression
Bhatia, 2003[27]		NS		2/5	Persistent BCR-ABL in CD34+ after CCR with I
Paschka, 2003[10]	II	400-800		4/6	Evidence of BCR-ABL in CCR
O'Dwyer, 2003[35]	II	Not stated	Matched controls	2/5	Abnormal cytogenetics in Ph cells

*Presented as peer-reviewed abstract only.
Abbreviations: Ara-C = cytarabine; I = imatinib; IFN = interferon; pts = patients; Ph = Philadelphia chromosome; Q-RT-PCR = quantitative reverse transcriptase polymerase chain reaction; QOL = quality of life

Table 1d. Details of included studies–Part 4 Studies included in the "Future Directions" only

First Author, Year	Trial Phase	Imatinib dose per day (mg)	Comparator	Quality	Comments
Additional articles included in Future Directions but not on other tables–Other factors					
Mechanism of action					
Kvasnicka, 2004[111]	Retro	400-600	Patients treated with IFN or hydroxy-urea	2/6	I is associated with reversal of bone marrow angiogenesis–suggesting an anti-angiogenic capacity not seen with IFN
*Soverini, 2004[Soverini, 2004 #858]	II	400		*	ABL mutations may be predictive of poor response
*Jabbour, 2004[112]	Obs	Not stated		*	Mutations in the p-loop and I binding pocket don't correlate with outcome
*Branford, 2004[113]	Unclear	Not stated		*	Frequency of BCR-A*BL* mutations persists even with continued CCR > 24 mos
*Corm, 2004[114]	II	400-600		*	Mutations in the p-loop and I binding pocket lead to poorer prognosis
*Deininger, 2004[115]	Obs	Not stated		*	Kinase domain mutations are correlated with phase of disease and clonal evolution
*Hochhaus, 2004[116]	Obs	Not stated		*	Kinase domain mutations are correlated with disease progression, especially p-loop
Approach to treatment					
Shimoni, 2003[117]	II	400-600		3/5	Use of I to induce remission in Ph+ leukemias prior to allogeneic SCT
*Lange, 2004[118]	II		Molecular response durability between allogeneic SCT and I	*	Responses after allogeneic SCT may be more durable
*Palandri, 2004[119]	Retro	400-600		*	Evidence of response with I in the setting of relapsed CML after allogeneic SCT
*Pautas, 2004[120]	Unclear	Not stated		*	Evidence of response with I in the setting of relapsed CML after allogeneic SCT
*Conneally, 2004[121]	Unclear	300-600		*	Evidence of response with I in the setting of relapsed CML after allogeneic SCT
*Laurence, 2004[122]	Obs	Not stated		*	BC can still occur even with CCR on I
*George, 2004[123]	Retro	Not stated		*	May be differential response to I by race and ethnicity
*Bassi, 2004[124]	II	400		*	I is well tolerated in patients ≥ 65 years
*Martino, 2004[125]	Retro	400-600		*	I well tolerated and efficacious in pts >70years

Table 1d. Details of included studies–Part 4 Studies included in the "Future Directions" only

First Author, Year	Trial Phase	Imatinib dose per day (mg)	Comparator	Quality	Comments
Diagnostic tests					
Soverini, 2004[126]	Retro	400		3/5	Denaturing-HPLC method to screen for ABL point mutations
*Issa, 2004[127]	Obs	Not stated		*	Peripheral blood FISH for Ph+ possible, although inferior to bone marrow samples and RT-PCR
*Thomazy, 2004[128]	Obs	Not stated		*	Plasma samples can be used for Q-RT-PCR monitoring
*Kagami, 2004[129]	Obs	Not stated		*	cDNA microarrays may be a useful strategy to predict response to I
*Vallespi, 2004[130]	Obs	400		*	Further confirmation that BCR-ABL transcript ratios decrease with response to I
*Paschka, 2004[131]	Obs	Not stated		*	Methods of quantitating molecular response
*Albitar, 2005[132]		II	800		*
Upcoming clinical trials					
*Berger, 2004[133]; *Hehlmann, 2005[134]	III	400 (with IFN, AraC, or after IFN)	All 4 arms contain I	*	*Berger, 2004[133]; *Hehlmann, 2005[134]
*Monroy, 2004[135]	III	400 vs 400 mg + AraC	Both arms contain I	*	*Monroy, 2004[135]
*Fruehauf, 2004[136]	I/II	600 with mitoxantrone, etoposide, and AraC		*	*Fruehauf, 2004[136]
*Cornelissen, 2004[137]	I/II	200-800 with Ara-C at 200-1000 mg/ m2/24hs		*	*Cornelissen, 2004[137]
*Rousselot, 2004[138]	I/II	600 mg AraC and daunorubicin		*	*Rousselot, 2004[138]
*Ceglarek, 2004[139]	II	300-800		*	*Ceglarek, 2004[139]
*Cortes, 2005[140]	II	800		*	*Cortes, 2005[140]

Presented as peer-reviewed abstract only.
Abbreviations: AP = accelerated phase; Ara-C = cytarabine; BC = blast crisis; BP = blastic phase; CP = chronic phase; CCR = complete cytogenetic response; HPLC = high performance liquid chromatography; I = imatinib; IFN = interferon; Obs = observational study; pts = patients; Ph = Philadelphia chromosome; Q-RT-PCR = quantitative reverse transcriptase polymerase chain reaction; QOL = quality of life; Retro = retrospective; SCT = stem cell transplant

Efficacy

Evidence of efficacy of imatinib in CML can be best considered in terms of the matrix presented in Figure 5. Discrete studies are available for the first three CP clinical settings with the imatinib resistant setting addressed in the Future Directions section. The AP and BP clinical settings are presented in studies of mixed populations, represented on the respective tables. In addition, Table 7 presents those studies of mixed phases and Table 8 includes studies of imatinib combined with other treatments. Table 9 presents efficacy in terms of quality of life.

Figure 5: The CML therapy matrix

		PHASE		
		Chronic phase	**Accelerated phase**	**Blastic Phase/blast crisis**
EXTENT OF PREVIOUS THERAPY	**Newly diagnosed**	Table 2	Table 5	Table 6
	Interferon resistant or refractory	Table 3	Table 5	Table 6
	Previous stem cell transplant/heavily pretreated	Table 4	Table 5	Table 6
	Imatinib refractory or intolerant	Future Directions	Future Directions	Future Directions

Chronic phase

The most convincing and highest quality data for imatinib in CML is derived from the large phase III trial of imatinib vs. interferon plus cytarabine published in 2003 by O'Brien et al., the International Randomized Study of Interferon versus STI571 (IRIS).[59] Prior to imatinib, interferon plus cytarabine was considered the standard of care for newly diagnosed CP CML when stem cell transplantation was not possible. In the RCT by Guilhot et al., published in 1997, interferon plus cytarabine was superior to interferon alone, with 41 percent achieving Major CR

for the combined intervention vs. 24 percent for interferon alone (p=0.001), and 15 percent vs. 9 percent Complete CR rates.[42] The estimated 3-year overall survival (OS) was 86 percent. The superior intervention from the Guilhot study was then the comparator for the IRIS trial.

In the IRIS phase III trial of imatinib vs. interferon plus cytarabine, imatinib was clearly superior with an 85 percent Major CR rate compared to 22% for interferon plus cytarabine, and Complete CR rates of 74 percent vs. 9 percent. While the OS presented in the original report was not different, PFS at 18 months was significantly better with imatinib (92 percent vs. 74 percent, p<0.0001). In a followup abstract report, the 30-month OS for imatinib was 95 percent (93-97 percent); OS for interferon plus cytarabine was not presented.[62] The efficacy of the interferon plus cytarabine arm was not as good in IRIS as in the original Guilhot study (Major CR rate in IRIS 22 percent, Guilhot et al 41 percent), however the 30-month OS rates with imatinib in IRIS (95 percent) are still substantially higher than the 36-month OS rates with interferon and cytarabine from the Guilhot et al RCT (86 percent).

In addition to clinical response rates, other important treatment-related insights that can be derived from this group of studies includes the molecular impact of imatinib, timing of maximal treatment effect, dosing parameters, and tolerability of stem cell transplantation after imatinib.

Imatinib is a targeted drug that interacts with the BCR-ABL tyrosine kinase protein and ultimately leads to apoptosis and destruction of CML cells. Reduction in CML cells should lead to fewer cells with the Ph and therefore fewer cells producing the BCR-ABL mRNA. Reduction in the number of CML cells with Ph is the "cytogenetic response" described previously. Reduction in the number of cells producing the mRNA transcripts is the "molecular response." Evidence of molecular response has been linked to survival,[6,11] In terms of imatinib efficacy, Hughes et al. demonstrated that among IRIS patients who achieved a Complete CR at 6 months, imatinib led to more molecular responses (42 percent vs. 13 percent, p=0.01). Branford and colleagues demonstrated that 71 percent of IRIS participants obtained a Major MR (defined by this group as $\geq$3 log reduction in BCR-ABL/ABL transcript numbers) by 3 years. The rate of Major MR continued to increase over the first 2 years, and after that did not appear to increase or decrease substantially.[32]

Karntarjian, Cortes, and colleagues provided further insight into the timing of the response to imatinib in one of their phase II trial reports.[63] Complete CR rates for imatinib increased from 34 percent to 60 percent over the period from 3 to 9 months. Meanwhile, the Complete CR rates for a group of historical controls that received interferon alone did not increase substantially after 3 months and, similarly, little increase was noted for interferon plus cytarabine patients after 6 months. A steady increase in the number of Complete CRs over 12 months was noted within studies of imatinib in the CP interferon refractory setting.[8,70,73] Taken together with the molecular response data from IRIS,[32] these data suggest that maximal responses to imatinib take longer than was previously seen with interferon-based regimens and that efficacy analyses need to be clearly presented in the context of duration of exposure to imatinib.

Uncontrolled phase II studies support the conclusion of the IRIS trial and provide additional clinical insight into the appropriate starting dose. Most convincingly, Kantarjian, Talpaz and colleagues treated patients with 800 mg of imatinib, and achieved better Complete CR rates as

compared to historical controls who had received 400 mg of imatinib (90 percent vs. 74 percent).[12] In an ongoing phase II trial by Hughes et al., the 600 mg dose appears to be leading to higher Major CR and Complete CR rates, as compared to a historical control group from the IRIS trial that received 400 mg.[65] Direct comparisons between doses are not currently available.

Finally, possibility of stem cell transplantation after progression on imatinib was evaluated in an abstract presentation by Guilhot et al.[62] Seventy-five IRIS participants went on to stem cell transplantation. There were no differences in survival after transplant between participants who received imatinib (N=30) and those who received interferon with cytarabine (N=45).

Table 2. Summary of efficacy of imatinib for CML–Chronic Phase, Newly diagnosed

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Complete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Chronic phase–newly diagnosed										
Phase III										
O'Brien, Guilhot, et al, 2003 [59]	400 mg (increased to 800mg for no CHR at 3 months or at least a Minor CR at 12 months) [19 mo]	1106 pts I: 553 50 [18-70] 62% M IFN + Ara-C: 553 51 [18-70] 56% M	I = 553 IFN + Ara-C = 553 Crossover from IFN + AraC to I = 318 Crossover from I to IFN + AraC = 11	85.2% 22.1% 55.7% 0%	73.8% 8.5% 39.6% 0%	11.4% 13.6% 16.0% 0%			95.3% 55.5% 82.4% 27.3%	Rate of MCR at 18 mos: I = 97% (CI 84-90%) IFN + AraC = 35% (29-40%) (p<0.001) Rate of CCR at 18 mos: I = 76% (CI 72-80%) IFN + AraC = 15% (10-19%) (p<0.001) PFS at 18 mos: I = 92% IFN+Ara-C= 74% (p<0.001) OS at 18 mos: I = 97% IFN+Ara-C= 96% (p=0.23)

Table 2. Summary of efficacy of imatinib for CML–Chronic Phase, Newly diagnosed

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Complete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Hughes 2003 sub-study[11]	[19 mo] only included pts with CCR	I: 333 51 [18-70] 41% M IFN + Ara-C: 37 50 [21-70] 43% M	 I = 333 6 mo IFN+AraC =37 6 mo		MMR (≥3 log reduction) 42% 13% (p=0.01)					
Branford 2003 sub-study[33]	[30 mo for first line therapy; 17 mo for crossovers]	55 pts - subset of above	I = 26 IFN + Ara-C = 27 Second line I (crossovers) = 24		79% 7.4% 75%					
*Guilhot, 2004 sub-study[62] Abstract only	[30 mo]		 I = 553 12 mo 30 mo		MMR (≥3 log reduction) 40% 90%					Estimated PFS at 30 mo = 88% (85-91%) Estimated OS at 30 mo = 95% (93-97%) 75 went on to SCT–no difference in OS after SCT between I (n=30) or IFN+Ara-C (n=45)

Table 2. Summary of efficacy of imatinib for CML–Chronic Phase, Newly diagnosed

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Complete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
*Branford, 2004 sub-study[32]	[42 mo]	32 pts–subset of above	I = 32	Med BCR-ABL log reduction	MMR (≥3 log reduction)	≥4 log reduction)				
Abstract only			12 mo(n=26) 18 mo(n=26) 24 mo(n=26) 30 mo(n=26) 36 mo(n=25) 42 mo(n=24)	3.0 3.2 3.4 3.6 3.9 4.2	46% 64% 68% 68% 71% 71%	4% 4% 7% 25% 32% 54%	(transcript level doesn't appear to increase much past 24 mo)			

Table 2. Summary of efficacy of imatinib for CML–Chronic Phase, Newly diagnosed

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Complete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Phase I/II										
Karntarjian, Cortes, et al., 2003[63]	400mg [9 mo]	50 pts (early phase CP) 50 historical controls 48 [15-79]; 26% > 60yrs 52%M 35 I pts had received short courses of hydroxyurea (33) or IFN (2; 2 wks) Historical controls = early phase CML-CP treated w/ hydroxyurea or IFN based regimens at single institution–only IFN and IFN+Ara-C historical control shown here	I = 50 3 mo 6 mo 9 mo Historical controls: IFN = 274 3 mo 6 mo 9 mo IFN + Ara-C = 257 3 mo 6 mo 9 mo	 74% 80% 77% 2% 11% 14% 9% 23% 23%	 34% 52% 60% 4% 3% 5% 1% 7% 8%					
Karntarjian, Talpaz, et al., 2004[12]	800 mg [15 mo]	114 pts 50 historical controls 48 [17-84] 61%M Historical controls were 50 pts with similar characteristics treated with Imatinib 400 mg	I = 114 Historical control = 50	95% 92%	90% 74%	5% 18%	1% 6%		98% 98%	At median f/u 15 mo (range, 3-27 mo), 112 pts (98%) on I at 800mg are alive in chronic phase Estimated transformation-free status at 24 mo from KM: I 800 mg = 100% vs. historical controls 90% (p=0.0004)

Table 2. Summary of efficacy of imatinib for CML–Chronic Phase, Newly diagnosed

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Complete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Kantarjian, O'Brien, 2003[98] Includes patients from Karntarjian, Cortes, et al., 2003[63] and Karntarjian, Talpaz, et al., 2004[12]	400-800 mg [19 mo]	I: 187 pts (pts derived from several studies) 26%>60yr Historical controls: 87 pts (pts derived from several studies) 26%>60yr Historical controls = received prior IFN therapy otherwise not well described	I =187 IFN Historical control = 650	92% 50%	81% 32%	11% 18%	3% 26%		97% 82%	Estimated from KM: OS at 2yr for I = 98% and IFN Historical Controls = 88% (p=0.01)
*Cortes, Talpaz, OBrien, Giles, et al., 2004[64] Abstract only	400-800 mg [36 mo for 400 mg group; 19 mo for 800 mg group]	400 mg = 49 pts 800 mg = 181 pts 48 [15-84]	I @ 400 mg = 49 I @ 800 mg = 181		81% 96% p=0.0002					MMR CMR 47% 8% 67% 24% (both p≤0.02)
*Hughes, 2004[65] Abstract only	600-800 mg [12 mo]	103 pts enrolled, data on 80 pts presented in abstract 47 [21-75] Gender not stated	I @ 600 mg = 80 I @ 400 mg = 556 in IRIS	94% 84% p=0.0004	89% 69% P<0.0001					MMR (≥3 log) 40% 47% p N/A

Abbreviations: * = abstract; Ara-C = Cytarabine; CR = cytogenetic response; CCR = complete cytogenetic response; CHR = complete hematological response; CMR = complete molecular response; f/u = followup; I = Imatinib; IFN = Interferon; K-M = Kaplan-Meier; OS = overall survival; M = Male; MMR = major molecular response; N = Number; NR = not reported; OS = Overall Survival; PFS = progression-free survival; pt(s)=patient(s); SCT = Stem cell transplant

Chronic Phase - Interferon resistant or refractory

CML that has been previously treated is expected to be more resistant to the next therapy. Leukemic cells develop genetic or other changes that protect the cell and help them evade subsequent treatments. Hence, imatinib treatment of CML in the interferon resistant or refractory setting should be less efficacious than the newly diagnosed setting. As with most new treatments, imatinib was first tested in the clinical setting of patients who were resistant or refractory to interferon-based therapies, the gold standard treatment at the time (when stem cell transplantation was not possible). This group of studies provides information on imatinib efficacy in the treatment resistant and refractory setting, timing of best imatinib response, duration of response (PFS), survival (OS) and dose response.

Several phase II studies of imatinib for interferon resistant or refractory disease exist (Table 3). In the first major published imatinib clinical trial, Druker and colleagues demonstrated that imatinib had activity in the interferon resistant or refractory setting, documenting Major CRs of up to 50 percent.[66] This was a landmark study, establishing that an oral targeted therapy could have dramatic activity in a disease resistant setting.

Kantarjian, Sawyers and colleagues conducted the largest phase II open-label study.[2] Efficacy estimates from this study of 400 mg daily with a median duration of imatinib treatment of 17.9 months indicated that the Major CR rate for the interferon resistant or refractory group of patients was 60 percent with a Complete CR rate of 41 percent. The imatinib dose was increased to 800 mg when patients had not achieved a CHR by 3 months, a Major CR by 12 months, or relapsed after CHR. These estimates have been pretty consistent across this entire group of studies.[8] Patients treated earlier in their course (early CP, i.e., <1 year since diagnosis) have fared better than those whose disease is in late CP (>1 year since diagnosis), with a 62 percent Complete CR rate for early CP and 41 percent for late.[44] The estimates were slightly higher than reported for interferon resistant or refractory CP in the 2002 FDA approval summary (Major CR 31 percent, Complete CR rate 13 percent).[82]

Reasons for needing to change from interferon-based therapy varied, and included resistance to the medication (failure to achieve the desired response within a defined timeframe), relapse (return of disease after response has been achieved), and intolerance (non-hematologic $\geq$ Grade 3 toxicity). Patients with hematologic or cytogenetic relapse after interferon-based therapy had higher response rates to imatinib than those with resistant disease after 6 months of therapy (cytogenetic relapse after interferon, 76 percent Complete CR with imatinib; cytogenetic resistance to interferon, 31 percent Complete CR with imatinib). Patients who were interferon intolerant had intermediate response rates, however this group was older than the other patient participants (50 percent with age $\geq$60 vs. 40 percent for rest of participants), consistent with the fact that they were not tolerating the side effects of interferon well.

As observed with the newly diagnosed group, cytogenetic responses continued to accrue after up to 12 months of imatinib therapy.[8, 73] Periods after 12 months were not reported. Importantly, though, patients who achieved any CR early (i.e., by 3 months) had substantially longer PFS and OS (OS if achieved Major or Minor CR by 3 months, 95 percent, if not 72 percent, $p<0.0001$).[72] Similarly, an early Major CR that is achieved by 6 months was also associated with longer PFS

and OS (OS if achieved Major CR by 6 months, 95 percent, if not 78 percent, p=0.001). Extending these findings to molecular responses, Rosti et al. report that overall survival is better is a major molecular response is achieved.[8]

Because the interferon resistant or refractory is the oldest group of longitudinal studies of imatinib in CML, the longest survival followup data are available for this group of patients. Duration of response and survival are reflected in the 4-year follow up study by Kantarjian, Cortes, and colleagues.[72] Among their full cohort of 261 patients they described a 4-year OS rate of 86 percent and PFS of 80 percent. They compared these PFS rates to a matched cohort of historical controls under treatment at their institution from 1982 to 1997. The historical cohort had a 4-year PFS of 43 percent (compared to the imatinib cohort $p<0.0001$).

Appropriate dosing continues to be a question. Phase I dose ranging studies with phase II outcomes correlates demonstrated that doses in the 500 mg range were most efficacious.[66] Some patients resistant to lower doses of imatinib achieved a response when the dose was increased to 800 mg .[71, 74] As expected, response rates were lower (Complete CR 5-19 percent) and less durable (43 percent with loss of response by 416 days). Similarly, increasing the dose could overcome relapses, such that patients who relapsed at 400 mg imatinib could still achieve a cytogenetic response when the dose was increased to 800 mg (18 percent Complete CR).[71] Finally, Cortes et al. reported 89 percent Complete CR rates when the initial imatinib dose was 800 mg, although only 33 participants were involved in this study.[69]

One challenge for this group of studies is that there are several publications presenting data from different combination of the same group of patients.[2, 70-72] These patients were recruited through several phase II industry-sponsored trials (Novartis 110, 112, 113) and the various publications represent different clinical questions, analyses, comparison groups, and followup periods. There is a risk of misinterpreting these as multiple independent datasets corroborating the efficacy estimate.

Table 3. Summary of efficacy of imatinib for CML –Chronic phase, interferon resistant or refractory

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Chronic phase–interferon resistant or refractory										
Phase I/II										
Druker, Talpaz, et al., 2001[66]	25-1000 mg/d [8.5 mo (1 wk to 8.5 yr)]	83 pts 55 [19-76] 66% M	I = 83 I Dose: < 50 mg= 6 85 = 4 140 =3 200-250=16 300-1000=54 Higher dose ranging: 330-350mg 400 500 600 750 800 1000 Total N = 54	 38% 50% 17% 50% 33% 12% 14% 31%				 15% 33% 17% 50% 0% 25% 1% 22%		77% 0% 25% 33% 56% 99%	Median time to best cytogenetic response = 147 days
Braziel, 2002 sub-study[67]	300-600 mg [mean 3.5 yr; range 1.1-9.1 yr.]	19 pts 57[19-70] 47% M	I = 19	64%	32%	32%			95%	All pts with CCR were still cytogenetically negative at 14 mo; 5/6 also with CMR

Table 3. Summary of efficacy of imatinib for CML –Chronic phase, interferon resistant or refractory

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Kantarjian, Sawyers, et al., 2002[2]	400 mg (increased to 800 mg for no CHR at 3 months, no MCR at 12 months, or relapse after CHR) [med duration of treatment with I = 17.9 mo (0.5-20.3)]	532 pts 57 yrs. [18-81] 60% M 454 of these were confirmed chonic phase patients	I = 454 *IFN/ hematologic failure:* Resistance = 63 Relapse = 70 *IFN/ cytogenetic failure:* Resistance = 119 Relapse= 41 IFN intolerant = 161	60% 41% 57% 55% 83% 66%	41% 25% 41% 31% 76% 47%	19% 16% 16% 24% 7% 19%	5% 8% 1% 8% 2% 2%	11% 16% 16% 9% 2% 11%	95% 89% 99% 97% 98% 93%	Median 18 mo PFS = 89% (95% CI, 86 to 92%) Median 18 mo OS = 95% Median time to cytogenetic relapse 12 mo (range 6-19) and 6 mo (range 3-14) from time of MCR If dose increase necessary, CHR in 9% and CR in 11%
Marin, Marktel, Szydlo, et al., 2003 sub-study [68]		Subset of 143 pts >60yr = 24% 54%M Historical controls = 246 CML CP pts from the Medical Research Council CML 3 trial of IFN vs busulfan or hydroxyurea who didn't respond to IFN	I = 143 Historical control = 246	55%	34%	19%	4%			Treatment with I: RR for mortality 0.54 (CI 0.31-0.93, p=0.026) RR for PFS 0.40 (CI 0.20-0.77, p=0.0065)

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Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Cortes, Giles, et al, 2003[69]	800 mg [15 mo]	33 pts 47 [30-75] 22% >60 yr 42% M	I = 33	90% 97% durable	89%					All alive at 16 mo median f/u, except two that stopped therapy (1 = arthritis; 1= noncompliant)
Karntarjian, Talpaz, et al., 2002[70] Includes some patients presented in Kantarjian, Sawyers, et al., 2002[2]	400 mg (increased to 800mg for no CHR at 3 months, no MCR at 12 months, or relapse after CHR) [17 mo (1-21)]	249 pts 34% >60 yrs 57%M	I = 249 3 mo 6 mo 12 mo	62% 44% 47% 57%	45% 25% 28% 38%					18 mo PFS = 93% 18 mo OS = 96% Any cytogenetic response at 3 months: Yes–PFS at 18 mo = 100% No–PFS at 18 mo = 85% (p<0.001) Yes–OS at 18 mo = 100% No–OS at 18 mo = 95% (p<0.001)

Table 3. Summary of efficacy of imatinib for CML –Chronic phase, interferon resistant or refractory

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Karntarjian, Talpaz, et al., 2003[71] Includes patients from Kantarjian, Sawyers, et al., 2002[2] and Karntarjian, Talpaz, et al., 2002[70]	400-800 mg Planned dose escalation from 400 mg to 800 mg, or to 600 mg daily if the dose had been reduced to 300 mg daily if no CHR at 3 mo, no MCR at 12 mo, heme relapse, or cytogenetic relapse, defined as an increase of Ph+ cells by at least 30% [Median duration of I = 13mo]	54pts 58 [24-77] 43% >60 yrs 57%M	I = 54 High dose I for no response to 400mg N=20 High dose I for cytogenetic relapse N=34	43% 5% 38%	18%	20%			65%	

Table 3. Summary of efficacy of imatinib for CML –Chronic phase, interferon resistant or refractory

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Kantarjian, O'Brien, 2004[44] Includes patients from Kantarjian, Sawyers, et al.,.2002[2], Karntarjian, Talpaz, et al., 2002[70] and Karntarjian, Talpaz, et al., 2003[71]	400 mg (increased to 800 mg for no CHR at 3 months, no MCR at 12 months, or relapse after CHR) [34 mo for I; 109 mo for historical control]	Early CP: I = 261 pts 34% > age 60; Historical control = 204 pts 19% > age 60 Late CP: I = 147 pts 39% > age 60; Historical control = 95 pts 9% > age 60 Historical controls = CML-CP treated w/ IFN based regimens from 1982-1997 whose disease progressed and were treated with some other subsequent therapy	Early CP I = 261 Historical control = 204 Late CP I = 147 Historical control = 95	73% 24% 59% 11%	62% 19 % (p<0.001) 41% 7 % (p<0.001)	11% 5% 18% 4%	10% 13%		97% 53% 95% 58%	Estimated 2 yr OS from KM I (early CP)= 95% Historical control = 70%

Table 3. Summary of efficacy of imatinib for CML –Chronic phase, interferon resistant or refractory

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Karntarjian, Cortes, et al., 2004[72] Includes patients from Kantarjian, Sawyers, et al., 2002[2], Karntarjian, Talpaz, et al., 2002[70] and Karntarjian, Talpaz, et al., 2003[71]	400 mg (increased to 800 mg for no CHR at 3 months, no MCR at 12 months, or relapse after CHR) [45 mo for I; 109 mo for historical control]	I = 261 pts 34% > age 60 Historical control = 251 pts 17% > age 60 Historical controls = CML-CP treated w/ IFN based regimens from 1982-1997 whose disease progressed and were treated with some other subsequent therapy	I=261 Historical control = 251	73%	63%	10%	5%	Major MR 43%	Complete MR 26%	Estimated K-M: For imatinib: 4-yr OS = 86% 4-yr PFS = 80% Major or Minor CR at 3 mo: Yes - 4-yr PFS = 93% 4-yr OS = 95% No - 4-yr PFS = 55% 4-yr OS = 72% (p for both analyses ≤0.001) Major CR at 6 mo: Yes - 4-yr PFS = 93% 4-yr OS = 95% No - 4-yr PFS = 65% 4-yr OS = 78% (p for both analyses ≤0.001) For historical control: 4-yr PFS = 43%
Le Coutre, 2003[73]	400 mg [9mo]	39 pts 56 [23-80]	I = 39 3 mo (N=33) 6 mo (N=27) 9 mo (N=13) 12 mo (N=3)	 21% 33% 62% 67%	 6% 30% 62% 33%	 15% 3% 0% 33%				

Table 3. Summary of efficacy of imatinib for CML –Chronic phase, interferon resistant or refractory

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Marin, Goldman, et al., 2003[74]	600-1000 mg [416 days (212-790)]	36 pts (27 IFN refractory and 9 newly diagnosed)–all treated with higher dose I for failure to achieve CCR on I 400mg age/gender not stated	I = 36	39%	19%	20%				Cytogenetic response short-lasting–43% with loss of response at med f/u (timeframe not clearly stated)
Marin, Marktel, Bua, et al., 2003[75]	200-800 mg [not stated]	145 pts 53 [17-76] (>65 yr = 17%) 47%M All IFN refractory; 14% received autoSCT	I = 145	29%	19%					12 mo OS = 87% (CI 92-80%) 24 mo OS = 63% (CI 78-56%) 12 mo PFS = 75% (CI 68-83%) 24 mo PFS = 52% (CI 47-60%)
Rosti, 2004[8]	400mg [26 mo]	191 pts age/gender not stated	I = 191 3 mo 6 mo 9 mo 12 mo	61% 41% 44% 42% 48%	44% 16% 27% 29% 33%				89% 89% 89% 86% 80%	At med f/u 26 mo, OS estimated from KM: MCR achieved 97% MCR not achieved 92% (p=0.037)

Abbreviations: * = abstract; CI = 95% confidence interval; CML = Chronic myelogenous leukemia; CP = chronic phase; CR = cytogenetic response; CCR = complete cytogenetic response; CHR = complete hematological response; CMR = complete molecular response; f/u = follow-up; I = Imatinib; IFN = Interferon; K-M = Kaplan-Meier; M = Male; MCR = major cytogenetic response; N = Number; OS = Overall Survival; PFS = progression-free survival; pt(s)=patient(s); RR = relative risk; SCT = Stem cell transplant

Chronic phase - Previous stem cell transplant and heavily pretreated

As the number and intensity of previous treatment increases, there is progressive decrease in the chance of response to new treatments. A critical question for imatinib is whether it is an option for patients who have become resistant to multiple prior therapies, and whether it precludes other subsequent therapy. Of particular interest is stem cell transplantation (SCT, a.k.a. bone marrow transplantation), which includes intensive myelosuppressive cytotoxic chemotherapy often with multiple agents. Allogeneic transplant also carries a substantial risk of graft versus host disease (GVHD).

Cervantes et al. demonstrated that 400 mg of imatinib yielded substantial Complete CR rates for 33 patients with prior autologous SCT (33 percent at 12 months), similar to that of the comparison sample of 65 interferon refractory patients who had not had a transplant (38 percent; Table 4).[37] Similar response rates were substantiated across this group of trials, with some studies noting even substantially higher Complete CR rates (33-85 percent).

Table 4. Summary of efficacy of imatinib for CML –Chronic phase, Previous stem cell transplant/heavily pretreated

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Chronic phase –previous stem cell transplant/heavily pretreated										
Phase I/II										
Cervantes, 2003[37]	400 mg [f/u not stated; at least 12 mo.]	Prior autoSCT: 33 pt 53 yr [24-70] 61% M	Prior autoSCT: I = 33 3 mo 6 mo 12 mo	 42% 45% 55%	 21% 24% 33%	 21% 21% 22%	 14% 10% 11%			PFS = 93.7%
		No autoSCT/IFN refractory: 65 pt 53 yr [17-80] 54% M	No autoSCT IFN refractory: I = 65 3 mo 6 mo 12 mo	 47% 52% 66%	 20% 35% 38%	 27% 17% 28%	 20% 19% 8%			PFS= 96.7% (p NS)
		Both groups received I								
Fischer, 2002[77]	400 mg [28 wk]	24 pt–disease relapse after autologous transplant 56 yr. [25-64] 58% M (only 15 CML-CP pt reported here; f/u period for AP and BP not long enough for endpoints)	I for CP relapse after autoSCT = 15	61%	46%	15%	8%	8%	100%	

Table 4. Summary of efficacy of imatinib for CML –Chronic phase, Previous stem cell transplant/heavily pretreated

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Kantarjian, O'Brien, et al., 2002[78]	400-1000 mg [16 mo]	28 pt 43 yr [25-64] 57% M (All with prior allogeneic SCT; 1 CP in CHR, 4 CP active, 3 AP in CHR, 12 AP active, 8 BP; 23 evaluable)	I = 28 (23 evaluable)	58%	35%	23%			74%	OS 1-yr 74% for all, and 100% treated in CP
O'Brien, Giles, et al., 2003[79]	Not stated [46 mo]	90 pt 46 [25-64] (age >60yr 4%) 51% M	I = 90 (given after relapse from IFN, Ara C, and homoharringtonine +/- allogeneic SCT)	78%	65%	13%	5%			Estimated 5-yr OS = 88%
Hess, 2004[80]	400 mg [381 day]	37 pt	I = 37 (given for CP relapse after allogeneic SCT)		85% of 11/13 with cytogenetic relapse only					25/27 (67%) achieved CMR 1 mild reactivation of GVHD OS at 1.7 yr = 100%
*Corsetti, 2004[81] Abstract only	400 mg for CP 600 mg for AP [36 mo]	50 pt Age & gender not specified CML-CP & AP relapsed after autoSCT & IFN	I =		CCR 61%	Major 70%				At median f/u of 36 mo: PFS 78% OS 87%

Abbreviations: * = abstract; AP = Accelerated phase; Ara-C = Cytarabine; BP = Blastic phase; CML = Chronic myelogenous leukemia; CP = chronic phase; CR = cytogenetic response; CCR = complete cytogenetic response; CHR = complete hematological response; CMR = complete molecular response; f/u = follow-up; GVHD = graft versus host disease; I = Imatinib; IFN = Interferon; M = Male; N = Number; OS = Overall Survival; PFS = progression-free survival; pt(s)=patient(s); SCT = Stem cell transplant

Accelerated phase

CML that is more advanced at presentation has a poorer prognosis. Imatinib is still efficacious in the accelerated phase setting, as demonstrated by Talpaz et al. (Table 5).[87] Complete CR rates ranged from 11 to 19 percent, with the 600 mg dose being more efficacious than 400 mg. In a subsequent follow up abstract, the Major CR rate was 48 percent with a median follow up of 38 months and the median survival had not been reached. A group of historical controls (accelerated phase, not otherwise described) were reported to have a median survival of 21 months.[88] The 3-year OS was estimated at 53 percent.

Table 5. Summary of efficacy of imatinib for CML–Accelerated phase

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Accelerated Phase: Phase I/II										
Talpaz, 2002[87]	400-800 mg [median treatment duration 10-11 months; median f/u not stated] (initially at 400 mg daily, later increased to 600 mg, and subsequently 800 mg allowed for inadequate response)	235 pts (235 pts enrolled but only 181 pts with confirmed diagnosis presented) 58 [22-86] 50%M 34% previously untreated 66% previously treated	I = 181 I @ 400mg = 62 I @ 600mg = 119	24% 16% 28%	17% 11% 19%	7% 5% 8%	7% 8% 6%	17% 15% 18%		TTP estimated K-M > 1-yr: All doses = 59% (CI 52-66%) 400mg I = 44% (CI 31-56%) 600mg I = 67% (CI 59-76%) (p=0.002) 1 yr OS estimated K-M: All doses = 74% (CI 68-81%) 400mg I = 65% (CI 53-77%) 600mg I = 78% (CI 70-87%)
Follow up data in abstract: *Cortes, Talpaz, OBrien, Gracia-Manero, et al., 2004[88]	[38 mos]		I = 171	48%						Median survival not reached at med of 38 mo f/u (21 mo for historical controls)– estimated at 53% at 3 yr

Abbreviations: * = abstract; AP = Accelerated phase; CHR = complete hematologic response; CI = 95% confidence interval; CML = Chronic myelogenous leukemia; CP = chronic phase; CR = cytogenetic response; I = Imatinib; K-M = Kaplan-Meier; M = Male; N = Number; OS = Overall Survival; PFS = progression-free survival; pt(s)=patient(s); TTP = time to progression

Blastic phase/blast crisis

During the chronic phase there is massive clonal expansion of CML cells. In the blastic phase the cells lose the ability to differentiate and the leukemia advances rapidly. Blastic phase CML has the poorest prognosis with an expected survival of 3-6 months. Historically it has been poorly responsive to any therapy. Median survival is 21-29 weeks, even with aggressive acute leukemia treatment plans.[141] Database review studies have indicated a 10-year survival after bone marrow transplantation of 0 percent (1996 report).[142]

Imatinib has been shown to have efficacy in the blastic setting (Table 6). Sawyers et al. report the largest Phase II trial involving 260 participants with a median duration of treatment of 4 months.[3] A total of 31 percent had a sustained CHR for over 4 weeks and 7 percent had a Complete CR. For those who did respond to imatinib, the estimated median response duration was 10 months. OS was estimated as 6.9 months (95 percent CI, 5.7-8.7 months) with 43 percent survival at 9 months and 20 percent at 18 months. In all studies that evaluated response by blast type, lymphoid blast crisis had better response rates than non-lymphoid (myeloid) blast crisis.[89, 90] Previously untreated patients always had a better response than those who were previously treated.[3] Doses ranged from 400-1000 mg without a clear pattern for maximal efficacy. Sawyers et al. started with 400 mg and increased to a maximum of 800 mg when the disease was resistant or refractory.[3]

Table 6. Summary of efficacy of imatinib for CML –Blastic phase/blast crisis

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Blastic Phase/Blast Crisis										
Phase I/II										
Druker, Sawyers, et al., 2001[89]	300-1000 mg dose escalation [74 days (1-349 days)]	58 pts 48 yr [24-76] 60% M	I in Myeloid BC=38						11%	TTP = 84 days [42-194]
		BC or Ph+ ALL resistant or refractory to standard induction	I in Lymphoid BC and Ph+ALL= 20						20%	TTP = 58 days [42-123]

Table 6. Summary of efficacy of imatinib for CML –Blastic phase/blast crisis

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Kantarjian, Cortes, 2002[90]	300-1000 mg [11 mos]	75 pts 53 yr [27% >60 yr]	I = 75		6%	3%	3%		21%	Median OS = non-lymphoid BC =6.5 mo
		67% previously untreated 33% previously treated	I in Nonlymphoid BC = 65		5%	3%	3%		23%	28% 1 yr survival for non-lymphoid BC
			I in Lymphoid BC = 10		10%					Lymphoid BC =7.0 mos.
										Compared to historical controls that received standard Ara-C based induction chemotherapy, I = 55% objective response rate vs 29% with Ara-C (p=0.001); 4-week mortality = 4% with I and 15% with Ara-C (p=0.07); median survival was 7 mo with I and 4 mo with Ara-C (p=0.04)

Table 6. Summary of efficacy of imatinib for CML –Blastic phase/blast crisis

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Sawyers, 2002[3]	400 mg (later in study dose escalation for treatment resistance was allowed to max 800 mg) [median duration of treatment 4 mos, f/u not stated]	260 pts 56 [19-81] 52% 57% previously untreated 43% previously treated	I = 260 Previously untreated = 148 Previously treated = 81	16% 16% 17%	7% 8% 6%	9% 7% 11%	2% 2% 1%	13% 15% 10%	52% Sustained >4wks = 31% Sustained = 36% Sustained = 21%	Estimated PFS at 6 mos = 68% (CI 57-79%) Estimated median response duration = 10ms (CI 7.2-12.6) OS estimated from KM = median 6.9 mos (CI, 5.7-8.7) with 43% survival at 9 mos and 20% at 18 mos
Sureda, 2003[4]	600 mg [f/u not stated]	30 pts 50 [18-72] 53%M All pretreated, 70% with multiple previous regimens	I = 30	3%	0%	3%	10%		30%	Median response duration of CHR = 5 mos (range 4-18) EFS at 1 yr = 29% (SD 8%) OS at 1 yr = 36% (SD 13%)

Abbreviations:
***** = abstract; ALL = Acute Lymphocytic Leukemia; Ara-C = Cytarabine; BC = Blastic crisis; BP = Blast phase; CI = 95% confidence interval; CML = Chronic myelogenous leukemia; CR = cytogenetic response; CHR = complete hematological response; EFS = event-free survival; f/u = followup; M = Male; N = Number; OS = Overall Survival; PFS = progression-free survival; Ph+ = Philadelphia chromosome positive; pt(s)=patient(s); TTP = time to progression

Additional efficacy tables

Table 7 reviews three reports that presented response to imatinib across phases. Two reports were summed from the three large phase II Novartis trials submitted to the FDA as part of the 2002 imatinib approval process.[82, 83] These studies are instructive in that they provide validation of the differential effect of imatinib therapy by phase of disease and the efficacy estimates previously presented, as well as additional estimates of treatment durability. With a median follow up of 40 months 64 percent of CP participants were still taking imatinib.[83] Among CP patients with Major CR, 82 percent were still on imatinib at 3 years, with PFS 80 percent and OS 88 percent. For AP and BP the 3-year PFS was 55 percent and 5 percent, respectively. A third study conducted with 128 patients who had a prior allogeneic SCT also validates the differential effect of imatinib by phase and the activity of imatinib in the heavily pretreated post-allogeneic SCT setting.[84] The overall and CP Complete CR rates of 42 percent and 58 percent described were consistent with the previous group of allogeneic studies.

Table 8 presents two additional studies that did not naturally fit into the other tables. Both of these were preliminary trials assessing the tolerability and efficacy of drug combinations including imatinib in newly diagnosed CP CML. Gardembas and colleagues described imatinib combined with cytarabine[38] and Baccarani et al. reported imatinib plus pegylated interferon.[91] Both trials reported Complete CR rates that were no better than those seen in the IRIS study with imatinib alone. Interpretation of these trials is limited by the shorter follow up periods; additional cytogenetic and molecular responses may accumulate with time making these combination therapies more interesting as the data mature.

Table 7. Summary of efficacy of imatinib for CML–Mixed phases

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Mixed Phases										
Phase I/II										
Cohen, 2002[82]	Phase I = 25-1000 mg	IFN refractory CP: 83 pts	I in IFN refractory CP = 83	31%	13%				98% [when dose > 300 mg]	
	Phase II = 400-600 mg	CP: 532 pts 57 yr. [18-90] 59% M	I in CP = 532	49%	30%				88%	
This is the FDA Approval Summary–most of these patients are presented elsewhere predominantly as the 3 large phase II Novartis trials–see individual tables		AP: 235 pts 56 yr [22-86] 50% M	I in AP = 235	21%	14%				63%	Median time to hematologic progression for CML-AP = >6 mo
		BC: 260 pts 56 yr [19-81] 52% M	I in BC = 260	13.5%	5%				26%	Median time to hematologic progression for CML-BC = 5.6 mo

Table 7. Summary of efficacy of imatinib for CML–Mixed phases

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Silver, 2004[83] Follow up data presented in abstract form only	CP–400 mg AP / BP–400-600 mg Dose escalation to 800 mg allowed in later parts of the studies [40 mos for CP participants]	CP–532 pts (all late CP) AP–235 pts BP–260 pts Unclear how many are IFN refractory	I - CP = 532 I - AP = 235 I - BP = 260	65%	52%	13%				CP: 64% still on I 82% of those with MCR continue @ 3 yr 3 yr OS = 88% 3 yr PFS = 80% AP: 25% still on I When at 600mg dose, 55% 3yr PFS BP: 5% still on I When at 600mg dose, 14% 3yr PFS
Olavarria, 2003[84]	400-600 mg [9 mos]	128 pts 45 yr [17-65] 62% M All with previous allogeneic SCT; 40% received donor lymphocyte infusion; heavily pretreated	I = 123 I in CP after alloSCT = 50 I in AP after alloSCT = 29 I in BP after alloSCT = 44	54% 71% 67% 44%	42% 58% 48% 22%	12% 13% 19% 22%			71% 98% 83% 32%	Estimated 2-yr OS: All = 65% AP = 86% BP = 12% (p for AP vs BP <0.0001)

Table 7. Summary of efficacy of imatinib for CML–Mixed phases

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Lahaye, 2005[85]	400-600 mg.	300 pts 56.2 yr [14.6-79.6] 57% M	300 pts							
	CP [33 mo, 6-49]	CP = 139 pts 55.9 yr [18.5-76.6] 56% M	CP: I = 139 [median duration = 34 mo (19-49)		49%	12%	4%	27%	97%	@30 mo, estimated DFS = 83%; CHR @ 30 mo = 79% MCR after 3 mo =longer DFS (p=0.009) MCR after 6 mo = longer DFS (p=0.004) MCR after 12 mo= longer DFS (p=.0001) & improved OS (p=0.021)
	AP [28 mo, 0.4-50]	AP = 80 pts 60.9 yr [30.9-81.8] 66% M	AP: I= 80 [median duration = 28 mo(0.4-50)		26%	5%	9%	36%	61%	AP: DFS & OS were not predictive
	BC [6 mo, 0.1-52]	BC = 76 pts	BC: I = 76		8%	4%	3%	34%	18%	BC: Estimated survival @ 12 mo =32% @ 24 mo = 18% OS = 6 mo (0.9-52)

Table 7. Summary of efficacy of imatinib for CML–Mixed phases

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Deshmukh, 2004[86]	"Recommended doses"	174 pts	CP, I = 97	50%	31%				92%	
	[Not stated]	Participant profile not described								
Abstract only			CP (early CP subset), I =24	63%	21%				100%	
		CP = 97 pts (of which 24 = early CP)								
		AP = 47 pts	AP, I = 47	21%	6%				55%	
		BP = 30 pts								
			BP, I = 30	23%	13%				37%	

Abbreviations: * = abstract; AP = Accelerated phase; BC = Blast crisis; BP = Blastic phase; CI = 95% confidence interval; CML = Chronic myelogenous leukemia; CP = chronic phase; CR = cytogenetic response; CHR = complete hematological response; DFS = Disease free survival; I = Imatinib; IFN = Interferon; M = Male; MCR = major cytogenetic response; N = Number; OS = Overall Survival; PFS = progression-free survival; pt(s)=patient(s); QOL = Quality of life; RR = relative risk; SCT = Stem cell transplant

Table 8. Summary of efficacy of imatinib for CML–Other types of studies

Study ID	Imatinib dose [median length of follow up]	No. of patients, age, sex, additional CML characteristics	N	Major CR	Com-plete CR	Partial CR	Minor CR	Minimal CR	CHR	Survival/ Other
Imatinib efficacy/other										
Phase I/II										
Gardembas, 2003[38]	400 mg (with Ara-C SQ 20 mg/m^2/d on d15-28) [12 mo] median 6 cycles of Ara-C	30 pts 48 yrs [22-81] 67% M Newly diagnosed CML-CP	I+AraC= 30 3 mo 6 mo 9 mo 12 mo	70% 73% 77% 83%	23% 57% 53% 70%	47% 17% 23% 13%	6% 10% 6% 6%		100% 100% 100% 97%	No CCR @ 3 mos = 6% No CCR @ 6 mos. = 6% No CCR @ 9 mos. = 3% No CCR @ 12 mos. = 3 %
Baccarani, 2004[91]	400 mg (with pegylated IFN at 50 mcg/d, 100 mcg/d, or 150 mcg/d) [min 6 mo]	76 pts 47 yrs [18-68] 58%M Newly diagnosed CML-CP	I+PegIFN= 76	83%	70%	13%			97%	CCR similar in all IFN cohorts 47% with BCR-ABL transcript reduction by >3 log

Abbreviations: ***** = abstract; CML = Chronic myelogenous leukemia; CP = chronic phase; CR = cytogenetic response; CHR = complete hematological response; I = Imatinib; IFN = Interferon; M = Male; N = Number; OS = Overall Survival; pt(s)=patient(s)

Quality of Life

Quality of life (QOL) is another important efficacy outcome. Hahn and colleagues investigated the QOL of newly diagnosed CP patients receiving imatinib vs. interferon plus cytarabine in the IRIS study.[60, 61] The Functional Assessment of Cancer Therapies–Biologic Response Modifiers (FACT-BRM) instrument was used.[143] The primary QOL outcome was the Trial Outcome Index (TOI; 27 items, score range 0-108) and secondary endpoints included social/family well-being (SFWB; 7 items range 0-28) and emotional well being (EWB; 6 items, range from 0-24). Higher scores indicated better QOL. Quality of life was measured at baseline, monthly for 6 months, then at 9, 12, and 18 months. Imatinib treated patients scored significantly higher on all of these QOL measurements. The mean TOI across the trial was 84.4 for imatinib treated patients and 67.7 for patients on interferon plus cytarabine ($p<0.001$). Patients on the interferon plus cytarabine arm had a substantially greater decrease in TOI across time than those on imatinib. This work was recently repeated in a phase II study conducted by Pasquini and colleagues in Brazil.[76] Imatinib led to clinically significant increases in TOI at 1, 6 ,and 12 months.

Table 9. Summary of efficacy of imatinib for CML–Quality of Life

Study ID	QOL scales used/measurements obtained	Imatinib dose [length of follow up]	No. of patients, age, sex, additional CML characteristics	QOL outcomes
Hahn, 2003[60, 61]	FACT-BRM Within the FACT-BRM , the primary outcome was the TOI; (27 items, score range 0-108) Secondary endpoints included SFWB (7 items range 0-28) and EWB (six items, range from 0-24). Higher scores are better. baseline monthly for 6mo and then at 9, 12, and 18 mo	400 mg (increased to 800mg for no CHR at 3 months or at least a Minor CR at 12 months) [19 mo] [30 mo for first line therapy; 17 mo for crossovers]	CP newly diagnosed 1049 pts Imatinib: 530 50 [18-70] 62% M IFN+AraC: 519 51 [18-70] 56% M	TOI (mean across trial) Imatinib 84.4 IFN+AraC 67.7 (p<.001) SFWB (mean across trial) Imatinib 22.8 IFN+AraC 21.6 (p<.001) EWB (mean at 18 mo timepoint) Imatinib 19.5 IFN+AraC 17.7 (p<.001) Based upon 1,3,6,9, and 12 mo data: % of participants with clinically meaningful <u>decrease</u> in TOI by 5 or more points (goal = increased TOI) Imatinib 22-29% across timepoints IFN+AraC 52-73% across timepoints p<0.001 % of participants with clinically meaningful <u>increase</u> in TOI by 5 or more points Imatinib 29-43% across timepoints IFN+AraC 9-25% across timepoints p not stated
*Pasquini, 2004[76] Abstract only	FACT-BRM Primary outcome = TOI Baseline monthly for 6mos and then at mos 9,12,and 18	00-600 mg	CP - IFN refractory 230 pts All received imatinib 46 [18-76] 56%M	% of participants with clinically meaningful increase in TOI by 5 or more points All received I: 1 mo–increase by 5.4 (p<0.0001) 6 mo–increase by 7.4 (p<0.0001) 12 mo–increase by 9.8 (p<0.0051)

Abbreviations: * = abstract; AraC = Cytarabine; CML = chronic myelogenous leukemia; CP = chronic phase; emotional well being (EWB); FACT-BRM = Functional Assessment of Cancer Therapies - Biologic Response Modifiers; I = Imatinib; IFN = Interferon; M = Male; N = Number; pt(s) = patient(s); QOL = Quality of life; social/family well-being (SFWB); Trial Outcome Index (TOI)

Adverse events

Table 10 reviews the adverse events reported across the studies. In the IRIS trial, imatinib most commonly caused neutropenia (61 percent), thrombocytopenia (57 percent), superficial edema (56 percent), nausea (44 percent), and abnormal liver function results (43 percent).[59] Interferon plus cytarabine most commonly caused thrombocytopenia (79 percent), abnormal liver function results (74 percent), neutropenia (67 percent), fatigue (66 percent), nausea (61 percent), anemia (55 percent), and headache (43 percent). The incidence of grade 3/4 side effects was primarily hematological with imatinib (neutropenia 14 percent and thrombocytopenia 8 percent) whereas interferon plus cytarabine included fatigue (24 percent) and hematological (neutropenia 25 percent and thrombocytopenia 17 percent). The incidence of side effects increased with imatinib dose and phase of illness, with hematologic side effects particularly increasing with advancing phases of illness.

In addition to the adverse events commonly described across this group of studies, four individual reports of adverse events were identified. Valeyrie and colleagues prospectively followed 54 patients started on imatinib [94] Eighty-nine percent experienced at least one cutaneous reaction; 67 percent had rashes, 65 percent edema and 41 percent pruritis. Six percent had severe enough rash to discontinue therapy either temporarily or permanently. The rate of rash increased with imatinib dose. In a similar study of 78 patients by Drummond et al., 12 percent of patients had rashes that could be directly attributed to imatinib.[92] Steegmann reported a prospective study of gamma globulin levels in 36 patients receiving imatinib for CML when resistant to or intolerant of interferon. Low serum IgG, IgA, and IgM levels were identified in 28 percent, 14 percent and 22 percent of patients, respectively.[93] Finally, Al-Ali and colleagues identified that imatinib caused elevated creatinine kinase (CK) levels of >50 percent above baseline in 81% of the 113 patient cohort studied; elevation was highest for those who reported cramps or myalgias.[95] Patients whose CK levels were elevated after 6 months of imatinib had higher rates of Major CR (p=0.048).

Phase of CML	Chronic phase - newly diagnosed							Chronic phase - interferon resistant or refractory												
First Author, Year	Obrien [51]				Kantarjian [55]	Kantarjian [56]		Drucker [28]									Le Coutre [66]	Rosti [69]			Kantarjian, Cortes [65]
Drug / dosage	imatinib	IFN/AraC	imatinib	IFN/AraC	Varied Doses	800mg/d		25-140mg/d		200-300mg/d		350-500mg/d		600-1000mg		total	% AE's related to Imatimib # of pts with event	# of AE's			Median Follow-up = 45 Months
n	n=551	n=553	n=551	n=553		n=114		n=14		n=23		n=18		n=28		n=83					n=261
constituitional																		158	45	9	
edema or fluid retention						1%	0%	25%	0%	27%	0%	40%	0%	66%	8%	39%		77	14	2	0%
superficial edema	56%	9%	0.9%	0.6%													46%				
periorbital																					
leg																					
face																					
othersite																					
eyelid																					
nausea	44%	61%	0.7%	5.1%				25%	0%	36%	0%	60%	0%	71%	0%	43%	5.1%				
nausea/vomiting						1%	0%														0%
diarrhea	33%	42%	1.8%	3.2%		1%	0%	17%	0%	5%	0%	40%	0%	46%	4%	25%					0%
myalgia or musculoskeletal pain	1%	1%	1.5/2.7%	1.0%	0.02	3%	2%	25%	0%	63%	0%	40%	7%	34%	17%	41%					1%
mucscle cramps	38%	11%	1.3%	0.2%													25.6%				0%
fatigue	35%	66%	1.1%	24.4%	0.02	1%	2%	17%	0%	27%	0%	13%	0%	29%	4%	20%					
dermatitis or rash	34%	25%	2.0%	2.3%	0.06	6%	6%	8%	0%	20%	0%	13%	0%	34%	4%	19%	15.4%	47	21	4	2%
headache	31%	43%	0.4%	3.2%																	
abdominal pain	2%	25%	2.4%	3.9%																	
flatulence																					
vomiting	17%	27%	1.5%	3.4%				0%	0%	16%	0%	13%	0%	41%	0%	18%					
hemorrhage	21%	21%	0.7%	1.5%														27	5	2*	
tumor hemorrhage																					
cerebral hemorrhage																					
upper GI tract																					
dyspepsia	16%	9%	0.0%	0.8%				17%	0%	16%	0%	34%	0%	20%	0%	18%					
increased lacrimation																					
loose stools																					
taste disturbance																					
neutropenia	61%	67%	14.3%	25.0%		36%	20%	0%	0%	11%	5%	7%	7%	0%	29%	14%	8.0%				
abdominal distension																					
abnormal liver-function results	43%	74%	5%	7%	4%	7%	10%											nr	9	9	
leukopenia																					
arthralgia								0%	0%	5%	0%	7%	0%	34%	4%	13%					
paresthesia																					
esophageal reflux																					
pruritus	7%	12%	0.2%	0.2%																	
pain																					
blurred vision																					
photosensitivity																					
nasopharyngitis	22%	8%	0.0%	0.2%																	
pyrexia	13%	39%	0.7%	2.8%																	

Phase of CML	Chronic phase - newly diagnosed							Chronic phase - interferon resistant or refractory												
First Author, Year	Obrien [51]				Kantarjian [55]	Kantarjian [56]		Drucker [28]									Le Coutre [66]	Rosti [69]			Kantarjian, Cortes [65]
Drug / dosage	imatinib	IFN/AraC	imatinib	IFN/AraC	Varied Doses	800mg/d		25-140mg/d		200-300mg/d		350-500mg/d		600-1000mg		total	% AE's related to Imatimib # of pts with event				Median Follow-up = 45 Months
n	n=551	n=553	n=551	n=553		n=114		n=14		n=23		n=18		n=28		n=83		# of AE's			n=261
insomnia	12%	19%	0.0%	2.3%																	
upper respiratory tract infection	15%	8%	0.2%	0.4%																	
granulocytopenia					20%																62%
thrombocytopenia	57%	79%	8%	17%	8%	25%	12%	0%	0%	5%	0%	13%	7%	8%	29%	16%	41.0%				22%
anemia	45%	55%	3%	4%	8%	10%	4%										12.8%				14%
GI symptoms																		125	24	0	
weight increase																					
cough	15%	22%	0.2%	0.6%																	
dyspnea	7%	14%	1.5%	1.5%																	
anorexia	5%	32%	0.0%	2.4%																	
constipation	9%	14%	0.7%	0.2%																	
nasopharingitis																					
night sweats	7%	16%	0.2%	0.4%																	
epitaxis																					
hypokalemia																					
petechiae																					
pneumonia																					
weakness																					
asthenia	6%	19%	0.2%	4%																	
mucositis																					
neuro symptoms																		8	8	0	
cardiac						4%	2%														0.8%
bone or joint aches	28%	40%	2.4%	7%													2.6%				1%
infection																		33	12	0	
weight gain	13%	2%	0.9%	0.2%													12.8%				
dizziness	15%	24%	0.9%	3.4%																	
prolonged wound healing																	2.6%				
pharyngolaryngeal pain	16%	13%	0.2%	0.2%																	
depression	10%	36%	0.4%	13%																	0.8%
anxiety	7%	11%	0.2%	3%																	
rigors	7%	34%	0.0%	0.8%																	
influenza like illness	7%	19%	0.0%	0.8%																	
alopecia	4%	22%	0.0%	0.6%																	
increased sweating	4%	15%	0.0%	0.4%																	
weight loss	3%	17%	0.2%	1.3%																	
stomatitis	3%	12%	0.0%	0.2%																	
dry mouth	2%	10%	0.0%	0.2%																	
mucosal inflammation	1%	10%	0.0%	3.2%																	
psychiatric																		10	8	0	
cardiovascular																		10	4	3*	
other																		36	6	2**	
hematologic																		ade 4 AE's which were recorded			

Phase of CML	Chronic phase - previous stem cell transplant/heavily pretreated			Mixed phased													Accelerated phase				
First Author, Year	Cervantes [28]		Kantarjian [72]	Cohen [76]						LaHaye [79]						Talpaz [81]				
				phase 1	phase 2																
Drug / dosage	ASCT	no ASCT			CML-BC		CML-AP		CML-CP IFN failures		CML-CP				CML-AP	CML-BC					
n			varied doses		n=260 600mg n=223 400mg n=37		600mg n=158 400mg n=77		n=532 400mg		n=139		n=80		n=76		n=235 events reported in atleast 5% of pts		all pts n=235	400mg n=77	600mg n=158
constituitional																					
edema or fluid retention	21%		10%	39%	67%	10%	68%	6%	52%	2%							64%	3%			
superficial edema					63%	5%	66%	4%	51%	1%											
periorbital			7%																		
leg			7%								29%	0%	36%		29%						
face																					
othersite			4%		16%	6%	9%	3%	2%	1%											
eyelid											46%	0%	38%		45%						
nausea				43%	68%	3%	68%	5%	55%	2%	29%	1%	31%		47%		65%	3%			
nausea/vomiting			4%																		
diarrhea			0%	25%	39%	3%	49%	4%	33%	9%							37%	0%			
myalgia or musculoskeletal pain			4%	41%	37%	8%	39%	7%	27%	1%							13%	1%			
mucscle cramps	0.15				25%	0%	34%	0%	46%	1%	53%	0%	39%		32%		32%	0%			
fatigue					24%	2%	33%	3%	25%	0%							11%	3%			
dermatitis or rash	0.03	11% GVHD related			32%	4%	39%	4%	36%	3%	18%	5%	24%		26%		22%	1%			
headache					24%	4%	26%	2%	28%	0%							13%	1%			
abdominal pain					23%	5%	26%	2%	20%	0%											
flatulence																					
vomiting					49%	3%	54%	3%	28%	1%							49%	1%			
hemorrhage					48%	16%	35%	8%	13%	0%							12%	2%			
tumor hemorrhage																					
cerebral hemorrhage					4%	2%	1%	0%	0%	0%											
upper GI tract					5%	2%	3%	1%	0%	0%											
dyspepsia					9%	0%	19%	0%	18%	0%							16%	0%			
increased lacrimation																					
loose stools											24%	0%	20%		29%						
taste disturbance																					
neutropenia												19%		48%		57%			22%/35%	21%/35%	25%/35%
abdominal distension																					
abnormal liver-function results	3%		18%	% (gd 2 or >)																	
leukopenia												14%		36%		54%			33%/14%	27%/18%	35%/13%
arthralgia					21%	3%	26%	5%	24%	1%							12%	3%			
paresthesia																					
esophageal reflux																					
pruritus					6%	1%	10%	0%	9%	1%							9%	0.4%			
pain																	11%	1%			
blurred vision																					
photosensitivity																					
nasopharyngitis																					
pyrexia			4%		38%	7%	35%	7%	14%	1%											

Phase of CML	Chronic phase - previous stem cell transplant/heavily pretreated			Mixed phased													Accelerated phase				
First Author, Year	Cervantes [28]		Kantarjian [72]	Cohen [76]						LaHaye [79]							Talpaz [81]				
				phase 1	phase 2																
Drug / dosage	ASCT	no ASCT		CML-BC		CML-AP		CML-CP IFN failures		CML-CP				CML-AP	CML-BC						
n			varied doses	n=260 600mg n=223 400mg n=37		600mg n=158 400mg n=77		n=532 400mg		n=139		n=80		n=76			n=235 events reported in atleast 5% of pts		all pts n=235	400mg n=77	600mg n=158
insomnia																					
upper respiratory tract infection																					
granulocytopenia	33%	32%	43%																		
thrombocytopenia	27%	17%	27%								16%		40%		64%				31%/12%	30%/14%	32%/11%
anemia	12%	5%									6%		39%		41%				33%/6%	35%/9%	32%/15%
GI symptoms	18%																7%	0.4%			
weight increase					4%	0%	6%	1%	14%	2%											
cough					12%	1%	22%	1%	9%	0%											
dyspnea					12%	4%	16%	5%	5%	0%											
anorexia					10%	2%	14%	1%	3%	0%							8%	1%			
constipation					13%	1%	13%	1%	4%	0%											
nasopharingitis					5%	0%	10%	0%	9%	0%											
night sweats					10%	1%	10%	1%	8%	0%											
epitaxis					12%	3%	9%	0%	3%	0%											
hypokalemia					12%	3%	9%	1%	2%	0%											
petechiae					10%	1%	4%	1%	1%	0%											
pneumonia					10%	5%	7%	5%	1%	0%											
weakness					10%	3%	8%	2%	5%	0%											
asthenia																					
mucositis																					
neuro symptoms																					
cardiac																					
bone or joint aches			7%																		
infection			4%																		
weight gain																	11%	1%			
dizziness																					
prolonged wound healing																					
pharyngolaryngeal pain																					
depression																					
anxiety																					
rigors																					
influenza like illness																					
alopecia																					
increased sweating																					
weight loss																					
stomatitis																					
dry mouth																					
mucosal inflammation																					
psychiatric																					
cardiovascular																					
other																					
hematologic																	9%	0.4%			

Phase of CML	Blastic phase											imatinib efficacy/other	
First Author, Year	Drucker [59]							Sawyers [85]		Sureda [86]		Gardembas [30]	
Drug / dosage	300mg/d		400-500mg/d		600-1000mg/d		total					400mg combined with Ara-C	
n	n=8		n=17		n=33		n=58	n=260		n=30		n=30	n=16
constituitional													
edema or fluid retention	43%	21%	31%	10%	78%	10%	41%	57%	6%	40%			
superficial edema								55%	4%			50%	0%
periorbital													
leg													
face													
othersite								9%	3%				
eyelid													
nausea	43%	21%	60.0%	10.0%	95%	21%	55%	63%	2%	30%	3%	83%	0%
nausea/vomiting													
diarrhea	0%	0%	21.0%	0.0%	41%	0%	17%	24%	1%	23%		40%	0%
myalgia or musculoskeletal pain	43%	0%	31.0%	0.0%	36%	0%	21%	12%	1%	3%	3%	50%	0%
mucscle cramps								25%	1%			37%	0%
fatigue	21%	0%	41.0%	0.0%	5%	0%	10%	8%	2%	37%			
dermatitis or rash	0%	0%	31.0%	0.0%	26%	10%	17%	23%	4%		6%	23%	0%
headache								10%	1%			30%	0%
abdominal pain								27%	1%			53%	10%
flatulence													
vomiting	66%	0%	60.0%	10.0%	57%	16%	41%	44%	1%	23%		63%	13%
hemorrhage								10%	2%				
tumor hemorrhage													
cerebral hemorrhage													
upper GI tract													
dyspepsia								7%	0%				
increased lacrimation													
loose stools													
taste disturbance													
neutropenia									16/48%	37%	20%	53%	27%
abdominal distension													
abnormal liver-function results										14%	6%		
leukopenia													
arthralgia								8%	1%	13%			
paresthesia													
esophageal reflux													
pruritus												13%	0%
pain													
blurred vision													
photosensitivity													
nasopharyngitis												27%	0%
pyrexia													

Phase of CML	Blastic phase											imatinib efficacy/other	
First Author, Year	Drucker [59]							Sawyers [85]		Sureda [86]		Gardembas [30]	
Drug / dosage	300mg/d		400-500mg/d		600-1000mg/d		total					400mg combined with Ara-C	
n	n=8		n=17		n=33		n=58	n=260		n=30		n=30	n=16
insomnia													
upper respiratory tract infection													
granulocytopenia													
thrombocytopenia	5								29/33%	23%	20%	50%	37%
anemia	5								41/11%			10%	7%
GI symptoms													
weight increase													
cough													
dyspnea													
anorexia	21%	0	33%	0	10%	0	10%					13%	0%
constipation													
nasopharingitis													
night sweats													
epitaxis													
hypokalemia													
petechiae													
pneumonia													
weakness													
asthenia												21%	2%
mucositis												13%	0%
neuro symptoms												3%	0%
cardiac													
bone or joint aches													
infection													
weight gain													
dizziness													
prolonged wound healing													
pharyngolaryngeal pain													
depression													
anxiety													
rigors													
influenza like illness													
alopecia													
increased sweating													
weight loss													
stomatitis													
dry mouth													
mucosal inflammation													
psychiatric													
cardiovascular													
other													
hematologic										67%	23%		

Predictors

Ideally, treatment is matched to those patients most likely to respond to that treatment. Certain clinical and molecular characteristics can be used to predict which patients with CML are more or less likely to respond to imatinib. These predictors of response to imatinib are distinct from the disease characteristics that correlate with prognosis irrespective of treatment plan. For example, the most important prognostic factor is the phase of disease. Some prognostic factors are also associated with response to treatment. Clinical characteristics predicting response were presented in the Efficacy section and included:

- phase of disease (CP, AP and BP; early vs. late CP);
- previous treatment before imatinib (interferon, stem cell transplantation);
- reason that previous treatments were discontinued (resistant, refractory, intolerant); and,
- dose.

Many authors have reviewed the correlation between clinical prognostic factors (e.g., splenomegaly, percentage of blasts in the peripheral blood, platelet count) and tumor response or survival with imatinib. As expected, most of the known prognostic factors can be used to identify high risk and low risk patients in the setting of imatinib therapy in a similar manner to other treatment settings. A full review of the hazard ratios for these clinical prognostic factors is outside the scope of this review. Here we concentrate on molecular factors that predict response to imatinib and are likely to be related to the targeted action of the drug.

The molecular predictors can be arbitrarily divided into four groups. The first three groups are based upon whether the assessment focuses on genetic material (DNA), production of the RNA message, or the tyrosine kinase protein and its interaction with imatinib. A fourth group includes other miscellaneous predictors. Group 1 includes DNA predictors are related to the formation of Ph, the evidence of impact of imatinib on the Ph, the accumulation of other DNA abnormalities within the CML cells, or genetic profiling to predict imatinib responders. Group 2 includes RNA predictors that relate to the production of the BCR-ABL mRNA transcripts including trends in production over time. Group 3 relates to changes in the tyrosine kinase protein that influence the activity of imatinib. Group 4 includes other related predictors that were identified in this review such as bone marrow cellularity and myelosuppresssion. These groups can be further divided into characteristics identified at the start of imatinib therapy and characteristics that can be evaluated during therapy to predict response (subclassification A or B).

Assessment of study quality is reviewed in Chapter 2. Quality scores reflect study reporting quality from a clinical research standpoint, not the quality of the basic science. In a broad review of the literature such as this one, it is difficult to determine which predictors have been exhaustively scientifically validated and which ones are only investigational. The volume of studies citing an individual predictor is used as a proxy indicator. These tables have been arranged so that potential predictors with a large number of supporting studies are cited at the beginning of the tables and emerging predictors are cited at the end.

Molecular predictors: Group 1A--DNA factors at the start of imatinib therapy

Ph+ cells measured during cytogenetic analysis is a measurement of burden of disease. This is represented in terms of "percentage of Ph+ metaphases" at the start of imatinib therapy. Five studies evaluated the relationship between this predictor and tumor response, progression, or survival. There were significantly more patients with a Major CR when <90 percent of metaphases where Ph+ at the start of therapy.[1, 2] A similar trend for survival was seen, but not statistically significant.[1] There were significantly more patients with a Complete CR when <100 percent of metaphases where Ph+ at the start of therapy; overall survival was longer too.[75] For those patients increased to 800 mg of imatinib due to disease resistance at 400 mg, complete and partial cytogenetic response were again more likely if Ph+ cells represented <100 percent of metaphases.[74] In terms of disease progression, there was not a statistically significant relationship between CML hematologic relapse and those patients with >98 percent Ph+ metaphases at the beginning of therapy, but the trend for relapse followed that previously seen.[96] These secondary analyses were predominantly from studies of patients with CML in chronic phase that is resistant or refractory to interferon (CP-IFN-r); one study included other CP patients and AP patients.[1] In general, patients with a smaller burden of disease at the start of imatinib therapy were more likely to have a Major CR, Complete CR, and/or improved overall survival.

Chromosomal abnormalities in addition to the Ph have been repeatedly investigated as a potential prognostic and therapeutic predictor in CML. Cytogenetic abnormalities have been investigated both at the time of initial diagnosis and with clinical disease progression (e.g., from chronic to accelerated phase). The language that various authors use to describe this process is imprecise, including descriptions of "other chromosomal abnormalities," "complex cytogenetics," and "cytogenetic clonal evolution". Overall, the most common terminology in "clonal evolution" and therefore this grouping will be used to represent this category of predictive markers.

Clonal evolution at the time of initial diagnosis may be a marker for more advanced or aggressive disease. Indeed, larger studies of patients in AP and BP supported that clonal evolution at baseline predicted poorer survival ($p<0.005$)[3, 4] and likely predicted disease progression ($p=0.086$).[87] Smaller studies did not support these findings.[67, 90] Cytogenetic clonal evolution is often a hallmark of CML as it progresses from chronic to more advanced phases. Similar to phase being a clinical predictor of response to imatinib, clonal evolution may be a molecular predictor. Ten studies including patients in CP and CP-IFN-r considered cytogenetic clonal evolution as a predictor of tumor response, although it was likely that these studies reflected multiple presentations of the same patient populations. Taken together these studies suggested that cytogenetic clonal evolution inconsistently predicted disease response,[1, 2, 70, 75] but was a major predictor of the risk of disease relapse (relative risks (RR) reported 4.34, 4.912, and 14.8)[96, 97, 99] and survival.[1, 44, 70, 72, 75]

CD34 is an antigen that is selectively expressed on myeloid and lymphoid hematopoetic progenitor cells. Marin and Elliot both presented abstracts that indicated that the percent of CD34+ cells in the bone marrow in CML correlated with tumor response.[100, 101]

Variant Ph translocations occur in up to 10 percent of cases of CML. The variant Ph may lead to variant BCR-ABL tyrosine kinase proteins and therefore affect imatinib's efficacy. Prior to the era of imatinib, variant Ph was not associated with prognosis except perhaps abnormalities involving chromosome 17.[49] In an analysis that included patients in CP and AP, El-Zamaity and colleagues did not identify a significantly shorter duration of response with variant Ph as compared to other patients with CML.[97]

Deletions of the resultant DNA on chromosome 9 can be seen in up to 15 percent of cases of CML.[50] Chromosome 9 deletions are known to negatively affect prognosis, decreasing survival by up to 20 percent at 5 years.[53, 54] These studies were conducted predominantly in patients on interferon-based therapies.[50] In the setting of imatinib, chromosome 9 deletions lead to poorer PFS in CP, AP and BP settings (p=0.02).[51] Another study found no differences in major CR or complete CR in CP patients.[144] Overall survival was not significantly different in either study with median follow-up of 48 months. Longer periods of followup may be needed.

Investigations of genetic patterns are underway. A number of genes are known to be related to drug resistance and programmed cell death (apoptosis) in leukemic cells. Evaluation of gene expression suggested that *MRP-1* was overexpressed in blast crisis CML, and that *MRP-1* overexpression was significantly correlated with poor tumor response to imatinib.[102] Using gene microarray techniques, McLean and colleagues identified a genomic profile and microarray pattern characteristic of tumor response in CP CML. Patients whose CML met this ideal microarray profile had a substantially greater likelihood of Complete CR (odd ratio (OR) 200, 95% CI 19-3096) and Major CR (OR 19.9, 95% CI 6-67).[103]

In summary, DNA factors at the start of imatinib therapy that predict poorer tumor response and/or survival include the following:

- 90-100 percent of metaphases are Ph+ at the start of imatinib;
- Clonal evolution in AP or BP;
- Clonal evolution in CP (predicts risk of relapse and poorer survival);
- Higher percentage of CD34+ cells in the bone marrow;
- Chromosome 9 deletions; and,
- Genetic profiles.

Table 11. Tumor characteristics predictive of disease response or survival: Group 1A -- DNA factors at the start of imatinib therapy

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
% of Ph+ metaphases at the start of therapy	Cortes, Talpaz, et al.., 2003[1] (quality = 6/6) CP & AP	Relationship to Major CR: Ph+ <90%: N= 295 91% p<0.0001 Ph+ >90%: N = 270 54%	Relationship to survival: Ph+ <90% N= 295 96% p=0.08 Ph+ >90% N = 270 81%
	Kantarjian, Sawyers, et al.,2002[2] (quality = 6/6) CP-IFN-r	Relationship to Major CR: Ph+ <90%: N= 55 89% p<0.001 Ph+ >90%: N = 378 56%	
	Marin, Goldman, et al., 2003[74] (quality 1/5) CP-IFN-r	Predictor of response to I at 800 mg (when resistant to I at 400 mg): Ph+ < 100%: N=18 28% CCR, 16% MCR + minorCR Ph+ = 100%: N=18 0% CCR, 6% MCR + minorCR p<0.05	
	Marin, Marktel, Bua, et al., 2003[75] (quality 2/5) CP-IFN-r	Relationship to CCR: Ph+ < 100%: N= 20 80% p=<0.0001 Ph+ = 100%: N = 122 21%	Relationship to OS: Ph+ < 100%: N= 20 100% p=<0.02 Ph+ = 100%: N = 122 68%
	O'Dwyer, 2004[96] (quality 2/5) CP-IFN-r	Relationship to hematologic relapse: Ph+ <99%: N= 20 2% p=0.2478 Ph+ = 99%+: N = 118 17%	
Clonal evolution (AP and BP/BC)	Kantarjian, Cortes, 2002[90] (quality 5/6) BP	Relationship to Major CR: None: N = 28 64% p=0.15 Clonal evolution: N = 43 47%	None: N = 28 median survival = 7.5 mo Clonal evolution: N = 43 median survival = 4.5 mo p=0.49
	Sawyers, 2002[3] (quality 5/6) BP		None: N = 67 median survival = 10.5 mo Clonal evolution: N = 111 median survival = 5.5 mo p=0.003
	Sureda, 2003[4] (quality 4/5) BC		Ph+ only: N= 18 1-yr OS = 57% (SD 18%) Clonal evolution: N = 12 1-yr OS = 0% p=0.0043
	Talpaz, 2002[87] (quality 5/6) AP	Relationship to disease progression: None: N = 100 38% p=0.086 Clonal evolution: N = 60 50%	
Cyotgenetic clonal evolution (likely overlapping patient populations)	Braziel, 2002[67] (quality = 3/6) CP-IFN-r	Presence or absence of clonal evolution not related to response (3 of 19 pts with complex cyto–were distributed among three response groups)	
	Cortes, Talpaz, et al.., 2003 [1](quality = 6/6) CP	Relationship to Major CR: None: N= 295 65% p=0.1 Clonal evolution: N = 270 54%	Relationship to survival: None: N= 295 92% p=0.002 Clonal evolution: N = 270 77%
	El-Zimaity, 2004[97] (quality = 3/6) CP & AP	Shorter duration of response RR 4.34 (SE 0.47) p=0.002	

Table 11. Tumor characteristics predictive of disease response or survival: Group 1A -- DNA factors at the start of imatinib therapy			
Prognostic factor	**Studies indicating an association and quality**	**Strength of association with tumor response**	**Strength of association with survival**
	Kantarjian, Sawyers, et al.,2002[2] (quality = 6/6) BP	Relationship to Major CR: None: N = 379 61% p=0.18 Clonal evolution: N = 54 52%	
	Karntarjian, Talpaz, et al., 2002[70] (quality 5/5) CP-IFN-r	Relationship to Major CR: None: N= 222 65% p=0.02 Clonal evolution: N = 27 41%	Relationship to survival: None: N= 222 98% p<0.01 Clonal evolution: N = 27 84%
	Kantarjian, O'Brien, 2004[Kantarjian, 2004 #151 (quality 5/6) CP-IFN-r		None: 2 yr survival = 87% 4 yr survival = 66% Clonal evolution: 2 yr survival = 66% 4 yr survival = 55% p=0.05
	Kantarjian, O'Brien, 2003[98] (quality 3/6) CP-new diagnosis		Relationship to estimated 5-yr survival: None: N= 779 66% p=0.95 Clonal evolution: N = 58 65% (only 187 received I; others = IFN)
	Karntarjian, Cortes, et al., 2004[72] (quality 5/6) CP-IFN-r		Relationship between baseline clonal evolution and 4-yr survival: None: N= 237 88% p=0.007 Clonal evolution: N = 24 69%
	Marin, Marktel, et al., 2003[75] (quality 2/5) CP	Relationship to CCR: None: N= 24 33% p=0.41 Clonal evolution: N = 31 24%	Relationship to OS: None: N= 111 81% p<0.0001 Clonal evolution: N = 31 32%
	Marktel, 2003[99] (quality 5/6) CP-IFN-r	Relationship to PFS at 18 mos: None: N= 50 94% p<0.0001 Clonal evolution: N = 10 34% Confirmed in multivariate model (RR 14.8, CI 2.8-76.6)	
	O'Dwyer, 2004[96] (quality 2/5) CP-IFN-r	Relationship to hematologic relapse: None: N= 119 9% p<0.0001 Clonal evolution: N = 22 50% HR 4.912 (CI 1.944-12.409)	
CD34+ cells in the bone marrow	*Marin, 2004[100] (quality *) CP	Relationship to PFS: CD34+ % of BM cells ≤2% (N=44)–PFS @ 3-yr = 77% CD34+ % of BM cells >2% (N=14)–PFS @ 3-yr = 36% p=0.006	
	*Elliot, 2004[101] (quality *) phase unclear	CD34+ cells/10hpf predicts CCR	

Table 11. Tumor characteristics predictive of disease response or survival: Group 1A -- DNA factors at the start of imatinib therapy

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
Variant Ph translocations	El-Zimaity, 2004[97] (quality = 3/6) CP & AP	Shorter duration of response RR 1.33 (SE 0.76) p=0.71	
Chromosome 9 deletions	Huntly, 2003[51] (quality = 2/6) CP-new diagnosis, AP, BP	Progression free survival for CP patients with (N = 35) and those without deletions (N=172) is significantly different; those with deletions did worse. p=0.02 Progression free survival for AP + BP patients with (N = 15) and those without deletions (N=106) is significantly different; those with deletions did worse. p=0.02	Overall survival for patients with (n = 54) and those without deletions (n=297) not significantly different; median follow up 48 months. p=0.18
Genes known to be related to apoptosis and drug resistance in leukemia cells	Lange, 2003[102] (quality 4/6) BC	8 candidate genes studied via Q-RT-PCR; when compared to healthy controls, BCL-XL, MDR-1, BAX, MRP-1 and survivin is overexpressed in BC (all p<0.05) MDM-2 is underexpressed (p=0.001) The only candidate gene correlated with tumor response was MRP-1 (med <24 10/16 responses, ≥24 5/21, p=0.018; multivariate model OR of no response with high MRP-1 = 14.4 (p=0.011)	
Genomic microarrays	McLean[103] (quality 5/6) CP	Used microarray technology to evaluate the signature of >1000 genes and develop a genomic expression profile that is characteristic of CR in CP-CML Pt met ideal microarray profile: OR for CCR = 200 (19-3096; N=66) OR for MCR = 19.9 (6-67; N=90)	

Abbreviations: * = abstract; AP = Accelerated phase; BC = Blast crisis; BM = bone marrow; BP = Blastic phase; CI = 95% confidence interval; CML = Chronic myelogenous leukemia; CP = chronic phase; CR = cytogenetic response; CCR = complete cytogenetic response; cyto = cytogenetics; hpf = high powered fields; HR = Hazard Ratio; I = Imatinib; IFN = Interferon; M = Male; MCR = major molecular response; N = Number; NR = not reported; OR = Odds ratio; OS = Overall Survival; PFS = progression-free survival; Ph+ = Philadelphia chromosome positive; pt(s)=patient(s); RR = relative risk;

Molecular predictors: Group 1B—DNA factors monitored during imatinib therapy

Cytogenetic response (CR) is the most commonly used surrogate marker of tumor response for CML. Its relationship to PFS and OS in the setting of imatinib therapy has been confirmed by at least seven studies involving all phases of CML.[8, 62, 68, 72, 75, 83, 96] Timing of the CR is also important. Across the analyses that evaluated the time course of the CR, CR by 3 or 6 months strongly predicted PFS and OS. [62, 72, 75] In the only study that compared timepoints, partial CR by 6 months was most predictive of survival[72]

Similarly, the degree of reduction in CD34+ cells in the bone marrow can be considered another surrogate marker of tumor response. Marin demonstrated that the degree of reduction of CD34+ cells in CML in the setting of imatinib treatment correlated with progression free survival (RR 0.88, 95 percent CI 0.53-0.93).[100] This is consistent with imatinib decreasing the percentage of blasts and normalization to a CHR.

In summary, DNA factors monitored during therapy that predict better tumor response and/or survival include the following:

- Cytogenetic response; and,
- Degree of reduction of CD34+ cells in the bone marrow.

Table 12. Tumor characteristics predictive of disease response or survival: Group 1B—DNA factors evaluated during imatinib therapy

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
Cytogenetic response to imatinib	Marin, Marktel, Szydlo, et al., 2003[68] (quality 5/5) CP-IFN-r	Achieved at least a minor CR with I: RR for PFS = 0.09 (CI 0.03-0.25, p<0.0001) No cytogenetic response with I: RR for OS = 1.94 (CI 1.22-3.01, p=0.0053)	Achieved at least a minor CR with I: RR for OS = 0.13 (CI 0.05-0.39, p=0.0002) No cytogenetic response with I: RR for OS = 1.69 (CI 1.09-2.64, p=0.02) Adjusted probabilities of OS at 8 years were 78% (CI 51-93%) for responders, 23% (CI 18-29%) for IFN refractory historical controls not getting I, and 6% (CI 2-17%) for non-responders
	O'Dwyer, 2004[96] (quality 2/5) CP-IFN-r	Relationship of MCR to hemotologic relapse: No MCR: N= 77 26% p=0.0339 MCR: N = 64 3% HR 0.193 (CI 0.042-0.883)	
	Rosti, 2004[8] (quality 4/5) CP		Achieved at least a MCR with I: OS estimated from KM at 26 mo median f/u No MCR = 92% p=0.037 MCR = 97%
	Silver, 2004[83] (quality *) CP, AP, BP		AP: Relationship between MCR at 3 mo and 3-yr survival: MCR at 3 mo - 85% 3-yr OS No MCR - 52% 3-yr OS p<0.001 CP: Relationship between at least a MinorCR at 6 mos and 3-yr survival: MinorCR at 6 mo - 96% 3-yr OS No MinorCR at 6 mo - 86% 3-yr OS p<0.001
	Karntarjian, Cortes, et al., 2004[72] (quality 5/6) CP-IFN-r	Relationship between Major or Minor CR and 4-yr PFS: CR = 93% No CR = 55% p<0.0001 Relationship between Major CR at 6 mo and 4-yr PFS: CR = 94% No CR = 51% p<0.0001	Relationship between MCR or MinorCR and 4-yr OS: CR = 95% No CR = 72% p<0.0001 Relationship between MCR or MinorCR at 6 mo and 4-yr OS: CR = 96% No CR = 70% p<0.0001 In multivariate analysis, MinorCR or MCR at 3 and 6 mo predict survival (p=0.03 and 0.01, respectively).

Table 12. Tumor characteristics predictive of disease response or survival: Group 1B—DNA factors evaluated during imatinib therapy

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
	*Guilhot, 2004[62] (quality *) CP-new diagnosis Marin, Marktel, Bua, et al., 2003[75] (quality 2/5) CP	Relationship between MCR at 6 mo and 30-mo PFS: MCR at 6 mo (n=407) - 97% No MCR at 6 mo (n=124) - 89% p<0.001 Relationship to PFS (described in terms of % of Ph+ metaphases at 3 months): Ph+ 0-65% (Minor CR + MCR): N= 52 83% p=<0.0001 Ph+ > 65% (No CR): N = 88 32%	Relationship between MCR at 6 mo and 30-mo OS: MCR at 6 mo (n=407) - 97% No MCR at 6 mo (n=124) - 92% p=0.0162 Relationship to OS: Ph+ 0-65%: N= 52 96% p=<0.0001 Ph+ > 65%: N = 88 52%
Change in CD34+ cells in the bone marrow	*Marin, 2004[100] (quality *) CP	Degree of reduction of CD34+ cells–RR for PFS = 0.88 (CI 0.53-0.93) p=0.006	

Abbreviations: * = abstract; AP = Accelerated phase; BP = Blastic phase; CI = 95% confidence interval; CP = Chronic phase; f/u = follow up; HR = Hazard Ratio I = Imatinib; IFN = Interferon; IFN-r = IFN refractory; K-M = Kaplan-Meier; OS = overall survival; EFS = event-free survival; M = Male; MCR = major molecular response; minorCR= minor molecular response; OS= Overall Survival; PFS = progression-free survival; pt(s)=patient(s); RR = relative risk

Molecular predictors: Group 2–Production of the RNA message

All of the RNA factors identified related to quantification of BCR-ABL mRNA transcripts and evaluation of their time course using Q-RT-PCR. All phases of CML were studied. A decrease in mRNA transcripts with treatment is a "molecular response" (MR), and is a surrogate marker of CML tumor response. RNA factors can also be considered in terms of evaluation prior to initiation of imatinib therapy and then followup evaluation during treatment.

Nine studies support the association between MR and overall tumor response.[5-12] An individual patient's best MR predicts survival and those with very low levels of residual disease (median ratio <0.1 percent) have the more durable Complete CRs.[10] Among all patients in the IRIS study who achieved a Complete CR, those who received imatinib had a greater MR than those who received interferon plus cytarabine (p=0.036).[11]

Response to imatinib is independent of BCR-ABL mRNA transcript number at the start of treatment.[6, 55, 104] However, molecular monitoring during imatinib therapy is predictive of overall tumor response. Generally, this is considered in terms of transcript level or log reduction in transcript levels at 1, 3, 6, or 12 months. Median log reduction of > 2 at both 3 and 6 months was predictive of continued tumor response at 24 months.[33] Median log reduction of $\geq$ 3 at 12 months was also predictive of continued tumor response at 24 months.[11] Similarly, when the BCR-ABL/ABL ratio is <50 percent at 4 weeks, the PFS at 500 days is 100 percent, vs. 45 percent for those who do not achieve a ratio of <50 percent.[48] Based upon data from the IRIS study, BCR-ABL transcript levels did not decrease substantially after 24 months on imatinib treatment.[8, 113] There are also substantially more IRIS patients that received imatinib with $\geq$3 log reductions in transcript levels than those who received interferon plus cytarabine.[11]

In summary, factors related to production of the RNA message that are monitored during therapy and predict better tumor response include the following:

- Molecular response;
- > 2 log reduction in BCR-ABL mRNA transcripts at 3 or 6 months;
- $\geq$ 3 log reduction in BCR-ABL mRNA transcripts at 12 months; and,
- BCR-ABL/ABL ratio <50 percent at 4 weeks.

Table 13. Tumor characteristics predictive of disease response or survival: Group 2–Production of the RNA message		
Prognostic factor	**Studies indicating an association and quality**	**Strength of association with tumor response**
Molecular response as a marker of tumor response	Paschka, 2003[10] (quality = 4/6) CP-IFN-r	Best individual molecular ratios in patients who achieved a MCR and subsequently relapsed were significantly higher than that of patients who remained in CCR, median f/u 13 mo (p=0.0017) BCR-ABL/ABL Median All pts = 0.086 (0-3.9) Relapse = 1.4 (0.013-7.8) Continuous CCR = 0.071 (0-3.9) All pt who achieved median ratio <0.1% are in CCR
	Müller, 2003[104] (quality 5/6) CP-new diagnosis	Median BCR-ABL/ABL ratio at start of I (N=98) was 51% (1-210%) Median for CR pts (N=85): 0.067% (0-5.7%) Median for PR pts (N=5): 1.4% (0.18-11%) Median for MinorR pts (N=7): 27% (6-69%) Median for pts in NR (N=2): 42% (38-45%)
	Hughes 2003 (quality = 6/6)[11] CP- new diagnosis	Relationship between CCR and reduction in level of transcripts: I-treated in CCR (N=333): 2.5 log reduction IFN+cytarabine in CCR (N=37): 2.2 log reduction p=0.036
	Merx, 2002[105] (quality = 5/5) CP-IFN-r	Median BCR-ABL/ABL ratio at start of I (N=120) was 67% (0.01-100%) Median for CR pts (N=50): 0.85% (0.018-21%) Median for PR pts (N=42): 6.7% (0.5-94%) Median for Minor R pts (N=33): 45% (6-100%) Median for NR pts (N=50): 46% (6-100%) CR to PR ($p < 0.0001$) PR and MinorR ($p < 0.0001$), MinorR and NR (p NS)
	Rosti, 2004[8] (quality 4/5) CP-IFN-r	>2 log reduction in the BCR-ABL/B_2 microglobulin transcript ratio in 76/85 (89%) pt in CCR with I and 0/23 (0%) pt in PCR
	Stentoft, 2001[7] (quality 4/5) AP & CP	Longitudinal plots of BCR-ABL transcripts derived from blood and bone marrow samples correlate (i.e. peripheral blood assessments are adequate) On plots, 1 log reduction in BCR-ABL transcript levels correlate with CCR (strength of association not given)
	Wu, 2002[6] (quality 3/5) CP, AP & BC	Longitudinal plots of BCR-ABL transcript copy numbers correlate with cytogenetic response
	*Cortes, Talpaz, OBrien, Giles, et al., 2004[5] (quality *) CP-new diagnosis	Relationship between increasing transcript levels and relapse at 24 mos: <0.05 increase–0/44 (0%) loss of CCR 0.05-1 increase–6/33 (18%) >1–5/11 (45%) p=0.0001

Table 13. Tumor characteristics predictive of disease response or survival: Group 2–Production of the RNA message		
Prognostic factor	**Studies indicating an association and quality**	**Strength of association with tumor response**
	Moravcova, 2004[9] (quality 3/6) CP-IFN-r	6/11 CP pts achieved CCR with rapid decrease in transcript 18-2600 fold at 6 mo, and 37-12500 fold at 12 mo; no BP or AP pt (0/8) showed this trend
	Karntarjian, Talpaz, et al., 2004[12] (quality = 5/5) CP-IFN-r	If BCR-ABL/ABL is <0.05%, then all pt (N=71) had a CCR and none relapsed by 10 mo median f/u
Prognostic value of baseline transcript levels	Müller, 2003[104] (quality 5/6) CP-new diagnosis	Median BCR-ABL/ABL ratio at start of I (n=98) was 51% (1-210%) Response to I was independent of BCR-ABL level at start of therapy
	Hochhaus, 2002[55] (quality = 3/6) CP	Relationship between presence of higher ratio and resistance expressed as the ration of BCR-ABL/G6PD: Prior to Imatinib 4.6 % With Imatinib resistance 6.0% p=NS
	Wu, 2002[6] (quality 3/5) CP, AP & BC	BCR-ABL copy number at baseline was not significantly different among I treated patients who ultimately did or did not have cytogenetic response (p=0.09)
Prognostic value of transcript trends while on imatinib treatment	Branford, 2003[33] (quality = 5/6) CP-new diagnosis	Among I-treated pts (n=28), median log reduction is associated with MMR at 24 mo ▪ Med log reduction > 2 versus < 2 at 3mo (100% vs. 54%; p<0.001 by K-M) ▪ Med log reduction > 2 versus < 2 at 6 mo (86% vs. 0%; p<0.001 by K-M) and incidence of progression • Med log reduction <2 versus > 2 at 6 mo (56% vs 4%; p=0.002 by K-M)
	Hughes 2003 (quality = 6/6)[11] CP- new diagnosis	Relationship between ≥3 log reduction@ 12 mo & being progression free @ 24 mo: ≥3 log reduction @ 12 mo: 100% <3 log reduction: 95% no CCR: 85% p=<0.001 Relationship between ≥3 log reduction and CCR: ≥3 log reduction at 6 months: I-treated in CCR: 42% IFN+cytarabine in CCR: 13% p=0.03 ≥3 log reduction at 12 months: I-treated in CCR: 57% IFN+cytarabine in CCR: 24% p=0.003

Table 13. Tumor characteristics predictive of disease response or survival: Group 2–Production of the RNA message		
Prognostic factor	**Studies indicating an association and quality**	**Strength of association with tumor response**
	Rosti, 2004[8] (quality 4/5) CP-IFN-r	Median transcript level in pt who reached CCR in <6 mo after start of I: Baseline 0.2330 3 mo 0.0039 6 mo 0.0003 12 mo 0.0005 24 mo 0.0001 Median transcript level in pt who reached CCR in 9-12 mo after start of I: Baseline 0.2490 3 mo 0.0213 6 mo 0.0046 12 mo 0.0034 24 mo 0.0002
	Müller, 2003[104] (quality 5/6) CP-new diagnosis	After 3 mo, CCR within the first year could be predicted using the ratio BCR-ABL/ABL (p=0.0026) or BCR-ABL/G6PD (p=0.0074). Empirically derived statistical cutoff point for best prediction of CCR after 12 mo was a ratio BCR-ABL/ABL of 10% at 3 months with a positive predictive value of 71% and a negative predictive value of 82% Empirically derived statistical cutoff point for best prediction of CCR after 12 mo was a reduction of the ratio BCR-ABL/G6PD of 0.3 log after 3 mo with a positive predictive value of 76% and a negative predictive value of 80%, respectively
	*Müller, 2004[106] (quality *) CP, AP & BC	BCR-ABL/ABL ratios after 12mo were lower in I pts in CCR than I pts with subsequent relapse (0.18-0.60%, p=0.04) In n=132 pt from the IRIS study, no pt with BCR-ABL/ABL <0.12% (>3 log reduction) after 12 mo relapsed
	*Branford, 2004[32] (quality *) CP	BCR-ABL levels do not appear to decrease substantially after 24 mo on I (see efficacy table, IRIS trial)
	*Cortes, Talpaz, OBrien, Giles, et al., 2004[5] (quality *) CP-new diagnosis	Relationship between 1 log reduction in transcript levels after 3 mo and 3 log reduction at 24 mo: >1 log: 90% < 1 log: 55% p=0.0002
	*Press, 2004[107] (quality *) CP	Relationship between ≥2 log reduction in transcripts at time of CCR and relapse over 29 mo median f/u ≥2 log reduction–3/10 (10%) relapsed <2 log reduction–22/49 (45%) relapsed OR 7.1 (CI 1.9-26)

Table 13. Tumor characteristics predictive of disease response or survival: Group 2–Production of the RNA message		
Prognostic factor	**Studies indicating an association and quality**	**Strength of association with tumor response**
	Wang, 2003[48] (quality 2/5) All phases and relapse states including after allogeneic SCT	Relationship to PFS at 500 days estimated from K-M: BCR-ABL/ABL ratio @ 4 wk <50% - 100% BCR-ABL/ABL ratio @ 4 wk >50% - 45% p=0.01 BCR-ABL/ABL ratio @ 3 mo <10% - 100% BCR-ABL/ABL ratio @ 3 mo >10% - 38% p=0.003
	Wu, 2002[6] (quality 3/5) CP, AP & BC Merx, 2002[105] (quality = 5/5) CP-IFN-r	BCR-ABL copy number at 3mos was significantly reduced among I treated patients who had a cytogenetic response (p=0.02) and this trend increased with time (p=0.04 at 6 mo, p=0.005 at 9 mo, and p=0.0008 at 12 mo) Median BCR-ABL/ABL ratio at start of I (n=120) was 67% (0.01-100%) Median for CR pts (n=50): 0.85% (0.018-21%) Median for PR pts (n=42): 6.7% (0.5-94%) Median for Minor R pts (n=33): 45% (6-100%) Median for NR pts (n=50): 46% (6-100%) CR to PR (p < 0.0001) PR and MinorR (p < 0.0001), MinorR and NR (p NS) Probability of MCR after 6 mo was higher when ratio <20% at 2 mo (p=0.007)

Abbreviations: * = abstract; AP = Accelerated phase; BP = Blastic phase; CI = 95% confidence interval; CML = Chronic myelogenous leukemia; CP = chronic phase; CR = cytogenetic response; CCR = complete cytogenetic response; f/u = follow-up; I = Imatinib; IFN = Interferon; K-M = Kaplan-Meier; M = Male; MMR = major molecular response; NR = no response; NS = not significant; OR = Odds ratio; OS = Overall Survival; PCR = polymerase chain reaction; PFS = progression-free survival; PR = partial response; pt(s)=patient(s); RR = relative risk; SCT = Stem cell transplant

Molecular predictors: Group 3–Interaction between the tyrosine kinase protein and imatinib

Mutations in the tyrosine kinase protein have been an active area of inquiry. Only three studies met the eligibility requirements for this review and were therefore included on Table 14.[55, 108, 145] These studies were of lower quality than the majority of included articles, mainly because they were basic science reports with minor clinical correlations. Since they focused on the basic science, there was less attention in the manuscript to the traditional quality reporting items that are usually considered during secondary clinical research summaries. Further, several studies did not meet the explicit criteria for this review and therefore were highlighted within the "future directions" studies only (Table 1d, "Mechanism of action"). These studies were excluded primarily because they did not clearly provide quantitative assessment of the correlation between the molecular findings and response to imatinib. Taken together, the group of studies presented in Tables 1d and 14 suggest that there is substantial current research effort focusing on the molecular mechanisms of imatinib resistance at the protein level. Some of this work focuses on the gene expression corresponding to imatinib resistance, such as the *MRP-1* studies described previously. Others evaluate the relationship between mutations in the tyrosine kinase domain that lead to changes in the protein which might confer imatinib resistance.[Shah, 2002 #292; Hochhaus, 2002 #285; Soverini, 2004 #858] Of particular interest are mutations in the p-loop of the protein where ATP binds and the protein pocket where imatinib binds.[112, 114-116] These data are in development; clear evidence of the clinical utility of such information for predicting tumor response and overall survival with imatinib is not available yet.

White and colleagues described an in vitro assay to predict imatinib's ability to inhibit phosphorylation of the adaptor protein Crkl.[145] Crk1 binds BCR-ABL directly and plays a functional role in BCR-ABL-mediated transformation to cancerous CML cells by linking the kinase signal to downstream effector pathways.[146] Previous in vitro studies have shown that Crkl phosphorylation correlated with untreated disease and relapse after imatinib, while lack of phosphorylation correlated with response to imatinib.[146] White et al.. measured in vitro levels of Crkl phosphorylation of the patients CML cells in the setting of imatinib; using a scoring system of high and low levels of Crkl phosphorylation measured by the IC50, they correlated the IC50 to Major MR. Among newly diagnosed CP CML patients, low IC50 at diagnosis correlated with ability to achieve a Major MR at 12 months. This correlation was particularly strong for those patients with low Sokal scores.

In summary, protein factors related to the interaction between the tyrosine kinase protein and imatinib that can be monitored during therapy and that predict <u>better</u> tumor response include the following:

- In vitro evidence of imatinib's ability to reduce Crkl phosphorylation.

Table 14. Tumor characteristics predictive of disease response or survival: Group 3–Interaction between the tyrosine kinase protein and imatinib

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response
Mutations in tyrosine kinase domain (may lead to I resistance)	Hochhaus, 2002[55] (quality = 3/6) CP, AP & BC	Median time to relapse: Mutation present (35%)=237 days Mutation not present (65%)= 251 days p=NS
	Shah, 2002[108] (quality 1/6) CP & AP	3/4 pt with CP CML with CHR on I and with kinase domain mutations progressed, whereas 1/9 without mutations progressed
Adapter protein phosphorylation	*White, 2004[145] (quality *) CML-unclear phase-newly diagnosed	In vitro assay to predict imatinib inhibition of adaptor protein Crkl phosphorylation (measured by IC50). Relationship between IC50, Sokal score and Probability of achieving a MMR at 12mos: All (N=57 newly diagnosed CP CML patients prior to I): Low IC50: MMR = 47% High IC50: MMR = 23% p=0.034 Low Sokal (N=19): Low IC50: MMR = 67% High IC50: MMR = 20% p=0.037 Intermed Sokal (N=15): Low IC50: MMR = 50% High IC50: MMR = 22% p=NS Intermed Sokal (N=16): Low IC50: MMR = 17% High IC50: MMR = 0% p=NS

Abbreviations: *= abstract; AP = Accelerated phase; BC = Blast crisis; CML = Chronic myelogenous leukemia; CP = chronic phase; CHR = complete hematological response; I = Imatinib; MMR = major molecular response; minor = minor response; NS = not significant

Molecular predictors: Group 4—Other factors

Several other molecular studies are presented in Table 15. Bone marrow cellularity decreases when CML responds to imatinib, an expected finding.[109] Myelosuppression due to imatinib of ≥ Grade 3 predicts poorer Major MR rates with imatinib, and if the myelosuppression persists for > 2 weeks the chance of Major MR is even lower.[110]

The concept of "cure" and complete disease eradication in CML is murky. Even when patients are in CCR, evidence of CML can be found. Bhatia and colleagues showed that all of the 15 patients in Complete CR studied had evidence of BCR-ABL in their CD34+ cells as identified by FISH or RT-PCR up to 61 months after starting imatinib.[27] O'Dwyer reported similar findings for seven patients in Major CR.[35] Using sensitive RT-PCR techniques Paschka et al. found evidence of BCR-ABL in all samples of CCR patients on imatinib.[10] Taken together, these data support the notion that complete remission in CML may be conversion to a low grade chronic disease with continuous potential for relapse over the long term. Using the previous definition from the transplantation literature that "cure" is continued Complete CR at 5 years,[13, 34] "cure" may be a relative state of disease control rather than complete eradication.

In summary, other factors monitored during therapy that predict poorer tumor response include the following:

- Myelosuppression due to imatinib of greater than Grade 2,
- Myelosuppression persisting for more than two weeks.

Table 15. Tumor characteristics predictive of disease response or survival: Group 4—Other factors

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
Bone marrow cellularity	Frater, 2003[109] (quality = 1/5) CP-IFN-r	BM cellularity 100% N =13 with decrease when responds to I	
Myelosuppression	Sneed, 2003[110] (quality 5/6) CP-IFN-r	Any myelosuppression ≥Grade 3: Yes (N=76) MCR 62% CCR 45% No (N=67) MCR 78% CCR 64% P=0.01 Any myelosuppression ≥Grade 3 for > 2wk duration: Yes (N=50) MCR 58% CCR 36% No (N=93) MCR 75% CCR 63% P=0.001	
Persistent BCR-ABL in CD34+ cells after CCR with I	Bhatia et al., 2003[27] (quality = 2/5) CP & AP	100% (N=15) had persistent evidence of BCR-ABL by FISH or RT-PCR up to 61 months (range 1–61) after starting I	
Evidence of BCR-ABL in CCR	Paschka, 2003[10] (quality = 4/6) CP, AP & BC	21/68 (31%) samples derived from pts in CCR by conventional cytogenetics have evidence of residual disease by HM-FISH All (N=234) samples of CCR patients had evidence of BCR-ABL by RT-PCR	
Abnormal cytogenetics in Ph- cells	O'Dwyer, 2003[35] (quality 2/5) CP-IFN-r	Clones with abnormal cytogenetics could be identified in the Ph- cells of 7 patients in MCR; link to disease outcome not presented	

Abbreviations: AP = Accelerated Phase; BC = Blast crisis; CP = Chronic Phase; CCR = complete cytogenetic response; I = Imatinib; MCR = Major cytogenetic response, Ph- = Philadelphia chromosome negative; pt(s) = patient(s)

Discussion

In this section we summarize the findings of the review in terms of answering the key questions initially posed, and then discuss the clinical and research implications of these data.

CML is a rare hematological cancer that affects <5,000 Americans yearly. An excessive number of abnormal white blood cells are produced that eventually take over the body's ability to produce normal cells. In at least 95 percent of cases, CML starts with the formation of the Philadelphia chromosome (Ph), also known as the 9;22 translocation that forms the BCR-ABL gene. BCR-ABL is transcribed into mRNA and then translated into the BCR-ABL tyrosine kinase protein. This tyrosine kinase is a continuously active protein that sends the cancer signal of uncontrolled cell division. Imatinib binds to the BCR-ABL tyrosine kinase protein and turns off this signal.

There are three clinical phases of CML–chronic phase, accelerated phase, and blastic phase/blast crisis. These phases are characterized by their tumor aggressiveness and prognosis. Therapeutic options include imatinib, interferon alpha with or without cytarabine, hydroxyurea, busulfan, other conventional chemotherapies, and stem cell transplantation (bone marrow transplantation, SCT). Allogeneic SCT is the only curative treatment for CML, however it is only available for 20-25 percent of patients due to lack of a suitable donor;[147] 15-30 percent treatment-related mortality can be expected with SCT.[17]

1. *In patients with chronic myeloid leukemia, what is the effect of imatinib compared to interferon alpha or best supportive care on overall survival, disease free survival, remission rates (PR, CHR, cytogenetic remission), and quality of life (QOL)?*

There is convincing evidence of the efficacy of imatinib for CML in all clinical settings as described in the matrix below. For many of these studies the results are still early and median survival has not been reached. This is especially true for those studies of CP CML. Thus, Complete CR (CCR) rates are compared across studies, as Complete CR is a major indictor of tumor response, is correlated with PFS and OS as demonstrated in Table 12, and is a major goal of therapy.[22]

Figure 6: The CML therapy matrix with Complete CR estimates

		PHASE		
		Chronic phase	**Accelerated phase**	**Blastic phase/blast crisis**
EXTENT OF PREVIOUS THERAPY	**Newly diagnosed**	Phase III: I: 74%[59] IFN + AraC: 9%,[59] 15%[42] IFN alone: 9%[42] Phase II: I 60-81%[63, 98] Historical control (includes IFN): 5-32%[63, 98]	I: 11-19%[82, 87] Estimated IFN: <5%	I: 0-10%[3, 4, 89, 90] Estimated IFN: <<5%
	Interferon refractory or intolerant	I: 31-62%[2, 44, 73, 148] Historical control with IFN: 7-19%[44]	I: 11-19%[82, 87] Estimated IFN: <5%	I: 0-10%[3, 4, 89, 90] Estimated IFN: <<5%
	Previous stem cell transplant/heavily pretreated	I: 33-85%[37 77-81] Historical control with IFN: 7-19%[44] (from above)	I: 11-19%[82, 87] Estimated IFN: <5%	I: 0-10%[3, 4, 89, 90] Estimated IFN: <<5%
	Imatinib refractory or intolerant	Future Directions	Future Directions	Future Directions

Abbreviations: I = Imatinib; IFN = interferon; Ara-C = cytarabine

The most compelling evidence for the efficacy of imatinib is the IRIS trial, an international multi-center phase III trial of imatinib vs. interferon plus cytarabine as initial therapy for newly diagnosed chronic phase CML.[59] A previous phase III study by Guilhot et al. had demonstrated that interferon plus cytarabine rendered superior cytogenetic response and survival when compared to interferon alone.[42] Another phase III study by Baccarini et al. of interferon vs. interferon plus cytarabine was more equivocal with interferon plus cytarabine yielding better cytogenetic responses but similar survival.[149] Complete CR rates were slightly better in the Guilhot study than the Baccarini study (15 percent vs. 8 percent, respectively). Thus, the IRIS comparison group of interferon plus cytarabine is as good as interferon alone, if not better. Use of the interferon plus cytarabine arm from the Guilhot study as a baseline comparator when needed is also reasonable.

In the IRIS study, imatinib was clearly superior to interferon plus cytarabine in terms of cytogenetic response (74 percent vs. 9 percent),[59] molecular response (42% vs. 13% of those with Complete CR at 6 months),[11] PFS (92% vs. 74% at 18 months),[59] and QOL (TOI 84.4 vs. 67.7).[60, 61] Estimates of OS were not significantly different between imatinib and interferon plus cytarabine in the original IRIS publication.[59] Since 58 percent of participants on the interferon plus cytarabine arm crossed over to imatinib in this trial, estimates of OS for the individual groups were difficult. In a follow up report on the IRIS trial, the 30-month OS for imatinib was 95 percent.[62] This compares favorably to the previously reported 36-month OS rates for interferon plus cytarabine of 86 percent in the Guilhot study.[42] QOL was studied as part of the IRIS trial, and patients receiving imatinib had significantly better total QOL, social/family well-being, and emotional well-being (Table 9).[60, 61] Pasquini el al. reported similar findings in a Phase II trial conducted in Brazil.[76]

There were some criticisms of the IRIS trial. Most notably, the overall mean dose intensity on the interferon plus cytarabine arm was only 58 percent of the target dose, with the dose intensity of the imatinib arm 97 percent of target.[147] This compares similarly to the Guilhot et al. trial of interferon vs. interferon plus cytarabine where only 57 percent achieved the target dose intensity with interferon.[42] The Baccarini study reported higher rates of achieving target dose intensity with interferon (70 percent),[149] but did not report different survival rates than those seen with the Guilhot et al. trial.[147] The other main criticism of the IRIS trial is that PFS was calculated using loss of CHR, loss of Major CR, or increases in WBC as criteria for progression.[147] This criticism is reflective of the variability in definition of disease progression in CML. For this reason, comparison of more uniform endpoints across trials such as Complete CR or OS may be a more objective measure of relative efficacy.

Efficacy is clearly different by phase of disease and timing within the treatment algorithm, as reflected in Figure 6. Earlier phases and patients treated in the first-line setting had the highest response rates. CP patients treated earlier in the course (i.e., <1 year from diagnosis) had better response rates with imatinib than those treated later in the CP period.[44] In the post-interferon setting, the reason that the interferon was discontinued influenced response rates.[2] Regardless, significant Complete CR rates are seen with imatinib in all treatment settings, including patients who are heavily pre-treated with myelotoxic chemotherapy with or without SCT. The response rates for the heavily pre-treated CP patients are similar to those of the interferon-refractory or intolerant CP patients. The historic control group for the interferon-refractory or intolerant CP patients likely reflects the same or better response rates than would an appropriate control group for the heavily pre-treated CP patients; this group has been used for the comparator group in the heavily-pretreated CP setting.

The AP and BP studies do not report comparator groups, however previous studies suggest that fewer than 5 percent of AP patients achieve a Major CR with interferon.[150] The Complete CR rate for AP treated with interferon can therefore be expected to be lower than 5 percent, and BP lower yet. Studies identified in this review reported Complete CR rates with imatinib of 11-19 percent for AP and 0-10 percent for BP (Figure 6). One year survival rates of 74 percent (95 percent CI 68-81 percent) for AP patients treated with imatinib compare favorably to the historic 6-18 month median life expectancy described in Figure 2.[87] Similarly, the median OS of 6.5-7 months for BP patients treated with imatinib is longer than the historic prognosis of 3-6 months.[2]

An important limitation to the assessment of efficacy is that many of the studies cited have overlapping populations. This does not necessarily subtract from the value of the analysis as the different reports and studies are usually addressing different issues, but needs to be kept in mind when considering sample sizes quotes. The estimation of efficacy and predictors of response is also limited by the rapidly evolving nature of this field–making it difficult to ensure that an evidence report is up-to-date after an arbitrary evidence review date.

Other important issues of imatinib efficacy include timing of effect, appropriate dose, and relationship to SCT. Efficacy analyses should be considered in terms of duration of exposure to imatinib. In the setting of newly diagnosed CP CML, molecular response rates to imatinib increased steadily over the first two years on imatinib and then did not change substantially after 24 months.[32] Complete CR rates on imatinib increased for at least 12 months after initiation of the drug,[8, 63, 70, 73] whereas Complete CRs did not increase after 6 months on interferon-based therapies. Some authors have argued that Complete CR rates do not increase after 6 months on imatinib,[22] however this current review demonstrated that they continue to increase for up to 12 months and that periods after 12 months have been poorly studied. Nonetheless, achieving molecular and cytogenetic responses were beneficial no matter how long it took to get there (Table 12 and 13).

Patients who achieved an early response as minimally defined by either molecular response by 4 weeks or some cytogenetic response by 3 months had better PFS and OS.[48, 72] The exact milestone cut-off that should be followed is unclear. Cytogenetic response milestones have been investigated at 3 and 6 months predominantly (Table 12), although changes can be identified out to 12 months (Table 3). Molecular response milestones have been investigated for 4 weeks, 3 months, 6 months, and 12 months (Table 13). These milestones can be used to identify patients who have had a suboptimal response to imatinib. Failure to achieve a significant cytogenetic response (Major or Complete) by 6–12 months is one criteria for suboptimal response that may indicate an increased dose of imatinib or shift in treatment plan. Similarly, molecular milestones are starting to be used when such laboratory facilities are available. Failure to achieve a >2 log reduction in the number of BCR-ABL mRNA transcripts by 3– 6 months could be considered evidence of suboptimal response;[33] failure to achieve a $\geq$3 log reduction by 6–12 months could be considered suboptimal.[11] These analyses were primarily conducted with patients receiving 400 mg imatinib daily.

Starting imatinib doses are usually 400 mg daily for CP and 600 mg daily for AP and BP.[148] In accordance with FDA recommendations based upon the IRIS study, imatinib is administered daily at a dose of 400 mg in newly diagnosed CP patients.[147] Patients not achieving a CHR at 3 months or a Major CR at 12 months may be escalated to 400 mg twice daily. For Grade 2 non-hematologic toxicity, imatinib is withheld until toxicity resolves. After resolution of grade 2 toxicity, the drug is resumed at 400 mg daily. After resolution of grade 3 or 4 toxicity, the drug is resumed at 300 mg daily. There is clearly a dose response relationship with imatinib.[148] Several studies in different clinical settings support the additional therapeutic advantage of increasing to 800 mg a day. Imatinib resistance or CML relapses at 400 mg can be overcome by increasing to 800 mg, as described in the CP-interferon refractory setting.[71] Further, starting at

the 600 or 800 mg dose may induce more Complete CRs,[65, 69] but with more adverse events (Table 10).

The IRIS trial also demonstrated that imatinib was tolerable and efficacious after progression on interferon-based therapy, and that patients receiving imatinib could still go on to SCT.[59] Numerous studies presented in Tables 3, 4, 7, and 8 also support these findings. Imatinib is effective and well tolerated in the setting of disease relapse after SCT,[119-121] and it does not preclude a patient from receiving a SCT.

Given the genetic variability of the American population, an important question for targeted drugs such as imatinib is whether the clinical research findings are limited to a specific portion of the population. Ethic and racial studies related to imatinib efficacy are few. IRIS was an international multi-site trial involving patients from at least 15 countries in North America, Europe, Australia and New Zealand.[59] Deshmukh and colleagues presented a similar imatinib experience to that reported in other studies evaluating a population recruited exclusively in India.[86] The Pasquini et al. study involved participants recruited exclusively in Brazil and reported similar QOL findings to that described in IRIS.[76] Meanwhile, a retrospective chart review by George and colleagues of 26 patients from the Chicago area suggested that non-Caucasian patients had poorer response rates to imatinib than Caucasians (Table 1d).[123] Complete CR was achieved in 100% of Caucasians (6/6) and 14% of non-Caucasians (2/14). Considering all of these studies, it appears that imatinib has efficacy across genetically diverse populations, however given the findings of George et al., further studies are needed, especially in the United States.

Is there a differential effect of imatinib for patients who are $\geq$65 years of age? Two abstracts were presented at the 2004 American Society of Hematology meeting that addressed this question (Table 1d).[124, 125] Both studies suggested that imatinib was efficacious and well tolerated in patients $\geq$65 or 70 years of age, although less so than younger patients. The study by Bassi et al. suggested that patients $\geq$65 years had significantly more adverse events than those <65 and therefore poorer tolerance of imatinib and fewer Complete CRs (36% vs. 57%, p=0.001).

Does imatinib lead to "cure"? Defining "cure" in CML is difficult. Even when imatinib-treated patients are in Complete CR, evidence of CML can be found.[27 10, 35] Blast crisis can still occur in patients who developed a Complete CR on imatinib.[122] Complete remission with imatinib in CML may be a conversion to a low grade chronic disease with continuous potential for relapse over the long term. For this reason, the debate between imatinib vs. SCT in early chronic phase when possible continues.

Finally, this review of efficacy is based upon a systematic review of prospective studies that met the criteria for inclusion. Efficacy summaries reflect an overview of statistically significant reported findings, and neither reflect review of other literature nor current clinical practice. The field is evolving so quickly that such a review quickly becomes outdated and regular updates are important.

2. *In patients with chronic myeloid leukemia, what is the effect of imatinib compared to interferon alpha or best supportive care on adverse effects, tolerability, and compliance with treatment?*

Imatinib has far fewer adverse effects (any grade and grade 3/4) compared with interferon. In the IRIS trial, imatinib most commonly caused neutropenia (61 percent), thrombocytopenia (57 percent), superficial edema (56 percent), nausea (44 percent), and abnormal liver function results (43 percent).[59] Interferon plus cytarabine most commonly caused thrombocytopenia (79 percent), abnormal liver function results (74 percent), neutropenia (67 percent), fatigue (66 percent), nausea (61 percent), anemia (55 percent), and headache (43 percent). The incidence of grade 3/4 side effects was primarily hematological with imatinib (neutropenia 14 percent and thrombocytopenia 8 percent) whereas interferon plus cytarabine included fatigue (24 percent) and hematological (neutropenia 25 percent and thrombocytopenia 17 percent). The incidence of side effects increased with imatinib dose and phase of illness, as expected (Table 10). In particular, the hematologic side effects increased with advancing phases of illness. As demonstrated by Sneed et al., Grade 3/4 myelosuppression predicts poorer tumor responses with imatinib, especially when the myelosuppression lasts for longer than 2 weeks (Table 15).[110]

Compliance with imatinib was not formally presented in the studies reviewed. Discussions with authors revealed that there is a forthcoming report investigating adherence to imatinib therapy using prescription data for a total of 4043 imatinib-treated patients tracked over 14 months[151]. Overall, the compliance rate was approximately 75 percent, and persistent continuation on therapy averaged 256 days of therapy over 12 months. Suboptimal adherence to imatinib therapy may be an under-recognized problem that requires active monitoring by healthcare professionals.

3. *What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy? In addressing this question, we will focus on the following: (1) predictive patient or tumor characteristics that are related to the mechanism of action of the drug (i.e., molecular target; performance status, while a powerful predictor of outcome, is not related to mechanism of action); (2) candidates for diagnostic testing (even if not commercially or clinically available currently (e.g., PCR)); and, (3) patient or tumor characteristics that are associated with clinically important differences in treatment response.*

As presented in the Introduction (Chapter 1), there is clear correlation between clinical prognostic factors (e.g., phase of disease, previous treatment, Sokal score, splenomegaly, percentage of blasts in the peripheral blood) and tumor response or survival with imatinib. These known prognostic factors can be used to identify high risk and low risk patients in the setting of imatinib therapy in a similar manner to other treatment settings. A full review of the hazard ratios for these clinical prognostic factors was outside the scope of this review. Here we concentrate on molecular factors that predict response to imatinib and are likely to be related to the targeted action of the drug.

Prognostic factors were divided into 5 groups: 1A) DNA factors assessed at the start of therapy, 1B) DNA factors monitored during therapy, 2) production of the RNA message, 3) interaction

between the tyrosine kinase protein and imatinib, and 4) other factors (Table 11-15). Many of these have already been reviewed in the preceding section on efficacy. Additional observations are presented here.

At the start of therapy, patients with a high burden of disease as evidenced by 90-100 percent of Ph+ metaphases during cytogenetic analysis or more CD34+ cells in the bone marrow were more likely to have a poor tumor response and decreased overall survival. Similarly, evidence of clonal evolution (complex cytogenetics) in the accelerated or blastic phases of illness predicted poorer survival and increased risk of tumor progression. Cytogenetic clonal evolution was a significant predictor of risk of relapse and shortened survival, but did not consistently predict disease response. Evidence of chromosome 9 deletions predicted poorer PFS but not OS. Once imatinib therapy was started, both evidence of cytogenetic response and reduction in the numbers of CD34+ cells in the bone marrow predicted improved PFS and OS. Cytogenetic response can be used as a surrogate marker of overall CML tumor response.

Factors that relate to production of the RNA message and that predict tumor response were highlighted in the efficacy discussion. BCR-ABL mRNA transcript levels measured before therapy starts are not predictive of outcome. Molecular response using Q-RT-PCR predicts survival and durability of the tumor response; it can be used as a surrogate marker of tumor response. When the log reduction was >2 at 3 or 6 months, patients had better PFS; similarly, when the log reduction was $\geq$3 at 12 months, patients had better PFS. Reduction in the *BCR-ABL/ABL* ratio to <50 percent at 4 weeks was also predictive of better PFS. Recently authors have suggested the need to rationally test different algorithms using molecular monitoring at defined timepoints.[132]

All of the predictors just described are currently available for clinical use. In particular, cytogenetic analysis including analysis of chromosome 9 is widely available. A recent abstract indicates that peripheral blood FISH analysis is possible, but it is inferior to bone marrow samples or RT-PCR.[127] Analysis of CD34+ cells by flow cytometry is available through most reference laboratories. Reliable Q-RT-PCR for molecular monitoring is available through specialized facilities and centralized laboratories, and may not be an option for all patients at present.[22]

Newer analyses looking at genetic profiles using microarrays are in development. McLean and colleagues demonstrated that they could identify a microarray pattern characteristic of tumor response in CP CML.[152] While not currently ready for widespread use as a diagnostic test, such genetic profiling has the future potential to assist in the identification of individuals likely to respond or not respond to imatinib.[129] Similarly, individual genes associated with drug resistance have been identified; overexpression of *MRP-1* was correlated with tumor response to imatinib.[102] These studies are preliminary and not ready for clinical application, but do suggest that genetic profiles or RT-PCR analyses of the expression of individual genes other than BCR-ABL may be used in the future to assist in tailoring the use of imatinib for individual patients.

There is an evolving literature on the molecular mechanisms of imatinib resistance at the protein level.[146, 153] The majority of this literature did not meet the criteria for this review because quantitative correlations with clinical outcomes were not presented. Mutations in the tyrosine

kinase domain of *BCR-ABL* that lead to changes in the protein may disturb imatinib binding and therefore lead to poorer tumor response with imatinib. Changes of particular interest are those that lead to protein alterations in the p-loop where ATP binds and the protein pocket where imatinib binds. Such mutations that affect imatinib binding may make the drug less efficacious. Thus far the evidence for direct clinical impact has been scant. Shah and colleagues demonstrated how more CML patients with mutations in the binding domain progressed than those without mutations.[108] In four abstracts presented at the American Society of Hematology meeting in December 2004, it was suggested that ABL, p-loop and binding pocket mutations were predictive of disease progression or aggressiveness, [Soverini, 2004 #858; Corm, 2004 #846; Deininger, 2004 #844; Hochhaus, 2004 #168] while a fifth abstract suggested that these did not correlate with outcome.[112] Ideally, patients who are unlikely to have a good response to imatinib due to such mutations would be identified early and transitioned to more appropriate therapy. Some groups have used molecular monitoring to predict mutational status.[154] Analysis of 214 IRIS participants treated with imatinib revealed that 61 percent of the 56 patients with a >2-fold increase in BCR-ABL mRNA transcript levels had mutations while only 0.6 percent of the 158 with stable transcript levels had mutations.

This work on mutations that lead to altered imatinib binding and efficacy is still in development, both in terms of identification of the important mutations and their clinical impact. In order for it to have widespread clinical applicability there must be practical methods of detecting protein mutations. Soverini et al. recently described a denaturing High Performance Liquid Chromotography (HPLC) method to screen for ABL point mutations that may make routine detection of mutations more practical.[126]

Finally, White and colleagues have described an in vitro assay to predict imatinib's ability to inhibit phosphorylation of the adaptor protein Crkl.[145] This assay could be used to predict those CML likely to achieve a Major MR at 12 months before imatinib was started. This work is in an early phase and has not been widely tested, but provides another opportunity to identify patients likely to respond to imatinib and those who may need to transition to other therapies.

This work can be summarized as follows:

Figure 7: Predictors of CML response with imatinib

Timing of use of the predictors of imatinib response	Currently widely available	Available in some areas	In development
At the start of therapy	Cytogenetic analysis: ▪ Cytogenetic clonal evolution ▪ % of Ph+ metaphases ▪ Chromosome 9 deletions Flow cytometry ▪ % of CD34+ cells in the bone marrow		▪ Genetic microarrays ▪ Expression of drug resistance genes ▪ Laboratory analyses that provide information n mutations that change the tyrosine kinase protein ▪ In vitro assay of Crkl phosphorylation with imatinib
During therapy	Cytogenetic analysis: ▪ Cytogenetic response at 6 or 12 months Flow cytometry ▪ Reduction in the % of CD34+ cells in the bone marrow	Q-RT-PCR ▪ Log reduction in BCR-ABL mRNA transcripts at 1, 3, 6, or 12 months	Q-RT-PCR ▪ Log reduction BCR-ABL mRNA transcripts as a predictor mutations in the protein binding of imatinib

This is a rapidly evolving area and new data are constantly emerging. This current review only reflects the landscape to June 2005. Some of these data will become more or less useful as new information is uncovered. New predictors are likely to be defined.

Current State of Clinical Use

According to the National Comprehensive Cancer Network (NCCN) guideline dated November 23, 2004, imatinib is the standard of care as first-line therapy for CP CML when patients are not eligible for SCT.[56] This recommendation of imatinib as first-line therapy is stronger than the previous NCCN guideline which presented imatinib and interferon-based therapy as more equal options. When patients are eligible for SCT, the choice of first-line therapy with imatinib or transplant is still under debate.

The recommended starting dose is 400 mg. The NCCN guideline recommends that therapy is modified if a CHR is not obtained by 3 months. Modification options include reconsideration of SCT, clinical trials, increasing the imatinib to 600-800 mg, or interferon with or without cytarabine. For patients who obtained a CHR at 3 months, 6 month evaluation should include cytogenetic analysis. Patients who achieve at least a Minor CR at 6 months should continue at their current dose or increase to 600-800 mg as tolerated. Potential therapy modifications for patients who do not achieve at least a Minor CR by 6 months again include reconsideration of SCT, clinical trials, increasing the imatinib to 600-800 mg, or interferon with or without cytarabine. For patients who achieve at least a Minor CR at 6 months, 12 month evaluation should again include cytogenetic analysis. Those in Complete CR should continue imatinib at the current dose. Those in Major CR should be increased to 600-800mg as tolerated, and those in Minor or no CR should proceed with therapy modification or continue imatinib with the goal of maintaining hematologic remission only. The option to start patients out at higher doses of imatinib is presented.

The NCCN guideline recommends bone marrow cytogenetic analysis even if FISH or Q-RT-PCR are available, because cytogenetic findings including clonal evolution may indicate the need to consider other treatment strategies (e.g., clinical trial, increased imatinib dose). Management strategies in the setting of chromosome 9 deletions are not discussed nor is the role of molecular monitoring.

According to the National Cancer Institute (NCI) clinical guide at www.cancer.gov, the timing and role of imatinib for newly diagnosed CP CML are not as clear.[19] This review was most recently updated in February 2005. Particular questions raised by the NCI reviewers include the following:

- What is the best dose of imatinib and should it be combined with other agents (such as interferon alfa and/or cytarabine)?
- What is the role of allogeneic stem cell transplantation for younger, eligible patients, and should it be offered before or after initiation of imatinib?
- Will transplantation be more or equally efficacious before or after failure on imatinib?
- Will responses on imatinib be durable for many years, or will responses be short-lived and the relapsing disease be more difficult to control?

Both the NCCN and NCI guidelines are less clear about the optimal management of newly diagnosed AP or BP. Patients with newly diagnosed AP may be enrolled in a clinical trial, undergo SCT, be treated with imatinib, or receive interferon-based therapies (interferon-based treatment is not recommended for AP in the NCCN document). Patients with newly diagnosed

BP may be enrolled in a clinical trial, undergo SCT, be treated with imatinib, or receive acute leukemia induction chemotherapy regimens (neither guideline recommends interferon). Imatinib is also a consideration in the relapsed or refractory disease settings when it has not previously been used.

When other treatment strategies have not been successful, chemotherapy with hydroxyurea or busulfan, transfusion support, or palliative care remain options for patients.

Implications for Future Research

Future directions of research on imatinib for CML fall into two main domains:

1. CLINICAL SCIENCES:
   - efficacy of imatinib therapy alone or in combination with other agents
   - better predictors of patients most likely to respond or at risk of poor response
   - better understanding of the relative efficacy across segments of the population including different racial, ethnic and age groups
   - long-term longitudinal follow up of imatinib in the various clinical settings [155]
   - understanding of the ideal timing of SCT
   - meaning of surrogate markers such as molecular response at specific intervals after the initiation of therapy
   - impact of minimal residual disease when patients are in Complete CR
   - treatment algorithms subjected to objective evaluation
   - safe discontinuation of imatinib when there is a good clinical response
   - multiple drug regimens that include imatinib (see Table 1d)
2. BASIC SCIENCES:
   - refined understanding of imatinib's mechanism of action (e.g., anti-angiogenic properties)
   - molecular understanding of mechanisms of drug resistance for imatinib and other targeted therapies
   - better ability to predict individuals likely to be resistant to imatinib
   - development of new technologies so that knowledge of genetic profiles[156157] and molecular predictors of resistance[158] can be translated into practical clinical tests
   - development of new targeted therapies that incorporate these molecular insights

Standardization of terminology in CML is also important to advancing understanding of this disease. Blastic phase is a distinct period of the illness and some authors indicate that blast crisis is a sub-stage within blastic phase. This review highlighted the imprecision with which the terms blastic phase and blast crisis were used. A common language is needed to ensure that similar periods in the disease are compared across studies. Methods sections of manuscripts on CML should include a definition of how these terms are used.

Similarly, there are different definitions for the percentage of peripheral blood or bone marrow blasts that distinguish accelerated phase from blastic phase. Reviewers of this document suggested that 15 percent is the most commonly used cut-off. The NIH website, www.cancer.gov, cites 30 percent. Actual cut-off used across studies was variable. In order to

ensure that assessment of efficacy by phase is accurate, it is critical that these definitinons are standardized and that common terminology is used across studies. Methods sections should always include the definition.

Terminology for cytogenetic or clonal evolution is also imprecise. This is an important descriptor of the baseline participant population in a CML study and also considered by many authors as a predictor of disease response. Definitions of clonal evolution are rarely cited. Again, standardization of terminology and inclusion of definitions in methods sections is critical.

References

1. Cortes JE, Talpaz M, Giles F, et al.. Prognostic significance of cytogenetic clonal evolution in patients with chronic myelogenous leukemia on imatinib mesylate therapy. Blood 2003;101(10):3794-3800.

2. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. New England Journal of Medicine 2002;346(9):645-652.

3. Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood 2002;99(10):3530-3539.

4. Sureda A, Carrasco M, de Miguel M, et al. Imatinib mesylate as treatment for blastic transformation of Philadelphia chromosome positive chronic myelogenous leukemia. Haematologica 2003;88(11):1213-1220.

5. Cortes J, Talpaz M, O'Brien S, et al. Clinical significance of molecular monitoring in chronic myeloid leukemia (CML) in chronic phase (CP) with imatinib therapy. Blood 2004;104(11):Abstract #272.

6. Wu CJ, Neuberg D, Chillemi A, et al. Quantitative monitoring of BCR/ABL transcript during STI-571 therapy. Leukemia & Lymphoma 2002;43(12):2281-2289.

7. Stentoft J, Pallisgaard N, Kjeldsen E, et al. Kinetics of BCR-ABL fusion transcript levels in chronic myeloid leukemia patients treated with STI571 measured by quantitative real-time polymerase chain reaction. European Journal of Haematology 2001;67(5-6):302-308.

8. Rosti G, Martinelli G, Bassi S, et al. Molecular response to imatinib in late chronic-phase chronic myeloid leukemia. Blood 2004;103(6):2284-2290.

9. Moravcova J, Zmekova V, Klamova H, et al. Differences and similarities in kinetics of BCR-ABL transcript levels in CML patients treated with imatinib mesylate for chronic or accelerated disease phase. Leukemia Research 2004;28(4):415-419.

10. Paschka P, Muller MC, Merx K, et al. Molecular monitoring of response to imatinib (Glivec) in CML patients pretreated with interferon alpha. Low levels of residual disease are associated with continuous remission. Leukemia 2003;17(9):1687-1694.

11. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. New England Journal of Medicine 2003;349(15):1423-1432.

12. Kantarjian H, Talpaz M, O'Brien SS, et al. High-dose imatinib mesylate therapy in newly diagnosed Philadelphia chromosome-positive chronic phase chronic myeloid leukemia. Blood 2004;103(8):2873-2878.

13. Goldman JM, Melo JV. Chronic myeloid leukemia—Advances in biology and new approaches to treatment. New England Journal of Medicine 2003;349(15):1451-1464.

14. Sawyers CL. Chronic myeloid leukemia. New England Journal of Medicine Apr 29 1999;340(17):1330-1340.

15. American Cancer Society. Cancer Facts and Figures 2005. 2005; http://www.cancer.org/docroot/STT/stt_0.asp. Accessed March 25, 2005, 2005.

16. Faderl S, Talpaz M, Estrov Z, et al. Chronic myelogenous leukemia: biology and therapy. Annals of Internal Medicine Aug 3 1999;131(3):207-219.

17. Lee SJ, Anasetti C, Horowitz MM, et al. Initial therapy for chronic myelogenous leukemia: playing the odds. Journal of Clinical Oncology Sep 1998;16(9):2897-2903.

18. Xie Y, Davies SM, Xiang Y, et al. Trends in leukemia incidence and survival in the United States (1973-1998). Cancer 2003;97(9):2229-2235.

19. National Cancer Institute. Chronic Myelogenous Leukemia (PDQ®): Treatment: Health Professional Version; 2005. [Accessed at http://www.cancer.gov/cancertopics/pdq/treatment/CML/healthprofessional/allpages September 23, 2005]

20. Savage DG, Szydlo RM, Goldman JM. Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. British Journal of Haematology 1997;96(1):111-116.

21. Kurzrock R, Gutterman JU, Talpaz M. The molecular genetics of Philadelphia chromosome-positive leukemias. New England Journal of Medicine 1988;319(15):990-998.

22. O'Brien S, Tefferi A, Valent P. Chronic myelogenous leukemia and myeloproliferative disease. Hematology (Am Soc Hematol Educ Program) 2004:146-162.

23. Bose S, Deininger M, Gora-Tybor J, et al. The presence of typical and atypical BCR-ABL fusion genes in leukocytes of normal individuals: biologic significance and implications for the assessment of minimal residual disease. Blood Nov 1 1998;92(9):3362-3367.

24. Onida F, Ball G, Kantarjian HM, et al. Characteristics and outcome of patients with Philadelphia chromosome negative, bcr/abl negative chronic myelogenous leukemia. Cancer Oct 15 2002;95(8):1673-1684.

25. Cortes JE, Talpaz M, Beran M, et al. Philadelphia chromosome-negative chronic myelogenous leukemia with rearrangement of the breakpoint cluster region. Long-term follow-up results. Cancer Jan 15 1995;75(2):464-470.

26. Martiat P, Michaux JL, Rodhain J. Philadelphia-negative (Ph-) chronic myeloid leukemia (CML): comparison with Ph+ CML and chronic myelomonocytic leukemia. The Groupe Francais de Cytogenetique Hematologique. Blood Jul 1 1991;78(1):205-211.

27. Bhatia R, Holtz M, Niu N, et al. Persistence of malignant hematopoietic progenitors in chronic myelogenous leukemia patients in complete cytogenetic remission following imatinib mesylate treatment. Blood 2003;101(12):4701-4707.

28. Kantarjian HM, Dixon D, Keating MJ, et al. Characteristics of accelerated disease in chronic myelogenous leukemia. Cancer 1988;61(7):1441-1446.

29. Kantarjian HM, Deisseroth A, Kurzrock R, et al. Chronic myelogenous leukemia: a concise update. Blood Aug 1 1993;82(3):691-703.

30. Sokal JE, Baccarani M, Russo D, et al. Staging and prognosis in chronic myelogenous leukemia. Seminars in Hematology Jan 1988;25(1):49-61.

31. Savage DG, Szydlo RM, Chase A, et al. Bone marrow transplantation for chronic myeloid leukaemia: the effects of differing criteria for defining chronic phase on probabilities of survival and relapse. British Journal of Haematology Oct 1997;99(1):30-35.

32. Branford S, Rudzki Z, Grigg A, et al. BCR-ABL levels continue to decrease up to 42 months after commencement of standard dose imatinib in patients with newly diagnosed chronic phase CML who achieve a major molecular response. Blood 2004;104(11):Abstract #274.

33. Branford S, Rudzki Z, Harper A, et al. Imatinib produces significantly superior molecular responses compared to interferon alfa plus cytarabine in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Leukemia 2003;17(12):2401-2409.

34. van Rhee F, Szydlo RM, Hermans J, et al. Long-term results after allogeneic bone marrow transplantation for chronic myelogenous leukemia in chronic phase: a report from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplantation 1997;20(7):553-560.

35. O'Dwyer ME, Gatter KM, Loriaux M, et al. Demonstration of Philadelphia chromosome negative abnormal clones in patients with chronic myelogenous leukemia during major cytogenetic responses induced by imatinib mesylate. Leukemia 2003;17(3):481-487.

36. Barrett AJ, Malkovska V. Graft-versus-leukaemia: understanding and using the alloimmune response to treat haematological malignancies. British Journal of Haematology 1996;93(4):754-761.

37. Cervantes F, Hernandez-Boluda JC, Odriozola J, et al. Imatinib mesylate (STI571) treatment in patients with chronic-phase chronic myelogenous leukaemia previously submitted to autologous stem cell transplantation. British Journal of Haematology 2003;120(3):500-504.

38. Gardembas M, Rousselot P, Tulliez M, et al. Results of a prospective phase 2 study combining imatinib mesylate and cytarabine for the treatment of Philadelphia-positive patients with chronic myelogenous leukemia in chronic phase. Blood 2003;102(13):4298-4305.

39. Radich JP, Gooley T, Bensinger W, et al. HLA-matched related hematopoietic cell transplantation for chronic-phase CML using a targeted busulfan and cyclophosphamide preparative regimen. Blood Jul 1 2003;102(1):31-35.

40. Kantarjian HM, O'Brien S, Cortes JE, et al. Complete cytogenetic and molecular responses to interferon-alpha-based therapy for chronic myelogenous leukemia are associated with excellent long-term prognosis. Cancer Feb 15 2003;97(4):1033-1041.

41. Anonymous. Interferon alfa versus chemotherapy for chronic myeloid leukemia: a meta-analysis of seven randomized trials: Chronic Myeloid Leukemia Trialists' Collaborative Group. Journal of the National Cancer Institute Nov 5 1997;89(21):1616-1620.

42. Guilhot F, Chastang C, Michallet M, et al. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. French Chronic Myeloid Leukemia Study Group. New England Journal of Medicine Jul 24 1997;337(4):223-229.

43. Hehlmann R, Heimpel H, Hasford J, et al. Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: prolongation of survival by hydroxyurea. The German CML Study Group. Blood Jul 15 1993;82(2):398-407.

44. Kantarjian H, O'Brien S, Cortes J, et al. Survival advantage with imatinib mesylate therapy in chronic-phase chronic myelogenous;eukemia (CML-CP) after IFN-alpha failure and in late CML-CP, comparison with historical controls. Clinical Cancer Research 2004;10(1 Pt 1):68-75.

45. Silver RT. Molecular Biology of CML. In: Bast RC, Kufe D, Pollock RE, et al., eds. Cancer Medicine 5 ed. Hamilton, Ontario: BC Decker; 2000.

46. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. Journal of the National Cancer Institute Jun 3 1998;90(11):850-858.

47. Thomas MJ, Irving JA, Lennard AL, et al, On behalf of the Northern Region Haematology Group. Validation of the Hasford score in a demographic study in chronic granulocytic leukaemia. Journal of Clinical Pathology Jun 2001;54(6):491-493.

48. Wang L, Pearson K, Ferguson JE, et al. The early molecular response to imatinib predicts cytogenetic and clinical outcome in chronic myeloid leukaemia. British Journal of Haematology 2003;120(6):990-999.

49. Johansson B, Fioretos T, Mitelman F. Cytogenetic and molecular genetic evolution of chronic myeloid leukemia. Acta Haematologica 2002;107(2):76-94.

50. Huntly BJ, Bench A, Green AR. Double jeopardy from a single translocation: deletions of the derivative chromosome 9 in chronic myeloid leukemia. Blood Aug 15 2003;102(4):1160-1168.

51. Huntly BJ, Guilhot F, Reid AG, et al. Imatinib improves but may not fully reverse the poor prognosis of patients with CML with derivative chromosome 9 deletions. Blood Sep 15 2003;102(6):2205-2212.

52. Huntly BJ, Bench AJ, Delabesse E, et al. Derivative chromosome 9 deletions in chronic myeloid leukemia: poor prognosis is not associated with loss of ABL-BCR expression, elevated BCR-ABL levels, or karyotypic instability. Blood Jun 15 2002;99(12):4547-4553.

53. Huntly BJ, Reid AG, Bench AJ, et al. Deletions of the derivative chromosome 9 occur at the time of the Philadelphia translocation and provide a powerful and independent prognostic indicator in chronic myeloid leukemia. Blood Sep 15 2001;98(6):1732-1738.

54. Sinclair PB, Nacheva EP, Leversha M, et al. Large deletions at the t(9;22) breakpoint are common and may identify a poor-prognosis subgroup of patients with chronic myeloid leukemia. Blood Feb 1 2000;95(3):738-743.

55. Hochhaus A, Kreil S, Corbin AS, et al. Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. Leukemia 2002;16(11):2190-2196.

56. U.S. Food and Drug Administration. Gleevac approved for the first line treatment of chronic myeloid leukemia (CML). December 20, 2002; http://www.fda.gov/bbs/topics/NEWS/2002/NEW00860.html. Accessed July 5, 2005.

57. Robinson KA, Dickersin KO. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. International Journal of Epidemiology 2002;31(1):150-153.

58. National Institute for Clinical Excellence. Guidance on the use of imatinib for chronic myeloid leukaemia. London: National Institute for Clinical Excellence; 2003.

59. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. New England Journal of Medicine 2003;348(11):994-1004.

60. Hahn EA, Glendenning GA, Sorensen MV, et al. Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low-dose cytarabine: results from the IRIS Study. Journal of Clinical Oncology 2003;21(11):2138-2146.

61. Hahn EA, Glendenning GA. Quality of life on imatinib. Seminars in Hematology 2003;40(2 Suppl 2):31-36.

62. Guilhot F. Sustained durability of responses plus high rates of cytogenetic responses result in long-term benefit for newly diagnosed chronic-phase chronic myeloid leukemia (CML-CP) treated with imatinib (IM) therapy: update from the IRIS Study. Blood 2004;104(11):Abstract #21.

63. Kantarjian HM, Cortes JE, O'Brien S, et al. Imatinib mesylate therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia: high incidence of early complete and major cytogenetic responses. Blood 2003;101(1):97-100.

64. Cortes J, Talpaz M, O'Brien S, et al. High-dose imatinib mesylate treatment in patients (pts) with previously untreated early chronic phase (CP) chronic myeloid leukemia (CML). Blood 2004;104(11):Abstract #999.

65. Hughes T, Branford S, Reynolds J, et al. Higher-dose imatinib (600 mg/day) with selective intensification in newly diagnosed CML patients in chronic phase; cytogenetic response rates at 12 months are superior to IRIS. Blood 2004;104(11):Abstract #1001.

66. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. New England Journal of Medicine 2001;344(14):1031-1037.

67. Braziel RM, Launder TM, Druker BJ, et al. Hematopathologic and cytogenetic findings in imatinib mesylate-treated chronic myelogenous leukemia patients: 14 months' experience. Blood 2002;100(2):435-441.

68. Marin D, Marktel S, Szydlo R, et al. Survival of patients with chronic-phase chronic myeloid leukaemia on imatinib after failure on interferon alfa. Lancet 2003;362:617-619.

69. Cortes J, Giles F, O'Brien S, et al. Result of high-dose imatinib mesylate in patients with Philadelphia chromosome-positive chronic myeloid leukemia after failure of interferon-alpha. Blood 2003;102(1):83-86.

70. Kantarjian HM, Talpaz M, O'Brien S, et al. Imatinib mesylate for Philadelphia chromosome-positive, chronic-phase myeloid leukemia after failure of interferon-alpha: follow-up results. Clinical Cancer Research Jul 2002;8(7):2177-2187.

71. Kantarjian HM, Talpaz M, O'Brien S, et al. Dose escalation of imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia. Blood 2003;101(2):473-475.

72. Kantarjian HM, Cortes JE, O'Brien S, et al. Long-term survival benefit and improved complete cytogenetic and molecular response rates with imatinib mesylate in Philadelphia chromosome-positive chronic-phase chronic myeloid leukemia after failure of interferon-alpha. Blood Oct 1 2004;104(7):1979-1988.

73. Le Coutre P, Kreuzer KA, Na IK, et al. Imatinib in Philadelphia chromosome-positive chronic phase CML patients: molecular and cytogenetic response rates and prediction of clinical outcome. American Journal of Hematology 2003;73(4):249-255.

74. Marin D, Goldman JM, Olavarria E, Apperley JF. Transient benefit only from increasing the imatinib dose in CML patients who do not achieve complete cytogenetic remissions on conventional doses. Blood 2003;102(7):2702-2704.

75. Marin D, Marktel S, Bua M, et al. Prognostic factors for patients with chronic myeloid leukaemia in chronic phase treated with imatinib mesylate after failure of interferon alfa. Leukemia 2003;17(8):1448-1453.

76. Pasquini R, Clementino NC, Zanichelli MA, et al. Observational study for evaluation of quality of life in patients with chronic myeloid leukemia (CML) in use of Gleevec® (Imatinib Mesilate). Blood 2004;104(11):Abstract # 2932.

77. Fischer T, Reifenrath C, Hess GR, et al. Safety and efficacy of STI-571 (imatinib mesylate) in patients with bcr/abl-positive chronic myelogenous leukemia (CML) after autologous peripheral blood stem cell transplantation (PBSCT). Leukemia 2002;16(7):1220-1228.

78. Kantarjian HM, O'Brien S, Cortes JE, et al. Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. Blood 2002;100(5):1590-1595.

79. O'Brien S, Giles F, Talpaz M, et al. Results of triple therapy with interferon-alpha, cytarabine, and homoharringtonine, and the impact of adding imatinib to the treatment sequence in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in early chronic phase. Cancer 2003;98(5):888-893.

80. Hess G, Bunjes D, Siegert W, et al. Durable molecular remissions in patients with relapsed CML post allogeneic stem cell transplantationupon treatment with imatinib-mesylate (Glivec®, STI-571). Follow-up results of a phase II open-label study. Blood 2004;104(11):Abstract #1004.

81. Corsetti MT, Beltrami G, Carella AM. Imatinib achieves high rates of complete citogenetic remission (CCR) in CML patients relapsed after autografting and IFN-alfa therapy. Blood 2004;104(11):Abstract # 4656.

82. Cohen MH, Williams G, Johnson JR, et al. Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. Clinical Cancer Research 2002;8(5):935-942.

83. Silver RT, Talpaz M, Sawyers CL, et al. Four years of follow-up of 1027 patients with late chronic phase (L-CP), accelerated phase (AP), or blast crisis (BC) chronic myeloid leukemia (CML) treated with imatinib in three large phase II trials. Blood 2004;104(11):Abstract #23.

84. Olavarria E, Ottmann OG, Deininger M, et al. Response to imatinib in patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. Leukemia 2003;17(9):1707-1712.

85. Lahaye T, Riehm B, Berger U, et al. Response and resistance in 300 patients with BCR-ABL-positive leukemias treated with imatinib in a single center: a 4.5-year follow-up. Cancer Apr 15 2005;103(8):1659-1669.

86. Deshmukh CD, Saikia T, Bakshi AV, et al.. Imatinib mesylate in chronic myeloid leukemia (CML): A single institution experience of 174 patients. Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: 6710. 2004.

87. Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002;99(6):1928-1937.

88. Cortes J, Talpaz M, O'Brien S, et al. Survival advantage for patients (pts) with chronic myeloid leukemia (CML) in accelerated phase (AP) treated with imatinib. Blood 2004;104(11):Abstract #1006.

89. Druker BJ, Sawyers CL, Kantarjian H, 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. New England Journal of Medicine 2001;344(14):1038-1042.

90. Kantarjian HM, Cortes J, O'Brien S, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. Blood 2002;99(10):3547-3553.

91. Baccarani M, Martinelli G, Rosti G, et al. Imatinib and pegylated human recombinant interferon-{alpha}2b in early chronic-phase chronic myeloid leukemia. Blood December 15, 2004 2004;104(13):4245-4251.

92. Drummond A, Micallef-Eynaud P, Douglas WS, Hay I, Holyoake TL, Drummond MW. A spectrum of skin reactions caused by the tyrosine kinase inhibitor imatinib mesylate (STI 571, Glivec). British Journal of Haematology 2003;120(5):911-913.

93. Steegmann JL, Moreno G, Alaez C, et al. Chronic myeloid leukemia patients resistant to or intolerant of interferon alpha and subsequently treated with imatinib show reduced immunoglobulin levels and hypogammaglobulinemia. Haematologica 2003;88(7):762-768.

94. Valeyrie L, Bastuji-Garin S, Revuz J, Bachot N, Giraudier SO. Adverse cutaneous reactions to imatinib (ST1571) in Philadelphia chromosome-positive leukemias: A prospective study of 54 patients. Journal of the American Academy of Dermatology 2003;48(2):201-206.

95. Al-Ali HK, Krahl R, Orth M, et al. Persistently increased creatine kinase levels in patients with chronic myeloid leukemia treated with imatinib correlate with major cytogenetic remission. Blood 2004;104(11):Abstract # 2933.

96. O'Dwyer ME, Mauro MJ, Blasdel C, et al. Clonal evolution and lack of cytogenetic response are adverse prognostic factors for hematologic relapse of chronic phase CML patients treated with imatinib mesylate. Blood 2004;103(2):451-455.

97. El-Zimaity MM, Kantarjian H, Talpaz M, et al. Results of imatinib mesylate therapy in chronic myelogenous leukaemia with variant Philadelphia chromosome. British Journal of Haematology 2004;125(2):187-195.

98. Kantarjian HM, O'Brien S, Cortes J, et al. Imatinib mesylate therapy improves survival in patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia in the chronic phase: comparison with historic data. Cancer 2003;98(12):2636-2642.

99. Marktel S, Marin D, Foot N, et al. Chronic myeloid leukemia in chronic phase responding to imatinib: the occurrence of additional cytogenetic abnormalities predicts disease progression. Haematologica 2003;88(3):260-267.

100. Marin D, Horncastle D, Andreasson C, et al. Prognostic impact of percentage CD34 expression in bone marrow trephines of patients with chronic myeloid leukaemia in chronic phase treated with imatinib. Blood 2004;104(11):Abstract #1019.

101. Elliot VJ, Marin D, Horncastle D, et al. Total Number of CD34 + cells per ten high power fields in bone marrow trephines of patients with chronic myeloid leukaemia correlates with probability of complete cytogenetic response during the first year of treatment with imatinib. Blood 2004;104(11):Abstract # 4664.

102. Lange T, Gunther C, Kohler T, et al. High levels of BAX, low levels of MRP-1, and high platelets are independent predictors of response to imatinib in myeloid blast crisis of CML. Blood 2003;101(6):2152-2155.

103. McLean LA, Gathmann I, Capdeville R, et al. Pharmacogenomic analysis of cytogenetic response in chronic myeloid leukemia patients treated with imatinib. Clinical Cancer Research 2004;10(1 Pt 1):155-165.

104. Muller MC, Gattermann N, Lahaye T, et al. Dynamics of BCR-ABL mRNA expression in first-line therapy of chronic myelogenous leukemia patients with imatinib or interferon alpha/ara-C. Leukemia 2003;17(12):2392-2400.

105. Merx K, Muller MC, Kreil S, et al. Early reduction of BCR-ABL mRNA transcript levels predicts cytogenetic response in chronic phase CML patients treated with imatinib after failure of interferon alpha. Leukemia 2002;16(9):1579-1583.

106. Mueller MC, Paschka P, LaHaye T, et al. Molecular long-term surveillance of CML patients on imatinib therapy. follow-up of german patients treated within the IRIS trial. Blood 2004;104(11):Abstract #1003.

107. Press RD, Love Z, Tronnes AA, et al. BCR-ABL RNA levels at the time of a complete cytogenetic response (CCR) predict the duration of CCR in imatinib-treated chronic myeloid leukemia patients. Blood 2004;104(11):Abstract #1098.

108. Shah NP, Nicoll JM, Nagar B, et al. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer Cell 2002;2(2):117-125.

109. Frater JL, Tallman MS, Variakojis D, et al. Chronic myeloid leukemia following therapy with imatinib mesylate (Gleevec). Bone marrow histopathology and correlation with genetic status. American Journal of Clinical Pathology 2003;119(6):833-841.

110. Sneed TB, Kantarjian HM, Talpaz M, et al. The significance of myelosuppression during therapy with imatinib mesylate in patients with chronic myelogenous leukemia in chronic phase. Cancer 2004;100(1):116-121.

111. Kvasnicka HM, Thiele J, Staib P, et al. Reversal of bone marrow angiogenesis in chronic myeloid leukemia following imatinib mesylate (STI571) therapy. Blood 2004;103(9):3549-3551.

112. Jabbour E, Kantarjian H, Jones D, et al. Long-term incidence and outcome of BCR-ABL mutations in patients (pts) with chronic myeloid leukemia (CML) treated with imatinib mesylate P-loop mutations are not associated with worse outcome. Blood 2004;104(11):Abstract #1007.

113. Branford S, Rudzki Z, Grigg A, et al. The frequency of detection of BCR-ABL mutations in imatinib treated patients with chronic phase CML who attain a complete cytogenetic response (CCR) does not diminish with increasing duration of CCR but the associated loss of response is usually gradual. Blood 2004;104(11):Abstract #271.

114. Corm S, Nicollini F, Borie D, et al. Mutation status of imatinib mesylate-resistants CML patients and clinical outcomes: a French multicenter retrospective study for the fiLMC group. Blood 2004;104(11):Abstract #275.

115. Deininger MW, Willis S, Lange T, et al. Detection of imatinib-resistant BCR-ABL mutants in drug-naïve patients: correlation with disease phase and clonal evolution but not with response to treatment. Blood 2004;104(11):Abstract #273.

116. Hochhaus A. Imatinib mesylate (Glivec, Gleevec) in the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST). Annals of Hematology 2004;83(Suppl 1):S65-66.

117. Shimoni A, Kroger N, Zander AR, et al. Imatinib mesylate (STI571) in preparation for allogeneic hematopoietic stem cell transplantation and donor lymphocyte infusions in patients with Philadelphia-positive acute leukemias. Leukemia 2003;17(2):290-297.

118. Lange T, Bumm T, Mueller M, et al. Molecular remission to imatinib in patients with chronic myeloid leukaemia (CML) is less durable compared to patients after allografting. Blood 2004;104(11):Abstract #276.

119. Palandri F, Martinelli G, Amabile M, et al. Imatinib therapy for chronic myeloid leukemia patients who relapse after allogeneic stem cell transplantation: a molecular analysis. Blood 2004;104(11):Abstract # 4655.

120. Pautas C, Nicolini F, Cony-Makhoul P, et al. Imatinib mesylate (IM), is an alternative to donor lymphocyte infusion (DLI) for chronic myelogenous leukemia (CML) in relapse after allogeneic stem cell transplantation: a 3-year follow-up report, on the behalf of the Société Française de Greffe de Moëlle et de Thérapie Cellulaire (SFGM-TC) and the France Intergroupe de la Leucémie Myéloïde Chronique (Fi-LMC). Blood 2004;104(11):Abstract #1017.

121. Conneally E, Carroll P, Neat M, et al. Imatinib mesylate treatment of patients with chronic myeloid leukaemia relapsing following allogeneic stem cell transplantation. Blood 2004;104(11):Abstract # 4659.

122. Laurence A, Marin D, Clark R, Shepherd P, Mackinnon S. Frequency of blast crisis after achieving complete cytogenetic remission in first chronic phase CML Patients Who recieved imatinib therapy within six months of diagnosis. Blood 2004;104(11):Abstract #1021.

123. George S, Horvath L, Molokie R, et al. Response to therapy with imatinib mesylate in patients with CML is poor in non-caucasian patients. Blood 2004;104(11):Abstract # 2937.

124. Bassi S, Castagnetti F, Amabile M, et al. Imatinib in the treatment of CML Patients $\geq$ 65 years old in late chronic phase: results of a Phase II ttudy of the GIMEMA CML Working Party. Blood 2004;104(11):Abstract # 2935.

125. Martino B, Vincelli Y, Ronco F, et al. Efficacy and safety of imatinib treatment in elederly patients with chronic myeloid leukemia. Blood 2004;104(11):Abstract # 4680.

126. Soverini S, Martinelli G, Amabile M, et al. Denaturing-HPLC-based assay for detection of ABL mutations in chronic myeloid leukemia patients resistant to Imatinib. Clinical Chemistry 2004;50(7):1205-1213.

127. Issa S, Holdsworth D, Oei P, et al. The utility of peripheral blood FISH in the quantitation of BCR/ABL in CML patients on imatinib mesylate: a comparison with bone marrow FISH and conventional cytogenetics. Blood 2004;104(11):Abstract # 2942.

128. Thomazy VA, Kantarjian HM, Imam M, et al. Use of plasma RNA for real-time quantitative RT-PCR to monitor imatinib therapy in patients with chronic myeloid leukemia. Blood 2004;104(11):Abstract #1099.

129. Kagami Y, Katagiri T, Kaneta Y, et al. Validation study on the prediction of response to imatinib mesylate in chronic myeloid leukemia (CML) patients by genome-wide cDNA microarray analysis. Blood 2004;104(11):Abstract # 2946.

130. Vallespí T, Borrego M, Colomé D, Jaen A, Rozman M, Massagué M. Quantitative polymerase chain reaction (qPCR) at diagnosis and follow-up of patients with chronic myeloid leukemia in treatment with imatinib. Blood 2004;104(11):Abstract # 4688.

131. Paschka P, Branford S, Lorentz C, Hehlmann R, Hughes T, Hochhaus A. Comparison of "log reduction from median pretherapeutic value" vs ratio BCR-ABL/ABL to express the therapeutic response in CML patients. Blood 2004;104(11):Abstract #1013.

132. Albitar M, Cortes J, Giles F, et al. Molecular monitoring of chronic phase chronic myeloid leukemia patients treated with 800mg imatinib. Journal of Clinical Oncology 2005;23(16S):abstract 6554.

133. Berger U, Hochhaus A, Reiter A, et al. Feasibility of imatinib combination therapies in a randomized trial for chronic myeloid leukemia: the German CML-Study IV - Pilot Phase. 2004;104(11):Abstract #24.

134. Hehlmann R, Hochhaus A, Berger U, Pfirrmann M, Hasford J. Concept and feasibility of the randomized comparison of imatinib with imatinib combination therapies for chronic myeloid leukemia: the German CML Study IV - Pilot Phase. Journal of Clinical Oncology 2005;23(16S):abstract 6574.

135. Monroy RH, Vargas-Viveros P, Cervera E, et al. Imatinib alone (IA) vs. imatinib + Ara-C (IMAC): a randomized phase III clinical trial for the treatment of early phase (EP) chronic myeloid leukemia (CML) Ph+. Preliminary report of Mexican Cooperative Leukemia Group (GRUMELA). Blood 2004;104(11):Abstract #1015.

136. Fruehauf, Topaly, Buss EC, et al. A multicenter Phase I/II Trial of the combination of imatinib mesylate with mitoxantrone/etoposide and cytarabine in patients with CML in myeloid blast crisis: a trend to a longer survival in patients receiving more aggressive treatment schedules. Blood 2004;104(11):Abstract # 2929.

137. Cornelissen JJVP, Verhoef GEG, Smit WM, et al. High rates of molecular response and low incidence of mutations in patients treated with newly diagnosed chronic myeloid leukemia (CML) treated with a dose-escalated combination of imatinib and cytarabin. Blood 2004;104(11):Abstract #19.

138. Rousselot P, Legros L, Guilhot J, et al. A Phase I/II dose escalating study of daunorubicin combined with imatinib mesylate and cytarabine as induction therapy for chronic myelogenous leukaemia in myeloid blast crisis. Preliminary results of the AFR01 trial. Blood 2004;104(11):Abstract #1002.

139. Ceglarek BB, Konopka LJ, Sikorska A, et al. Gleevec therapy in advanced phases of the CML - Polish study report. Blood 2004;104(11):Abstract # 4701.

140. Cortes J, Giles F, Salvado A, et al. High dose (HD) imatinib in patients with previously untreated chronic myeloid leukemia (CML) in early chronic phase (CP): preliminary results of a multicenter community based trial. Journal of Clinical Oncology 2005;23(16S):abstract 6518.

141. Sacchi S, Kantarjian HK, O'Brien S, et al. Chronic myelogenous leukemia in nonlymphoid blastic phase. Cancer 1999;86(12):2632-2641.

142. Gratwohl A, Hermans J. Allogeneic bone marrow transplantation for chronic myeloid leukemia. Working Party Chronic Leukemia of the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplantation May 1996;17 Suppl 3:S7-9.

143. Bacik J, Mazumdar M, Murphy BA, et al. The functional assessment of cancer therapy-BRM (FACT-BRM): a new tool for the assessment of quality of life in patients treated with biologic response modifiers. Qual Life Res Feb 2004;13(1):137-154.

144. Quintas-Cardama A, Kantarjian H, Talpaz M, et al. Imatinib mesylate therapy may overcome the poor prognostic significance of deletions of derivative chromosome 9 in patients with chronic myelogenous leukemia. Blood 2005;105(6):2281-2286.

145. White DL, Saunders VA, Branford S, Lyons B, Hughes TP. The combination of intrinsic sensitivity to imatinib and sokal prognostic score is strongly predictive of molecular response in newly diagnosed CML patients treated with imatinib. Blood 2004;104(11):Abstract #1008.

146. Gorre ME, Mohammed M, Ellwood K, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science Aug 3 2001;293(5531):876-880.

147. Johnson JR, Bross P, Cohen M, et al. Approval summary: imatinib mesylate capsules for treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase. Clinical Cancer Research 2003;9(6):1972-1979.

148. Cohen MH, Johnson JR, Pazdur R. U.S. Food and Drug Administration Drug Approval Summary: conversion of imatinib mesylate (STI571; Gleevec) tablets from accelerated approval to full approval. Clinical Cancer Research Jan 1 2005;11(1):12-19.

149. Baccarani M, Rosti G, de Vivo A, et al. A randomized study of interferon-alpha versus interferon-alpha and low-dose arabinosyl cytosine in chronic myeloid leukemia. Blood Mar 1 2002;99(5):1527-1535.

150. Kantarjian HM, Keating MJ, Estey EH, et al. Treatment of advanced stages of Philadelphia chromosome-positive chronic myelogenous leukemia with interferon-alpha and low-dose cytarabine. Journal of Clinical Oncology May 1992;10(5):772-778.

151. Personal communication with Kelly Moore. Novartis 5-19-2005.

152. McLean LA, Gathmann I, Capdeville R, Polymeropoulos MH, Dressman M. Pharmacogenomic analysis of cytogenetic response in chronic myeloid leukemia patients treated with imatinib. Clinical Cancer Research Jan 1 2004;10(1 Pt 1):155-165.

153. Savage DG, Antman KH. Imatinib mesylate—a new oral targeted therapy. New England Journal of Medicine 2002;346(9):683-693.

154. Branford S, Rudzki Z, Parkinson I, et al. Real-time quantitative PCR analysis can be used as a primary screen to identify patients with CML treated with imatinib who have BCR-ABL kinase domain mutations. *Blood.* Nov 1 2004;104(9):2926-2932.

155. Lange T, Bumm T, Mueller M, et al. Durability of molecular remission in chronic myeloid leukemia patients treated with imatinib vs allogeneic stem cell transplantation. Leukemia 2004;19:1262–1269.

156. Crossman LC, Mori M, Hsieh YC, et al. In chronic myeloid leukemia white cells from cytogenetic responders and non-responders to imatinib have very similar gene expression signatures. Haematologica 2005;90:459-464.

157. Kaneta Y, Kagami Y, Katagiri T, et al. Prediction of sensitivity to STI571 among chronic myeloid leukemia patients by genome-wide cDNA microarray analysis. Japanese Journal of Cancer Research 2002;93:849–856.

158. Crossman LC, Druker BJ, Deininger MW, et al. hOCT 1 and resistance to imatinib. Blood 2005;106(3):1133-1134.

Included Articles

Al-Ali HK, Krahl R, Orth M, et al. Persistently increased creatine kinase levels in patients with chronic myeloid leukemia treated with imatinib correlate with major cytogenetic remission. Blood 2004;104(11):Abstract # 2933.

Albitar M, Cortes J, Giles F, et al. Molecular monitoring of chronic phase chronic myeloid leukemia patients treated with 800mg imatinib. Journal of Clinical Oncology 2005;23:Abstract 6554.

American Cancer Society. Cancer Facts and Figures 2005. 2005; http://www.cancer.org/docroot/STT/stt_0.asp. Accessed March 25, 2005, 2005.

Anonymous. Interferon alfa versus chemotherapy for chronic myeloid leukemia: a meta-analysis of seven randomized trials: Chronic Myeloid Leukemia Trialists' Collaborative Group. Journal of the National Cancer Institute 1997;89(21):1616-20.

Baccarani M, Martinelli G, Rosti G, et al. Imatinib and pegylated human recombinant interferon-{alpha}2b in early chronic-phase chronic myeloid leukemia. Blood 2004;104(13):4245-51.

Baccarani M, Rosti G, de Vivo A, et al. Arandomized study of interferon-a versus interferon-a and low-dose arabinosyl cytosine in chronic myeloid leukemia. Blood 2002;99:527-1535.

Bacik J, Mazumdar M, Murphy B, et al. The functional assessment of cancer therapy-BRM (FACT-BRM): A new tool for the assessment of quality of life in patients treated with biologic response modifiers. Quality of Life Research 2004;13(1):137-54.

Barrett A, Malkovska V. Graft-versus-leukaemia: understanding and using the alloimmune response to treat haematological malignancies. . British Journal of Haematology 1996;93. 1996:754-61.

Bassi S, Castagnetti F, Amabile M, et al. Imatinib in the treatment of CML patients ≥65 years old in late chronic phase: Results of a phase II study of the GIMEMA CML Working Party. Blood 2004;104(11):Abstract # 2935.

Berger U, Hochhaus A, Reiter A, et al. Feasibility of imatinib combination therapies in a randomized trial for chronic myeloid leukemia: The German CML-Study IV - Pilot Phase. Blood 2004;104(11):Abstract #24.

Bhatia R., Holtz M., Niu N., et al. Persistence of malignant hematopoietic progenitors in chronic myelogenous leukemia patients in complete cytogenetic remission following imatinib mesylate treatment. Blood 2003;101(12):4701-7.

Bose S, Deininger MW, Gora-Tybor J, et al. The presence of typical and atypical BCR-ABL fusion genes in leukocytes of normal individuals: Biologic significance and implications for the assessment of minimal residual disease. Blood 92. 1998.

Branford S, Rudzki Z, Grigg A, et al. The frequency of detection of BCR-ABL mutations in imatinib treated patients with chronic phase CML who attain a complete cytogenetic response (CCR) does not diminish with increasing duration of ccr but the associated loss of response is

usually gradual. Blood 2004;104(11):Abstract #271.

Branford S, Rudzki Z, Grigg A, et al. BCR-ABL levels continue to decrease up to 42 months after commencement of standard dose imatinib in patients with newly diagnosed chronic phase CML who achieve a major molecular response. Blood 2004;104(11):Abstract #274.

Branford S, Rudzki Z, Harper A, et al. Imatinib produces significantly superior molecular responses compared to interferon alfa plus cytarabine in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Leukemia 2003;17(12):2401-9.

Branford S, Rudzki Z, Parkinson I, et al. Real-time quantitative PCR analysis can be used as a primary screen to identify patients with CMLtreated with imatinib who have BCR-ABL kinase domain mutations. Blood 2004;104(9):2926-32.

Braziel RM, Launder TM, Druker BJ, et al. Hematopathologic and cytogenetic findings in imatinib mesylate-treated chronic myelogenous leukemia patients: 14 months' experience. Blood 2002;100(2):435-41.

Ceglarek BB, Konopka LJ, Sikorska A, et al. Gleevec Therapy in Advanced Phases of the CML - Polish Study Report. Blood 2004;104(11):Abstract # 4701.

Cervantes F, Hernandez-Boluda JC, Odriozola J, et al. Imatinib mesylate (STI571) treatment in patients with chronic-phase chronic myelogenous leukaemia previously submitted to autologous stem cell transplantation. British Journal of Haematology 2003;120(3):500-4.

Cohen MH, Johnson JR, Pazdur R. U.S. Food and Drug Administration Drug Approval Summary: Conversion of Imatinib Mesylate (STI571; Gleevec) Tablets from Accelerated Approval to Full Approval. Clinical Cancer Research 2005;11:12-9.

Cohen MH, Williams G, Johnson JR, et al. Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. Clinical Cancer Research 2002;8(5):935-42.

Conneally E, Carroll P, Neat M, et al. Imatinib mesylate treatment of patients with chronic myeloid leukaemia relapsing following allogeneic stem cell transplantation. Blood 2004;104(11):Abstract # 4659.

Corm S, Nicollini F, Borie D, et al. Mutation status of imatinib mesylate-resistants cml patients and clinical outcomes: A French multicenter retrospective study for the fiLMC Group. Blood 2004;104(11):Abstract #275.

Cornelissen JJ, Valk P, Verhoef GEG, et al. High rates of molecular response and low incidence of mutations in patients treated with newly diagnosed chronic myeloid leukemia (CML) treated with a dose-escalated combination of imatinib and cytarabin. Blood 2004;104(11):Abstract #19.

Corsetti MT, Beltrami G, Carella AM. Imatinib achieves high rates of complete citogenetic remission (CCR) in CML patients relapsed after autografting and IFN-α Therapy. Blood 2004;104(11):Abstract # 4656.

Cortes J, Giles F, O'Brien S, et al. Result of high-dose imatinib mesylate in patients with Philadelphia chromosome-positive chronic myeloid leukemia after failure of interferon-alpha. Blood 2003;102(1):83-6.

Cortes J, Giles F, Salvado A, et al. High dose (HD) imatinib in patients with previously untreated chronic myeloid leukemia (CML) in early chronic phase (CP): preliminary results of a multicenter community based trial. Journal of Clinical Oncology 2005;20(162):abstract 6518.

Cortes J, Talpaz M, Beran M, et al. Philadelphia chromosome-negative chronic myelogenous leukemia with rearrangement of the breakpoint cluster region. Long-term follow-up results. Cancer 1995 Jan 15;75. 1995:464-70.

Cortes J, Talpaz M, Giles F, et al. Prognostic significance of cytogenetic clonal evolution in patients with chronic myelogenous leukemia on imatinib mesylate therapy. Blood 2003;101(10):3794-800.

Cortes J, Talpaz M, O'Brien S, et al. Survival advantage for patients (pts) with chronic myeloid leukemia (CML) in accelerated phase (AP) treated with imatinib. Blood 2004;104(11):Abstract #1006.

Cortes J, Talpaz M, O'Brien S, et al. High-dose imatinib mesylate treatment in patients (pts) with previously untreated early chronic phase (CP) chronic myeloid leukemia (CML). Blood 2004;104(11):Abstract #999.

Cortes J, Talpaz M, O'Brien S, et al. Clinical significance of molecular monitoring in chronic myeloid leukemia (CML) in chronic phase (CP) with imatinib therapy. Blood 2004;104(11):Abstract #272.

Crossman LC, Druker BJ, Deininger MW. hOCT 1 and resistance to imatinib. Blood 2005;106(3):1133-4.

Crossman LC, Mori M, Hsieh Y, et al. In chronic myeloid leukemia white cells from cytogenetic responders and non-responders to imatinib have very similar gene expression signatures. Haematologica 2005;90:459-64.

Deininger MW, Willis S, Lange T, et al. Detection of imatinib-resistant BCR-ABL mutants in drug-naïve patients: correlation with disease phase and clonal evolution but not with response to treatment. Blood 2004;104(11):Abstract #273.

Deshmukh CD, Saikia T, Bakshi AV, et al. Imatinib mesylate in chronic myeloid leukemia (CML): A single institution experience of 174 patients. Journal of Clinical Oncology 2004;22(14S):Abstract #6710.

Druker BJ. Taking aim at Ewing's sarcoma: is KIT a target and will imatinib work? Journal of the National Cancer Institute 2002;94(22):1660-1.

Druker BJ, Sawyers CL, Kantarjian H, 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. New England Journal of Medicine 2001;344(14):1038-42.

Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. New England Journal of Medicine 2001;344(14):1031-7.

Drummond A, Micallef-Eynaud P, Douglas WS, et al. A spectrum of skin reactions caused by the tyrosine kinase inhibitor imatinib mesylate (STI 571, Glivec). British Journal of Haematology 2003;120(5):911-3.

El-Zimaity MM, Kantarjian H, Talpaz M, et al. Results of imatinib mesylate therapy in chronic myelogenous leukaemia with variant Philadelphia chromosome. British Journal of Haematology 2004;125(2):187-95.

Elliot VJ, Marin D, Horncastle D, et al. Total number of CD34 + cells per ten high power fields in bone marrow trephines of patients with chronic myeloid leukaemia correlates with probability of complete cytogenetic response during the first year of treatment with imatinib. Blood 2004;104(11):Abstract # 4664.

Faderl S, Talpaz M, Estrov Z, et al. Chronic Myelogenous leukemia: biology and therapy. Annals of Internal Medicine 1999;131(3):207-19.

Fischer T, Reifenrath C, Hess GR, et al. Safety and efficacy of STI-571 (imatinib mesylate) in patients with bcr/abl-positive chronic myelogenous leukemia (CML) after autologous peripheral blood stem cell transplantation (PBSCT). Leukemia 2002;16(7):1220-8.

Frater JL, Tallman MS, Variakojis D, et al. Chronic myeloid leukemia following therapy with imatinib mesylate (Gleevec). Bone marrow histopathology and correlation with genetic status. American Journal of Clinical Pathology 2003;119(6):833-41.

Fruehauf, Topaly, Buss EC, et al. A multicenter phase I/II trial of the combination of imatinib mesylate with mitoxantrone/etoposide and cytarabine in patients with CML in myeloid blast crisis: a trend to a longer survival in patients receiving more aggressive treatment schedules. Blood 2004;104(11):Abstract # 2929.

Gardembas M, Rousselot P, Tulliez M, et al. Results of a prospective phase 2 study combining imatinib mesylate and cytarabine for the treatment of Philadelphia-positive patients with chronic myelogenous leukemia in chronic phase. Blood 2003;102(13):4298-305.

George S, Horvath L, Molokie R, et al. Response to therapy with imatinib mesylate in patients with CML is poor in non-caucasian patients. Blood 2004;104(11):Abstract # 2937.

Goldman J. M. , Melo J. V. Mechanisms of disease - Chronic myeloid leukemia - Advances in biology and new approaches to treatment. New England Journal of Medicine 2003;349(15):1451-64.

Gorre ME, Skaggs BJ, Sawyers CL. Imatinib-resistant BCR-ABL mutations alter oncogenic potency, kinase activity and substrate selection. Blood 2004;104(11):Abstract #556.

Gratwohl A, Hermans J. Allogeneic bone marrow transplantation for chronic myeloid leukemia. Working Party Chronic Leukemia of the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplantation 17 (Suppl 3):S7-9.

Guilhot F. Sustained durability of responses plus high rates of cytogenetic responses result in long-term benefit for newly diagnosed chronic-phase chronic myeloid leukemia (CML-CP) treated with imatinib (IM) therapy: update from the IRIS study. Blood 2004;104(11):Abstract #21.

Guilhot F, Chastang C, Michallet M, et al. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. French Chronic Myeloid Leukemia Study Group. New England Journal of Medicine 1997;337(4):223-9.

Hahn EA, Glendenning GA. Quality of life on imatinib. Seminars in Hematology 2003;40(2 Suppl 2):31-6.

Hahn EA, Glendenning GA, Sorensen MV, et al. Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low-dose cytarabine: results from the IRIS Study. Journal of Clinical Oncology 2003;21(11):2138-46.

Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. Journal of the National Cancer Institute 1998;90:850-8.

Hehlmann R, Heimpel H, Hasford J, 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(2):398-407.

Hehlmann R, Hochhaus A, Berger U, et al. Concept and feasibility of the randomized comparison of imatinib with imatinib combination therapies for chronic myeloid leukemia: the German CML Study IV - Pilot Phase. Journal of Clinical Oncology 2005;23(16S):abstract 6574.

Hess G, Bunjes D, Siegert W, et al. Durable molecular remissions in patients with relapsed CML post allogeneic stem cell transplantation upon treatment with imatinib-mesylate (Glivec®, STI-571). Follow-up results of a phase II open-label study. Blood 2004;104(11):Abstract #1004.

Hochhaus A. Imatinib mesylate (Glivec, Gleevec) in the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST). Annals of Hematology 2004;83(Suppl 1):S65-6.

Hochhaus A, Kreil S, Corbin AS, et al. Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. Leukemia 2002;16(11):2190-6.

Hughes T, Branford S, Reynolds J, et al. Higher-dose imatinib (600 mg/day) with selective intensification in newly diagnosed CML patients in chronic phase; cytogenetic response rates at 12 months are superior to IRIS. Blood 2004;104(11):Abstract #1001.

Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or

interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. New England Journal of Medicine 2003;349(15):1423-32.

Huntly B, Bench A, Delabesse E, et al. Derivative chromosome 9 deletions in chronic myeloid leukemia: poor prognosis is not associated with loss of ABL-BCR expression, elevated BCR-ABL levels, or karyotypic instability. Blood 2002;99(12):4547-53.

Huntly B, Guilhot F, Reid A, et al. Imatinib improves but may not fully reverse the poor prognosis of patients with CML with derivative chromosome 9 deletions. Blood 2003;102(6):2205-12.

Huntly B, Reid A, Bench A, et al. Deletions of the derivative chromosome 9 occur at the time of the Philadelphia translocation and provide a powerful and independent prognostic indicator in chronic myeloid leukemia. Blood 2001;98(6):1732-8.

Huntly BBA, Green A. Double jeopardy from a single translocation: deletions of the derivative chromosome 9 in chronic myeloid leukemia. Blood 2003;102(4):1160-8.

Issa S, Holdsworth D, Oei P, et al. The utility of peripheral blood FISH in the quantitation of BCR/ABL in CML patients on imatinib mesylate: a comparison with bone marrow FISH and conventional cytogenetics. Blood 2004;104(11):Abstract # 2942.

Jabbour E, Kantarjian H, Jones D, et al. Long-term incidence and outcome of BCR-ABL mutations in patients (pts) with chronic myeloid leukemia (CML) treated with imatinib mesylate. P-Loop mutations are not associated with worse outcome. Blood 2004;104(11):Abstract #1007.

Johansson B, Fioretos T, Mitelman F. Cytogenetic and molecular genetic evolution of chronic myeloid leukemia. Acta Haematologica 2002;107(2):76-94.

Johnson JR, Bross P, Cohen M, et al. Approval summary: imatinib mesylate capsules for treatment of adult patients with newly diagnosed philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase. Clinical Cancer Research 2003;9(6):1972-9.

Kagami Y, Katagiri T, Kaneta Y, et al. Validation study on the prediction of response to imatinib mesylate in chronic myeloid leukemia (CML) patients by genome-wide cDNA microarray analysis. Blood 2004;104(11):Abstract # 2946.

Kaneta Y, Kagami YKT, Tsunoda T, et al. Prediction of sensitivity to STI571 among chronic myeloid leukemia patients by genome-wide cDNA microarray analysis. Japanese Journal of Cancer Research 2002;93:849–856.

Kantarjian H, Cortes J, O'Brien S, et al. Long-term survival benefit and improved complete cytogenetic and molecular response rates with imatinib mesylate in Philadelphia chromosome-positive chronic-phase chronic myeloid leukemia after failure of interferon-alpha. Blood 2004;104(7):1979-88.

Kantarjian H, Cortes J, O'Brien S, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. Blood 2002;99(10):3547-

53.

Kantarjian H, Cortes J, O'Brien S, et al. Imatinib mesylate therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia: high incidence of early complete and major cytogenetic responses. Blood 2003;101(1):97-100.

Kantarjian H, Deisseroth A, Kurzrock R, et al. Chronic myelogenous leukemia: a concise update. Blood 1993;82(3):691-703.

Kantarjian H, Dixon D, Keating M, et al. Characteristics of accelerated disease in chronic myelogenous leukemia. Cancer 1988;61(7):1441-6.

Kantarjian H, Keating M, Estey E, et al. Treatment of advanced stages of Philadelphia chromosome-positive chronic myelogenous leukemia with interferon-ei and low-dose cytarabine. Journal of Clinical Oncology 1992;10(5):772-8.

Kantarjian H, O'Brien S, Cortes J, et al. Complete cytogenetic and molecular responses to interferon-alpha-based therapy for chronic myelogenous leukemia are associated with excellent long-term prognosis. Cancer 2003;94(7):1033-41.

Kantarjian H, O'Brien S, Cortes J, et al. Imatinib mesylate therapy improves survival in patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia in the chronic phase: comparison with historic data. Cancer 2003;98(12):2636-42.

Kantarjian H, O'Brien S, Cortes J, et al. Survival advantage with imatinib mesylate therapy in chronic-phase chronic myelogenous leukemia (CML-CP) after IFN-alpha failure and in late CML-CP, comparison with historical controls. Clinical Cancer Research 2004;10(1 Pt 1):68-75.

Kantarjian H, O'Brien S, Cortes J, et al. Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. Blood 2002;100(5):1590-5.

Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. New England Journal of Medicine 2002;346(9):645-52.

Kantarjian H, Talpaz M, O'Brien S, et al. Imatinib mesylate for Philadelphia chromosome-positive, chronic-phase myeloid leukemia after failure of interferon-alpha: follow-up results. Clinical Cancer Research 2002;8(7):2177-87.

Kantarjian H, Talpaz M, O'Brien S, et al. High-dose imatinib mesylate therapy in newly diagnosed Philadelphia chromosome-positive chronic phase chronic myeloid leukemia. Blood 2004;103(8):2873-8.

Kantarjian H, Talpaz M, O'Brien S, et al. Dose escalation of imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia. Blood 2003;101(2):473-5.

Kurzrock R, Gutterman J, Talpaz M. The molecular genetics of Philadelphia chromosome-

positive leukemias. New England Journal of Medicine 1988;319(15):990-8.

Kvasnicka HM, Thiele J, Staib P, et al. Reversal of bone marrow angiogenesis in chronic myeloid leukemia following imatinib mesylate (STI571) therapy. Blood 2004;103(9):3549-51.

Lahaye T, Riehm B, Berger U, et al. Response and resistance in 300 patients with BCR-ABL–positive leukemias treated with imatinib in a single center: a 4.5-year follow-up. Cancer 2005;103(8):1659-69.

Lange T, Bumm T, Mueller M, et al. Durability of molecular remission in chronic myeloid leukemia patients treated with imatinib vs allogeneic stem cell transplantation. Leukemia 2005;19:1262–1269.

Lange T, Bumm T, Mueller M, et al. Molecular remission to imatinib in patients with chronic myeloid leukaemia (CML) is less durable compared to patients after allografting. Blood 2004;104(11):Abstract #276.

Lange T, Gunther C, Kohler T, et al. High levels of BAX, low levels of MRP-1, and high platelets are independent predictors of response to imatinib in myeloid blast crisis of CML. Blood 2003;101(6):2152-5.

Laurence A, Marin D, Clark R, et al. Frequency of blast crisis after achieving complete cytogenetic remission in first chronic phase CML patients who recieved imatinib therapy within six months of diagnosis. Blood 2004;104(11):Abstract #1021.

Le Coutre P, Kreuzer KA, Na IK, et al. Imatinib in Philadelphia chromosome-positive chronic phase CML patients: molecular and cytogenetic response rates and prediction of clinical outcome. American Journal of Hematology 2003;73(4):249-55.

Lee S, Anasetti C, Horowitz M, et al. Initial therapy for chronic myelogenous leukemia: playing the odds. Journal of Clinical Oncology. 1998;16(9):2897-903.

Marin D, Goldman JM, Olavarria E, et al. Transient benefit only from increasing the imatinib dose in CML patients who do not achieve complete cytogenetic remissions on conventional doses. Blood 2003;102(7):2702-4.

Marin D, Horncastle D, Andreasson C, et al. Prognostic impact of percentage cd34 expression in bone marrow trephines of patients with chronic myeloid leukaemia in chronic phase treated with imatinib. Blood 2004;104(11):Abstract #1019.

Marin D, Marktel S, Bua M, et al. Prognostic factors for patients with chronic myeloid leukaemia in chronic phase treated with imatinib mesylate after failure of interferon alfa. Leukemia 2003;17(8):1448-53.

Marin D, Marktel S, Szydlo R, et al. Survival of patients with chronic-phase chronic myeloid leukaemia on imatinib after failure on interferon alfa. Lancet 2003;362:617-9.

Marktel S, Marin D, Foot N, et al. Chronic myeloid leukemia in chronic phase responding to

imatinib: the occurrence of additional cytogenetic abnormalities predicts disease progression. Haematologica 2003;88(3):260-7.

Martiat P, Michaux J, Rodhain J. Philadelphia-negative (Ph-) chronic myeloid leukemia (CML): comparison with Ph+ CML and chronic myelomonocytic leukemia. The Groupe Francais de Cytogenetique Hematologique. Blood 1991;78(1):205-11.

Martino B, Vincelli Y, Ronco F, et al. Efficacy and safety of imatinib treatment in elederly patients with chronic myeloid leukemia. Blood 2004;104(11):Abstract # 4680.

McLean LA, Gathmann I, Capdeville R, et al. Pharmacogenomic analysis of cytogenetic response in chronic myeloid leukemia patients treated with imatinib. Clinical Cancer Research 2004;10(1 Pt 1):155-65.

Merx K, Muller MC, Kreil S, et al. Early reduction of BCR-ABL mRNA transcript levels predicts cytogenetic response in chronic phase CML patients treated with imatinib after failure of interferon alpha. Leukemia 2002;16(9):1579-83.

Monroy RH, Vargas-Viveros P, Cervera E, et al. Imatinib Alone (IA) vs. Imatinib + Ara-C (IMAC): A randomized phase III clinical trial for the treatment of early phase (EP) chronic myeloid leukemia (CML) Ph+. Preliminary report of Mexican Cooperative Leukemia Group (GRUMELA). Blood 2004;104(11):Abstract #1015.

Moravcova J, Zmekova V, Klamova H, et al. Differences and similarities in kinetics of BCR-ABL transcript levels in CML patients treated with imatinib mesylate for chronic or accelerated disease phase. Leukemia Research 2004;28(4):415-9.

Müller MC, Gattermann N, Lahaye T, et al. Dynamics of BCR-ABL mRNA expression in first-line therapy of chronic myelogenous leukemia patients with imatinib or interferon alpha/ara-C. Leukemia 2003;17(12):2392-400.

Müller MC, Paschka P, LaHaye T, et al. Molecular long-term surveillance of CML patients on imatinib therapy. Follow-up of German patients treated within the IRIS trial. Blood 2004;104(11):Abstract #1003.

National Cancer Institute. Chronic Myelogenous Leukemia (PDQ®): Treatment: Health Professional Version; 2005. [Accessed at http://www.cancer.gov/cancertopics/pdq/treatment/CML/healthprofessional/allpages September 23, 2005]

National Comprehensive Cancer Network. Chronic Myelogenous Leukemia - Clinical Practice Guidelines in Oncology: Version 1.2006. [Accessed at - http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf September 23, 2005.]

National Institute for Clinical Excellence. Guidance on the use of imatinib for chronic myeloid leukaemia. London: National Institute for Clinical Excellence (NICE); 2003.

O'Brien S, Giles F, Talpaz M, et al. Results of triple therapy with interferon-alpha, cytarabine,

and homoharringtonine, and the impact of adding imatinib to the treatment sequence in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in early chronic phase. Cancer 2003;98(5):888-93.

O'Brien S, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. New England Journal of Medicine 2003;348(11):994-1004.

O'Brien S, Tefferi A, Valent P. Chronic myelogenous leukemia and myeloproliferative disease. 2004.

O'Dwyer ME, Gatter KM, Loriaux M, et al. Demonstration of Philadelphia chromosome negative abnormal clones in patients with chronic myelogenous leukemia during major cytogenetic responses induced by imatinib mesylate. Leukemia 2003;17(3):481-7.

O'Dwyer ME, Mauro MJ, Blasdel C, et al. Clonal evolution and lack of cytogenetic response are adverse prognostic factors for hematologic relapse of chronic phase CML patients treated with imatinib mesylate. Blood 2004;103(2):451-5.

Olavarria E, Ottmann OG, Deininger MW, et al. Response to imatinib in patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. Leukemia 2003;17(9):1707-12.

Onida F, Ball G, Kantarjian H, et al. Characteristics and outcome of patients with Philadelphia chromosome negative, BCR/ABL negative chronic myelogenous leukemia. Cancer 2002;95(8):1673-84.

Palandri F, Martinelli G, Amabile M, et al. Imatinib therapy for chronic myeloid leukemia patients who relapse after allogeneic stem cell transplantation: a molecular analysis. Blood 2004;104(11):Abstract # 4655.

Paschka P, Branford S, Lorentz C, et al. Comparison of "log reduction from median pretherapeutic value" vs ratio BCR-ABL/ABL to express the therapeutic response in CML patients. Blood 2004;104(11):Abstract #1013.

Paschka P, Muller MC, Merx K, et al. Molecular monitoring of response to imatinib (Glivec) in CML patients pretreated with interferon alpha. Low levels of residual disease are associated with continuous remission. Leukemia 2003;17(9):1687-94.

Pasquini R, Clementino NC, Zanichelli MA, et al. Observational study for evaluation of quality of life in patients with chronic myeloid leukemia (CML) in use of Gleevec® (imatinib mesilate). Blood 2004;104(11):Abstract # 2932.

Pautas C, Nicolini F, Cony-Makhoul P, et al. Imatinib mesylate (IM), is an alternative to donor lymphocyte infusion (DLI) for chronic myelogenous leukemia (CML) in relapse after allogeneic stem cell transplantation: a 3-year follow-up report, on the Behalf of the Société Française de Greffe de Moëlle et de Thérapie Cellulaire (SFGM-TC) and the France Intergroupe de la Leucémie Myéloïde Chronique (Fi-LMC). Blood 2004;104(11):Abstract #1017.

Press RD, Love Z, Tronnes AA, et al. BCR-ABL RNA levels at the time of a complete cytogenetic response (CCR) predict the duration of CCR in imatinib-treated chronic myeloid leukemia patients. Blood 2004;104(11):Abstract #1098.

Quintas-Cardama A, Kantarjian H, Talpaz M, et al. Imatinib mesylate therapy may overcome the poor prognostic significance of deletions of derivative chromosome 9 in patients with chronic myelogenous leukemia. Blood 2005;105(6):2281-6.

Radich J, Gooley T, Bensinger W, et al. HLA-matched related hematopoietic cell transplantation for chronic-phase CML using a targeted busulfan and cyclophosphamide preparative regimen. Blood 2003;102(1):31-5.

Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. International Journal of Epidemiology 2002;31(1):150-3.

Rosti G, Martinelli G, Bassi S, et al. Molecular response to imatinib in late chronic-phase chronic myeloid leukemia. Blood 2004;103(6):2284-90.

Rousselot P, Legros L, Guilhot J, et al. A Phase I/II dose escalating study of daunorubicin combined with imatinib mesylate and cytarabine as induction therapy for chronic myelogenous leukaemia in myeloid blast crisis. Preliminary results of the AFR01 trial. Blood 2004;104(11):Abstract #1002.

Sacchi S, Kantarjian H, O'Brien S, et al. Chronic myelogenous leukemia in nonlymphoid blastic phase. Cancer 1999;18(12):2632-41.

Savage D, Antman K. Imatinib mesylate--a new oral targeted therapy. New England Journal of Medicine 2002;346(9):683-93.

Savage D, Szydlo R, Chase A, et al. Bone marrow transplantation for chronic myeloid leukaemia: the effects of differing criteria for defining chronic phase on probabilities of survival and relapse. British Journal of Haematology. 1997;99(1):30-5.

Savage D, Szydlo R, Goldman JM. Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. British Journal of Haematology 1997;96(1):111-6.

Sawyers CL. Chronic myeloid leukemia - Review Article. New England Journal of Medicine 1999;340(17):1330-40.

Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood 2002;99(10):3530-9.

Shah NP, Nicoll JM, Nagar B, et al. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer Cell 2002;2(2):117-25.

Shimoni A, Kroger N, Zander AR, et al. Imatinib mesylate (STI571) in preparation for allogeneic hematopoietic stem cell transplantation and donor lymphocyte infusions in patients with Philadelphia-positive acute leukemias. Leukemia 2003;17(2):290-7.

Silver RT, Talpaz M, Sawyers CL, et al. Four years of follow-up of 1027 patients with late chronic phase (L-CP), accelerated phase (AP), or blast crisis (BC) chronic myeloid leukemia (CML) treated with imatinib in three large Phase II trials. Blood 2004;104(11):Abstract #23.

Sinclair P, Nacheva E, Leversha M, et al. Large deletions at the t(9;22) breakpoint are common and may identify a poor-prognosis subgroup of patients with chronic myeloid leukemia. Blood 2000;95(3):738-43.

Sneed TB, Kantarjian H, Talpaz M, et al. The significance of myelosuppression during therapy with imatinib mesylate in patients with chronic myelogenous leukemia in chronic phase. Cancer 2004;100(1):116-21.

Sokal J, Baccarani M, Russo D, et al. Staging and prognosis in chronic myelogenous leukemia. Seminars in Hematology. 1988;25(1):49-61.

Soverini S, Martinelli G, Amabile M, et al. Denaturing-HPLC-based assay for detection of ABL mutations in chronic myeloid leukemia patients resistant to Imatinib. Clinical Chemistry 2004;50(7):1205-13.

Soverini S, Martinelli G, Rosti G, et al. ABL mutations in late chronic phase chronic myeloid leukemia patients with up-front cytogenetic resistance to imatinib are associated with a greater likelihood of progression to blast crisis and shorter survival: a study by the GIMEMA working party on chronic myeloid leukemia. Journal of Clinical Oncology 2005;23(18):4100-9.

Steegmann JL, Moreno G, Alaez C, et al. Chronic myeloid leukemia patients resistant to or intolerant of interferon alpha and subsequently treated with imatinib show reduced immunoglobulin levels and hypogammaglobulinemia. Haematologica 2003;88(7):762-8.

Stentoft J, Pallisgaard N, Kjeldsen E, et al. Kinetics of BCR-ABL fusion transcript levels in chronic myeloid leukemia patients treated with STI571 measured by quantitative real-time polymerase chain reaction. European Journal of Haematology 2001;67(5-6):302-8.

Sureda A, Carrasco M, de Miguel M, et al. Imatinib mesylate as treatment for blastic transformation of Philadelphia chromosome positive chronic myelogenous leukemia. Haematologica 2003;88(11):1213-20.

Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002;99(6):1928-37.

Thomas M, Irving J, Lennard A, et al. Validation of the Hasford score in a demographic study in chronic granulocytic leukaemia. Journal of Clinical Pathology 2001;54(6):491-3.

Thomazy VA, Kantarjian H, Imam M, et al. Use of Plasma RNA for Real-Time Quantitative RT-

PCR to Monitor Imatinib Therapy in Patients with Chronic Myeloid Leukemia. Blood 2004;104(11):Abstract #1099.

U.S. Food and Drug Administration. Gleevec approved for first line treatment of chronic myeloid leukemia (CML). 2002. [Accessed at - http://www.fda.gov/bbs/topics/NEWS/2002/NEW00860.html, September 23, 2005]

Valeyrie L. , Bastuji-Garin S. , Revuz J. , et al. Adverse cutaneous reactions to imatinib (ST1571) in Philadelphia chromosome-positive leukemias: A prospective study of 54 patients. Journal of the American Academy of Dermatology 2003;48(2):201-6.

Vallespí T, Borrego M, Colomé D, et al. Quantitative polymerase chain reaction (qPCR) at diagnosis and follow-up of patients with chronic myeloid leukemia in treatment with imatinib. Blood 2004;104(11):Abstract # 4688.

van Rhee F, Szydlo R, Hermans J, et al. Long-term results after allogeneic bone marrow transplantation for chronic myelogenous leukemia in chronic phase: a report from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplantation 1997;20(7):553-60.

Wang L, Pearson K, Ferguson JE, et al. The early molecular response to imatinib predicts cytogenetic and clinical outcome in chronic myeloid leukaemia. British Journal of Haematology 2003;120(6):990-9.

White DL, Saunders VA, Branford S, et al. The combination of intrinsic sensitivity to imatinib and sokal prognostic score is strongly predictive of molecular response in newly diagnosed CML patients treated with imatinib. Blood 2004;104(11):Abstract #1008.

Wu CJ, Neuberg D, Chillemi A, et al. Quantitative monitoring of BCR/ABL transcript during STI-571 therapy. Leukemia & Lymphoma 2002;43(12):2281-9.

Xie Y, Davies S, Xiang Y, et al. Trends in leukemia incidence and survival in the United States (1973-1998). 2003;97(9):2229-35.

Excluded Articles

Abruzzese E, Bocchia M, Trawinska M, et al. Peptide-vaccine treatment associated with imatinib in patients with residual CML disease is able to induce both immunologic response and molecular remission. Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: 2517. 2004.

Abruzzese E, Gozzetti A, Zaccaria A, et al. Ph-abnormal clones emerged during imatinib therapy: clinical report and clonal analyses on 23 patients from GIMEMA working party (GWP) in CML registry. Blood 2004;104(11):Abstract # 2936.

Alvarez RH, Kantarjian H, Bueso-Ramos C, et al. Significance of marrow fibrosis in chronic phase chronic myelogenous leukemia (CML) post interferon-a failure treated with imatinib mesylate therapy. Blood 2004;104(11):Abstract # 2939.

Angstreich GR, Smith BD, Jones RJ. Treatment options for chronic myeloid leukemia: imatinib versus interferon versus allogeneic transplant. [Review]. Current Opinion in Oncology 2004;16(2):95-9.

Ausekar BV. Comparative study of survival off CML patients under treatment with busulphan, hydroxyurea, interferon A, imatinib. Journal of Clinical Oncology 2004;22(14S):Abstract #6783.

Azam M, Latek RR, Daley GQ. Mechanisms of autoinhibition and STI-571/imatinib resistance revealed by mutagenesis of BCR-ABL. Cell 2003;112(6):831-43.

Barbouti A, Ahlgren T, Johansson B, et al. Clinical and genetic studies of ETV6/ABL1-positive chronic myeloid leukaemia in blast crisis treated with imatinib mesylate. British Journal of Haematology 2003;122(1):85-93.

Berger U, Engelich G, Reiter A, et al. Imatinib and beyond--the new CML study IV. A randomized controlled comparison of imatinib vs imatinib/interferon-alpha vs imatinib/low-dose AraC vs imatinib after interferon-alpha failure in newly diagnosed chronic phase chronic myeloid leukemia. Annals of Hematology 2004;83(4):258-64.

Blasiak J, Drzewoski J, Poplawski T, et al. Imatinib (STI571) induces DNA damage in BCR/ABL-expressing leukemic cells but not in normal lymphocytes. Blood 2004;104(11):Abstract # 4353.

Borthakur G, Cortes J. Imatinib mesylate in the treatment of chronic myelogenous leukemia. [Review]. International Journal of Hematology 2004;79(5):411-9.

Brieger A, Boehrer S, Schaaf S, et al. In bcr-abl-positive myeloid cells resistant to conventional chemotherapeutic agents, expression of Par-4 increases sensitivity to imatinib (STI571) and histone deacetylase-inhibitors. Biochemical Pharmacology 2004;68(1):85-93.

Bueso-Ramos CE, Cortes J, Talpaz M, et al. Imatinib mesylate therapy reduces bone marrow

fibrosis in patients with chronic myelogenous leukemia. Cancer 2004;101(2):332-6.

Canadian Coordinating Office for Health Technology Assessment. 2001. [Accessed at - https://www.ccohta.ca/entry_e.html, September 23, 2005]

Cazzaniga G, Corradi B, Piazza R, et al. Highly sensitive mutations detection in BCR-ABL positive leukemia prior and during imatinib treatment. Blood 2004;104(11):Abstract #1985.

Champlin R, Ghosh S, McCormick G, et al. Sequential treatment with reduced intensity allogeneic stem cell transplantation and imatinib for chronic myelogenous leukemia (CML). Blood 2004;104(11):Abstract #812.

Chandra J, Tracy, Gorre M, et al. Effects of adaphostin, a novel tyrphostin inhibitor, in diverse models of imatinib mesylate resistance. Blood 2004;104(11):Abstract # 2097.

Corbin AS, Buchdunger E, Pascal F, et al. Analysis of the structural basis of specificity of inhibition of the Abl kinase by STI571. Journal of Biological Chemistry 2002;277(35):32214-9.

Cortes J. Randomized trial of therapy of early phase chronic myelogenous leukemia with high-dose imatinib mesylate (Gleevec) alone or in combination with peg-alpha interferon (PEG-Intron) and sargramostin (GM-CSF). National Institutes of Health, Clinicial Trials. 2003 [Accessed at - http://www.clinicaltrials.gov/ct/show/NCT00050531?order=45=, September 23, 2005]

Deininger MW, Druker BJ. Specific targeted therapy of chronic myelogenous leukemia with imatinib. [Review]. Pharmacological Reviews 2003;55(3):401-23.

Deininger MW, O'Brien S, Ford JM, et al. Practical management of patients with chronic myeloid leukemia receiving imatinib. [Review]. Journal of Clinical Oncology 2003;21(8):1637-47.

Deininger MW, Schleuning M, Sayer H-G, et al. Allografting after imatinib therapy. No evidence for increased transplant-related mortality and favorable results in patients transplanted in remission. A retrospective study by the EBMT. Blood;100:783a.

Demehri S, Lange T, Paschka P, et al. CML with E8A2 BCR-ABL fusion: the fourth breakpoint cluster region? Blood 2004;104(11):Abstract #1018.

Druker BJ. Signal transduction inhibition: results from phase I clinical trials in chronic myeloid leukemia. [Review]. Seminars in Hematology 2001;38(3 Suppl 8):9-14.

Druker BJ. Taking aim at Ewing's sarcoma: is KIT a target and will imatinib work? Journal of the National Cancer Institute 2002, 94: 1660-1

Druker BJ. Imatinib mesylate in the treatment of chronic myeloid leukaemia. [Review]. Expert Opinion on Pharmacotherapy 2003;4(6):963-71.

Ebnoether M, Stentoft J, Ford JM, et al. Cerebral oedema as a possible complication of treatment

with imatinib. Lancet 2002;359(9319):1751-2.

Elliot VJ, Marin D, Horncastle D, et al. Percentage of CD34 + cells in a minimum 500-cell count in bone marrow trephines of patients with chronic myeloid leukaemia provides the best correlation with aspirate blast count. Blood 2004;104(11):Abstract # 4663.

Engelich G, Berger U, Hochhaus A, et al. Randomized controlled comparison of imatinib vs. imatinib + interferon alpha vs. imatinib + low dose araC vs. interferon a standard therapy and determining the role of allografting vs. salvage chemotherapy in newly diagnosed chronic phase CML. Onkologie 2002;25(Suppl 4):174.

Faber E, Jarosova M, Nausova J, et al. Intermittent dosage of imatinib - a feasible strategy for patients with significant hematologic toxicity during standard therapy. Blood 2004;104(11):Abstract # 4657.

Gambacorti-Passerini C, Tornaghi L, Cavagnini F, et al. Gynaecomastia in men with chronic myeloid leukaemia after imatinib_ . Lancet 2003;361:1954–56.

Garside R, Round A, Dalziel K, et al. The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review. [Review]. Health Technology Assessment 2002;6(33):1-162.

Goldman JM. Chronic myeloid leukemia—still a few questions. Experimental Hematology 2004;32:2-10.

Gordois A, Scuffham P, Warren E, et al. Cost-utility analysis of imatinib mesilate for the treatment of advanced stage chronic myeloid leukaemia. British Journal of Cancer 2003;89(4):634-40.

Gratwohl A, Hermans J, Goldman JM, et al. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Lancet 1998;352:1087–92.

Griswold IJ, Bumm T, O'Hare T, et al. Investigation of the biological differences between BCR-ABL kinase mutations resistant to imatinib. Blood 2004;104(11):Abstract #555.

Guilhot F. Imatinib (Gleevec, Glivec) versus interferon (IFN) + cytarabine as initial therapy for patients with chronic myeloid leukaemia (CML) in chronic phase: results of a randomized study (for the IRIS group). Annals of Oncology 2002;13(Suppl 5):8, Abs. 27.

Guilhot F, O'Brien S, Druker BJ, et al. Imatinib (ST1571, Glivec(r)) as initial therapy for patients with CML: results of a randomized phase III study versus interferon (IFN) cytarabine. [abstract]. Hematology Journal 2002;3(Suppl 1):181.

Gulbas Z, Akay MO, Sahin F, et al. Chronic myeloid leukemia patients treated with imatinib show increased IFN-gamma synthesis in T Cells and hypogammaglobulinemia. Blood 2004;104(11):Abstract # 4698.

Gupta S, Berman E, Jhanwar S. Results of conventional cytogenetics and interphase FISH (I-

FISH) analyses in patients with a clinical and morphologic diagnosis of CML: analysis of 52 cases. Blood 2004;104(11):Abstract # 4423.

Hahn EA. The quality of life of patients with chronic phase chronic myeloid leukemia in the IRIS study of interferon-alpha plus ARA-C vs imatinib (ST1571, Glivec(r)). [abstract]. Hematology Journal 2002;3(Suppl 1):300.

Hahn EA, Sorensen MV, Hudgens SA, et al. Quality of life of patients with chronic phase chronic myeloid leukemia in the IRIS study of interferon-alpha plus Ara-C vs imatinib (ST1571, Glivec, Gleevec0. [abstract]. Blood 2002;100(11):94a.

Hehlmann R. Phase III randomized pilot study of imatinib mesylate alone or with interferon alfa or low-dose cytarabine versus interferon alfa standard therapy followed by allogeneic stem cell transplantation in patients with newly diagnosed chronic phase chronic myelogenous leukemia. National Institutes of Health, Clinical Trials 2003 [Accessed at - http://www.clinicaltrials.gov, September 23, 2005].

Homewood J, Watson M, Richards SM, et al. Treatment of CML using IFN-alpha: impact on quality of life. Hematology Journal 2003;4(4):253-62.

Hughes T, Branford S. Molecular monitoring of chronic myeloid leukemia. [Review]. Seminars in Hematology 2003;40(2 Suppl 2):62-8.

Husereau D. Imatinib mesylate for chronic myeloid leukemia: what do we really know? Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA) 2002.

Ichihara E, Costa FF, Busoli N, et al. High frequency of point mutations of BCR/ABL gene in CML patients resistant to imatinib therapy - report of a novel mutation. Blood 2004;104(11):Abstract # 4661.

Illmer T, Schaich M, Platzbecker U, et al. P-glycoprotein-mediated drug efflux is a resistance mechanism of chronic myelogenous leukemia cells to treatment with imatinib mesylate. Leukemia 2004;18(3):401-8.

Jiang X, Zhao Y, Chan WY, et al. Leukemic stem cells of chronic phase CML patients consistently display very high BCR-ABL transcript levels and reduced responsiveness to imatinib mesylate in addition to generating a rare subset that produce imatinib mesylate-resistant differentiated progeny. Blood 2004;104(11):Abstract # 711.

Jilani I, Vincente T, Faraji H, et al. Circulating myeloperoxidase (MPO) as a tumor marker in patients with chronic myeloid leukemia (CML). Blood 2004;104(11):Abstract # 4679.

Kai T, Ikeda K, Shiga Y, et al. Imatinib mesylate induced fatal hepatitis B virus (HBV) reactivation in a patient with CML. Blood 2004;104(11):Abstract # 4677.

Kantarjian H, Cortes J, O'Brien S, et al. Long-term results of imatinib mesylate therapy in philadelphia chromosome (Ph) positive chronic phase chronic myelogenous leukemia (CML) post interferon-a (IFN) failure. M.D. Anderson experience in 261 patients. Journal of Clinical

Oncology 2004;22(1: 4S (July 15 Supplement),):Abstract 6622.

Kantarjian H, O'Brien S, Cortes J, et al. Analysis of the impact of imatinib mesylate therapy on the prognosis of patients with Philadelphia chromosome-positive chronic myelogenous leukemia treated with interferon-alpha regimens for early chronic phase. Cancer 2003;98(7):1430-7.

Kim J, Kim D, Lee D, et al. Monitoring of BCR-ABL Transcirpt Levels after Discontinuation of Imatinib Therapy in Chronic Myelogenous Leukemia Patients Achieving Complete Cytogenetic Response. Blood 2004;104(11):Abstract # 4684.

Koyama N, Koschmieder S, Tyagi S, et al. Inhibition of phosphotyrosine phosphatase-1B (PTP1B) induces resistance to the ABL kinase inhibitor imatinib mesylate (Gleevec®) in BCR-ABL positive leukemic cells. Blood 2004;104(11):Abstract # 2095.

Kurzrock R, Talpaz M, Li L, et al. Distinct biological impact of dephosphorylation vs downregulation of p210 Bcr-Abl: implications for imatinib mesylate response and resistance. Blood 2004;104(11):Abstract # 4307.

Kwak J, Lee N, Song E, et al. The change of vascular endothelial growth factor and microvessel density following imatinib mesylate therapy and allogeneic bone marrow transplantation in chronic myeolid leukemia. Blood 2004;104(11):Abstract # 4669.

Larson RA, IRIS Study Group. Imatinib (ST1571, Gleevec) as initial therapy for patients with newly diagnosed Ph+ chronic myeloid leukemia (CML): results of a randomized Phase III study vs interferon-alfa + cytarabine (IFN+AraC). [abstract]. Blood 2002;100:4a.

Latagliata R, Breccia M, Carmosino I, et al. Association of hydroxyurea to imatinib is effective in patients with chronic myelogenous leukemia resistant to imatinib alone. Blood 2004;104(11):Abstract # 4693.

Leis JF, Stepan DE, Curtin PT, et al. Central nervous system failure in patients with chronic myelogenous leukemia lymphoid blast crisis and Philadelphia chromosome positive acute lymphoblastic leukemia treated with imatinib (STI-571). Leukemia & Lymphoma 2004;45(4):695-8.

Lickliter J, Arthur C, D'Rozario J, et al. Phase II pilot study of imatinib mesylate combined with induction chemotherapy in blast-phase CML and Ph+ ALL. Blood 2004;104(11):Abstract #4682.

Lin F, Drummond MW, O'Brien S, et al. Molecular monitoring in chronic myeloid leukemia patients who achieve complete cytogenetic remission on imatinib. Blood 2003;102(3):1143.

Martinelli G, Rosti G, Pane F, et al. Prediction of response to imatinib by prospective quantitation of BCR-ABL transcript in late chronic phase chronic myeloid leukemia patients by GIMEMA Working Party on CML. Blood 2004;104(11):Abstract # 4672.

Matsui W, Angstreich GR, Vala MS, et al. Chronic myeloid leukemia stem cells and their differentiated progeny display divergent drug sensitivities to imatinib mesylate and interferon-

alpha. Blood 2004;104(11):Abstract #1996.

McNamara C, Grigg A, Szer J, et al. Morphological effects of imatinib mesylate (STI571) on the bone marrow and blood of patients with Philadelphia chromosome (Ph) positive chronic myeloid leukaemia. Clinical & Laboratory Haematology 2003;25(2):119-25.

McPherson E, Shanmughan M, Huang SY, et al. Response of elevated serum soluble interleukin-2 receptor (sIL-2R) and overexpression of glucose-6- phosphate dehydrogenase (G6PD) in patients with chronic myelogenous leukemia treated with imatinib mesylate. Blood 2004;104(11):Abstract # 4695.

Miljus j, Melo JV, Boros L, et al. Metabolic profile of imatinib resistance in CML cells. Blood 2004;104(11):Abstract #1982.

Miyoshi T, Nagai T, Nakamura M, et al. Heme affects sensitivity to imatinib through regulation of Nrf2 Activity in BCR/ABL-positive cell lines. Blood 2004;104(11):Abstract #2092 .

National Institute for Clinical Excellence. Guidance on the use of imatinib for chronic myeloid leukaemia. London: National Institute for Clinical Excellence (NICE) 2002.

Neumann F, Teutsch N, Kliszewski S, et al. Gene expression profiling of Philadelphia chromosome (Ph) Negative CD34+ hematopoietic stem and progenitor cells of patients with Ph positive CML in complete molecular remission during therapy with imatinib. Leukemia 2005;104(19):458-60.

Novaretti MC, Fonseca GH, Conchon M, et al. First case of immune-mediated haemolytic anaemia associated to imatinib mesylate. European Journal of Haematology 2003;71(6):455-8.

O'Brien S, Deininger MW. Imatinib in patients with newly diagnosed chronic-phase chronic myeloid leukemia. Seminars in Hematology 2003;40(2 Suppl 2):26-30.

O'Brien S, Rule SA. Position paper on imatinib mesylate in chronic myeloid leukaemia. British Journal of Haematology 2002;119(1):268-72.

Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood 2002;100(6):1965-71.

Ptasznik A, Nakata Y, Kalota A, et al. Targeting lyn kinase with short interfering RNA (siRNA)-a novel therapeutic strategy for drug resistant chronic myelogenous leukemia (CML). Blood 2004;104(11):Abstract #554.

Radujkovic A, Schad M, Topaly J, et al. Synergism between 17-AAG and imatinib in imatinib-resistant CML Cells: inhibition of p-glycoprotein by 17-AAG as a new mechanism of increasing imatinib activity. Blood 2004;104(11):Abstract # 2094.

Reinhold U, Hennig E, Leiblein S, et al. FISH for BCR-ABL on interphases of peripheral blood neutrophils but not of unselected white cells correlates with bone marrow cytogenetics in CML

patients treated with imatinib. Leukemia 2003;17(10):1925-9.

Rosti G, Trabacchi E, Bassi S, et al. Risk and early cytogenetic response to imatinib and interferon in chronic myeloid leukemia. Haematologica 2003;88(3):256-9.

Sashida G, Tauchi T, Sumi M, et al. Specific inhibition of hTERT by shRNA sensitizes for imatinib mesylate in BCR-ABL-positive cells. Blood 2004;104(11):Abstract # 4339.

Sawyers CL. Research on resistance to cancer drug Gleevec. Science 2001;294:1834.

Schoch CSS, Bursch S, Gerstner D, et al. Comparison of chromosome banding analysis, interphase- and hypermetaphase-FISH, qualitative and quantitative PCR for diagnosis and for follow-up in chronic myeloid leukemia: a study on 350 cases. Leukemia 2002;16:53–59.

Segawa H, Kimura S, Kuroda J, et al. Zoledronate inhibits leukemia growth in bone marrow and synergizes with imatinib mesylate against Ph^+ primary leukemic cells. Blood 2004;104(11):Abstract # 2096.

Shah NP, Branford S, Hughes TP, et al. Major cytogenetic responses to BMS-354825 in patients with chronic myeloid leukemia are associated with a one to two log reduction in *BCR-ABL* transcript. Blood 2004;104(11):Abstract #1008.

Shah NP, Tran C, Lee FY, et al. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 2004;305:399-401.

Shimizu T, Miyakawa Y, Iwata S, et al. A novel mechanism for imatinib mesylate (STI571) resistance in CML cells: contribution of TC-PTP to modulating signals down-stream from the BCR-ABL fusion protein. Blood 2004;104(11):Abstract #1984.

Siciliano RD, Schmid M, Stussi G, et al. Continuous complete molecular remission after withdrawal of imatinib mesylate in relapsed CML after allogeneic stem cell transplantation. Blood 2004;104(11):Abstract # 4686.

Silver RT. Molecular Biology of CML. In RC Bast, D Kufe, RE Pollock, et al. Cancer Medicine (Ed. 5) Hamilton, Ontario: BC Decker 2000.

Silver RT, Peterson BL, Szatrowski TP, et al. Treatment of the chronic phase of chronic myeloid leukemia with an intermittent schedule of recombinant interferon alfa-2b and cytarabine: results from CALGB study 9013. Leukemia & Lymphoma 2003;44(1):39-48.

Sotiropoulos D, Adamidou D, Athanasiadou A, et al. two pregnancies resulting in a healthy newborn in a CML patient treated with imatinib. Blood 2004;104(11):Abstract # 4694.

Soverini S, Martinelli G, Rosti G, et al. ABL mutations in late-chronic phase chronic myeloid leukemia patients with cytogenetic refractoriness to imatinib are associated with a greater likelihood of progression to blast crisis and shorter survival. On Behalf of the GIMEMA Working Party on Chronic Myeloid Leukemia. Blood 2004;104(11):Abstract #1005.

Tipping AJ, Deininger MW, Goldman JM, et al. Comparative gene expression profile of chronic myeloid leukemia cells innately resistant to imatinib mesylate. Experimental Hematology 2003;31(11):1073-80.

Tsao AS, Kantarjian H, Cortes J, et al. Imatinib mesylate causes hypopigmentation in the skin. Cancer 2003;98(11):2483-7.

van Deventer HW, Hall MD, Orlowski RZ, et al. Clinical course of thrombocytopenia in patients treated with imatinib mesylate for accelerated phase chronic myelogenous leukemia. American Journal of Hematology 2002;71(3):184-90.

Vandenberghe P, Boeckx N, Ronsyn E, et al. Imatinib mesylate induces durable complete remission of advanced CML persisting after allogeneic bone marrow transplantation. Leukemia 2003;17(2):458-60.

Vidal, Kantarjian H, O'Brien S, et al. Sudden blastic transformation (SBT) in patients (pts) with chronic myeloid leukemia (CML) treated with imatinib mesylate. Blood 2004;104(11):Abstract # 2930.

Wassmann B, Gokbuget N, Bruck P *et al*. 2003.

Wassmann B, Gokbuget N, Scheuring UJ, et al. A randomized multicenter open label phase II study to determine the safety and efficacy of induction therapy with imatinib (Glivec, formerly STI571) in comparison with standard induction chemotherapy in elderly (>55 years) patients with Philadelphia chromosome-positive (Ph+/BCR-ABL+) acute lymphoblastic leukemia (ALL) (CSTI571ADE 10). Annals of Hematology 2003;82(11):716-20.

Zander AR, Zabelina T, Renges H, et al. Pretreatment with Glivec Increases Transplant-Related Mortality after Allogeneic Transplant. Blood 2003;102(21):468a.

Appendix A:
MEDLINE Search Strategy

Database: Ovid MEDLINE(R) <1966 to September Week 3 2004>
Search Strategy:

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4 randomized controlled trial.pt. (194192)
5 controlled clinical trial.pt. (67292)
6 Randomized Controlled Trials/ (34359)
7 Random Allocation/ (51911)
8 Double-Blind Method/ (79820)
9 Single-Blind Method/ (8433)
10 or/4-9 (329367)
11 Animal/ not Human/ (2838957)
12 10 not 11 (311915)
13 clinical trial.pt. (392148)
14 exp Clinical Trials/ (159166)
15 (clinic$ adj25 trial$).tw. (103424)
16 ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (76365)
17 Placebos/ (23320)
18 placebo$.tw. (86217)
19 random$.tw. (294378)
20 Research Design/ (38965)
21 (latin adj square).tw. (2126)
22 or/13-21 (693867)
23 22 not 11 (643785)
24 23 not 12 (342333)
25 Comparative Study/ (1152523)
26 exp Evaluation Studies/ (499768)
27 Follow-Up Studies/ (288858)
28 Prospective Studies/ (178265)
29 (control$ or prospectiv$ or volunteer$).tw. (1483791)
30 Cross-Over Studies/ (15073)
31 or/25-30 (2964552)
32 31 not 11 (2271429)
33 32 not (12 or 24) (1817997)
34 12 or 24 or 33 (2472245)

38 (imatinib or gleevec or glivec or STI571).mp. (1613)
39 exp leukemia, myeloid, chronic/ (9737)
40 38 and 39 (718)
41 40 and 34 (286)
42 limit 41 to english language (250)

Appendix B:
Quality Criteria

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups random?
   Adequate approaches to sequence generation
   - Computer-generated random numbers
   - Random numbers tables

   Inadequate approaches to sequence generation
   - Use of alternation, case record numbers, birth dates or weekdays
2. Was the treatment allocation concealed?
   Adequate approaches to concealment of randomization
   - Centralized or pharmacy-controlled randomization
   - Serially-numbered identical containers
   - On-site computer based system with a randomization sequence that is not readable until allocation
   - Other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients

   Inadequate approaches to concealment of randomization
   - Use of alternation, case record numbers, birth dates or weekdays
   - Open random numbers lists
   - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
3. Were the groups similar at baseline in terms of important prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were the point estimates and measure of variability presented for the primary outcome measure?
9. Did the analyses include an intention to treat analysis?

Quality criteria for assessment of observational studies

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

Cohort studies

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

Case-control studies

Is the case definition explicit?
Had the disease state of the cases been reliably assessed and validated?
Were the controls randomly selected from the source of population of the cases?
How comparable are the cases and controls with respect to potential confounding factors?
Were interventions and other exposures assessed in the same way for cases and controls?
How was the response rate defined?
Were the non-response rates and reasons for non-response the same in both groups?
Is it possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
Was an appropriate statistical analysis used (matched or unmatched)?

Case series

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

Appendix B. Table 16. Quality of included studies

Quality Question 1. Is the study based on a representative sample from a relevant population?
Quality Question 2. Are the criteria for inclusion explicit?
Quality Question 3. Did all individuals enter the survey at a similar point in disease progression?
Quality Question 4. Was follow up long enough for important events to occur?
Quality Question 5. Were outcomes assessed using objective criteria or was blinding used?
Quality Question 6. If comparisons of sub-series, was there a sufficient description of the series and distribution of prognostic factors?

First Author, Year	Quality 1:	Quality 2:	Quality 3:	Quality 4:	Quality 5:	Quality 6:	Total score
Baccarani, 2004[91]	Y	Y	Y	N	Y	N/A	4/5
Bhatia, 2003[27]	N	Y	N	Unclear	Y	N/A	2/5
Branford, 2003[33]	Y	Y	Y	Y	Y	N	5/6
Braziel, 2002[67]	N	Y	Unclear	Y	Y	N	3/6
Cervantes, 2003[37]	N	Y	N	N	Y	Y	3/6
Cohen, 2002[82]	Y	Y	Y	Unclear	Y	Y	5/6
Cortes, Giles, et al., 2003[69]	Y	Y	Unclear	N	Y	N/A	3/5
Cortes, Talpaz, et al., 2003[1]	Y	Y	Y	Y	Y	Y	6/6
Druker, Sawyers, et al., 2001[89]	Y	Y	Y	N	Y	Y	5/6
Druker, Talpaz, et al., 2001[66]							
Drummond, 2003[92]	Y	N	Unclear	Unclear	Y	N/A	2/5
El-Zimaity, 2004[97]	N	N	N	Y	Y	Y	3/6
Fischer, 2002[77]	N	N	N	N	Y	N	1/6
Frater, 2003[109]	Unclear	N	Unclear	Unclear	Y	N/A	1/5
Gardembas, 2003[38]	Y	Y	Y	Y	Y	N/A	5/5
Hahn, 2003 (2 full-text articles)[60, 61]	Y	Y	Y	Y	Y	N/A	5/5
Hochhaus, 2002[55]	Unclear	N	Unclear	Y	Y	Y	3/6
Hughes, 2003[11]	Y	Y	Y	Y	Y	Y	6/6
Huntly, 2003[51]	Unclear	N	N	N	Y	Y	2/6
Kantarjian, Sawyers, et al.,2002[2]	Y	Y	Y	Y	Y	Y	6/6
Karntarjian, Talpaz, et al., 2002[70]	Y	Y	Y	Y	Y	N/A	5/5
Karntarjian, Talpaz, et al., 2003[71]	N	Y	N	Y	Y	N	3/6
Karntarjian, Talpaz, et al., 2004[12]	Y	Y	Y	Y	Y	N/A	5/5
Kantarjian, Cortes, et al., 2002[90]	Y	Y	Y	Y	Y	N	5/6
Karntarjian, Cortes, et al., 2003[63]	Y	N	Y	N	Y	Y	6/6
Karntarjian, Cortes, et al., 2004[72]	N	Y	Y	Y	Y	Y	5/6
Kantarjian, O'Brien, et al., 2002[78]	N	Y	N	Y	Y	N	3/6
Kantarjian, O'Brien, et al., 2003[98]	N	N	Y	Y	Y	N	3/6
Kantarjian, O'Brien, et al., 2004[44]	N	Y	Y	Y	Y	Y	5/6
Kvasnicka, 2004[111]	N	N	N	Y	Y	N	2/6
Lahaye, 2005[75]	Y	Y	Y	Y	Y	N	5/6
Lange, 2003[102]	Y	N	Y	Y	Y	N	4/6
Le Coutre, 2003[73]	Y	Y	Y	N	Y	N/A	4/5

First Author, Year	Quality 1:	Quality 2:	Quality 3:	Quality 4:	Quality 5:	Quality 6:	Total score
Marin, Goldman, et al., 2003[74]	Unclear	N	Unclear	N	Y	N/A	1/5
Marin, Marktel, Bua, et al., 2003[75]	Y	N	N	Unclear	Y	N/A	2/5
Marin, Marktel, Szydlo, et al., 2003[75]	Y	Y	Y	Y	Y	N/A	5/5
Marktel, 2003[99]	Y	Y	Y	Y	Y	N	5/6
McLean[103]	Y	Y	Y	Y	Y	N	5/6
Merx, 2002[105]	Y	Y	Y	Y	Y	N/A	5/5
Moravcova, 2004[9]	N	N	Y	Y	Y	N	3/6
Müller, 2003[104]	Y	Y	Y	Y	Y	N	5/6
O'Brien, Giles, et al., 2003[79]	N	Y	N	Y	Y	N/A	3/5
O'Brien, Guilhot, et al., 2003 [59]	Y	Y	Y	Y	Y	N/A	5/5
O'Dwyer, 2003[35]	N	Y	Unclear	Unclear	Y	N/A	2/5
O'Dwyer, 2004[96]	N	N	Unclear	Y	Y	N/A	2/5
Olavarria, 2003[84]	Y	Y	N	Y	Y	N	4/6
Paschka, 2003[10]	Y	Y	Unclear	Y	Y	Unclear	4/6
Rosti, 2004[8]	Unclear	Y	Y	Y	Y	N/A	4/5
Sawyers, 2002[3]	Y	Y	Y	Unclear	Y	Y	5/6
Shah, 2002[108]	N	N	N	N	Y	N	1/6
Shimoni, 2003[117]	N	Y	N	Y	Y	N/A	3/5
O'Sneed, 2003[110]	Y	Y	Y	Y	Y	N	5/6
Soverini, 2004[126]	N	N	Y	Y	Y	N/A	3/5
Steegman, 2003[93]	N	Y	Y	Y	Y	N/A	4/5
Stentoft, 2001[7]	N	Y	Y	Y	Y	N/A	4/5
Sureda, 2003[4]	Y	Y	Y	Unclear	Y	N/A	4/5
Talpaz, 2002[87]	Y	Y	Y	Unclear	Y	Y	5/6
Valeyrie, 2003[94]	Y	Y	Y	Unclear	N	N/A	3/5
Wang, 2003[48]	N	N	N	Y	Y	N/A	2/5
Wu, 2002[6]	N	N	Y	Y	Y	N/A	3/5

Abbreviations: N = No; Y = Yes; N/A = not applicable