Imatinib in combination with Cytarabine as compared to Imatinib alone in patients with first chronic phase Chronic Myeloid Leukemia.

A prospective randomized phase III study

PROTOCOL

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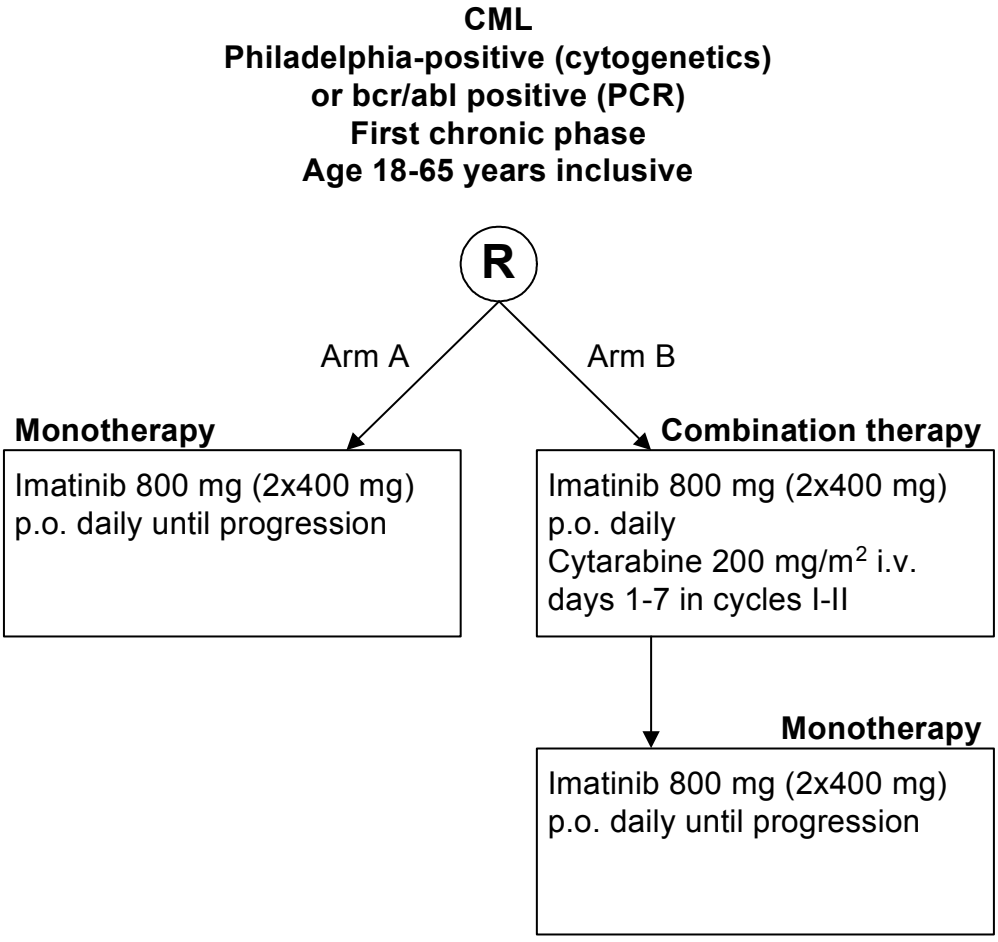
1 Scheme of study



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3 Synopsis

Study phase	Phase III
Study objectives	To determine the efficacy of the combination of imatinib with cytarabine as compared to imatinib alone in terms of the rate of molecular response at 12 months from randomization.
Patient population	Patients with Chronic Myeloid Leukemia, Philadelphia-positive (cytogenetics) or bcr-abl positive (PCR), in first chronic phase ≤ 2 months from diagnosis, age 18-65 years inclusive
Study design	Prospective, multicenter, randomized
Duration of treatment	Until progression
Number of patients	330 patients registered and randomized
Adverse events	Adverse events will be documented if observed, mentioned during open questioning, or when spontaneously reported
Planned start of recruitment	I 2006
Planned end of recruitment	I 2011

4 Investigators and study administrative structure

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5 Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by a reciprocal translocation between chromosome 9 and 22 (t(9;22)(q34;q11)) referred to as the Philadelphia chromosome. It results in the generation of a new oncogene (bcr-abl) encoding for a protein with constitutive tyrosine kinase activity causing a variety of cellular changes responsible for the malignant phenotype of CML (1). The disease is characterized by an initial indolent chronic phase usually followed after a median time of 4-5 years by a blastic transformation, highly resistant to further therapy. Classical treatment with hydroxyurea or busulphan does not alter the clinical course while interferon with or without cytarabine (Ara-C) can induce, mostly temporarily, cytogenetic responses in a minority of the patients resulting in a survival advantage (2). Complete eradication of the malignant clone is currently only achieved by (non-)myeloablative chemo/radiotherapy followed by an allogeneic stem cell transplantation (3). However this procedure is only applicable for a limited number of patients and is still associated with considerable morbidity and mortality. The introduction

of imatinib mesylate (IM, Glivec®) has dramatically changed the treatment of CML patients. IM exerts its tyrosine kinase inhibiting action by stabilizing the inactive non ATP-binding conformation of BCR-ABL. In Phase I and II studies that included interferon unresponsive, accelerated and blastic phase patients, remarkable clinical responses were attained, with relatively minor side effects. Currently IM is appreciated as a first line drug in the treatment of CML, resulting in hematological (98%), major (91%) and complete (84%) cytogenetic responses in newly diagnosed patients as reported in the 42 months update of the IRIS study at ASH 2004 (3-5). Also, molecular responses are noticed: approximately 40% of the patients achieve a greater than 3-log reduction of the BCR-ABL protein, leading to a sharp decline in the chance of progression (5). Currently, the major aim of treatment is not only to achieve a cytogenetic response, but, preferably to attain a molecular response.

Resistance against IM can be caused by a variety of mechanisms, including overexpression of BCR-ABL, P-glycoprotein overexpression, the emergence of additional chromosomal abnormalities and, probably most important, the occurrence of point mutations in the ATP binding and kinase domains of the BCR-ABL protein leading to interference of the IM-BCR-ABL interaction (6). So, despite the high success rate of IM in terms of cytogenetic and molecular responses that translate in prolonged overall and disease-free survival, patients with unsatisfactory responses still pose a considerable problem. Successors of the tyrosine kinase inhibitors effective against cell lines transfected with a variety of point-mutated bcr-abl fusion genes are now finding their way into early clinical studies, thus hopefully tackling the problem of IM resistance (7,8). Dose escalation and/or combination with chemotherapy has already been investigated in phase II studies and phase III studies for the most promising approaches are currently being developed or have recently started.

5.1 Imatinib dose escalation

A clear dose-response relationship for IM has been shown in preclinical models. In the phase I studies no maximum tolerated dose (MTD) was observed, while here, a dose response relationship was already obvious. Of patients with cytogenetic resistance to the standard dose of IM of 400 mg/day, 34% responded to 800 mg/day, while in the accelerated phase of the disease escalation to 600 mg led to higher cytogenetic response rates and significantly better TTP and OS (9). In a phase II study from the MD Anderson Cancer Center, Houston, 114 patients with newly diagnosed chronic phase CML were treated with 800 mg IM (10). A major cytogenetic response was achieved in 109 patients (96%), including 103 (90%) with a complete cytogenetic response. With a median follow-up of 15 months, no patient has progressed to accelerated or blastic phase. The estimated 2-year survival rate was 94%. By quantitative polymerase chain reaction (QPCR) studies, 71 (63%) of 112 patients showed bcr-abl/abl percentage ratios decrease to less than 0.05%, and 31 (28%) to undetectable levels. Compared with standard-dose IM, high-dose IM was associated with significantly better complete cytogenetic responses (P =.0005), major molecular responses (QPCR < 0.05%; P =.00001), and complete molecular responses (undetectable bcr-abl; P =.001). High-

dose IM was well tolerated but resulted in more frequent myelosuppression; 82% of patients continue to receive 600 mg or more of IM daily.

5.2 Dose escalation of imatinib in combination with cytarabine (HOVON 51 CML)

Cytarabine is an active drug in myeloid leukemia's, especially when intensified dosages are applied (11). In-vitro studies of IM and cytarabine showed synergistic anti-proliferative effects (12,13). With the aim to prevent resistance and to induce an early, high rate of molecular remissions, HOVON set out to evaluate the combination of IM and cytarabine in a dose-escalation study of consecutive cohorts treated with daily IM at dosages of 200 mg, 400 mg, 600 mg or 800 mg combined with intravenous cytarabine, added as 2 consecutive cycles of i.v. treatment at days 1-7 at a dose of 200 mg/m^2/24 hrs or 1,000 mg/m^2/24 hrs. Primary endpoints were dose-limiting-toxicity (DLT) and quantitative molecular response as assessed by standardized real-time QPCR of bcr-abl transcripts. Patients without a major molecular response after 12 months were evaluated for mutations by direct sequencing. From the start in August 2001 until September 2005, 159 pts have been included in cohorts I through V. According to pre-defined criteria, cohorts I-IV B were demonstrated feasible and accrual continues (cohort IV A) for evaluation of efficacy. At 12 months from the start of treatment, overall probabilities of developing a major (≥ 3log reduction of bcr-abl copies) or complete (> 4.5log) molecular response were 56% (s.e. 5%) and 17% (4%), respectively. Overall survival was 91% (3%) at 24 months and progression-free survival was 85% (4%). Significantly higher molecular response rates were observed in patients treated with 600 mg or 800 mg imatinib, irrespective of dose of cytarabine. Conversely, the higher dose of cytarabine (1,000 versus 200 mg) appeared not significantly associated with an even better molecular response. With a median follow-up of 21 months, six patients developed accelerated phase and 1 patient developed a blastic crisis. Among 30 pts without a major molecular response at 12 months, 2 pts acquired a point mutation of the Abl kinase domain resulting in amino-acid substitutions Phe359Val and Glu459Lys, respectively. These results suggest that the combination of escalated IM combined with standard or intensified cytarabine may prevent resistance and mirrors the synergy of both drugs that was found in-vitro (14).

5.3 Rationale of the study

Both in-vitro and in-vivo studies have now suggested synergistic activity of imatinib and cytarabine. Especially, patients treated with 800 mg imatinib and cytarabine within the HOVON 51 CML study developed a major molecular response in 76% (s.e. 10%) and a complete molecular response in 41% (12%) within 12 months from treatment (see section 17). For comparison, 60% of patients treated with 800 mg imatinib only at the MD Anderson (10) developed a major molecular response and 25-30% a complete molecular response at 12 months, which suggests that cytarabine significantly adds to the efficacy of imatinib. The importance of a rapid major molecular response is underscored by the virtual absence of disease progression in such patients as reported by several investigators (15,16). Therefore, in order to answer the question whether the combination of high

dose imatinib combined with i.v. cytarabine may result in a higher rate of major molecular response and a lower incidence of disease progression as high dose imatinib alone, it is proposed to perform a prospective randomized phase III study in patients with first chronic phase CML. Following the completion of the HOVON 51 CML study in 2005, it is expected that accrual in the new randomized study will start early in 2006.

6 Study objective

To assess the efficacy of imatinib combined with i.v. cytarabine as compared to imatinib alone in terms of:

- The rate and duration of major molecular response
- The rate and duration of complete molecular response
- The rate and duration of complete cytogenetic response
- The rate and duration of complete hematological response
- Progression-free survival
- Overall survival
- Safety profile
- Actual dose-intensity delivered
- Incidence of mutations of abl-kinase domain

In addition, proteomic and genomic analyses are planned to identify potential biomarkers predictive of response and progression-free survival.

7 Study design

This is a prospective, open label, randomized phase III study. Details of all treatments (dose and schedule) are given in section 9.

7.1 Registration, randomization and study treatment

Patients with newly diagnosed CML, Philadelphia-positive or bc/abl positive, in first chronic phase meeting all eligibility criteria (see section 8.1) and having provided informed consent will be randomized between:

Arm A: imatinib given orally at a total dose of 800 mg daily until progression

Arm B: imatinib given orally at a total dose of 800 mg daily, combined with 2 successive cycles of i.v. cytarabine 200 mg/m^2, at day 1-7, in cycles I and II, followed by imatinib monotherapy (800 mg daily) until progression

Treatment according to study arms A or B will start following cessation of preceding therapy with hydroxyurea (HU) or cessation of preceding therapy with imatinib. Preceding therapy with HU is allowed for no longer than 2 months and preceding therapy with imatinib is allowed for no longer than 1 month.

8 Study population

8.1 Eligibility for registration

All eligible patients have to be registered and randomized before start of treatment (see section 16). Patients have to meet all of the criteria mentioned below.

8.1.1 Inclusion criteria

- Newly diagnosed patients with CML in first chronic phase ≤ 2 months;
- Presence of Philadelphia chromosome or bcr-abl rearrangement;
- Age 18-65 years inclusive;
- WHO performance status ≤ 2 (see appendix E);
- Written informed consent.

8.1.2 Exclusion criteria

- CML in accelerated phase or blastic crisis as defined by the WHO criteria (see appendix A).
- Hepatic dysfunction (serum bilirubin ≥ 2 x N, and/or ALAT ≥ 4 x N, and/or ASAT ≥ 4 x N);
- Renal dysfunction (creatinine ≥ 200 μmol/l or 2.3 mg/dl);
- Severe cardiac dysfunction (NYHA classification II-IV, see appendix F);
- Severe pulmonary or neurologic disease;
- Pregnant or lactating females;
- Patients with a history of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma;
- Patients known to be HIV-positive;
- Patients with active, uncontrolled infections;
- Previous treatment other than hydroxyurea ≤ 2 months or imatinib ≤ 1 month;
- Male and female patients of reproductive potential who are not practicing effective means of contraception.

9 Treatments

9.1 Imatinib monotherapy (arm A)

Following registration and randomization, preceding therapy with hydroxyurea or imatinib is stopped and imatinib is started at a total dose of 800 mg daily, preferably 2 x 400 mg 12 hours apart. Imatinib is continued until progression or intolerance of treatment (see section 10).

9.1.1 Dose adjustments during imatinib monotherapy

Hematological toxicity

Grade 1 and 2:

No dose adjustments for grade 1 and 2 hematological toxicity will be made.

Grade 3 and 4:

If a patient experiences a grade ≥ 3 neutropenia and/or thrombocytopenia (i.e., ANC < $1.0x10^9$/l, or a platelet count < $50x10^9$/l), imatinib must be withheld until the toxicity has resolved to grade ≤ 2. ANC takes precedence over WBC in determining the degree of neutropenia. If the hematological toxicity resolves to grade ≤ 2 within 2 weeks, imatinib may be resumed at a dose of 800 mg/day, as appropriate. If the grade ≥ 3 hematological toxicity recurs or persists for longer than two weeks, imatinib must be withheld and reduced to 600 mg/day once toxicity has resolved to grade ≤ 2. If the grade ≥ 3 hematological toxicity recurs after dose reduction to 600 mg, imatinib must be witheld and may be resumed at 600 mg/day upon recovery to grade ≤ 2. If the grade ≥ 3 hematological toxicity recurs, imatinib must be withheld and reduced to 400 mg/day once toxicity has resolved to grade ≤ 2.

If the grade ≥ 3 neutropenia and/or thrombocytopenia recurs after dose reduction to 400 mg/day, imatinib must be withheld and resumed at 400 mg/day upon recovery to grade ≤ 2. If the grade ≥ 3 hematological toxicity recurs, imatinib must be withheld and reduced to 300 mg/day upon recovery to grade ≤ 2. If the grade ≥ 3 hematological toxicity recurs after dose reduction to 300 mg/day, imatinib must be witheld and resumed at 300 mg/day upon recovery to grade ≤ 2. If at any time the hematological toxicity does not resolve to grade ≤ 2 in 28 days, consult with the study coordinator.

No dose reductions will be performed for grade ≥ 3 anemia or lymphopenia. Patients developing anemia may be transfused or prescribed erythopoietin at the discretion of the treating physician.

Non-hematological toxicity

Grade 1:

No dose adjustments for grade 1 non-hematological toxicity will be made.

Grade 2:

If a patient experiences a grade 2 non-hematological toxicity that does not resolve despite

therapeutic intervention, imatinib must be withheld until the toxicity has resolved to grade ≤ 1. Imatinib may then be resumed at a dose of 800 mg. If the grade 2 toxicity recurs, imatinib must again be withheld until the toxicity has resolved to grade ≤ 1, and the dose of imatinib must be reduced to 600 mg daily. If the grade 2 toxicity recurs at 600 mg, imatinib must be withheld until the toxicity has resolved to grade ≤ 1, and resumed at 600 mg daily. If the grade 2 toxicity recurs at 600 mg, imatinib must again be withheld until the toxicity has resolved to grade ≤ 1, and imatinib must be resumed at 400 mg daily. If the grade 2 toxicity recurs at 400 mg, imatinib must be withheld until the toxicity has resolved to grade ≤ 1, and the dose of imatinib must be reduced to 300 mg daily.

Grade 3 and 4:

If a patient experiences grade ≥ 3 non-hematological toxicity, imatinib must be withheld until the toxicity has resolved to grade ≤ 1. Imatinib may then be restarted at a reduced dose of 600 mg daily. If the grade ≥ 3 toxicity recurs at 600 mg, imatinib must be withheld until the toxicity has revolved to grade ≤ 1. Imatinib may then be reintroduced at a dose of 400 mg daily. If the toxicity recurs with grade ≥ 3 at 400 mg, imatinib must be withheld until the toxicity has resolved to grade ≤ 1. Imatinib may then be reintroduced at a dose of 300 mg daily. If at any time the non-hematological toxicity does not resolve to grade ≤ 1 in 28 days, consult with the study coordinator. A documented grade ≥ 3 non-hematological toxicity that recurs despite dose reduction to 300 mg daily is considered intolerance of treatment and the patient should be discontinued from study treatment.

Dose	Hematological toxicity		Non-hematological toxicity	
	Grade 1 and 2	Grade ≥ 3	Grade 2	Grade ≥ 3
800 mg/day	No dose reduction	Hold therapy and resume at 800 mg after recovery to grade ≤ 2 If toxicity recurs, hold therapy and resume at 600 mg after recovery to grade ≤ 2	Hold therapy and resume at 800 mg after recovery to grade ≤ 1 If toxicity recurs, hold therapy and resume at 600 mg after recovery to grade ≤ 1	Hold therapy and resume at 600 mg after recovery to grade ≤ 1
600 mg/day	No dose reduction	Hold therapy and resume at 600 mg after recovery to grade ≤ 2 If toxicity recurs, hold therapy and resume at 400 mg after recovery to grade ≤ 2	Hold therapy and resume at 600 mg after recovery to grade ≤ 1 If toxicity recurs, hold therapy and resume at 400 mg after recovery to grade ≤ 1	Hold therapy and resume at 400 mg after recovery to grade ≤ 1
400 mg/day	No dose reduction	Hold therapy and resume at 400 mg after recovery to grade ≤ 2 If toxicity recurs, hold therapy and resume at 300 mg after recovery to grade ≤ 2	Hold therapy and resume at 300 mg after recovery to grade ≤ 1	Hold therapy and resume at 300 mg after recovery to grade ≤ 1
300 mg/day	No dose reduction	Hold therapy and resume at 300 mg after recovery to grade ≤ 2 If toxicity recurs at 300 mg, consult with the study coordinator	If toxicity recurs at 300 mg, consult with the study coordinator	Discontinue therapy

9.1.2 Dose re-escalation during imatinib monotherapy

Every attempt to increase the dose of imatinib to the previously administered dose level prior to any dose reduction should be made. The dose of imatinib should be increased if the following criteria are met at least one month after dose reduction:

- there is not recurrence of the toxicity which led to dose reduction;
- there are no additional grade ≥ 2 non-hematological toxicities.

This applies to either dose reductions due to hematological or non-hematological toxicities.

For patients whose imatinib has been reduced to 300 mg, the imatinib dose would be increased to 400 mg. After at least one month the same criteria should once again be met for further dose re-escalations.

9.1.3 Special management orders in conjunction with imatinib monotherapy

- Myelosuppression can occur at any time during imatinib therapy, but it generally occurs within 2 to 4 weeks. Use of growth factors (G-CSF and GM-CSF) may be initiated with recurrent grade ≥ 3 neutropenia. Dose titration is recommended to keep ANC > $1.5x10^9$/l. Dose adjustments should be made according to section 9.1.1.
- In most cases rash is mild, self-limiting and manageable with antihistamines or topical steroids. A short course of oral steroids may be initiated for the management of more severe cases. Prednisone 25 mg is recommended for one week or until rash has resolved.
- Patients should be monitored closely for peripheral edema and rapid weight gain. The use of diuretics may be initiated for the management of edema. In severe cases imatinib should be withheld and the edema may be controlled with diuretics. Imatinib can be resumed, while maintaining or increasing diuretic therapy.
- Routine liver function tests should be performed throughout the study. It is also recommended that patients be screened for viral hepatitis at the screening visit. Dose reduction may be warranted and the decision to continue imatinib needs to be made in light of the clinical situation.

9.2 Imatinib and cytarabine combination therapy (arm B)

Following registration and randomization, preceding therapy with hydroxyurea or imatinib is stopped and imatinib is started at a total dose of 800 mg daily, preferably 2 x 400 mg. The first cycle of i.v. cytarabine is started as soon as possible, preferably within 14 days from the start of imatinib, and at the latest 4 weeks from the start of imatinib. Dose adaptations are outlined in section 9.2.1. During combination therapy, patients will receive imatinib at a total dose of 800 mg, preferably 400 mg twice daily, continuously. Cytarabine is added as a 7 day course of i.v. chemotherapy. Cytarabine is given at a dose of 200 mg/m^2/day in 500 ml NaCl 0.65% (or 0.9%) as 1-2 hours infusion, once daily. The second cycle of cytarabine will be started if there is evidence of hematopoietic recovery (platelets > $100x10^9$/l and WBC > $2.0x10^9$/l), when evaluation procedures after cycle I have been performed and when all toxicities have resolved to grade ≤ 1. Cycle II should be started within 8 weeks from the start of cycle I. If start of cycle II within 8 weeks from start of cycle I is not possible, patients should continue with imatinib monotherapy.

Combination therapy may be administered on an outpatient basis. However, it is advocated to admit patients clinically in case of grade 4 hematological toxicity (e.g. ANC < $0.5x10^9$/l). Alternatively patients may be followed up frequently (3 times per week) in the outpatient clinic, with immediate clinical admittance in case of fever.

9.2.1 Dose adjustments during imatinib and cytarabine combination therapy

Dose adjustments outlined below should be adhered to from the start of cytarabine until hematological recovery following the last combination therapy cycle given. Hereafter dose adjustments should be made according to 9.1.1.

Hematological toxicity

Imatinib is continued during the phase of cytopenia following combination therapy. However, grade 4 hematological toxicity, which persists for more than 4 weeks, should be followed by interruption of imatinib until resolution of hematological toxicity to grade ≤ 2. Thereafter imatinib should be resumed at the targeted dose and subsequent adaptations of dose should be made according to 9.1.1.

Non-hematological Toxicity

No dose modifications will be made for cytarabine.
No dose modifications of imatinib will be made for grade 1, 2 and 3 toxicity (except for grade 3 liver toxicity).
If a patient experiences any of the following toxicities, imatinib must be withheld until toxicity has resolved to grade < 2 and then be resumed at the targeted dose:

- grade 4 stomatitis which persists for longer than 1 week;
- grade 3 or 4 liver toxicity;
- any other grade 4 toxicity (except hematological toxicity, nausea and vomiting).

9.2.2 Special management orders in conjunction with combination therapy

- Infections should be controlled before start of chemotherapy.
- Anti-bacterial prophylaxis and anti-fungal prophylaxis should be given, for example oral ciprofloxacin 500 mg (2 x) and oral fluconazole tablets 200 mg (1 x), or according to local protocols, from the start of neutropenia.
- Patients experiencing grade 4 neutropenia (ANC < $0.5x10^9$/l) for longer than 1 week may receive granulocyte colony-stimulating factor (G-CSF) until neutropenia has resolved (ANC > $1.0x10^9$/l). G-CSF should be given at a dose of 5 μg/kg s.c. once daily.
- After cytarabine therapy 200 mg/m^2/day, special attention should be given to prevent bacteremias by α-hemolytic Streptococci, for example, by oral azithromycin.
- Cytarabine 200 mg/m^2/day should be discontinued in case of nystagmus or cerebellar symptoms. If those symptoms resolve within 24 hours, cytarabine may be resumed. After

interruption of the cycle, it should not be prolonged after day 7.

9.3 Imatinib monotherapy following combination therapy (arm B)

Following full hematological recovery after the second cycle of i.v. cytarabine and when evaluation procedures have been completed, monotherapy therapy is started. Patients will continue with imatinib at a dose of 800 mg until progression of disease or intolerance of treatment, whichever occurs first (see section 10). Dose adaptations during imatinib monotherapy are outlined in section 9.1.1.

9.4 Concomitant medication

- In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed.
- The concomitant administration of investigational drugs is NOT allowed. However, the administration of any other anticancer agents including chemotherapy and biologic agents is NOT permitted.
- Because of the possible risk of either reduced activity or enhanced toxicity of the concomitant medication and/or imatinib, drugs known to interact with the same CYP450 isoenzymes (CYP2D6 and CYP3A4) as imatinib should be used with caution. Patients using concomitant medications known to be metabolized by these cytochrome P450 enzymes will not be excluded from the study. However, the patients must be carefully monitored for potentiation of toxicity due to individual concomitant medication. Consideration should be given to using alternative agents with less potential for interaction with imatinib.
- Special care has to be given to the concomitant use of acetaminophen/paracetamol with imatinib. Patients should be counseled to limit the use of over-the-counter medications that contain acetaminophen/paracetamol.
- Concomitant use of levothyroxine should be carefully monitored and the cumulative dose of levothyroxine should be doubled at start of imatinib treatment.
- In general, the use of warfarin is discouraged on this protocol. Since warfarin is metabolized through the CYP450 system, patients on therapy with warfarin should have their INR closely monitored. For example, monitoring is suggested every two days during the first two weeks of simultaneous treatment with imatinib, twice per week for the following two weeks, and every 2 weeks until discontinuation of either imatinib or warfarin. As an alternative, therapeutic anticoagulation may be accomplished using low-molecular weight heparin or heparin. Mini-dose warfarin (e.g. 1 mg q.d.) is permitted for prophylaxis of central venous catheter thrombosis, at the discretion of the treating physician.
- Patients on anticonvulsants should have regular monitoring of plasma concentration of these agents. The routine use of systemic corticosteroid therapy is permitted. Growth factors may be initiated with recurrent grade 3 neutropenia. Prophylactic anti-emetics may be allowed if the patient has experienced grade > 1 nausea or vomiting.

- Prophylactic use of loperamide (with suggested dosing as start: 4 mg p.o. x 1, than 2 mg p.o. after each loose stool, max 16 mg/day) may be initiated for patients experiencing grade ≥ 2 diarrhea, before dose interruption.

10 End of protocol treatment

Reasons for going off protocol treatment are:

1. Progression*
2. Excessive toxicity (including toxic death) / intolerance of treatment
3. Intercurrent death
4. No compliance of the patient (especially refusal to continue treatment)
5. Major protocol violation

* The following events are considered progression:

- progression to accelerated phase (see appendix A);
- progression to blastic crisis (see appendix A);
- progression without prior complete hematological response (see appendix C);
- progression with prior complete hematological response (see appendix C);
- progression from major cytogenetic response (see appendix C);
- clonal evolution (see appendix C).

11 Required clinical evaluations

Aim of the clinical evaluation at entry is to know in which stage of disease the patients are. Aim of the clinical evaluation during treatment and follow up is to determine toxicities and response. Evaluation of response is described in section 11.3 and appendix C. The Sokal score will be determined at the HOVON Data Center based on data determined at diagnosis (see appendix B) and will be used for stratification prior to randomization (see section 16).

11.1 Time of clinical evaluations

Arm A:

- At entry: before start imatinib*
- ≤ 12 months from entry: at 3, 6 and 12 months after start imatinib
- > 12 months from entry: every 6 months
- Follow up: every 6 months

Arm B:

- At entry: before start imatinib*
- After cytarabine cycle I: approximately 4 weeks after start cycle I
- After cytarabine cycle II: approximately 4 weeks after start cycle II

- Imatinib monotherapy: every 6 months, with the first clinical evaluation at 6 months after entry
- Follow up: every 6 months

* For patients treated with imatinib prior to entry in the study baseline evaluations are those performed before start imatinib, if available. If unavailable, baseline evaluations should be performed at entry.

11.2 Required investigations

	at entry[1]	during cycle I and II (arm B)	after cycle I (arm B)[2]	month 3 (arm A) after cycle II (arm B)	month 6	month 12	month 18	months 24, 36, 48, etc.	months 30, 42, 54, etc.
Medical history	X		X	X	X	X	X	X	X
Physical examination	X		X	X	X	X	X	X	X
Hematology	PB		PB	PB	PB	PB	PB	PB	PB
Blood chemistry	PB		PB	PB	PB	PB	PB	PB	PB
Bone marrow									
Bone marrow biopsy	BMB								
Bone marrow aspirate	BMA			BMA[2]	BMA	BMA		BMA	
Storage for future studies	BMA				BMA	BMA[3]			
Cytogenetic analysis	BMA			BMA[2]	BMA	BMA		BMA	
Molecular analysis	PB + BMA		PB	PB + BMA	PB + BMA	PB + BMA	PB	PB + BMA	PB
Specific investigations									
Ultrasonogram spleen/liver	X		o.i.	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.
X-thorax	X		o.i.	o.i.	o.i.				
ECG	X								
Additional investigations	X	X[4]							

o.i. On indication

PB Peripheral blood sample

BMB Bone marrow biopsy

BMA Bone marrow aspirate

1 For patients treated with imatinib prior to entry in the study baseline evaluations are those performed before start imatinib, if available. If unavailable, baseline evaluations should be performed at entry.

2 If a patient in arm B only receives one cytarabine cycle, evaluations scheduled after cycle II should be performed after cycle I.

3 Hereafter also at progression.

4 See 11.2.10.

11.2.1 Medical history

Standard medical history, with special attention for:

- WHO performance status
- Toxicities
- Infections

Only at entry:

- Prior and present other diseases
- Antecedent hematological or oncological diseases
- Previous chemotherapy

11.2.2 Physical examination

Standard physical examination including body weight and height, with special attention for:

- Spleen size in cm below mid left costal margin
- Toxicities
- Infections

11.2.3 Hematology

Complete hematogram with special attention for:

- Hemoglobin
- WBC
- WBC differential count including description of circulating erythroblasts, reticulocytes
- Platelet count
- Recovery of peripheral blood cells after cycle I and II (arm B)

11.2.4 Blood chemistry

- BUN
- Creatinine
- ASAT (SGOT)
- ALAT (SGPT)
- Alkaline phosphatase
- γ-GT
- Total bilirubin
- LDH

11.2.5 Bone marrow

- Bone marrow biopsy at entry for histology including reticulin stain (Gomori's stain)
- Bone marrow aspirate for cytology and differential
- Bone marrow aspirate for cytogenetic analysis as described in 11.2.6

In addition to these investigations, all patients are asked for informed consent to store biological material at entry, 6 and 12 months after entry and at progression, for future studies. These studies include proteomic and genomic analysis to identify potential biomarkers predictive of response and

progression-free survival. All materials are anonymized and stored for a maximum of 15 years after inclusion has been completed, after which the samples will be destroyed. Any study to be undertaken on these materials must be approved of by the study coordinators and relevant ethical authorities prior to undertaking the studies.

11.2.6 Cytogenetic analysis

- Conventional cytogenetic analysis of at least 20 metaphases
- FISH analysis for Philadelphia chromosome (optional)

11.2.7 Molecular analysis (see also appendix C)

- At entry real-time quantitative PCR for bcr-abl on both bone marrow and peripheral blood samples
- Real-time quantitative PCR for bcr-abl on both bone marrow and peripheral blood samples at 3, 6 and 12 months after entry (Arm A)
- Real-time quantitative PCR for bcr-abl on both bone marrow and peripheral blood samples after cycles I and II and at 6 and 12 months after entry (Arm B)
- Real-time quantitative PCR for bcr-abl on peripheral blood samples during monotherapy and follow up every 6 months after entry starting at 12 months after entry

11.2.8 Specific investigations

- Ultrasonogram spleen and liver (size in cm)
- X-Thorax
- ECG

11.2.9 Additional investigations

- HLA-typing (A, B) for platelet transfusions
- Platelet antibodies: auto and (optional) allo
- Neutrophil alkaline phosphatase score (optional)

11.2.10 Additional investigations during cytarabine treatment

- Platelet count, WBC and differential at least 2-3 times weekly
- BUN, creatinine, sodium, potassium, calcium, glucose daily during chemotherapy, and thereafter at least twice weekly
- ALAT, ASAT, alkaline phosphatase, γ-GT, bilirubin and LDH at least weekly
- Routine urine analysis weekly
- X-Thorax once during the first week, thereafter as clinically indicated

11.3 Evaluation of response

Response will be evaluated according to the criteria in appendix C. Response will be assessed after cycle I (arm B), after cycle II (arm B), after 3 months (arm A) and thereafter approximately every 6

months during imatinib monotherapy and follow up starting at 6 months after entry.

12 Toxicities

All chemotherapeutic agents used in the protocol can cause pancytopenia and can induce septic or hemorrhagic complications.
Cytarabine can cause anorexia, nausea, vomiting, hepatic dysfunction, skin rash, pneumonitis, fever.
Imatinib can cause nausea, muscle spasms, arthralgia, headache, peri-orbital edema and liverfunction abnormalities.

Toxicities will be scored according to the NCI Common Terminology Criteria for Adverse Events, version 3.0 (see appendix D).

13 Reporting serious adverse events

Adverse event (AE)
An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject during protocol treatment. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse reaction (AR)
Adverse reactions (AR) are those AE's of which a reasonable causal relationship to any dose administered of the investigational medicinal product and the event is suspected.

Serious adverse event (SAE)
A serious adverse event is defined as any untoward medical occurrence that at any dose results in:

- death
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization
- significant / persistent disability
- a congenital anomaly / birth defect
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above)

Note that ANY death, whether due to side effects of the treatment or due to progressive disease or due to other causes is considered as a serious adverse event.

Unexpected SAE

Unexpected Serious Adverse Events are those SAE's of which the nature or severity is not consistent with information in the relevant source documents. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as a source document in that country.

Suspected unexpected serious adverse reaction (SUSAR)

All suspected AR's which occur in the trial and that are both unexpected and serious.

Protocol treatment period

The protocol treatment period is defined as the period from the first study-related procedure until 30 days following the last dose of protocol treatment or until the start of another systemic anti-cancer treatment off protocol, if earlier.

13.2 Reporting of (serious) adverse events

Adverse event

AE's will be reported on the CRF. All adverse events of Grade 2 or higher, with the exception of progression of disease, occurring during the protocol treatment period will be reported. Adverse events occurring after that period should also be reported if considered related to protocol treatment.

SAE and Unexpected serious adverse event

All SAE's occurring during the protocol treatment period must be reported to the HOVON Data Center by fax **within 24 hours of the initial observation of the event**, except hospitalizations for:

- a standard procedure for protocol therapy administration. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a Serious Adverse Event.
- the administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- a procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- a procedure that is planned (i.e., planned prior to starting of treatment on study; must be documented in the CRF). Prolonged hospitalization for a complication considered to be at least possibly related to the protocol treatment remains a reportable serious adverse event.

All details should be documented on the **Serious Adverse Event and Death Report**. In circumstances where it is not possible to submit a complete report an initial report may be made giving only the mandatory information. Initial reports must be followed-up by a complete report within a further 2 working days and sent to the HOVON Data Center. All SAE Reports must be dated and signed by the responsible investigator or one of his/her authorized staff members.

At any time after the protocol treatment period, *unexpected* Serious Adverse Events that are considered to be at least suspected to be related to protocol treatment must also be reported to the HOVON Data Center using the same procedure, **within 24 hours after the SAE was known to the investigator**.

The investigator will decide whether the serious adverse event is related to the treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the serious adverse event form. The assessment of causality is made by the investigator using the following:

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship to the protocol treatment (also include pre-existing conditions)
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

13.3 Processing of serious adverse event reports

The HOVON Data Center will forward all reports within 24 hours of receipt to the study coordinator and the study central datamanager. The report of an SAE will be the signal for the central datamanager to ask the investigator or the responsible local datamanager to complete and send as soon as possible all relevant CRF's for the involved patient with details of treatment and outcome.

14 Endpoints

Primary endpoint

1. Rate of major molecular response at 12 months from randomization.

Secondary endpoints

2. Rate and duration of major and complete molecular response;
3. Rate and duration of major and complete cytogenetic response;
4. Rate and duration of complete hematological response;
5. Progression-free survival (i.e. time from registration to progression or death from any cause, whichever occurs first);
6. Overall survival measured from the time of registration. Patients still alive or lost to follow up are censored at the date they were last known to be alive;
7. Toxicity;
8. Actual dose-intensity of imatinib delivered;
9. Incidence of mutations of abl-kinase domain.

15 Data collection

Data will be collected on Case Report Forms (CRF) to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. Data collected on the CRF are derived from the protocol and will include at least:

- inclusion and exclusion criteria;
- baseline status of patient including medical history and stage of disease;
- timing and dosage of protocol treatment;
- adverse events;
- parameters for response evaluation;
- any other parameters necessary to evaluate the study endpoints;
- survival status of patient;
- reason for end of protocol treatment.

Each CRF page will be identified by a pre-printed trial number, and a unique combination of patient study number (assigned at registration), hospital and patient namecode (as documented at registration) to be filled out before completing the form.
The CRF will be completed on site by the local investigator or an authorized staff member. Each page must be dated and signed by the local investigator upon completion. All CRF entries must be based on source documents. The CRF and written instructions for completing the CRF will be provided by the HOVON Data Center.
Copies of the CRF will be kept on site. The original CRF pages must be sent to the HOVON Data Center at the requested timepoints. How and when to send in forms is described in detail in the CRF

header and the CRF instructions.
All data from the CRF will be entered into the study database by the HOVON Data Center.

16 Randomization

Eligible patients should be registered within 2 months of diagnosis. Patients can be registered at the HOVON Data Center of the Erasmus MC – Daniel den Hoed by phone call: +31.10.4391568 or fax +31.10.4391028 Monday through Friday, from 09:00 to 17:00, or via the Internet through TOP (Trial Online Process; https://www.hdc.hovon.nl/top). A logon to TOP can be requested at the HOVON Data Center for participants.

The following information will be requested at registration:

- Protocol number
- Institution name
- Name of caller/responsible investigator
- Patient's initials or code
- Patient's hospital record number (optional)
- Sex
- Date of birth
- Date of diagnosis CML
- Eligibility criteria

All eligibility criteria will be checked with a checklist. Patients will be randomized, stratified by center and Sokal score with a minimization procedure, ensuring balance within each stratum and overall balance. The randomization result and a unique patient study number will be given immediately by TOP or phone and confirmed by fax or email.

17 Statistical considerations

17.1 Sample size and power considerations

This study is designed to establish whether addition of two 7-days' cycles of cytarabine 200 mg/m^2/day to daily imatinib 800 mg treatment, will improve outcome as compared to treatment with 800 mg imatinib daily alone.

Results in 114 newly diagnosed chronic phase CML patients who were treated with monotherapy imatinib 800 mg daily (Kantarjian; Blood 2004; 103:2873-2878) suggest 1-year major molecular response (MMR) of about 60% and a 1-year complete molecular response (CMR) of 25-30%. This is much higher than obtained in the IRIS-study (Hughes; NEJM 2003; 349:1423-1432), where imatinib 400 mg daily resulted in about 40% MMR and about 5% CMR at 12 months.

Data on imatinib treatment combined with two 7-days' cycles of cytarabine are only available from the HOVON 51 CML-trial. The primary goal of this trial was to investigate the feasibility of imatinib treatment (between 200 and 800 mg daily) combined with 2 cycles of cytarabine (200 or 1000 mg/m^2/day) in 7 different combinations. Preliminary data available as of September 2005 have confirmed the feasibility of the first 6 dose levels; data of the highest dose level are currently awaited.

A secondary end point of this trial was MMR. Combined for all dose levels, an actuarial estimate of the overall MMR at 12 months of about 53% was achieved, with a standard error (s.e.) of 5%. Moreover, a failure rate of 8% (s.e. 3%) was observed, while 38% (s.e. 5%) of all patients neither had a MMR nor a failure (acceleration, blastic crisis or death within 12 months). An actuarial 12-months MMR rate of 76% was seen in those patients with imatinib 800 mg/day, as compared to about 40% in patients treated with 400 mg/day, which confirmed the results of Hughes and Kantarjian, which established the choice for imatinib 800 mg/day in both treatment arms for the current trial. Whether cytarabine 200 mg/m^2/day is better than no cytarabine at all is not clear, and will therefore be evaluated in this trial. It should be noted that preliminary results of about 68 patients in the HOVON 51 CML-trial (daily imatinib 800 mg, dose levels IV A and V) showed an actuarial 12-months' MMR of 76% (s.e. 10%) and a 12-months' CMR of 41% (s.e. 12%).

Data from the IRIS-study show the impact of MMR, as they did not observe any progression of death in patients who were in MMR at 12 months, for a follow up period of 12-18 months. However, because long-term follow up data of patients who achieve a MMR are lacking, we will consider MMR at 12 months as the primary end point for this trial.

Patients who have achieved a MMR at 12 months after randomization, will be considered a success. Patients will be considered a failure in case of:

- loss of hematological, cytogenetic or molecular response, accelerated phase, blastic crisis, clonal evolution or death before 12 months;
- no MMR achieved within 12 months.

In order to detect with 80% power an improvement in 12-months' MMR from 60% to 75% (2-sided significance level α=0.05), 330 patients are required. This will be achieved in about 5 years, as an accrual of 60-70 patients per year is expected.

17.2 Statistical analysis

All analyses will be according to the intention to treat principle.

17.2.1 Efficacy analysis

The main endpoint for the comparison between the two treatment arms is the proportion of patients

with a MMR at 12 months. The proportions will be compared between the two treatment arms using logistic regression. In addition, an exploratory logistic regression with adjustment for baseline Sokal score will be performed to evaluate the effect of Sokal score on the MMR rate at 12 months.

Secondary end points include the rates of hematological response, complete cytogenetic response (CcyR), major molecular response (MMR) and complete molecular response (CMR), time to CcyR, MMR and CMR, progression-free survival and overall survival from randomization.

Actuarial survival curves for all time-to-event end points will be computed using the Kaplan-Meier method, 95% confidence intervals will be constructed, and survival curves will be compared using the log-rank test for illustrative purposes, without and with stratification based on the Sokal score.

17.2.2 Toxicity analysis

The analysis of treatment toxicity will be done primarily by tabulation of the incidence of side effects and infections with CTCAE grade 2 or more (see appendix D) by treatment arm (and cycle cytarabine, arm B only).

17.2.3 Additional analyses

Additional analyses involve the analysis of prognostic factors, especially the Sokal score and Euro-hazard score (see appendix B), with respect to 12-months' MMR-rate, and time to MMR, PFS and OS. Logistic regression and Cox regression analysis will be used for this purpose.

17.3 Data and safety monitoring board

A data and safety monitoring board (DSMB) will be installed before start of the study. Results of the planned interim analysis stated in paragraph 17.4 and eventually other unplanned interim analyses, will be presented confidentially to the DSMB. Only if the DSMB recommends that the study should be stopped or modified, the results will become available to the principal investigator for further decisions. The presented reports include by treatment arm the number of entered patients and at that time evaluable patients, treatment given, the number of failures, types of failures and incidence of SAE's and other adverse events (CTCAE grade).

17.4 Interim analyses and safety monitoring

One formal interim analysis is focused on efficacy and is planned, primarily to guard against unfavorable results in the experimental arm (imatinib + cytarabine). This analysis will be performed after 12-months molecular response data of the first 150 patients (75 per treatment arm) are available, and is expected to take place 3.5-4 years after the start of the trial.

The DSMB is free in its recommendations to the study coordinators, but the following guidelines apply:

- A worse 12-months' MMR-rate in the experimental arm with a P-value < 0.1 is a good reason to recommend the stopping of the trial or recommendations for modifications.
- A better 12-months MMR-rate in the experimental arm is in general no reason to recommend early stopping of the study, unless the associated P-value is very extreme (P < 0.001).

The study will be closely and sequentially monitored before the interim analysis. Monitoring will be based on the reported SAE's which are not subjected to data delay. The difference in the number of patients with an SAE in both arms and the difference in the number of deaths in both arms are tested using the binomial test. It will be repeatedly tested whether those incidences in the experimental arm are higher at a significance level of 0.05, adjusted for multiple testing (adjustment based on simulation). If one of both incidences is significantly higher in the experimental arm an early report will be presented to the DSMB.

18 Ethics

18.1 Independent ethics committee or Institutional review board

The study protocol and any amendment that is not solely of an administrative nature will be approved by an Independent Ethics Committee or Institutional Review Board.

18.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and the ICH-GCP Guidelines. The local investigator is responsible for ensuring that the study will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

18.3 Patient information and consent

Written informed consent of patients is required before registration. The procedure and the risks and the opinions for therapy in chronic myeloid leukemia will be explained to the patient.

19 Trial insurance

HOVON will ensure that insurance is in place for all participating sites.

HOVON will provide risk insurance to cover all patients from participating sites in the Netherlands according to Dutch law (WMO).

In case of an intergroup study, risk insurance of patients from centers participating within another cooperative group will be provided by that group, according to all applicable laws and regulations.

Individual participating centers from outside the Netherlands have to arrange risk insurance of their

own patients according to all applicable laws and regulations.

20 Publication policy

The final publication of the trial results will be written by the study coordinator(s) on the basis of the statistical analysis performed at the HOVON Data Center. A draft manuscript will be submitted to the Data Center, all co-authors and the sponsor for review. After revision by the Data Center, the other co-authors and the sponsor, the manuscript will be sent to a peer reviewed scientific journal.

Authors of the manuscript will include the study coordinator(s), the lead investigators of the major groups (in case of intergroup studies), investigators who have included more than 5% of the evaluable patients in the trial (by order of number of patients included), the statistician(s) and the HOVON datamanager in charge of the trial, and others who have made significant scientific contributions.

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, but no comparisons between randomized treatment arms may be made publicly available before the recruitment is discontinued.

Any publication, abstract or presentation based on patients included in this study must be approved by the study coordinator(s). This is applicable to any individual patient registered/randomized in the trial, or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomized treatment arms nor an analysis of any of the study end-points unless the final results of the trial have already been published.

21 Glossary of abbreviations

(in alphabetical order)

γ-GT	Gamma Glutamyl Transferase
AE	Adverse Event
ALAT	Alanine Amino Transferase
ANC	Absolute Neutrophil Count
Ara-C	Cytarabine, cytosine arabinoside
ASH	American Society of Hematology
ASAT	Aspartate Amino Transferase
ATP	Adenosine Triphosphate
BM	Bone Marrow
BCR-ABL	Breakpoint Cluster Region – Abelson
BUN	Blood Urea Nitrogen
CKTO	"Commissie voor Klinisch Toegepast Onderzoek"
CML	Chronic Myeloid Leukemia
CMR	Complete Molecular Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	Cytochrome P450
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FISH	Fluorescent In Situ Hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HOVON	"Stichting Hemato-Oncologie voor Volwassenen Nederland" (Dutch-Belgian Hemato-Oncology Cooperative Group)
HU	Hydroxyurea
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IM	Imatinib, Glivec®
INR	International Normalized Ratio

i.v.	Intravenous
LDH	Lactate Dehydrogenase
Lys	Lysine
METC	Medical Ethical review committee
MMR	Major Molecular Response
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute (USA)
NYHA	New York Heart Association
o.i.	On Indication
OS	Overall Survival
PB	Peripheral Blood
PCR	Polymerase Chain Reaction
PFS	Progression-Free Survival
Ph	Philadelphia
Phe	Phenylalanine
p.o.	“Per Os” (orally)
q.d.	“Quaque Die” (every day)
QPCR	Quantitative Polymerase Chain Reaction
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SAE	Serious Adverse Event
s.e.	Standard Error
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvate Transaminase
TOP	Trial Online Process
TTP	Time To Progression
Val	Valine
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen
WBC	White Blood Count

22 References

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A Diagnostic criteria Chronic Myeloid Leukemia

Jaffe ES, Harris NL, Stein H, Vardiman JW (Eds) World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. IARC press: Lyon 2001; p20-27

Chronic phase

Chronic phase is defined as not meeting any of the criteria for accelerated phase and blastic crisis.

Accelerated phase

Accelerated phase is defined by the presence of any one of the following signs or symptoms:

- 10% ≤ blasts < 20% in peripheral blood or bone marrow;
- basophils ≥ 20% in peripheral blood;
- persistent thrombocytopenia (platelets < $100x10^9$/l), not related to therapy;
- persistent thrombocytosis (platelets ≥ $1000x10^9$/l), unresponsive to therapy;
- increasing spleen size and increasing WBC count, unresponsive to therapy.

Megakaryocytic proliferation with marked fibrosis and/or severe granulocytic dysplasia are suggestive for accelerated phase, but should be confirmed by the presence of any of the signs or symptoms mentioned above.

Blastic crisis

Blastic crisis is defined by the presence of any one of the following signs:

- blasts ≥ 20% in peripheral blood or bone marrow;
- extra medullary blastic proliferation;
- large foci or clusters of blasts in bone marrow biopsy.

B CML risk assessment

Sokal score

(Blood 1984; 63: 789-799)

The Sokal score is based on the following data determined at diagnosis:

age (in years), spleen size (in cm below mid left costal margin), platelet count (in 10^9/l) and percentage blasts (in %) in the peripheral blood differential.

$$\text{Sokal score} = \exp(0.0116 \times \text{age} + 0.0345 \times \text{spleen} + 0.1880 \times (\text{platelets}/700)^2 + 0.0887 \times \text{blasts} - 1.0456)$$

Patients are then divided into the appropriate one of three risk groups:

Low risk: Sokal < 0.8

Intermediate risk: $0.8 \leq$ Sokal ≤ 1.2

High risk: Sokal > 1.2

Euro-hazard score

(J NCI 1998; 90: 850-858)

The Euro-hazard score is based on the following data determined at diagnosis:

age (in years), spleen size (in cm below mid left costal margin), percentage blasts (in %) in the peripheral blood differential, percentage eosinophils (in %) in PB, percentage basophils (in %) in PB and platelet count (in 10^9/l).

$$\text{Euro-hazard score} = 1000 \times (0.6666 \times I_{\{\text{age} \geq 50\}} + 0.0420 \times \text{spleen} + 0.0584 \times \text{blasts} + 0.0413 \times \text{eosinophils} + 0.2039 \times I_{\{\text{basophils} \geq 3\}} + 1.0956 \times I_{\{\text{platelets} \geq 1500\}})$$

where $I_{\{x \geq a\}}$ is the indicator function:

$I_{\{x \geq a\}} = 0$ if $x < a$

$I_{\{x \geq a\}} = 1$ if $x \geq a$

Patients are then divided into the appropriate one of three risk groups:

Low risk:	Euro-hazard $\leq$ 780
Intermediate risk:	780 < Euro-hazard $\leq$ 1480
High risk:	Euro-hazard > 1480

C Response criteria for Chronic Myeloid Leukemia

Hematological response

Complete hematological remission

Requires all of the following:

- Normalization of leukocyte count: WBC < $10x10^9$/l;
- Normal differentials without circulating immature forms; a percentage of circulating immature cells ≤ 2% is compatible with complete hematological remission, provided that it concerns no immature forms other than myelocytes and metamyelocytes:
  blasts = 0%, promyelocytes = 0%, myelocytes+metamyelocytes ≤ 2%;
- Normalization of platelet count: platelets < $450x10^9$/l;
- Disappearance of all clinical symptoms and signs of disease including palpable splenomegaly.

Partial hematological remission

Not fulfilling all the criteria for complete hematological remission, with WBC ≤ $20x10^9$/l.

Failure

WBC > $20x10^9$/l, or progression of disease to accelerated phase or blastic crisis without prior complete hematological remission.

Cytogenetic response

At least 20 metaphases analysed by conventional cytogenetic analysis or 200 metaphases/interphases analysed by FISH.

Complete: Ph^+ chromosomes = 0%

Partial: Ph^+ chromosomes > 0% and Ph^+ chromosomes < 35%

Minimal: Ph^+ chromosomes ≥ 35% and Ph^+ chromosomes < 100%

Absent: Ph^+ chromosomes = 100%

Patients with either complete or partial cytogenetic response are considered to have achieved a major cytogenetic response.

Molecular response

Complete response: ≥ 4.5 log decrease of bcr-abl mRNA detectable by real-time quantitative RT-PCR

Major Response: ≥ 3 log decrease of bcr-abl mRNA detectable by real-time quantitative RT-PCR

Partial Response: ≥ 1 log and < 3 log decrease of bcr-abl mRNA detectable by real-time quantitative RT-PCR

No response: < 1 log decrease of bcr-abl mRNA detectable by real-time quantitative RT-PCR

Molecular responses will be monitored by means of real-time quantitative RT-PCR for the bcr-abl fusion transcript. Protocols for real-time quantitative RT-PCR for bcr-abl will be standardized by the Dutch Network for Molecular Diagnostics. Quality control will also be performed under the supervision of the Dutch Network for Molecular Diagnostics.

The real-time RT-PCR analyses will only be carried out in laboratories qualified according to the quality standards defined by the Dutch Network for Molecular Diagnostics. Samples from other hospital laboratories should be sent to one of the reference laboratories (for information please contact Dr. P. Valk, Erasmus MC, Rotterdam, tel.: +31.10.4087975). The real-time quantitative RT-PCR results obtained in this study will be reviewed by the Dutch Network for Molecular Diagnostics. For patients in arm A real-time quantitative RT-PCR will be performed at entry, at 3, 6 and 12 months after entry and at 6 months intervals thereafter. For patients in arm B real-time quantitative RT-PCR will be performed at entry, after cycle I, after cycle II, at 6 and 12 months after entry and at 6 months intervals thereafter (Arm B).

Progression

Progression from complete hematological response

Requires any of the following after complete hematological response, confirmed by a second determination at least one month later:

- WBC > $20x10^9$/l while under continuous imatinib treatment and in the absence of the use of steroids and/or growth factors;
- Appearance of blasts or promyelocytes in PB
- Myelocytes + metamyelocytes > 5% in PB
- Platelets > $600x10^9$/l
- Progressing splenomegaly to a size of > 5 cm below the mid left costal margin to be confirmed on two occasions at least 4 weeks apart

Progression without prior complete hematological response

A doubling of WBC confirmed by a second determination at least one month later with at least the second value > $20x10^9$/l.

Progression from major cytogenetic response

An increase in Ph^+ cells in BM by at least 30 percentage points (e.g. from 20% to 50%, or from 30% to 60%) from the best achieved response and confirmed by a second cytogenetic analysis at least one month later.

Clonal evolution

The appearance of additional chromosomal abnormalities other than the Ph chromosome. Ph chromosome variants or complex Ph chromosome translocations are not considered to indicate disease acceleration.

D Toxicity criteria

The grading of toxicity and adverse events will be done using the NCI Common Terminology Criteria for Adverse Events, CTCAE version 3.0, published December 12, 2003. A complete document (72 pages) may be downloaded from the following sites:

http://ctep.info.nih.gov/reporting/ctc.html
http://www.hovon.nl (under Studies > Documents)

A hardcopy may be obtained from the HOVON Data Center on request.

E ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

2 Some bed time, but to be in bed less than 50% of normal daytime

3 Needs to be in bed more than 50% of normal daytime

4 Unable to get out of bed

F NYHA* scoring list

Grade 1	No breathlessness
Grade 2	Breathlessness on severe exertion
Grade 3	Breathlessness on mild exertion
Grade 4	Breathlessness at rest

The *New York Heart Association functional and therapeutic classification applied to dyspnoea.