Amendment to the
Randomized Controlled Comparison of Imatinib vs.
Imatinib/Interferon-α vs. Imatinib 800 mg

Quality assurance protocol for the
Treatment Optimization Trial in Chronic Myeloid Leukemia (CML)
CML-Study IV

Running Title: „GEIST"

(German for „SPIRIT":
German **E**valuation of **I**nterferon α, **S**TI-571 and **T**ransplantation in CML)

Amendment to: The main phase study protocol dated May 10, 2005

New insights in tyrosine kinase inhibition and internationally standardized definitions of outcome parameters resulted in the need for the present CML IV study protocol amendment. Results of the CML-Study IV have been presented at national and international congresses (ASH 2008 and 2009, EHA 2009, DGHO 2008 and 2009, ASCO 2010) and are prepared for publication. The part on transplantation outcome in the imatinib era has been published (Saussele et al, Blood 2010; 115: 1880 – 1885).

Status of recruitment

The main phase of the CML study IV consists of a recruitment phase of 5 years (2005 -2010) and a 5-year observation phase (2010-2015).
By 27.04.2010, 1.452 newly diagnosed CML patients in chronic phase had been randomized (pilot phase and main phase).
By the end of 2010 approximately 400 patients will be recruited in each of the three main phase arms.

Update of definitions and target parameters

Based on the recommendations of the expert panel of the European LeukemiaNet (Baccarani et al., Blood 2006 und Baccarani et al., JCO 2009), definitions and designations of the following parameters will be updated.

Accelerated phase (new definition of 3.2.2)

An accelerated phase is present, if *one* of the following criteria is fulfilled in the peripheral blood or in the bone marrow (Baccarani et al., Blood 2006):

- Blasts 15-29%
- Blasts and promyelocytes > 30%, when blasts < 30%
- Basophils ≥ 20%
- Permanent therapy independent thrombocytopenia with platelets < 100 x 10^9/L

Complete hematologic remission (new definition of 3.3.1)

A complete hematologic remission is present if all following criteria are fulfilled (Baccarani et al., JCO 2009):

- Leukocytes < 10 x 10^9/L
- Basophils < 5%
- No myelocytes, no promyelocytes, no blasts
- Platelets < 450 x 10^9/L
- No palpable spleen, or sonographic spleen size < 12x5 cm

If there was no enlarged spleen at diagnosis, a complete remission may be assumed in the face of a missing spleen statement as long as all laboratory parameters fulfil the remission criteria. A reference to the initial spleen statement is not valid as soon as the complete hematologic remission has been lost.

Exceptions: If the spleen is permanently enlarged, other reasons for splenomegaly have to be taken into consideration such as post infectious, chronic hemolysis, spleen vein thrombosis, liver cirrhosis).

Loss of complete hematologic remission (new introduction)

A loss of a complete hematologic remission is not acceptable in the case of complete cytogenetic remission or major molecular remission. The loss of complete hematologic remission is defined by at least one of the following criteria:

- Leukocytes > 20x10^9/L
- Blasts or promyelocytes > 0%
- Myelocytes + metamyelocytes >5%
- Platelets >550x10^9/L
- Spleen >1cm palpable or sonographic > than 12x5 cm and larger than last report

(cave: Since each of these criteria may have reactive causes, the diagnosis should be supplemented by cytogenetic and molecular diagnostics. Patients with blasts or promyelocytes = 1% and without any other criteria should be revisited.
To exclude reactive changes, a query to the family doctor is needed if at least one of the criteria is positive.

Cytogenetic remission (new definition of 3.3.2)

The upper limit of partial remission is defined by 35% instead of 34% Ph-metaphases (Baccarani et al., JCO 2009).
Complete and partial remissions together form the category of “major remission”.
Calculation base is the evaluation of at least 20 metaphases.

Interphase-FISH can be used as a substitute for the banding analysis for complete cytogenetic remission, if there are < 1% positive cells in at least 200 interphases.

If only molecular diagnosis is available, a stable major molecular remission (definition see below) is equivalent to complete cytogenetic remission. A stable major molecular remission is present if it is demonstrated in two consecutive analyses at least 3 months apart.

- Complete remission: 0% Ph+-metaphases
- Partial remission: 1 – 35% Ph+-metaphases
- Minor response: 36 – 65% Ph+-metaphases
- Minimal response: 66 – 95% Ph+-metaphases
- No response: > 95% Ph+-metaphases

Loss of cytogenetic remission (new introduction)

After the achievement of a complete cytogenetic remission, loss of cytogenetic remission is defined by an increase of Ph-metaphases to > 35% demonstrated by chromosomal banding analysis of at least 10 metaphases (FISH not acceptable).

Molecular response (new definition, elimination and amendment of 3.3.3)

a) major molecular remission (MMR, new definition)

A major molecular remission is defined by a BCR-ABL transcript level ≤ 0.10% (international scale).
(This definition may only be used in patients with b2a2 or b3a2 transcripts.)

b) complete molecular remission (CMR)

A complete molecular remission is defined by a negative result of a quantitative Real-Time PCR and/or nested PCR of defined sensitivity:

CMR^{4} defines complete molecular remission with a sensitivity of 1:10.000 (4 log).
$CMR^{4.5}$ defines complete molecular remission with a sensitivity of 1:32.000 (4.5 log).
CMR^{5} defines complete molecular remission with a sensitivity of 1:100.000 (5 log)

Loss of major molecular remission

The loss of major molecular remission is defined by a five-fold increase of transcripts with concurrent increase above the 0,1% transcript level.

Progression free survival (PFS, new definition of 3.3.4)

In accordance with international definitions, progression free survival is defined as time from diagnosis to start of accelerated phase, blast phase, or death.

Failure-free survival (FFS, new definition, amendment of 15.4.4)

What has been called time to progression previously (see 15.4.4), nowadays corresponds to the definition of failure free survival (Baccarani et al., JCO 2009).

Definition of imatinib failure:
- No complete hematologic remission by 3 months (interval up to 4.5 months).
- No complete cytogenetic remission by 18 months (interval up to 21 months).

- Loss of cytogenetic remission after achievement of a complete cytogenetic remission
- Progression to accelerated phase or blast crisis
- Death

Event-free survival (EFS, new introduction)

The following events terminate the period of event free survival, in addition to all events that define failure free survival:

- Intolerance
- Toxicity

Toxicities and intolerance have to exhibit a severeness that requires therapy change. This has to be documented by a CRF 3, including the reason for therapy change.

Statistical analyses

Comments 15.4.1

The analysis planned in 15.4.1 has been performed according to the protocol. The planned sequential analyses for the primary outcome "molecular remission" were conducted in the years 2007, 2008, and 2009. In accordance with the international ELN guidelines (Baccarani et al., JCO 2009), the outcome "molecular remission" was specified as "major molecular remission" and the boundary for an actual "major molecular remission" (major molecular remission = yes) was changed from ≤ 0.12% to ≤ 0.10%. Any higher percentages led to the classification (major molecular remission = no). The reason for this change in cut-point was international standardisation.

The sequential analyses of the primary outcome "major molecular remission" resulted in the rejection of null hypothesis 1: "Equal percentages of (major) molecular remissions after 12 month of therapy in the treatment arm "imatinib 800 mg" in comparison to the treatment with "imatinib 400 mg" (with or without addition of interferon alpha)."

Comments to 15.4.3

Aspect A) For the arms of the pilot phase: The point mentioned with regard to the arm "imatinib + araC" stays unchanged.

Aspect B) For the main phase arms "imatinib + interferon alpha", "imatinib 400 mg", and "imatinib 800 mg" the following will now apply:

About 400 patients will be randomised into each of the three arms by the second half of 2010. Druker et al. (NEJM, 2006) published 5-year survival probabilities of 0.89 for patients randomised to imatinib 400 mg monotherapy in the IRIS study.

Under the hypothesis of a 5-year survival probability of 0.90 for patients treated with imatinib 400 mg, an improvement of the 5-year survival probability to ≥ 0.95 or a decline to ≤ 0.84 can be shown when all following conditions apply:

- comparing 400 patients in each arm
- recruiting over 5 years (2005-2010)
- following-up 5 additional years
- using an alpha = 0.05
- assuming exponentially distributed survival curves

In this case, the power needed to be able to identify one of the above survival differences would be just a little higher than 80%.

Thus there is a realistic chance for an appropriate prospective testing of null hypothesis 2 by using the log-rank test with a power of at least 80%:

Null hypothesis 2:

H_0: "The survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 800 mg" are not different"
versus
H_1: "The survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 800 mg" are different"

A confirmatory test with alpha = 0.05 is possible by using a prospective hypotheses order. If the first hypothesis was rejected at the 0.05 significance level (as it was the case with null hypothesis 1: "Equal percentages of (major) molecular remissions after 12 months") the next hypothesis may be tested at the same significance level.

According to the protocol of May 10th 2005, the planned second analysis was a comparison of the times to progression:
"The analysis of "time to progression" is conducted after the final analysis of the first main outcome "molecular remission at 12 months".

With the unforeseeable, now given possibility to compare the survival probabilities of two treatment arms with sufficient power, the comparison of overall survival probabilities is preferred to the comparison of "time to progression". Overall survival has the advantage that the focus is on the actual primary outcome in oncology, with death due to any cause as the only event. Unlike other events, the day of death is usually known exactly and the problem of a measurement bias due to left truncation does not apply.

Survival can still be linked to the randomised therapies, also because the percentage of patients who have so far changed to another TKI has reached only about 10% after five years.

After the question has been answered whether imatinib 800 mg leads to a higher percentage of major molecular remissions when compared to imatinib 400, the comparison of overall survival was the next logical step. Now, if it is possible to reject null hypothesis 2, the next question is to investigate whether the combination of imatinib 400 mg and IFN will lead to an improved overall survival, too:

Null hypothesis 3:
H_0: "The survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 400 mg + IFN" are not different"
versus

H_1: "The survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 400 mg + IFN" are different"

Confirmatory testing is performed with the log-rank test and a significance level of 0.05. Because recruitment started in 2002 for both arms, the power will be higher than for null hypothesis 2.

The sequence of hypotheses is continued by:

Null hypothesis 4:
H_0: „The progression-free survival probabilities (following the definition in 3.3.4) between the treatment arms "imatinib 400 mg" and "imatinib 800 mg" are not different"
versus
H_1: „The progression-free survival probabilities (following the definition in 3.3.4) between the treatment arms "imatinib 400 mg" and "imatinib 800 mg" are different"

Null hypothesis 5:
H_0: "The progression-free survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 400 mg + IFN" are not different"
versus
H_1: "The progression-free survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 400 mg + IFN" are different"

Null hypothesis 6:
H_0: "The failure-free survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 800 mg" are not different"
versus
H_1: "The failure-free survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 800 mg" are different"

Null hypothesis 7:
H_0: "The failure-free survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 400 mg + IFN" are not different"
versus
H_1: "The failure-free survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 400 mg + IFN" are different"

Null hypothesis 8:
H_0: "The event-free survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 800 mg" are not different"
versus
H_1: "The event-free survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 800 mg" are different"

Null hypothesis 9:
H_0: "The event-free survival probabilities between the treatment arms "imatinib 400 mg" and "imatinib 400 mg + IFN" are not different"
versus

H_1: "The event-free survival probabilities between the treatment arms "imatinib 400 mg" and the "imatinib 400 mg + IFN" are different"

Working with significance level alpha=0.05 is possible until the first null hypothesis cannot be rejected. The result of all following tests may only be reported as exploratory results. All analyses will be conducted five years after the recruitment of the last patient. In all cases the log-rank test will be performed.

Comments 15.4.4

Progression-free survival was defined in accordance with the ELN guidelines. What was formerly understood as "progression-free survival" was renamed to "failure-free survival". The test of differences in failure-free survival was embedded into the sequence of above hypotheses.

Other changes of the protocol

1.1. Steering Committee
Prof. A. Hochhaus, Jena (new Adresse)
Prof. S. Krause, Erlangen (new Adresse)
Prof. G. M. Baerlocher substitutes Prof. Tobler
Prof. Dominik Heim substitutes Prof. Gratwohl
Prof. Th. Fischer resigned.

1.2. Protocol Writing Committee
Dr. S. Saußele and Dr. A. Leitner substitute Dr. G. Engelich and Dr. U. Berger,

1.3 Coordinating Center
New adress:
Pettenkoferstr. 22
68169 Mannheim
Phone.: 0621-3836952
Fax 0621-3836969

Dr. S. Saußele substitutes Dr. U. Berger. Prof. Reiter instead PD Reiter.

1.4. Biometry
M. Lauseker in addition

1.5. Central Diagnostics and Quality Control (see also 11.2 und 11.3)
The reference laboratory for cytogenetics in Switzerland is leaded since 2010 by Prof. Jacqueline Schoumans. The name of PD Dr. C. Schoch changed to PD Dr. C. Haferlach. Since 2010, molecular monitoring is performed in Mannheim by PD Dr. M. C. Müller and In Jena by Prof. Dr. A. Hochhaus (new adress: Abt. Hämatologie und Onkologie, Universitätsklinikum Jena).

1.6. Participating Centers
Updated list see appendix 6.

2. Synopsis
Estimated number of cases corrected to 1500

3.4.4 Evidence-Based Practice Guidelines of CML Treatment
All gidelines and recommendations were adapted to ELN criteria (Baccarani et al. Blood 2006, JCO 2009)

6. Participating Investigators/Institutions
s. section 1.6

9. Treatment Plan
Defined on the basis of the ELN management recommendation published in 2009 (Baccarani et al. Blood 2006, JCO 2009)

10.2 Follow-up Investigations (CRF 2)
Monitoring is adapted according to ELN-criteria, especially intervals for bone marrow biopsy

16 Data Management
CRF2 is adapted.

CML-Studie IV	Alle 3 Monate, ab Jahr 3 nach Diagnose alle 6 Monate Gleichzeitig zu Bogen 3,4,5,6 Zusätzlich nach Erreichen einer kompl. hämatologischen oder einer part. bzw. kompl. zytogenetischen Remission.	**Bogen 2** Verlaufsbogen

Klinik-Nr. ___
Patienten-Nr. ___
Geburtsdatum ___ ___ ___
Geschlecht ☐ männl. ☐ weibl.

Patienten-Initialen ___
(Vorname, Nachname)
Beurteilungsdatum ___ ___ ___
Nummer des Verlaufsbogens ___

k.A = keine Angabe
n.d. = nicht durchgeführt
n.v. = nicht verwertbar

Bisherige Therapie im Intervall	**Beginn**	**Ende**	**Therapietage**	**Gesamtdosis**	**Vorzeit. Absetzen**	**Grund des Absetzens***
Bitte stets so angeben:	TT.MM.JJ	TT.MM.JJ			Ja nein	U A S Grund
Imatinib 400 mg				mg	☐ ☐	☐ ☐ ☐ ____
Imatinib 800 mg				mg	☐ ☐	☐ ☐ ☐ ____
Roferon® ☐ Intron A® ☐ PEG-IFN® ☐				Mio.E.	☐ ☐	☐ ☐ ☐ ____
Wöchentliche Dosis____ ☐ 3 x 3 Mio.E/µg ☐ 3 x 1,5 Mio.E/µg ☐ andere: __ x __ Mio.E/µg						
ARA-C				mg	☐ ☐	☐ ☐ ☐ ____
HU				g	☐ ☐	☐ ☐ ☐ ____

Andere CML-Therapie: ☐ nein
ja, welche: ☐ Dasatinib seit ___
☐ Nilotinib seit ___
☐ Andere ________ ___

Begleitmedikation mit Dosisangaben:
1. 2.
3. 4.
5. 6.

*
U = Unverträglichkeit
A = Ablehnung
S = Sonstiges

Krankheitsstadium zum Zeitpunkt der Beurteilung
Chronische Phase ☐
Akzelerierte Phase ☐ Diagnose am ___
Blastenphase ☐ Diagnose am ___
Kriterium: ☐ Diff-BB ☐ KM ☐ Extramed. Manifestation,
(z.B. LK, Haut, usw.) welche:__________

KM-Zytologie ☐ *n.d.* ☐ *n.v.* am ___
Blasten ___ % Promyelozyten ___ %
Basophile ___ % Eosinophile ___ %
Untersucher/Ort:__________ Präparat Nr.:__________

KM Histologie ☐ *n.d.* ☐ *n.v.* am ___
Fibrose ☐ *k.A.* ☐ vorhanden ☐ nicht vorhanden

	k.A.	vermindert	normal	vermehrt	Reifungsstörung nein	Reifungsstörung ja
Granulopoese	o	o	o	o	o	o
Erythropoese	o	o	o	o	o	o
Megakaryopoese	o	o	o	o	o	o
Zellularität	o	o	o	o		

Untersucher/Ort:__________ Präparat Nr.________

Klinischer Befund am ___
Gewicht ___ kg
Milzgröße (palpiert) ☐ nein ☐ ja
wenn tastbar ___ cm
Milzlänge (sonographisch) ___ cm
Lebergröße (in MCL gemessen) ___ cm

Laborwerte am ___

Leukozyten	___ . ___	10^9/L
Blasten	___	%
Promyelozyten	___	%
Myelozyten, Metamyelozyten	___	%
Stabkernige	___	% } Neutrophile
Segmentkernige	___	% } Neutrophile
Eosinophile	___	%
Basophile	___	%
Monozyten	___	%
Lymphozyten	___	%
Normoblasten	___	%
Retikulozyten	___	‰
Thrombozyten	___	10^9/L
Hb	___ . ___	g/dL (oder mmol/l)
LDH	___ (Normalwert: ___)	U/L (oder µkat/l)

Summe des Diff.-blutbildes sollte 100 % sein

☐ **Zytogenetik** ☐ FISH ☐ *n.d.* ☐ *n.v.* am ___
Philadelphia-Chromosom ☐ neg. ☐ pos.
Anzahl der ausgewerteten Mitosen ___
Anzahl Ph-pos. Mitosen ___ in % ___
Andere klonale Chromosomenanomalien ☐ nein ☐ ja
ja, welche:__________
Material: ☐ Knochenmark ☐ Blut
Untersucher/Ort:__________ Präparat Nr.:__________

Molekularbiologie ☐ *n.d.* ☐ *n.v.* am ___
RT-PCR ☐ neg. ☐ pos.
BCR-ABL/ABL-Quotient (IS) ___ . ___ %
Alternativer Quotient:__________ ___ . ___ %
Material: ☐ Knochenmark ☐ Blut
Mutation: ☐ nein ☐ ja, welche:__________
Untersucher/Ort:__________ Präparat Nr.:__________

Unerwünschte Wirkungen (Kodierschlüsse s. Protokollanhang) sind aufgetreten: ☐ nein ☐ ja

Art der Nebenwirkung	**Nr. (s. Anhang im Protokoll)**	**Schweregrad**	**Datum des 1. Auftretens**	**Verlauf**	**Therapiebezug**	**Symptomatische Behandlung**
	___ . ___					
	___ . ___					
	___ . ___					
	___ . ___					
	___ . ___					

Klinik: __________ Datum: __________ Unterschrift: __________

Befundkopien und Arztbriefe erleichtern vor allem bei besonderen Befunden (z.B. komplexe zytogenetische Anomalien) die Auswertung und ersparen Rückfragen.