Treatment Optimization Trial in Chronic Myeloid Leukemia (CML)

Randomized Controlled Comparison of Imatinib vs. Imatinib/Interferon-α vs. Imatinib/Low-Dose AraC vs. Interferon-α Standard Therapy and Determination of the Role of Allografting in Newly Diagnosed Chronic Phase

Running Title: CML-Study IV

Pilot Phase

Version: December 13, 2002

This study is conducted by the CML-Study Group (CML-SG), the BMBF-sponsored Competence Network "Acute and Chronic Leukemias", the Süddeutsche Hämoblastosegruppe (SHG) e.V. and the Schweizerische Arbeitsgruppe für Klinische Krebsforschung (SAKK)

Study Coordinator: Prof. Dr. med. R. Hehlmann, Mannheim

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ABBREVIATIONS

ALL	Acute Lymphocytic leukemia
ANC	Absolute Neutrophil Count
AraC	Arabinosylcytosin
ATG	Antithymocyte Globulin
CBC	Complete Blood Count
CCR	Complete Cytogenetic Remission
CHR	Complete Hematologic Remission
CML	Chronic Myeloid Leukemia
CML-SG	CML-Study Group
CMML	Chronic Myelomonocytic Leukemia
CRF	Case Report Form
CSP	Cyclosporine
EBMT Score	European Blood and Marrow Transplant Prognosis Score
EBMTR	European Blood and Marrow Transplantation Registry
G-CSF	Granulocyte-Colony Stimulating Factor
GvHD	Graft versus Host Disease
GvL	Graft versus Leukemia
HLA	Human Leukocyte Antigen
HMG CoA	Hydroxymethylglutaryl Coenzym A
HU	Hydroxyurea
IBE	"Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie der LMU München"
IBMTR	International Bone Marrow Transplantation Registry
IFN	Interferon alpha
MCL	Medioclavicular Line
MCR	Major Cytogenetic Response
MMF	Mycophenolate Mofetil
MTX	Methotrexate
PCR	Polymerase Chain Reaction
Pegasys®	Pegylated Interferon alpha 2a
PEG-Intron®	Pegylated Interferon alpha 2b
Ph	Philadelphia Chromosome
RT- PCR	Reverse Transcriptase-Polymerase Chain Reaction
SAKK	"Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung"
SHG	"Süddeutsche Hämoblastosegruppe"
SCT	Stem Cell Transplantation
TBI	Total Body Irradiation
TRM	Transplant Related Mortality
WBC	White Blood Cell
WHO	World Health Organization

1 Organization and Committees

1.1 Steering Committee

Prof. Dr. R. Hehlmann, Mannheim

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Prof. Dr. A. Gratwohl, Basel (SAKK)

Prof. Dr. A. Tobler, Bern (SAKK)

Honorary Member: Prof. Dr. H. Heimpel, Ulm

1.2 Protocol Writing Committee

Prof. Dr. R. Hehlmann, Priv.-Doz. Dr. A. Reiter, Dr. G. Engelich,

Priv.-Doz. Dr. A. Hochhaus, Prof. Dr. J. Hasford

Prof. Dr. H.-J. Kolb, Prof. Dr. D. Niederwieser

1.3 Coordinating Center

Prof. Dr. R. Hehlmann (Study Coordinator)

Dr. U. Berger, Priv.-Doz. Dr. A. Hochhaus, Priv.-Doz. Dr. A. Reiter

III. Medizinische Universitätsklinik

Fakultät für Klinische Medizin Mannheim der Universität Heidelberg

Wiesbadener Str. 7-11

68305 Mannheim

Phone. : Documentation: 0621/383 4168 (Sekretariat Prof. Hehlmann: 383 4115)

Fax: Documentation: 0621/383 4239 (Sekretariat Prof. Hehlmann: 383 4201)

E-mail: CML.Studie@urz.uni-heidelberg.de

Registration and Randomization: Phone : (0621)-383-4168, fax: (0621)-383-4239

1.4 Biometry and Data Management

Prof. Dr. J. Hasford, Prof. Dr. K. Überla, Dipl.-Stat. M. Pfirrmann

Institut für Medizinische Informationsverarbeitung,

Biometrie und Epidemiologie der Universität München (IBE)

1.5 Central Diagnostics and Quality Control

a) Histology Panel

Prof. Dr. H. H. Kreipe, Priv.-Doz. Dr. T. Buhr, Dr. G. Büsche; Hannover

b) Cytogenetics Panel

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Prof. Dr. B. Schlegelberger, Hannover

Prof. Dr. M. Jotterand, Lausanne

c) Molecular Genetics

Priv.-Doz. Dr. A. Hochhaus, Priv.-Doz. Dr. A. Reiter; Mannheim

d) Safety Monitoring Board for SCT

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Prof. Dr. G. Ehninger, Dresden

Prof. Dr. A. Gratwohl, Basel (SAKK)

Prof. Dr. H.-J. Kolb, München

Prof. Dr. A. Zander, Hamburg

1.6 Participating Centers

Refer to appendix 6

SIGNED BY:

Steering Committee: **Date**

Prof. Dr. R. Hehlmann: _____

Prof. Dr. G. Ehninger (Dresden): _____

PD Dr. T. Fischer (Mainz): _____

Prof. Dr. J. Hasford (München): _____

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Prof. Dr. D. K. Hossfeld (Hamburg): _____

Prof. Dr. H.-J. Kolb (München): _____

PD Dr. S. Krause (Regensburg): _____

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Prof. Dr. H. Pralle (Giessen): _____

Prof. Dr. A. Gratwohl (Basel, SAKK): _____

Prof. Dr. A. Tobler (Bern, SAKK): _____

Honorary Member: Prof. Dr. H. Heimpel (Ulm): _____

2 Synopsis

Title of the Study	Randomized controlled treatment optimization trial in chronic myeloid leukemia (CML): imatinib vs. imatinib/interferon- vs. imatinib/low-dose araC vs. interferon- -based standard therapy, and allografting vs. salvage chemotherapy in chronic phase CML.
Coordinator	Prof. Dr. med. R. Hehlmann, Mannheim
Steering Committee	refer to section 1.1
List of Investigators	refer to section 1.6
Study Period	July 2002 until 2010
Objectives	1) Imatinib-based vs. interferon-alpha(IFN)-based therapy (hematologic, cytogenetic and molecular response, overall-, risk group dependent- , and progression free survival, time to progression). 2) Imatinib vs. imatinib/IFN vs. imatinib/low-dose araC (hematologic, cytogenetic, molecular response, overall-, risk group dependent- , and progression free survival, time to progression). 3) Allografting vs. imatinib-based therapy in patients eligible for transplantation. 4) Standard- vs. reduced-intensity conditioning in patients older than 45 years of age. **Additional objectives:** 1) Time of first appearance and duration of hematologic, cytogenetic and molecular responses. 2) Correlation of quality of responses with survival times. 3) Comparison of short- and long-term adverse effects of imatinib-based mono- and combination therapies and of IFN standard therapy. 4) Duration of blastic phase and immunophenotype of blasts in dependence of treatment. 5) Survival and outcome of high-risk patients (New CML Score) after early allografting. 6) Hematologic, cytogenetic and molecular responses of imatinib as salvage therapy after IFN failure. 7) Validation of the New CML Score or development of a new prognostic score adapted for imatinib-based therapies. 8) Impact of normal or subnormal WBC counts during the course of treatment for the duration of chronic phase and effect on survival. 9) Novel drug therapies for relapsing or refractory CML. 10) Risk-adapted treatment strategies (e.g., imatinib + chemotherapy, intensive chemotherapy, autografting) in non-responders to imatinib-based therapy (protocol amendments to follow). 11) Influence of pretransplant therapies on the outcome of allografting. 12) Analysis of complete cytogenetic responders within the different treatment groups.
Trial Design	Randomization into 4 treatment arms: imatinib, imatinib + IFN, imatinib + low-dose araC, and IFN ± hydroxyurea (HU) (± low dose araC). High-risk patients will be randomized to receive imatinib or imatinib combination therapy only.

Patient Numbers	Total number of subjects enrolled n=1600, 400 in each arm.
Inclusion Criteria	• Newly diagnosed BCR-ABL-positive CML in chronic phase. • Pretreatment with HU or anagrelide is permitted. • No age limit. • Informed consent.
Exclusion Criteria	• Pretreatment with chemotherapy, IFN or radiation. • Second malignancy, if it requires therapy and the estimated life expectancy is shorter than the median survival of CML. • Other serious diseases, pregnancy including lactation period or other conditions which could prevent the required protocol-compliance. • Participation in another trial • No informed consent.
Treatment Plan	**Arm I:** 400mg* Imatinib p.o. qd. **Arm II:** 400mg* Imatinib p.o. qd + IFN, initially 1,5-3 x 10^6 IU flat dose s.c. qd, later IFN dose to be adjusted according to CBC. **Arm III:** 400mg* Imatinib p.o. qd + araC, initially 10 mg flat dose up to 2 x five days/month, later araC dose to be adjusted according to CBC. **Arm IV:** IFN, initially 5 x 10^6 IE/m^2 s.c. qd, later IFN dose adjustments made according to CBC and attainment of hematologic response. Switch to imatinib after IFN failure. Patients eligible for an allotransplant who failed imatinib are randomized genetically whether or not an HLA-identical related or unrelated donor is available to undergo allografting or to continue any form of salvage therapy. Patients older than 45 years of age will be further randomized to receive an age adjusted standard (8 Gy) conditioning regimen or reduced-intensity preparative regimen (minitransplant). *Dose increased to 600mg, if no hematologic response after 3 mos
Study Endpoints	Primary: overall- , risk group dependent- , and progression free survival, hematologic, cytogenetic and molecular responses; time to progression. efficacy parameters: clinical exam, CBC + differential, cytogenetics, PCR, bone marrow exam. Secondary: adverse drug effects (recorded by WHO), quality of life (approximated by analysis of symptoms, performance status, and adverse drug effects)
Sample Size Calculation	refer to section 15.1
Statistics	refer to section 15.3

2.1 Rationale

In CML therapy, an entirely new situation has emerged due to the introduction of the tyrosine kinase inhibitor imatinib. Hematologic and cytogenetic response rates are much higher with imatinib than with interferon alpha (IFN) at lower toxicity. Although the rate of progression seems to be less with imatinib than with IFN, the observation times under imatinib with a median of 14-18 months are too short to allow any definite estimate concerning survival and long term toxicity. In addition, patients in complete cytogenetic response (CCR) under imatinib retain BCR/ABL transcripts as markers of residual disease, and resistance to imatinib can evolve after relatively short intervals.

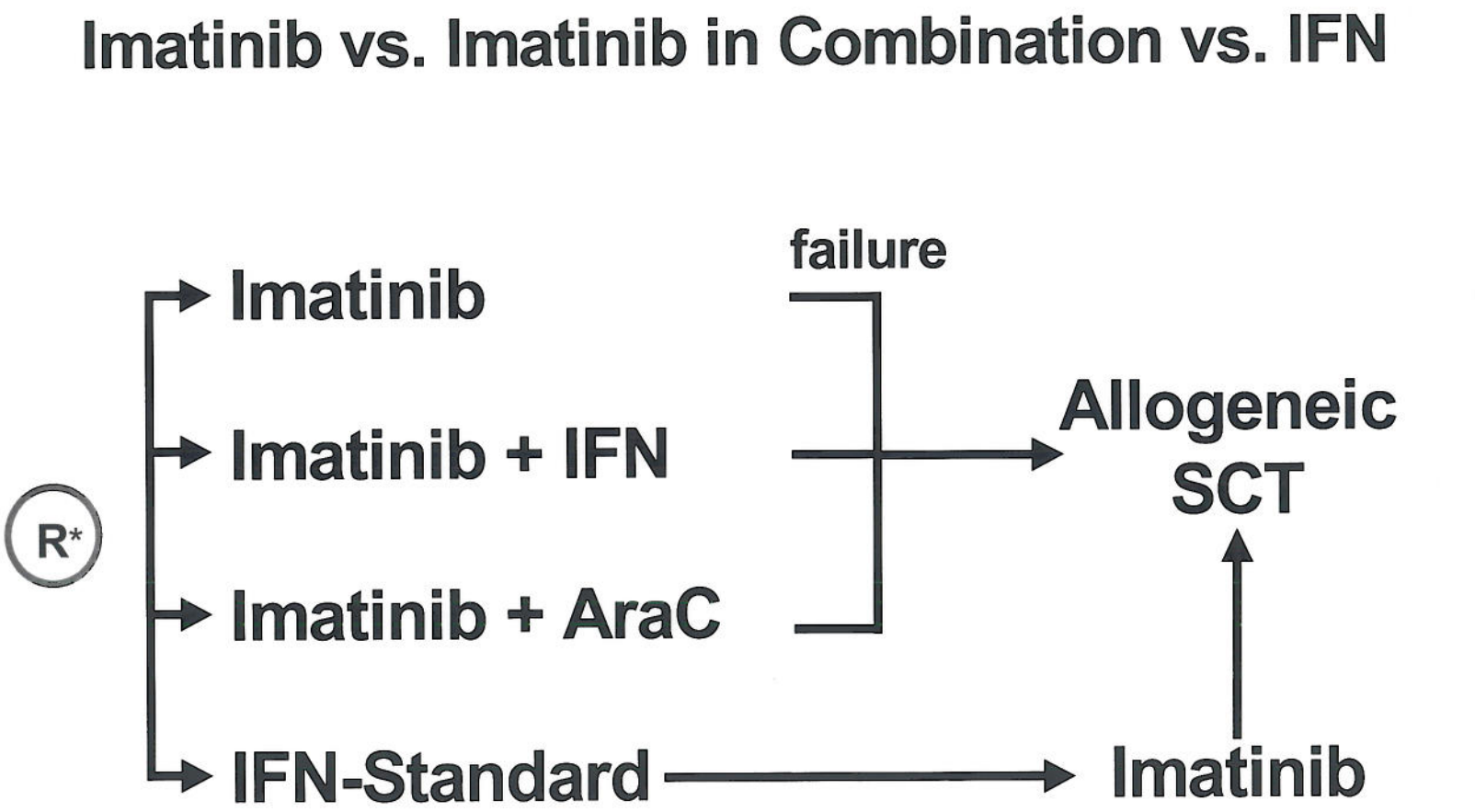
There is international consensus that combinations of imatinib with IFN and arabinosylcytosine (AraC) which are synergistic in vitro might offer further improvement of outcome and should be studied. In favor of combinations is the fact that drugs with different modes of action are combined (e.g., competitive inhibition by imatinib vs. immune modulation by IFN).

In CML-Study IV, combinations of imatinib with IFN or AraC are compared with imatinib as single agent and IFN standard therapy. High-risk patients are restricted to the imatinib arms. The IFN standard arm is important in view of the superior 10-year-survival rates with IFN and the short observation times with imatinib, the persistence of BCR/ABL transcripts in CCR and the development of imatinib resistance. IFN can be combined with hydroxyurea (HU) any time. In the case of IFN failure, crossover to imatinib is provided. The sequential treatment design with IFN followed by imatinib might also yield a survival advantage.

After imatinib failure, an allogeneic stem cell transplantation (SCT) is recommended for all patients with an available donor. This design aims to determine the role of allogeneic SCT in the imatinib era. In an effort to reduce transplant related mortality (TRM) reduced intensity conditioning will be evaluated in patients 46 years or older.

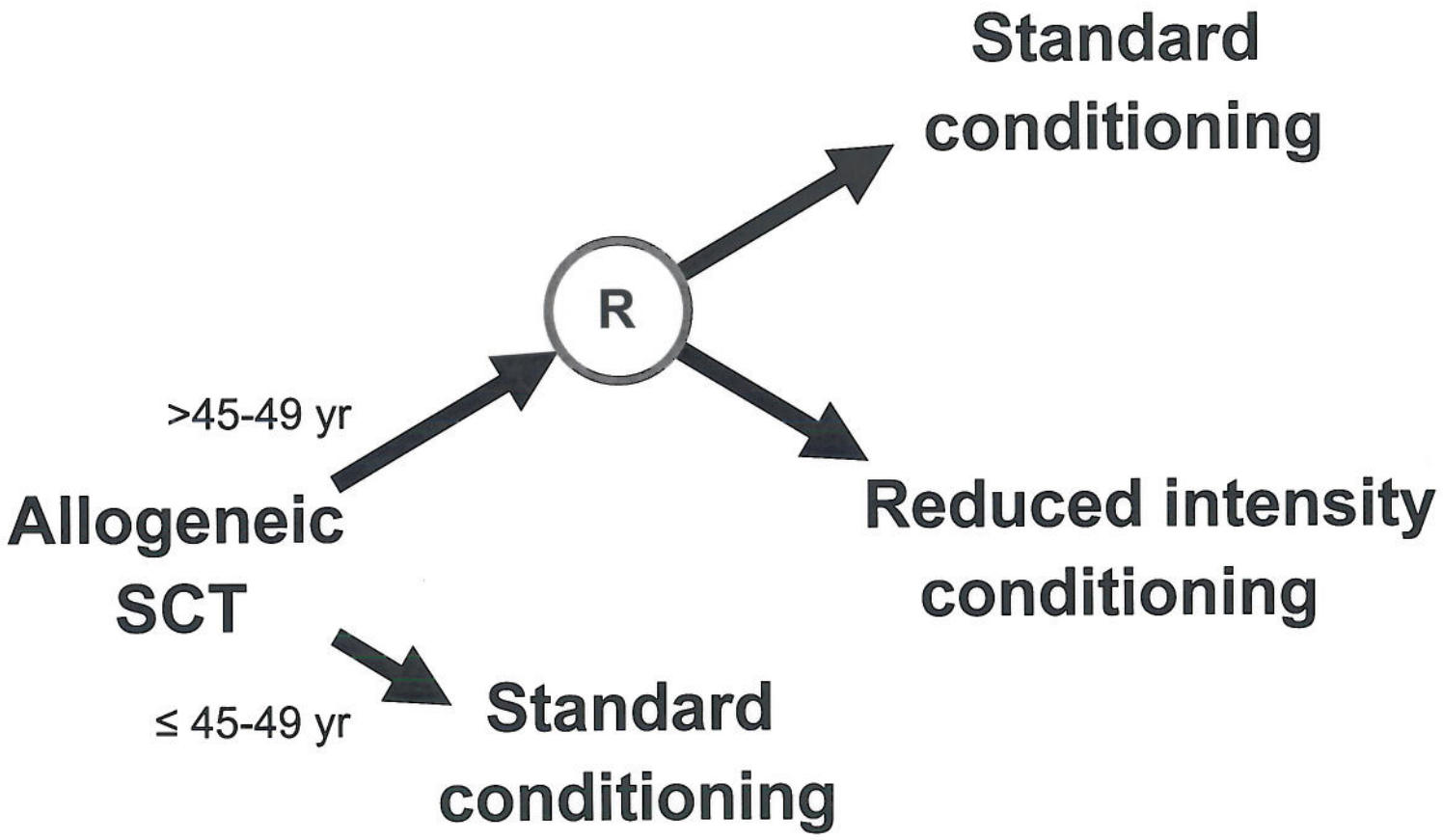
The CML-Study IV with its comprehensive concept and sequential treatment strategy offers an optimized treatment to essentially any patient with CML. Furthermore, it can be expected that the rational, quality controlled treatment strategy within the study protocol will be more cost effective in the long run than treatment outside the study.

2.2 Study Design, Primary Objectives 1 and 2



* High risk patients: Randomization only for imatinib-based therapies; early allogeneic SCT recommended.

2.3 Study Design, Primary Objectives 3 and 4



3 Scientific Background, Definitions and Therapy

3.1 Background

The CML-Study Group (CML-SG), Süddeutsche Hämoblastosegruppe (SHG) and Schweizerische Arbeitsgruppe für Klinische Krebsforschung (SAKK) aim as their long-term goal to improve therapy and prognosis in patients with CML. Emerging new therapies will be incorporated into current study protocols as long as it is methodologically possible.

In the first trial (CML-Study I) CML-SG demonstrated that HU and IFN prolong survival and the duration of chronic phase in patients with CML compared to the previous standard busulfan.[1;2] The subsequent CML Study II[3] – final results will be published shortly - demonstrated that the combination of IFN and HU as compared to HU monotherapy prolongs survival. In CML-Studies III and IIIA the role of allogeneic SCT was addressed. In view of the high peritransplant mortality outcomes of allotransplants were compared to best available conventional non-transplant therapy. Furthermore, subgroup analysis should identify individuals who would gain the greatest benefit from allogeneic SCT. In addition, novel strategies such as dose intensified chemotherapy regimens (CML-Study III) and/or autologous transplantation (CML- Study IIIA) were evaluated in terms of their impact on survival.

The fourth randomized trial now compares imatinib monotherapy, imatinib in combination with IFN or low-dose araC, and IFN-based standard therapy and aims to assess survival and hematologic, cytogenetic and molecular response rates as primary study endpoints. In addition, the role of allotransplant and reduced-intensity conditioning (i.e., patients 46 years or older) will be randomly evaluated.

CML-study IV is founded on the scientific results and conclusions drawn from the predecessor trials, CML-Studies I-IIIA. Moreover, CML-Study IV can rely on a well collaborating study group, experienced review panels, quality controlled documentation and well functioning data analysis.

3.2 Definitions

Chronic myeloid leukemia (CML) is a clonal disorder of pluripotent hematopoietic stem cells. In about 95% of the patients, a reciprocal translocation between the long arms of the chromosomes 9 and 22, the t(9;22)(q34;q11) is found. The shortened chromosome 22 is designated Philadelphia-chromosome (Ph).[4] On a molecular level the BCR-gene localized on 22q11 fuses with the translocated ABL-gene from the 9q34 region.[5-7] BCR-ABL-rearrangement is detected in 95%, the reciprocal ABL-BCR-rearrangement in 70% of cases.[8] Detection of Ph-chromosome or BCR-ABL-rearrangement is diagnostic for CML.

Characteristics of CML:

1. Increase of ANC in the peripheral blood (as a rule more than a 30.000/µl).
2. Appearance of myeloid precursors in the peripheral blood (myelocytes, promyelocytes and/or myeloblasts).
3. Hypercellular bone marrow consistent with a chronic myeloproliferative disorder
4. Lack of morphologic criteria for acute leukemia.
5. Lack of criteria for other myeloproliferative disorders (e.g., agnogenic myeloid metaplasia, essential thrombocythemia, polycythemia vera, chronic myelomonocytic leukemia [CMML]).[9]

In about 30% of the Ph-negative CML the typical BCR-ABL-rearrangement as noted in virtually all Ph-positive CMLs is demonstrable by molecular methods. The clinical course in this situation does not differ from the classical Ph-

positive CML. However, Ph- and BCR-ABL-negative so called ‚atypical CML' runs a different clinical course associated with an unfavorable prognosis compared to Ph-positive CML.[10-12] Diagnostic distinction from other myeloproliferative disorders including CMML may sometimes be challenging and a clear cut diagnosis is made only in retrospect.[9] **Hence, a positive BCR-ABL-rearrangement is mandatory for inclusion into this study.**

CML runs a triphasic clinical course: the chronic, accelerated, and blastic phases.

3.2.1 Chronic Phase

Chronic Phase is characterized by an autonomous, unregulated proliferation of white blood cell - and partly megakaryopoietic precursors. Patients in the chronic phase manifest a leukocytosis, hypercellular bone marrow, splenomegaly, and no evidence of disease progression into accelerated or blastic phases (see below).

The Ph- or BCR-ABL-positive CML requires treatment without exception; treatment decision is not influenced by peripheral blood cell numbers or the clinical presentation.

The end of the chronic phase is marked by an evolution into an unstable phase, that may clinically be heterogenous. It may become apparent by a resistance to therapy (i.e., uncontrolled cell numbers despite intensified treatment). Disease progression into a blast crisis, which follows an accelerated phase, is more clearly defined. In some cases bone marrow aplasia (i.e., biopsy proven failure of hematopoietic marrow) may be the most conspicuous sign.

3.2.2 Accelerated Phase

Definition of accelerated phase (according to international imatinib studies, one feature suffices):

- Presence of blasts in peripheral blood or bone marrow ≥ 10%, but < 30%.
- Presence of blasts **and** promyelocytes in peripheral blood or bone marrow ≥ 20%.
- Presence of basophils in peripheral blood ≥ 20%.
- Therapy-unrelated thrombocytopenia < 100 x 10^9/L.
- Enlarging spleen size ≥ 10 cm below the left costal margin noted at two exams at least 4 weeks apart or a more than 50 % increase of spleen size within 4 weeks.
- Additional cytogenetic abberations.

3.2.3 Blastic Phase

Definition of blastic phase (according to international imatinib studies):

- Presence of blasts in peripheral blood or bone marrow ≥ 30%.
- Extramedullary blastic infiltrates except in spleen, lymph nodes or liver.

3.3 Definitions of Response Criteria

The same definition of response criteria were applied in CML-Studies I-IIIA and will be used according to Talpaz et al.[13] and the international phase II imatinib trials:

3.3.1 Hematologic Response

Complete hematologic response (all of the following must be present)

- WBC count less than 10.000/µl.
- Platelets in the range of 140.000 – 400.000/µl.
- No blasts, promyelocytes, myelocytes or metamyelocytes in the peripheral blood.
- No evidence of disease-related symptoms and extramedullary disease including hepatosplenomegaly.

Partial hematologic response (one suffices)

- Reduction of leukocytes to less than 20.000/µl and less than 50% of baseline.
- Reduction of platelets and spleen size to less than 50% of baseline.
- Normal peripheral blood counts, i.e., WBC count less than 10.000/µl, platelets less than 400.000/µl with persistent splenomegaly.

No response

- None of mentioned response criteria are met.

3.3.2 Cytogenetic Response

Complete response:	Eradication of Ph-positive metaphases
Major response:	1-34% Ph-positive metaphases
Minor response:	35-65% Ph-positive metaphases
Minimal response:	66-95% Ph-positive metaphases
No response:	96-100% Ph-positive metaphases

3.3.3 Molecular Response

Qualitative PCR-Analysis:

Performed by two-step-(‚nested') PCR, detection level 10^{-6} leukemic cells.

Complete response:

No evidence of BCR-ABL-fusion transcripts, provided the cDNA used is of good quality.

Quantitative PCR-Analysis:

Quantification of BCR-ABL-transcripts in relation to a reference gene (Ratios BCR-ABL/ABL and BCR-ABL/G6PD).

3.4 Scientific Foundation of Therapy

When planning the treatment of CML basically two treatment options are available: allogeneic SCT, the only potentially curative treatment modality, can be offered to 35% of patients with CML dependent on eligibility and donor availability; and the non-transplant conventional therapy, by which as a rule the disease is not curative.

3.4.1 Drug Therapy

For a long time drug treatment was considered palliative. In first conducted observational studies a modestly improved survival was noted with splenic irradiation and busulfan. But this supposed benefit was more likely due to flawed study

design (i.e., selection bias, such as unbalanced inclusion of high-risk patients, Ph-negative CML, or heralding blast crisis) rather than true efficacy of those therapies.[14] For the first time a significantly improved survival benefit was shown by HU and IFN. Table 1 lists median survival rates with a number of different treatment modalities.

Table 1. Median survival under various therapies for CML

Therapy	Months	Reference
None	31	15
Splenic irradiation	28	16
Busulfan	35-52	1;2;17-21
Hydroxyurea	48-69	1;2;18;19;22-24
Dose-intensive chemotherapy	45-55	25-32
Interferon alpha	55-89	1;2;13;21;23;24;33-39
Imatinib (STI571)	3.5*	40
Allogeneic Stem Cell Transplantation	40-80% 5-year survival	41-49

* Increase in survival during blast crisis

3.4.1.1 Hydroxyurea

Hydroxyurea (HU) inhibits the enzyme ribonucleotidereductase. There are several advantages that make HU the drug of choice during initiation of therapy: a rapidly inducible treatment effect, low toxicity rates, and the improved survival compared to busulfan. Adverse effects of HU include mainly dermatitis, skin- and nail atrophy, and gastrointestinal symptoms. Typically, red blood cells are macrocytic. Rarely, HU is associated with exanthema and ulcerations at the calfs and ankles, very rarely with drug fever.

Early on, small retrospective studies reported a survival benefit when using HU in chronic phase CML.[18;19] Therefore, CML-SG launched a randomized trial (CML-study I) to evaluate survival and duration of chronic phase with HU or busulfan as single agents. Treatment with HU resulted in improved median survival (approximately 1 year) compared to busulfan.[1] A metaanalysis of three available randomized studies[22] confirmed the evident survival benefit (median survival of 48-69 months) for HU-treated patients.[1;2;18;19;23;24]

3.4.1.2 Interferon alpha

Beginning in the 1980's IFN has gained a significant role in treating CML. Hematologic responses have been noted in the majority of patients (approximately 80 % of cases) and CCR were noted in a small percentage of patients (approximately 13 %),[50] which were durable when IFN was discontinued.[51] Talpaz and coworkers firstly reported on 7 of 51 Ph-positive patients with CML, who achieved CCR.[33] Since then, rates of CCR reported in monocentric studies varied considerably (up to 38%) dependent on the risk profile.[1;13;21;23;24;34-36;38;39]

In an effort to identify at diagnosis patients with an unfavorable prognosis reliable scores have been developed, most recently the **New CML Score,**[53] which impact on outcome more heavily than any given therapy.[52] Patients are stratified into three separate risk groups with clearly different odds of survival (**Figure 1**). Besides an excellent prognosis of low-risk patients high-risk patients on the other hand do not seem to benefit from any drug therapy, even when they achieved CCR.[50]

3.4.1.3 Hydroxyurea/Interferon alpha ± Low-Dose AraC

Recently, a number of studies evaluated combinations of IFN with HU or low-dose araC. In a French randomized trial combination of IFN/HU and low-dose araC (20 mg/m²/day) administered on 10 – 15 days per month was superior to IFN/HU monotherapy in both cytogenetic response and survival.[39] These results were confirmed only in part by an Italian randomized trial.[63] In this study, despite improved major and complete cytogenetic responses like in the French trial, no survival benefit was discerned. A metaanalysis of both trials is planned. A third smaller randomized trial albeit with limited follow-up also failed to prove a survival advantage with IFN/low-dose araC.[64] Retrospective data from Houston showed similar results namely improved cytogenetic response rates but no improved survival with combined therapy.[65]

Table 2: Rates of hematologic and cytogenetic responses and survival in patients with chronic phase CML treated with combined therapy IFN and low-dose araC (review[66]).

Number of Patients	Low Risk (Sokal) %	Dose of AraC	Complete Hematologic Response (%)	Cytogenetic Response %		Overall Survival % (years of f/u)	Reference
				Major	Complete		
721	47	40 mg 10 – 15 days/months	67	41	15	87 (3)	Guilhot et al., 1997 [39]
538	50	40 mg 10 days/months	62	28	14	85 (3)	Baccarani et al., 2002 [63]
64	-	10 -15 mg 4 – 5 days/week	74	27	16	95 (3)	Giles et al., 2000 [64]

3.4.1.4 Imatinib (STI571, Glivec®)

An abnormal tyrosine kinase activity is causal in the pathogenesis of CML leading to enhanced tyrosine phosphorylation of a series of cytoplasmic proteins which regulate proliferation, differentiation and apoptosis in BCR-ABL expressing cells.[67-69] In an effort to identify compounds, which could selectively inhibit the aberrantly enhanced tyrosine kinase, imatinib, a-phenylaminopyrimidinderivative, was found.[70] It competitively inhibits the ATP binding site of BCR-ABL-tyrosine kinase and, by inhibiting tyrosine phosphorylation, imatinib blocks the BCR-ABL signal transduction cascade. Imatinib is highly selective for inhibiting BCR-ABL, ABL, PDGF-R and c-kit[71] without inhibiting the proliferation of BCR-ABL-negative cells.[72]

Imatinib is well absorbed from the gut. Peak plasma levels are reached after 2-4 hours. A single oral dose of 400 mg/day reaches a steady state plasma concentration which exceeds the minimal required concentration for inhibiting cellular phosphorylation and causes lysis of BCR-ABL-positive cell lines *in vitro*. The half time of imatinib is 13 to 16 hours on average.[73]

In a phase I study 83 IFN refractory patients in chronic phase were treated with imatinib.[73] Median time of IFN pre-treatment was 8.5 months (1 wk - 8.5 yr), the median time of the imatinib therapy was 310 days (17 -607 days). CHR was noted in 53 of 54 patients treated with more than 300 mg of imatinib (criteria: leukocytes < 10.000/µl und platelets < 450.000/µl for at least 4 weeks). Hematologic responses were attained generally within the first four weeks of imatinib therapy and were durable in 51 of 53 patients with a median follow-up of 265 days (17 -468 days). A MCR was noted in 17 (31%), CCR in 7 patients (13%).

Median time to best cytogentic response was 148 days (48 -331 days). The side effects (i.e., nausea, diarrhea, myalgias and periorbital edema) were relatively frequent (25 -43 %) but mostly mild (WHO grade I and II).

In some patients abnormal liver function tests were noted. An initial drop of hemoglobin of 1 -2 g/dl, which was dose related, occured frequently. Leukopenia and thrombocytopenia (WHO grade III) occurred in 14% and 16%, respectively, and was not dose limiting. The maximally tolerable dose of imatinib was not defined, the highest dose administered was 1000 mg.

In a second phase I study 58 patients with myeloid (n = 38) or lymphoid blast crisis or ALL (n = 20) were treated with 300 - 1000 mg of imatinib. [74] Median age was 48 years (24 -76 yr). Additional chromosomal abnormalities were noted in 58% and 65%, respectively. 21 patients with myeloid blast crisis (55%) achieved a hematologic response, which was complete in 4 patients (11%). In 12 patients (32%) less than 5% blasts were noted in the bone marrow.
In patients with lymphatic blast crisis hematologic response rate was 70%, which was complete in 20%. In 11 patients (55%) less than 5% blasts were noted in the bone marrow. 7 of 58 patients (12%) attained MCR, which was complete in 5 patients (3 and 2 patients, respectively from each group). Response rates were not closely related to the administered doses. Of the 21 patients with myeloid blast crisis who had attained a hematologic response, 9 patients relapsed after a median of 84 days (42 -194 days). All patients with lymphoid blast crisis except one relapsed after a median of 58 days. The side effect profiles were comparable to the aforementioned study in chronic phase CML. Overall, 16 patients died due to disease progression.

Phase-II-trials were conducted in blast crisis (n = 260), accelerated phase (n = 235) and IFN resistance or intolerance (n = 532). In patients with blast crisis hematologic response rate was 52% (complete in 8%), major cytogenetic responses were 16%, with 7% of the responses being complete.[40] Time to progression and median survival were significantly shorter in pre-treated patients. In patients with accelerated phase imatinib induced sustained hematologic responses lasting at least 4 weeks in 69% (complete in 34%).[75] MCR rate was 24%. Estimated 12-month overall survival was 74%. In IFN refractory or –intolerant patients in chronic phase CML imatinib induced CHR in 95%, MCR in 60%, with 41% of the responses being complete.[76] The median time to onset of CHR was 0.7 months, of MCR 2.9 months. A phase III study, which randomly compares single agents imatinib and IFN as primary treatment in patients with early chronic phase, completed accrual January 2001. Interim results (ASCO, May 2002) demonstrate that hematologic and cytogenetic response rates are much higher with imatinib than with IFN at lower toxicity. Altough the rate of progression seems to be less with imatinib than with IFN, the observation times under imatinib with a median of 14-18 months are too short to allow any definite estimate concerning survival and long term toxicity. In addition, in view of emergence of imatinib resistance[80-82] and the failure to eradicate residual BCR-ABL transcripts even in patients with CCR[118] the prospects of curing CML with imatinib monotherapy seem unlikely. As a solution of these long term risks of imatinib therapy, combinations of imatinib with other effective CML drugs are studied.

Table 3: Rates of hematologic and cytogenetic responses with imatinib, (phase II-studies).[40;75;76]

	Median Duration of Therapy (Months)	Recruited	Hematologic Response		Cytogenetic Response (≤ 35% Ph-positive metaphases)	
			n	%	N	%
Chronic Phase	18	532	454	95	454	60
Accelerated Phase	8	235	148	63	49	21
Myeloid Blast Crisis	6	260	133	51	35	14

To evaluate drug combinations of imatinib + IFN, araC, and HU *in vitro* equivoval results were seen. Thiesing *et al.* demonstrated additive and synergistic inhibition of imatinib combined with IFN and araC, respectively, but antagonistic effects when imatinib was combined with HU.[77] Topaly *et al.* made similar observation with araC and HU.[78] Accordingly, imatinib combined with different compounds of IFN were synergistic , with araC and HU additive on cell growth inhibition of BCR-ABL positive cell lines.[79] In summary, at least additive effects cell growth inhibition were noted with the combinations of imatinib + IFN and imatinib + araC. The final results of the phase I/II studies imatinib + IFN, imatinib + PEG Intron®, Imatinib + Pegasys®, imatinib + araC (Mannheim, Bologna, Houston and Portland, USA, Newcastle, U.K.) are awaited and considered in the dosage recommendations.

3.4.2 Allogeneic Stem Cell Transplantation

Allogeneic SCT is the only curative treatment modality and therefore plays a distinct role in the treatment of CML. A variety of prognostic factors have been identified to predict disease-free survival post allotransplant and put together in the EBMT transplantation risk score (**Table 4, Figure 2**)[49]

Table 4: Transplant risk score for CML.[49] The score is calculated by the sum of each parameters.

Donor	HLA-identical sibling	0
	Unrelated donor	1
Stage of Disease	1st chronic phase	0
	Disease progression	1
	Blast crisis or 2./3. Chronic phase	2
Age of Recipient	< 20 years	0
	20 – 40 years	1
	> 40 years	2
Gender Recipient/Donor	All, except	0
	Male recipient/female donor	1
Time Elapsed from Diagnosis until SCT	< 12 months	0
	> 12 months	1

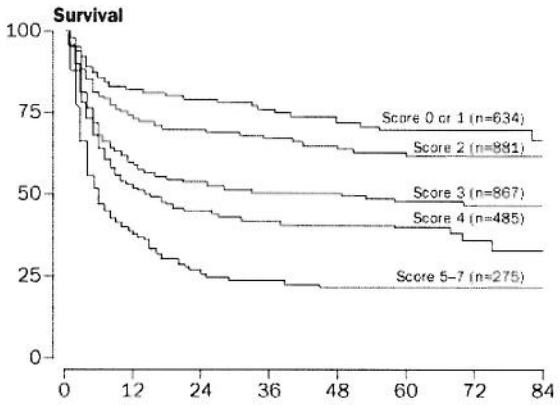


Figure 2: Survival probability of risk groups according to the EBMT score.[49]

Disease-free survival rates post allogeneic SCT with related donors vary according to center and age selection of the patients between 38% and 75%.[41-49] The outcome is more favorable when SCT is carried out within the first two to three years after diagnosis.[43;47;83] Results may even be improved when allogeneic SCT is carried out within the first 6 months after diagnosis (IBMTR and EBMTR data). A decade ago survival rates from patients with an unrelated allograft were 10-15% inferior. However, within the last years utilizing more stringent selection criteria (age less than 50 years, allele typing techniques) results have clearly improved and are nowadays equivalent to related donor transplants. The best results of unrelated transplants are reported from Seattle with 5-year survival rates of 75%.[47;84;85] Comparing unrelated with related allografts from our data bank results were equivalent (preliminary data). Unequivocally, in unrelated allografts graft failure and graft versus host disease (GvHD) appears more likely and leukemia relapse less likely due to graft versus leukemia (GvL) effects. For appropriate methodology of immunogenetic donor search we refer to the German Consensus practice guidelines. [86]

Transplant-related morbidity and mortality are considerable. Risks include infections, acute GvHD as well as long-term impairment of quality of life by chronic GvHD, radiation sequelae, and toxicities related to the conditioning regimen. No prospective trials comparing allogeneic SCT and IFN have been reported, as yet. A retrospective analysis has been performed comparing the outcome of allogeneic transplants reported to the IBMTR to those patients treated with IFN or HU in the CML-Study I[87] and analyzing IFN-treated or transplanted patients from the Italian Cooperative Study Group[88]. In low-risk patients the overall survival advantage for transplantation became significant not before eight and ten years, respectively. The randomized trial CML-Study III comparing allogeneic SCT to medical therapy by assigning patients with HLA-matched donors to transplantation and those without histocompatible donor to medical therapy is currently underway. Interim analyses, so far confirm the retrospective data. The debate with respect to optimal treatment in CML is likely to intensify with the introduction of tyrosine kinase inhibitor imatinib which proved to be highly active in the treatment of chronic phase CML. However, information about survival and long-term side effects of this drug are pending.

In view of the significant TRM it is reasonable to evaluate first line non-transplant treatment strategies for low- and intermediate-risk patients with allogeneic SCT used as salvage once patients have failed IFN or imatinib. By prospective analysis it appears safe to use IFN prior to allogeneic SCT, provided IFN is discontinued at least 3 months before.[89] In recent years non-myeloablative SCT has yielded encouraging results with respect to reduction of TRM

(**Table 5**).[90-93] It offers acceptable toxicity profiles, which is of particular importance in patients older than 45 years of age[90]. Facing a bewildering array of various conditioning regimens and dosages used unfortunately no standard conditioning has emerged.[94] Conceptually, non-myeloablative SCT is based on the insight that engraftment can be accomplished by using less intensive and therefore less toxic doses of preparative regimens, resulting in reduced TRM particularly within the early peritransplant period and secondly on eliminating the residual malignant clones by exploiting the "graft versus leukemia"effect.

Table 5: Non-myeloablative SCT in hematological and non-hematological malignancies.

	Storb et al. (2001)[95]	McSweeney et al. (2001)[90]	Slavin et al. (1998)[92]	NIH/Childs et al. (1999)[93]	Khouri et al. (1998)[96]	Giralt et al. (1997)[91]
Age (median)	18 – 72 (54)	31 – 72 (56)	1 – 56 (34)	23 – 68 (51)	47 – 71 (60)	27 – 71 (60)
Conditioning Regimen	2 Gy TBI (n = 73) Flu + 2Gy TBI (n = 83)	2 Gy TBI	Flu + Bu + ATG	Cy/Flu	Flu/Cy	FLAG 2-Cda/AraC
CML in CP/Total, n	17/156	4/45	6/26	4/50	0/15	0/15
Graft Failure (%)	18 w/o Flu, rarely w/ Flu	20	0	2	0	0
Acute GvHD (Grade II – III) (%)	50	47	19	8 (I + II)	0	20 (I + II)
Acute GvHD (Grade IV) (%)	7	-	5	6 (III + IV)	6 (III + IV)	0
Chronic GvHD (%)	65	51	36	23	13	0 (n = 5)
Median Follow-up (days)	220	417	240	-	180	100
Progression free Survival (%)	50 (0.6 y)	-	81 (0.7 y)	55 (0.5 y)		13 (0.3 y)
Overall Survival (%)	62 (0.6 y)	67 (1.1 y)	85 (0.7 y)	75 (0.5 y)	50 (1 y)	40 (0.3 y)

The source of hematopoietic stem cells (peripheral blood vs. bone marrow derived) has no significant impact on the long-term outcome post allogeneic SCT (**Table 6**).

Table 6: Peripheral blood stem cells versus bone marrow for allografting.

	Ringden et al. (1999)[97]		Elmaagacli et al. (2002)[98]		Schmitz et al. (2002)[99]		Bensinger et al. (2001)[100]	
Study Design	Matched-pair Unrelated		Retrospective Unrelated		Randomized Related		Randomized Related	
CML, N	42 / 90		91 / 91		350		57 / 172	
	BM	PB	BM	PB	BM	PB	BM	PB
Days (median) until ANC > 0.5 X 10^9/L	20 *	16 *	22 *	17 *	15 *	12 *	21 *	16 *
TRM (%)	21 (1 y)	27 (1 y)	30 * (2.7 y)	5 * (2.7 y)	NS	NS	30 (2 J)	21 (2 J)
Acute GvHD (Grade II – IV) (%) (100 days)	20	30	43	41	39 *	52 *	57	64
Acute GvHD (Grade III– IV) (%) (100 days)	16	14	24 *	8 *	16 *	28 *	12	15
Chronic GvHD	85	59	81	83	53 *	74 *	35	46
Disease free Survival (%)	48 (1 y)	46 (1 y)	30 * (2.7 y)	64 * (2.7 y)	NS	NS	45 * (2 y)	65 * (2 y)
Overall Survival (%)	53 (1 y)	54 (1 y)	66 * (2.7 y)	94 * (2.7 y)	NS	NS	54 (2 y)	66 (2 y)

* $P<.05$; NS, not significant.

In younger patients ≤ 45 years the choice of conditioning (BuCy oder CyTBI) has no impact on survival of patients with CML (**Table 7**).

Table 7: Patient characteristics from four randomized trials[102-104, 117] and one metaanalysis[101] that correlated post transplant outcome with the conditioning regimens busulfan/cyclophosphamide (Bu/Cy) versus cyclophosphamide/TBI (Cy/TBI). Projected 10-year survival and disease-free survival as well as long-term side effects were equivalent except that an increased risk of cataracts were noted in the Cy/TBI group.

	Disease	Stage	N	% of Subjects with Longterm Follow-Up	Median Age (yr)	Time of Follow-Up (mos)
Blaise et al[117]	AML	CR1	101	100	32	23±11
Clift et al[102]	CML	CP	147	96.5	37	Minimum 12
Devergie et al[104]	CML	CP	120	98.3	36	42
Ringden et al[103]	CML/AML	CP/CR1	46/51	98.4	33	1-50
	CML/AML	Advanced	11/19			

CR, complete response; CP, chronic phase.

3.4.3 Dose-Intensive Therapy and Autologous Transplantation

High-dose therapy with autologous stem cell rescue may represent an alternative option for IFN- and imatinib-refractory patients lacking a suitable donor, or who are excluded from an allograft because of other reasons. Uncontrolled studies support its use (i.e., Carella et al.[105] Simonsson et al.[106]). In CML-Study IIIA and likewise in similar European trials high-dose treatment protocols have been randomly evaluated in IFN-resistant patients. As yet, due to brief observation periods no final conclusions can be drawn from those trials. So far, the procedure has become more simple and effective over the years by employing peripheral blood stem cell mobilization and in vivo purging.[105] At present, having at hands the highly effective drug imatinib, autologous transplantation remains an experimental

procedure and possible indications may be limited to salvage of patients who lack a suitable donor and have failed conventional drug therapy. The high economic burden of this procedure should be kept in mind, as well.

3.4.4 Evidence-Based Practice Guidelines of CML Treatment

On behalf of the American Society of Hematology an international expert panel examined the evidence for a variety of treatment options in chronic phase CML (i.e., chemotherapy, IFN, allogeneic SCT) and made a series of recommendations attributing the strongest evidence to results from randomized controlled trials that had survival as the main study endpoint.[56]

3.4.4.1 Medical Therapy

- Patients with a favorable risk profile being in early chronic phase should be treated with IFN or combined treatment of IFN with chemotherapy (i.e., HU, low-dose araC), which is associated with the highest likelihood of survival.
- Trials that reported the highest survival rates, had administered maximally tolerable doses of IFN targeting a WBC count in the range 2.000 – 4.000/µl, a platelet count exceeding 50.000/µl and absence of signs of toxicity (lower IFN doses proved also to be effective).[107]
- Currently available controlled trials do not give sufficient information on the optimal time frame of IFN therapy.
- Those patients who attain MCR or CCR under IFN therapy, have the greatest likelihood of prolonged survival.
- No evidence exists with regard to an upper age limit of IFN therapy.
- Based on data from controlled trials there is no evidence that IFN is effective in patients with advanced chronic phase.
- Patients who prefer conventional chemotherapy over IFN, should take HU rather than busulfan. HU compared to busulfan prolongs survival and is less toxic.

3.4.4.2 Allogeneic Stem Cell Transplantation

- If physicians and patients expect evidence for a survival advantage by allogeneic SCT on the basis of randomized, controlled trials, then such an evidence is not available.
- Allogeneic SCT is a viable treatment option, if the patient has a suitable HLA-matched donor and no comorbid disease exclusive to the procedure.
- On the basis of the available information a patient must be fully informed so that he understands chances and risks of the transplant procedure with regard to the potential long-term benefits, the mainly short-term risks of transplant-related complications and death.
- Allogeneic SCT should be ideally performed within the first two years after the diagnosis was made, in order to achieve the highest likelihood of survival.
- Younger patients benefit more likely from an allotransplant.
- Evidence obtained from observational studies indicates that IFN therapy does not diminish success rates of the subsequent allogeneic SCT (provided that IFN is discontinued at least 90 days prior to allogeneic SCT).[89]

Table 8 summarizes probabilities of survival based on treatment modality, risk status, and the time elapsed from time of diagnosis.

Table 8: Survival after allogeneic SCT or IFN-based therapy within low- intermediate- and high-risk groups.[53]

	Survival %		
	3-Year	**5-Year**	**10-Year**
Early Transplantation	55 – 75	50 – 75	50 – 65
IFN Therapy:			
Low Risk	95	75	40
Intermediate , High Risk	75 – 80	50	20

3.5 Study Questions

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The following questions are formulated based on the body of scientific knowledge and the capabilities of the CML-SG.

- **Question 1:** Does imatinib-based therapy cause higher rates of hematologic, cytogenetic and molecular response, prolonged survival or longer duration of the chronic phase than a IFN standard therapy?
  Reasoning: Imatinib is a novel compound which in phase I and II studies produced high rates of CHR and CCR with minimal toxicity, far superior than previously achieved with IFN-based therapy. 68% of imatinib-treated patients attained a CCR (preliminary results, phase III-study). However, long-term survival rates and adverse effects of imatinib are not available, as yet. Conversely, IFN-based therapy offers a 10-year survival probability of 72 – 82% among patients with CCR. The study therefore aims to examine whether the high hematologic and cytogenetic response rates obtained with an imatinib-based therapy will confer improved survival compared to conventional IFN standard therapy and whether such a survival advantage will be risk group dependent.

- **Question 2:** Are there any differences between imatinib "monotherapy" and combined treatment of imatinib+IFN and imatinib+araC, respectively, in terms of attaining hematologic, cytogenetic and molecular response rates, survival, or duration of chronic phase?
  Reasoning: *In vitro* data demonstrated synergism of combining imatinib with IFN or araC. It is hypothesized that by combining active drugs efficacy is enhanced and overall toxicity lessened.

- **Question 3:** Does allogeneic SCT offer a survival advantage in patients who failed imatinib-based therapy compared to alternative medical treatment options?
  Reasoning: So far, allogeneic SCT is the only curative treatment modality. However, limitations are the excessive transplant-related morbidity and -mortality. Intensified chemotherapy may be an alternative option, which has certainly less severe side effects. However, it remains to be determined, which of these therapies ultimately may offer the best chances of survival.

- **Question 4:** What conditioning, reduced-intensity- (minitransplants) or standard-dose preparative regimens are superior in terms of survival (mortality) and toxicity (morbidity)?
  Reasoning: Transplant-related mortality is substantially influenced by the intensity of the preparative regimen. Curtailing toxicity by reducing dose intensity without jeopardizing the antileukemic effect of conditioning and by the same token enhancing "graft versus leukemia" effect with donor lymphocytes are primary objectives of non-myeloablative SCT. This procedure is particularly useful in the high-risk group of patients older than 45 years of age.

3.6 Risk-Benefit Assessment

Imatinib in combination with IFN or araC is compared to imatinib as single agent and secondly, imatinib-based therapies to conventional IFN standard therapy in terms of differences in hematologic and cytogenetic responses and survival. Based on preliminary data, it appears likely - although needs to be determined with a clinical trial - that imatinib-based therapies are in effect superior in the first line treatment of chronic phase CML. Long-term survival probabilities and toxicities of imatinib are not known yet. Thus, assignments of patients into imatinib- and 'non-imatinib'-based treatment arms is ethically correct and justifiable. In addition, therapeutic strategies employing or

omitting allografting will be compared. But these investigations do not impose additional risks. Evaluating minitransplants (reduced-intensity conditioning) the benefit of reduced transplant-related toxicity and the risk of less proven efficacy are balanced.

4 Study Objectives

4.1 Primary Objectives

1. Imatinib-based vs. IFN-based therapy (hematologic, cytogenetic and molecular response, overall- , risk group dependent- , and progression free survival, time to progression), refer to study question 1.

2. Imatinib vs. imatinib/IFN vs. imatinib/low dose araC (hematologic, cytogenetic and molecular response, overall- , risk group dependent- , and progression free survival, time to progression), refer to study question 2.

3. Allografting vs. imatinib-based therapy in patients eligible for allogeneic SCT, refer to study question 3.

4. Standard vs. reduced-intensity conditioning in patients older than 45 years of age, refer to study question 4.

4.2 Secondary Objectives

1. Time to first appearance and duration of hematologic, cytogenetic and molecular responses.
2. Association of these variables with survival.
3. Comparison of short- and long-term adverse effects of imatinib and IFN therapies.
4. Analysis of differences in the presentation, duration and responses to therapy of accelerated and blastic phases among the four treatment arms.
5. Analysis of survival of high-risk patients after early allografting.
6. Hematologic, cytogenetic and molecular responses to imatinib after IFN failure.
7. Validation of the New CML Score or development of a new prognostic score adapted and validated for imatinib-based therapies.
8. Retrospective analysis of the significance of WBC counts for duration of chronic phase and prolongation of survival during the course of treatment.
9. Novel drug therapies in relapsing or refractory patients.
10. Analysis of risk-adapted treatment strategies (e.g. imatinib + chemotherapy, intensive chemotherapy, autografting) after imatinib failure (protocol amendments to follow).
11. Analysis of outcome post allotransplant in dependence of therapy received prior to transplant.
12. Comparison of outcomes of patients who attained CCR with different treatments.

5 Investigational Plan

5.1 Study Design

CML-Study IV is a randomized controlled trial designed for optimizing treatment in CML. Study scheme is as follows:

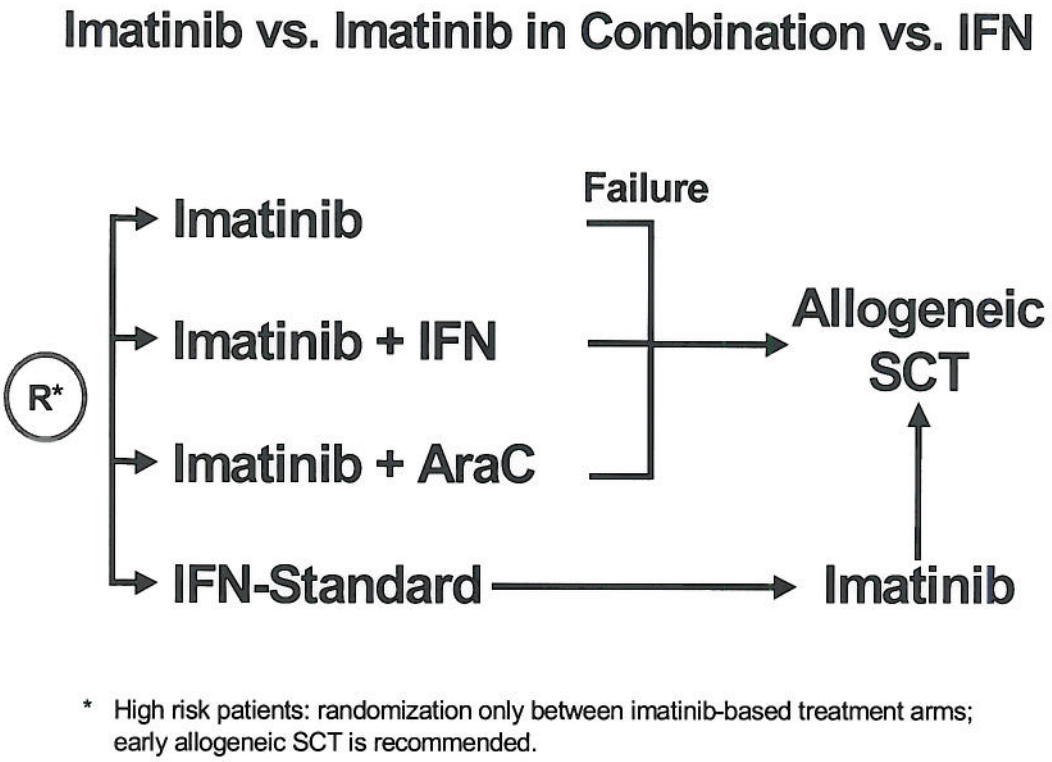

Figure 4: Study scheme – Randomization into 4 treatment arms, refer to primary objectives 1 and 2.

For patients who failed imatinib therapy and are considered for allogeneic SCT the scheme is outlined as follows:

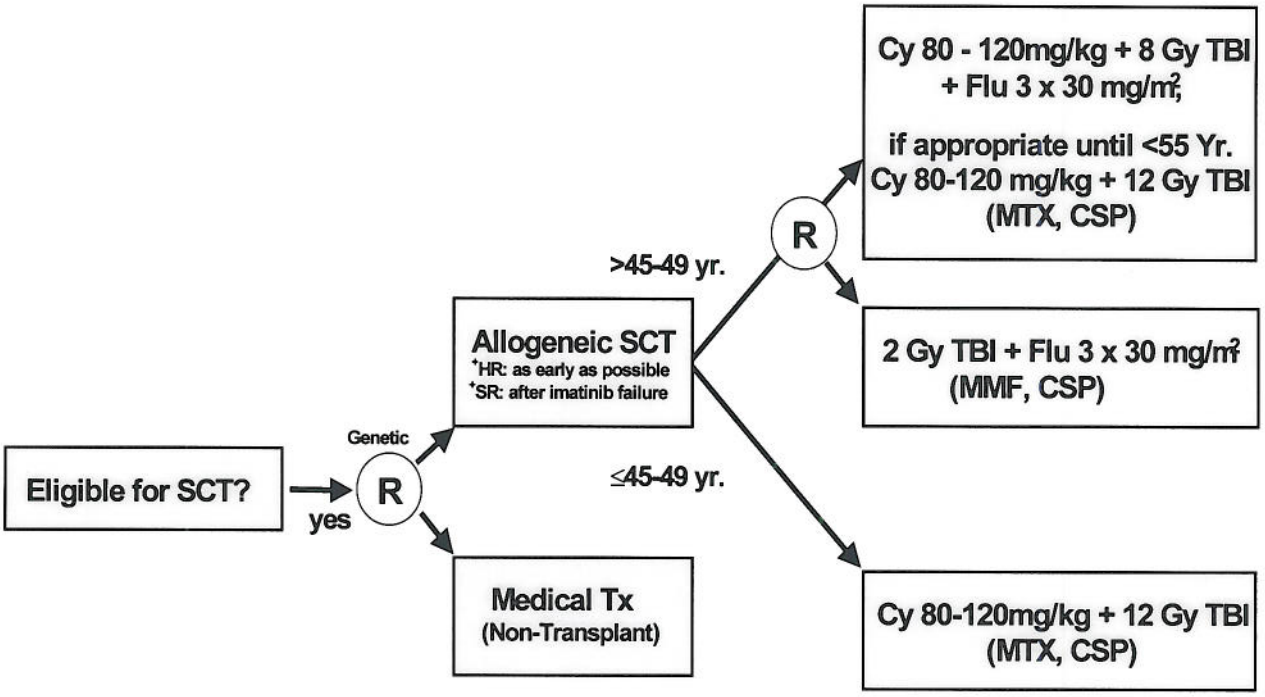

Figure 4: Study scheme – Role of allografting after imatinib failure, refer to primary objectives 3 and 4.

5.2 Recruitment Period, Sample Size

Patients are recruited over 4, if necessary 5 years, and followed-up after the last enrollment at a minimum over 5 years. Overall, 1600 patients are to be recruited. Based on previous experience it is projected that 350 – 400 patients are possibly recruited per year. Patients suitable for an allogeneic SCT are included into the calculation. Assuming that 20-30% of all randomized patients will eventually undergo an allotransplant and assuming further that 5% are high-risk patients not eligible for SCT then 400 subjects per arm should be randomized, annually. The initial randomization procedure is balanced and stratifies by participating centers. Subjects will be recruited and randomized regardless if an allogeneic SCT is considered later on. Patients do not decide at the time of randomization if they should undergo allogeneic SCT at any time in the future. But physicians should seek to determine whether patients would be suitable and willing to give consent for an allotransplant.

6 Participating Investigators/Institutions

Participating investigators and institutions constitute the CML Study Group (CML-SG), see list in appendix 6. The CML-SG has demonstrated to be qualified and highly experienced in conducting large scale, multicenter trials. Each investigating institution has agreed in advance to participate and to comply with the study protocol. By exception, the agreement of participation may be sent successively.

7 Study Population

7.1 Inclusion Criteria

- Newly diagnosed BCR-ABL-positive CML in chronic phase.
- Pretreatment with HU or anagrelide is permitted.
- No age limit.
- Informed consent.

7.2 Exclusion Criteria

- Pretreatment with IFN or chemotherapy other than HU or anagrelide.
- Second malignancy, if treatment is required and the estimated life expectancy is shorter than the median survival of CML.
- Other serious illness, pregnancy including lactation period or other conditions which could prevent the required protocol compliance.
- Participation with another clinical trial
- No informed consent.

8 Enrollment

8.1 Randomization

All newly diagnosed BCR-ABL-positive CML patients in chronic phase will be randomized. Low- and intermediate-risk patients, (New CML Score [**www.pharmacoepi.de**]), will be randomized into one of four treatment arms, imatinib vs. imatinib + IFN vs. imatinib + low-dose AraC vs. IFN standard therapy. High-risk patients will only be randomized into one of the three imatinib-based treatment arms, as IFN has not been shown to prolong survival in this group of patients even if CCR is achieved. These patients are candidates for early allografting.

If the study inclusion criteria are met, the patient is randomized at the Study Coordinating Office by telephone (**+49-621-383-4168**) utilizing a web-based randomization program which stratifies according to the New CML Score.

All patients will be randomized regardless if an allotransplant is planned later on. The patient does not need to decide at the time of randomization, whether an allotransplant should be pursued. However, it is crucial to clarify whether the patient would be willing to give consent for the procedure in order to initiate donor search as soon as possible. In general, patients are eligible for transplantation if they are younger than 70 years of age without major comorbid illness or other obvious reasons exclusive for an allotransplant. Candidates eligible transplantation will be genetically randomized into 'non-transplant, medical therapy' and allografting according to availability of a donor. A search for related HLA-compatible donor is mandatory in all cases and should be initiated at time of diagnosis.

Low- and intermediate-risk patients are referred for allografting only after they have failed imatinib-based therapy. Patients randomized for IFN-based therapy are switched to imatinib first in case of IFN failure. In the age group above 45 years of age transplantable patients will be randomized into standard- or reduced-intensity conditioning in an attempt to decrease TRM.

9 Treatment Plan

9.1 Non-Transplant Therapy

9.1.1 Hydroxyurea

All patients randomized into the IFN standard arm should initially receive cytoreductive therapy with HU (40 mg/kg/day). In the imatinib-based treatment arms initial cytoreduction with HU is optional, preferably to avoid leukostasis. If done, HU should be discontinued if WBC count is less than 50.000/µl because of possible drug antagonism between imatinib and HU. Patients in the standard arm should initiate IFN if the WBC count is in the range of 10.- 20.000/µl. During cytoreduction, oral administration of allopurinol 300 mg once daily or urinary alkalinization, e.g., uralyt U or sodium bicarbonate, are mandatory measures for prevention of tumor lysis.

9.1.2 Imatinib

9.1.2.1 Imatinib-Monotherapy

Imatinib is administered once daily at a dose of 400 mg. Preferably, the drug should be administered with food as single dose while the patient is in a sitting position. The use of grapefruit juice as diluent is discouraged. It is suggested to check CBC counts during the lead-in time at least twice weekly. If the patient fails to attain CHR within the first **2 months** or MCR after **6 months** imatinib is escalated up to a daily dose of 600 mg. Disease progression should be carefully ruled out by bone marrow examination and cytogenetics. These diagnostic steps should be meticulously documented. The concomitant administration of HU should be avoided by all means except for the initial phase of cytoreduction. If no MCR is achieved after **12 months** of imatinib therapy an HLA-matched allogeneic SCT should be considered. For patients not suitable for an allotransplant options of risk-adapted therapies will be suggested, a protocol amendment is to follow.

If the patient experiences intolerance to imatinib then the single daily dose of 400 mg imatinib can be split into two doses administered twice daily at doses of 200 mg.The most frequent side effects to imatinib are nausea, vomiting, diarrhea, muscle cramps and peripheral edema, preferentially at eye lids. These side effects rarely exceed WHO grade II. In previous trials, only 1% of patients in chronic phase experienced toxicity to imatinib that resulted in discontinuation of the drug. Muscle cramps may recede with oral magnesium, edemas with small doses of diuretics. Exanthema occurs in approximately 10% of patients which responds well to topical steroids. Anemia is commonly observed and reversible. WHO grades III and IV neutropenia and/or thrombocytopenia occur rarely in chronic phase but frequently in advanced stages of the disease. Severe hematologic toxicity, in general, reflects poor bone marrow reserve of BCR-

ABL negative precursors rather than toxicity to hematopoietic progenitor cells. Therefore, overall bone marrow cellularity should be taken into account when assessing the capacity of the marrow to regenerate and if dose reductions of imatinib may be indicated.

Except for cases of bone marrow aplasia (cellularity less than 10%) dose reduction below 300 mg should be avoided by all means because the drug's efficacy may be jeopardized. Imatinib is withheld when WBC and platelet counts drop below 1 x 10^9 and 50 x 10^9/L, respectively. Imatinib is resumed at the same dose when WBC and platelet counts rise to more than 1.5 x 10^9 and 75 x 10^9/L. However, imatinib should be reduced to 300 mg when after re-challenge severe cytopenias ensue. Severe hepatic toxicity reportedly occurs with a frequency of 1.1 – 3.5%, which has lead to permanent discontinuation of imatinib in less than 0.5% of cases. During the initial phase of imatinib therapy liver function tests should be checked monthly and even more closely in patients with a history of liver dysfunction. Imatinib should be discontinued if bilirubin rises to more than threefold or the transaminases to more than fivefold of the upper limit of normal. If bilirubin drops below 1.5-fold and the transaminases below 2.5-fold of upper limit of normal, imatinib can be resumed after the dose has been reduced from 400 to 300 and from 600 to 400 mg, respectively. The use of G-CSF is recommended in neutropenic patients with infections or in asymptomatic patients with persistent neutropenia.

Inhibitors of the cytochrome P-450-isoenzyme (CYPA4) - ketoconazole, itraconazole, erythromycin, clarithromycin – cause decreased metabolization and increased plasma concentration of imatinib. Conversely, inducers of this family of enzymes (i.e., dexamethason, phenytoin, carbamazepine, rifampicin, phenobarbital) cause increased metabolization and decreased plasma concentration. Furthermore, imatinib leads to increased plasma concentrations of HMG CoA reductase inhibitors, cyclosporine, triazole benzodiazepines and calcium antagonists of the dihydropyridin-type. Women in the childbearing age should use a form of contraception. Insufficient data concerning long-term adverse effects (e.g., renal- and hepatic- immune suppression) are available at present. Women should be discouraged to fall pregnant. Since the year 2001 imatinib is approved for the therapy of IFN-refractory and –intolerant CML in Germany and Switzerland. There is no upper age limit, (for further drug information, refer to appendix 8).

Imatinib-failure

In patients who fail imatinib (i.e., insufficient control of underlying disease or emergence of resistence) an allogeneic SCT should be pursued according to availability of a donor and patient's status. In those who are not eligible for allografting alternative treatment options are conventional chemotherapy with HU/araC or high-dose chemotherapy with autologous stem cell rescue.

Definition of imatinib failure:

- No complete hematologic response within 3 months.
- No sufficient cytogenetic response (no minor response, 35-94% Ph+) within 6 months with concomitant cytopenias that exclude imatinib dose escalation of imatinib to 600 mg daily at the 2 and 6 months of imatinib therapy checkpoints.
- No major cytogenetic response within 12 months (no 1-34% Ph+ cells) .
- Loss of complete hematologic or of any previously attained cytogenetic response.

- Rise of BCR/ABL transcript levels by at least one log in previously complete cytogenetic responders.

Patients randomized to the IFN standard arm will be switched to imatinib in the event of IFN failure (IFN resistence or IFN intolerance). Thereafter, criteria of imatinib failure are applied.

9.1.2.2 Imatinib + Interferon alpha

Imatinib is dosed and administered as described above. The addition of IFN should be commenced not earlier than 3 months after initiation of imatinib-therapy. IFN should be started with a dose of 1.5 – 3 mio IU as a flat dose thrice weekly and gradually escalated thereafter. Recommendations with respect to the target dose of IFN will be made as soon as the final results of the phase I studies will be available. Ideally, imatinib should be given at a dose of 400 mg/ day and IFN should be adjusted to reach a maximally tolerated dose with a WBC count ranging between 2 - 4 x 10^9 /L. WBC and platelet counts should never be allowed to drop below 1 x 10^9 and 50 x 10^9 /L, respectively.

If ANC is less than 1 x 10^9 and/or platelets are less than 100 x 10^9 /L IFN dose should be cut in half and withheld if cell numbers are less than 0.5 x 10^9 and/or 50 x 10^9 /L, respectively. If liver function tests are elevated (transaminases 2.5-fold and/or bilirubin 1.5-fold of upper limit of normal) then at first, IFN and later imatinib are withheld, the latter, if transaminases are 5-fold and/or bilirubin 3-fold of upper limit of normal increased). Imatinib can be resumed at a lower dose (400 to 300 mg and 600 to 400 mg, respectively), if transaminases are less than 2.5-fold and/or bilirubin less than 1.5-fold of upper limit of normal). In the event of psychiatric complaints (i.e., confusion , depression) IFN should be withheld first. Severe toxicity precludes further therapy. Then both drugs should be withheld immediately and resumed at first with imatinib as single agent, if symptoms have resolved.

9.1.2.3 Imatinib + Low-Dose AraC

Imatinib is dosed and administered as described above. The addition of low-dose araC (arabinosylcytosin, Alexan®) should be commenced not earlier than 3 months after the start of imatinib-therapy. AraC should be started as a daily flat dose of 10 mg s.c. daily given up to a maximum dose of 2 x five days per month. AraC can be escalated thereafter up to 20 mg/m^2 given intermittently at up to 10 days per month. The use of the oral araC (YNK01) may be permitted in the future pending the results of ongoing studies (separate protocol amendment is to follow). Recommendations with respect to the target dose of araC will be made as soon as the final results of the phase I studies will be available. AraC should be cut in half if ANC and platelet counts drop below 1 x 10^9 and 100 x 10^9 /L and discontinued below 0.5 x 10^9 and 50 x 10^9 /L, respectively.

Both drugs may cause gastrointestinal toxicity. At first araC and later, if symptoms do not cease, imatinib is withheld. Imatinib can be resumed at a lower dose (e.g., 400 to 300 mg and 600 to 400 mg, respectively), dependent upon resolution of toxicity. Severe toxicity precludes further therapy. Then both drugs should be withheld immediately and resumed at first with imatinib as single agent, if symptoms have resolved.

9.1.3 Interferon Standard Therapy

9.1.3.1 Management

After initial cytoreduction with HU (40mg/kg/day) IFN therapy (Roferon® or Intron A®) is administered initially with a daily flat dose of 3 x 10^6 IU s.c. and gradually escalated thereafter. IFN should be given with or without HU to achieve a target WBC count in the range of 2 - 4 x 10^9 /L. In the absence of CHR **after 3 months** of therapy low-dose araC can be added to the IFN/HU combination and dosed either with 20 mg/m^2 s.c. given at 10 – 15 days/month or as a 10 mg daily flat dose. AraC should be on hold if platelets drop below 100 x 10^9 /L. Conversely, araC can be escalated up to the maximum dose of 40 mg/m^2 administered at 15 days/month in the absence of a sufficient hematologic response. If side effects are encountered, in doubt we recommend to discontinue araC first from the three- drug combination.

If patients attain CHR within 3 months or MCR within 9 to 12 months under IFN-based therapy, this is highly predictive for ultimately attaining CCR. 10-year survival probability of low-risk patients is approximately 40%, of those with CCR as best response, 80%. Thus, IFN therapy should be continued in good responders. AraC should be discontinued, if two subsequent cytogenetic analyses document a durable CCR.

9.1.3.2 Interferon-Failure (Resistance or Intolerance)

In the event of IFN failure (intolerance or resistance) patients are crossed over to the imatinib treatment arm. IFN resistance is defined with absent CHR after 6 months or absent MCR (no 1-34% Ph+ cells) after 21 months of IFN therapy. Prior to the planned crossover to imatinib these cases should be carefully reviewed with members of the Steering Committee or the Study Coordinating Office. A detailed documentation of the reasons for the crossover is warranted. IFN intolerance is difficult to define and entirely relies on the personal judgement of the treating physician and patient. Patients, who experience severe symptoms of IFN intolerance (WHO grades III and IV), are switched over to imatinib therapy. Also for this case crossover needs to be discussed with members of the Steering Committee or the Study Coordinating Office. A detailed documentation should be provided. In order to make valid conclusions of study results stringent adherence of assigned patients to the IFN standard arm is of utmost importance. In addition, quality assurance measures will be taken to monitor compliance in a blinded manner with respect to investigators and quality of documentation within the IFN standard arm. Physicians are encouraged to discuss challenging management problems with members of the Study Coordinating Center.

Definition of IFN Failure:

- No complete hematologic response within 6 months.
- No major cytogenetic response within 21 months (>34% Ph+ cells).
- Loss of complete hematologic response or loss of any cytogenetic response.
- IFN intolerance as defined by any sustained severe IFN related toxicity (WHO-grade (II) III or IV).

In case of IFN resistance or -intolerance patients may crossover to receive imatinib. Prior to the crossover these cases are carefully reviewed by members of the Steering Committee or the Study Coordinating Office. Patients who develop resistance to imatinib should be considered for allogeneic SCT.

9.1.3.3 How To Proceed in case of Interferon- and Imatinib Failure

In patients who fail imatinib (i.e., insufficient control of underlying disease or emergence of resistance) an allogeneic SCT should be pursued according to availability of a donor (related or unrelated) and patient's status. In those who are not eligible for allografting alternative treatment options are conventional chemotherapy with HU/araC, high-dose chemotherapy with autologous stem cell rescue followed by IFN- or imatinib-based therapy.

9.1.3.4 Choice of Interferon Drug Formulation

Each investigating center should choose and then keep to one of the available IFN brand names (e.g., Roferon® , Intron A®). Pegylated IFNs may be used as soon as they are approved. A protocol amendment will then follow.

9.1.3.5 IFN Adverse Effects

Adverse effects are more likely encountered with IFN than HU or busulfan,[62] whereby fatalities occur very rarely and are unheard of in the usual dose range of IFN. The quality of life is clearly compromised in a number of patients. Table 9 summarizes frequencies of main side effects of IFN according to WHO Common Toxicity Criteria. Patients often experience flu-like symptoms, particularly within the first weeks of treatment. In this period patients should be encouraged to adhere to IFN. These flu-like symptoms (i.e., fever, chills, headache, fatigue, aching, back pain, loss of appetite, dry mouth) are ameliorated with 1 g of paracetamol p.o. or p.r. when administered one hour prior to IFN intake (maximum recommended dose 3 x 1g paracetamol daily, if used with imatinib/IFN combination 1g daily).

Reduce IFN dose by 50% in the event of one of the following adverse effects:

- Deterioration of overall well being (drop of performance scale index of more than 20%, significant weight loss, fever).
- Neurologic toxicity (e.g., depression, parkinsonian syndrome, loss of memory, delirium)
- Newly developed cardiac arrhythmias.
- Rise of ASAT- or ALAT above 100 U/L.
- Rise of creatinine above 1,7 mg/dL (150 mmol/L).
- Platelets less than 50 x 10^9/L.

Table 9: Rates of IFN adverse effects in CML-Study I, n = 133

			1	3	6	12	18	24	30	36	42	48
			Months after randomization									
Number of Patients Treated		127	127	102	76	46	46	36	29	26	21	17
	WHO-Grade	**Number of pts with AE (%)**	**Number of patients with AEs in corresponding Time Interval**									
Flu-like Syndrome	1	15 (12)	16	16	17	5	11	4	3	7	6	
	2	43 (34)	45	23	8	12	5	7	5	1	2	2
	3	40 (31)	27	7	6	4	3	3	1	4	1	1
	4	10 (8)	3	1	1	1		2		1		
Total		**108 (85)**	**91**	**47**	**32**	**22**	**19**	**16**	**9**	**13**	**9**	**3**
Gastrointestinal	1	22 (17)	14	14	10	6	8	4	5	1	1	
	2	29 (23)	21	7	7	3	1	1	2	2	1	
	3	17 (13)	10	3	2	2	1				2	1
	4	3 (2)	1	1						1		
Total		**71 (56)**	**46**	**25**	**19**	**11**	**10**	**5**	**7**	**4**	**4**	**1**
Dermatologic	1	22 (17)	10	13	8	6	4	1		1		
	2	31 (24)	11	14	12	1	1	2	1	1	2	2
	3	6 (5)		3	2			1				
	4	2 (2)				1			1			
Total		**61 (48)**	**21**	**30**	**22**	**8**	**5**	**4**	**2**	**2**	**2**	**2**
Neuro-/psychiatric	1	17 (13)	11	13	8	5	4	2	2	2	1	3
	2	22 (17)	9	11	6	5	2	1		2	1	
	3	10 (8)	1	2	3	3	1	2		1		
	4	5 (4)	4		1			1	1			
Total		**54 (43)**	**25**	**26**	**18**	**13**	**7**	**6**	**3**	**5**	**2**	**3**
Other**	1	34 (27)	11	10	8	1	8	1		2	2	2
	2	21 (17)	8	4	4	1	4	3	3	1	1	
	3	23 (18)	8	5	3	3	1	2		1		
	4	4 (3)	2	1							1	1
Total		**82 (65)**	**29**	**20**	**15**	**5**	**13**	**6**	**3**	**4**	**4**	**3**

* 33 Flu-like, 1 gastrointestinal, 6 dermatologic, 10 neuro-/psych., 25 other AEs had been present prior to initiation of treatment (baseline), ** abnormal lab values, local symptoms, cardiac-related.

Intolerable side effects which lead to permanent withdrawal of IFN therapy, are mainly neurological (i.e., psychosis) and cardiovascular (i.e., arrhythmias). The remainder of side effects are managed with temporary dose reduction followed by renewed dose escalation up to maximally tolerated dose. Supportive measures, in particular psychological support, are a mainstay of proper management. Facing a deadly disease and the potential impact of IFN therapy, patients should be encouraged to accept mild toxicity. If more severe adverse effects persist, further dose reductions by 50% are justified. In case of WHO grade III or IV adverse effects IFN should be discontinued until symptoms have resolved and then restarted at half of the previous dose. If adverse effects recur IFN is discontinued until symptoms are resolved and then restarted at the 25% intensity of the initial dose. In cases of relentless severe adverse effects IFN is discontinued permanently.

9.2 Stem Cell Harvest

Stem cell harvest is optional in all suitable patients and it is best done after patients have attained MCR or CCR. The rationale is to rescue patients with high-dose therapy in an event of relapse. Sufficient numbers of stem cells can be collected with G-CSF at a dose of 10 µg/kg/day administered over five days.

9.3 Allogeneic Stem Cell Transplantation

9.3.1 When Should Allogeneic SCT Be Done?

In patients with standard risk (i.e., low- and intermediate-risk) allogeneic SCT is performed after imatinib failure (refer to 9.1.2.1) provided a suitable donor (related or unrelated) is available according to genetic randomization.

High-risk patients or subjects younger than 20 years of age should be transplanted as early as possible. In older patients reduced-intensity- vs. standard conditioning will be evaluated.

9.3.2 Conditioning

Patients 45 years of age or younger should receive standard conditioning with 12 Gy fractionated TBI (2x/day over 3 days) followed by cyclophosphamide at a total dose of 80 - 120 mg/kg.[102] By exception, due to logistical reasons, cyclophosphamide may precede TBI. High-dose busulfan at a dose of 16mg/kg can replace TBI if not available.[97;102;108] The role of ATG will be evaluated by a separate protocol.

Patients 46 years of age or older (50 years or older for biologically young and healthy subjects) undergoing an allotransplant are randomized to receive a reduced-intensity conditioning regimen with 2 Gy fractionated TBI + fludarabine 3 x 30 mg/m^2 and GvHD prophylaxis with mycophenolate and cyclosporine (CSP) according to the protocol of Mc Sweeney et al., *Blood* 2001 vs. an age-adapted standard conditioning regimen with 8 Gy fractionated TBI + cyclophosphamide 2 x 40 - 60 mg/kg, fludarabine 3 x 30 mg/m^2 and GVHD-prophylaxis with MTX and CSP (Munich protocol, for detailed scheme see appendix 9). Patients up to the age of 54 may receive 12 Gy TBI + CY 80 – 120 mg/kg as preparative regimen. A reduced-intensity conditioning regimen with fludarabine 6 x 30mg/m^2/day plus busulfan 4 mg/kg/day x 2 plus CSP as GvHD-prophylaxis is an alternative if TBI is not available.

Since non-myeloablative SCT is still considered experimental, a "Safety Monitoring Board" will carefully review transplant results of all treated patients beyond the age of 46 years.

9.3.3 Patients Lacking a Donor

Patients lacking a suitable donor should be treated with conventional (non-transplant) therapy, refer to 9.1.3.3. Therapeutic options are conventional chemotherapy with HU/araC, high-dose chemotherapy with autologous stem cell rescue followed by IFN- or imatinib-based therapy, or HU/araC.

9.3.4 Management Issues in Preparation For an Allogeneic Stem Cell Transplant

The following issues should be appropriately taken into consideration:

- In patients suitable for allogeneic SCT HLA-typing and donor search should be initiated at the time of diagnosis (as done in the CML-Study III and IIIA). Donor search may be expanded under certain indications in the wider family. If unsuccessful, a donor search within the unrelated donor pool should be done (please obtain insurance coverage for the planned procedure). In 50-60% of the cases an allele typed HLA-identical unrelated donor can be identified.

- Until recently, current practice was to proceed to transplant after diagnosis as early as possible. But this strategy may be ill-founded in patients receiving IFN or imatinib-based therapies. The only data available stem from retrospective analyses of patients, who had received HU or busulfan as pretransplant therapy. Analyses by individual risk groups are lacking.

- The New CML Score[53] was designed and validated by analyzing IFN-treated patients. Standard risk patients probably do not benefit from early allogeneic SCT. Conversely, high-risk patients seem not to benefit from IFN therapy even if they achieve cytogenetic response. It remains to be determined for how long low-risk IFN-treated patients provided they attained a durable cytogenetic response may defer allogeneic SCT without compromising outcome . However, it is evident that high-risk patients should proceed to allogeneic SCT as soon as possible.

- Patients, who are appropriate candidates for an allograft should be fully informed about the procedure itself, donor-related issues, post-transplant care and possible complications. To reiterate, allogeneic SCT is indicated for standard risk patients after imatinib failure, for high-risk patients or subjects with very low transplantation risk like those younger than 20 years of age as soon as possible after diagnosis. High-risk patients probably do not benefit from IFN therapy even if they achieve CCR. If allogeneic SCT is carried out within the next 3 months, the patients should only be treated with HU. In patients transplanted at a later time, IFN therapy should be discontinued at least 3 months prior to the planned SCT. So far, only little can be said whether pretreatment with imatinib influences outcome post allotransplant. Transplant centers take responsibility for cryoconserving marrow or peripheral blood stem cells as a back-up. In patients, who lack an HLA-identical related donor, stem cells can be obtained at the time of diagnosis to serve as rescue after an allogeneic or autologous transplantation later on.

Contact persons (members of the Study Steering Committee) for issues on allogeneic SCT:

Prof. Dr. H.-J. Kolb
III. Medizinische Klinik
Klinikum Großhadern der LMU München
Tel: 089/7095-4241
Fax: 089/7095-4242

Prof. Dr. A. Gratwohl
Kantonsspital Basel
Abteilung für Hämatologie
Tel.: +41/61/265-2525
Fax: +41/61/265-4450

9.4 Compliance

Quality control is paramount and will be monitored closely. At certain time points compliance (i.e., adherence to the study protocol) will be checked at the level of the investigating centers and the coordinating center. In a specially designed "patient passport" (appendix 7) salient lab data and treatment changes will be recorded. This should facilitate monitoring. Interim analyses will be provided frequently. Herein protocol violations or any changes significantly affecting the conduct of the trial, updated rates of accrual and study drop-outs will be reported.

10 Clinical Assessment

10.1 Initial Investigations (CRF 1)

- Medical history (symptoms, comorbid illnesses, performance status).
- Physical examination: spleen size measured in cm below costal margin and by ultrasound, liver span in cm at MCL, extramedullary disease (lymph nodes, skin), height, weight.
- CBC + differential, reticulocytes, LDH, ALT/GPT, AST/GOT, bilirubin, alkaline phosphatase, creatinine, electrolytes, urinanalysis.
- ECG.
- Cytogenetics: chromosomal analysis (banding) for detection of Ph chromosome.
- Molecular genetics with multiplex-PCR for typing of dominant BCR-ABL-transcript and for detection of BCR-ABL-transcripts.[109-111] Detection of 9q+ deletions
- Bone marrow aspirate.
- Bone marrow biopsy.
- 30 ml EDTA-peripheral blood to be sent to Study Coordinating Center (tissue- and serum archive).
- Documentation of randomized treatment arm and date of randomization.
- Patient consent.

In subjects eligible for allogeneic SCT:

- HLA – typing.
- Number of sibling, gender, HLA-typing

10.2 Follow-up Investigations (CRF 2-6)

10.2.1 Every 3 Months (CRF2)

- Current medical condition and physical examination (assessment of extramedullary disease, spleen size, liver span, current weight).
- CBC + differential for assessing hematologic response, reticulocytes.
- Creatinine, ALT/GPT, AST/GOT, bilirubin, alkaline phosphatase, electrolytes, LDH, urinalysis.
- ECG.
- Drug doses administered (patient passport, appendix 7) and tolerance.
- Adverse effects: record symptoms, severity grade (WHO), relationship to therapy administered.

10.2.2 After 3 and 6 Months Since Diagnosis, Then Every 6 Months (CRF2)

For assessing efficacy of treatment and the individual risk of the patient it is crucial that appropriate bone marrow-, cytogenetic- and molecular investigations are performed at certain timepoints. Investigations at 3, 6, 12, 15, 18 and 21 months are mandatory, thereafter optional dependent on the clinical situation. It should be noted that expected rates of CCR are beyond 50%. For those, qualitative and quantitative PCR are effective diagnostic tools for disease monitoring. It is expected that subtle differences of efficacy between treatment arms are detectable solely by molecular techniques. Peripheral blood samples are sufficient.

10.2.3 Every 12 Months

Bone marrow biopsy (at the same time obtain bone marrow aspirate for cytology, cytogenetics, and molecular studies).

10.2.4 Additional Follow-up Investigations (CRF 3-6)

- After attaining CHR or CCR, unless covered by regular assessment schedule (additional CRF 2).
- Switch of randomized therapy (CRF 3).
- Resistance to therapy/blast crisis: immunophenotyping of blastic cells (CRF 5) and entire follow up assessment (CRF 2).
- At time of allogeneic SCT: assessment to be completed by the transplant center (CRF 4).
- After relapse post transplantation choice of therapy is free, follow up assessment at 6-month intervals.
- Ph- and BCR-ABL-negativity by PCR post transplant: follow up assessment at 6-month intervals, by year 3 post transplant at 12-month intervals, for monitoring quantitative PCR may replace cytogenetics.
- Demise or withdrawal from study: documentation of cause of death, reason for drop-out (CRF 6 and CRF 2).
- Safety examination for subjects withdrawing from study: follow up assessment (CRF 2).

10.3 Optional "Bolt-on" Scientific Studies

Participating in scientific "bolt on" studies is optional but greatly appreciated. You may receive more detailed information on those studies from the principal investigators themselves (appendix 11).

11 Diagnostics/ Sample Retrieval and Shipment

11.1 Bone Marrow Aspirate

Approximately 10 bone marrow smears are prepared and stained according to May-Grünwald-Giemsa technique within 24 hours. For quality control purposes additional unstained smears should be available. The report should be based on assessment of at least 200 enumerated marrow nucleated cells.

11.2 Cytogenetics

Cytogenetic analysis is usually performed from **bone marrow**. Samples are examined centrally at designated reference laboratories, Prof. Dr. Schlegelberger in Hannover, Dr. Schoch in Munich, and Professor Dr. Jotterand in Lausanne (for the SAAK). In exceptional cases cytogenetic analysis may be done on site if satisfactory quality can be assured. For karyotyping a minimum of 25 metaphases should be examined. The cytogenetic samples are archived in order to be available for review by an expert panel, if

requested. A copy of the cytogenetic report should be sent to the treating physician and the Study Coordinating Center.

Retrieval of bone marrow: aspirate 2-4 ml of into a sterile heparinized tube (approx. 2000 IU Heparin additive, no EDTA anticoagulant). Cytogenetic analysis can be performed from the peripheral blood, if at least 10% myeloid precursors in the differential are present (myelocytes, promyelocytes, blasts) and WBC count exceeds 10 x 10^9/L.

Retrieval of peripheral blood: 10 ml of blood from a peripheral vein into a sterile heparinized tube (approx. 2000 IU Heparin additive, no EDTA anticoagulant).

Shipment: pack the blood or marrow sample in a **sterile** shatterproof container and send it via overnight express mail to the cytogentic laboratory (sample retrieval form, see appendix 10).

Important: please obtain samples for cytogenetic analysis preferably monday to wednesday.

Prof. Dr. B. Schlegelberger
Medizinische Hochschule Hannover
Institut für Zell- und Molekularpathologie
Carl Neuberg-Str. 1
30623 Hannover
Tel.: 0511 532 4522
Fax: 0511 532 4521
E-Mail: schlegelberger.brigitte@mh-hannover.de

Dr. C. Schoch
Medizinische Klinik III
Labor für spezielle Leukämie-Diagnostik
Klinikum Großhadern
Marchioninistr. 15
81377 München
Tel.: 089-7095-4977
Fax: 089-7095-4978
E-Mail: claudia.schoch@med3.med.uni-muenchen.de

Prof. Dr. M. Jotterand
Division of Medical Genetics, CHUV
CH-1011 Lausanne
Tel.: +41/21-314-3387/3383
Fax: +41/21-314-3444
E-Mail: Martine.Jotterand@chuv.hospvd.ch

11.3 Molecular Genetics

Multiplex PCR will be performed for screening and typing of BCR-ABL transcripts at diagnosis. Thereafter, for follow up assessments quantitative PCR will be performed on marrow samples in conjunction with cytogenetics. A minimum of 1 – 5 x 10^7 cells are sufficient. Samples may be drawn from peripheral vein (EDTA or heparinized blood 20-30 ml) and/or bone marrow (citrate additive). For shipment please always use overnight express mail.

For monitoring of BCR-ABL positive patients please send samples, 20ml of EDTA-peripheral blood and bone marrow to Priv. Doz. Dr. Hochhaus/Priv. Doz. Dr. A. Reiter, Mannheim for pretherapeutic diagnostics and then every 3 months, from year 3 on every 6 months. Unused material will be archived.

Priv.-Doz. Dr. A. Hochhaus / Priv.-Doz. Dr. A. Reiter
III. Medizinische Universitätsklinik
Klinikum Mannheim
Wiesbadener Str. 7-11
68305 Mannheim
Tel.: 0621/383-4232
Fax: 0621/383-4201
E-Mail: andreas.hochhaus@med3.ma.uni-heidelberg.de; andreas.reiter@med3.ma.uni-heidelberg.de

11.4 Bone Marrow Biopsy

All the bone marrow biopsies should be sent to the reference pathologist Prof. Dr. H. Kreipe, Hannover, for review. If biopsies are examined elsewhere, the Study Coordinating Center should be informed, which will help to arrange that additional cuts of the cell block are sent to the reference pathologist.

Prof. Dr. H. Kreipe
Institut für Pathologie
Med. Hochschule Hannover
Carl-Neuberg-Str. 1
30601 Hannover
Tel.: (0511) 532-4500
Fax: (0511) 532-5799
E-Mail: kreipe.hans@mh-hannover.de

12 Duration of the Study

12.1 End of Planned Follow-up

Subjects are followed up until termination of the trial or demise.

12.2 Premature Termination of the Trial

A number of reasons are specified that may cause suspension of the entire trial, treatment arm, or investigating centers:

- Inadequate recruitment that makes achievement of the study objectives unlikely (termination of the trial).
- Poor tolerance of individual treatment regimens (closure of treatment arm).
- Significant survival differences between treatment arms (closure of treatment arm or termination of the trial)
- Inadequate protocol compliance that jeopardizes the validity of the study (withdrawal of an investigating center)
- Pregnancy (subject's withdrawal and counseling).
- Personal request of patient (subject's withdrawal). In this case, although patients are treated off-protocol, data are recorded according to intent-to-treat principle. In addition, drop-out patients should have a final safety examination (CRF 2), and followed up at regular intervals.

13 Efficacy Assessment

13.1 Checkpoints

Refer to section 10.1

13.2 Methodology

Refer to section 11.1 – 11.4

13.3 Documentation

Refer to section 10.1 and 10.2. CRFs analogous to those used in previous trials will be finalized and issued upon termination of the pilote phase and activation of the study.

13.4 Response Criteria

Refer to section 3.3

14 Safety Assessment

It is the responsibility of the Study Coordinating Center to review and monitor all reported serious adverse events. Management of adverse events is outlined in the study protocol. Severity of adverse events are recorded according to standardized Common Toxicity Criteria (WHO). Patients older than 45 years of age who are considered for allogeneic SCT will be carefully reviewed by a "Safety Monitoring Board". Quality of life assessments will be derived in approximation from analysis of side effect profiles. Such a feasibility analysis is underway sponsored by a project of the "Competence Network Acute and Chronic Leukemias".

15 Statistical Design

15.1 Duration of the Study, Sample Size

The recruitment will last for 4, if necessary 5 years, follow up will last 5 years. Per year, a minimum of 280 evaluable CML patients are projected. Assuming that 20-30% of randomized patients will be transplanted and 5% are representing high-risk patients not eligible for SCT then 400 patients per arm are to be randomized each year. If median survival for low- and intermediate-risk patients is projected 77 months when treated with standard therapy, then the statistical power is 75% with $\alpha = 0{,}04294$ (final analysis, refer to section 15.3, sample size calculator program PS Version 1.0.15) to achieving a survival difference of 24 months (imatinib based therapies n = 840, IFN-based therapy n = 280). A difference of this magnitude would be certainly clinically relevant. With respect to comparison of the three imatinib-based treatment arms with each other, assuming n=280 subjects in each arm and a median survival of 101 months for the entire group, Table 10 shows projected differences of survival (months) between two treatment arms (arbitrarily designated as group A and B) in order to reach statistical significance (α=0,04294, statistical power 75%, final analysis). Such calculations suppose an exponential distribution of survival within each treatment arm.

Table 10: One-sided deviation (minimum) of median survival within group B (Med. S. B) from supposed median survival within group A (Med. S. A), in order to reach statistical significance: α=0,04294, statistical power 75%, sample size per arm: n = 280.

Med. S. A	72	73	74	75	76	77	78	79	80	81	82
Med. S. B	**101**	**102**	**103**	**105**	**107**	**108**	**109**	**111**	**112**	**114**	**116**
Med. S. A	83	84	85	86	87	88	89	90	91	92	93
Med. S.. B	**117**	**119**	**121**	**122**	**124**	**126**	**127**	**129**	**131**	**132**	**134**
Med. S. A	94	95	96	97	98	99	100	101			
Med. S. B	**136**	**137**	**139**	**141**	**142**	**144**	**146**	**147**			
Med. S. A	102	103	104	105	106	107	108	109	110	111	112
Med. S. B	**73**	**74**	**74**	**75**	**75**	**76**	**77**	**77**	**78**	**79**	**79**
Med. S. A	113	114	115	116	117	118	119	120	121	122	123
Med. S. B	**80**	**81**	**81**	**82**	**82**	**83**	**84**	**84**	**85**	**86**	**86**
Med. S. A	124	125	126	127	128	129	130	131	132	133	134
Med. S. B	**87**	**87**	**88**	**89**	**89**	**90**	**90**	**91**	**92**	**92**	**93**
Med. S. A	135	136	137	138	139	140	141	142	143	144	145
Med. S. B	**93**	**94**	**95**	**95**	**96**	**96**	**97**	**98**	**98**	**99**	**99**
Med. S. A	146	147									
Med. S. B	**100**	**101**									

It was further assumed that both groups A and B do not deviate extremely from 101 months, the supposed median survival of all 3 imatinib treatment arms. For a given situation that one arm exhibits at least one median survival of 101 months, if survival in the other arm is less or conversely, that one arm exhibits a maximum survival of 101 months, if survival in the other arm is greater, all scenarios with median survival deviations reaching extremes of 73 and 160 months are taken into account. Example: assuming one imatinib treatment arm designated as group A achieves a median survival of 133 months. Table 10 indicates a maximum median survival of 92 months in group B in order to reach statistical significance. Alternatively, an excess median survival within group B, far beyond 133 months, would also be statistically significant but this would contradict the initial hypothesis that median survival of all imatinib-treated patients is close to 101 months.

Table 10 represents a selection of possible results, which already considers probable and extreme situations. The tests of Marcus, Peritz and Gabriel[116] are applied (i.e., before two of the three imatinib treatment arms are compared the three imatinib arms have to be statistically significant by logrank test. With respect to the primary objective imatinib-based- vs. IFN-based therapy (section 15.3) is valid. If there are statistically significant differences between at least two imatinib arms, it is no longer meaningful in the context of the above-mentioned primary objective to test the IFN-based therapy arm against all three imatinib arms. Under these circumstances first and second objectives should be combined and all four treatment arms should be tested together whereby the procedure by Marcus, Peritz and Gabriel[116] is applied.

In order to show more distinctly subtle statistical differences between the treatment arms it may be necessary to merge data with other ongoing trials (e.g., the SPIRIT Study or planned trials of the Italian and Scandinavian cooperative groups). Based on international consensus it may be considered in the future to drop the treatment arm imatinib/araC. This may increase patient numbers in the other arms and consequently statistical power. If the IFN standard arm has to be closed prematurely (due to lack of compliance) then comparison of imatinib-based treatment arms with IFN-treated historical controls is entertained.

With respect to the primary objective 4 standard vs. reduced-intensity conditioning in patients older than 45 years of age we postulate that TRM in the experimental arm with reduced-intensity conditioning will be halved from 40-70%, depending on the transplantation risk to 20-35%. If one estimates the sample size necessary for this difference (α: 5%, two-sided; β: 20%), then it should have 31 to 82 patients per arm. There is no doubt that these sample numbers are reached. Analysis of cytogenetic response, the second main endpoint of the study, is done in the same manner as survival analysis.

15.2 Study Endpoints

Refer to sections 5.1 and 5.2

15.3 Statistical Considerations

Over the course of the trial period compliance of study patients assigned to the standard arm will be closely monitored by using statistical descriptive analyses as well as frequent assessments of the quality of documentation in the CRFs. Records of those who have withdrawn from the study (dropouts) will be scrutinized in the same way as well as records selected randomly.

This is followed by an analysis of structural similarity (i.e., comparability of treatment arms) of baseline variables and distribution of well known prognostic markers. Data will be described descriptively by using point estimators and confidence intervals. For estimation of survival probabilities as the primary endpoints Kaplan-Meier estimator[112] will be used. Survival probabilities within the treatment arms will be compared by logrank test.[113] The error probability is $\alpha \leq 0{,}05$ (two-sided).

The secondary endpoints will be analyzed by applying appropriate statistical inference methods according to data type and study question. Then, well-known prognostic markers and models will be validated and if necessary new models developed. For this the Cox's proportional hazards model[114] and the CART methodology[115] will be applied. Interim analyses of the primary study endpoints will be performed in the years 4, 6, and 8 since study activation. While protecting the type I error probability of $\alpha \leq 0{,}05$ the group sequential design according to O'Brien-Fleming[117] will be used. According to this model error probabilities are

α (4^{th} yr.) $\leq$ 0,00005,

α (6^{th} yr.) $\leq$ 0,00420,

α (8^{th} yr.) $\leq$ 0,01942

and α (final analysis) $\leq$ 0,04294.

Treatment tolerance will be analyzed chiefly by descriptive methods using contingency tables.
IBE is capable of utilities for data gathering, management and analysis (networks: Unix, WindowsNT, software: SAS, Oracle).

15.4 Publication of Results

The data obtained from this study will be published. Participating investigators will be named coauthors if the number of patients accrued is more than 5% of the entire study population. It is agreed upon that the individual of the Study Steering Group who prepares the manuscript will be named as first author, followed by coauthors. Besides the first

author, other members of the Steering Committee, investigators focused on special research aspects and those who had accrued large number of subjects should be appropriately acknowledged as such. The remainder of investigators will be mentioned as "For the German CML Study Group" in a footnote following the list of authors or at the end of the manuscript. Study results, including those relating to individual centers, may be published only with the prior consent of the Study Steering Committee.

16 Data Management

- Data will be recorded on prepared case report forms (CRFs), see sections 10.1 and 10.2.
- All patient-related and protocol-required information will be gathered in an anonymized fashion. Each patient is unmistakably identified by a patient number assigned at the time of registration, patient initials, date of birth and gender.
- The randomization lists are furnished centrally by the IBE Munich.
- At diagnosis (i.e., prior to initiation of treatment) CRF 1 has to be completed. At randomization (unless coincidental with time of diagnosis) another CRF 1 has to be completed.
- At regular intervals during the course of the study every 3 months (starting from year 3 since diagnosis every 6 months) follow-up CRF 2 have to be completed – additionally, after attaining CHR, MCR and/or CCR, unless already covered by 3 and/or 6-monthly follow-up CRFs.
- CRF 3 has to be completed when a randomized treatment is changed (please give detailed information about reasons for the change).
- CRF 4 has to be completed after allogeneic SCT.
- The onset of blast crisis is documented with CRF 2 and CRF 5.
- Termination of the study (demise, withdrawal, end of study) is documented with CRF2 and CRF 6.
- Serious and unexpected adverse events are reported on SAE Report Form (appendix 12).

The original CRFs remain at the investigating center, while the two copies are sent to the Study Coordinating Center. The Study Coordinating Center checks the received CRFs and may ask the individual center for clarification or further documentation in case of missing data. One copy of the CRF remains at the Study Coordinating Center, the other is sent to the statistics center (IBE), where the data are subjected to a cross check and then entered into the system.

17 Quality Control

17.1 Centralized Quality Assurance

- Peripheral blood, bone marrow smears, bone marrow biopsies and cytogenetic analyses are stored and archived ready to be submitted if requested to a review panel as described in the sections 11.1 -11.4.
- Members of the histology, cytology, cytogenetic and molecular genetics panels review the rigorous exactness and quality of diagnostic tests as well as the uniformity how the tests are read.
- Quality of data is regularly assessed by the IBE (plausibility, completeness, check of randomization etc.).
- How often these assessments are necessary is determined by the panel members.
- Arising clinical and methodical problems are brought up and discussed at regular meetings of the Study Group.

17.2 Monitoring

At regular intervals during the course of the study it is agreed upon to check protocol compliance – understood as the adherence to all the trial-related requirements and the applicable regulatory requirements – both overall and at each center, so that prompt corrective measures may be taken, if necessary. The patient passport (appendix 7) is helpful in this regard. Any protocol violations, their nature and extent, are carefully documented for interpreting later study results.

All serious and unexpected adverse events must be notified as promptly as possible indicating their nature, severity and relationship to the study treatment by completing a SAE Report Form (appendix 12), which is sent to the Study Coordinating Center. The Study Coordinating Center and IBE report on monitoring at the regular meetings of the Study Group.

17.3 Reference Institutions

Contact addresses of the reference institutions are listed in the sections 11.1 – 11.4.

18 Ethical Principles

18.1 Declaration of Helsinki, Drug Legislation, Institutional Review Board

This trial protocol conforms with the World Medical Association's Declaration of Helsinki amended (2000 Edinburgh, Scotland) with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP) and the German law (AMG) to use pharmaceutical drugs – excerpt from the last amendment, July 2000 (appendices 3 and 4). The study protocol and the copy of the Institution's Ethical Commission (Ethical Commission of the Fakultät für Klinische Medizin Mannheim der Universität Heidelberg) was submitted to the "Regierungspräsidium Karlsruhe" and the German Federal Drug Agency (BfArM). According to § 40 AMG patients' insurance coverage has been contracted with the insurance company "Gothaer Allgemeine Versicherung AG, Köln"; the insurance policy number is 11.444.546060 .

18.2 Informed Patient Consent

Patients are provided with information about the study in accordance with standards and legal guidelines. The information entails treatment strategies in CML, drugs employed (interferon alpha, imatinib, araC, HU), allogeneic SCT, study objectives, purpose and procedure of randomization. Patients are randomized only after they have given informed consent. **Patient Consent Form** and **Guidelines for Physicians** are used for obtaining an informed patient consent (appendices 1 and 2). Patients who refuse to give consent are not randomized. However, their planned treatment and course of disease should be documented. Should by interim analyses one treatment arm be significantly superior over the others, then all study patients will be treated with the superior therapy.

References

1. Hehlmann R, Heimpel H, Hasford J, Kolb HJ, Pralle H, Hossfeld DK, Queisser W, Löffler H, Heinze B, Georgii A, v.Wussow P, Bartram C, Griesshammer M, Bergmann L, Essers U, Falge C, Hochhaus A, Queisser U, Sick C, Meyer P, Schmitz N, Verpoort K, Eimermacher H, Walther F, Westerhausen M, Kleeberg UR, Heilein A, Käbisch A, Barz C, Zimmermann R, Meuret G, Tichelli A, Berdel WE, Kanz L, Anger B, Tigges FJ, Schmid L, Brockhaus W, Zankovich R, Schäfer U, Weissenfels I, Mainzer K, Tobler A, Perker M, Hohnloser J, Messerer D, Thiele J, Buhr T, Ansari H, and the German CML Study Group: Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: prolongation of survival by hydroxyurea. The German CML Study Group. Blood. 82: 398-407, 1993

2. Hehlmann R, Heimpel H, Hasford J, Kolb HJ, Pralle H, Hossfeld DK, Queisser W, Löffler H, Hochhaus A, Heinze B, Georgii A, Bartram CR, Griesshammer M, Bergmann L, Essers U, Falge C, Queisser U, Meyer P, Schmitz N, Eimermacher H, Walther F, Fett W, Kleeberg UR, Käbisch A, Nerl C, Zimmermann R, Meuret G, Tichelli A, Kanz L, Tigges FJ, Schmid L, Brockhaus W, Tobler A, Reiter A, Perker M, Emmerich B, Verpoort K, Zankovich R, Wussow PV, Prümmer O, Thiele J, Buhr T, Carbonell F, Ansari H, and the German CML Study Group: Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. The German CML Study Group. Blood. 84: 4064-4077, 1994

3. Hehlmann R, Heimpel H, Hossfeld DK, Hasford J, Kolb HJ, Loffler H, Pralle H, Queisser W, Hochhaus A, Tichelli A, Fett W, Schmitz N, Reiter A, Griesshammer M, Pfeifer W, Baumler M, Kamp T, Tobler A, Eimermacher H, Kuse R, Berger U, Ansari H, and the German CML Study Group: Randomized study of the combination of hydroxyurea and interferon alpha versus hydroxyurea monotherapy during the chronic phase of chronic myelogenous leukemia (CML Study II). Bone Marrow Transplant. 17, Supp.3: S21-S24, 1996

4. Nowell PC, Hungerford DA: A minute chromosome in human chronic granulocytic leukemia. Science. 132: 1497-1501, 1960

5. Bartram CR, de Klein A, Hagemeijer A, van Agthoven T, Geurts van Kessel A, Bootsma D, Grosveld G, Ferguson Smith MA, Davies T, Stone M, Heisterkamp N, Stephenson JR, Groffen J: Translocation of c-*abl* oncogene correlates with the presence of a Philadelphia chromosome in chronic myelocytic leukaemia. Nature. 306: 277-280, 1983

6. Heisterkamp N, Stephenson JR, Groffen J, Hansen PF, de Klein A, Bartram CR, Grosveld G: Localization of the c-ab1 oncogene adjacent to a translocation break point in chronic myelocytic leukaemia. Nature. 306: 239-242, 1983

7. Shtivelman E, Lifshitz B, Gale RP, Canaani E: Fused transcript of abl and bcr genes in chronic myelogenous leukaemia. Nature. 315: 550-554, 1985

8. Melo JV, Gordon DE, Cross NCP, Goldman JM: The ABL-BCR fusion gene is expressed in chronic myeloid leukemia. Blood. 81: 158-165, 1993

9. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick H, Sultan C, Cox C: The chronic myeloid leukaemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Proposals by the French-American- British Cooperative Leukaemia Group. Br.J.Haematol. 87: 746-754, 1994

10. Hochhaus A, Hehlmann R, Bartram CR, Ansari H, Heimpel H, Heinze B, Reiter A, Hossfeld DK: Clinical heterogeneity of Philadelphia chromosome negative chronic myelogenous leukemia correlates with prognosis: molecular analysis of 49 cases and division into four subgroups. Blood. 84, Supp.1: 154a, 1994

11. Kantarjian HM, Keating MJ, Walters RS, McCredie K, Smith TL, Talpaz M, Beran M, Cork A, Trujillo JM, Freireich EJ: Clinical and prognostic features of Philadelphia chromosome-negative chronic myelogenous leukemia. Cancer. 58: 2023-2030, 1986

12. Kurzrock R, Kantarjian HM, Shtalrid M, Gutterman JU, Talpaz M: Philadelphia chromosome-negative chronic myelogenous leukemia without breakpoint cluster region rearrangement: a chronic myeloid leukemia with a distinct clinical course. Blood. 75: 445-452, 1990

13. Talpaz M, Kantarjian H, Kurzrock R, Trujillo JM, Gutterman JU: Interferon-alpha produces sustained cytogenetic responses in chronic myelogenous leukemia. Ann.Intern.Med. 114: 532-538, 1991

14. Hehlmann R, Ansari H, Hasford J, Heimpel H, Hossfeld DK, Kolb HJ, Löffler H, Pralle H, Queisser W, Reiter A, Hochhaus A, and the German CML Study Group: Comparative analysis of the impact of risk profile and drug therapy on survival in CML using Sokal's index and new score. Br.J.Haematol. 97: 76-85, 1997

15. Minot GR, Buckman TE, Isaacs R: Chronic myelogenous leukemia. J.Am.Med.Assoc. 82: 1489-1494, 1924

16. Medical Research Council's Working Party for Therapeutic Trials in Leukaemia: Chronic Granulocytic Leukemia: Comparison of radiotherapy and busulphan therapy. Br.Med.J. 1: 201-208, 1968

17. Galton DA: Chemotherapy of chronic myelocytic leukemia. Sem.Hematol. 6: 323-343, 1969

18. Rushing D, Goldman A, Gibbs G, Howe R, Kennedy BJ: Hydroxyurea versus busulfan in the treatment of chronic myelogenous leukemia. Am.J.Clin.Oncol. 5: 307-313, 1982

19. Bolin RW, Robinson WA, Sutherland J, Hamman RF: Busulfan versus hydroxyurea in long-term therapy of chronic myelogenous leukemia. Cancer. 50: 1683-1686, 1982

20. Haut A, Abbott WS, Wintrobe MM, Cartwright GE: Busulfan in the treatment of chronic myelocytic leukemia. The effect of long-term intermittent therapy. Blood. 17: 1-19, 1961

21. Ohnishi K, Ohno R, Tomonaga M, Kamada N, Onozawa K, Kuramoto A, Dohy H, Mizoguchi H, Miyawaki S, Tsubaki K, Miura Y, Omine M, Kobayashi T, Naoe T, Ohshima T, Hirashima K, Ohtake S, Takahashi I, Morishima Y, Naito K, Asou N, Tanimoto M, Sakuma A, Yamada K, and the Kouseisho Leukemia Study Group: A randomized trial comparing interferon-alpha with busulfan for newly diagnosed chronic myelogenous leukemia in chronic phase. Blood. 86: 906-916, 1995

22. Chronic Myeloid Leukemia Trialists' Collaborative Group. Hydroxyurea versus busulphan for chronic myeloid leukaemia: an individual patient data meta-analysis of three randomized trials. Br.J.Haematol. 110: 573-576. 2000

23. The Italian Cooperative Study Group on Chronic Myeloid Leukemia: Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. N.Engl.J.Med. 330: 820-825, 1994

24. The Benelux CML Study Group.: Randomized study on hydroxyurea alone versus hydroxyurea combined with low-dose interferon-α2b for chronic myeloid leukemia. Blood. 91: 2713-2721, 1998

25. Sharp JC, Joyner MV, Wayne AW, Kemp J, Crofts M, Birch ADJ, McArthur G, Lai S, Sterndale H, Williams Y: Karyotypic conversion in Ph^1-positive chronic myeloid leukaemia with combination chemotherapy. Lancet. 1370-1372, 1979

26. The Italian Cooperative Study Group on Chronic Myeloid Leukemia: Long-term follow-Up of the Italian trial of interferon-alpha versus conventional chemotherapy in chronic myeloid leukemia. Blood. 92: 1541-1548, 1998

27. Cunningham I, Gee T, Dowling M, Chaganti R, Bailey R, Hopfan S, Bowden L, Turnbull A, Knapper W, Clarkson B: Results of treatment of Ph'+ chronic myelogenous leukemia with an intensive treatment regimen (L-5 protocol). Blood. 53: 375-395, 1979

28. Hehlmann R: Cytostatic therapy of chronic myelogenous leukemia: review and perspectives, in Huhn D, Hellriegel KP, Niederle N (eds): Chronic myelocytic leukemia and interferon. Berlin Heidelberg, Springer, 1988, pp 102-112

29. Kantarjian HM, Vellekoop L, McCredie KB, Keating MJ, Hester J, Smith T, Barlogie B, Trujillo J, Freireich EJ: Intensive combination chemotherapy (ROAP 10) and splenectomy in the management of chronic myelogenous leukemia. J.Clin.Oncol. 3: 192-200, 1985

30. Hester JP, Waddell CC, Coltman CA, Morrison FS, Stephens RL, Balcerzak SP, Baker LH, Chen TT: Response of chronic myelogenous leukemia patients to COAP-splenectomy. Cancer. 54: 1977-1982, 1984

31. Kantarjian HM, Talpaz M, LeMaistre CF, Spinolo J, Spitzer G, Yau J, Dicke K, Jagannath S, Deisseroth AB: Intensive combination chemotherapy and autologous bone marrow transplantation leads to the reappearance of Philadelphia chromosome-negative cells in chronic myelogenous leukemia. Cancer. 67: 2959-2965, 1991

32. Kantarjian HM, Talpaz M, Keating MJ, Estey EH, O'Brien S, Beran M, McCredie K, Gutterman J, Freireich EJ: Intensive chemotherapy induction followed by interferon-alpha maintenance in patients with Philadelphia chromosome-positive chronic myelogenous leukemia. Cancer. 68: 1201-1207, 1991

33. Talpaz M, Kantarjian HM, McCredie K, Trujillo JM, Keating MJ, Gutterman JU: Hematologic remission and cytogenetic improvement induced by recombinant human interferon $alpha_{2a}$ in chronic myelogenous leukemia. N.Engl.J.Med. 314: 1065-1069, 1986

34. Alimena G, Morra E, Lazzarino M, Liberati AM, Montefusco E, Inverardi D, Bernasconi P, Mancini M, Donti E, Grignani F, et al: Interferon alpha-2b as therapy for Ph'-positive chronic myelogenous leukemia: a study of 82 patients treated with intermittent or daily administration. Blood. 72: 642-647, 1988

35. Ozer H, George SL, Schiffer CA, Rao K, Rao PN, Wurster Hill DH, Arthur DD, Powell B, Gottlieb A, Peterson BA, Rai K, Testa JR, Lebeau M, Tantravahi R, Bloomfield CD: Prolonged subcutaneous administration of recombinant alpha 2b interferon in patients with previously untreated Philadelphia chromosome-positive chronic-phase chronic myelogenous leukemia: effect on remission duration and survival: Cancer and Leukemia Group B study 8583. Blood. 82: 2975-2984, 1993

36. Allan NC, Richards SM, Shepherd PC: UK Medical Research Council randomised, multicentre trial of interferon-alpha n1 for chronic myeloid leukaemia: improved survival irrespective of cytogenetic response. The UK Medical Research Council's Working Parties for Therapeutic Trials in Adult Leukaemia. Lancet. 345: 1392-1397, 1995

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

38. Kantarjian HM, Smith TL, O'Brien S, Beran M, Pierce S, Talpaz M, and the Leukemia Service: Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon-α therapy. Ann.Intern.Med. 122: 254-261, 1995

39. Guilhot F, Chastang C, Michallet M, Guerci A, Harousseau JL, Maloisel F, Bouabdallah R, Guyotat D, Cheron N, Nicolini F, Abgrall JF, Tanzer J, for the French Chronic Myeloid Leukemia Study Group.: Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. N.Engl.J.Med. 337: 223-229, 1997

40. Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller C, Ottmann OG, Schiffer CA, Talpaz M, Guilhot F, Deininger MWG, Fischer T, O'Brien SG, Stone R, Gambacorti-Passerini C, Russell N, Reiffers J, Shea T, Chapuis B, Coutre S, Tura S, Mora E, Larson RA, Saven A, Peschel C, Gratwohl A, Mandelli F, Ben-Am M, Gathmann I, Capdeville R, Paquette RL, Druker BJ: Gleevec/Glivec™ (imatinib mesylate) induces hematologic and cytogenetic responses in patients with chronic myeloid leukemia in myeloid blast crisis: results of a phase II study. Blood. 99: 3530-3539, 2002

41. Goldman JM, Apperley JF, Jones L, Marcus R, Goolden AWG, Batchelor R, Hale G, Waldman H, Reid CD, Hows J, Gordon Smith E, Catovsky D, Galton DAG: Bone marrow transplantation for patients with chronic myeloid leukemia. N.Engl.J.Med. 314: 202-207, 1986

42. Thomas ED, Clift RA: Indications for marrow transplantation in chronic myelogenous leukemia. Blood. 73: 861-864, 1989

43. Goldman JM, Szydlo R, Horowitz MM, Gale RP, Ash RC, Atkinson K, Dicke KA, Gluckman E, Herzig RH, Marmont A, Masaoka T, McGlave PB, Messner H, O'Reilly RJ, Reiffers J, Rimm AA, Speck B, Veum-Stone JA, Wingard JR, Zwaan FE, Bortin MM: Choice of pretransplant treatment and timing of transplants for chronic myelogenous leukemia in chronic phase [see comments]. Blood. 82: 2235-2238, 1993

44. Horowitz MM, Rowlings PA, Passweg JR: Allogeneic bone marrow transplantation for CML: a report from the International Bone Marrow Transplant Registry. Bone Marrow Transplant. 17, Supp.3: S5-S6, 1996

45. Gratwohl A, Hermans J, for the Working Party Chronic Leukemia of the European Group for Blood and Marrow Transplantation (EBMT): Allogeneic bone marrow transplantation for chronic myeloid leukemia. Bone Marrow Transplant. 17, Supp.3: S7-S9, 1996

46. Clift RA, Storb R: Marrow transplantation for CML: the Seattle experience. Bone Marrow Transplant. 17, Supp.3: S1-S3, 1996

47. Hansen JA, Gooley TA, Martin PJ, Appelbaum F, Chauncey TR, Clift RA, Petersdorf EW, Radich J, Sanders JE, Storb RF, Sullivan KM, Anasetti C: Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia in chronic phase. N.Engl.J.Med. 338: 962-968, 1998

48. Clift, R. A., Radich, J., Appelbaum, F. R., Martin, P., Flowers, M. E. D., Deeg, H. J., Storb, R., and Thomas, E. D. Long-term follow-up of a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide for patients receiving allogeneic marrow transplants during chronic phase of chronic myeloid leukemia. Blood. 94: 3960-3962. 1999.

49. Gratwohl A, Hermans J, Goldman JM, Frassoni F, Devergie A, Carreras E, Kolb HJ, Gahrton G, Arcese W, Vernant JP, Ruutu T, de Witte T, van Rhee F, Apperley J, for the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT): Risk assessment for patients with chronic myeloid leukemia before allogeneic blood or marrow transplantation. Lancet. 352: 1087-1092, 1998

50. Bonifazi F, De Vivo A, Rosti G, Guilhot F, Guilhot J, Trabacchi E, Hehlmann R, Hochhaus A, Shepherd PC, Steegmann JL, Kluin-Nelemans HC, Thaler J, Simonsson B, Louwagie A, Reiffers J, Mahon FX, Montefusco E,

Alimena G, Hasford J, Richards S, Saglio G, Testoni N, Martinelli G, Tura S, Baccarani M: Chronic myeloid leukemia and interferon-alpha: a study of complete cytogenetic responders. Blood. 98: 3074-3081, 2001

51. Mahon FX, Delbrel X, Cony-Makhoul P, Faberes C, Boiron JM, Barthe C, Bilhou-Nabera C, Pigneux A, Marit G, Reiffers J: Follow-up of complete cytogenetic remission in patients with chronic myeloid leukemia after cessation of interferon alfa. J.Clin.Oncol. 20: 214-220, 2002

52. Hehlmann R, Ansari H, Hasford J, Heimpel H, Hossfeld DK, Kolb HJ, Loffler H, Pralle H, Queisser W, Reiter A, Hochhaus A: Comparative analysis of the impact of risk profile and of drug therapy on survival in CML using Sokal's index and a new score. German chronic myeloid leukaemia (CML)-Study Group. Br.J.Haematol. 97: 76-85, 1997

53. Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC, Alimena G, Steegmann JL, Ansari H: A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. J.Natl.Cancer Inst. 90: 850-858, 1998

54. Hasford J, Baccarani M, Hehlmann R, Ansari H, Tura S, Zuffa E: Interferon-α and hydroxyurea in early chronic myeloid leukemia: a comparative analysis of the Italian and German chronic myeloid leukemia trials with interferon-α. Blood. 87: 5384-5391, 1996

55. Chronic Myeloid Leukemia Trialists' Collaborative Group: Interferon alfa versus chemotherapy for chronic myeloid leukemia: a meta-analysis of seven randomized trials. J.Natl.Cancer Inst. 89: 1616-1620, 1997

56. Silver RT, Woolf SH, Hehlmann R, Appelbaum FR, Anderson J, Bennett C, Goldman JM, Guilhot F, Kantarjian HM, Lichtin AE, Talpaz M, Tura S: An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: Developed for the American Society of Hematology. Blood. 94: 1517-1536, 1999

57. Mahon FX, Montastruc M, Faberes C, Reiffers J: Predicting complete cytogenetic response in chronic myelogenous leukemia patients treated with recombinant interferon α. Blood. 84: 3592-3594, 1994

58. Hochhaus A, Lin F, Reiter A, Skladny H, van Rhee F, Shepherd PCA, Allan NC, Hehlmann R, Goldman JM, Cross NCP: Variable numbers of BCR-ABL transcripts persist in CML patients who achieve complete cytogenetic remission with interferon-α. Br.J.Haematol. 91: 126-131, 1995

59. Hochhaus A, Lin F, Reiter A, Skladny H, Mason PJ, van Rhee F, Shepherd PCA, Allan NC, Hehlmann R, Goldman JM, Cross NCP: Quantification of residual disease in chronic myelogenous leukemia patients on interferon-α therapy by competitive polymerase chain reaction. Blood. 87: 1549-1555, 1996

60. Reiter A, Marley SB, Hochhaus A, Sohal J, Raanani P, Hehlmann R, Gordon MY, Goldman JM, Cross NCP: BCR-ABL positive progenitors in chronic myeloid leukaemia patients in complete cytogenetic remission after treatment with interferon-α. Br.J.Haematol. 102: 1271-1278, 1998

61. Hochhaus A, Reiter A, Saussele S, Reichert A, Emig M, Kaeda J, Schultheis B, Berger U, Shepherd PC, Allan NC, Hehlmann R, Goldman JM, Cross NC: Molecular heterogeneity in complete cytogenetic responders after interferon-alpha therapy for chronic myelogenous leukemia: low levels of minimal residual disease are associated with continuing remission. German CML Study Group and the UK MRC CML Study Group. Blood. 95: 62-66, 2000

62. Quesada JR, Talpaz M, Rios A, Kurzrock R, Gutterman JU: Clinical toxicity of interferons in cancer patients: a review. J.Clin.Oncol. 4: 234-243, 1986

63. Baccarani M, Rosti G, De Vivo A, Bonifazi F, Russo D, Martinelli G, Testoni N, Amabile M, Fiacchini M, Montefusco E, Saglio G, Tura S, for the Italian Cooperative Study Group on Chronic Myeloid Leukemia: A randomized study of interferon-a versus interferon-a and low-dose arabinosyl cytosine in chronic myeloid leukemia. Blood. 99: 1527-1535, 2002

64. Giles FJ, Shan J, Chen S, Advani SH, Supandiman I, Aziz Z, Caviles AP, Tee GY, Chasen MR, Fahed Z, Chaoj TY, Aydogdu I, Lynott AM: A prospective randomized study of alpha-2b interferon plus hydroxyurea or cytarabine for patients with early chronic phase chronic myelogenous leukemia: the International Oncology Study Group CML1 study. Leuk.Lymphoma. 37: 367-377, 2000

65. Kantarjian HM, O'Brien S, Smith TL, Rios MB, Cotes J, Beran M, Koller C, Giles FJ, Andreeff M, Kornblau S, Giralt S, Keating M, Talpaz M: Treatment of Philadelphia chromosome-positive early chronic phase chronic myelogenous leukemia with daily doses of interferon alpha and low-dose cytarabine. J.Clin.Oncol. 17: 284-292, 1999

66. Reiter, A., Hochhaus, A., Berger, U., Kuhn, C., and Hehlmann, R. AraC-based pharmacotherapy of chronic myeloid leukaemia. Expert.Opin.Pharmacother. 2: 1129-1135. 2001.

67. Daley GQ, van Etten RA, Baltimore D: Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. Science. 247: 824-830, 1990

68. Kelliher MA, McLaughlin J, Witte ON, Rosenberg N: Induction of a chronic myelogenous leukemia-like syndrome in mice with v-abl and BCR/ABL [published erratum appears in Proc Natl Acad Sci U S A 1990 Nov;87(22):9072]. Proc.Natl.Acad.Sci.U.S.A. 87: 6649-6653, 1990

69. Lugo TG, Pendergast AM, Muller AJ, Witte ON: Tyrosine kinase activity and transformation potency of bcr-abl oncogene products. Science. 247: 1079-1082, 1990

70. Buchdunger, E., Zimmermann, J., Mett, H., Meyer, T., Müller, M., Druker, B. J., and Lydon, N. B. Inhibition of the Abl protein-tyrosine kinase *in vitro* and *in vivo* by a 2-phenylaminopyrimidine derivative. Cancer Res. 56: 100-104. 1996.

71. Buchdunger, E., Cioffi, C. L., Law, N., Stover, D., Ohno-Jones, S., Druker, B. J., and Lydon, N. B. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J.Pharmacol.Exp.Ther. 295: 139-145. 2000.

72. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB: Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat.Med. 2: 561-566, 1996

73. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, Sawyers CL: Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N.Engl.J Med. 344: 1031-1037, 2001

74. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, Capdeville R, Talpaz M: Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N.Engl.J Med. 344: 1038-1042, 2001

75. Talpaz M, Silver RT, Druker BJ, Goldman JM, Gambacorti-Passerini C, Guilhot F, Schiffer CA, Fischer T, Deininger MW, Lennard AL, Hochhaus A, Ottmann OG, Gratwohl A, Baccarani M, Stone R, Tura S, Mahon FX, Fernandes-Reese S, Gathmann I, Capdeville R, Kantarjian HM, Sawyers CL: Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase II study. Blood. 99: 1928-1937, 2002

76. Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, Niederwieser D, Resta D, Capdeville R, Zoellner U, Talpaz M, Druker B: Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N.Engl.J Med. 346: 645-652, 2002

77. Thiesing JT, Ohno-Jones S, Kolibaba KS, Druker BJ: Efficacy of STI571, an abl tyrosine kinase inhibitor, in conjunction with other antileukemic agents against bcr-abl-positive cells. Blood. 96: 3195-3199, 2000

78. Topaly, J., Zeller, W., and Fruehauf, S. Synergistic activity of the new ABL-specific tyrosine kinase inhibitor STI571 and chemotherapeutic druigs on BCR-ABL-positivbe chronic myelogenous leukemia cells. Leukemia. 15(3), 342-347. 2001.

79. Kano, Y., Akutsu, M., Tsunoda, S., Mano, H., Sato, Y., Honma, Y., and Furukawa, Y. In vitro cytotoxic effects of a tyrosine kinase inhibitor STI571 in combination with commonly used antileukemic agents. Blood. 97, 1999-2007. 2001.

80. Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Rao PN, Sawyers CL: Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science. 293: 876-880, 2001

81. Hochhaus A, Kreil S, Corbin A, La Rosee P, Lahaye T, Berger U, Cross NC, Linkesch W, Druker BJ, Hehlmann R, Gambac, Corneo G, D'Incalci M: Roots of clinical resistance to STI-571 cancer therapy. Science. 293: 2163, 2001

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

83. Clift RA, Appelbaum FR, Thomas ED: Treatment of chronic myeloid leukemia by marrow transplantation. Blood. 82: 1954-1956, 1993

84. McGlave PB, Shu XO, Wen W, Anasetti C, Nademanee A, Champlin R, Antin JH, Kernan NA, King R, Weisdorf DJ: Unrelated donor marrow transplantation for chronic myelogenous leukemia: 9 years' experience of the national marrow donor program. Blood. 95: 2219-2225, 2000

85. Dini G, Lamparelli T, Rondelli R, Lanino E, Barbanti M, Costa C, Manfredini L, Guidi S, Rosti G, Alessandrino EP, Lacatelli F, Marenco P, Soligo D, Di Bartolomeo P, Aversa F, La Nasa G, Busca A, Majolino I, De Laurenzi A, Bacigalupo A: Unrelated donor marrow transplantation for chronic myelogenous leukaemia. Br.J.Haematol. 102: 544-552, 1998

86. Ottinger HD, Muller CR, Goldmann SF, Albert E, Arnold R, Beelen DW, Blasczyk R, Bunjes D, Casper J, Ebell W, Ehninger G, Eiermann T, Einsele H, Fauser A, Ferencik S, Finke J, Hertenstein B, Heyll A, Klingebiel T, Knipper A, Kremens B, Kolb HJ, Kolbe K, Lenartz E, Lindemann M, Muller CA, Mytilineos J, Niederwieser D, Runde V, Sayer H, Schaefer UW, Schmitz N, Schroder S, Schulze-Rath R, Schwerdtfeger R, Siegert W, Thiele B, Zander AR, Grosse-Wilde H: Second German consensus on immunogenetic donor search for allotransplantation of hematopoietic stem cells. Ann.Hematol. 80: 706-714, 2001

87. Gale RP, Hehlmann R, Zhang MJ, Hasford J, Goldman JM, Heimpel H, Hochhaus A, Klein JP, Kolb HJ, McGlave PB, Passweg JR, Rowlings PA, Sobocinski KA, Horowitz MM, and the German CML Study Group: Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia (CML). Blood. 91: 1810-1819, 1998

88. The Italian Cooperative Study Group on Chronic Myeloid Leukemia and the Italian Group for Bone Marrow Transplantation: Monitoring treatment and survival in chronic myeloid leukemia. J.Clin.Oncol. 17: 1858-1868, 1999

89. Hehlmann R, Hochhaus A, Kolb HJ, Hasford J, Gratwohl A, Heimpel H, Siegert W, Finke J, Ehninger G, Holler E, Berger U, Pfirrmann M, Muth A, Zander A, Fauser AA, Heyll A, Nerl C, Hossfeld DK, Löffler H, Pralle H, Queisser W, Tobler A, for the German CML-Study Group and the SAKK: Interferon before allogeneic bone marrow transplantation in chronic myelogenous leukemia does not affect outcome adversely, provided it is discontinued at least 90 days before the procedure. Blood. 94: 3668-3677, 1999

90. McSweeney PA, Niederwieser D, Shizuru JA, Sandmaier BM, Molina AJ, Maloney DG, Chauncey TR, Gooley TA, Hegenbart U, Nash RA, Radich J, Wagner JL, Minor S, Appelbaum FR, Bensinger WI, Bryant E, Flowers ME, Georges GE, Grumet FC, Kiem HP, Torok-Storb B, Yu C, Blume KG, Storb RF: Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus- tumor effects. Blood. 97: 3390-3400, 2001

91. Giralt S, Estey E, Albitar M, Van Besien K, Rondon G, Anderlini P, O'Brien S, Khouri I, Gajewski J, Mehra R, Claxton D, Andersson B, Beran M, Przepiorka D, Koller C, Kornblau S, Korbling M, Keating M, Kantarjian H, Champlin R: Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood. 89: 4531-4536, 1997

92. Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M, Cividalli G, Varadi G, Kirschbaum M, Ackerstein A, Samuel S, Amar A, Brautbar C, Ben Tal O, Eldor A, Or R: Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood. 91: 756-763, 1998

93. Childs R, Clave E, Contentin N, Jayasekera D, Hensel N, Leitman S, Read EJ, Carter C, Bahceci E, Young NS, Barrett AJ: Engraftment kinetics after nonmyeloablative allogeneic peripheral blood stem cell transplantation: full donor T-cell chimerism precedes alloimmune responses. Blood. 94: 3234-3241, 1999

94. Barrett J, Childs R: Non-myeloablative stem cell transplants. Br.J.Haematol. 111: 6-17, 2000

95. Storb R, Champlin R, Riddell S, Murata M, Bryant S, Warren EH: Non-myeloablative transplants for malignant disease. Hematology 2001.American Society of Hematology Education Program Book 375-391, 2001

96. Khouri IF, Keating M, Korbling M, Przepiorka D, Anderlini P, O'Brien S, Giralt S, Ippoliti C, von Wolff B, Gajewski J, Donato M, Claxton D, Ueno N, Andersson B, Gee A, Champlin R: Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. J.Clin.Oncol. 16: 2817-2824, 1998

97. Ringden O, Remberger M, Runde V, Bornhauser M, Blau IW, Basara N, Holig K, Beelen DW, Hagglund H, Basu O, Ehninger G, Fauser AA: Peripheral blood stem cell transplantation from unrelated donors: a comparison with marrow transplantation. Blood. 94: 455-464, 1999

98. Elmaagacli AH, Basoglu S, Peceny R, Trenschel R, Ottinger H, Lollert A, Runde V, Grosse-Wilde H, Beelen DW, Schaefer UW: Improved disease-free-survival after transplantation of peripheral blood stem cells as compared with bone marrow from HLA-identical unrelated donors in patients with first chronic phase chronic myeloid leukemia. Blood. 99: 1130-1135, 2002

99. Schmitz N, Beksac M, Hasenclever D, Bacigalupo A, Ruutu T, Nagler A, Gluckman E, Russell N, Apperley J, Gorin N, Szer J, Bradstock K, Varet B, Clark P, Borkett K, Gratwohl A: A randomised study from the European Group for

Blood and Marrow Transplantation comparing allogeneic transplantation of filgastrim-mobilised peripheral blood progenitor cells with bone marrow transplantation in 350 patients (pts) with leukemia. Blood. 96: 481a, 2001

100. Bensinger, W. I., Martin, P. J., Storer, B., Clift, R., Forman, S. J., Negrin, R., Kashyap, A., Flowers, M. E. D., Lilleby, K., Chauncey, T. R., Storb, R., and Appelbaum, F. R. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. N.Engl.J.Med. 344, 175-181. 2001.

101. Socie G, Clift RA, Blaise D, Devergie A, Ringden O, Martin PJ, Remberger M, Deeg HJ, Ruutu T, Michallet M, Sullivan KM, Chevret S: Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. Blood. 98: 3569-3574, 2001

102. Clift RA, Buckner CD, Thomas ED, Bensinger WI, Bowden R, Bryant E, Deeg HJ, Doney KC, Fisher LD, Hansen JA, .: Marrow transplantation for chronic myeloid leukemia: a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide. Blood. 84: 2036-2043, 1994

103. Ringden O, Ruutu T, Remberger M, Nikoskelainen J, Volin L, Vindelov L, Parkkali T, Lenhoff S, Sallerfors B, Ljungman P, .: A randomized trial comparing busulfan with total body irradiation as conditioning in allogeneic marrow transplant recipients with leukemia: a report from the Nordic Bone Marrow Transplantation Group. Blood. 83: 2723-2730, 1994

104. Devergie A, Blaise D, Attal M, Tigaud JD, Jouet JP, Vernant JP, Bordigoni P, Ifrah N, Dauriac C, Cahn JY, .: Allogeneic bone marrow transplantation for chronic myeloid leukemia in first chronic phase: a randomized trial of busulfan-cytoxan versus cytoxan-total body irradiation as preparative regimen: a report from the French Society of Bone Marrow Graft (SFGM). Blood. 85: 2263-2268, 1995

105. Carella AM, Lerma E, Corsetti MT, Dejana A, Basta P, Vassallo F, Abate M, Soracco M, Benvenuto F, Figari O, Podesta M, Piaggio G, Ferrara R, Sessarego M, Parodi C, Pizzuti M, Rubagotti A, Occhini D, Frassoni F: Autografting with Philadelphia chromosome-negative mobilized hematopoietic progenitor cells in chronic myelogenous leukemia. Blood. 93: 1534-1539, 1999

106. Simonsson B, Oberg G, Bjoreman M, Bjorkholm M, Carneskog J, Gahrton G, Hast R, Karl H, Lanng-Nielsen J, Lofvenberg E, Malm C, Turesson I, Uden AM, Vilen L, Weis-Bjerrum O, for the Danish-Swedish CML group: Intensive treatment in order to minimize the Ph-positive clone in CML. Bone Marrow Transplant. 17, Supp.3: S63-S64, 1996

107. Shepherd P, Kluin-Nelemans HC, Richards S, Le Cessie S, on behalf of the MRC Adult Leukaemia Working Party and the HOVON 20 CML Group: A randomised comparison of low or high dose IFN-alpha in newly diagnosed CML patients shows no difference in major cytogenetic response rate or survival between the two groups. Blood. 98: 727a, 2001

108. Hartman AR, Williams SF, Dillon JJ: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs total body irradiation: a meta-analysis. Bone Marrow Transplant. 22: 439-443, 1998

109. Hochhaus A, Reiter A, Skladny H, Melo JV, Sick C, Berger U, Guo JQ, Arlinghaus RB, Hehlmann R, Goldman JM, Cross NC: A novel BCR-ABL fusion gene (e6a2) in a patient with Philadelphia chromosome-negative chronic myelogenous leukemia. Blood. 88: 2236-2240, 1996

110. Melo JV: The diversity of BCR-ABL fusion proteins and their relationship to leukemia phenotype. Blood. 88: 2375-2384, 1996

111. Pane F, Frigeri F, Sindona M, Luciano L, Ferrara F, Cimino R, Meloni G, Saglio G, Salvatore F, Rotoli B: Neutrophilic-chronic myelogenous leukemia (CML-N): a distinct disease with a specific marker (BCR-ABL with c3a2 junction). Blood. 88: 2410-2414, 1996

112. Kaplan EL, Meier P: Nonparametrical estimation for incomplete observations. J.Am.Stat.Assoc. 53: 457-481, 1958

113. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. J Natl.Cancer Inst. 22: 719-748, 1959

114. Cox DR: Regression models and life-tables. JRSS B 34: 187-220, 1972

115. Breimann: CART-Verfahren: Classification and regression trees. Belmont, CA: Wadsworth, 1984

116. O'Brien PC, Fleming TR: Multiple testing procedure for clinical trials. Biometrics. 35: 549-556, 1979

117. Blaise D, Maraninchi D, Archimbaud E, et al. Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: a randomized trial of a busulfan-cytoxan versus cytoxan-total body irradiation as preparative regimen: a report from the Groupe d'Etudes de la Greffe de Moelle Osseuse. Blood. 79: 2578-2582, 1992.

118. Merx K, Müller MC, Kreil S, Lahaye T, Paschka P, Schoch C, Weisser A, Kuhn C, Berger U, Gschaidmeier H, Hehlmann R, Hochhaus A: 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 16:1579-83, 2002

to inform the patients about the CML-Study IV, which should be modified according to the regulations of the participating center, the conversational style of the physician who obtains the consent, and the patient's specific medical and psychosocial situation.

It is the **aim** of the information process:

1. to enable the patient to participate in the decision in accordance with the ethical and legal principles of the treatment contract which is premised on the autonomy of the patient decision;
2. to convince the patient of the necessity and value of the treatment, including participation in the study, as a precondition for ensuring stable compliance for the entire duration of the treatment and study;
3. to protect the responsible medical and nursing staff from unjustified accusations that could lead to an arbitration process, malpractice law suit or criminal proceedings;
4. bearing in mind the wide and varied communication from cancer patients treated in studies, to influence in a positive way public opinion on the value and necessity of medically and psychologically sound treatment studies; reference can be made here to the well-documented fact that cancer patients participating in therapeutic studies have a better prognosis in general than those treated outside studies.

The discussion below deals only with the initial period of the information process, up to the actual start of the study or treatment. This in no way detracts from the need for a continued, systematic flow of information during the treatment of study patients. The information process, described below, consists of three phases, which may overlap in time, depending on the specific situation.

1. Information on diagnosis, prognosis and general treatment goals

When patients first meet the physicians responsible for the study and its planned treatments, many patients already have prior information, which must be ascertained from the referral letter, possible further consultations with the referring physician and/or in conversation with the patient. With due adaptation to medical and individual variables, the patient is informed – in keeping with normal standards – about the nature and name of CML, its good medium-term prognosis even if untreated, and the general goals and options of treatment. If for no other reason than the current expansion of information sources (books, information acquired from friends or on the Internet, e.g. info@kompetenznetz-leukaemie.de, etc), it may also be necessary to decide whether to mention modalities that are not needed or not possible in the present case. Whether the question of study participation should be raised at the first meeting must be decided according to the individual situation. A step-by-step approach, which gives the patient time to understand and process the information received, is almost always possible in CML, unlike for example in most patients with acute leukemia.

2. Information on study and study participation

Assuming that time has elapsed since the first phase of the information process, it is always possible to involve "supporters" (trusted relatives, friends, etc) of the patient's choice in the second phase. This is generally desirable, not only for humanitarian and psychological reasons, but also to reinforce the stability of consent.

No later than the start of the second information phase the physicians involved should be aware of the following variables:

- Social situation, language level, prior information, "supporters"
- Special treatment risks due to concomitant disorders not leading to exclusion from the study
- Prognostic factors of CML
- In transplantable patients, number, age and availability of siblings
- If possible, findings important for prognosis or choice of treatment, in particular BCR-ABL-status.

Based on this information, it should first be ascertained whether the patient meets the study entry criteria for CML-study IV. At this point of time eligible patients are to be informed about objectives and rationale of the study.

In CML therapy, an entirely new situation has evolved due to the introduction of the tyrosine kinase inhibitor imatinib. Hematologic and cytogenetic response rates are much higher with imatinib than with interferon alpha (IFN) at lower toxicity. Although the rate of progression seems to be less with imatinib than with IFN, the observation times under imatinib with a median of 18-20 months are too short to allow any definite estimate concerning survival and long term toxicity. In addition, patients in complete cytogenetic response (CCR) under imatinib retain BCR/ABL transcripts as markers of residual disease, and resistance to imatinib can evolve after relatively short intervals. Thus, many uncertainties accompany imatinib therapy.

IFN therapy, on the other hand, offers 10-year-survival estimates of 40% in low-risk patients and 75% in low- and intermediate-risk patients with major cytogenetic response at low toxicity.

There is international consensus that combinations of imatinib with IFN and arabinosylcytosin (araC) which are synergistic in vitro might offer further improvement of outcome and should be studied. In favor of combinations is the fact that drugs with different modes of action are combined (e.g. competitive inhibition by imatinib vs. immune modulation by IFN). In the CML study IV, the combinations of imatinib with IFN or araC are compared with imatinib as single agent and IFN standard therapy. High-risk patients are restricted to the imatinib arms.

The IFN standard arm is important in view of the superior 10-year-survival rates with IFN and the short observation times with imatinib, the persistence of BCR/ABL transcripts in CCR and the development of imatinib resistance. IFN can be combined with hydroxyurea (HU) any time. In the case of IFN failure, crossover to imatinib is provided. The sequential treatment design with IFN followed by imatinib might also yield a survival advantage.

After failure of imatinib, an allogeneic stem cell transplantation is recommended for all eligible patients who have an available donor. This design aims to determine the role of allogeneic transplantation in the imatinib era. In an effort to reduce transplant related mortality (TRM) reduced-intensity conditioning will be evaluated in patients 46 years or older.

The CML-Study IV with its comprehensive concept and sequential treatment strategy offers an optimized treatment to essentially any patient with CML. Furthermore, it can be expected that the rational, quality controlled treatment strategy within the study protocol will be more cost effective in the long run than treatment outside the study

This patient group is informed in the normal way about the randomization process. The approach corresponds to that for conventional prospective, randomized, comparative chemotherapy studies. In addition, transplantable patients are genetically randomized according to availability of a donor.

All newly diagnosed Ph- or BCR-ABL-positive CML patients in chronic phase will be randomized regardless if an allotransplant is planned later on. The decision to undergo an allotransplant is solely made by the physician and the patient and is dependent on the patient's risk profile and the imatinib response

Patients are randomized only with knowledge of the individual risk score determined by the New CML Score (www.pharmacoepi.de). This is because high-risk patients will only be randomized among the three imatinib-based treatment arms, as in this risk group IFN has not been shown to prolong survival even when a complete cytogenetic response is achieved. For these patients allografting early on in the course is recommended.

Low- and intermediate-risk patients will be randomized between the 4 therapy arms (imatinib vs. imatinib + IFN vs. imatinib + low-dose araC vs. IFN standard therapy). If the study inclusion criteria are met, the patient is randomized at the Study Coordinating Office by telephone (**+49-621-383-4168**) utilizing a web-based randomization program which stratifies according to the New CML Score. The patient does not need to decide at the time of randomization, whether an allotransplant should be pursued. However, it is crucial that at this point of time the patient's consent for the procedure is obtained and a donor search is initiated. Indication for allografting is dependent upon clinical response and donor availability. Patient, treating physician and the transplant center are partners in this decision-making process. For non-transplantable patients medical therapy including autologous transplantation will be provided, which is guided by the established scores and treatment variables such as hematologic and cytogenetic response.

It is of utmost importance that protocol compliance in the IFN standard arm is not violated. Lacking well defined criteria for IFN failure there is no justification for switching patients to imatinib. It has to be stressed that long-term results of low- and intermediate-risk patients treated with IFN are excellent. For instance, 10-year-survival rates of patients in complete cytogenetic response are up to 80%. Conversely, it remains to be determined whether imatinib prolongs survival compared to IFN, whether imatinib produces long-term toxicity. This uncertainties of imatinib therapy concerning impact on long-term survival and toxicity (despite high response rates) has to be weighed against a proven survival benefit, known response rates and toxicity profile of IFN.

A key factor for the success of any information process oriented towards patient autonomy and stable compliance is that all decisions not reached by randomization must be settled in advance among the participating physicians and centers.

3. Documentation of consent to participate in study, including planned randomization steps and treatment measures

Patient consent should generally be documented in writing (see Patient Consent Form). It is important to ensure that the patient or his legal representative understands the written declaration of consent, and has before signing been allowed sufficient time for reflection and consultation with "supporters" or other physicians (see Informed Consent for CML-study IV, Appendix 2).

In exceptional cases (e.g. inadequate mastery of the language), informed consent can be obtained verbally in the presence of witnesses (nurse, other physician, if possible, additional "supporters"). In such cases a protocol should be prepared which includes the statement that the content corresponds to the study schedule and the text of the written declaration of consent. The witnesses then sign the protocol in an identifiable fashion and indicate their professional qualification or relationship to the patient.

4. Second opinion, withdrawal of consent, informing other physicians involved in treatment, response to refusal of consent

Both physicians and insurance institutions are increasingly stressing the importance of obtaining a second opinion. It has been found that the mere offer of a second opinion, even if not accepted, strengthens the doctor-patient relationship and increases compliance. As possible candidates for consultation the patient should be given the names of hematologists participating in the study or with specialist knowledge in the treatment of CML. All prospective study patients should be told that they are free to withdraw their consent at any time. To maintain study compliance it is important to keep other physicians treating the patient (general physicians or hematologists in community practice, general practitioners) informed about the conduct and aims of the study.
Patients refusing consent must be guaranteed that they will be treated according to the current standard procedure with the same quality of care.

Patient Consent Form

Randomized Controlled Comparison of Imatinib vs. Imatinib/Interferon-α vs. Imatinib/low-dose AraC vs. Interferon-α Standard Therapy and Determination of the Role of Allografting in Newly Diagnosed Chronic Phase CML (CML Study IV)

Patient: .....
(full name)

.....
(date of birth)

Diagnoses: .....

The patient was given the study information on: .....
(date)

by: .....

Witness: .....
(full name, position, address)

The patient was informed about the diagnosis on: .....
(date)

by: .....

Please tick the points discussed.

1. Nature of Disease

You have been diagnosed with chronic myeloid leukemia (CML). The disease is characterized by a chronic phase of variable duration and a progression to acute leukemia, which is usually not amenable to therapy. CML needs to be treated during all stages of the disease. In the chronic phase several treatment options are available, allogeneic transplantation on one hand and non-transplant drug therapy on the other hand. In the latter group two therapeutic options are at hands, which differ with respect to their efficacy and toxicity profiles.

2. Allogeneic Bone Marrow or Stem Cell Transplantation

Transplantation of bone marrow or peripheral blood stem cells from a healthy donor is the only curative modality in CML, at present. The prerequisites for undergoing allogeneic transplantation are a suitable donor (either a family member or someone unrelated but matched to be suitable) and physical fitness of the candidates (appropriate age and no serious other diseases). The success rate is 50-65% when patients are transplanted in the chronic phase. But the outcome has to be weighed against a transplant related mortality of up to 25-30%. The causes of death shortly after transplantation are due

to graft-versus-host-reaction, (i.e., intolerance of transplanted cells derived from donor and recipient organs [liver, gut, skin]), infection during immunosuppression, or failure of the engrafted donor marrow. Later on, although the disease may recur, effective treatment in this case is available.

3. Hydroxyurea, Interferon alpha and Cytosinarabinoside (AraC)

These drugs represent the current standard treatment for patients who are not candidates for bone marrow transplantation due to age limitations or no available donor. Compared with the previous standard therapy hydroxyurea alone, this treatment regimen prolongs survival by one to two years and even far more in low-risk patients and those, who respond well to interferon alpha (IFN) therapy. We know from long-term studies that 40% of patients with low-risk disease can expect to live after 10 years, and 75% of low- or intermediate-risk patients who achieve a cytogenetic response to IFN. These patients experience only mild adverse effects to IFN.

Adverse effects to hydroxyurea are rare and include skin discoloration and pruritus, impaired skin and nail growth, and – remotely – nausea. Fever also has been observed in very rare cases.

Adverse effects to IFN, on the other hand, are common but in general fully reversible and mild. These are mainly flu-like symptoms such as fever, chills, headache, aching limbs, fatigue, loss of appetite, and mild to moderate hair loss. Rarely, after long intake of IFN patients may feel depressed and worn out resulting in somnolence, attention deficit, muscle weakness, or gait imbalance. Other rare side effects include skin changes, altered sensation, vomiting and diarrhea. In very rare cases IFN has been associated with abnormal kidney function, arrhythmias in patients with pre-existing coronary heart disease, and occasionally arthritis-like complaints.

The main adverse effects to araC are hematologic (e.g., a transient decreased production of blood cells in the bone marrow that requires transfusions of blood products and antibiotics) and gastrointestinal (e.g., nausea, vomiting, diarrhea). These side effects are reversible and usually do not interfere when given at the prescribed doses with normal daily activities. For women of child-bearing age contraceptives are recommended with IFN use although normal pregnancies have been reported.

4. Treatment With the Tyrosine Kinase Inhibitor Imatinib (Glivec®)

CML is caused by an increased, uninhibited activity of a specific enzyme, the so called bcr-abl tyrosine kinase. Enzymes by definition are proteins, which let take place certain chemical reactions within the cell, e.g., transduction of cell signals. The altered protein moiety of the bcr-abl enzyme, which leads to unrestricted cell signaling, is the result of fusion of genes called chromosomal translocation (exchange of genetic material occurring during partition of cells). The chromosomal translocation in CML is called Philadelphia chromosome. Recently, the drug imatinib (Glivec®) has been made available that inhibits the enzyme activity of bcr-abl with a fair degree of specificity. Imatinib offers high response rates at low toxicity. It can be assumed that response rates to imatinib therapy may be even further improved when imatinib is combined with the already potent drugs IFN and araC.

Adverse effects to imatinib comprise nausea, vomiting, muscle cramps and fluid congestion=edema (particularly around the eye lids). In general, these untoward effects are readily treatable so that drug discontinuation is not warranted. Other side effects are blood- (i.e., concerning reduction of red-, white blood cells, and platelets in the peripheral blood) and liver-related. The latter is commonly transient but in rare cases imatinib needs to be discontinued permanently, because of more severe liver dysfunction. Therefore, particularly during the first weeks of administration liver function tests need to be checked closely, once or twice weekly. As yet, no information about long-term side effects of imatinib is available. This fact represents an uncalculated risk of long-term imatinib administration.

5. Combinations of Imatinib with IFN or AraC

Combinations of the most potent drugs are promising to pan out into a survival benefit. As yet, it has not been demonstrated that a combination therapy is superior compared to imatinib as single agent or to conventional therapy with IFN. But this might quite possibly be the case in view of emerging imatinib resistance although uncertainties with regard to increased long-term side effects have to be taken into account. Randomization into the different treatment arms is ethical and the study has been approved by the Internal Review Boards (IRB).

6. Rationale of the Study

The main study objective is to determine whether combinations of imatinib with other drugs (IFN or araC) are superior compared to imatinib as single agent. In addition, imatinib-based therapies are evaluated and compared to IFN standard therapy. Study endpoints for evaluating efficacy are survival time, time of chronic phase, and response rates with an acceptable toxicity profile.

7. Purpose of Randomization

In general, in order to be confident which therapy is better than the other the two patient cohorts must not differ except for the therapy they were allocated to. This conformity of patient cohorts is achieved by randomization = random assignment to a treatment arm. It is a fundamental prerequisite to meaningfully compare two therapies.

8. Duration of the Study

It is planned to follow up on the patients until the end of the study or until the patient's death. At certain predetermined checkpoints you agree to have your blood and bone marrow tested for assessment of disease progression. Lab work at 3, 6, 12, 18, and 24 months is mandatory, later on tests are planned on an individual basis. The CML central offices are ready to counsel you anytime about your individual case or when you have general questions such as the latest developments in the field.

9. Use of Blood and Bone Marrow Specimens for Research Purposes

You agree that residual blood or bone marrow which are left over from above mentioned diagnostic tests, can be stored anonymously and used at a later time to try to answer scientific questions in well designed research projects. In general, no extra blood or bone marrow is needed. The quantities that are to be obtained are stated in the protocol. Besides diagnostic use blood and bone marrow specimens will be solely used for research.

If you do not want residual blood specimens to be used for research purposes, please indicate by tick at number 14.

10. Participation of Individuals Younger than 18 Years of Age

Imatinib has not been specifically approved for use in individuals 18 years or younger. This is called "off-label" use of the drug.

11. Insurance Coverage and –Conditions

During the study patients are insured to cover for impairments of health and body (§ 40 AMG) that occur as a result of study drugs or study procedures. This insurance lasts up to three years after the end of the study. The following conditions are excluded: worsening of preexisting health disorders, genetic diseases, or health problems if these occurred as result of a flagrant violation against recommendations of study physicians. If requested the letter of the patient's insurance contracted between the "Deutsche Krebsgesellschaft" and the insurance company can be forwarded. The name of the insurance company is "Gothaer Versicherung" (insurance policy number 11.444.546060). The address and contact person of the insurance company are: Gothaer Allgemeine Versicherung AG 50598 Cologne, phone: +49 (0) 221 308-1370, Werner Bührmann. The insurance contract is regulated by law (AMG).

12. Patient's Freedom to Decide

It is your free will to decide about participating and to be randomized. If you are deemed eligible for allogeneic transplantation the procedure can be done anytime. By participating in the study you probably will make a contribution for improving CML treatment, since clinical studies are key elements in the scientific progress. Later on, you may withdraw from the study without giving further reasons anytime. In this case you will be asked to have a final check done by your treating physician and to agree that the data relating to your disease may be used for documentation. You agree that the data are stored anonymously and to be used for analysis. Your personal data are handled confidentially at all times. Data concerning your name or identification will not appear in the publications of the study, they must never be made public and they are protected by law and the Good Clinical Practice Guidelines (ICH-GCP) which the study physicians abide to.

Emergency care is provided at all times without prior notification and acknowledgment.

13. The Unticked Points Were Not Discussed

Reason:

Refusal by patient ❑

Hazard to patient ❑

14. Patient's Will About Participation, Randomization and Use of Anonymous Data

Will participate ❑

Will not participate ❑

Informing physician: .....
(signature, date)

Witness: .....
(signature, date)

Patient:

(or legal guardian if less than 18 years of age) (signature, date)

The Patient will receive a copy of the consent form

I do **not** authorize that my blood or bone marrow will be used for research purposes
❑

For further questions please contact: Dr. U. Berger and colleagues of the CML Central Office, III. Medizinische Universitätsklinik, Fakultät für Klinische Medizin Mannheim der Universität Heidelberg, Wiesbadener Str. 7-11, 68305 Mannheim, phone: (0621)-383-4168