Treatment Optimization Trial in Chronic Myeloid Leukemia (CML)

CML-Study IV
Randomized Controlled Comparison of Imatinib vs. Imatinib/Interferon-α vs. Imatinib 800 mg
and
Determination of the Role of Allografting in Newly Diagnosed Chronic Phase

Running Title: „GEIST“

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

Version: May 10, 2005

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 Group of Blood and Marrow Transplant Prognosis Score
EBMTR	European Group of 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

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Refer to appendix 6

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2 Synopsis

Title of the Study	Randomized controlled treatment optimization trial in chronic myeloid leukemia (CML): imatinib vs. imatinib/interferon-α vs. imatinib/low-dose araC vs. imatinib after interferon-α-failure; main phase vs. imatinib 800 mg and determination of the role of allografting in newly diagnosed chronic phase CML patients
Coordinator	Prof. Dr. med. R. Hehlmann, Mannheim
Steering Committee	refer to section 1.1
List of Investigators	refer to appendix 6
Study Period	July 2002 until 2012
Objectives	1) Primary imatinib-based vs. imatinib after interferon-alpha(IFN)-failure; main phse v. imatinib 800 mg (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 imatinib after IFN-failure. 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 (3) treatment arms: imatinib, imatinib + IFN, imatinib + low-dose araC, or imatinib after failure of IFN ± hydroxyurea (HU) (± low dose araC). High-risk patients who do not profit from primary IFN will be randomized instead to receive primary imatinib 800 mg. Main Phase: imatinib 400 mg , imatinib + IFN or imatinib 800

	mg.
Patient Numbers	Total number of subjects enrolled n=1600 (total), 400 per treatment group (=n=1200 for the main phase)
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:** 800mg Imatinib p.o. qd **Arm III (pilot phase):** 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 (pilot phase):** IFN, initially 3 x 10^6 IU s.c. qd, later IFN dose increase made according to CBC and attainment of hematologic response. Imatinib, 400 mg p.o.qd. after IFN failure. High risk: primary imatinib 800 mg p.o. qd.
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 the two hitherto most effective anti-CML drugs IFN and arabinosylcytosine (AraC) which are synergistic in vitro might offer further improvement of outcome (delay or prevention of development of resistance, reduction of minimal residual disease) 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 with sequential therapy of imatinib after IFN-failure. High-dose imatinib is studied in high-risk patients.

The treatment arm imatinib after IFN-failure retains the chance of an IFN-induced cytogenetic remission with superior 10-year-survival rates (70-80%) in view of the limited 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 imatinib after IFN-failure might also yield a survival advantage. High-risk patients are restricted to primary imatinib-based therapy.

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.

After termination of the pilot phase the protocol is amended due to the scientific progress as follows:

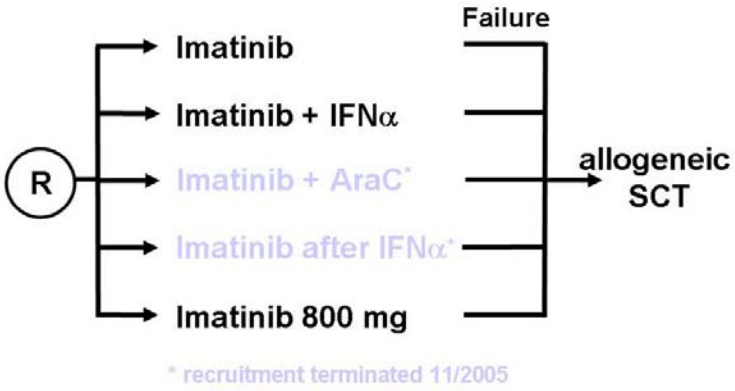
1. Randomization also of low and intermediate risk patients to the imatinib 800 mg arm
2. Closure of the imatinib after IFN failure arm
3. Closure of the imatinib + araC arm

Rationale: all recently published and ongoing studies demonstrate a more rapid achievement of cytogenetic and molecular remissions with imatinib 800 mg compared to imatinib 400 mg. This could translate into better survival by a more rapid reduction of the Ph-clone and postponement of progression and clonal evolution. The

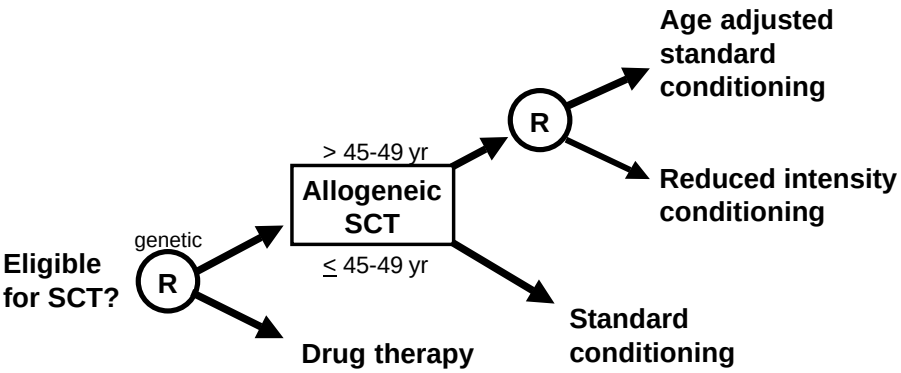
inforcement of the imatinib 800 mg arm represents the logical adaptation of the protocol to the current state of knowledge.

The early termination of treatment arms was defined under certain conditions in section 15.1 (feasibility, compliance). Closure of both treatment arms imatinib after IFN-failure and imatinib + araC was due to feasibility reasons.

2.2 Study Design, Primary Objectives 1 and 2



2.3 Study Design, Primary Objective 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 demonstrated that the combination of IFN and HU as compared to HU monotherapy prolongs survival[3]. 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 (400mg) vs. imatinib in combination with IFN vs imatinib 800 mg (pilot phase vs imatinib in combination with low-dose araC and imatinib after IFN-failure) 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 neutrophil count 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. Increase of basophiles and eosinophiles
4. Hypercellular bone marrow consistent with a chronic myeloproliferative disorder
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

C**hronic 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 heterogeneous. 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** (at least 3 criteria have to be fulfilled)

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

- Presence of blasts in peripheral blood or bone marrow ≥ 10%, but < 30%.under therapy
- 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 aberrations.

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 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 < 450.000/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 molecular 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).

Molecular remission

BCR-ABL/ABL ratio <0,12% (according to 3log reduction as defined by Hughes et al [14-16]

3.3.4 Time to progression

In addition to loss of hematologic and cytogenetic remission with therapy resistance disease progression is defined as an increase of the BCR-ABL/ABL ratio:

1. of 1 log in case of complete cytogenetic remission (CCR)
2. of > 0,12% in case of prior BCR-ABL negativity (CMR)

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[17]. 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	[18]
Splenic irradiation	28	[19]
Busulfan	35-52	[1,2,20-24]
Hydroxyurea	48-69	[1,2,21,22,25-27]
Dose-intensive chemotherapy	45-55	[28-35]
Interferon alpha	55-89*	[1,2,13,24,26,27,36-42]
Imatinib (STI571)	98% alive after 18 months	[43]
Allogeneic Stem Cell Transplantation	40-80% 5-year survival	[44-51,51,52]

* in patients with CCR > 10 years

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.[21,22] 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[25] confirmed the evident survival benefit (median survival of 48-69 months) for HU-treated patients.[1,2,21,22,26,27]

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 %), which were durable when IFN was discontinued[53]. Talpaz and coworkers firstly reported on 7 of 51 Ph-positive patients with CML, who achieved CCR.[36] Since then, rates of CCR reported in monocentric studies varied considerably (up to 38%) dependent on the risk profile.[1,13,24,26,27,37-39,41,42]

In an effort to identify at diagnosis patients with an unfavorable prognosis reliable scores have been developed, most recently the **New CML Score,**[54] which impact on outcome more heavily than any given therapy.[17] 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.[55,56]

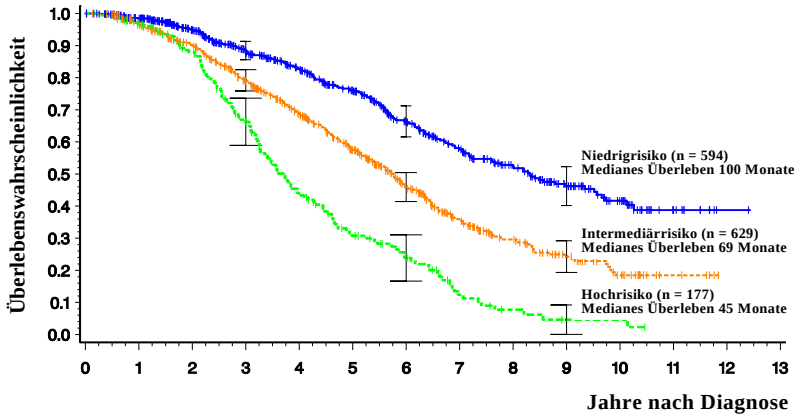


Figure 1: New CML Score.[54] The score is calculated from six clinical variables at diagnosis: age, spleen size in cm below costal margin, platelet count, the percent blasts, eosinophils, and basophils in the peripheral blood (www.pharmacoepi.de). Based on these parameters the score distinctly separates three risk groups with low- (< 780), intermediate- (780 – 1480), and high-risk of death (> 1480). Median 10-year survival rate is 40% for low-risk patients.

Patients on IFN who achieve a cytogenetic response may expect a significant survival advantage.[26,55] The CML-SG could demonstrate such a survival advantage for patients treated with IFN compared to busulfan but not to HU. The smaller differences with respect to survival times and response rates reported in the German randomized trial are explained by a greater proportion of high-risk patients included (e.g., proportion of low- to high-risk patients 0.71 in CML-Study I, 1.79 in the Italian study and 2,26 in the study reported by Kantarjian and Talpaz).[26,41] Comparing results of the German and Italian trials after adjusting for different inclusion- and exclusion criteria survival curves were nearly identical and IFN was superior in the treatment of early chronic phase CML.[57] A meta-analysis of seven randomized trials confirmed the improved survival of IFN compared to busulfan and HU.[58] The evidence-based treatment guidelines issued by the American Society of Hematology[59] advocate a treatment approach that optimally should contain IFN and HU as first line drugs. According to current evidence optimum IFN-treatment should be combined with HU as needed[3].

The median time to major or complete cytogenetic response is 12 months (from 3 to 75 months, n = 104) according to Kantarjian und Talpaz[41] and 17 months (CCR, n = 20) according to Mahon et al[60]. The most reliable predictor of achieving a cytogenetic response is a complete hematologic response (CHR) within 3 months of therapy. For instance, 82% of patients with a CHR within 3 months subsequently achieved CCR[60]. These

findings are in accordance with results of the CML-Study I, in which all cytogenetic responses were preceded by CHR. For patients treated with IFN, who do not achieve a CHR within the first 9 months or at least a major cytogenetic response within 12-18 months, alternative therapies should be considered. On the other hand for patients attaining CCR the estimated overall 10-year survival is 72-78% and in the low-risk group 81% (n=457) [55,61].

By sensitive RT-PCR it was shown that almost all patients with CCR harbor residual BCR-ABL-transcripts. The transcript levels may range 4 logs suggesting a high degree of variability in the quality of cytogenetic responses[62,63-65] BCR-ABL transcript levels are predictive for duration of response as patients who relapsed later on had significantly higher transcript levels at the time of remission[65].

IFN is often fraught with side effects and may compromise quality of life more often than with HU or busulfan[66]. However, life-threatening adverse effects are very rare and unheard of in the usual dose ranges. Common adverse effects and their frequencies (derived from CML-Study I) are summarized in Table 9 (section 9.1.3.5).

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[42]. These results were confirmed only in part by an Italian randomized trial[67]. 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[68]. Retrospective data from Houston showed similar results namely improved cytogenetic response rates but no improved survival with combined therapy[69].

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[70]).

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 [42]
538	50	40 mg 10 days/months	62	28	14	85 (3)	Baccarani et al., 2002 [67]
64	-	10 -15 mg 4 – 5 days/week	74	27	16	95 (3)	Giles et al., 2000 [68]

3.4.1.4 Pegylated interferons

To improve pharmakokinetics two pegylated IFN preparation are being developed by binding polyethyleneglykol (PEG) to IFN: A 1:1 formulation of PEG ^{12000} with IFNα 2b (PEG-Intron) has a half life of 31 and an activity duration of 144 hours[71]. The formulation of a branched PEG ^{40000} with IFNα 2a (Pegasys) has a half life of 77 and an activity duration of 168 hours[72]. Pegylated IFNs are expected to show at least the same efficacy as conventional IFNs with easier application mode (only once weekly) and lower toxicity. In some instances of resistance against conventional IFN a response to PEG-IFN was observed.

A randomized comparison of Pegasys with Roferon demonstrated superiority of Pegasys with regard to hematologic and cytogenetic (Ph+ <35%) remission rates[73].

3.4.1.5 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[74],[75,76]. In an effort to identify compounds, which could selectively inhibit the aberrantly enhanced tyrosine kinase, imatinib, a-phenylaminopyrimidinderivative, was found[77]. 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[78] without inhibiting the proliferation of BCR-ABL-negative cells[79].

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[80].

In a phase I study 83 IFN refractory patients in chronic phase were treated with imatinib[80]. 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 and 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 cytogenetic 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, occurred 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[81]. 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[82]. 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%, Table 3)[83]. 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[84]. The median time to onset of CHR was 0.7 months, of MCR 2.9 months. Cytogenetic response is predicted by early reduction of BCR-ABL-transcript levels[85].

Table 3: Rates of hematologic and cytogenetic responses with imatinib, (phase II-studies).[82-84]

	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

A randomized comparison of primary imatinib vs. IFN in early chronic phase (June 2000 until January 2001, n=1106, IRIS-trial) confirmed the high hematologic (95.3% vs. 55.5%) and cytogenetic remission rates (76.2% vs. 14.5%) for imatinib in comparison to IFN (18 months data) [43].

To evaluate drug combinations of imatinib + IFN, araC, and HU *in vitro* equivocal 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.[86] Topaly *et al*. made similar observation with araC and HU[87]. 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[88]. 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.) will be considered in the dosage recommendations.

Despite of the promising data regarding hematologic and cytogenetic response rates at low adverse event rates with imatinib even in blast crisis, long-term survival and toxicity are unknown. The curative potential of the drug seems to be low in view of observed resistance [89-91] and persistence of BCR-ABL transcripts even in patients with complete cytogenetic remission[14].

Primary therapy with imatinib 800 mg

Several studies suggest that high-dose imatinib (600-800 mg) is more effective than the standard dose of 400 mg. Increasing imatinib concentrations enhance the anti-proliferative effect on BCR-ABL positive cells [79].

A dose-activity relationship could be demonstrated in the phase I clinical trial with imatinib: the cytogenetic response rate with 300-1000 mg/d was 54%, but decreased to less than 10% at dosages of < 300 mg. A toxicity-limiting dosage was not reached at 1000 mg [80].

A comparison of imatinib 800 mg with historical data with imatinib 400 mg of the IRIS-trial demonstrated a higher rate of cytogenetic remissions for patients treated with imatinib 800 mg in late chronic phase patients after IFN-failure [92].

A monocentric phase-II-Study[93] confirmed the superiority of imatinib 800 mg in newly diagnosed CML patients. 103 (90%) of 114 patients achieved a complete cytogenetic remission after a median follow-up of 15 months. Compared to a historical control treated with imatinib 400 mg, patients on imatinib 800 mg achieved a cytogenetic response earlier, and the rates of complete cytogenetic (90% vs. 70%, p=0.0005), molecular and complete molecular (BCR-ABL transcripts not detectable; 28% vs. 7%, p=0.001) remissions were higher. High-dose imatinib was well tolerated with somewhat more myelosuppression. After one year, 66% of 70 evaluable patients were still on 800 mg/d.

In another study, newly diagnosed CML-patients selectively received dose intensification. The rate of patients treated with a median daily dose of 600 mg and achieving a complete cytogenetic response after 12 months was higher than in patients treated with a lower median daily dose (93% vs. 78%, p=0.0015). The probability to achieve a molecular remission was higher for patients treated with 600 mg (58%) than for patients treated with a median daily dose of 500-599 mg (33%) or less than 500 mg (32%) [94].

A meta-analysis [95] of three studies (50 patients on imatinib 400 mg and two studies with 172 patients on imatinib 800 mg (400 mg twice a day) with identical inclusion criteria demonstrated an advantage for high dose imatinib: significantly more patients achieved a major (67% vs. 47%, p=0.0007) and a complete molecular remission (24% vs. 8%, p=0.02) with imatinib 800 mg.

In summary, high-dose imatinib (800 mg) treatment seems to be superior to treatment with imatinib 400 mg with regard to cytogenetic and to molecular remission. The clinical benefit for patients in early chronic phase remains to be determined.

3.4.2 Allogeneic Stem Cell Transplantation (SCT)

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**)[52].

Table 4: Transplant risk score for CML[52]. 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

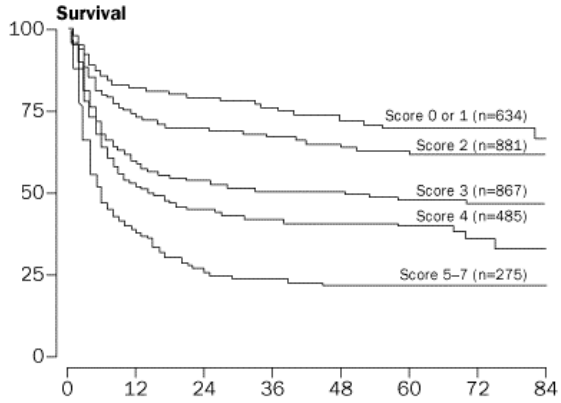


Figure 1: Survival probability of risk groups according to the EBMT score[52].

Disease-free survival rates post allogeneic SCT with related donors vary according to center and age selection of the patients between 38% and 75%[44,45-52]. The outcome is more favorable when SCT is carried out within the first two to three years after diagnosis[96]. 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%.[50,97,98] 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[99].

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[100] and analyzing IFN-treated or transplanted patients from the Italian Cooperative Study Group[101]. 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[102].

In recent years **non-myeloablative SCT** has yielded encouraging results with respect to reduction of TRM (**Table 5**)[103-107] . It offers acceptable toxicity profiles, which is of particular importance in patients older than 45 years of age[103]. Facing a bewildering array of various conditioning regimens and dosages used unfortunately no standard conditioning has emerged[108]. 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)[109]	**McSweeney et al. (2001)**[103]	**Slavin et al. (1998)**[106]	**NIH/Childs et al. (1999)**[107]	**Khouri et al. (1998)**[110]	**Giralt et al. (1997)**[105]	**Or et al, (2003)**[104]
Age (median)	18 – 72 (54)	31 – 72 (56)	1 – 56 (34)	23 – 68 (51)	47 – 71 (60)	27 – 71 (60)	3 – 63 (35)
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	Flu + Bu + ATG
CML in CP/Total, n	17/156	4/45	6/26	4/50	0/15	0/15	24/24
Graft Failure (%)	18 w/o Flu, rarely w/ Flu	20	0	2	0	0	0
Acute GvHD (Grade II – III) (%)	50	47	19	8 (I + II)	0	20 (I + II)	37.5
Acute GvHD (Grade IV) (%)	7	-	5	6 (III + IV)	6 (III + IV)	0	12.5
Chronic GvHD (%)	65	51	36	23	13	0 (n = 5)	54
Median Follow-up (days)	220	417	240	-	180	100	42 (months)
Progression free Survival (%)	50 (0.6 y)	-	81 (0.7 y)	55 (0.5 y)		13 (0.3 y)	85 (5 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)	85 (5 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)[111]	**Elmaagacli et al. (2002)**[112]	**Schmitz et al. (2002)**[113]	**Bensinger et al. (2001)**[114]

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[115,116] and one metaanalysis[117] 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[118]	AML	CR1	101	100	32	23±11
Clift et al[119]	CML	CP	147	96.5	37	Minimum 12
Devergie et al[120]	CML	CP	120	98.3	36	42
Ringden et al[121]	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.[122] Simonsson et al.[123]). 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[124]. 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 (ASH) 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[59].

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)[125].
- 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)[102].

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[54].

	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

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

- **Question 1:** Does primary imatinib-based therapy (main phase: therapy with imatinib 800 mg) cause higher rates of hematologic, cytogenetic and molecular response (main phase: within 12 months), prolonged survival or longer duration of the chronic phase than the strategy imatinib after IFN failure (main phase: than therapy with imatinib 400 mg)?
  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. In a phase III study 76% of imatinib-treated patients attained a CCR. 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 – 81% among patients with CCR. In several studies (observational and historical comparisons) a higher rate of cytogenetic and molecular response for patients on imatinib 800 mg compared to imatinib 400 mg could be demonstrated. The study therefore aims to examine whether the high hematologic and cytogenetic response rates obtained with an imatinib-based therapy (main Phase. imatinib 800 mg) will confer improved survival compared to conventional IFN standard therapy (main phase: imatinib 400 mg) 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 with acceptable toxicity.

- **Question 3: What is the role of HSCT in the imatinib era?** 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 potential 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, primary imatinib-based therapies to imatinib after IFN failure 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. Comparison of primary imatinib-based vs. imatinib after IFN-failure therapy (main phase: imatinib 800 mg vs. imatinib 400 mg and imatinib + IFN) (hematologic, cytogenetic and molecular response (main phase: at 12 months), 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 primary imatinib and sequential imatinib after IFN-failure strategies.
4. Analysis of differences in the presentation, phenotype, 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 (imatinib 800mg and others) in high risk patients and 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:

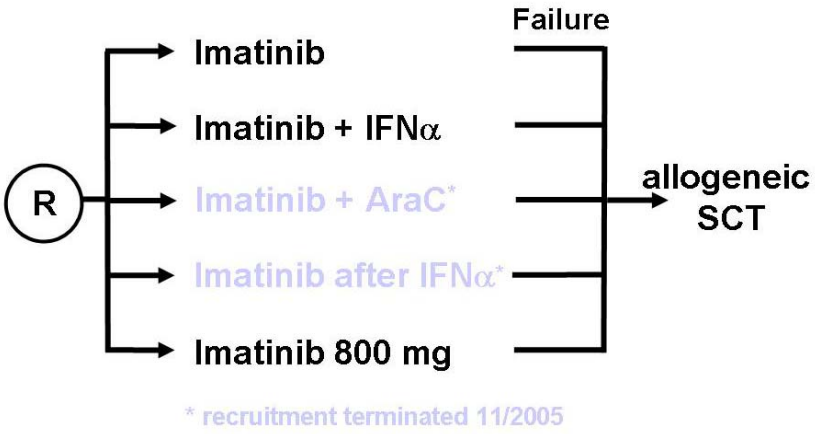


Figure 3: Study scheme – Randomization into 4 treatment arms, refer to primary objectives 1 and 2.

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

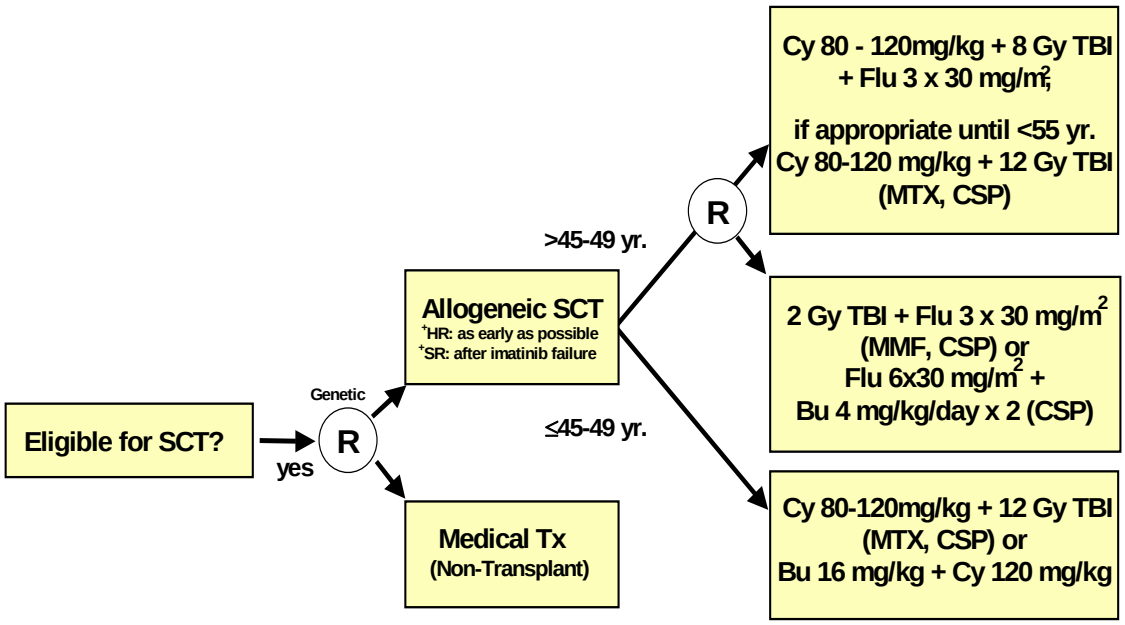


Figure 4: Study scheme – Role of allografting after imatinib failure and of conditioning with reduced intensity, refer to primary objectives 3 and 4. Flu = Fludarabin, Cy = Cyclophosphamide, Bu = busulfan, MTX = methotrexate, CSP = Cyolosporin A, TBI = total body irradiation.

5.2 Recruitment Period, Sample Size

Patients are recruited over 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 10% 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 recruitment phase may be extended until 1600 patients are included. The randomization procedure is 2:1.1 in favour of imatinib 800 mg until recruitment is equal in all arms. Afterwards it 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, anagrelide and imatinib until 6 weeks prior to randomization 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 (main phase: three) treatment arms, imatinib vs. imatinib + IFN vs. imatinib + low-dose AraC vs. imatinib after IFN-failure (Main phase: imatinib 800 mg). High- risk patients will only be randomized into primary imatinib-based therapies, 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. A fourth treatment arm with primary high dose imatinib (800 mg/die) is offered for this group of patients. Free drug is provided by Novartis Company for the dosage exceeding the standard dose of 400 mg/die.

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 for 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 imatinib after IFN-failure are switched to imatinib 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 and 800 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.

Imatinib 800 mg is administered similarly.

If the patient experiences intolerance to imatinib then the single daily dose of 400 (800) mg imatinib can be split into two doses administered twice daily at doses of 200 (400) 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 since 2002 for primary therapy of CML in all phases. 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 resistance) 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 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 or 800 mg daily at the 2 and 6 months of imatinib therapy checkpoints.
- No major cytogenetic response within 12 months (no 1-34% Ph+ cells) despite dose escalation to 600 8800) mg after months 2 and 6.
- 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 or BCR-ABL/ABL ratio >0,12% for patients with prior complete molecular remission
- Newly detected BCR-ABL mutations.

Patients randomized to imatinib after IFN-failure will be switched to imatinib in the event of IFN failure (IFN resistance or IFN intolerance). Thereafter, criteria of imatinib failure are applied.

Treatment with imatinib 800 mg starts after 6 weeks treatments with imatinib 400 mg (to avoid cytopenias).

9.1.2.2 Imatinib + Interferon alpha

Imatinib is dosed and administered as described above for imatinib 400 mg. The addition of IFN should be commenced not earlier than 6 weeks after initiation of imatinib-therapy. IFN should be started with a dose of 1.5 mill. IU as a flat dose thrice weekly and gradually escalated to 3 mill IU thrice weekly 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 neutropenia persists in spite of

interruption of IFN, imatinib is discontinued until recovery of neutrophils. A reduction of imatinib to less than 300 mg/day should be avoided because of the risk of developing imatinib resistance. 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.
The initial dose of PEGASYS in combination with 400 mg imatinib is 135 µg Pegasys/week which can be increased to 180 µg/week dependent on tolerability. If neutrophils drop below 1,000/µl or platelets below 75,000/µl, Pegasys should be interrupted.

Economic considerations: The recommended initial dose of IFN of 4.5 Mill. IU per week in combination represents 7% of the recommended dose of IFN of 63 Mill. IU per week for IFN-monotherapy. These marginal additional costs will most probably be compensated by interruption of imatinib in those cases in which discontinuation of IFN does not improve neutropenia rapidly enough.

9.1.2.3 Imatinib + Low-Dose AraC

Imatinib is dosed and administered as described above for imatinib 400 mg. The addition of low-dose araC (arabinosylcytosin, Alexan®) should be commenced not earlier than 6 weeks 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 Imatinib after IFN-failure

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.

If PEGASYS is used, the initial dose of PEGASYS after cytoreduction with HU is 180 µg Pegasys/week. HU should be decreased accordingly. To avoid adverseevents paracetamol (0.5 – 1 g) should be administered 1-4h after injection. In case of intolerability PEGASYS dose should be decreased step by step.

9.1.3.2 Interferon-Failure (Resistance or Intolerance)

In the event of IFN failure (intolerance or resistance) patients are crossed over to imatinib. 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 sequential treatment 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. 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 available (registration or free drug).

9.1.3.5 IFN Adverse Effects

Adverse effects are more likely encountered with IFN than HU or busulfan[66], 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 to four hours 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 (see scheme in Fig 4, chapter 5.1).

High-risk patients with very low transplantation risks (EBMT score 0 and 1) should be transplanted as early as possible.

In older patients reduced-intensity vs. standard conditioning will be evaluated (see EBMT protocol).

9.3.2 Conditioning

Patients 45 years of age or younger should receive conditioning with

- 12 Gy fractionated TBI (2x/day over 3 days) followed by cyclophosphamide at a total dose of 2 x 60 mg/kg[119] **or** with
- high-dose busulfan at a dose of 16mg/kg plus cyclophosphamide 30 mg/kg for 4 days [111,126].

By exception, due to logistical reasons, cyclophosphamide may precede TBI. 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 McSweeney et al., Blood 2001

  or fludarabine 6 x 30mg/m^2/day plus busulfan 4 mg/kg/day x 2 plus CSP as GvHD-prophylaxis according to the protocol of Or and Slavin, Blood 2003 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 conditioning regimen.

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.

Each center decides with the first patient which conditioning regimen will be used, but has then to adhere to this decision for all future study patients transplanted at the center.

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[54] 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 all patients after imatinib failure, for high-risk patients or subjects with very low transplantation risk (EBMT score 0-1) 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:

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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).
- Demographic data: education, marital status, occupation, smoking habits.
- Physical examination: spleen size (measured in cm below costal margin and/or by ultrasound), liver span in cm at MCL, extramedullary disease (lymph nodes, skin), height, weight.
- CBC + differential, reticulocytes, normoblasts, LDH.
- 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[127]. Detection of 9q+ deletions[128,129]
- Bone marrow aspirate (combined with cytogenetics).
- 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.
- Allocation to SCT according to eligibility and donor availability.

10.2 Follow-up Investigations (CRF 2)

10.2.1 Every 3 months during the first 2 years, every 6 months thereafter

- Current medical condition and physical examination (assessment of extramedullary disease, spleen size, liver span, current weight)
- **CBC + differential for assessing hematologic response**, reticulocytes, normoblasts, LDH
- SCT – donor availability
- Disease stage
- Drug doses administered (patient passport, appendix 7) and tolerance
- Adverse effects: record symptoms, severity grade (WHO), relationship to therapy administered
- **Cytogenetics for assessment of cytogenetic remission**
- **Molecular genetics for assessment of molecular remission**

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. Documentations every 3 months during the first 2 years are mandatory, thereafter every 6 months. 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.

10.2.2 Every 12 months

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

10.3 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).

10.4 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, PD Dr. Schoch in Munich, and Prof. 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 10×10^9/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 cytogenetic laboratory (sample retrieval form, see appendix 10).

Important: please obtain samples for cytogenetic analysis preferably Monday to Wednesday.

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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 Prof. 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.

Prof. Dr. A. Hochhaus / Priv.-Doz. Dr. A. Reiter
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68305 Mannheim
Tel.: 0621/383-4232
Fax: 0621/383-4201
E-Mail: andreas.hochhaus@uni-hd.de; andreas.reiter@medma.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
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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 pilot 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 5 years, follow up will also 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 α = 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[130] 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[130] 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 and depending on remission rates observed in this study, it may be considered in the future to drop one treatment arm, e.g. imatinib/araC. This may increase patient numbers in the other arms and consequently statistical power. If the arm imatinib after IFN-failure has to be closed prematurely (e.g. due to lack of compliance) then comparison of imatinib-based treatment results with results from metaanalyses of IFN-treated patients within the Collaborative Prognostic Factor Project is planned. The analysis of high risk patients treated with 800 mg imatinib is planned together with a projected Italian study that compares 400 and 800 mg imatinib in high risk patients.
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[131] will be used. Survival probabilities within the treatment arms will be compared by logrank test[132]. 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[133] and the CART methodology[134] will be applied.

Interim analyses of the primary study endpoints will be performed in the years 4, 6, and 8 since study activation. Analyses of the hematologic, cytogenetic and molecular remission rates will be performed also in the years 2, 3 and 5. While protecting the type I error probability of $\alpha \leq 0{,}05$ the group sequential design according to O'Brien-Fleming[130] will be used. According to this model error probabilities are

α (4th yr.) $\leq$ 0,00005,

α (6th yr.) $\leq$ 0,00420,

α (8th 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, Windows NT, software: SAS, Oracle).

15.4 Duration of the study and sample size calculation (main phase)

15.4.1 Molecular remission at 12 months as new primary outcome parameter

Molecular remission is defined by a BCR-ABL/ABL-ratio < 0.12%.
With regard to the analyses of the outcome parameters „Time to progression" and „Survival", during the main phase patients are randomised into three arms with a ratio of 1 (imatinib 400 mg) : 2 (imatinib 800 mg) : 1 (imatinib + IFN), until equal sample sizes have been achieved in each of the three arms. Afterwards, the ratio will be changed to 1:1:1.
Since between the treatment arms "imatinib + IFN" and "imatinib 400 mg" no difference with respect to the rate of molecular remission at 12 months is expected, these arms are analyzed together.
Hence, the null hypothesis H0 with regard to molecular remission at 12 months is given by:
The rate of molecular remission under "imatinib 800 mg" (A) = the rate of molecular remission under "imatinib + IFN" and "imatinib 400 mg" (B)
Accordingly the alternative hypothesis H1 is given by:
The rate of molecular remission under "imatinib 800 mg" ≠ the rate of molecular remission under "imatinib + IFN" and "imatinib 400 mg"
Relating to preliminary data [e.g. MDACC Houston, however, with another definition of molecular response [93] relevant differences can be expected, which might be established before the termination of recruitment. Hence, a group-sequential analysis plan according to O'Brien-Fleming was chosen [130]. With this procedure it is possible to test the null hypothesis at three different time points (2007, 2008, 2009) while adhering to an overall α-level of 0.05 (two-sided). Significance levels for the singular tests are given by

$\alpha 1 = 0.00052$ (first test)

$\alpha 2 = 0.01411$ (second test)

$\alpha 3 = 0.04507$ (final test)

A power of 0.8 was selected.

Given rates p1 = 25% patients with molecular remission and p2 = 50%, a total of n = 68 patients per group (A) and (B) would be needed to falsify the null hypothesis with a probability of 80% using Fisher's exact test with the final $\alpha 3 = 0.04507$ (sample size calculation with software PS Version 1.0.15). Accordingly, 68 patients will have to be randomized into the treatment arm "imatinib 800 mg" and 34 patients into each of the treatment arms "imatinib + IFN" and "imatinib 400 mg".

When considering all available remission data at 12 months for the patients randomized until July 2005, the sample size ratio would be 1 to 2 for (A) vs. (B). Under otherwise equal assumptions for the sample size calculation, the enclosure of 100 patients of the arms "imatinib + IFN" and "imatinib 400 mg" (B), randomized either earlier or from 2005 onwards, would afford the additional remission data of only n = 50 patients newly randomized into the arm (A) "imatinib 800 mg".

15.4.2 Securing the answer to the previous main comparison: IFN-based therapy vs. imatinib-based therapy

For patients with low- or intermediate-risk51, the primary focus was the comparison of survival between patients that had been randomized to an IFN-based first-line therapy (median survival had been assumed to be 77 months) and patients, which had originally been randomized to an imatinib-based first-line therapy (median survival had been assumed to be ≥ 101 months). With termination of the arm "imatinib after IFN-failure", which will comprise about 125 patients until July 2005, the previous main question cannot be answered with patients from the CML study IV alone. In this case, it was determined in the study protocol of 18th November 2003 that data of several hundreds of IFN-treated patients from the Collaborative Prognostic Factors Project will be included. The exact number depends on the completeness of the baseline factors adjusting for different risks in survival which is necessary for this (historical) comparison. Furthermore, all patients that have been or will be randomised into the imatinib-based arms will be considered. The answer to the former primary question is thus not endangered.

15.4.3 Consequences for the answer to the former second main question: Comparison of three imatinib-based therapies

A: Comparison of "imatinib + IFN", "imatinib 400 mg", and "imatinib+AraC" (until July 2005).

Also from July 2005, randomization in the treatment arms "imatinib + IFN" and "imatinib 400 mg" will continue. Until July 2005, the treatments arm "imatinib + araC" will comprise about 160 patients. A comparison of survival probabilities between all three arms will be possible on the basis of a co-operation with other European study groups. There is a corresponding agreement with the French colleagues, who examine the same question, i.e. the comparison of survival probabilities of "imatinib + araC" vs. "imatinib 400 mg". Thus, the complete answering of the second former main question is secured.

B: Comparison of "imatinib + IFN", "imatinib 400 mg", and "imatinib 800 mg" (from July 2005).

Since July 2002 about 480 patients have been randomised into the three imatinib-based first-line treatment arms. So far, less than 10% have been transplanted, so that the assumed sample size reduction of 30% due to allogeneic SCT in first chronic phase can be corrected downwards. Under the assumption of 10% SCT in first chronic phase, about 140 patients per arm will stay at risk for the endpoint of interest i.e. survival under imatinib-based therapy according to intention to treat analysis.

The former assumption to be able to recruit 320 patients per year (1600 patients in 5 years, respectively) did not hold. In the judgment of the study steering committee, some study centers did not report their patients to the CML study IV because of their reservations regarding the arm "imatinib after failure of IFN-based first-line therapy". Under the assumption to be able to randomize about 250 patients per year from July 2005 onwards, the formerly calculated sample size of n = 280 would be reached after three years, if randomization is conducted with a ratio of 2 (imatinib 800 mg): 1 (imatinib 400 mg): 1 (imatinib + IFN). If randomization is terminated after 760 patients in July 2008, 190 patients should have been randomized into each of the two latter arms. With a sample size reduction of 10%, about 170 patients per arm would be available. In addition to the 140 patients mentioned above, 310 patients could thus be under investigation. The recruitment of 380 patients for the arm "imatinib 800 mg" would lead to 340 evaluable patients, again considering a 10% sample size reduction due to SCT in first chronic phase. Until July 2005, an additional number of 10 high-risk patients were randomized into the "imatinib 800 mg" arm

Even under the more optimistic assumption to be able to randomize 300 patients per year, recruitment should last for at least 3 years. Thus, the power to detect small differences would be increased. This might be particularly important with regard to median event times differing considerably from the assumed ones which could only be prognosticated in all study arms.

Originally, differences in the survival probabilities should be tested in a confirmatory fashion. The testing was based on the closed test procedure of Marcus et al. 118 within the framework of a group-sequential analysis plan and with a chosen significance level α=0.04294 for the final test. Due to the change in randomisation, it is no longer possible to perform the confirmatory testing with the closed test procedure. Instead, intention to treat analysis with regard to survival will be performed descriptively.

15.4.4 Primary outcome "Time to progression"

While for "imatinib 800" rapid advantages with regard to molecular remission are expected, rather long-term differences between "imatinib 400 mg" and "imatinib + IFN" are assumed. For this reason, these two arms are distinguished, too. Apart from survival time, duration of chronic phase, rates of hematological, cytogenetic and molecular remission, the endpoint "time to progression" will be compared between the three arms. The advantage of "time to progression" over overall survival and duration of chronic phase is its closer relation to the randomized "intention-to-treat (ITT)" therapy. Results are rather interpretable as a consequence of the randomized treatment, especially when therapy strategies have completely changed a long time before the end of chronic phase.

Considering the definition of imatinib failure, the following events are specified for "time to progression":

a. No complete hematological remission at three months (examination at this time point is mandatory, to give each therapy the same chance of success, three months should actually have passed).

b. No complete cytogenetic remission at 12 months (examination at this time point is mandatory, to give each therapy the same chance of success, 12 months should actually have passed).
c. Loss of complete cytogenetic remission after achievement of complete cytogenetic remission within the first 12 months (regular patient examination is needed)
d. End of chronic phase (i. e. accelerated phase, blast crisis)
e. Death

Also for the analysis of the primary outcome "time to progression", recruitment duration of three years is meaningful. Again, the median times to event have not been observed to date and had to be prognosticated.
The analysis of "time to progression" is conducted after the final analysis of the first primary outcome parameter "molecular remission at 12 months" has been performed.

The null hypothesis H0 is given by:
"Time to progression" under "imatinib 800 mg" (A) = "Time to progression" under "imatinib+IFN" (BA) = "Time to progression" under "imatinib 400 mg" (BB)

The alternative hypothesis H1 is given by:
"Time to progression" under (A) ≠ "Time to progression" under (BA) and / or "Time to progression" under (A) ≠ "Time to progression" under (BB) and / or "Time to progression" under (BA) ≠ "Time to progression" under (BB)

A refusal of H0 means that statistically significantly there had been no equality between the three therapies. At this stage, this does not allow any conclusion with regard to statistically significant differences between two particular therapies. However, with the closed test procedure of Marcus et al.[135] it is possible to test the sub-hypotheses H0_A_BA: (A) vs. (BA), H0_A_BB: (A) vs. (BB), and H0_BA_BB: (BA) vs. (BB) with the same α-level as for H0 under the condition, that H0 was refused. However, if H0 was not refused, no sub-hypothesis is allowed to be tested.
Under the consideration that differences may possibly be identifiable earlier, the group-sequential analysis plan of O'Brien-Fleming [130] was chosen again. With a total α-level of 0.05 (two-sided) H0 and, if applicable, the three sub-hypotheses are tested at three time points (2008, 2010, and 2012):

$\alpha 1 = 0.00052$ (first test)
$\alpha 2 = 0.01411$ (second test)
$\alpha 3 = 0.04507$ (final test)

Given 310 evaluable patients per arm, a recruitment period of three years, an additional follow-up of four years, and assuming exponential distribution for all three arms and a median event time of 72 months for one of the arms, under the final $\alpha 3 = 0.04507$ (two-sided) it would be possible to identify a statistically significantly different median event time ≤ 52 months or ≥ 104 months with a power of 0.8 under application of the log-rank test (sample size calculation with software PS Version 1.0.15).
Under consideration of a higher number of evaluable patients, either randomized earlier and / or additionally recruited, it would be possible to detect even smaller statistically significant differences.

"Time to progression" is an outcome where events can be analyzed within a reasonable amount of time and where events are closely linked to the current medical understanding of therapy failure. However, regular

evaluation of hematological, cytogenetic, and molecular data is inevitable for the correct analysis of this parameter.

15.4.5 Other (exploratory) analyses (all with differentiation and comparison of the randomized therapies)

Complete hematological remission

Rates of patients achieving a complete hematological remission are compared. Time to first observation of complete hematological remission is analyzed.

With respect to valid and reliable results for the analysis of the primary outcome parameter "time to progression" (definition see above), a regular examination of hematological remission is essential, especially in the first year of therapy.

Cytogenetic remission

Rates of patients receiving a certain quality of cytogenetic remission at medically relevant time points (e.g. at the time when a decision about imatinib failure is made) are investigated. Prognostic relevance for progression and, if possible, for survival is examined. Time to first observation of at least partial remission and time to first observation of complete cytogenetic remission are analyzed.

With respect to valid and reliable results for the analysis of the primary outcome parameter "time to progression" (definition see above), a regular examination of cytogenetic remission is essential.

Molecular remission

Additionally to the comparison of the primary outcome, rates of patients receiving a (complete) molecular remission are determined at medically relevant time points (e.g. at the time when a decision about further imatinib therapy is made), absolute BCR-ABL/ABL-quotients are compared, the prospective establishment of a cut-off value with prognostic relevance for progression and, if possible, for survival is intended and the time to the first observation of (complete) molecular remission is analyzed.

With respect to valid and reliable results for the analysis of the primary outcome parameter "time to progression" (definition see above), a regular examination of molecular remission is essential.

15.5 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.

Reference List

(1) Hehlmann R, Heimpel H, Hasford J et al. Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: Prolongation of survival by hydroxyurea. Blood. 1993;82:398-407.

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