Feasibility study using repeated intensive chemotherapy courses for patients with primary acute lymphoblastic leukemia in adults age 18 - 39 years inclusive

A phase II study

PROTOCOL

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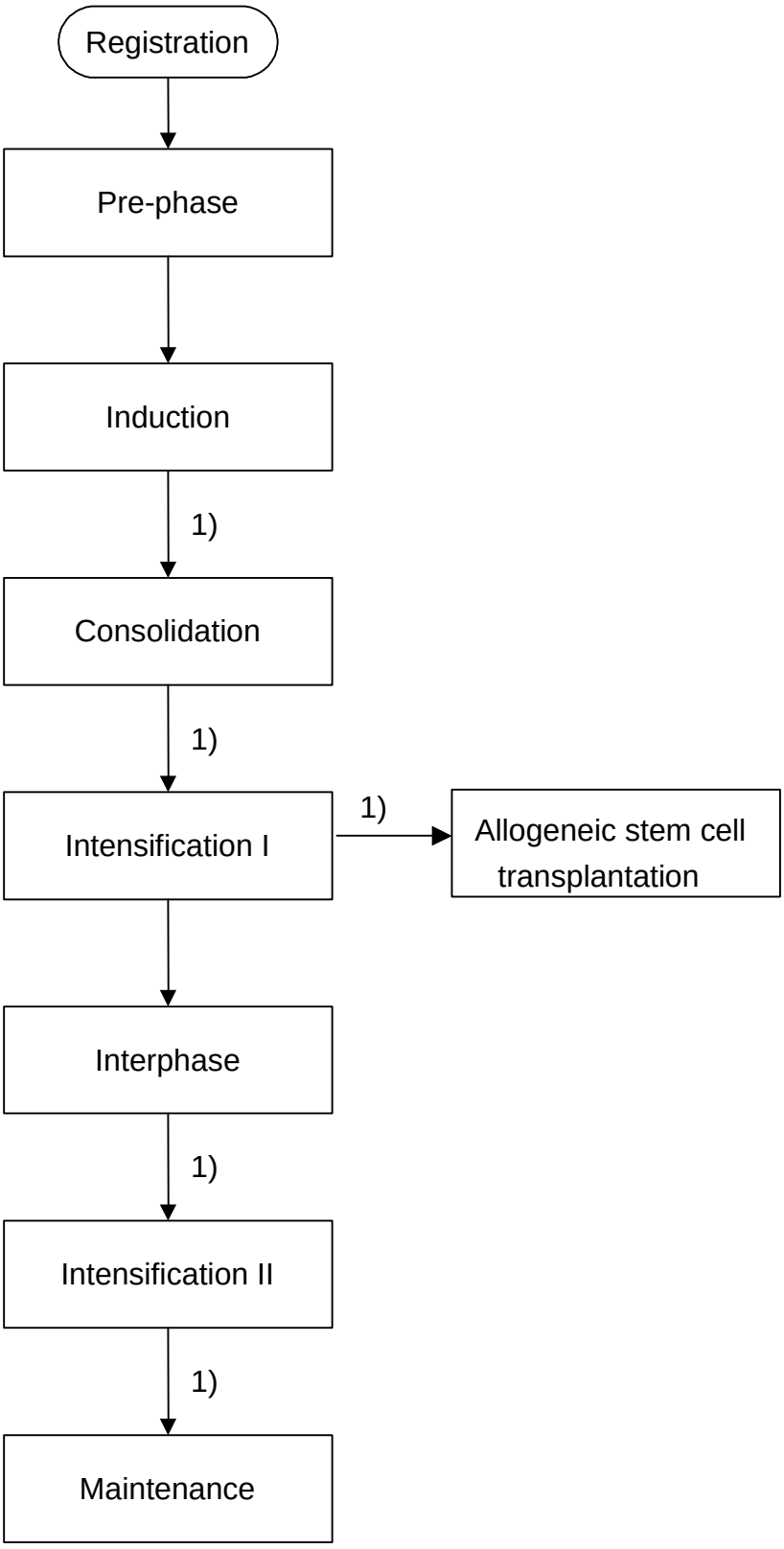
1 Scheme of study



1) Patients in CR, otherwise off protocol treatment

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3 Synopsis

Study phase	Phase II
Study objectives	Evaluation of feasibility of an intensified treatment protocol in adult patients with ALL
Patient population	Patients, with ALL, non-mature B cell, previously untreated, age 18-39 years inclusive
Study design	Prospective, multicenter, non-randomized
Duration of treatment	Expected duration of pre-phase, induction, consolidation, intensification I, interphase and intensification II will be at most 10 months; maintenance will continue until 2 years after day 1 of pre-phase
Number of patients	50
Adverse events	Adverse events will be documented if observed, mentioned during open questioning, or when spontaneously reported.
Planned start and end of recruitment	Start of recruitment: II 2005 End of recruitment: II 2007

4 Investigators and study administrative structure

Responsibility	Name	Affiliation/Address
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4.1 Cytological immunophenotype review

Review by the HRC will be performed at diagnosis.
4 unstained blood and 6 unstained bone marrow smears should be sent together with a filled out HRC cytology form and a copy of the report of the immunological marker analysis to Dr. M.B. van 't Veer, Hematocytology Review Committee, Erasmus MC – Daniel den Hoed, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands, at the time of registration. Confirmation of diagnosis is not necessary for registration or start of treatment.

4.2 Cytogenetic review

Central review will be performed for cytogenetic analysis at diagnosis.
Each cytogeneticist, responsible for the cytogenetic analysis of the patients in a hospital will be notified automatically by email of the registration of a patient from that hospital in the study. A filled out cytogenetic form together with 2 representative karyotypes and a copy of the original cytogenetic report is requested to be sent within 3 months to the HOVON Data Center for central review.
If additional FISH analysis was performed, a filled out FISH form together with a copy of the original FISH report is also requested to be sent with the cytogenetic data for central review.

5 Introduction

5.1 Acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is a malignant disease that originates from B- or T-lymphocyte precursors. Malignant transformation is a consequence of somatic mutation in a single lymphoid progenitor cell. This mutation might occur at different stages of B- or T-cell development. The level of differentiation of the dominant leukemic clone is well established by immunophenotyping of the leukemic cells. Analysis of T-cell receptor gene or immunoglobulin gene rearrangements have been frequently used to document the clonal origin of the disease.
Treatment regimens for acute lymphoblastic leukemia (ALL) have evolved empirically into complex schemes that use numerous agents in various doses, combinations, and schedules. Unfortunately few of the individual treatment components have been tested rigorously in randomized trials. Thus, it is difficult to analyze critically the absolute contribution of each drug or dose schedule to the ultimate outcome. Numerous non-randomized trials have attempted to answer these questions, but

multiple alterations in study design between sequential trials have made it difficult to assess the exact merit of each modification (1-7).

5.2 Remission induction

In adolescents and adults during the last 20 years of EORTC-LCG ALL studies the treatment results have improved. At the beginning CR rate and long term disease free survival were 40-50% and 20%, respectively. Current combinations of vincristine, corticosteroids, an anthracycline, asparaginase and cyclophosphamide result in a complete remission rate of more than 80% in adult patients (1-7). In vitro and in vivo sensitivity to corticosteroids in the remission induction phase seems to predict for prognosis (GIMEMA) (7). In children dexamethasone gave better results than prednisone. For adults the EORTC ALL-4 trial currently investigates this question. Induction therapy has been further intensified by increasing the dose of cyclophosphamide, cytarabine and methotrexate or by adding a new drug. The attempt of such approach is to destroy leukemic cells before they develop selective drug resistance. In childhood ALL, L-asparaginase appears to prolong DFS when given during consolidation (8,9).

5.3 Post-remission therapy

To improve the prognosis of adult patients with ALL the current consensus is not to use a single protocol for all ALL patients but to use, after achievement of complete remission, different protocols according to well defined risk groups (3, 10). More rapid cytoreduction during the induction course may not increase the already high CR rate, but it is too early to tell whether it will produce demonstrably longer remission durations.

Consolidation with high dose Ara-C and/or methotrexate has definitely improved the prognosis of certain subsets of ALL (mature B, T ALL, pro-B ALL), but its value remains unproven or is absent in other subsets (2, 3). Allogeneic SCT has only been shown more valuable than autologous SCT or intensive maintenance in younger patients with poor prognosis ALL (Ph+ALL) (7, 10). Deleting long-term maintenance treatment is probably detrimental in certain subgroups of ALL (common/pre-B ALL) but randomized trials are not available.

Since the beginning of the eighties the EORTC Leukemia Group performed 4 successive randomized studies on adult ALL. The ALL-3 study included high dose Ara-C consolidation and a randomization between an intensive maintenance regimen and autologous stem cell transplantation; allogeneic stem cell transplantation was offered to those who had an HLA-compatible family donor. Meta-analysis with the more or less similar French LALA trial did not show a difference in DFS and survival between the two arms (unpublished data). The most recent

study (ALL-4) compared longterm intensive maintenance courses with autologous stem cell transplantation followed by low maintenance; allogeneic stem cell transplantation was part of the study for those with a HLA identical donor. The current complete remission rate after the remission induction regimen in the ALL-4 is approximately 70% and after "consolidation" approximately 80%. Differences between the randomized arms are currently not apparent. Survival at 5 years is in the range of 35-40%. The relapse rate during the first 2 years of remission is high.
The results from the HOVON studies (HOVON 18 and 37) are comparable to the EORTC-LG and French LALA findings. They also utilized autologous and allogeneic stem cell transplantation, with a complete remission rate of 82% after two cycles of induction treatment and an overall survival for all patients of 33% at 5 years, for those following autologous SCT 38% and after allogeneic SCT 58%, respectively (unpublished data). Donor/no donor comparisons showed a trend towards superiority of allogeneic stem cell transplantation in the EORTC-LG ALL-4 trial and a significant difference with respect to disease-free and overall survival in favour of allogeneic stem cell transplantation in the HOVON trials.

5.4 New developments on intensification therapy

Boissel et al. (11) compared the outcome of adolescents (15-20 years) with ALL treated in France in either the pediatric FRALLE 93 or the adult LALA-94 (= almost similar to the EORTC ALL-4 protocol) clinical trial. With a median follow up of about 3.5 years, the CR rate (94% vs 83%), eventfree survival at 5 years (67% vs 41%), and the DFS for the CR patients (72% vs 49%) were far superior in the pediatric group and multivariate analysis confirmed the independent effect of the treatment trial on outcome. The major differences between the pediatric or adult approach were the actually given dosages of asparaginase, corticosteroids and vinca-alkaloids. Another difference was the strict discipline with which the treatment courses were administered by the pediatricians compared by the flexibility of the internists.
Analyses with similar outcome have been reported by comparing ALL patients aged 15 till 21 years treated in Dutch and British children and adult protocols (12, 13).
The feasibility of an actualization of the FRALLE 93, called the FRALLE 2000, was tested in 2003/2004 in Paris, Leiden, Roma and Zagreb in 18 adult untreated and 4 relapsed ALL patients (age 16-59 years). Seventeen of 18 untreated patients and 2 of 4 relapsed patients reached a complete remission. No treatment related mortality was encountered, but grade 3 - 4 toxicities included a considerable number of severe infections, liver function abnormalities, unexpected peripheral neuropathies and denutrition. These toxicities increased with age. Over the age of 40 the protocol was considered too toxic. Most of the chemotherapy courses could be administered in the day care center, except the induction course and the high dose methotrexate. The average

time spent in the hospital was for the induction course 33.5 days, consolidation course 24.5 days, intensification phase I 14 days, interphase 10.5 days and intensification phase II 9 days. The adherence discipline with respect to timeliness to the treatment schedules was successful in at least 50% of the limited number of patients studied so far.

5.5 Minimal residual diseases and relapse of ALL

Most of the patients who achieve a complete response will experience a relapse and will die of leukemia. Relapse is thought to result from residual leukemic cells that remain following achievement of "complete" remission, but are below the limits of detection using conventional morphologic assessment. However, sensitive techniques are now available to detect subclinical levels of residual leukemia, termed minimal residual disease (MRD). A variety of techniques have been studied for the detection of residual disease, including cytogenetics, cell culture systems, fluorescence in situ hybridization (FISH), Southern blotting, immunophenotyping, and polymerase chain reaction (PCR) techniques. Immunophenotyping techniques using multicolor-gated flow cytometry are based on aberrant expression of antigens by the leukemic cell population. Sequential MRD monitoring using multiparameter flow cytometry has been shown to be a valuable predictor of relapse in a study of 128 children with ALL(14). In one study, the cumulative rate of relapse for those negative for MRD by flow cytometry was 10 percent, whereas it was 23, 43, and 72 percent for those with MRD of < 0.1, 0.1 to < 1.0, and ≥ 1.0 percent, respectively (15).
Amplification of a DNA or cDNA sequence unique to the leukemic clone using the polymerase chain reaction (PCR) technique permits identification of one malignant cell among 10^4 to 10^6 normal cells. Two targets can be used for MRD in ALL patients, namely immunoglobulin (Ig) or T-cell receptor (TCR) gene rearrangements, or leukemia-specific chromosomal rearrangements.
As a result of the random deletions and insertions of nucleotides that occur during immunoglobulin (Ig) and T-cell receptor (TCR) gene rearrangement, unique junctional sequences are generated that can serve as leukemic clone-specific markers. The precise nucleotide sequence of the junctional region of the Ig or TCR genes in the leukemic cells can be identified at the time of diagnosis, allowing for the design of junctional region-specific oligonucleotides. These can be used as patient-specific probes (or primers) for MRD detection during and following anti-leukemic treatment (16).
Leukemia-specific breakpoint fusion regions resulting from chromosomal rearrangements may be used as PCR targets. In ALL, DNA based PCR for MRD has been successfully performed for (16-22) T-lineage ALL with TAL1 gene deletions (SIL-TAL1), (11;14)(p13;q11) involving RHOM1-TCRD, t(1;14)(p32;q11) involving TAL1-TCRD and t(10;14)(q24;q11) involving HOX11-TCRD.

In most of the chromosomal translocations more common to adult ALL, MRD detection and monitoring depends on identification of the resultant leukemia-specific fusion mRNA. This fusion mRNA can be used as a target for MRD analysis using PCR after the fusion mRNA (consisting of transcribed coding exons with the non-coding introns excised) is converted to cDNA using the enzyme reverse transcriptase (RT). This technique is known as RT-PCR. In ALL, RT-PCR has been used to detect the following transcripts: BCR/ABL resulting from t(9;22), E2A/PBX1 in cases pre-B ALL with t(1;19), MLL/AF4 in t(4;11) leukemia and TEL/AML1 resulting from t(12;21) in precursor-B ALL (16-22).
Quantitative analysis of the reaction product after amplification is completed depends on multiple dilutions or co-amplification of internal or external standards, and is technically demanding. Newer automated PCR techniques, however, are likely to allow for more precise and consistent quantitation of residual leukemic clones.
Oligoclonality of Ig and TCR gene rearrangements at diagnosis are a relatively frequent phenomenon. Primary and secondary rearrangements occurring during the course of the disease might result in the loss of specific junctional regions initially identified at diagnosis; therefore, it appears prudent to monitor ALL patients with two or more independent PCR targets in order to prevent false-negative results during follow-up (9-21).
These studies will also provide clues to the pathogenesis of the leukemias and the biological properties of residual leukemic cells. Residual disease is a dynamic process, with the numbers of residual leukemic cells fluctuating over time (22). Although levels of residual disease may fall below the detection limit of even highly sensitive molecular assays shortly after therapy, the leukemic cells do not necessarily disappear when the patient enters into clinical remission. They may subsequently increase until clinically overt disease recurs, or they may fall below the threshold of detection again. A "positive" to "negative" to "positive" pattern of PCR results is commonly seen. As a result, "molecular relapse" does not always predict subsequent clinical relapse, nor does a negative result guarantee leukemia-free survival.

5.6 Rationale

Since more than 80 percent of newly diagnosed adults with ALL enter a complete remssion, it has become difficult to demonstrate incremental improvements in initial response rates in a statistically significant way. However, disease-free survival, relapse incidence and overall survival did not improve considerable during the last decades. Intensification of induction, consolidation, post-consolidation treatment in younger patients is directed to improve the duration of the remission and survival times.

This feasibility study intends to apply (a slight modification of) the French FRALLE-2000 protocol in patients under the age of 40 years. In addition, we will acquire experience with a protocol for patients from 40 until 70 years (HOVON 71). The efficacy of these regimens will be assessed by morphological and immunophenotyping techniques. Minimal residual disease after therapy will be afterwards investigated with PCR techniques for Ig and TCR gene rearrangement as well as for leukemia-specific breakpoint fusion regions.
This study is designed to investigate the feasibility in all participating centers of more intensified treatment of adult patients with ALL before a randomized question can be added in a multicenter phase III setting.

6 Study objective

To assess the feasibility of an intensified treatment protocol in adult patients with ALL.

7 Study design

Details of all treatments (dose and schedule) are given in paragraph 9.
This is a multicenter feasibility study. Primary previously untreated ALL patients under the age of 40 years will be registered and will receive an intensified treatment regimen.
All CR-patients will be eligible for an allogeneic stem cell transplantation after Intensification I in case a suitable stem cell donor is available.
In addition to the more classical evaluation methods (morphology, immunophenotyping), the leukemic mass will be studied afterwards from stored blood and bone marrow samples by using the PCR technique for Ig and TCR gene rearrangement as well as for leukemia-specific breakpoint fusion regions at diagnosis, after the remission induction, after the intensification course I and after the intensification course II.

8 Study population

8.1 Eligibility for registration

All eligible patients have to be registered before start of treatment (see 16).

8.1.1 Inclusion criteria

- Age 18 - 39 years inclusive
- Primary previously untreated ALL (including Philadelphia chromosome or BCR-ABL positive ALL)
- WHO performance status 0, 1, or 2 (appendix C)
- Negative pregnancy test at inclusion if applicable
- Written informed consent

8.1.2 Exclusion criteria

- Mature B-cell ALL
- Acute undifferentiated leukemia
- Severe cardiovascular disease (arrhythmias requiring chronic treatment, congestive heart failure or symptomatic ischemic heart disease)
- Severe pulmonary dysfunction (CTCAE grade III-IV, see appendix D)
- Severe neurological or psychiatric disease
- Significant hepatic dysfunction (serum bilirubin or transaminases $\geq$ 3 times normal level)
- Significant renal dysfunction (serum creatinine $\geq$ 3 times normal level)
- History of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma
- Active, uncontrolled infections
- Patient known to be HIV-positive
- Patient is a lactating woman
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule

9 Treatments

9.1 Pre-phase

Agent	Dose/day	Route	Days
Prednisone	60 mg/m^2, divided in 2 daily doses	p.o.	1-7
MTX	15 mg	i.t.	On day 1 or at the time that most blast cells have disappeared from the blood

Blood morphology should be performed on day 8 to determine corticosteroid sensitivity.

9.2 Induction

No dose modification due to hematological toxicity should be made during induction treatment.

Agent	Dose/day	Route	Days
Prednisone	40 mg/m^2, divided in 3 daily doses	p.o.	8-28, then taper to 0 within 7 days
Vincristine	1.5 mg/m^2, maximum 2 mg	i.v.	8, 15, 22, 29
Daunorubicin	40 mg/m^2	i.v. in 60 minutes	8, 15, 22
Cyclophosphamide	1000 mg/m^2	i.v. in 60 minutes	8
L-Asparaginase*	6000 IU/m^2	i.m. or i.v. in 60 minutes	8, 10, 12, 15, 17, 19, 22, 24, 26
MTX	15 mg	i.t.	8, 15, in case of CNS localisation also on day 22
G-CSF	150 μg/m^2 (lenograstim)	s.c. or i.v. in 30 minutes	From day ANC < 0.5 x 10^9/l until ANC > 1.0 x 10^9/l or D43

* see Appendix F

Response (see appendix B) after induction treatment will be evaluated on day 43. Patients in CR will continue with consolidation treatment. Furthermore, patients who do not meet the first CR-criterion of <5% malignant cells but who have 5-10% blast cells by morphology and <1% malignant cells by immunophenotypical analysis and attain all of the other CR-criteria may also continue with consolidation treatment. Patients who did not achieve CR nor meet the above mentioned criteria will go off protocol treatment. In these patients intensive reinduction and consolidation by high dose Ara-C and an anthracyclin followed by (autologous or) allogeneic stem cell transplantation is advised.

9.3 Consolidation

9.3.1 Eligibility criteria for consolidation treatment

- Patient in CR or patient with 5-10% blast cells by morphology and <1% leukemic cells by immunophenotyping and meeting all other criteria for CR.
- Absence of severe renal and liver function abnormalities, i.e. creatinine ≤ 1.5 x upper limit of normal and bilirubin/transaminases ≤ 3 x upper limit of normal
- WHO performance status 0, 1, or 2
- Absence of severe cardiac, pulmonary, neurologic or metabolic disease
- Absence of uncontrolled infections

Treatment should be postponed until the eligibility criteria are met.

9.3.2 Consolidation A

Consolidation treatment starts as soon as ANC > 1.0 x 10^9/l and platelets > 100 x 10^9/l, providing that the eligibility criteria (see 9.3.1) have been fulfilled.
Consolidation treatment will be considered delayed if it starts after day 45 (with D1 being start of pre-phase treatment), whatever the reason. If consolidation treatment has not started on day 75, the patient will go off protocol treatment.

Agent	Dose/day	Route	Days
6-Thioguanine	60 mg/m^2	p.o.	1-21
Cyclophosphamide	1000 mg/m^2	i.v. in 60 minutes	1, 15
ARA-C	60 mg/m^2, divided in 2 daily doses	s.c.	1, 2, 8, 9, 15, 16
MTX	15 mg	i.t.	1, 15

9.3.3 Consolidation B

The second part of the consolidation treatment starts no sooner than day 29 (with D1 being start consolidation treatment A) and as soon as ANC > 0.5 x 10^9/l and platelets > 50 x 10^9/l. Consolidation B will be considered delayed if it starts after day 30, whatever the reason. If consolidation treatment has not been resumed on day 60, the patient will go off protocol treatment.

Agent	Dose/day	Route	Days
Prednisone	40 mg/m^2, divided in 3 daily doses	p.o.	29-35
Vincristine	1.5 mg/m^2, maximum 2 mg	i.v.	29, 43
6-Mercaptopurine	50 mg/m^2	p.o.	29-49
MTX*	5000 mg/m^2	i.v.	29, 43
MTX	25 mg/m^2	p.o.	36
MTX*	15 mg	i.t.	29, 43 (at hour 24 of high dose MTX i.v.)

* see Appendix G (re-check liver and renal functions before high dose MTX administration)

Response (see appendix B) after consolidation treatment will be evaluated between days 50 and 57. Patients with CR will continue with intensification treatment. Patients not in a CR or with a relapse after CR will go off protocol treatment.

9.4 Intensification I

9.4.1 Eligibility criteria for starting intensification treatment I

- Patient in CR
- Absence of severe renal and liver function abnormalities, i.e. creatinine ≤ 1.5 x upper limit of normal and bilirubin/transaminases ≤ 3 x upper limit of normal
- WHO performance status 0, 1, or 2
- Absence of severe cardiac, pulmonary, neurologic or metabolic disease
- Absence of uncontrolled infections

Treatment should be postponed until the eligibility criteria are met.

9.4.2 Intensification IA

Intensification treatment starts no sooner than day 58 (with D1 being start consolidation treatment A) and as soon as ANC > 1.0 x 10^9/l and platelets > 100 x 10^9/l, providing that the eligibility criteria (see 9.4.1) have been fulfilled.
Intensification treatment will be considered delayed if it starts after day 60, whatever the reason. If intensification treatment has not started on day 90, the patient will go off protocol treatment.

Agent	Dose/day	Route	Days
Dexamethasone	10 mg/m^2, divided in 3 daily doses	p.o.	1-14, then taper to 0 within 7 days
Vindesine	3 mg/m^2, maximum 4 mg	i.v.	1, 8, 15
Adriamycine	25 mg/m^2	i.v. in 60 minutes	1, 8, 15
L-Asparaginase*	6000 IU/m^2	i.m. or i.v. in 60 minutes	4, 6, 8, 10, 12, 15
MTX	15 mg	i.t.	1, in case of initial CNS localisation also on day 15

* see Appendix F

9.4.3 Intensification IB

The second part of the intensification treatment starts no sooner than day 29 (with D1 being start intensification treatment IA) and as soon as ANC > 1.0 x 10^9/l and platelets > 100 x 10^9/l.

Intensification IB will be considered delayed if it starts after day 30, whatever the reason. If intensification IB has not been resumed on day 60, the patient will go off protocol treatment.

Agent	Dose/day	Route	Days
6-Thioguanine	60 mg/m^2	p.o.	29-49
Etoposide	150 mg/m^2	i.v. in 60 minutes	29, 36, 43
ARA-C	60 mg/m^2, divided in 2 daily doses	s.c.	29, 30, 36, 37, 43, 44
MTX	15 mg	i.t.	29

Response (see appendix B) after intensification treatment I will be evaluated between days 50 and 57. Patients with CR will continue with interphase treatment. Patients with a relapse after CR will go off protocol treatment.
Patients in CR with a suitable stem cell donor may proceed to allogeneic stem cell transplantation (see 9.9).

9.5 Interphase

9.5.1 Eligibility criteria for starting interphase treatment

- Patient in CR
- Absence of severe renal and liver function abnormalities, i.e. creatinine ≤ 1.5 x upper limit of normal and bilirubin/transaminases ≤ 3 x upper limit of normal
- WHO performance status 0, 1, or 2
- Absence of severe cardiac, pulmonary, neurologic or metabolic disease
- Absence of uncontrolled infections

Treatment should be postponed until the eligibility criteria are met.

9.5.2 Interphase A

Interphase treatment starts no sooner than day 29 (with D1 being start intensification treatment IB) and as soon as ANC > 1.0 x 10^9/l and platelets > 100 x 10^9/l, providing that the eligibility criteria (see 9.5.1) have been fulfilled.

Interphase treatment will be considered delayed if it starts after day 30, whatever the reason. If interphase treatment has not started on day 60 the patient will go off protocol treatment.

Agent	Dose/day	Route	Days
Prednisone	40 mg/m^2, divided in 3 daily doses	p.o.	1-7
Vincristine	1.5 mg/m^2, maximum 2 mg	i.v.	1, 15
6-Mercaptopurine	50 mg/m^2	p.o.	1-22
MTX*	5000 mg/m^2	i.v.	1, 15
MTX	25 mg/m^2	p.o.	8, 22
MTX*	15 mg	i.t.	1, 15 (at hour 24 of high dose MTX i.v.)

* see Appendix G

9.5.3 Interphase B

The second part of the interphase treatment starts no sooner than day 29 (with D1 being start interphase treatment A) and as soon as ANC > 0.5 x 10^9/l and platelets > 50 x 10^9/l.
Interphase B will be considered delayed if it starts after day 30, whatever the reason. If interphase treatment has not been resumed on day 60, the patient will go off protocol treatment.

Agent	Dose/day	Route	Days
Prednisone	40 mg/m^2, divided in 3 daily doses	p.o.	29-35
Vincristine	1.5 mg/m^2, maximum 2 mg	i.v.	29, 43**
6-Mercaptopurine	50 mg/m^2	p.o.	29-49
MTX*	5000 mg/m^2	i.v.	29, 43**
MTX	25 mg/m^2	p.o.	36
MTX*	15 mg	i.t.	29, 43** (at hour 24 of high dose MTX i.v.)
Cranial irradiation** (only in case of CNS localisation at diagnosis)	24 Gy	-	Between day 40-55

* see Appendix G (re-check liver and renal functions before high dose MTX administration)

** in case of cranial irradiation, Vincristine, Methotrexate 5000 and i.t. only on day 29, not on day 43.

9.6 Intensification II

9.6.1 Eligibility criteria for starting intensification treatment II

- Patient without signs of relapse
- Absence of severe renal and liver function abnormalities, i.e. creatinine ≤ 1.5 x upper limit of normal and bilirubin/transaminases ≤ 3 x upper limit of normal
- WHO performance status 0, 1, or 2
- Absence of severe cardiac, pulmonary, neurologic or metabolic disease
- Absence of uncontrolled infections

Treatment should be postponed until the eligibility criteria are met.

9.6.2 Intensification IIA

Intensification treatment II starts no sooner than day 58 (with D1 being start interphase treatment A) and as soon as ANC > 1.0 x 10^9/l and platelets > 100 x 10^9/l, providing that the eligibility criteria (see 9.6.1) have been fulfilled.
Intensification treatment II will be considered delayed if it starts after day 60, whatever the reason. If intensification treatment II has not started on day 90, the patient will go off protocol treatment.

Agent	Dose/day	Route	Days
Prednisone	40 mg/m^2, divided in 3 daily doses	p.o.	1-14, then taper to 0 within 7 days
Vincristine	1.5 mg/m^2, maximum 2 mg	i.v.	1, 8, 15
Daunorubicin	30 mg/m^2	i.v. in 60 minutes	1, 8, 15
L-Asparaginase*	6000 IU/m^2	i.m. or i.v. in 60 minutes	4, 6, 8, 10, 12, 15
MTX	15 mg	i.t.	1 (not in case of previous cranial irradiation)

* see Appendix F

9.6.3 Intensification IIB

The second part of intensification treatment II starts no sooner than day 29 (with D1 being start intensification treatment IIA) and as soon as ANC > 1.0 x 10^9/l and platelets > 100 x 10^9/l. Intensification IIB will be considered delayed if it starts after day 30, whatever the reason. If Intensification IIB has not been resumed on day 60, the patient will go off protocol treatment.

Agent	Dose/day	Route	Days
6-Thioguanine	60 mg/m^2	p.o.	29-49
Cyclophosphamide	1000 mg/m^2	i.v. in 60 minutes	29
ARA-C	60 mg/m^2, divided in 2 daily doses	s.c.	29, 30, 36, 37, 43, 44
MTX	15 mg	i.t.	29 (not in case of previous cranial irradiation)

Response (see appendix B) after intensification II treatment will be evaluated between days 50 and 57. Patients with CR will continue with maintenance treatment. Patients with a relapse after CR will go off protocol treatment.

9.7 Maintenance

9.7.1 Eligibility criteria for starting maintenance treatment

- Patient in CR
- Absence of severe renal and liver function abnormalities, i.e. creatinine ≤ 1.5 x upper limit of normal and bilirubin/transaminases ≤ 3 x upper limit of normal
- WHO performance status 0, 1, or 2
- Absence of severe cardiac, pulmonary, neurologic or metabolic disease
- Absence of uncontrolled infections

Treatment should be postponed until the eligibility criteria are met.

9.7.2 Maintenance treatment

Maintenance treatment starts starts no sooner than day 58 (with D1 being start intensification treatment IIA) and as soon as ANC > 1.0 x 10^9/l and platelets > 100 x 10^9/l, providing that the eligibility criteria (see 9.7.1) have been fulfilled.
Maintenance treatment will be considered delayed if it starts after day 60 (with D1 being start intensification treatment IIA), whatever the reason. If maintenance treatment has not started on day 90, the patient will go off protocol treatment.
Maintenance treatment will be continued until 2 years after day 1 of pre-phase or until relapse, whichever comes first.
When maintenance treatment is interrupted for more than 8 weeks, it is regarded as end of maintenance treatment and the patient will go off protocol treatment

Agent	Dose/day	Route	Days
6-Mercaptopurine	75 mg/m^2	p.o.	Daily
MTX	25 mg/m^2	p.o.	Weekly

6-Mercaptopurine and Methotrexate should be stopped during the monthly reinduction courses (see 9.7.2.2).

9.7.2.1 Dose adjustments of maintenance treatment

Target WBC numbers during maintenance are: ANC 0.8-1.2 x 10^9/l and lymphocytes > 0.5 x 10^9/l.
The dose of oral Methotrexate (MTX) and/or 6-mercaptopurine (6-MP) during maintenance will be adjusted according to the following scheme:

	ALT < 5 x ULN	ALT 5 –10 x ULN	ALT > 10 x ULN
ANC < 0.5 x10^9/l	Stop until resolved	Stop until resolved	Stop until resolved
ANC 0.5- 0.8 x10^9/l	Decrease 6-MP and MTX with 33% until resolved	Decrease 6-MP with 33% and stop MTX until resolved	Stop until resolved
ANC 0.8 –1.2 x10^9/l	No modification	Decrease 6-MP with 33% and stop MTX until resolved	Stop until resolved
ANC> 1.2 x10^9/l	No modification	Decrease 6-MP with 33% and stop MTX until resolved	Stop until resolved

9.7.2.2 Reinduction courses

During the first year of maintenance patients will receive a reinduction course once a month. 6-mercaptopurine and Methotrexate should be stopped during the monthly reinduction courses.
The first reinduction course will be given after 4 weeks of maintenance treatment. The first reinduction course will be considered delayed if it starts after day 28 (with D1 being start maintenance treatment). Each following reinduction course will be considered delayed if it starts after day 35 (with D1 being start previous reinduction course).
Reinduction courses will be stopped when 12 reinduction courses have been administered or when 2 years since day 1 of pre-phase have passed, whichever comes first.
Any delay, interruption or stopping of reinduction courses is no reason to go off protocol treatment as long as maintenance treatment is continued.

Agent	Dose/day	Route	Days
Prednisone	40 mg/m^2, divided in 3 daily doses	p.o.	1-7
Vincristine	1.5 mg/m^2, maximum 2 mg	i.v.	1
Methotrexate	15 mg	i.t.	day 1 of courses 3, 6 and 9

Response will be evaluated every 6 months. Patients in CR will continue maintenance treatment. Patients with a relapse after CR will go off protocol treatment.

9.8 Special management orders during treatment

Attempts should be made prior and during treatment to control any medical problems, such as infection, metabolic complications and bleeding.

- Tumor lysis syndrome (even possible during prednisone pre-phase) should be prevented by allopurinol, sodium bicarbonate, hyperhydration and furosemide.
- Electrolyte abnormalities should be monitored and corrected if indicated.
- The indications for prophylactic platelet transfusion are recommended to be given according to the guidelines developed by Gmür (23).
- During periods with high corticosteroids: “prophylactic” blood cultures are strongly recommended.
- Patients with fever should be treated with empiric broad spectrum antibiotics.

- Antibiotics should be given as prescribed by the in vitro sensitivity tests, whenever a pathogen has been isolated.
- Protective environment and selective intestinal tract decontamination are recommended for prophylaxis of infection during remission induction therapy.
- Monitoring of cytomegalovirus infections is advised.
- Because of increased risk for pneumocystis carinii pneumonia or herpes infection prophylaxis with cotrimoxazole and valaciclovir during the whole treatment period is strongly recommended.
- Major denutrition has been observed in the majority of patients: a high protein oral regimen and early parenteral nutrition in case of decrease of albumine levels or of weight loss (>5-10%) is strongly advised.
- Anticonceptive measures if applicable, should be taken.

9.9 Allogeneic stem cell transplantation

Patients in CR after intensification I with a suitable stem cell donor should proceed to allogeneic stem cell transplantation. HLA typing of patient and siblings should be performed at study entry. Allogeneic SCT will be carried out according to the standard guidelines and general procedures operational in the local allogeneic transplantation centers.
Patients receiving an allogeneic stem cell transplantation will go off protocol treatment at the day of stem cell reinfusion and will not receive interphase, intensification II and maintenance therapy.

9.10 Imatinib treatment in Philadelphia positive ALL patients

Philadelphia-positive (Ph^+) ALL patients are eligible for this study. Imatinib 600 mg per day orally will be given from the day of detection of the t(9;22) translocation or the BCR/ABL product until relapse, allogeneic stem cell transplantation or end of maintenance treatment, whichever comes first. Because of increased risk of thrombosis and CNS toxicity imatinib must be withheld during the periods when L-Asparaginase is administered, i.e. day 8-26 during induction and day 4-15 during intensification I and II. Since also interactions with other cytostatic drugs have been described, regular monitoring of imatinib levels in the blood is advised.

10 End of protocol treatment

Reasons for going off protocol treatment are:

1. Normal completion of protocol treatment
2. Allogeneic stem cell transplantation
3. Not eligible to start with consolidation treatment
4. No CR after consolidation treatment
5. Relapse (bone marrow or extra-medullary)
6. Excessive extra-medullary drug toxicity
7. Death whatever the cause
8. No compliance of the patient (especially refusal to continue treatment)
9. Major protocol violation*
10. Delay or interruption of treatment, exceeding the limits described in paragraph 9

* Major protocol violation defined as:
other ALL treatment given than as described in paragraph 9, or not meeting eligibility criteria for inclusion as described in paragraph 8.1.

11 Required clinical evaluations

11.1 Time of clinical evaluations

- At entry: baseline before start of protocol treatment
- After pre-phase: determine corticosteroid sensitivity on day 8
- After induction treatment: clinical evaluation and response assessment on day 43
- After consolidation treatment: clinical evaluation and response assessment between days 50 and 57
- After intensification treatment I: clinical evaluation and response assessment between days 50 and 57
- After interphase treatment: clinical evaluation and response assessment between days 50 and 57
- After intensification treatment II: clinical evaluation and response assessment between days 50 and 57
- During maintenance treatment: clinical evaluation and response assessment every 6 months
- Follow up after end of protocol: clinical evaluation and response assessment every 6 months

11.2 Required investigations

	At entry	Pre-phase	Induction	Consolidation	Inter-phase	Intensification I&II	Maintenance	FU
Medical history	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X
PB immunophenotyping	X		X	X[1)]	X[1)]	X	X[1)]	X[1)]
PB PCR BCR/ABL	X		X[3)]	X[3)]	X[3)]	X[3)]	X[3)]	X[3)]
PB storage	X		X			X		
Blood chemistry	X	X	X	X	X	X	X	
Bone marrow aspirate								
Morphology	X		X	X	X[1)]	X	X[1)]	X[1)]
BM immunophenotyping	X		X	X[1)]	X[1)]	X	X[1)]	X[1)]
Cytogenetics	X		X[2)]	X[2)]				
BM PCR BCR/ABL	X		X[3)]	X[3)]	X[3)]	X[3)]	X[3)]	X[3)]
BM storage	X		X			X		
Specific investigations								
Chest X-ray	X							
ECG	X							
CSF examination	X	X	X	X	X	X	o.i.	o.i.
EMD examination	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.
Virological tests	X	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.
Microbiological tests	X	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.
HLA typing	X							

o.i. on indication

1) only on clinical and laboratory signs of relapse

2) at achievement of morphologic CR if aberrant karyotype at diagnosis

3) if applicable (see 11.2.9)

Complete blood count (CBC) and platelets during induction treatment twice weekly, during consolidation, interphase and intensification I & II every week.
Blood chemistry tests during induction treatment twice weekly, during consolidation, interphase and intensification I & II every week.

11.2.1 Medical history

Standard medical history, with special attention for:

- WHO performance status
- Adverse events
- Infections

- Bleeding
- Symptoms for CNS involvement
- Concomitant therapy

Only at entry:

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

11.2.2 Physical examination

Standard physical examination, with special attention for:

- Height (only at entry)
- Body weight
- Blood pressure
- Pulse
- Temperature (daily during induction treatment)
- Bleeding tendency
- Lymph node enlargement
- Liver and spleen size
- Any sign of possible extramedullary disease

11.2.3 Hematology

- Hemoglobin
- Hematocrit
- Reticulocytes
- Platelets
- WBC
- WBC differential
- Immunophenotyping (see 11.2.7)
- Molecular analysis (see 11.2.9)

Also CBC and platelets during induction treatment twice weekly, during consolidation, interphase and intensification I & II every week.

11.2.4 Blood chemistry

- Urea
- Creatinine
- Total bilirubin
- AST (SGOT)
- ALT (SGPT)
- Alkaline phosphatase
- Gamma GT
- LDH
- Total proteins
- Albumin
- CRP
- Glucose
- Calcium
- Phosphate
- Sodium
- Potassium
- Uric acid

At entry and at least twice weekly during asparaginase administration:

- Fibrinogen
- Anti-thrombine
- Amylase
- Lipase

Also blood chemistry tests during induction treatment twice weekly, during consolidation, interphase and intensification I & II every week.

11.2.5 Bone marrow aspirate

- Morphology
- Immunophenotyping (see 11.2.7)
- Cytogenetic analysis (see 11.2.8)
- Molecular analysis (see 11.2.9)

11.2.6 Specific investigations

- X-Thorax
- ECG
- Cerebral spinal fluid examination
- Pathology of other suspected extramedullary disease
- Virological tests (including CMV)
- Microbiological tests
- HLA typing of patient and family (at diagnosis or as soon as possible thereafter)

11.2.7 Immunophenotyping

Immunophenotyping of blood and bone marrow by flowcytometry will be performed at diagnosis in all patients. In virtually all cases the malignant lymphoblasts will express a phenotype which can be used for detection of minimal residual disease after treatment. Every time the bone marrow is examined, flowcytometry should be performed to quantitate the level of residual lymphoblast by a technique which is able to detect at least one malignant cell among 1,000 bone marrow cells.

Review by the HRC will be performed (see 4.1).

11.2.8 Cytogenetic analysis

Conventional cytogenetic analysis should be performed in all patients at diagnosis and in case of an aberrant karyotype repeated at the first achievement of morphologic CR. For Philadelphia chromosome positivity the detection of BCR/ABL will be required.

Central review will be performed for cytogenetic analysis (see 4.2).

11.2.9 Molecular analysis

Blood and bone marrow cells should be investigated for BCR/ABL at diagnosis. In case of BCR/ABL positivity follow up investigations for BCR/ABL should be performed at all bone marrow examinations mentioned in this protocol.

Blood and bone marrow cells should be stored for further analysis in the future of minimal residual disease by using a PCR technique for Ig and TCR gene rearrangement as well as for leukemia-specific breakpoint fusion regions.

Diagnostic and follow-up samples should be sent to the local laboratory. If necessary this local laboratory will forward the samples to a central laboratory as agreed within the Network for Molecular Diagnostics.

11.2.10 Corticosteroid sensitivity

Corticosteroid sensitivity will be determined on day 8 of the pre-phase.

Corticosteroid-sensitivity: leukemic blasts < 1 x 10^9/l in the blood

Corticosteroid-resistance: leukemic blasts > 1 x 10^9/l in the blood

11.3 Response assessment

Response will be assessed after the induction and intensification courses by evaluation of the bone marrow aspirate according to the definitions described in appendix B. After interphase treatment, during maintenance treatment and later on, bone marrow examination will only be performed when relapse is suspected based on unexpected abnormalities of blood cell counts, appearance of circulating blasts, or clinical abnormalities originating in the CNS. Definitions for CNS involvement, i.e. meningeal leukemia (ML) are described in appendix A.

11.4 Risk assessment

Several parameters which correlate with response rate and response duration in adult ALL have been identified and will be documented in this study but will not affect the treatment, all patients being treated by the same regimen. Factors correlating with poor prognosis are:

- WBC >30x10^9/l (especially in B-lineage ALL)
- WBC >100x10^9/l (especially in T-lineage ALL)
- unfavorable karyotype, i.e. t(9;22) , t(4;11) and other 11q23 abnormalities, and hypodiploidy
- pro-B cell ALL
- increasing age, variably defined as >30 and <30 years.

Less well defined prognostic factors are:

- LDH >4x ULN
- t(1;19), +8, and complex structural and numerical chromosomal abnormalities
- meningeal involvement at diagnosis
- hepatomegaly/splenomegaly

In addition, response to therapy is a major determinant of outcome:

- level of minimal residual disease (MRD) after remission induction and consolidation.

12 Toxicities

12.1 Chemotherapeutic agents

All chemotherapeutic agents used in this protocol cause prolonged pancytopenia during 3-6 weeks and can induce septic or hemorrhagic complications.
Congestive heart failure is a major complication of anthracyclines, frequently observed after high cumulative doses. The doses used are considerably lower than those associated with congestive heart failure.
Non-hematological drug toxicities include:
Adriamycine/daunorubicine: hair loss, mucositis, cardiomyopathy, nausea, vomiting, colitis, infertility.
Cytarabine (Ara-C) low-dose <100 mg/m^2: anorexia, nausea, vomiting, hepatic dysfunction, skin rash, fever.
Etoposide: nausea, vomiting, mucositis, hepatic dysfunction, neurotoxicity, skin rash.
L-Asparaginase: allergy, pancreatitis, hypofibrinogenemia, hepatic dysfunction.
Vincristine, vindesine: peripheral neuropathy, obstipation.
Methothrexate: nausea, vomiting, mucositis, hepatic dysfunction.
G-CSF (granulocyte colony-stimulating factor): fever, diarrhoea, abdominal pain, vomiting, skin rash, headache, bone pain and injection site reactions have been reported following the use of G-CSF.

12.2 Toxicities

Toxicities will be scored according to the NCI Common Terminology Criteria for Adverse Events, CTCAE version 3.0, published December 12, 2003 (Appendix D).

13 Reporting serious adverse events

An Adverse Event (AE) is any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs during or following treatment regardless of the causal relationship. This can include any unfavourable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the treatment.

Serious Adverse Events (SAE) are defined as any undesirable experience occurring to a patient, whether or not considered related to the treatment. Adverse events which are considered as serious are those which result in:

- death
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization
- severe/permanent disability
- a congenital anomaly

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

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

Reporting Serious Adverse Events

During protocol treatment all deaths, all SAE's that are life threatening and any *unexpected* SAE must be reported to the HOVON Data Center by fax **within 48 hours of the initial observation of the event**. All details should be documented on the **Serious Adverse Event and Death Report**. In circumstances where it is not possible to submit a complete report an initial report may be made giving only the mandatory information. Initial reports must be followed-up by a complete report within a further 14 calendar days and sent to the HOVON Data Center. All SAE Reports must be dated and signed by the responsible investigator or one of his/her authorized staff members.

At any time after the completion of protocol treatment, *unexpected* Serious Adverse Events that are considered to be possibly related to protocol treatment and ANY death (regardless the cause) must also be reported to the HOVON Data Center using the same procedure, **within 48 hours after the SAE or death was known to the investigator**.

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

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

The HOVON Data Center will forward all reports within 24 hours of receipt to the study coordinator and the study central datamanager. The report of an SAE will be the signal for the central datamanager to ask the investigator or the responsible local datamanager to complete and send as soon as possible all relevant CRF's for the involved patient with details of treatment and outcome. It is of utmost importance that all SAE's (including all deaths due to any cause) are reported in a timely fashion. Patients without a report of an SAE are implicitly considered alive without SAE. This information will be used in monitoring the incidence of SAE's, the estimation of overall survival and monitoring of safety of experimental treatments.

14 Endpoints

14.1 Primary endpoint

- Percentage of patients that reach a CR, complete all intensive phases of the protocol, and start with maintenance therapy within 11 months after start pre-phase or receive an allogeneic stem cell transplantation within 7.5 months after start pre-phase.

14.2 Secondary endpoints

- CR rate after remission induction, consolidation, intensification, and maintenance.
- Toxicity profile related to each treatment step and intervals between treatment steps.
- Event-free survival (i.e. time from registration until no CR on protocol, relapse or death, whichever comes first); Event-free survival for patients without a CR is set at one day.
- Disease-free survival (i.e. time from achievement of CR to day of relapse or death from any cause, whichever occurs first).
- Overall survival measured from time of registration.

15 Data collection

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

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

Each CRF page will be identified by a pre-printed trial number, and a unique combination of patient study number (assigned at registration), hospital and patient namecode (as documented at registration) to be filled out before completing the form.
The CRF will be completed on site by the local investigator or an authorised staff member. Each page must be dated and signed by the local investigator upon completion. All CRF entries must be

based on source documents. The CRF and written instructions for completing the CRF will be provided by the HOVON Data Center.
Copies of the CRF will be kept on site. The original CRF pages must be sent to the HOVON Data Center at the requested timepoints. How and when to send in forms is described in detail in the CRF header and the CRF instructions.
All data from the CRF will be entered into the study database by the HOVON Data Center.

16 Registration

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

The following information will be requested at registration:

1. Protocol number
2. Institution name
3. Name of caller/responsible investigator
4. Patient's initials or code
5. Patient's hospital record number (optional)
6. Sex
7. Date of birth
8. Eligibility criteria

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number, which will be given immediately by TOP or phone and confirmed by fax or email.

17 Statistical considerations

17.1 Sample size and power considerations

The aim of this study is to assess in young adults of 18-39 years inclusive the feasibility of and the response to several intensive chemotherapy courses, which have been used in the childhood FRALLE study. Patients will continue with maintenance therapy when they are in 1st CR after intensification II. Patients with a donor will be offered an allogeneic transplantation when they are in 1st CR after intensification I; these patients will not receive interphase, intensification II and maintenance therapy.

From the previous HOVON 18 ALL trial and an interim analysis of 130 patients of the HOVON 37 ALL trial, we derive the following results for this subgroup of patients:

Trial	# patients	Age, median	CR %	$EFS_{10\ months}$ (95% CI)	$EFS_{2\ years}$ (95% CI)
HOVON 18 ALL	114	24	87%	64% (55-72)	42% (33-51)
HOVON 37 ALL	83	27	86%	64% (53-73)	41% (30-52)

It is expected that about 85% of the patients will reach a CR and that, in total, about 70% of patients will reach the maintenance phase within 11 months from start pre-phase (theoretical period is 9 months) or the allogeneic transplantation within 7.5 months (theoretical period is 6 months).

Patients count as a failure at the earliest time point at which one of the following events occur:

- No CR
- Relapse after CR
- Off protocol before allogeneic transplantation or start maintenance
- Such a delay in treatment that completion of protocol treatment by allogeneic transplantation within 7.5 months or by start maintenance within 11 months has become impossible

Patients without a failure within 11 months are considered as a success. In order to monitor the failures, we define failure-free duration (FFD). Events for FFD are failures as defined before. FFD at 11 months ($FFD_{11\ mo}$) will be considered as primary end point for the sample size calculation.

- Let P_0 be the largest $FFD_{11\ mo}$ probability which, if true, implies that the feasibility/therapeutic activity is too low and therefore the present HOVON-70 schedule does not warrant further investigation. In the present trial, P_0 has been taken as 50%.

- Let P_1 be the lowest $FFD_{11\ mo}$ probability which, if true, implies that the feasibility/therapeutic activity is sufficiently high and therefore the proposed HOVON-70 schedule warrants further investigation in clinical trials. In the present trial, P_1 has been taken as 70%.
- Let α be the accepted probability of recommending for further investigation a regimen with a true "success" rate equal to or lower than P_0. In the present trial, α has been taken as 0.10.
- Let β be the accepted probability of rejecting from further trials a regimen with a true "success" rate at least equal to P_1. In the present trial, β has been taken as 0.10.

The required number of eligible patients is 50.

- One interim analysis will be performed as soon as 9 "failures" have been reported. The total time at risk for all patients who entered the trial will be calculated. Assuming an exponential distribution for the FFD during the first 11 months, we calculate the hazard rate, estimate $FFD_{11\ mo}$ and its 90% confidence interval (CI), and the trial will be considered for early termination when the upper limit of the 90% CI is less than 70%
- If the trial was not discontinued early, the final analysis will be performed when complete information is available for all eligible patients. If the upper limit of the 90% CI of $FFD_{11\ mo}$ is less than 70% (which is the case if of the 50 patients 29 or less are a success; 29/50 = 58%; 90% CI = (45.4, 69.9)), the trial will conclude that the proposed HOVON-70 schedule is not active enough. Otherwise, the trial will conclude that the treatment is active and warrants further investigation in this patient population

10,000 Monte Carlo simulations were performed to obtain the following operations characteristics of the monitoring schedule:

True $FFD_{11\ mo}$	Probability to recommend HOVON-70	Probability of early termination	Expected number of patients entered
50%	0.081	0.563	36.7
70%	0.918	0.051	48.9

In order to have up-to-date data for the interim analysis, a short questionnaire will be sent out every 2 months starting 2 months after entry of the 9th patient until 9 failures have been observed.

During the past 10 years about 20-25 patients aged 18-39 years were entered per year in HOVON trials. In this trial the University Hospital Groningen will also participate, as well as the LUMC Leiden, UMC St. Radboud Nijmegen and other individual EORTC centers. Therefore, with an expected

accrual of at least 30 patients per year, the required number of patients would be achieved within 2 years.

17.2 Analyses

All eligible patients who start with the pre-phase will be included in the analysis.

The estimated success rate along with a 90% CI interval will be presented. A 90% CI is chosen because for the primary endpoint, $\alpha = 0.10$.

The estimated CR rate along with a 95% CI interval will be presented.

The actuarial curves for FFD, EFS, DFS and OS will be computed using the Kaplan-Meier method and 95% CIs will be constructed.

Actuarial probabilities of relapse after CR or death in CR with corresponding standard errors will be calculated using the competing risk method.

The analysis of toxicity will be done primarily by tabulation of the incidence of side effects and infections with CTCAE grade 2 or more (appendix D) by treatment phase.

The average duration of each treatment phase will be calculated.

17.3 Interim analysis

One formal interim analysis is planned as described above.

17.4 Data and safety monitoring board

A data and safety monitoring board will not be installed.

18 Ethics

18.1 Independent ethics committee or Institutional review board

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

18.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (Edinburgh, Scotland, 2000) and the ICH-GCP Guidelines of 17 January 1997. The local investigator is responsible for ensuring that the study will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

18.3 Patient information and consent

Written Informed consent of patients is required before registration. The procedure and the risks and the opinions on treatment for ALL will be explained to the patient.

19 Trial insurance

The HOVON insurance program covers all patients from participating centres in the Netherlands according to Dutch law (WMO). The WMO insurance statement can be viewed on the HOVON Web site www.hovon.nl.
Individual participating centers from outside the Netherlands have to inform the HOVON about the national laws regarding the risk insurance of patients participating in a study. If necessary, HOVON will extend the insurance to cover these patients.

19.1 Intergroup studies

The HOVON insurance program does not cover the risk insurance of patients from centers participating within another cooperative group taking part in an intergroup study. The other participating groups will cover the insurance of patients registered through their offices.

20 Publication policy

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

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

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

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

21 Glossary of abbreviations

(in alphabetical order)

6-MP	6-Mercaptopurine
6-TG	6-Thioguanine
AE	Adverse Event
ALT	Alanine Amino Transferase
ALL	Acute Lymphoblastic Leukaemia
ANC	Absolute Neutrophil Count
Ara-C	Cytarabine, cytosine arabinoside
ASNase	L-Asparaginase
AST	Aspartate Amino Transferase
BM	Bone Marrow
CBC	Complete blood count
CKTO	Commissie voor Klinisch Toegepast Onderzoek
CMV	Cytomegalovirus
CNS	Central nervous system
CPM	Cyclophosphamide
CR	Complete Remission
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DEX	Dexamethasone
DFS	Disease free Survival
DNR	Daunorubicin
DOX	Adriamycine
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
EMD	Extra medullary disease
EORTC	European Organization for Research and Treatment of Cancer
EORTC-LCG	EORTC Leukemia Group
ETO	Etoposide
FFD	Failure-free duration
FFP	Fresh frozen plasma
FISH	Fluorescence in situ hybridization
FRALLE	French Acute Lymphoblastic Leukemia Group
FU	Follow up
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GIMEMA	Italian Group for Hemato-Oncology
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte histocompatibility antigen

HOVON	Dutch/Belgian Hemato-Oncology Cooperative Group
HRC	Hematocytology Review Committee
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IM	Intramuscular
IT	Intrathecal
(I)ULN	(Institutional) Upper Limit of Normal
IV	Intravenous
LDH	Lactate Dehydrogenase
METC	Medical Ethical review committee
ML	Meningeal leukemia
MPO	Myeloperoxidase
MRD	Minimal residual disease
MTX	Methotrexate
MUD	Matched unrelated donor
NCI	National Cancer Institute
NR	No response
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OS	Overall Survival
PB	Peripheral Blood
PCR	Polymerase chain reaction
PDN	Prednisone
PO	Per os
PR	Partial Response
RT	Reverse transcriptase
SAE	Serious Adverse Event
SC	Subcutaneous
SCT	Stem cell transplantation
TCR	T-cell receptor
VCR	Vincristine
VDS	Vindesine
WBC	White Blood Count
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen

22 References

1. Stryckmans, P, De Witte, T, Marie, JP, et al. Therapy of adult ALL: overview of 2 successive EORTC studies: (ALL-2; ALL-3). The EORTC Leukemia Cooperative Study Group. Leukemia 1992; 6 Suppl 2:199.
2. Hoelzer, D, Gokbuget, N. New approaches to acute lymphoblastic leukemia in adults: where do we go?. Semin Onco, 2000, l 27:540.
3. Hoelzer D, Gökbuget N, Ottmann O. Clinical management of adult ALL. In: Acute lymphoblastic leukemia. Hematology, American Society of Hematology Education Program Book. 2002; 162-168.
4. Parentesis JP. Why is age such an important independent prognostic factor in acute lymphoblastic leukemia ? Leukemia. 1997, suppl 4: S4-S7.
5. Dekker AW et al. Postremission Treatment with Autologous Stem Cell Transplantation (Auto-SCT) or Allogeneic Stem Cell Transplantation (allo-SCT) in Adults with Acute Lymphoblastic Leukemia (ALL). A phase II Clinical Trial (HOVON 18 ALL). Blood, 2001; 98: 859a.
6. Daenen S, van Imhoff GW, van den Berg E, et al. Improved outcome of adult acute lymphoblastic leukaemia by moderately intensified chemotherapy which includes a “pre-induction” course for rapid tumour reduction: preliminary results on 66 patients. Brit J Haematol. 1998; 100: 273-282.
7. Annino, L, Vegna, ML, Camera, A, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. Blood 2002; 99:863.
8. Rubnitz JE, Pui C-H. Recent advances in the treatment and understanding of childhood acute lymphoblastic leukaemia. Cancer Treat Rev. 2003; 29: 31-44.
9. Pui C, H, Campana, D, Evans W, E. Childhood acute lymphoblastic leukaemia--current status and future perspectives. Lancet Oncol 2001; 2:597.
10. Groupe Française de Cytogénétique Hématologigue. Cytogenetic abnormalities in adult acute lymphoblastic leukemia: correlations with hematologic findings and outcome. A collaborative study of the Groupe Française de Cytogénétique Hématologigue. Blood. 1996; 87: 3135-3142.
11. Boissel N, Auclerc MF, Lheritier V, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults ? Comparison of the French FRAILLE-93 and LALA-94 trials. J Clin Oncol. 2003; 21: 774-780.
12. de Bont JM, van der Holt B, Dekker AW, van der Does-van den Berg A, Sonneveld P, Pieters R. Significant difference in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric vs adult protocols in the Netherlands. Leukemia. 2004 Dec;18(12):2032-5.

13. Chessells JM, Hall E, Prentice HG, Durrant J, Bailey CC, Richards. The impact of age on outcome in lymphoblastic leukaemia; MRC UKALL X and XA compared: a report from the MRC Paediatric and Adult Working Parties. Leukemia. 1998; 12: 463-473.
14. Coustan-Smith, E, Behm, FG, Sanchez, J, et al. Immunological detection of minimal residual disease in children with acute lymphoblastic leukaemia. Lancet 1998; 351:550.
15. Coustan-Smith, E, Sancho, J, Hancock, ML, et al. Clinical importance of minimal residual disease in childhood acute lymphoblastic leukemia. Blood 2000; 96:2691.
16. van Dongen, JJ, Szczepanski, T, de Bruijn, MA, et al. Detection of minimal residual disease in acute leukemia patients. Cytokines Mol Ther 1996; 2:121.
17. Beishuizen, A, Hahlen, K, Hagememeijer, A, et al. Multiple rearranged immunobloublin genes in childhood acute lymphoblastic leukemia of precursor B-cell origin. Leukemia 1991; 9:316.
18. Steenbergen, EJ, Verhagen, OJ, van den, Berg H, et al. Rearrangement status of the malignant cell determines type of secondary IgH rearrangement (V-replacement or V to DJ joining) in childhood B precursor acute lymphoblastic leukemia. Leukemia 1997; 11:1258.
19. van Dongen, JJ, Seriu, T, Panzer-Grumayer, ER, et al. Prognostic value of minimal residual disease in acute lymphoblastic leukaemia in childhood. Lancet 1998; 352:1731.
20. Roberts, WM, Estrov, Z, Ouspenskaia, MV, et al. Measurement of residual leukemia during remission in childhood acute lymphoblastic leukemia. N Engl J Med 1997; 336:317.
21. Janossy, G, Bollum, FJ, Bradstock, KF, Ashley, J. Cellular phenotypes of normal and leukemic hemopoietic cells determined by analysis with selected antibody combinations. Blood 1980; 56:430.
22. De Haas, V, Oosten, L, Dee, R, et al. Minimal residual disease studies are beneficial in the follow-up of TEL/AML1 patients with B-precursor acute lymphoblastic leukaemia. Br J Haematol 2000; 111:1080.
23. Gmur J, Burger J, Schanz U, et al. Safety of stringent prophylactic platelet transfusion policy for patients with acute leukemia. Lancet 338; 1223-1226, 1991.
24. Mahmoud HH, Rivera GK, Hancock ML, et al. Low leukocyte counts with blast cells in cerebrospinal fluid of children with newly diagnosed acute lymphoblastic leukemia. New Engl. J. Med. 1993; 329: 314-9.

A. Diagnostic criteria for ALL

Morphologic criteria for ALL:

- >20% blasts in a representative bone marrow aspirate or otherwise in a bone marrow biopsy
- Myeloperoxidase (MPO) or Sudan Black positivity of the blasts < 3% (cytochemistry)

Classification of ALL according to immunological phenotype:

B-cell lineage		
	Pro-B ALL	cytCD79^{+}, CD19^{+}, HLA-DR^{+}, TdT^{+}, CD10^{-}
	Common ALL	cytCD79^{+}, CD19^{+}, HLA-DR^{+}, TdT^{+}, CD10^{+}
	Pre-B ALL	cytCD79^{+}, CD19^{+}, HLA-DR^{+}, TdT$^{+/-}$, CD10$^{+/-}$, cytμ^{+}
T-cell lineage		
	Prothymocyte ALL	cytCD3^{+}, CD2^{-}, CD7$^{+/(-)}$, HLA-DR^{+}, TdT^{+}
	Immature thymocyte	cytCD3^{+}, CD2^{+}, CD7^{+}, TdT^{+}, CD5^{+}, HLA-DR^{-}
	Common thymocyte	cytCD3^{+}, CD2^{+}, CD7^{+}, CD1^{+}, CD4^{+}, CD8^{+}, TdT^{+}
	Mature thymocyte	cytCD3^{+}, CD2^{+}, CD7^{+}, CD1-, CD4^{+}, or CD8^{+}, TdT^{+}

Indicated are the minimal requirements for subtyping; additional markers are advisable.

Meningeal leukemia (ML), if present, will be classified as follows:

- definite: clinical neurological signs of CNS involvement (mainly cerebral palsy) and/or > 5 blasts/ml CSF on cytological examination;
- probable: 1-5 blasts/ml CSF (24);
- dubious: pleiocytosis of CFS with increased protein level, in absence of blasts on cytological examination.

B. Response criteria for ALL

Complete response (CR) requires *all* of the following:

- <5% leukemic cells by morphology in a representative* bone marrow aspirate or otherwise in a bone marrow biopsy.
- Peripheral blood without leukemic cells by morphology, in case of doubt to be confirmed by immunophenotyping.
- Absence of extramedullary leukemia.

Partial response (PR) requires *all* of the following:

- 5-25% malignant cells by morphology in a representative* bone marrow aspirate or otherwise in a bone marrow biopsy.
- 0-25% malignant cells by immunophenotypical analysis in a representative* bone marrow aspirate or otherwise in a bone marrow biopsy.
- Absence of extramedullary leukemia.

No response (NR):

- Not meeting the criteria for CR, PR or relapse.

Relapse from CR requires at least one of the following:

- Reappearance of leukemic cells by morphology in the blood.
- Reappearance of leukemic cells by immunophenotyping in the blood.
- More than 5% leukemic cells by morphology and more than 1% leukemic cells by immunophenotyping in a representative* bone marrow aspirate or bone marrow biopsy.
- Appearance or reappearance of extramedullary leukemia, proven by biopsy or cytology.

* representative bone marrow aspirate defined as >20 % cellularity

C. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

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

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

4 Unable to get out of bed

D. Common Terminology Criteria for Adverse Events

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

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

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

E. Summary of therapeutic regimens

Prephase (days 1-7)

Day	1	2	3	4	5	6	7
PDN 2 x 30 mg/m²	X	X	X	X	X	X	X
MTX 15 mg IT	X*						

** or a few days later when blast cells have disappeared from the blood*

Induction treatment (days 8-29)

Day	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
PDN 40 mg/m²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	#
VCR 1.5 mg/m² (max 2 mg)	X							X							X							X
DNR 40 mg/m²	X							X							X							
CPM 1,000 mg/m²	X																					
ASNase 6,000 U/m²	X		X		X			X		X		X			X		X		X			
MTX 15 mg IT	X							X							X*							
Lenograstim 150 µg/m²**																						

** only in case of CNS localisation (at diagnosis);* *# thereafter taper off within one week*

*** from the day that ANC drops to < 0.5 x 10^9/L until ANC > 1.0 x 10^9/L or until day 42*

Consolidation treatment

Day 1 - 21 (starts when neutrophils > 1 x 10^9/l and platelets > 100 x 10^9/l)

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
6-TG 60 mg/m²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CPM 1,000 mg/m²	X														X						
Ara-C 2x30 mg/m²	X	X						X	X						X	X					
MTX 15 mg IT	X														X						

Day 29 - 49 (starts day 29 or as soon as neutrophils > 0.5 x 10^9/l and platelets > 50 x 10^9/l)

Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49
PDN 40 mg/m²	X	X	X	X	X	X	X														
VCR 1.5 mg/m² (max 2 mg)*	X*														X*						
6-MP 50 mg/m²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MTX 5,000 mg/m²	X														X						
MTX 25 mg/m²								X													
MTX 15 mg IT	X														X						

** decrease dose or delete in case of progressing neuropathy*

Intensification phase I

Day 1-15 (starts as soon as neutrophils > 1 x 10^9/l and platelets > 100 x 10^9/l)

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
DEX 10 mg/m²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	#
VDS 3 mg/m² (max 4 mg)	X							X							X
DOX 25 mg/m²	X							X							X
ASNase 6,000 U/m²				X		X		X		X		X			X
MTX 15 mg IT	X														X*

 # thereafter taper off within one week ** only in case of CNS localisation (at diagnosis)*

Day 29 - 49 (starts day 29 or as soon as neutrophils > 1 x 10^9/l and platelets > 100 x 10^9/l)

Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49
6-TG 60 mg/m²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ETO 150 mg/m²	X							X							X						
Ara-C 2x30 mg/m²	X	X						X	X						X	X					
MTX 15 mg IT	X																				

Interphase

Day 1-22 (starts when neutrophils > 1 x 10^9/l and platelets > 100 x 10^9/l)

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
PDN 40 mg/m²	X	X	X	X	X	X	X															
VCR 1.5 mg/m² (max 2 mg)	X														X							
6-MP 50 mg/m²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MTX 5,000 mg/m²	X														X							
MTX 25 mg/m²								X														X
MTX 15 mg IT	X														X							

Day 29-49 (starts day 29 or as soon as neutrophils > 0.5 x 10^9/l and platelets > 50 x 10^9/l)

Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55
PDN 40 mg/m²	X	X	X	X	X	X	X																				
VCR 1.5 mg/m² (max 2 mg)	X														X*												
6-MP 50 mg/m²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
MTX 5,000 mg/m²	X														X*												
MTX 25 mg/m²								X																			
MTX 15 mg IT	X														X*												
Cranial irradiation (24 Gy)**																											

** not in case of cranial irradiation*

*** in case of CNS localisation (at diagnosis) between days 40-55*

Intensification phase II

Day 1-15 (starts as soon as neutrophils > 1 x 10^9/l and platelets > 100 x 10^9/l)

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
PDN 40 mg/m²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	#
VCR 1.5 mg/m² (max 2 mg)	X							X							X
DNR 30 mg/m²	X							X							X
ASNase 6,000 U/m²				X		X		X		X		X			X
MTX 15 mg IT*	X*														

 # thereafter taper off within one week ** not in case of previous cranial irradiation*

Day 29 – 49 (starts day 29 or as soon as neutrophils > 1 x 10^9/l and platelets > 100 x 10^9/l)

Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49
6-TG 60 mg/m²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CPM 1,000 mg/m²	X																				
AraC 2x30 mg/m²	X	X						X	X						X	X					
MTX 15 mg IT*	X*																				

** not in case of previous cranial irradiation*

Maintenance

(starts as soon as neutrophils > 1 x 10^9/l and platelets > 100 x 10^9/l)

6-MP 75 mg/m²/d PO	until 2 years from start of pre-phase
MTX 25 mg/m²/week PO	until 2 years from start of pre-phase

(except for during the monthly reinduction courses; target WBC counts: neutrophils 0.8-1.2 x 10^9/l and lymphocytes > 0.5 x 10^9/l) plus (during first year of maintenance):

<u>monthly reinduction courses</u> consisting of:

Day	1	2	3	4	5	6	7
PDN 40 mg/m²	X	X	X	X	X	X	X
VCR 1.5 mg/m² (max 2 mg)	X						
MTX 15 mg i.t.*	X						

*only in courses 3, 6 and 9

F. Administration of L-Asparaginase

L-asparaginase stands for E. coli asparaginase, unless Erwinia asparaginase is mentioned.

- Intramuscular administration is preferred over the intravenous route if thrombocytes are > 50 x 10^9/l (spontaneously or after thrombocyte transfusion). In all other cases, L-asparaginase will be administered IV in 60 minutes
- Keep antihistamines, corticosteroids and adrenaline ready during each L-asparaginase administration
- Observe the patient for at least 1 hour after L-asparaginase administration
- Dose adjustments should be made according to the following table:

Event	Dose adjustment
Fibrinogen < 1.0 g/l	administer FFP to keep fibrinogen > 1.0 g/l
Fibrinogen < 0.5 g/l	withhold L-asparaginase and administer FFP until fibrinogen has increased to more than 1g/l
Antithrombine < 60%	administer antithrombine or FFP; aim at antithrombine levels of 80 - 100%
Pancreatitis	withhold L-asparaginase until resolved
Amylase > 2x ULN	withhold L-asparaginase until resolved
Liver toxicity (bilirubin and/or transaminases > 3x ULN)	withhold L-asparaginase until resolved
Allergic reaction	change to Erwinia asparaginase or PEG-asparaginase 1500 IU/m^2 once weekly

G. Administration of high dose MTX

- stop cotrimoxazol from 3 days before until 5 days after the high dose MTX
- check for possible interactions with azoles, quinolones, macrolides, NSAIDs, thiazide diuretics and aminosides
- Start when neutrophils > 0.5 x 10^9/l, platelets > 50 x 10^9/l, creatinine ≤ 1.5 x upper limit of normal and bilirubin/transaminases ≤ 3 x upper limit of normal

Dosage

5000 mg/m^2 in continuous IV infusion for 24 hours with:
1/10 of the dose = 500 mg/m^2 in 60 minutes (diluted in glucose 5%)
9/10 of the dose = 4,500 mg/m^2 in 23 hours (diluted in glucose 5%)

The intrathecal MTX therapy will be given at hour 24 (H24) of the high dose MTX infusion.

Hyperhydration and alkalinisation

Timepoint	Action
H -1	infuse 6 ml/kg (1 mEq/kg) sodium bicarbonate 1.4% in 30 minutes
H0 until H72	hydration (iv or po): 2000 ml/m^2/d with 1/3 of sodium bicarbonate 1.4% and 2/3 of glucose 5% (+ 2 g/l KCl)

- Make sure that the pH of the urine is > 7 before start of the MTX infusion
- Determine plasma levels of methotrexate at H24, H36, H48, H72 and H96; if MTX level is >2x10^{-7} M (≥ 0.2 micromol/L) folinic acid rescue must be applied

Folinic acid rescue

Folinic acid rescue is given from H36 (from the start of the MTX infusion) until MTX blood levels reach ≤ 2 x 10^{-7} mol/l (≤ 0.2 micromol/L). Folinic acid will be administered once every 6 hours according to the following table:

MTX level $.10^{-7}$ M/L	MTX level µmol/L	H36	H48	H72	H96	> H96
> 100	> 10	45 mg p.o. x 2	50 mg/m^2 i.v. x 4	200 mg/m^2 i.v. x 4	200 mg/m^2 i.v. x 4	200 mg/m^2 i.v. x 4
> 50	> 5	45 mg p.o. x 2	45 mg p.o. x 4	100 mg/m^2 i.v. x 4	200 mg/m^2 i.v. x 4	200 mg/m^2 i.v. x 4
> 10	> 1	45 mg p.o. x 2	45 mg p.o. x 4	50 mg/m^2 i.v. x 4	100 mg/m^2 i.v. x 4	200 mg/m^2 i.v. x 4
> 5	> 0.5	45 mg p.o. x 2	45 mg p.o. x 4	45 mg p.o. x 4	50 mg/m^2 i.v. x 4	100 mg/m^2 i.v. x 4
> 2	> 0.2	45 mg p.o. x 2	45 mg p.o. x 4	45 mg p.o. x 4	45 mg p.o. x 4	50 mg/m^2 i.v. x 4
$\leq$ 2	$\leq$ 0.2	no rescue	no rescue	no rescue	no rescue	no rescue

H. Patiënteninformatie

Uitvoerbaarheidsonderzoek naar een geïntensiveerd behandelingsprotocol bij volwassen patiënten van 18 tot en met 39 jaar met acute lymfatische leukemie

Inleiding

Geachte Heer, Mevrouw,

Uw behandelend arts heeft u voorgesteld aan het hierboven genoemde onderzoek deel te nemen en heeft al het één en ander uitgelegd. Uw toestemming of weigering moet u kunnen baseren op goede voorlichting onzerzijds. Daarom ontvangt u deze schriftelijke informatie, die u rustig kunt (her)lezen en in eigen kring bespreken. Ook daarna kunt u altijd nog vragen voorleggen aan de artsen die aan het einde van deze informatie genoemd staan.

Uw medische situatie en de bestaande mogelijkheden tot behandeling

Uit onderzoek is gebleken dat in uw beenmerg leukemie cellen aanwezig zijn, welke de normale bloedaanmaak belemmeren. Als het aantal leukemiecellen meer dan twintig procent van het totale aantal beenmergcellen bedraagt wordt er gesproken over een acute lymfatische leukemie (ALL), één van de vormen van leukemie. In de folder van het Koningin Wilhelmina Fonds (Nederlandse Kankerbestrijding) over Acute Leukemie kunt u hierover nog aanvullende informatie vinden.

De gebruikelijke behandeling bij ALL bij volwassenen bestaat uit twee of drie fasen. De eerste fase wordt de inductiefase genoemd en bestaat uit een kuur met verschillende leukemie-dodende geneesmiddelen (chemotherapie of cytostatica; zie ook verder). Het doel van deze inductiefase is de leukemiecellen te doden. Als dit lukt zijn er geen leukemiecellen meer zichtbaar in het beenmerg en herstellen de normale bloedcellen zich weer volledig. Dit wordt een complete remissie genoemd. De volgende fase betreft het consolideren van het bereikte resultaat. Deze fase bestaat uit een of enkele chemotherapiekuren. Ook een beenmergtransplantatie kan deel uit maken van deze fase. De laatste fase betreft de onderhoudsbehandeling voor de patienten die geen beenmergtransplantatie hebben ondergaan. De onderhoudsbehandeling duurt iets meer dan een jaar. Ondanks deze intensieve behandelingen is er geen garantie dat de ziekte nooit meer terug kan keren. De medische wetenschap blijft daarom zoeken naar behandelingen die (nog) beter werken.

Doel en achtergrond van het onderzoek

De laatste tijd is duidelijk geworden bij de behandeling van jongvolwassenen (16-20 jarigen) dat de behandelingsprotocollen zoals toegepast door de kinderartsen/hematologen betere resultaten op de langere termijn geven dan de protocollen die worden gegeven door hematologen. Redenen hiervoor zijn niet zeker, maar de veronderstelling is dat de kinder-behandelschema's intensiever van aard zijn en dat de schema's gedisciplineerder op de afgesproken tijden worden toegediend. Aangezien de resultaten van de kinderschema's mogelijk beter zijn gebleken, worden momenteel protocollen ontwikkeld om ook volwassen patienten een dergelijke intensieve behandeling te kunnen bieden. Doel van dit onderzoek is, om de uitvoerbaarheid van een kinderprotocol voor patienten van 18 tot en met 39 jaar te testen. De haalbaarheid wordt gemeten aan de hoeveelheid chemotherapie die aan volwassen patienten kan worden toegediend en aan de lengte van de intervallen tussen de kuren in vergelijking met de resultaten bij jongvolwassenen.

Behandelingsplan

De totale behandeling bestaat uit drie fasen. De eerste fase is bedoeld om een complete remissie te bereiken. De tweede fase is bedoeld om het bereikte resultaat de versterken en de derde fase wordt gegeven om het terugkomen van de ziekte te voorkomen.

De eerste fase (remissie-inductiebehandeling)

Tijdens deze kuur wordt u in het ziekenhuis opgenomen. De precieze opnameduur is niet aan te geven, maar u moet rekenen op 5-6 weken. De cytostatica worden door een speciaal infuus gegeven, dat in een van de grotere bloedvaten wordt ingebracht. De eerste kuur bestaat uit een pre-fase van een week waarin dagelijks prednison en eenmalig MTX middels een lumbaalpunctie (ruggeprik) wordt gegeven. Na die week wordt in het bloed onderzocht hoe de leukemie hierop heeft gereageerd. Vervolgens begint de remissie inductie behandeling die bestaat uit eenmalig cyclofosfamide, dagelijks prednison, wekelijks vincristine en daunorubicine, een tiental injecties met asparaginase en enkele lumbaalpuncties waarbij het middel methotrexaat wordt ingespoten. Nadat de bloedcellen hersteld zijn, wordt bloed en beenmergonderzoek verricht om het resultaat van de behandeling te beoordelen.

Bijwerkingen.

De cytostatica hebben de bekende bijwerkingen van misselijkheid en haaruitval tot gevolg. Verder onderdrukken zij tijdelijk de bloedaanmaak. Daardoor zullen de bloedplaatjes en witte bloedcellen tijdelijk naar lage waarden dalen, maar soms zijn deze waarden als gevolg van de leukemie bij voorbaat al sterk verlaagd. In deze periode worden regelmatig bloedtransfusies gegeven en krijgt u

regelmatig antibiotica ter voorkoming en ter behandeling van infecties. Ook krijgt u middelen ter bestrijding van de misselijkheid. Nadere informatie over algemene bijwerkingen van chemotherapie kunt u vinden in de folder over Chemotherapie van het Koningin Wilhelmina Fonds (Nederlandse Kankerbestrijding). De behandeling met cytostatica leidt (tijdelijk) tot verminderde vruchtbaarheid. Toch moet de kleine kans op zwangerschap tijdens chemotherapie koste wat kost worden voorkomen, middels betrouwbare anticonceptie, aangezien de chemotherapie tot ernstige afwijkingen aan het kind kan leiden.

Consolidatiefase

Nadat een complete remissie is vastgesteld, begint u aan de consolidatiefase van het behandelingsprotocol. De fase bestaat uit een viertal kuren: de consolidatiekuur, de intensificatiekuur I, de interfase en de intensificatiekuur II. Deze kuren duren elk ongeveer 7 weken en worden zoveel mogelijk poliklinisch en/of in dagverpleging toegediend. Behalve dat geprobeerd wordt zoveel mogelijk de berekende dosering van de cytostatica te geven, is het ook belangrijk de kuren op de afgesproken tijden toe te dienen. Dat waren namelijk de argumenten die gebruikt werden om te verklaren waarom de resultaten van de kinder-behandelschema's zoveel beter waren dan de protocollen voor de volwassenen.

Deze "consolidatiekuren" bestaan uit combinaties van een aantal cytostatica die u reeds had ontvangen en nieuwe middelen. De werking van de cytostatica impliceert weer een tijdelijke vermindering van uw bloedlichaampjes met bloedarmoede, infectierisico's en bloedingsrisico's tot gevolg. Bijwerkingen betreffen voorts misselijkheid, braken, diarree, leverfunctieafwijkingen, allergieën, zenuwaandoeningen (tintelingen, gevoelloosheid), etc.

Na de tweede kuur wordt opnieuw een bloed en beenmergonderzoek gedaan naar de activiteit van de leukemie. Na de tweede kuur van deze consolidatiefase dient ook besloten te worden of u in aanmerking komt voor een beenmergtransplantatie met stamcellen van een donor. De beslissing tot transplantatie is niet alleen afhankelijk van uw persoonlijke omstandigheden, maar ook van het verloop van de leukemie en komt daarom in deze fase pas aan de orde.

De onderhoudsfase

Deze fase duurt ongeveer 14 maanden en bestaat uit medicamenten die u dagelijks (6-mercaptopurine) en wekelijks (methotrexaat) inneemt, en uit maandelijkse reinductiekuren bestaande uit 7 dagen prednison en een injectie vincristine. U wordt hiertoe ook maandelijks op de polikliniek gecontroleerd. Alleen bij verdenking op een recidief (terugkeer) van de leukemie wordt beenmergonderzoek gedaan.

Extra belasting in verband met dit onderzoek.

De dosering van de medicamenten is veelal wat hoger dan gebruikelijk voor volwassen patiënten. Ten opzichte van de standaardbehandeling voor volwassen patiënten met acute lymfatische leukemie betekent ook het aantal kuren in de consolidatiefase een verzwaring (vier in plaats van een of twee). Voorts betekent het zorgvuldig volgen van de protocol voorschriften dat u opnieuw behandeld zou moeten worden terwijl u het gevoel kunt hebben er nog niet helemaal aan toe te zijn. Mocht overigens blijken uit de bijwerkingen die zich bij u voordoen of uit gegevens van de gehele groep patiënten die met dit protocol behandeld wordt, dat het onderzoek een voor u ongunstiger verloop heeft/kan hebben, dan zal de behandeling volgens het protocol opgeschort worden. Wij zullen u in zo'n geval een goed alternatief bieden.

Voor- en nadelen.

Indien u besluit aan dit onderzoek mee te doen is er een kans dat uw leukemie beter reageert door de hogere doseringen chemotherapie en de intervallen waarin die gegeven worden. De kans op bijwerkingen is echter ten gevolge van deze hogere doseringen ook groter dan bij de standaard behandeling.

Vertrouwelijkheid (Privacy)

Tot uw persoon herleidbare onderzoeksgegevens kunnen slechts met uw toestemming door daartoe bevoegde personen worden ingezien. Deze personen zijn medewerkers van het onderzoeksteam, medewerkers van de Inspectie voor de Gezondheidszorg of bevoegde inspecteurs van een buitenlandse overheid, en leden van de Medisch Ethische Toetsings Commissie. Inzage kan nodig zijn om de betrouwbaarheid en kwaliteit van het onderzoek na te gaan. Onderzoeksgegevens zullen worden gehanteerd met inachtneming van de Wet Bescherming Persoonsgegevens en het privacyreglement van het ziekenhuis waar u behandeld wordt.

Persoonsgegevens die tijdens deze studie worden verzameld, zullen worden vervangen door een codenummer. Alleen dat nummer zal gebruikt worden voor studiedocumentatie, in rapporten of publicaties over dit onderzoek. Slechts degene, die de sleutel van de code heeft (de onderzoeker of de behandelend arts) weet wie de persoon achter het codenummer is. De gegevens worden bewaard gedurende het onderzoek en na afloop vernietigd, of (indien van toepassing) de gegevens worden, indien u daar toestemming voor geeft, gedurende 15 jaar bewaard.

Schade

Voor de deelnemers aan dit onderzoek is een verzekering afgesloten. Deze verzekering dekt schade door dood of letsel die het gevolg is van deelname aan het onderzoek, en die zich gedurende de deelname aan het onderzoek openbaart, of binnen vier jaar na beëindiging van de deelname aan het onderzoek. De schade wordt geacht zich te hebben geopenbaard wanneer deze bij de verzekeraar is gemeld.

(In geval van schade kunt u zich direct wenden tot de verzekeraar.)
De verzekeraar van het onderzoek is:

Naam:	Gerling Allgemeine Versicherungs-AG
Adres:	Postbus 2636
	1000 CP Amsterdam
Telefoonnummer:	020 – 54 92 213
Contactpersoon:	mr. P. Oosterveen

De verzekering biedt een maximum dekking van € 450.000 per proefpersoon en € 3.500.000 voor het gehele onderzoek. De dekking van specifieke schades en kosten is verder tot bepaalde bedragen beperkt. Dit is opgenomen in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Informatie hierover kunt u vinden op de website van de Centrale Commissie Mensgebonden Onderzoek: www.ccmo.nl.

Voor deze verzekering gelden een aantal uitsluitingen. De verzekering dekt niet:

- schade waarvan op grond van de aard van het onderzoek zeker of nagenoeg zeker was dat deze zich zou voordoen;
- schade aan de gezondheid die ook zou zijn ontstaan indien u niet aan het onderzoek had deelgenomen;
- schade die het gevolg is van het niet of niet volledig nakomen van aanwijzingen of instructies;
- schade aan nakomelingen, als gevolg van een nadelige inwerking van het onderzoek op u of uw nakomeling;
- bij onderzoek naar bestaande behandelmethoden: schade die het gevolg is van één van deze behandelmethoden;
- bij onderzoek naar de behandeling van specifieke gezondheidsproblemen: schade die het gevolg is van het niet verbeteren of van het verslechteren van deze gezondheidsproblemen.

Weigeren voor en tijdens het onderzoek

Het is, zoals gezegd, niet precies bekend of deze behandeling gemakkelijk uitvoerbaar is. Dit geldt zowel voor de inductie en postinductie fase. Daarom heeft uw arts u verteld over het doel van dit onderzoek en u gevraagd om hier aan mee te werken. Als u besluit mee te doen met het onderzoek, dan verzoek ik u dat uiterlijk binnen 24 uur aan uw arts te melden. U bent uiteraard vrij uw medewerking aan dit onderzoek te weigeren. Als u besluit niet mee te doen, zal u de gebruikelijke “standaard”-behandeling voorgesteld worden. Die “standaard” behandeling is niet in elk deelnemend centrum exact hetzelfde. Het “standaard” protocol zal u voorafgaande aan de behandeling zorgvuldig uitgelegd worden. Ook indien u nu toestemming geeft, kunt u die later zonder opgave van redenen weer intrekken. Wat u ook besluit, het zal geen consequenties hebben voor de verzorging en begeleiding van uzelf en uw familie. De behandeling wordt zo nauwkeurig mogelijk volgens vooropgesteld plan uitgevoerd. Het kan natuurlijk gebeuren dat uw lichamelijke reacties of nieuw ontdekte feiten ons tot veranderingen dwingen. Die zullen direct met u besproken worden, zodat u de gelegenheid krijgt te overwegen al of niet met het onderzoek door te gaan. Wel vragen wij van u de voorschriften van uw behandelend arts goed op te volgen en u niet, zonder diens medeweten, elders te laten behandelen.
Tenslotte, u bent verzocht deel te nemen aan medisch wetenschappelijk onderzoek. Dat onderzoek wordt uitgevoerd nadat positief oordeel is verkregen van de Raad van Bestuur/directie van het ziekenhuis na advies van de Medisch Ethische Commissie. De voor dit onderzoek internationaal vastgestelde richtlijnen zullen nauwkeurig in acht worden genomen.
Voor het stellen van de diagnose ALL en voor het evalueren van de effecten van de behandeling wordt er regelmatig bloed en beenmerg afgenomen. Het materiaal ondergaat verschillende bewerkingen maar meestal blijft er wat over (uit voorzorg wordt voldoende afgenomen om bij twijfel of bij technische problemen het onderzoek te kunnen herhalen). Aan de deelnemers aan het onderzoek wordt apart toestemming gevraagd voor het opslaan van een deel van dit materiaal in ingevroren toestand, met het doel hiermee later wetenschappelijk onderzoek te doen, dat meer inzicht moet geven in de ziekte ALL. Het is volstrekt mogelijk om in te stemmen met de voorgestelde behandeling en toch te weigeren om bloed en beenmerg in te vriezen voor onderzoek dat buiten het kader van de studie valt.

Hoe te handelen bij klachten

Als u klachten heeft over het onderzoek, kunt u dit melden aan de onderzoeker. Wilt u dit liever niet, dan kunt u contact opnemen met de onafhankelijke klachtencommissie van het ziekenhuis:
.....

Nadere informatie

Mocht u verdere vragen hebben, dan kunt u die voorleggen aan uw behandelend specialist of aan:

.....[naam/namen betrokken specialisten]

.....

.....

Voor meer informatie kunt u ook contact opnemen met een onafhankelijk arts die zelf niet bij het onderzoek betrokken is, maar wel deskundig is op het gebied van dit onderzoek:

.....[naam en telefoonnummer onafhankelijk arts]

*Bijlagen: (Nederlandse Kankerbestrijding)

- Folder Wetenschappelijk onderzoek bij patiënten met kanker (Nederlandse Kankerbestrijding)
- Folder Acute Leukemie (Nederlandse Kankerbestrijding)

Folder Instituut voor Gezondheidsethiek

TOESTEMMINGSVERKLARING
voor deelname aan het wetenschappelijk onderzoek:

Uitvoerbaarheidsonderzoek naar een geïntensiveerd behandelingsprotocol bij volwassen patiënten van 18 tot en met 39 jaar met acute lymfatische leukemie

Ik ben naar tevredenheid over het onderzoek geïnformeerd. Ik heb de schriftelijke informatie goed gelezen. Ik ben in de gelegenheid gesteld om vragen te stellen over het onderzoek. Mijn vragen zijn naar tevredenheid beantwoord. Ik heb goed over deelname aan het onderzoek kunnen nadenken. Ik heb het recht mijn toestemming op ieder moment weer in te trekken zonder dat ik daarvoor een reden behoef te geven.
Ik stem vrijwillig toe met deelname aan het onderzoek.
Ik geef toestemming mijn persoonsgegevens (indien van toepassing) na afloop van de studie gedurende maximaal 15 jaar te bewaren.

Naam : .....

Adres : .....

Woonplaats : .....

Geboortedatum : .....

Handtekening : ..... Datum: .....

Ik heb geen / wel bezwaar tegen het opslaan van mijn bloed voor wetenschappelijk onderzoek.

Ik heb geen / wel bezwaar tegen het opslaan van mijn beenmerg voor wetenschappelijk onderzoek.

Ik heb begrepen dat ik na het onderzoek eventueel opnieuw benaderd kan worden voor (vervolg)onderzoek en stem daarmee wel / niet in.

Handtekening : ..... Datum: .....

Ondergetekende verklaart, dat de hierboven genoemde persoon zowel schriftelijk als mondeling over het bovenvermelde onderzoek geïnformeerd is. Hij/zij verklaart tevens, dat een voortijdige beëindiging van de deelname door bovengenoemde persoon, van geen enkele invloed zal zijn op de zorg die hem of haar toekomt.

Naam : .....

Functie : .....

Handtekening : ..... Datum: .....

Dit formulier is bestemd voor onderzoek met meerderjarigen, die wilsbekwaam zijn. Bij dit soort onderzoek moet door de betrokkenen zelf toestemming worden verleend.