Treatment of acute lymphoblastic leukemia (ALL) in adults age 40 - 70 years inclusive with chemotherapy including a "pre-induction course" for rapid tumor load reduction and prolonged maintenance chemotherapy

A phase II multicenter study

PROTOCOL

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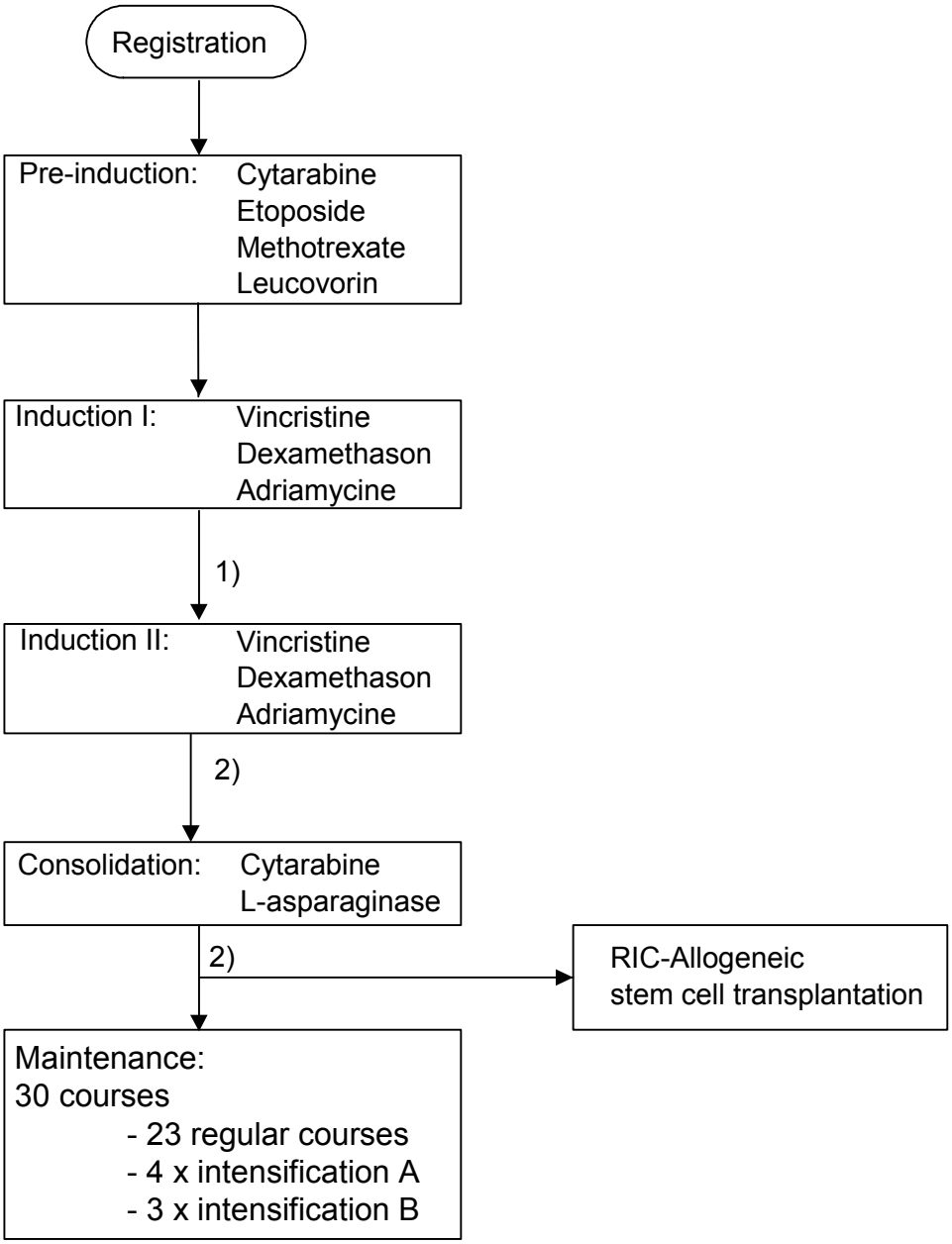
1 Scheme of study



1) Patients in CR or PR

2) Patients in CR

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3 Synopsis

Study phase	Phase II
Study objectives	Evaluation of efficacy and safety of an intensified treatment protocol in adult patients with ALL
Patient population	Patients 40 - 70 years inclusive of age with newly diagnosed ALL, previously untreated
Study design	Prospective, multicenter, non-randomized
Duration of treatment	Expected duration of treatment is 10 weeks in hospital and 30 months at outpatient department
Number of patients	55
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: IV 2007

4 Investigators and study administrative structure

Responsibility	Name	Affiliation/Address
Study Coordinators	S.M.G.J. Daenen	University Medical Center, Groningen
	J.J. Cornelissen	Erasmus MC, Rotterdam
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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

Despite ever more intensive chemotherapy, ALL in adults still has an unfavorable outcome, in marked contrast to ALL in children where the prognosis is rather good and the long-term survival rate nowadays exceeds 70% (1). In recent studies, complete remission (CR) rates in adults with induction courses consisting of corticosteroids, vincristine, and adriamycine, whether or not in combination with asparaginase or cyclophosphamide, are in excess of 80%, but disease-free (DFS) and overall survival (OS) rates at 3 to 5 years are (only) 30-40% (2-4). However, it appeared that adolescents who were treated according to childhood protocols had a better outcome than adolescents treated according to adult protocols (5-6). This suggested that the treatment schemes used in childhood were superior to the ones used in adults. The HOVON and EORTC cooperative groups thus decided to initiate a feasibility study in young adults up to 40 years of age with a treatment schedule developed for children, in this case the FRALLE 2000 study (with minor modifications). But this intensive schedule was considered too toxic for older adults who obviously do not tolerate intensified chemotherapy as well as children with high-risk ALL. Furthermore, there are additional reasons for the differences between adults and children; e.g. increasing age per se

has an unfavorable prognosis (7-8) and age correlates with several markers of poor prognosis such as immunophenotype and karyotypic abnormalities (9-12). Therefore, ALL in adults has a different biological behavior and other solutions instead of progressive intensification of chemotherapy in the way it is applied in children might be required. Alternatively, in order to prevent excessive toxicity, chemotherapy might be applied in a more prolonged way.

At the University Medical Center in Groningen promising experience has been obtained in adult ALL with treatment based on prolonged maintenance and the introduction of a new “pre-induction course”. The various phases of chemotherapy were adapted slightly in comparison to other treatment schemes. As an example, asparaginase which is often used as a fourth drug during remission induction but was reported not to be effective as such in adults (13) was applied during consolidation where it demonstrated benefit in children (14,15). Furthermore, consolidation with asparaginase was combined with intermediate dose Ara-C because this combination was shown to be synergistic (16). Patients up to the age of 55 years in first CR were eligible for sibling donor stem cell transplantation (SCT) after the consolidation course. But the innovative part of the approach was mainly the introduction of a pre-induction course, thus named because it preceded standard remission induction. It consisted of cytarabine (Ara-C) and etoposide (VP16) and was meant to obtain rapid tumor load reduction with non cross-reacting cytostatic drugs before the initiation of standard induction courses. The doses of the drugs were low in order not to cause profound aplasia and not to delay the subsequent chemotherapy. Indeed, this pre-induction course led to a marked reduction of high white blood cell counts (WBC) within a few days and seemed to contribute to early attainment of complete remission (CR), generally believed to correlate with favorable outcome (17, 18). The results of the first cohort, in which the pre-induction course was given only to patients with high WBC, was reported in 1998 (19); it showed a DFS of 45% and OS of 50% after a median follow-up of 7 years. Remarkably, the OS measured 86% in patients with WBC between $30x10^9$/l and $100x10^9$/l who actually had received the pre-induction course compared to 48% in patients with WBC $<30x10^9$/l who had not, suggesting a survival advantage for patients receiving the pre-induction course. The concept of rapid tumor load reduction with non cross-resistant cytostatic drugs combined with prolonged maintenance appeared promising and provided a rational basis for further investigation. However, prognosis for patients with WBC $>100x10^9$/l remained rather poor (19).
The next logical step was to include the pre-induction course with Ara-C and VP16 for all adults with ALL (not restricting it to patients with high WBC) and to combine Ara-C-VP16 with MTX for patients with an enhanced risk. Evaluation of the first 42 patients treated with this renewed scheme

showed an OS of 60% and a DFS of 67% combined with a low relapse rate of approximately 20% at 4 years. WBC >100x10^9/l was no longer a marker of poor prognosis (20).
Toxicity of the Groningen scheme in the younger patients was relatively low, mucositis being the most frequent side effect often requiring temporary opioids. The scheme appeared also feasible in older patients. Special attention was required for adequate nutrition in older patients since they could develop a wasting syndrome and in two cases even death probably due to corticosteroids-induced catabolism.
Promising as the Groningen results seem to be, they have been obtained at a single institution and in a relatively low number of approximately 100 patients, divided over subgroups with somewhat changing treatment schedules over time. The value of this approach has to be confirmed in a larger patient population and in the setting of a multicenter study. For adults who are not eligible for the HOVON 70 ALL protocol because of age ≥40 years, the Groningen scheme which showed beneficial effects also in patients up to 70 years will form the basis for treatment at the HOVON and EORTC centers. In order to prevent formation of subgroups, a single type of pre-induction course will be used for all patients independent of risk assessment. All patients will thus receive Ara-C, VP16 and MTX before the start of the remission induction courses.

5.1 Allogeneic stem cell transplantation

Adult ALL patients with an HLA-identical sibling donor mostly undergo SCT in first CR as survival benefit in comparison to conventional chemotherapy was formally proven as well for high-risk patients (21-22) as for standard-risk patients in the MRC-ECOG study (reported by Goldstone, ASH meeting, 2004). A donor/no donor comparison of combined HOVON 18/HOVON 37 data showed a significant difference with respect to disease-free survival and overall survival in favor of allogeneic stem cell transplantation. An allo-SCT in first CR appeared also superior to maintenance therapy for patients treated by the Groningen scheme (20). High treatment related morbidity and mortality, however, limit the applicability of allo-SCT in older patients. Non-myeloablative allogeneic SCT, also called reduced intensity conditioning allogeneic stem cell transplantation (RIC allo-SCT), with less intensive conditioning regimens has been developed aiming at elimination of residual leukemia by immunological means (graft versus leukemia effect, GvL) rather than direct cytostatic effects. It appeared less toxic and more tolerable even at increasing age. But ALL was at first considered less amenable for this type of SCT because donor lymphocyte infusion (DLI) appeared only marginally effective in relapse ALL after allo-SCT.
Nevertheless, many observations indicate that a GvL effect occurs also in ALL: the relapse rate is lower in ALL patients with GvHD after HLA-matched or matched unrelated donor (MUD) transplantation (23-25), and DLI is still able to induce a second remission in individual patients.

Preliminary results show that RIC allo-SCT can potentially rescue ALL patients with advanced-stage disease (26-28). At the same time, outcome could be improved by applying RIC SCT earlier, i.e. in first CR (26-28). These data form the rationale for investigating RIC SCT for ALL patients in first CR on a larger scale and compare RIC allo-SCT with maintenance chemotherapy. Patients in CR1 with an HLA-identical sibling donor will be eligible for RIC allo-SCT while CR1 patients without a donor who continue chemotherapy will serve as controls. MUD transplantations will not be standard treatment in this study and will be limited to patients with the most unfavorable characteristics at the discretion of the treating physician.

6 Study objective

Primary objective is to assess the efficacy and safety of a treatment protocol including a “pre-induction” course and prolonged maintenance chemotherapy in patients 40 - 70 years inclusive of age with ALL.
A secondary objective is to document the outcome of RIC allo-SCT with HLA-identical sibling donor stem cells in ALL patients from 40 to 65 years in first CR and to compare RIC allo-SCT to maintenance chemotherapy in this patient population.

7 Study design

Details of all treatments (dose and schedule) are given in paragraph 9.
All patients will be treated with the pre-induction course and a first remission induction course (ODA). Patients at least in PR will receive a second ODA course. CR patients will then continue with a consolidation course and will subsequently receive outpatient maintenance therapy for 30 months or until relapse, whichever comes first. Patients with an allogeneic donor will be offered a reduced intensity conditioning allogeneic stem cell transplantation (RIC allo-SCT) after the consolidation phase.
All patients will receive intrathecal or intraventricular CNS prophylaxis or therapy.
ALL patients with a Philadelphia chromosome will in addition receive imatinib for at least three years except for the asparaginase course.

8 Study population

8.1 Eligibility for registration

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

8.1.1 Inclusion criteria

- Age 40 - 70 years inclusive
- Primary previously untreated ALL*
- WHO performance status 0, 1, or 2
- Negative pregnancy test at inclusion if applicable
- Written informed consent

*Patients with mediastinal mass defining the so-called T-lymphoblastic leukemia/lymphoma are eligible for this trial. ALL patients with Philadelphia chromosome - t(9;22) and variants - are also eligible for this trial. However, when an alternative trial for Philadelphia chromosome positive patients becomes available, patients should be included in that trial by preference.

8.1.2 Exclusion criteria

- Mature B-cell ALL, i.e. Burkitt leukemia/lymphoma
- Acute undifferentiated leukemia (AUL)
- Severe cardiovascular disease (arrhythmias requiring chronic treatment, congestive heart failure or symptomatic ischemic heart disease)
- Severe pulmonary dysfunction (CTCAE grade III-IV)
- Severe neurological or psychiatric disease
- Significant hepatic dysfunction (serum bilirubin or transaminases $\geq$ 3 times normal level) except when caused by leukemic infiltration
- Significant renal dysfunction (serum creatinine $\geq$ 3 times normal level after rehydration and correction of hyperuricemia)
- History of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma
- History of anthracycline use exceeding a cumulative dose of 300 mg/m^2 doxorubicin (or its biological equivalent)
- 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-induction

Agent	Dose/day	Route	Days
Cytarabine (Ara-C)	200 mg/m^2	i.v. in 60 minutes	1, 8
Etoposide (VP16)	120 mg/m^2	i.v. in 60 minutes	1, 8
Methotrexate (MTX)	500 mg/m^2	i.v. in 120 minutes	4, 11
Leucovorin	120 mg divided in 4 doses of 30 mg strictly every 6 hours until disappearance of MTX from plasma	First dose i.v. thereafter i.v. or p.o.	5, 12, i.e. 24 hr after MTX

9.1.1 Special management orders during pre-induction

Doses of MTX used in pre-induction necessitate hydration and alkalinity of the urine for renal clearance and prevention of toxicity. 6-hourly leucovorin i.v. or orally (first dose i.v.!) must be given 24 hours after the end of MTX infusion and continued until elimination of MTX from blood.

9.2 ODA induction

Agent	Dose/day	Route	Days
Dexamethason	<60 kg : 8 mg 60-80 kg : 10 mg >80 kg : 12 mg	p.o.	1 – 21
Vincristine	1 mg	i.v.	1, 8, 15
Adriamycine	40-60 yr: 40 mg/m^2 61-70 yr: 30 mg/m^2	i.v.	2 – 4

Response (see appendix B) after each ODA course will be evaluated after regeneration of peripheral blood, around day 22 to 29. Regeneration of peripheral blood means a leukocyte count (WBC) >3x10^9/l. Patients in CR or PR after ODA 1 will continue with a second ODA induction course. Patients who did not achieve at least PR will go off protocol treatment.

The second ODA induction course will start after regeneration of peripheral blood, mostly between day 22 and 29 (with day 1 being the start of ODA 1). ODA 2 will be considered delayed if it starts

after day 29, whatever the reason. If ODA 2 has not started on day 42, the patient will go off protocol treatment.

Patients in CR after ODA 2 will continue with a consolidation course. Patients who did not achieve CR and patients with a relapse after CR will go off protocol treatment.

9.3 Consolidation

The consolidation course will start after regeneration of peripheral blood (WBC >3x10^9/l), mostly between day 22 and 29 (with day 1 being the start of ODA 2). Consolidation will be considered delayed if it starts after day 29, whatever the reason. If consolidation has not started on day 35, the patient will go off protocol treatment.

Agent	Dose/day	Route	Days
Cytarabine (Ara-C)	1000 mg/m^2/12 hr	i.v. in 60 minutes	1, 2
L-Asparaginase*	6000 IU/m^2	i.v. in 60 minutes	3 – 12

* see Appendix E

Response (see appendix B) after consolidation will be evaluated after regeneration, around day 22 to 29.

Patients still in CR after consolidation will continue with maintenance treatment. Patients with a relapse after CR will go off protocol treatment.
Patients in CR who have a suitable donor may proceed to allogeneic stem cell transplantation (see 9.8.)

9.4 Maintenance

9.4.1 Eligibility criteria for starting maintenance treatment

- Patient in CR
- Absence of liver function abnormalities, i.e. bilirubin/transaminases ≤ 3 x upper limit of normal
- Absence of concomitant disease, mainly active infection or persistent therapy related side effects
- Any effects of asparaginase on the coagulation, especially reduction of antithrombin (AT), have been resolved

9.4.2 Maintenance schedule

Maintenance treatment will start on day 29 (with day 1 being the start of consolidation) providing that the eligibility criteria (see 9.4.1) have been fulfilled.
Maintenance treatment will be considered delayed if it starts after day 29, whatever the reason. If maintenance treatment has not started on day 35, the patient will go off protocol treatment.
When maintenance treatment is interrupted for more than 5 weeks, it is regarded as end of maintenance treatment and the patient will go off protocol treatment
Maintenance treatment will be continued until 30 months after start of maintenance treatment or until relapse, whichever comes first.

Maintenance treatment will consist of 30 courses every 4 weeks, which are 23 regular (R) courses interspersed with 4 courses of intensification A and 3 courses of intensification B, according to the following schedule:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
R	R	R	A	R	R	R	B	R	R	R	A	R	R	R	B	R	R	R	A	R	R	R	B	R	R	R	A	R	R

Intensification courses A and B may be postponed for one month in case of intercurrent infections or other side effects. Regular courses must be continued in that case (e.g. course A in month 4 is postponed to month 5, in month 4 a regular course R is given instead).

9.4.3 Regular maintenance course

Agent	Dose/day	Route	Days
Prednisone	1 mg/kg	p.o.	1 – 7
Vincristine	40-60 yr: 1.4 mg/m^2, max 2 mg 61-70 yr: max 1 mg	i.v.	1
Methotrexate (MTX)	15 mg/m^2	p.o.	8, 15, 22
6-Mercaptopurine	75 mg/m^2	p.o.	8 – 28

9.4.4 Maintenance intensification A

Agent	Dose/day	Route	Days
Prednisone	1 mg/kg	p.o.	1 – 7
Vincristine	40-60 yr: 1.4 mg/m^2, max 2 mg 61-70 yr: max 1 mg	i.v.	1
Cytarabine (Ara-C)	200 mg/m^2	i.v. in 60 minutes	8, 15, 22
Etoposide (VP16)	120 mg/m^2	i.v. in 60 minutes	8, 15, 22

9.4.5 Maintenance intensification B

Agent	Dose/day	Route	Days
Prednisone	1 mg/kg	p.o.	1 – 7
Vincristine	40-60 yr: 1.4 mg/m^2, max 2 mg 61-70 yr: max 1 mg	i.v.	1
Mitoxantrone	8 mg/m^2	i.v. infusion	8
Cyclophosphamide	750 mg/m^2	i.v. infusion	8
Medication-free period	None	-	9 – 28

9.4.6 Dose adjustments of maintenance treatment

Event	Dose adjustment
WBC >4 x 10^9/l	increase MTX with 2.5 mg/day and/or 6-MP with 25 mg/day
WBC <3 x 10^9/l	reduce MTX with 2.5 mg/day and/or 6-MP with 25 mg/day
Transaminases >3 x ULN	reduce MTX by 25%; if insufficient results: further reduction of MTX by 25% and/or reduce 6-MP by 25%
Intolerance of 6-MP	substitution by 6-thioguanine 80 mg/m^2/day
Concomitant use of allopurinol	reduce 6-MP to 25 mg/m^2

9.5 CNS prophylaxis and treatment

CNS prophylaxis has to start early, i.e. in the first week of diagnosis of ALL.

Agent	Dose/day	Route	Days
Methotrexate (MTX)	40-60 yr: 15 mg 61-65 yr: 10 mg 66-70 yr: 7.5 mg	i.t. or i.v.t. injections	1x/week during the first 4 weeks, 1x/every 4 weeks during the following 6 months

When the meninges are involved in the leukemic process at diagnosis, therapeutic intervention according to institutional standards is to be applied. This has to include more frequent injections of MTX and/or Ara-C. Irradiation may be necessary but should be delayed if possible in order not to interfere with systemic chemotherapy.
To neutralize a possible effect of MTX leaking from the CNS on mucositis, leucovorin may be given 24 hours after the it. or ivt. injection of MTX

9.6 Dose adjustments during treatment

In case of severe polyneuropathy or abdominal ileus, vincristine has to be withdrawn temporarily and restarted later at 50% of the original dose.
When severe pancytopenia or persistent pancytopenia after reduction of the dose of cytostatic drugs develops during maintenance therapy, relapse rather than overdose of cytostatics should be considered and bone marrow examination would be mandatory for definite diagnosis.

9.7 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. All precautions which are generally taken during intensive chemotherapy for hematological malignancies are applied according to local rules, as long as these are in accordance with accepted standards. Supportive care includes the institution of antibiotic prophylaxis and therapy; transfusion of blood products; prevention of vomiting and hyperuricemia, and treatment of mucositis.
When the tumor load is high, there is a small but definite risk for the cell lysis syndrome, especially when the creatinine level is increased. Cornerstones of prevention are: hydration and, if necessary, diuretics in order to secure a urinary output of at least 200 ml per hour; prevention of hyperuricemia

by allopurinol or rasburicase; moderate doses of bicarbonate to neutralize (but not alkalify) urinary pH (7.0-7.5); assessment and correction of K, Ca, P, and Mg, and timely preparation for possible hemodialysis.
If applicable, patients should take precautions to prevent pregnancy for the whole duration of treatment.

9.8 Reduced intensity conditioning allogeneic stem cell transplantation (RIC allo-SCT)

All patients aged ≤ 65 years will have HLA typing at entry in the study and a search for an HLA-identical sibling donor will be performed. MUD transplantations will not be standard treatment in this study and will be limited to patients with the most unfavorable characteristics [e.g. t(9;22) or t(4;11)] at the discretion of the treating physician.
Patients aged ≤ 65 years in CR after consolidation treatment with a suitable HLA-identical sibling stem cell donor may proceed to reduced intensity conditioning allogeneic SCT. Patients receiving RIC allo-SCT will not receive maintenance therapy.

9.8.1 Conditioning regimen

Agent	Dose/day	Route	Days
Fludarabine	30 mg/m^2	i.v.	-4, -3, -2
Total Body Irradiation (TBI)*	2.0 Gy at 10-20 cGy/min.		-1
PBSC infusion**			0

* TBI to be administered between 11.00 and 14.00 hrs to avoid interference with immunosuppressive drugs

** Additional measures: In case of ABO blood group incompatibility and a high load of red blood cells ($\geq$200x10^9), and/or an anti-A or anti-B titer of $\geq$1/16:

- prehydration 1L NaCl 0.9% over 4 hrs
- antihistamines, e.g. clemastine 2 mg IV before infusion of stem cells
- infuse stem cells slowly starting with 1 ml/min., to be doubled after 30 min. and then further increased to 3 ml/min. if no adverse reactions occur

9.8.2 Donor peripheral blood stem cell (PBSC) collection

Day -5: start G-CSF 5 µg/kg s.c. b.i.d.

Day 0: leucapheresis aimed at harvesting 5–10x10^6 $CD34^+$ PBSC/kg body weight of the recipient. If the stem cell harvest provides an insufficient number of PBSC, continue G-CSF b.i.d. and repeat apheresis daily as long as necessary; consider doubling the dose of G-CSF.

9.8.3 Immunosuppression

For *prevention of GVHD* the following applies:

Day -3: start cyclosporine A (CSA) 4.5 mg/kg p.o. b.i.d.

Adjust CSA dose after transplantation to trough levels between 200 and 400 µg/ml until day +120 in the absence of GVHD, or day +180 if GVHD develops. Then taper over 2 weeks (per week 50% reduction of the starting dose), or over 10 weeks (per week 10% reduction), respectively.

Day 0: start mycophenolate mofetil (MMF) 15 mg/kg p.o. b.i.d. until day +84 in the absence of GVHD, then discontinue. If acute GVHD develops continue until disappearance of signs of GVHD, then stop.

For *treatment of GVHD*, CSA dose will be optimized and prednisone 2 mg/kg/day for 10 days will be added. Thereafter, the prednisone dose will be tapered by 50% reduction every 5 days. When GVHD persists and does not respond to this intervention, further therapy will be variable at the discretion of the treating physician.

9.8.4 Scheme of treatment

Day number	-4	-3	-2	-1	0	+84	+120	+134	+180	+250
Fludarabine	START	→	STOP							
Cyclosporine A		START	→	→	→	→	TAPER[1]	STOP	TAPER[2]	STOP[2]
TBI				2.0 Gy						
Stem cell infusion					Infusion					
MMF					START	STOP[3]				
Prednisone[4]										

1 Tapering will be a dose reduction by 50% of the starting dose per week leading to withdrawal in 2 weeks *in the absence of GVHD*

2 CSA trough levels between 200 and 400 µg/ml will be maintained until day +180 *in case GVHD develops*, then CSA will be tapered by 10% of the starting dose per week leading to withdrawal in 10 weeks

3 If GVHD develops continue until resolution of signs of GVHD

4 In case GVHD develops prednisone 2 mg/kg/d for 10 days will be added to the optimized CSA dose. Thereafter, the prednisone dose will be tapered by 50% reduction every 5 days.

Patients will go off protocol treatment on day +180. Until day +180 clinical evaluation will take place every month. Response assessment, including a bone marrow evaluation, has to be carried out at least once, on day +100. From day +180 onwards clinical and laboratory assessment of patients who underwent RIC allo-SCT will be as for patients who did not undergo RIC allo-SCT.

9.9 Special management orders during RIC allo-SCT

Prophylaxis against bacterial and viral infections, and Pneumocystis carinii pneumonitis will be performed according to common practice in (regular) allogeneic SCT. Monitoring of CMV and EBV will be performed following standard procedures and pre-emptive therapeutic intervention will be initiated at the first signs of viral reactivation.

Blood will be investigated for donor chimerism at weeks 4, 8, 12, 26, 39, 52, 65, 78, 91 and 104 after transplantation. Consider first reducing immunosuppressive therapy when the number of recipient blood cells does not decrease sufficiently or lymphoblasts reappear in peripheral blood or

bone marrow. As a following step, *donor lymphocyte infusion (DLI)* should be given according to the institutional rules.

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, liver function test abnormalities and CNS toxicity, Imatinib must be withheld during the periods when L-asparaginase is administered, i.e. days 3-12 of consolidation.

10 End of protocol treatment

Reasons for going off protocol treatment are:

1. Normal completion of protocol treatment
2. Less than PR after ODA 1
3. No CR after ODA 2
4. Relapse (BM or extra-medullary)
5. Excessive extra-medullary drug toxicity
6. Death whatever the cause
7. No compliance of the patient (especially refusal to continue treatment)
8. Major protocol violation*
9. Delay 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 induction treatment I & II: clinical evaluation and response assessment on day 22-29
- After consolidation treatment: clinical evaluation and response assessment on day 22-29
- During maintenance treatment: clinical evaluation every 4 weeks, response assessment every 6 months
- End of maintenance treatment: clinical evaluation and response assessment
- After RICallo-SCT: clinical evaluation every month until day +180, response assessment at least once on day +100
- Follow up after end of protocol: clinical evaluation as indicated below and response assessment when clinical evaluation suggests the possibility of relapse, or yearly for two years

  Year 1: every 2 months
  Year 2: every 3 months
  Year 3: every 4 months
  Year 4-5: every 6 months
  Year >5: every 12 months

11.2 Required investigations

	At entry	Induction I&II	Consolidation	RIC allo-SCT	Maintenance	End of maintenance	FU
Medical history	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X
PB immunophenotyping	X[1)]	X[1)]	X[1)]	X[1)]	X[1)]	X[1)]	X[1)]
Blood chemistry	X	X	X	X	X	X	X
Bone marrow aspirate							
Morphology	X	X	X	X[5)]	X	X	X[1)]
BM immunophenotyping	X	X	X	X[5)]	X	X	X[1)]
Cytogenetics	X	X[3)]	X[3)]	X[3)]			
BM PCR BCR/ABL	X	X[2)]	X[2)]	X[2)]	X[2)]	X[2)]	X[2)]
BM storage	X	X	X	X			
Specific investigations							
Chest x-ray	X	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.
ECG	X	o.i.	o.i.	o.i.	o.i.	o.i.	o.i.
CSF examination	X	X[4)]	X[4)]	X[4)]	X[4)]	X[4)]	o.i.
Virological tests	X	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.
HLA typing	X						

o.i. on indication

1) only in case of failure of bone marrow immunophenotyping at entry or on clinical and laboratory signs of relapse

2) if applicable (see 11.2.9)

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

4) concomitant with every prophylactic or therapeutic intrathecal drug administration

5) at least on day +100

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 during hospitalisation blood cell count and quantitative platelets daily, and WBC count and differential at least every other day until recovery of peripheral blood.

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 (AT)
- Amylase
- Lipase

Also during hospitalisation kidney and liver function tests, uric acid, calcium and phosphate twice weekly.

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 concomitant with every prophylactic or therapeutic intrathecal drug administration

- Virological tests (including CMV)
- Microbiological tests
- HLA typing of patient and family for patients ≤ 65 years of age (at diagnosis or as soon as possible thereafter)

11.2.7 Immunophenotyping

Immunophenotyping of blood and bone marrow by flow cytometry 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 (although differentiation of common ALL-type lymphoblasts from hematogones may pose some problems). Every time the bone marrow is examined, flow cytometry 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 also be required.

Central review will be performed for cytogenetic analysis at diagnosis only (see 4.2).
For analysis at first CR, a filled out cytogenetic form and a copy of the cytogenetic report is also requested to be sent within 3 months to the HOVON Data Center, together with a filled out FISH form and report if applicable.

11.2.9 Molecular analysis

Blood and bone marrow cells should be investigated for BCR/ABL and MLL gene translocation at diagnosis. In case of BCR/ABL positivity or abnormality of the MLL gene follow up investigations for these abnormalities 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.

11.3 Response assessment

Following each phase of treatment starting with the first induction course the response will be assessed by evaluation of blood- and bone marrow aspirate according to the definitions described in appendix B. During the phase of 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, >35, >50, or >60 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:

- time to CR, i.e. > or < than 4 weeks after initiation of therapy
- level of minimal residual disease (MRD) after remission induction and consolidation.

12 Toxicities

12.1 Chemotherapeutic agents

From (single institution) experience with the present treatment regimen in several dozens of patients it was learned that toxicity was manageable but could still be considerable, especially in older patients. The most frequent side effects were:

- mucositis of moderate to severe grade in about half the patients
- liver function test abnormalities most frequently correlated with dexamethasone and asparaginase but also with supportive care (antibiotics, orgametril)
- diabetes mellitus due to corticosteroids
- infection and FUO.

Occasional but sometimes severe or debilitating side effects were:

- polyneuropathy, preventable by timely reduction of vincristine dose and early institution of laxatives
- bleeding or thrombosis
- cardiac arrhythmia
- aseptic necrosis of bone, probably due to dexamethasone and/or MTX
- psychic disturbance (possibly corticosteroid-related)

Hematological toxicity, i.e. pancytopenia, was generally mild and of limited duration, but was severe and prolonged in up to 20% of patients. As mentioned above, febrile episodes and infection did occur regularly mainly during the phase of remission induction; sometimes, dexamethasone appeared to suppress fever probably leading to delay in diagnosing infection.

12.2 Fludarabine

Fludarabine is a drug used to treat lymphomas. It has been used in stem cell transplants to try to reduce the risk of rejection. Its main side effects include lowering of blood counts and infections. In early studies some patients who received high doses experienced nerve damage, but in doses used in this study this side effect would not be expected. Hemolytic anemia has occurred in some patients with chronic lymphocytic leukemia who received fludarabine.

12.3 Cyclosporine

The immediate effects of this drug may include nausea or vomiting when given orally. Other side effects include the possibility of developing high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. These effects are generally reversible upon decreasing the dose of the drug. An occasional patient has had a seizure but it is unclear whether cyclosporine, other drugs, or a combination of drugs was responsible. Some patients given intravenous cyclosporine for the treatment of GVHD experienced painful sensation in hands or feet or both. The pain subsided with the improvement of the GVHD or when the cyclosporine was switched from the intravenous to the oral form.

Patients may experience a change of liver or kidney function, in which case, the dose may be reduced or possibly even stopped for a while. This effect on kidneys seems to increase when other drugs which might cause kidney problems are given at the same time, especially certain antibiotics. Occasionally the kidney damage is severe enough to require the use of an artificial kidney machine (hemodialysis). During treatment cyclosporine blood levels will be monitored to determine if there are increased risks of side effects that warrant changing the dose.

12.4 Total body irradiation

The dose of TBI used in this protocol is approximately one-sixth of that used in conventional transplant protocols, and severe side effects from the TBI are not expected. TBI has been associated with causing sterility and there is a risk of major genetic damage to any children produced soon after transplantation.

12.5 Peripheral blood stem cell transplant

Side effects include low blood count, infections, bleeding, and failure of the donor stem cells to grow. Supportive care with red cell and platelet transfusions and antibiotic therapy may be necessary. Graft-versus-host disease (inflammation of skin, liver and gastrointestinal system), may also occur and require treatment with immune suppressing drugs. In addition, organ damage may occur as a result of radiation or the treatment with immune suppressing drugs. There is a risk that the patient will reject the donor's PBSC and that donor cells will not be detected after transplant. The dose of radiation used is not be expected to cause permanent marrow suppression in the event that graft rejection occurs.

12.5.1 Graft-versus-Host Disease (GVHD)

The major toxicity associated with allografting or infusion of donor PBMC is GVHD. GVHD has occurred in > 50% of patients.

Diagnosis of GVHD: Skin involvement will be assessed by biopsy with percentage of body surface area involved recorded. GI symptoms suspicious for GVHD will be evaluated by biopsy as indicated. Acute GVHD and chronic GVHD will be graded according to established criteria (Appendix F).

12.6 Mycophenolate mofetil

MMF is a relatively new drug used for suppressing the immune system and it has not been used frequently in bone marrow transplantation. Preliminary studies here indicate that this drug is reasonably well tolerated in the transplant setting. There are a small number of patients who have received solid organ transplants and had reversible fall in their red cell or white cell count while receiving MMF. The blood counts will be watched closely and, if significant decrease is noted, dose adjustments or stopping MMF may be indicated. Other uncommon side effects include nausea, vomiting, diarrhea, and abdominal discomfort. Cases of intestinal bleeding have also been reported.

12.7 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

- Disease-free survival (i.e. time from achievement of CR to day of relapse or death from any cause, whichever comes first).

14.2 Secondary endpoints

- CR rate after remission induction and consolidation.
- 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.
- Overall survival measured from time of registration;
- Outcome of patients with a reduced intensity conditioning allogeneic stem cell transplantation.

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 trialnumber, 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 accrual

The aim of this study is to assess in adults of 40-70 years inclusive the efficacy of pre-induction, remission induction and consolidation chemotherapy, followed by maintenance therapy, according to the Groningen scheme. Patients with an HLA-identical sibling donor will be offered a reduced

intensity conditioning allogeneic stem cell transplantation when they are in 1st CR after consolidation treatment.

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

Trial	# patients	Age, median (range)	CR %	$DFS_{1\ year}$ (95% CI)	$DFS_{3\ years}$ (95% CI)
HOVON 18 ALL	65	49 (41-60)	72%	43% (28-56)	26% (14-38)
HOVON 37 ALL	38	52 (41-59)	82%	35% (19-52)	26% (11-43)
Groningen	38	51 (40-73)	76%	73% (51-86)	68% (46-83)

It is expected that about 75% of the patients will reach a CR. The table suggests that disease-free survival from CR (DFS) in Groningen was highly improved compared to the HOVON. DFS is defined as the time from CR until the earliest time point at which one of the following events occur:

- Relapse after CR
- Death from any cause

From the table it is also clear that most events for DFS appear in the first year after CR. Therefore DFS at 1 year (DFS_{1y}) will be considered as primary end point for the sample size calculation.

- Let P_0 be the largest DFS_{1y} probability which, if true, implies that the therapeutic activity is too low and therefore the present HOVON-71 schedule does not warrant further investigation. In the present trial, P_0 has been taken as 40%.
- Let P_1 be the lowest DFS_{1y} probability which, if true, implies that the therapeutic activity is sufficiently high and therefore the proposed HOVON-71 schedule warrants further investigation in clinical trials. In the present trial, P_1 has been taken as 65%.
- 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 CR patients is 40. To reach these, 55 patients will be entered.

- One interim analysis will be performed as soon as 9 events have been reported. The total time at risk for all patients who entered the trial will be calculated. Assuming an exponential distribution for the DFS during the first 12 months, we calculate the hazard rate, estimate DFS_{1y} and its 90%

confidence interval, and the trial will be considered for early termination when the upper limit of the 90% CI is less than 65%

- 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 DFS_{1y} is less than 65% (which is the case if of 40 CR patients 20 or less are a success; 20/40 = 50%; 90% CI =(36.1, 63.9)), the trial will conclude that the proposed HOVON-71 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 DFS_{1y}	Probability to recommend HOVON-71	Probability of early termination	Expected number of patients entered
40%	0.061	0.667	27.3
65%	0.923	0.049	39.1

In order to have up-to-date data for the interim analysis, a short questionnaire will be sent out every 2 months starting 3 months after entry of the 12th patient until 9 events have been observed.

During the past 10 years about 10-15 patients aged 40-60 years were entered per year in HOVON trials. In this trial the upper age limit has been extended to 70 years, 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 20-25 patients per year, the required number of patients would be achieved in 2.5-3 years.

17.2 Analyses

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

The estimated DFS at 1 year 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 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.

The results of the patients who received a reduced intensity conditioning allogeneic transplantation will be presented.

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/randomized 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 (and the sponsor, where applicable) for review. After revision by the Data Center, the other co-authors (and the sponsor), the manuscript will be sent to a peer reviewed scientific journal.

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

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

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

21 Glossary of abbreviations

(in alphabetical order)

6-MP	6-Mercaptopurine
AE	Adverse Event
ALT	Alanine Amino Transferase
ALL	Acute Lymphoblastic Leukaemia
allo-SCT	Allogeneic stem cell transplantation
Ara-C	Cytarabine, cytosine arabinoside
AST	Aspartate Amino Transferase
AT	Antithrombin
BM	Bone Marrow
Ca	Calcium
CI	Confidence interval
CKTO	Commissie voor Klinisch Toegepast Onderzoek
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete Remission
CRF	Case Report Form
CRP	C-Reactive Protein
CSA	Cyclosporine A
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease free survival
DLI	Donor lymphocyte infusion
EBV	Epstein Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
EORTC	European Organization for Research and Treatment of Cancer
FFP	Fresh frozen plasma
FISH	Fluorescence in situ hybridization
FRALLE	French Acute Lymphoblastic Leukemia study group
FU	Follow up
FUO	Fever of unknown origin
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GI	Gastro-intestinal
GvHD	Graft versus host disease
GvL	Graft versus leukemia
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
IT	Intrathecal
(I)ULN	(Institutional) upper limit of normal
IV	Intravenous
IVT	Intraventricular
K	Potassium
LDH	Lactate dehydrogenase
METC	Medical Ethical Review Committee
Mg	Magnesium
ML	Meningeal leukemia
MMF	Mycophenolate mofetil
MPO	Myeloperoxidase
MRD	Minimal residual disease
MRC	Medical Research Council
MTX	Methotrexate
MUD	Matched unrelated donor
NaCl	Sodium chloride
NCI	National Cancer Institute
NMSCT	Non-myeloablative stem cell transplantation
NR	No response
ODA	Oncovin, dexamethason, adriamycine
OS	Overall Survival
PB	Peripheral blood
PBMC	Peripheral blood mononuclear cells
PBSC	Peripheral blood stem cell
PCR	Polymerase chain reaction
PO	Per os
PR	Partial Response
RIC allo-SCT	Reduced intensity conditioning allogeneic stem cell transplantation
SAE	Serious Adverse Event
SCT	Stem cell transplantation
TBI	Total body irradiation
TCR	T-cell receptor
VP16	Etoposide
WBC	White Blood Count
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen

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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 (29);
- 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. Administration of L-asparaginase

- Intramuscular administration can replace 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 < 0.5 g/l	Consider withholding L-asparaginase until fibrinogen has increased > 1g/l or administer fresh frozen plasma (FFP)
Antithrombine < 60%	Consider administration of antithrombine aiming at blood 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

F. Grading of GVHD

Acute GVHD

Severity of organ involvement

Skin	+1 maculopapular eruption involving less than 25% of the body surface
	+2 maculopapular eruption involving 25-50% of the body surface
	+3 generalized erythroderma
	+4 generalized erythroderma with bullous formation and often with desquamation
Liver	+1 moderate increase in AST* (150-170 IU) and bilirubin (20-40 μmol/l)
	+2 bilirubin rise 40-75 μmol/l with or without an increase in AST
	+3 bilirubin rise 75-200 μmol/l with or without an increase in AST
	+4 bilirubin rise to > 200 μmol/l with or without an increase in AST
GI	Diarrhea, nausea and vomiting graded +1 to +4 in severity
	The severity of GI involvement is assigned to the most severe involvement noted
Diarrhea	+1 > 500 ml of stool/day
	+2 > 1000 ml of stool/day
	+3 > 1500 ml of stool/day
	+4 > 2000 ml of stool/day

* increases in AST temporally related to either the onset or worsening of the skin rash

Severity of acute GVHD

Grade I +1 to +2 skin rash
no GI involvement
no more than +1 liver involvement
no decrease in performance

Grade II +1 to +3 skin rash
+1 to +2 GI involvement and/or
+1 to +2 liver involvement
mild decrease in performance

Grade III +2 to +4 skin rash and
+2 to +4 GI involvement with or without +2 to +4 liver involvement
marked decrease in performance with or without fever

Grade IV pattern and severity of GVHD similar to grade III with extreme constitutional symptoms

Chronic GVHD

Limited Localized skin involvement and/or liver function abnormalities

Extensive Generalized skin involvement, or localized skin involvement and/or liver function abnormalities + other organ involvements

G. Patiënteninformatie

Behandeling van acute lymfatische leukemie (ALL) bij 40-70 jarigen met chemo-therapie op basis van een "pre-inductiekuur" en langdurige onderhoudsbehandeling

Geachte Heer, Mevrouw,

Van uw behandelende artsen vernam u dat u lijdt aan acute lymfatische leukemie of "ALL", een kwaadaardige bloedziekte die onbehandeld op korte termijn fataal kan verlopen. De ziekte is wel behandelbaar met corticosteroïden en celdodende middelen (cytostatica). Er is een redelijke kans op genezing maar de behandeling is zwaar en langdurig en succes kan niet worden gegarandeerd. De behandeling bestaat uit verschillende fases en bevat meerdere elementen. Zij worden hier toegelicht, samen met enkele "nieuwe" aspecten, die beloftevolle resultaten opleverden in een relatief kleine groep van honderd patiënten. Uw medewerking wordt gevraagd voor een onderzoek waarin deze nieuwe behandelaspecten worden opgenomen, met de vraag of de eerdere gunstige resultaten bevestigd kunnen worden in een grotere groep patiënten die behandeling krijgen in meerdere ziekenhuizen, verspreid over Europa.

De standaardbehandeling van ALL bestaat uit één of twee *remissie-inductiekuren* met het doel een zgn. complete remissie te bereiken. Dit is een toestand waarbij de leukemie in bloed en beenmerg niet meer aantoonbaar is en die beschouwd wordt als voorwaarde voor langdurige overleving en (kans op) genezing. Deze kuren bevatten altijd minstens corticosteroïden (m.n. prednison of dexamethason), vincristine (Oncovin) en adriamycine, vaak in combinatie met een vierde of een vijfde middel. De inductiekuren worden gevolgd door *consolidatiekuren* met wisselende cytostatica. Vervolgens wordt meestal gedurende wisselend lange tijd een *onderhoudsbehandeling* of *maintenance-therapie* gestart met o.a. 6-mercaptopurine (6-MP) en methotrexate (MTX). Deze onderhoudskuren zijn poliklinisch, de voorafgaande kuren in principe klinisch. Omdat ALL zich ook gemakkelijk in de hersenvliezen (meningen) kan vestigen maar het merendeel van de genoemde cytostatica daar niet doordringen, is er daarnaast een specifieke behandeling nodig van het centrale zenuwstelsel, waarbij stoffen als MTX en Ara-C rechtstreeks in het ruggemergkanaal worden ingebracht, bvb via een ruggemergprik (= lumbaalpunktie). Patiënten in complete remissie komen in aanmerking voor een stamceltransplantatie (SCT), tenminste als ze een geschikte donor hebben, omdat hierdoor de kans op genezing toeneemt. Deze verhoogde overlevingskans moet echter afgewogen worden tegen de toegenomen risico's op ernstige complicaties maar als er een

geschikte donor is, adviseren de artsen meestal om wel een SCT te ondergaan. Sinds enkele jaren is er een nieuwe vorm van SCT, de RIC SCT (voor Reduced Intensity Conditioning SCT) die veel minder complicaties geeft en derhalve vooral geschikt lijkt voor patiënten boven 40 jaar maar de effectiviteit van RIC SCT bij ALL is nog niet goed geëvalueerd. Als u in aanmerking komt voor deze behandeling, dan zullen de voor- en nadelen en de procedures uitgebreid met u besproken worden, vooraleer eventueel tot SCT over te gaan.

Opzet van de studie

Het voorliggende onderzoek volgt dit schema maar voegt een “pre-inductiekuur” van twee weken toe, waarin bij het begin van elke week eenmaal Ara-C en etoposide (VP) wordt toegediend en halfweg de week MTX. Doel is om met deze voorbehandeling een groot aantal leukemische cellen op te ruimen nog vóór de start van de standaardbehandeling. Voor de consolidatie wordt gebruik gemaakt van Ara-C en asparaginase in optimale volgorde. Daarenboven wordt de poliklinische maintenancebehandeling langer dan gebruikelijk, namelijk 2,5 jaren, voortgezet en wordt er onderweg om de 4 maanden een wat intensievere kuur gegeven met afwisselend Ara-C en VP (als bij de pre-inductie) of cyclofosfamide (Endoxan) en novantrone (Mitoxantrone). Patiënten die een familielid hebben met een identiek weefseltype (d.w.z. identiek HLA-type) komen in aanmerking voor een RIC SCT na de consolidatiekuur. De doelgroep voor het onderzoek zijn patiënten die 40 jaar zijn of ouder, maar jonger dan 71 jaar.

Bijwerkingen

In het onderzoek worden geen nieuwe of experimentele middelen gebruikt, maar wordt de timing, de behandelduur, de dosering en volgorde van de bestaande middelen aangepast. Er zijn geen nieuwe bijwerkingen te verwachten maar de gebruikelijke bijwerkingen van intensieve cytostatische kuren kunnen wel optreden. Zo zal de bloedaanmaak bijna altijd zo sterk onderdrukt worden dat er gedurende enige tijd bloed– en bloedplaatjestransfusies nodig zijn. Een groot deel van de patiënten die reeds volgens dit schema behandeld werden, kreeg last van pijnlijke slijmvliesontsteking in de mond (mucositis), waarvoor tijdelijk pijnstilling en soms intraveneuze voeding nodig was. Andere veel voorkomende complicaties waren: infecties met bacteriën of schimmels, leverfunctiestoornissen en ontregeling van het suikermetabolisme. In zeldzame gevallen was de bijwerking zo ernstig of zo lang durend dat de behandeling moest worden afgebroken, in enkele gevallen had een infectie of andere complicatie zelfs een fataal beloop. Uw behandelende dokters verplichten zich er natuurlijk toe om de bijwerkingen zoveel mogelijk te voorkomen, o.a. door het geven van antibiotica, en om infecties optimaal te behandelen, als ze toch optreden. De bijwerkingen van deze kuren zijn van tijdelijke aard en na enkele dagen of

weken treedt herstel op. Overigens wijzen we er ook op dat de gegeven medicijnen toxisch kunnen zijn voor ongeboren en (via moedermelk) pasgeboren kinderen. Voor patiënten in de vruchtbare leeftijd is het belangrijk te zorgen voor goede zwangerschapspreventie tijdens en in de maanden na de behandeling.

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.

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 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 ons ziekenhuis. 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 behandelende arts) weet wie de persoon achter het codenummer is. De gegevens worden bewaard gedurende 15 jaar na het beëindigen van het onderzoek en na afloop vernietigd. Op deze wijze zal uw privacy gewaarborgd blijven.

Schade

De opdrachtgever van dit onderzoek, de Stichting HOVON (Hemato-Oncologie voor Volwassenen Nederland), heeft u verzekerd in verband met eventuele schade die u zou kunnen lijden als gevolg van uw deelname aan dit onderzoek. Het betreft de schade door overlijden of letsel die zich openbaart gedurende de deelname aan dit onderzoek en deze verzekering is een zogenaamde risicoverzekering. Dit houdt in dat de verzekeraar ongeacht of het onderzoek verwijtbaar

onzorgvuldig is uitgevoerd, de schade door overlijden of letsel zal uitkeren tot maximaal de daarvoor gestelde bedragen. Het bedrag waarvoor de verzekering is gesloten is maximaal € 450.000,00 voor de schade per proefpersoon, met een maximum van € 3.500.000,00 voor de schade van alle proefpersonen tezamen die deelnemen aan het onderzoek.
Indien bovengenoemde bedragen de schade niet volledig dekken en aangetoond kan worden dat de uitvoering van het onderzoek onzorgvuldig is geweest, dan kunt u hiernaast ook het ziekenhuis dat opdracht gegeven heeft tot het onderzoek of het ziekenhuis waar het onderzoek is uitgevoerd, aansprakelijk stellen.

De verzekering dekt niet de:

1. schade die het gevolg is van het uitblijven van een vermindering van de gezondheidsproblemen van de proefpersoon, danwel het gevolg is van de verdere verslechtering van de gezondheidsproblemen van de proefpersoon, indien de deelname van de proefpersoon aan het wetenschappelijk onderzoek geschiedt in het kader van de behandeling van deze gezondheidsproblemen.
2. schade door aantasting van de gezondheid van de proefpersoon die zich ook zou hebben geopenbaard wanneer de proefpersoon niet aan dit onderzoek had deelgenomen.
3. schade door aantasting van de gezondheid van de proefpersoon in het geval deze deelneemt aan een vergelijkend onderzoek als bedoeld in artikel 4 tweede lid van de Algemene Maatregel van Bestuur en aannemelijk is dat de schade het gevolg is van de in dat lid bedoelde reeds toegepaste handeling waaraan de proefpersoon wordt onderworpen.
4. schade die zich bij nakomelingen openbaart als gevolg van een nadelige inwerking van medisch-wetenschappelijk onderzoek op de proefpersoon en/of de nakomeling.
5. schade waarvan op grond van de aard van het onderzoek (nagenoeg) zeker was dat deze zich bij de proefpersoon zou voordoen.
6. schade, die het gevolg is van het niet of niet volledig opvolgen door de proefpersoon van aanwijzingen en instructies zoals deze in de patiënteninformatiebrief beschreven staan, voor zover de proefpersoon daartoe in staat is.

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

Weigeren voor en tijdens het onderzoek

U bent uiteraard vrij uw medewerking aan dit onderzoek te weigeren. Omdat het een acute ziekte betreft die op korte termijn behandeld dient te worden, stellen we voor dat u binnen 24 uur een beslissing neemt. Ook als u nu uw toestemming geeft, bent u gerechtigd om later te allen tijde uw goedkeuring in te trekken, zelfs zonder opgave van reden. Als u besluit niet mee te doen, of als u later uw toestemming intrekt, dan zult u de gebruikelijke standaard-behandeling krijgen. 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 behandelende 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 directie van het ziekenhuis, na advies van de Medisch Ethische Commissie. De voor dit onderzoek internationaal vastgestelde richtlijnen zullen nauwkeurig in acht worden genomen.

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 behandelende specialist of aan: …..[naam/namen betrokken specialisten]

…..

…..

Voor meer informatie kunt u ook contact opnemen met een onafhankelijke 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:

Behandeling van acute lymfatische leukemie (ALL) bij 40 tot en met 70 jarigen met chemotherapie op basis van een "pre-inductiekuur" en langdurige onderhoudsbehandeling

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 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.

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.