ALCL-Relapse

Treatment protocol for relapsed anaplastic large cell lymphoma of childhood and adolescence

An European Inter-group Co-operation on Childhood Non-Hodgkin Lymphoma (EICNHL) International Multicentre Therapy Study

Therapiestudie der GPOH

amended Version I
April 2004

Participating Groups:
AIEOP: Associazione Italiana di Ematologia ed Oncologia Pediatrica
BFM Austria, Czechia, Germany and Switzerland
BSPHO: Belgian society of paediatric haematology/oncology
DCOG: Dutch Childhood Oncology Group
NOPHO: Nordic Society of Pediatric Haematology and Oncology
PPLLSG: Polish Paediatric Leukaemia/Lymphoma Study Group
SFCE: Société Française des Cancers de l'Enfant
SHOP: Spanish Leukemia Group
UKCCSG: United Kingdom Children Cancer Study Group

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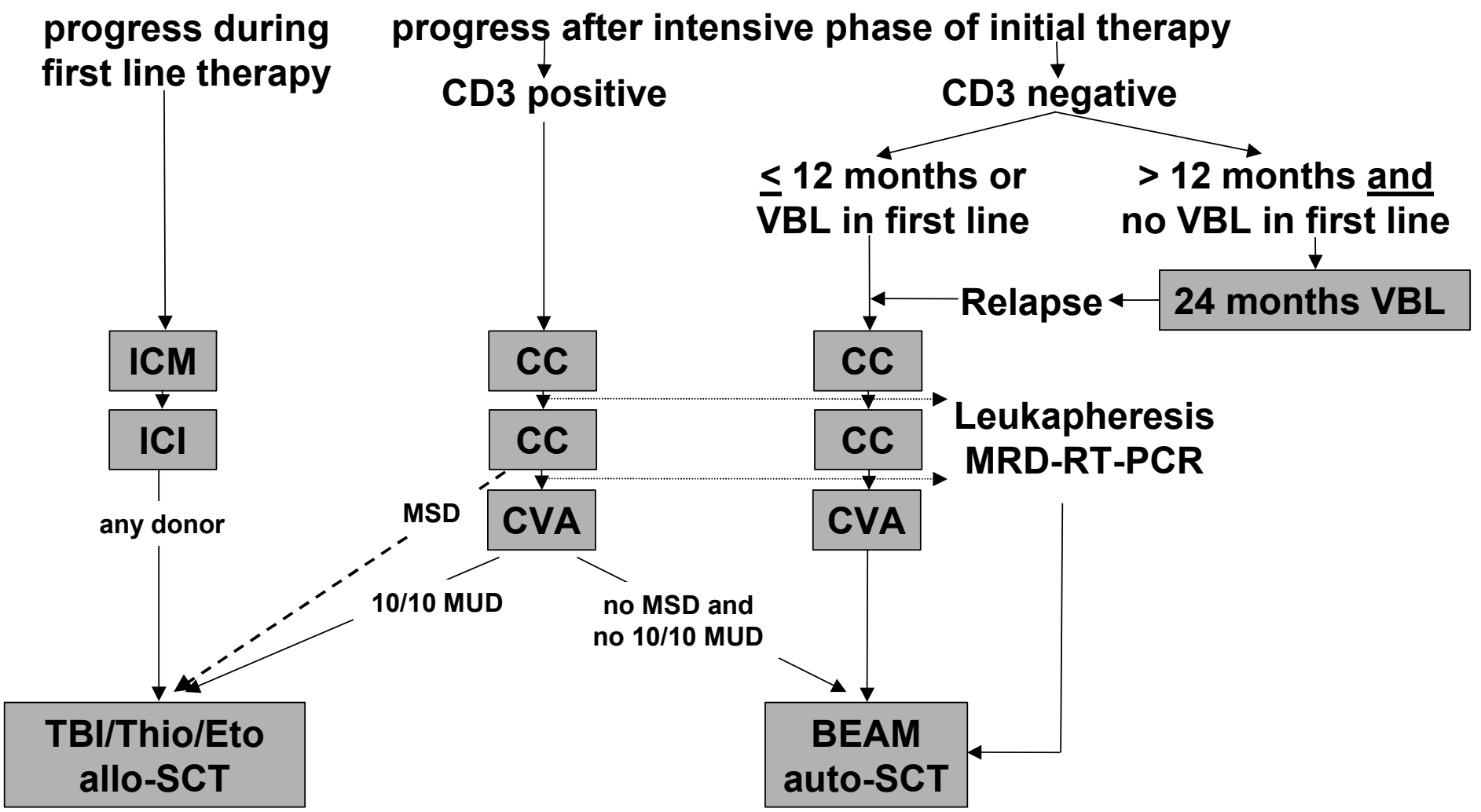
Treatment plan of ALCL Relapse



ALCL-Relapse

Version of the protocol	April 2004
Start of patient recruitment	April 2004
estimated end of patient recruitment	April 2010

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Important note

This document is intended to describe collaborative studies in relapsed anaplastic large cell lymphoma and to provide information for entering patients. The International Study Committee does not intend it to serve as a guide for the treatment of unregistered patients. The present study protocol does not represent recommendations for the standard treatment and is solely for the purpose of the current study. Whether the objectives of the study will be reached remains open. Treatment of patients according to the present protocol without consultation of the International Study Committee is not justifiable.

Before entering patients into the study clinicians must ensure that the study protocol has received clearance from their Ethical Committee and accomplishes regulatory requirements.

The completion of the protocol has been conducted with great care. Amendments may be necessary; these will be circulated to known participants of the trial, but institutions entering patients are advised to contact the responsible study centres to confirm the correctness of the protocol on their hand. Despite our best efforts the possibility of errors within this document cannot be entirely discounted. We therefore remind investigators that the responsibility for any therapy given lies with the attending physician alone and the authors of this protocol do not take responsibility for any adverse consequences arising from application of the recommendations in this protocol.

The content of the protocol is confidential and may not be passed on to centres not involved in the study, without the approval of the International Study Committee.

Protected labels are marked with the symbol following ®. The absence of ® does not imply that the term is free.

Table of Contents

1 Synopsis

Title

ALCL-Relapse
Treatment protocol for relapsed anaplastic large cell lymphoma of childhood and adolescence

Start of study

April/May 2004

Participating groups

- AIEOP
- BFM
- BSPHO
- DCOG
- NOPHO
- PPLLSG
- SFCE
- SHOP
- UKCCSG

Type of study

prospective multicentre trial

Stratification

therapeutic subgroups hierarchically stratified by
- time from initial diagnosis until the occurrence of relapse
- immunophenotype of ALCL
- availability of MSD or 10/10 MUD Sc-donor
- Vinblastine administration during frontline therapy

Randomisation

none

Inclusion criteria

- progression or relapse of ALCL
- age < 22 years
- slides of relapsed lymphoma available for national pathological and/or cytomorphology review
- signed informed consent of patient/guardians for participation in the study ALCL-Relapse
- no evidence of pregnancy or lactation period; assured contraception
- no participation in another clinical study, recruitment in study ALCL-Relapse during run time of the study

Patients who fulfil the eligibility criteria of the study but who meet one of the following criteria are not evaluable for trial's results. Nevertheless, they should be registered and documented in the study.
- 2nd, or subsequent relapse of ALCL
- significant pre-treatment for 1st relapse
- no adequate hepatic, renal and cardiac function
- HIV infection or AIDS, severe immunodeficiency
- previous organ transplantation
- previous malignancy prior to the anaplastic large cell lymphoma
- pre-existing disease prohibiting treatment as per instruction of protocol

Objectives

Primary objectives of the study are:
1. to improve the probability of event free survival in children and adolescents with early progression of ALCL or/and a relapse of ALCL with CD3 positive immunophenotype
2. to test whether in patients with relapse of CD3 negative ALCL occurring after the intensive phase of frontline treatment BEAM conditioning regimen (without TBI) for autologous stem cell transplantation is an effective treatment
3. to test the impact of Vinblastine in patients with late relapse of an CD3 negative ALCL

Primary endpoint

The endpoint for the 1st, 2nd and 3rd study question is the is the Event Free Survival (EFS), defined as minimum time from the date of diagnosis of relapse to the first event (death from any cause, 2nd relapse, progressive disease, secondary malignancy, late event).
EFS will be estimated using the Kaplan-Meier method.

Statistical considerations

In patients who are eligible for allogeneic SCT the test for difference will be considered significant if the lower limit of a one-sided 95% confidence interval of pEFS is above 31%.
In patients who are eligible for autologous SCT the test will be considered significant if the lower limit of a one-sided 95% confidence interval of pEFS is above 31%.
In patients who are eligible for Vinblastine alone the test will be considered significant if the lower limit of a one-sided 95% confidence interval of pEFS is above 31%.
With a type I error of 5 % the number of patients required to reach a power of 80% is 43 (test for difference in patients who are eligible for allogeneic SCT, null hypothesis pEFS=31%, expected rate 50%) and 33 (test for equivalence in patients who are eligible for autologous SCT, expected pEFS 53%, lower limit acceptable pEFS=31%).
With a type I error of 5 % the number of patients required to reach a power above 80% is 9 for patients who are eligible for VBL only with an expected pEFS 75% and a lower limit for the acceptable pEFS of 31%.

The expected number of patients diagnosed with relapse of ALCL in Europe is about 16 per year. Of these about 50% are expected to be eligible for allogeneic SCT (early relapse during front line therapy or CD3 positive). About 15% are expected to be eligible for Vinblastine only (very late relapse >1 year after diagnosis and CD3 negative without Vinblastine pre-treatment). The remaining 35% of the patients are eligible for autologous SCT. A total of about 96 patients is necessary to reach the required number of patients for each of the above mentioned study questions. With 16 patients per year, the duration of the recruitment will be 6 years.

2 Background and rationale

Anaplastic large cell lymphoma (ALCL) was first described as a clinicopathological entity by Stein and co-workers in 1985[1]. Morphologically it is characterized by large pleomorphic cells which express CD30, often together with epithelial membrane antigen (EMA) and the interleukin 2 (IL-2) receptor[2,3]. Lymphoid lineage specific antigens are of T- cell phenotype in the majority of cases. The relative frequency of T-cell immunology varied between different studies on pediatric and adolescent ALCL between 45% and 81%[1,4]. On the molecular level, almost 80% of pediatric and adolescent ALCL are characterized by a translocation involving the ALK receptor tyrosine kinase on chromosome 2[3,5]. Most often, the ALK gene gets fused to the NPM gene on chromosome 5, leading to a NPM-ALK fusion protein. The NPM-ALK protein can be detected by the ALK-1 monoclonal antibody and used as a diagnostic test for the presence of the NPM-ALK translocation. Recent reviews even suggest defining ALK–positive lymphomas as a distinct group of NHL[3-7].

ALCL accounts for 10 – 15% of all childhood and adolescence NHL. Clinically they are characterized by a predominance of B-symptoms and frequent extranodal involvement, particularly skin, lung, bone and soft tissue[8-11].
Like other childhood lymphomas, ALCL are highly chemosensitive with complete remission rates ranging from 65 to over 90% with various multiagent chemotherapy regimens[8,9,11-13]. Therapy for primary ALCL varied considerably in different study groups. Most of the European groups applied a short-pulse intensive chemotherapy strategy proven to be effective for mature B-cell neoplasms. Based on the experiences with different protocols, the European Intergroup Cooperation on Childhood NHL (EICNHL) instituted a common treatment strategy for primary ALCL in 1999 based on the protocol of the BFM group.

However, 25 – 40% of patients develop a relapse of the disease, usually during the first year after diagnosis. Risk factors for a relapse include skin, lung, mediastinal and visceral involvement[8,9,11-13]. A striking observation in the first ALCL relapse patients treated in France and Germany, however, was the favourable chance of survival after relapse of these patients in contrast to children or adolescents suffering from other subtype of NHL. 88% of 41 patients reported by the French Society of Pediatric Oncology (SFOP) achieved a second remission, of whom 25 patients when treated with CCNU, vinblastine, ara-C and bleomycin (after 1991). The final results were an overall and disease free survival of 69% and 44% at three years[14]. In this French series, weekly vinblastine led to long-lasting remissions even after failure of stem cell transplantation. However, this series included patients who relapsed between 1975 and 1997, and roughly half of the patients (20/41) relapsed after a primary treatment according to protocols which are no longer considered optimal treatment for patients with ALCL. Moreover, the role of high dose chemotherapy with autologous blood stem cell support in the treatment of ALCL relapses could not be further clarified. The United Kingdoms Children's Cancer Study Group (UKCCSG) reported their experience with 13 children with ALCL who relapsed after intensive frontline treatment between 1990 and 1997[13]. Most of these children relapsed early (6 patients within 5 months from diagnosis) and the outcome was less favourable (9 of the 13 children died due to second relapse/progression). Other reported series of relapse patients are small and stamped by the lack of a consistent approach to second line therapy[15-20].

No clear guide to the most appropriate treatment after relapse of an ALCL can be extracted from the studies reported so far. The promising drug Vinblastine has been incorporated into the frontline therapy in the ALCL 99 treatment protocol so that it no longer may be applicable for second line treatment[21].

The analysis of the outcome of patients with an ALCL relapse after BFM frontline therapy treated according to a recommendation in the NHL-BFM 90 and 95 protocol in Germany, Austria and Switzerland can be used for preliminary conclusions to define prognostic factors and get hinds for a risk-tailored therapy for relapse patients. Altogether, 80 patients were diagnosed with a relapse of an ALCL between February 1990 and February 2003 after intensive frontline therapy comparable to the current frontline protocol. The protocols NHL-BFM 90 and 95 recommended the strategy CC (dexamethasone, HD-ara-C and etoposide, triple drug i.t. therapy), followed by AA (Dexa, MTX, Ifosfamide, Vincristine, Cytarabine, Etoposide, triple drug

i.t. therapy) and BB (Dexa, MTX, Cyclophosphamide, Vincristine, Doxorubicine, triple drug i.t. therapy) for induction of a second remission. Autologous blood stem cell transplantation should be used as consolidation therapy. In individual patients treating physicians decided to perform allogeneic transplantations instead. The conditioning protocol included 12 Gy TBI (6x 2Gy), etoposide (40 mg/kg) and cyclophosphomide (2x 60mg/kg) for both transplant procedures. Supportive therapy and GvHD prophylaxes were at the discretion of each transplant center.
43 patients are alive in CR at January 2004 (Overall survival 53%). 31 patients (39%) died from ALCL-progression and 6 patients from treatment (TRM 8%) (Table 1). Two patients were diagnosed with a lymphomatoid papulomatosis; both of them have a wax-and-wane course of the disease with and without chemotherapy. They were not included in the further analyses of prognostic factors. The influence of therapy, localization of the relapse, time of the relapse from first diagnosis and of the immunophenotype on the outcome of the patients were analysed.

Table 1: Outcome after a first relapse of an ALCL

patients	80		(relapse diagnosis 10/86 – 2/03, update 3/04)
Survival	43	(53%)	
DOD	31	(39%)	
TRM	6	(8%)	

DOD, dead of disease, TRM, treatment related mortality

1. Influence of therapy on outcome (Table 2):
Four patients died of lymphoma progression after receiving no or palliative therapy. Four patients were treated with chemotherapy only. Two of them died of disease, one achieved a second CCR and one patient was lost to follow up. Of the 67 patients who were scheduled for either autologous or allogeneic blood stem cell transplantation (BSCT), 10 died before reaching the transplantation, 9 due to lymphoma progression and one due to TRM. Of the 57 patients who underwent a transplant procedure, 42 were treated by high dose therapy with autologous stem cell support. 20 patients (48%) achieved a second CCR and live free of disease. Two patients died from therapy and 20 patients relapsed a second time. Surprisingly, all five patients who underwent a secondary allogeneic BSCT after second relapse achieved a third CCR and survived. Ten of the 15 patients (65%) who received a primary allogeneic BSCT are in second CCR; TRM of the allogeneic procedure was 20% (3 patients).
Preliminary conclusions may be drawn from these results: Over 40% of patients with a relapse of an ALCL survive without disease after high dose therapy with autologous BSCT. Some patients can be rescued even after failure of high dose therapy by an allogeneic BSCT. There are some patients for whom the induction chemotherapy with CC may not be appropriate since 15% of patients relapsed before a scheduled transplant procedure.

Table 2: Influence of therapy on outcome of ALCL relapses (n=78)

				chemotherapy and BSCT		
	unknown	no/palliativ	chemother.	dead before SCT	autologous SCT	allogeneic SCT
patients	3	4	4	10	42	15
2. CCR	2		1		20 (48%)	10 (64%)
TRM		0	0	1	2	3
Progress	1	4	2	9	20	2
DOD	1	4	1 (1 lfu)	9	12	2

2. Influence of the localization of the relapse on outcome:
There was no influence of the localization of the relapse on the outcome of the patients. Neither the occurrence of new localisations nor the involvement of skin or bone marrow decreased the prognosis of the patients. The only exception are patients with the very rare situation of an ALCL relapse occuring in the CNS.

3. Influence of the immunophenotype on outcome:

When patients are grouped according to the expression of the major T-cell antigen CD3, 41 ALCL were CD3 negative, 23 CD3 positive and two patients carried B-cell-marker. The CD3 status of the remaining 12 patients could not be extracted from pathology reviews. Survival of the CD3 negative patients was 61% compared to 43.5% for the patients whose tumours expressed CD3. In order to see if the CD3-expression status of the primary tumor can define a group of patients who do not profit from high dose therapy we focussed our analyses to those patients who were treated by BSCT. A clear prognostic impact of the immunophenotype on the outcome after autologous BSCT can be made (Table 3): 19 (79%) of the 24 CD3 negative patients who received high dose therapy with autologous BSCT reached a second CCR compared to only 2 (15%) of the 13 CD3 positive patients. Altogether 6 patients with relapse of a CD3 positive ALCL underwent an allogeneic BSCT (4 after a second relapse after autologous BSCT and 2 after first relapse). All 6 patients are in second/third CCR. Relapse patients with CD3 positive tumours do not profit from an autologous BSCT (ABSCT), however, there is a first hint for a graft versus ALCL-effect against CD3 positive ALCL by allogeneic BSCT. These data suggest that patients with a CD3 negative relapse of an ALCL should be treated by ABSCT while CD3 positivity should qualify for an allogeneic BSCT.

Table 3: Influence of the immunophenotype on outcome of ALCL relapse patients who underwent a SCT

	autologous SCT		allogeneic SCT	
CD3	CD3 neg	CD3 pos	CD3 neg	CD3 pos
Patients	24	13	10	2
2. CCR	19 (79%)	2 (15%)	6	2
TRM	0	1	2	0
Progress	5	10	2	0
3. CCR	1 (allo)	4 (4 allo)		
DOD	3	7	2	0

4. Influence of time of the relapse after first diagnosis on outcome:

ALCL which stain positive for CD3 clearly define a bad risk group of patients. However, the prognosis of those patients who had a relapse during therapy for the primary ALCL (i.e., within 3 – 4 months after diagnosis of the first lymphoma) was even worse independent of the immunophenotype. Only three of the 17 patients (20%) who experienced their relapse within 4 months from diagnosis survived compared to 38 of 61 (62%) with a relapse later then 4 months. The main cause of death for the “early” relapse patients was the disease (74%). Hints for a treatment strategy for these patients again can be drawn from the analyses of the treatments performed (Table 4): 4 patients received no or palliative therapy; all 6 patients who underwent an ABSCT relapsed a second time and 5 of them died; two of the 6 patients who got an allogeneic BSCT survived (one even in second relapse during reinduction chemotherapy). These data suggest that patients with a relapse during frontline chemotherapy can not be rescued by high dose therapy with autologous BSCT, while an allogeneic approach may be a viable option.

Table 4: Outcome of the patients with a relapse of an ALCL during the first 4 months after primary diagnosis according to their relapse treatment

			Chemotherapy and BSCT	
	no or palliative chemotherapy	dead before SCT	autologous SCT	allogeneic SCT
Patients	4	1	6	6
2. CCR	0		0	2
TRM			0	2
Progress	4		6	2
3. CCR			1	0
DOD	4	1	5	2

Less then half of the patients who experience a relapse during treatment or shortly thereafter and who were treated according to the recommendation in the BFM-protocol (CC – AA – (BB)) reached the SCT without a second relapse. Therefore, these patients need more efficacious reinduction chemotherapy. There is a center experience (Gießen/Germany) with individual patients with refractory NHL including ALCL (progression during treatment, second or third relapse) treated with a chemotherapy cycle consisting of Mitoxantrone, Carboplatin and Ifosfamide followed by a second cycle with Idarubicine, Carboplatin and Ifosfamide. Complete lymphoma remissions were observed even in patients in whom CC has failed and the toxicity profile of this therapy compared favourable to CC (see Table 5).

Table 5: Toxicity profile of courses ICI and ICM in 5 patients

	course I (ICM)(N= 6)		**course II (ICI)(N= 4)**	
Toxicity	NCI grade III	NCI grade IV	NCI grade III	NCI grade IV
Haematology				
Haemoglobin	**3**	**3**	**1**	**3**
Leukocytes		**6**		**4**
Granulocytes				
Thrombocytes	**1**	**5**		**4**
Infection				
Infection	**1**		**1**	
Fever				
Mukositis				
Stomatitis				
Diarrhoea		**2**		
Liver				
Bilirubin				
SGOT/SGPT	**1**			
Neurotoxicity				
central	**1**			
peripheral				
other toxicities				
	haem. Cystitis			

There were no grade III/IV toxicities neither cardiac toxicities (arrhythmia or function), nor renal toxicities, thrombosis/embolism or anaphylaxis.
Therefore, in the current study the feasibility and efficacy of these regimens as reinduction for high risk relapse patients, i.e. patients with an early relapse during frontline therapy will be evaluated.

Risk groups
Treatment results for children with relapsed ALCL are generally superior to other diagnostic subgroups of NHL. However the heterogenity in the group of children with a relapse of an ALCL calls for risk group adapted therapy intensity. With a combination of the factors immunophenotype and time to progression 3 risk groups can be separated:
A: early relapse or/and CD3 positive: pEFS (2y) = 31%, SE 9% (N=26, events: 18) and pEFS (4y) = 22%, SE 8% (N=26, events: 20)
B: intermediate time to relapse and CD3 negative: pEFS (2y/4y) = 53%, SE 12% (N=18, events 8)
C: late relapse and CD3 negative: pEFS (2y/4y) = 75%, SE 13% (N=12, events 3)

With the exception of two events in risk group A all subsequent events occurred during the frist two years after diagnosis of relapase. Test for the difference revealed significant differences between group A vs B (p=.03) and A vs. C (p<.001).
Of 64 patients 34 could be classified to group A (53%) (8 patientes who received allogeneic SCT were excluded form the analysis of outcome; see above), 18 to group B (28%) and 12 to group C (19%).

3 Study objectives and design

3.1 Study objectives

The aim of the study is to test the feasibility and efficacy of a treatment strategy for relapsed anaplastic large cell lymphoma consisting for the majority of patients of reinduction chemotherapy followed by allogeneic or autologous stem cell transplantation, respectively (stratified for time of relapse, immunophenotype, Sc-donor availability and VBL administration during frontline therapy).

Primary objectives of the study are:
1. to improve the probability of event free survival in children and adolescents with early progression of ALCL or/and a relapse of ALCL with CD3 positive immunophenotype
2. to test whether in patients with relapse of CD3 negative ALCL occurring after the intensive phase of treatment BEAM conditioning regimen (without TBI) for autologous stem cell transplantation is an effective treatment
3. to test the impact of Vinblastine in patients with late relapse of an CD3 negative ALCL who have not received Vinblastin during frontline therapy

Secondary objectives of the study are to test the reproducibility of the newly introduced stratification criteria, to control protocol adherence measured by the proportion of patients who are treated according to the protocol among all patients who meet the inclusion criteria of the protocol and to monitor acute and late toxicity of the treatment.

Criteria of assessment for the primary objectives
The endpoint for the 1st, 2nd and 3rd study question is the is the Event Free Survival (EFS), defined as minimum time from the date of diagnosis of relapse/progress to a subsequent event (death from any cause, second relapse, progressive disease, secondary malignancy).
EFS will be estimated using the Kaplan-Meier method.

Criteria of assessment for the secondary objective
The end point for the question of reproducibility of the newly introduced stratification criteria is the proportion of patients who are eligible for allogeneic SCT (early progression, or/and CD3 positive immunophenotype).
The endpoint of the control of protocol adherence is the proportion of patients who are treated according to the protocol among all patients who meet the inclusion criteria of the protocol. A patient is judged to be treated according to the protocol if he is transplanted according to his risk classification within 4 months from beginning of relapse therapy.

Secondary end points
- overall survival: defined as time from relapse to death of any cause
- acute and long term toxicity
- rate of acute and chronic GvHD in patients with allogeneic stem cell transplantation
- treatment related mortality

3.2 Study design

ALCL-Relapse is a prospective non randomised international multicentre trial.

Patient recruitment starts in April/May 2004. With an expected recruitment of 16 patients per year, the duration of the study will be about 6 years.

The study includes:
- registration of all patients of participating centres with newly diagnosed relapse of an anaplastic large cell lymphoma
- stratified treatment-plan for salvage chemotherapy and stem cell transplantation
- program of investigations to identify prognostic factors highly predictive for failure of current treatment

The treatment of patients with relapsed anaplastic large cell lymphoma will be stratified by the following criteria (see page 2):

- time of progression/relapse
- immunophenotype of lymphoma cells
- stem cell donor availability
- VBL administration during frontline therapy

According to those stratification criteria there will be five arms (for details see chapter "Classification of therapeutic groups and treatment plan", page 28):

	time point of relapse	**immuno-phenotype**	**donor availibility**	**VBL in frontline therapy**	**salvage chemotherapy**	**SCT**
Arm1	early progression during intensive chemotherapy	CD3 positive or CD3 negative	any donor		ICM, ICI	allogeneic SCT
Arm 2a	relapse after end of intensive therapy	CD3 positive	MSD or 10/10 MUD available		CC, CC, (CVA)	allogeneic SCT
Arm 2b	relapse after end of intensive therapy	CD3 positive	no MSD and no 10/10 MUD available		CC, CC, CVA	autologous SCT
Arm 3	relapse after end of intensive therapy	CD3 negative		VBL in frontline therapy or relapse ≤ 12 months after diagnosis of ALCL	CC, CC, CVA	autologous SCT
Arm 4	relapse > 12 months after diagnosis of ALCL	CD3 negative		no VBL in frontline therapy	24 months VBL	none

3.3 Expected duration of patient's participation in the trial

For patients in the treatment arms 1, 2a, 2b, and 3 the individual duration of the treatment is estimated to be about 9 months. The actual duration depends on the clinical course of the individual patient. For patients in the treatment arm 4 the duration of the study is 24 months and if necessary additional 9 months after diagnosis of 2nd relapse and shift to treatment arm 3.
The follow-up period is at least 10 years.

4 Participating Groups

Participating groups are:

- AIEOP: Associazione Italiana di Ematologia ed Oncologia Pediatrica
- BFM Germany - Switzerland - Czechia
- BFM Austria
- BSPHO Belgian society of paediatric haematology/oncology
- DCOG: Dutch Childhood Oncology Group
- NOPHO for Scandinavian group
- PPLLSG Poland
- SFCE: Société Française des Cancers de l'Enfant
- SHOP Spain
- UKCCSG: United Kingdom Children's Cancer Study Group

These groups form the core collaborative group. Other national groups may join this study after discussion with the core group.

Participating groups are expected

- to register all patients with relapsed ALCL diagnosed in one of the participating centres of that group in order to avoid patient selection bias
- to provide diagnostic material for central review and research projects

All centres are expected to obtain approval for the study from their local research ethical committee according to their national policy and to control whether the protocol matches with GCP-guidelines and local law and regulatory requirements. Further more all participating centres have to agree to the contract of participation and all centres have to declare to adhere to the ALCL-Relapse protocol.

For the participating centres see appendix "Participating groups and centres", page 149.

5 Patient eligibility

5.1 Eligibility to the study

Patients meeting the following criteria are admitted to the study:

- Progression or relapse of anaplastic large cell lymphoma diagnosed either by histomorphological or cytomorphological characterisation
- slides of relapsed lymphoma available for national/international pathological and/or cytomorphology review
- age < 22 years
- signed informed consent of patient/guardians for participation in the study ALCL-Relapse
- no evidence of pregnancy or lactation period; assured contraception
- no participation in another clinical study and recruitment in study ALCL-Relapse during run time of the study

All patients fulfilling these eligibility criteria will be registered in the study. A registration fax must be sent to the responsible Co-ordination Centre as soon as the diagnosis of relapse is confirmed. For the registration form see appendix, page 97. In return the treating hospital will receive a confirmation of registration.
A subsequent exclusion of a patient is allowed only if it turns out that diagnosis of relapse was incorrect.

5.2 Patients not evaluable for trial's results

Patients who fulfil the eligibility criteria for the study but who meet one of the following criteria will not be included in the results of this trial. Nevertheless, they should be registered and documented in the study and the data will be analysed for defined questions. The national study co-ordinator should be contacted for potential therapy modifications before the start of treatment.

- 2^{nd} or subsequent relapse of ALCL
- significant pre-treatment for 1^{st} relapse (previous chemotherapy or radiotherapy within two months prior to the beginning of therapy according to the protocol ALCL-Relapse, exept in emergency situations)
- no adequate hepatic, renal and cardiac function
- HIV infection or AIDS, severe immunodeficiency
- previous organ transplantation
- previous malignancy prior to the anaplastic large cell lymphoma
- pre-existing disease prohibiting chemotherapy as per instructions of the protocol
- pre-condition prohibiting the conditioning regimen as per instruction of the protocol (see page 43)

6 Diagnostics

A histological or cytological/genetical confirmation of the relapse is mandatory for participation in the trial ALCL-Relapse. In addition the histo- or cytological diagnosis of the anaplastic large cell lymphoma must be confirmed by the national central pathology review panel of the respective participating national/cooperative group.

6.1 Initial diagnostic procedures

To establish the diagnosis of relapse of the anaplastic large cell lymphoma the least invasive procedure should be preferred. It is important to notice, however, that fine-needle or trocar needle biopsy is usually not recommended. Tissue specimen gained by needle biopsy is mostly insufficient for complete characterisation of the disease. Therefore, needle biopsy should be restricted to those patients to whom a more invasive intervention poses undue risk.

In case of suspected relapse all other options to establish the diagnosis should be considered before surgery is performed:

- examination of blood and bone marrow
- in case of pleural effusion/ascites: puncture and cytological and immunophenotypic examination by immuncytochemistry and genetics

In case of malignant effusions and/or significant bone marrow infiltration the diagnosis can be established by means of cytomorphology on cytospin preparations, FISH or PCR to evidence t(2;5) (or variant translocations) and immunophenotyping of cell suspensions.

Only if the diagnosis of relapse cannot be established using these simple techniques surgery should be performed. Surgery is primarily performed to confirm the diagnosis of suspected relapse. Complete resection should not be intended, except if possible, without any risk and functional loss for the patient. The most peripheral lesion should be chosen for biopsy, e.g. in case of a mediastinal tumour, extra-thoracic manifestations should be carefully sought, which can be used for a biopsy.

Material has to be ascertained in the following way:

- Tumour touch imprints
- formol fixated material for histologic and immunhistochemical examination
- fresh material in cell culture media (cell culture media or NaCl 0.9% if media is not available) for:
    1. MRD
    2. Cytogenetics
    3. Tumour cell banking
- shock frozen lymphoma material (liquid nitrogen, -80°C) for:
    1. Matrix comparative genomic hybridisation (CGH)
    2. Gene expression profiling
    3. Proteomics studies

If only limited biopsy material is available for carrying out all the diagnostic and research studies described above, tumour processing must follow a priority algorithm.

1. Assurance of diagnosis
2. MRD
3. Cytogenetics
4. Matrix-CGH
5. Gene expression profiling
6. Surface enhanced lasser desorption/inosation (SELDI)
7. Tumour cell banking

The following procedure is recommended:
Ideally, the paediatric oncologist or the pathologist should take over the biopsy specimen directly in the surgery room for appropriate processing. As a first step, the biopsy should be subdivided into one-third to two-thirds of volume. The two-third portion is kept sterile. Prepare

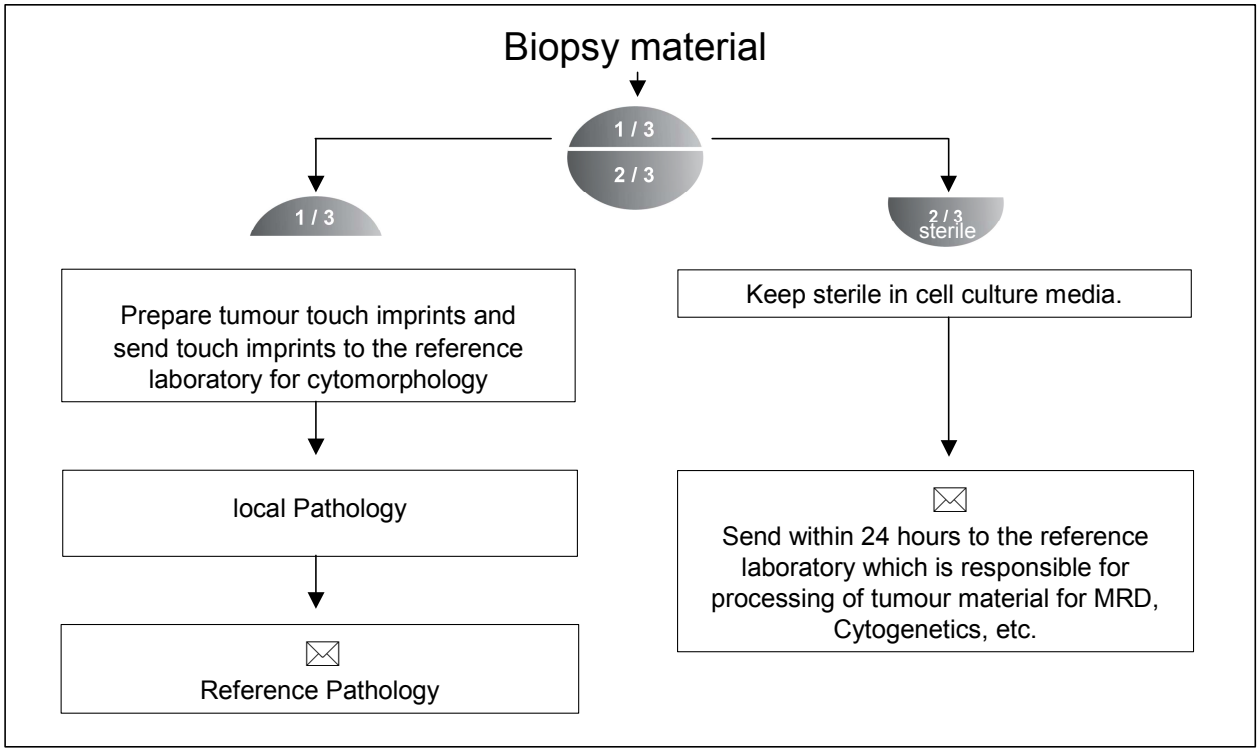
touch preparations from the one-third proportion. Use the one-third proportion for pathology, if sufficient according to the agreement of the pathologist. Use the two-thirds proportion for further biological studies according to the priority list above. The tissue for further biological studies should be sent as one sterile piece within 24 hours to a national central laboratory for further processing of tumour material (see schema below).

Important note: Central histological review is necessary to enter the study. A block of paraffin embedded material or 16 unstained slides will be requested for each patient.

The processing and shipment of the tumour material (biopsy, effusions, bone marrow, blood) is described in details (see chapter "Processing of tumour material", page 22).

6.2 Schema for the processing of tumour material

The following schema summarises the recommended processing of tumour material. Note, that the tumour material sent to pathological examinations must be enough to ensure diagnosis and to perform immunhistochemistry.



6.3 Processing of tumour material and blood samples at diagnosis of relapse

Material	Processing	Investigation	send to
Lymphoma	formol fixated	Histology Immunohistochemistry	**National Reference Pathology**
	in culture media or, if not available, 0,9% NaCl	Cytogenetics Molecular genetics/MRD Cell banking	**National Reference Genetics/Morphology**
Tumour touch imprints	preparations, unstained	Morphology, FISH	**National Reference Genetics/Morphology**
Bone marrow	20-25 ml with heparin*	Molecular genetics/MRD Cytogenetics Cell banking	**National Reference Genetics/Morphology**
	10 slides, unstained	Cytomorphology	
Liquor	2 cytospin preparations, unstained	Cytomorphology	**National Reference Morphology**
Blood	10 slides, unstained	Cytomorphology	**National Reference Genetics/Morphology**
	10 ml with heparin*	Molecular genetics/MRD Cell banking	
	10 ml with EDTA – send as quickly as possible	Study of B cell and T cell response to ALK	
Pleural effusion/Ascites	10 cytospin preparations, unstained	Cytomorphology	**National Reference Genetics/Morphology**
	as much as possible with heparin*	Cytogenetics Molecular genetics/MRD Cell banking	

*) Use heparin without stabilizer.

National Reference institute for genetics (MRD)	National Reference institute for morphology	National Reference Pathology	Immunresponse to ALK
Prof. Dr. J. Harbott Dr. K. Busch Onkogenetisches Labor Universitäts-Kinderklinik Pädiatrische Hämatologie und Onkologie Feulgenstr. 12 D – 35385 Gießen	Prof. A. Reiter Dr. W. Wößmann Universitäts-Kinderklinik Pädiatrische Hämatologie und Onkologie Feulgenstr. 12 D – 35385 Gießen	Prof. Dr. Dr. h.c. R. Parwaresch Institut für Hämatopathlogie Universität Kiel Niemannsweg 11 D – 24105 Kiel oder ein anderes Referenzpathologisches Institut der NHL-BFM Studie siehe S. 4	Karen Pulford Nuffield Department of Clinical Laboratory Sciences, Room 4A11, Level 4, Academic block, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, U.K. karen.pulford@ndcls.ox.ac.uk kamel.ait-tahar@ndcls.ox.ac.uk

6.4 Staging

6.4.1 Observation of tumour extension

- detailed clinical examination with careful attention to
  - general condition and B-symptoms
  - skin lesions (sometimes limited to a few pink macular papules)
- Performance status (Karnofsky/Lansky)
- detailed description of all initially involved sites
- x-ray of chest (p.a. and lateral) and, in case of a mediastinal mass, chest CT.
- Ultrasound scan of abdomen/pelvis, thorax (pleural effusion, pericardial effusion), testes
- abdominal MRI (magnetic resonance imaging) or CT with contrast in case of equivocal results in ultrasound
- BM aspirate (2 sites)
- CSF (cerebrospinal fluid) cytospin and cell number. Even if there is no apparent infiltrate, an initial cytospin preparation should be performed
  Recommendations for cytospin preparations

cells in CSF	filling quantity	revolutions/min	time
< 100/µl	0.5 ml	1 000/min	5 min.
100-1 000/µl	0.2 ml	1 000/min	5 min.
>1 000/µl	0.05 ml	1 100/min	3 min.

- Cytology of pleural fluid/ascites (cytospin preparations)
- immunological examinations and genetics of pleural fluid/ascites/BM (if involved)
- cranial MRI (if not available: CT with contrast medium)
- spinal MRI in case of neurological signs
- bone scan and local x-ray in case of local bone symptoms or of any suspicious areas identified on bone scan

further examinations:

- full blood count and film
- electrolytes, urea, creatinine, uric acid, calcium, phosphate, alkaline phosphatase
- GFR (glomerular filtration rate), if there is any evidence of renal dysfunction
- LDH (lactate dehydrogenase)
- tests for inherited thrombophilia (if not performed at time of initial diagnosis)
- echocardiography

6.4.2 Definition of organ involvement

6.4.2.1 Bone marrow involvement

Bone marrow involvement is diagnosed if there are morphologically identified lymphoma cells in bone marrow aspirates.

6.4.2.2 CNS involvement

CNS involvement is considered if:

- morphologically identified tumor cells or cells with t(2;5) (or variant translocations) are present in CSF cytospin preparations
- cerebral/medullary infiltrates on cranial/spinal MRI
- cranial nerve palsy that cannot be explained by extradural lesions

6.4.2.3 Liver involvement

Liver involvement is diagnosed if

- Liver enlargement exceeds the age related norm in ultrasound or other imaging techniques by 5 cm or more, or if liver is palpable 5 cm or more below the costal arch and/or
- nodular liver involvement is seen in ultrasound or other imaging techniques.

6.4.2.4 Lung involvement

Lung involvement should be confirmed by x-ray and/or CT-scan. If the histopathological diagnosis of relapse can be performed by biopsy of other sites, such as peripheral lymph nodes, a lung biopsy should not be carried out since it might compromise the patient.

6.4.2.5 Mediastinal involvement

Mediastinal involvement should be confirmed by x-ray and/or CT-scan. If the histopathological diagnosis of relapse can be performed by biopsy of other sites, such as peripheral lymph nodes, invasive methods, such as mediastinoscopy or thoracotomy, should not be carried out, since it might compromise the patient.

6.4.2.6 Skin involvement

Skin involvement should be confirmed by biopsy. In case of isolated skin relapse diagnosis of a lymphomatoid papulosis must be ruled out definitely.

6.4.2.7 Spleen involvement

Spleen involvement is diagnosed if

- spleen enlargement exceeds the age related norm in ultrasound or other imaging techniques by 5 cm or more, or if the spleen is palpable 5 cm or more below the costal arch and/or
- nodular spleen involvement is seen in ultrasound or other imaging techniques.

6.5 Staging system

St. Jude's Classification[22]

Stage	Criteria for extent of disease
I	A single tumour (extra nodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen or epidural.
II	A single tumour (extra nodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extra nodal) tumours with or without regional node involvement on the same side of the diaphragm. A primary gastrointestinal tumour usually in the ileocaecal area with or without involvement of associated mesenteric nodes only, grossly completely resected.
III	Two single tumours (extra nodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All primary intra-thoracic tumours (mediastinal, pleural, thymic). All extensive primary intra-abdominal disease. All paraspinal or epidural tumours regardless of other tumour site(s). Multilocular bone involvement.
IV	Any of the above with initial CNS and/or bone marrow involvement.

Ann Arbor staging classification

Stage	Criteria for extent of disease
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of an extralymphatic organ or site and one or more lymph node region on the same side of the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by involvement of the spleen (IIIS) or by localised involvement of an extralymphatic organ or site or both (IIIE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement

6.6 Diagnostic procedures during and after the end of therapy

6.6.1 Monitoring of minimal residual disease (MRD), chimerism and immune response to ALK

Time point	MRD***	Chimerism**		Immune response***
	3-5 ml EDTA BM* 10 ml EDTA blood	2x3ml EDTA blood	3ml BM	10 ml EDTA blood see page 59
at diagnosis of relapse	**X**			**X*** **
after the 2nd course of chemotherapy				
before SCT	**X**	**X**	**X**	**X*** **
day +7		**X**		
day +14		**X**		
day +21		**X**		
day +28	**X**	**X**	**X**	**X*** **
day +35		**X**		
day +42		**X**		
day +49		**X**		
day +60	**X**	**X**	**X**	**X*** **
day +74		**X**		
day +88		**X**		
day +100	**X**	**X**	**X**	**X*** **
4 month after SCT		**X**		
5 month after SCT		**X**		
day +180	**X**	**X**	**X**	**X*** **
day +360	**X**	**X**	**X**	**X*** **

* In patients who receive no SCT but Vinblastine for 24 months BMP as follow up of disease status should be performed only in case of BM-involvement at relapse and evidence of lymphoma cells in BM in previous examination. Examination of blood will be performed.

** Only after allogenic SCT.

*** Send the samples for MRD and immune response to the national reference laborytory for genetics in Gießen (for address see page 4 and 69).

6.6.2 Follow-up studies of disease status

Routine follow up studies are to be performed to follow and document the status of the disease. Recommended imaging methods for follow up studies depend on localisation.

localisation	Method for follow up studies
mediastinal tumour, lung	x-ray , if inconclusive CT
head, brain, spinal	clinical symptoms: MRI
peripheral nodes	Physical examination, ultrasound
abdominal sites	Ultrasound, if doubtful: CT or MRI
bone	clinics, if symptoms: x-ray, MRI
soft tissue	Physical examination, ultrasound, MRI
skin	Physical examination
testes	Physical examination

The following table gives recommendations for the time points of disease status evaluation.

Time points of follow up studies of disease status			
time point	**local manifestations** appropriate imaging as described above	**BM/blood**	**CSF** only in case of CNS involvement
before 2nd course	**X**	**X**	**X**
before 3rd course (autologous SCT)	**X**	**X**	**X***
before SCT	**X**	**X**	**X***
day 28 after SCT	**X**	**X**	**X***
day 42	**X**		
day 60	**X**	**X**	
day 100	**X**	**X**	
day 130	**X**		
day 160	**X**		
day 180	**X**	**X**	
day 181-365	2-monthly	**X**	
2nd year	3-monthly		
3rd year	6-monthly		
4th year	once a year		
Later	if progression suspected		

*) only in case of apparent lymphoma-cells in CSF at previous examination

Additional time points and examinations if progression is suspected.

6.6.3 Monitoring of late effects

The evaluation of late effects of the recommended therapy represents one aim of the study. For this analysis, follow up data will be requested in constant intervals (see chapter "Follow-up", page 55). In case of diagnosis of a late effect the corresponding part of the follow up form (see appendix page 134 or 142) has to be filled in and sent to the national data centre.
Furthermore the monitoring of late effects may be performed according to local practice.
In the following some basic recommendations are given.

time after SCT	**month**							**year**			
	0	**3**	**6**	**9**	**12**	**18**	**24**	**3**	**4**	**5**	**8**
transaminases	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
bilirubin	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
creatinine	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
blood pressure	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
height	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
weight	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
electrocardiogram (ECG)	**X**	**(X)**	**X**		**X**		**X**	**X**	**X**	**X**	**X**
echokardiography	**X**	**(X)**	**X**		**X**		**X**	**X**	**X**	**X**	**X**
X-ray thorax	**X**	**(X)**	**X**	**(X)**	**X**	**(X)**	**X**	**X**	**X**	**X**	**X**
Karnofsky/Lansky	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
capacity of learning	**X**		**X**		**X**		**X**	**X**	**X**	**X**	**X**
neurological status	**X**		**X**		**X**		**X**	**X**	**X**	**X**	**X**
pulmonary function	**X**		**X**		**X**		**X**		**X**		**X**
clotting tests	**X**		**X**		**X**		**X**		**X**		
status of the eyes	**X**				**X**		**X**	**X**	**X**	**X**	**X**
T3/4, TSH	**X**				**X**		**X**	**X**	**X**		**X**
LH/FSH/oestradiol/testosterone	**X**				**X**		**X**		**X**		**X**

7 Classification of therapeutic groups and treatment plan

The treatment of patients with relapsed anaplastic large cell lymphoma will be hierarchically stratified by the following criteria (see page 2):

- time of progression/relapse
- immunophenotype of lymphoma cells
- availability of MSD or 10/10 matched Sc-donor
- Vinblastine administration during frontline therapy

7.1 Arm 1: Early progression

The occurrence of relapse is regarded as early progression if tumour progression is diagnosed during the phase of intensive initial chemotherapy of the ALCL. In this therapeutic group there is no further differentiation of patients according to the immunophenotype of the lymphoma or compatibility of a Sc-donor.
Patients with early progression receive salvage chemotherapy consisting of one course ICM and one course ICI followed by allogeneic stem cell transplantation. There are no further restrictions concerning the HLA-compatibility between Sc-donor and recipient. The conditioning regimen is based on total body irradiation, Thiotepa and Etoposide.

7.2 Arm 2: Relapse and CD3 positive lymphoma cells

Patients with CD3-positivity in immunohistochemical examination of tumour slides of ALCL and the occurrence of relapse after the end of frontline therapy belong to this treatment group. Patients are stratified by the criterion of Sc-donor availability:

- **Arm 2a:** If a matched sibling donor or a 10/10 matched non-sibling donor is available, patients receive salvage chemotherapy consisting of two courses CC followed by allogeneic stem cell transplantation. For patients without a matched sibling donor and with ongoing search for a 10/10 matched non-sibling donor an additional course CVA after the two courses CC may be implemented until the completion of the SC-donor search. The conditioning regimen is based on total body irradiation, Thiotepa and Etoposide.
- **Arm 2b:** If there is no matched sibling donor or a 10/10 matched non-sibling donor available patients receive re-induction consisting of two courses CC and one course CVA, followed by BEAM conditioning regimen and autologous SCT (see chapter "Arm 3: Relapse and CD3 negative immunophenotype", page 28).

7.3 Arm 3: Relapse and CD3 negative immunophenotype

The criteria for patients belonging in this treatment group are

- time of relapse after the end of intensive frontline chemotherapy of ALCL
- CD3-negativity at immunohistochemical examinations of the ALCL
- relapse of ALCL within 12 months after the initial diagnosis
- or relapse of ALCL more than 12 months after the initial diagnosis of ALCL but Vinblastine received during frontline therapy

Patients in this therapeutic subgroup receive three courses of chemotherapy (CC, CC and CVA) with leukapheresis after the first and/or second CC course (the first course is preferred) followed by autologous SCT with the BEAM regimen of conditioning.

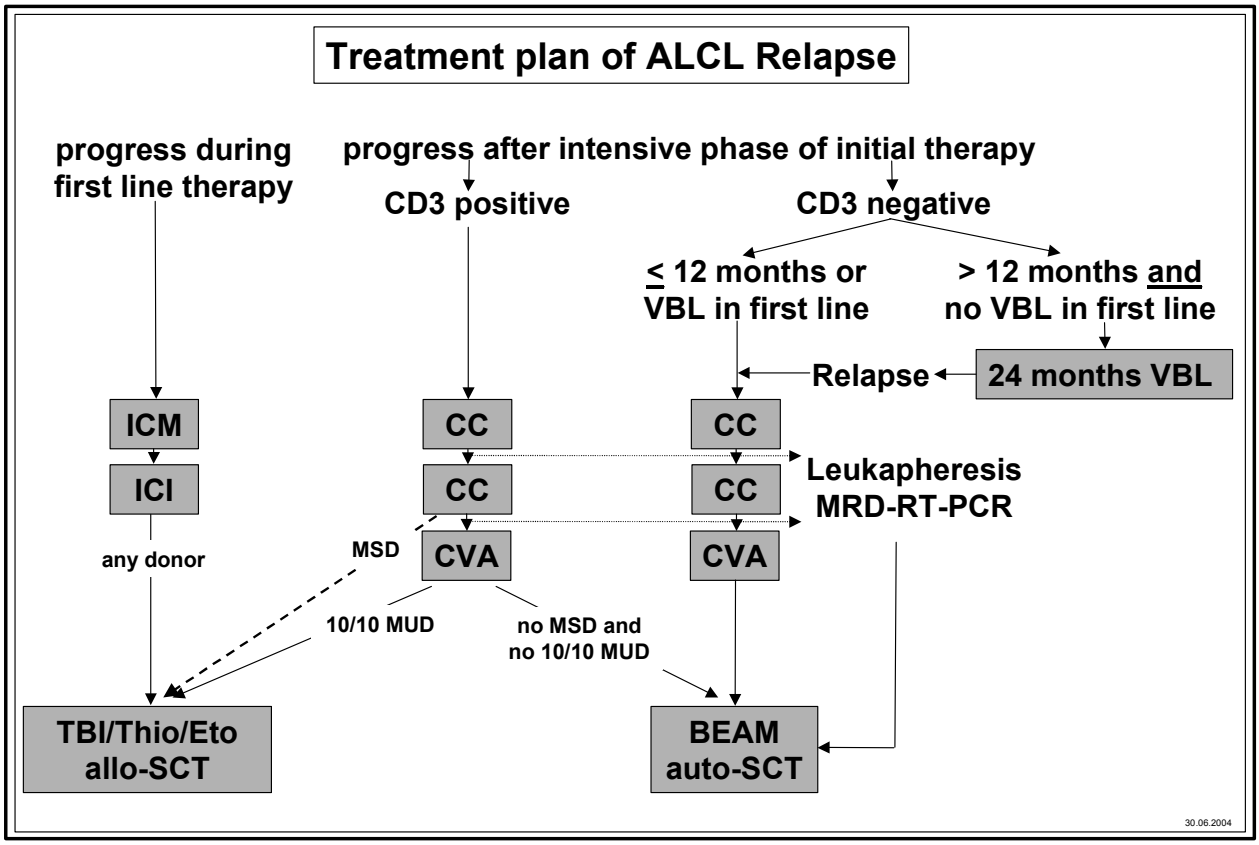
7.4 Arm 4: Late relapse and CD3 negative immunophenotype

Patients who fulfill all of the following three criteria

- relapse of ALCL more than 12 months after the initial diagnosis **and**
- CD3 negative immunophenotype **and**
- no Vinblastine received during frontline therapy

receive 24 months Vinblastin given once a week.
In case of progression during or after the administration of Vinblastine, patients receive therapy according to "Arm 3: Relapse and CD3 negative immunophenotype", page 28 with autologous SCT.

The classification and treatment of therapeutic groups is summarised in the following figure:



In case of an ALCL relapse **during** frontline treatment according to protocol ALCL 99 in the **low risk arm**, patients receive allogeneic SCT (see chapter "Arm 1: Early progression", page 28). For the tratment of patients who relapsed **after** frontline treatment in the low risk arm please contact the national study centre for advice.

8 Guidelines for timing of treatment and dose calculation

Adhere to the protocol as close as possible. Interruptions in a therapy element which has already begun should be avoided, except in case of a severe infection or serious toxicity. There are no planned adjustments to drug doses (except after consultation with the national study co-ordinator). If necessary, a postponement of a chemoherapy course is preferable. Special guidelines are given within the description of each treatment element or the description of the drug, respectively (e.g. Carboplatin, Ifosfamide).

8.1 Recommended requirements for the continuation of treatment

- The treatment according to the Protocol ALCL-Relapse should start as soon as the diagnosis of relapse is confirmed.
- In case of high tumour volume Rasburicase for the prophylaxis of a tumour lysis syndrome is recommended.
- Ensure sufficient bowel motility prior to the start of treatment.
- The timing of treatment should be adjusted to the recovery of the bone marrow and the clinical condition of the patient.
- minimal interval between the beginning of two subsequent courses: 16 days
- Before the start of a course, the patient should be free of fever for al least 3 days, there should be no signs of infection and the patient should be in good general condition.
- haematological requirements for the continuation of treatment:
    - recovery of peripheral counts with rising tendency following post-chemotherapy nadir
    - ANC ≥ 0.5 x 10^9/L
    - platelets ≥ 50 x 10^9/L
- renal and hepatological requirements for the continuation of treatment:
    - creatinine/creatinine-clearance within normal limits corrected for age
    - SGOT/SGPT ≤ 5 x upper normal limit
    - Bilirubin ≤ 3 upper normal limit
- Prior to the administration of Anthracyclines sufficient cardiac function should be ensured.

8.2 Guidelines for dose calculation

Systemic therapy
Dosage is based on body surface area (BSA), which is determined before every therapy element. Infants receive reduced chemotherapy dosage according to age:

Age	Dosage according to BSA
Birth - ≤ 6 months	2/3 of the calculated dose
7 - < 12 months	3/4 of the calculated dose
≥ 1 year	full dose

Intrathecal therapy
Dose according to age. The age at the time of administration is the determining factor.

Age	Methotrexate i.t. (mg)	Cytarabine i.t. (mg)	Prednisolone i.t. (mg)
<1 year	6	16	4
1 -< 2 years	8	20	6
2 -< 3 years	10	26	8
≥ 3 years	12	30	10

9 Re-induction chemotherapy: Treatment elements

The elements of salvage chemotherapy differ between the three respectively four therapeutic subgroups. For details see chapter "Classification of therapeutic groups and treatment plan", page 28 and page 2.

9.1 Course CC

day	1	2	3	4	5
Dexamethasone	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●
Vindesin	●				
Cytarabine (ARA-C)	● ●	● ●			
Etoposide (VP-16)			● ●	● ●	●
MTX/ARA-C/PRED i.t.					●
Hydration	●	●	●	●	●

Dexamethasone	**20 mg/m²/d, p.o. or iv** in 3 divided doses, **days 1-5**
Vindesin	**3 mg/m², iv (maximum single dose 5 mg), day 1** one hour before first dose of Cytarabine
Cytarabine (ARA-C)	**3 g/m²/single dose, iv over 3h, day 1 and 2** **(4 administrations at intervals of 12 hours)** days 1-3: supportive therapy → **lacrimal fluid,** **every 8 hours** 2-3 drops per eye; **Vitamin B_6** 150 mg/m², every 12 hours **cave:** in case of nystagmus/ataxia: termination of infusion. In case of persistent nystagmus/ataxia no further Cytarabine-Infusion (Purkinje-cell-degeneration)
Etoposide (VP-16)	**100 mg/m²/single dose, iv over 2h, day 3-5,** **(5 administrations at intervals of 12 hours)** dilution 1:50 to 1:100 in NaCl 0,9%; start at day 3 in the morning **cave:** hypotension, anaphylaxis and arrhythmia ⇒ monitoring during and 5 hours after the end of infusion
MTX/ARA-C/PRED i.t.	**Methotrexat, Cytarabin, Prednisolon intrathecally at day 5** in age-adjusted dose:

age	Methotrexat i.t. [mg]	Cytarabine i.t. [mg]	Prednisolon i.t. [mg]
< 1 year	6	16	4
1 - < 2 years	8	20	6
2 - < 3 years	10	26	8
≥ 3 years	12	30	10

After i.t. application lowered head position for at least 2 hours

Hydration	**3 000 ml/m²/d, iv**

9.2 Course CVA

day	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**
CCNU	●							
Vinblastine	●					●	●	●
Cytarabine (ARA-C)	●	●	●	●	●			

CCNU	**100 mg/m², p.o. day 1**
Vinblastine	**6 mg/m²/d (maximum single dose 10 mg), iv, days 1, 8, 15, 22**
Cytarabine (ARA-C)	**100 mg/m²/d, iv over 1 h, days 1-5**

9.3 Course ICM

day	1	2	3	4	5	6	7	8	9
MTX/ARA-C/PRED i.t.	●								
Mitoxantrone	●	●							
Carboplatin		▬	▬	▬	▬				
Ifosfamide		▬	▬	▬	▬	▬			
Mesna (1)		●							
Mesna (2)		▬	▬	▬	▬	▬	▬	▬	
Hydration	▬	▬	▬	▬	▬	▬	▬	▬	

MTX/ARA-C/PRED i.t.

Methotrexat, Cytarabin, Prednisolon intrathecally at day 1
in age-adjusted dose:

age	Methotrexat i.t. [mg]	Cytarabine i.t. [mg]	Prednisolon i.t. [mg]
< 1 year	6	16	4
1 - < 2 years	8	20	6
2 - < 3 years	10	26	8
≥ 3 years	12	30	10

After i.t. application lowered head position for at least 2 hours

Mitoxantrone

8 mg/m²/d, iv over 0,5h, day 1 and day 2

Carboplatin

200 mg/m²/d, continuous infusion over 4 days (96h), start at day 2

For dose modifications in case of reduced renal function see chapter "Drugs", page 48.

Ifosfamide

2 g/m²/d, continuous infusion over 5 days (120h), start at day 2

For treatment of Ifosfamide-induced neurotoxicity see chapter "Drugs", page 48.

Mesna (1)

500 mg/m², iv, day 2, before start of Ifosfamide

Mesna (2)

3 000 mg/m²/d, continuous infusion over 7 days (168h), start at day 2

Hydration

3 000 ml/m²/d, iv, if specific gravity of urine > 1010, increase of hydration to 150%

9.4 Course ICI

day	1	2	3	4	5	6	7	8	9
MTX/ARA-C/PRED i.t.	●								
Idarubicine	●	●							
Carboplatin		▬	▬	▬	▬				
Ifosfamide		▬	▬	▬	▬	▬			
Mesna (1)		●							
Mesna (2)		▬	▬	▬	▬	▬	▬	▬	
Hydration	▬	▬	▬	▬	▬	▬	▬	▬	

MTX/ARA-C/PRED i.t.

Methotrexat, Cytarabin, Prednisolon intrathecally at day 1
in age-adjusted dose:

age	Methotrexat i.t. [mg]	Cytarabine i.t. [mg]	Prednisolon i.t. [mg]
< 1 year	6	16	4
1 - < 2 years	8	20	6
2 - < 3 years	10	26	8
≥ 3 years	12	30	10

After i.t. application lowered head position for at least 2 hours

Idarubicine

10 mg/m²/d, iv over 4 h, day 1 and day 2

Carboplatin

200 mg/m²/d, continuous infusion over 4 days (96h), start at day 2

For dose modifications in case of reduced renal function see chapter "Drugs", page 48.

Ifosfamide

2 g/m²/d, continuous infusion over 5 days (120h), start at day 2

For treatment of Ifosfamide-induced neurotoxicity see chapter "Drugs", page 48.

Mesna (1)

500 mg/m², iv, day 2, before start of Ifosfamide

Mesna (2)

3 000 mg/m²/d, continuous infusion over 7 days (168h), start at day 2

Hydration

3 000 ml/m²/d, iv, if specific gravity of urine > 1010, increase of hydration to 150%

9.5 Vinblastine

Vinblastine: 6 mg/m^2 (maximum single dose 10 mg) iv bolus every week for a total duration of 24 months.

Dose modifications:

- A blood count should be carried out every 14 days and treatment should be stopped if the neutrophil count is < 0.5 x 10^9/l (or in case that there is no differential if leucocyte count is < 1 x 10^9/l) or the platelets are < 50 x 10^9/l. Vinblastine is recommenced once the neutrophil count is > 0.5 x 10^9/l and the platelets are > 50 x 10^9/l.
- The dose of Vinblastine should be reduced to 4 mg/m² in case of prolonged cytopenia necessitating an interruption of more than 2 injections. If the next two courses are well tolerated, the standard dose of 6 mg/m^2 should be tried again.
- Neurological examination as part of clinical evaluation should be carried out monthly. It is suggested that the Vinblastine dose should be reduced to half (3 mg/m^2) if there is evidence of symptomatic peripheral neuropathy. In this situation please contact the study co-ordinator.

9.6 Supportive therapy during salvage chemotherapy

Supportive therapy is primarily the responsibility of the physician in charge. In this chapter only recommendations are given for the patient management in certain situations. The national study co-ordinators are available for consultation. For supportive care during the period of SCT see chapter "Supportive care**:** minimal standard" page 38.

Substitution of blood products
Substitution of blood products should be performed according to local/national standards. All blood products have to be irradiated with a minimum of 30 Gy and leukocyte depleted. Substituted blood should be CMV-negative for CMV-negative patients.

Infection prophylaxis and therapy
The attending physician has the responsibility for the prophylaxis of infection. The following suggestions are meant as a general reference and are not considered binding guidelines.
The most important infection prophylaxis is a thorough disinfection of hands before and after every contact with a patient, as well as detailed patient and parent education about neutropenia and risk of infection. The administration of non-absorbable antibiotics for the purpose of complete or selective decontamination of the digestive tract may select for resistant bacteria and has not yet clearly been shown to be effective[23,24]. An oral antimycotic chemoprophylaxis with Amphotericin B-suspension or Fluconazole inhibits the colonisation by most Candida species, but does not inhibit the incidence of systemic Candida and Aspergillus mycoses[25]. Constipation and ileus favour the growth of bacteria and fungi in the intestinal lumen and the invasion into the mucous membrane, especially if damage due to cytostatic agents and/or infiltration has occurred. It is therefore important to assure a daily bowel movement, for instance through administration of lactulose p.o. If this treatment is not successful, then stimulant laxatives might be indicated.

Pneumocystis carinii prophylaxis
All patients should receive a prophylaxis with Trimethoprim-Sulfamethoxazole (Cotrimoxazol) during the entire phase of chemotherapy to prevent a Pneumocystis carinii-pneumonia. In the case of a TMP-SMZ intolerance it is possible to treat alternatively with pentamidine inhalation[26].

Medication	Dosage
TMP-SMZ	5 mg TMP/kg/d, p.o. in two doses on three consecutive days, e.g. during the weekend
alternatively: Pentamidine Aerosol	< 4 years: 150 mg/month in 5 ml aq. dest. Inhaled over 20 - 30 min ≥ 4 years: 300 mg/ month in 5 ml aq. dest. Inhaled over 20 - 30 min

Varicella exposure
Contact between ALCL patients during chemotherapy and individuals with varicella or varicella zoster must be avoided. If exposure does occur, there is a risk of illness for at least 28 days, regardless of serological status, although sero-positive patients do have a markedly decreased risk[27]. In individual cases, the degree of immunosuppression at the time of exposure determines the therapeutic measures[28-31].

Patient status	Recommendation
has had Varicella (history, scars, titer)	observation; exception: after SCT patients should always receive treatment.
not yet had varicella ± immunosuppression	Aciclovir 80 mg/kg/d, p.o. in 4 SD for 14-28 days + varicella-zoster hyperimmunoglobin within 48 hours after exposition
Varicella appearance	Aciclovir 3 x 15 mg/kg/d, iv (over 1 h) Until all efflorescences have dried up (minimum 5 days)

Active immunisation of contact persons against Varicella (if they have not had natural exposure) can reduce the risk of Varicella infection of the patient.

Fever and Neutropenia

Definition

- temperature oral/rectal ≥ 38.5°C
- neutrophils < 0.5 x 10^9/l

Diagnostics

Implementation/supplementation of tests according to clinical situation

- cultures: blood (every catheter channel), stool if diarrhoe (incl. Clostridium difficile toxin), urine
- swabs from throat, skin and mucous membrane lesions, anus
- PCR for mycetes if possible
- chest x-ray, consider CT if pulmonary symptoms and x-ray negative
- if the x-rays of the lungs are reported abnormal a diagnostic bronchial lavage is recommended if the patient is considered clinically stable

Therapy

Broad spectrum antibiotic therapy:

The antibiotic therapy must be adapted to the unique situation of each patient and each clinic's bacterial spectrum.

- start with a combination of a cephalosporin (3. generation) and an aminoglycoside
  alternative depending on individual risk: monotherapy with a cephalosporin (3. generation) or aminoglycoside and broad-spectrum penicilline
  adapt therapy to detected microbes
- abdominal symptoms: consider additional therapy with vancomycin orally 4x250 mg/d or Metronidazol
  (discuss catheter explantation if contaminated)
- change antibiotic therapy, if fever, infection parameter and clinical symptoms do not decrease after 2 - 3 days
- if fever is persistent > 3 - 5 d, or returns after iv antibiotics: additional therapy with antimycotic agents
- for suspected anaerobic infection: additional Clindamycin/Metronidazol

10 Stem cell transplantation (SCT)

After re-induction chemotherapy patients receive SCT (except patients in the Vinblastine treatment arm).

10.1 Transplantation groups

This study differentiates between two stem cell transplantation groups. Patients will be stratified by the following criteria: time of relapse, immunophenotype and availability of Sc-donor to receive either an allogeneic SCT or an autologous SCT (see chapter "Classification of therapeutic groups and treatment plan", page 28).

10.2 Time of SCT

The interval between the start of last chemotherapy and the start of the conditioning regimen should be 4 to at most 6 weeks. If infection or toxicity require that the start of the conditioning regimen needs to be postponed, patients should receive risk adapted chemotherapy e.g. weekly Vinblastine, to bridge the time until transplantation.
For patients in treatment arm 2a without a matched sibling donor and with ongoing search for a 10/10 matched non-sibling donor an additional course CVA after the two courses CC may be implemented until the completion of the SC-donor search (see chapter "Arm 2: Relapse and CD3 positive lymphoma cells" page 28).

10.3 Supportive care: minimal standard

Isolation
At the latest with the beginning of bone marrow aplasia, preferably after the end of irradiation or at the beginning of chemo-conditioning, the patient should be nursed in a reverse isolation unit. HEPA or laminar air-flow units are recommended.

Oral supportive measures
Starting one week before the conditioning regimen and continued until the end of severe neutropenia (ANC>500/µl) or until control of potential GvHD >II the following supportive measures should be applied:

- oral decontamination in accordance with local standards
- Trimethoprim-Sulfomethoxazol as pneumocystis-carinii-prophylaxis: before SCT until day –1 and from day +14 until 4 weeks after the end of immunosuppression on three days per week
- careful oral hygiene (including mucosa) in accordance with local standards

Intravenous supportive measures

- central-venous access
- Aciclovir (3x10mg/kg/day) as prophylaxis against herpes simplex:
  starting by day +1 until at least day +100
- intravenous substitution of immunoglobulins:
  on days –1 and +14 400mg/kg BW each, then adapted to target level (target level of serum IgG >500mg/dl) until normal values have been achieved
- substitution of packed red cells in cases of Hb levels below 8 g/dl; substitution of platelet concentrates according to local practice; note: in cases of haemorrhage or sepsis the number of platelets should be kept higher
- all blood products should be irradiated, filtered and leukocyte depleted

Hydration
During the entire period of the conditioning regimen sufficient hydration (3l/m²) and excretion needs to be taken care of.

Nutrition
Sufficient enteral and, if necessary, parenteral nutrition should be ensured in order to prevent catabolic metabolism after SCT. Enteral nutrition needs to be low in bacteria in accordance with the local standards. These measures may be loosened after the end of immunosuppression, if

no signs of an intestinal GvHD are observed. Enteral nutrition should be given preference over parenteral one.

Patient adjusted anti-emetic and pain therapy
Together with the conditioning regimen antiemetic therapy should be initiated in accordance with local protocols. In the presence of oropharyngeal mucositis, patient adjusted pain therapy should be carried out.

Monitoring of bacterial, viral and fungal infections
Virus antibodies in the donor as well as recipient should be serologically determined (at least HIV, hepatitis A, B, C, CMV, EBV, varicella-zoster) before transplantation.
The patient's CMV virus load should be evaluated at least once a week by means of PCR-VNA or pp65 antigen test, as CMV may have a significant influence on the occurrence and course of GvHD. Especially in SCT from MMD a long lasting severe immunodeficiency can be expected. Bacterial and fungal surveillance cultures and viral monitoring (adeno, CMV, EBV) should be performed during the treatment in accordance with local standards.

Pre-emptive therapy with Ganciclovir in cases of CMV-PCR positivity
CMV-VNA evidence in the serum (PCR: >1x10³ copies/ml) or pp65 antigenaemia should initiate pre-emptive treatment with Ganciclovir or alternatively with Foscarnet[32-36].

Infection therapy
In the presence of fever and/or other signs of infection, empirical treatment with broad-spectrum antibiotics in accordance with local standards is necessary. If no improvement can be seen, appropriate systemic antifungal drugs, which also include the aspergillus species, should be used.

10.4 Allogeneic SCT

Patients of Arm 1 and Arm 2a with an early progression and patients with CD3 positive ALCL are to receive allogeneic SCT (see chapter "Classification of therapeutic groups and treatment plan", page 28).

10.4.1 HLA-Typing

For those patients with an indication of allogeneic SCT (arm 1 and arm 2, see page 28) HLA-typing will be done as soon as possible. At the same time, HLA typing of parents and siblings should be done. If the HLA typing of the family does not render a genotypic identical sibling donor or a ≥ 10/10 compatible non-sibling donor, patients should be immediately entered into a search programme for unrelated donors. An extended family analysis could be useful in case of special HLA constellations (e.g. consanguinity or HLA homocygosis of the patient). It is advisable to discuss these possibilities with the laboratory responsible for HLA-typing.

The minimum requirement for HLA typing is as follows:
The loci A, B, C, DRB1 and DQB1 are to be determined. For possibly suitable sibling donors the definition of the HLA I features via the so-called “medium resolution” method could be sufficient. In case of no available sibling donor the HLA class I and the HLA class II for the patient and the unrelated donors and possible none-sibling family donors need to be done at the high resolution level ("four digit").

Furthermore, blood groups and CMV status of the patient and the potential donor as well as donor age should be regarded.

It is essential to start early with the search for a suitable unrelated donor, in order to be able to carry out the transplantation at the earliest possible time. Likewise the SCT centre should be contacted in time to discuss necessary preliminary steps and possible alternative strategies, and to correlate dates. Also the selection of donors needs to be co-ordinated with the SCT centre.

10.4.2 Sc-donor selection

This study differentiates between four stem cell donor groups. This division is not based on the family relationship between donor and recipient, but on the HLA compatibility. The assignment to a group determines the transplantation regimen (stem cell source, stem cell manipulation, conditioning regimen, GvHD prophylaxis).

MSD: **M**atched **S**ibling **D**onor:
HLA identical sibling donor

10/10 HLA-matched non-sibling donor (related or unrelated):
Related or unrelated SC donors 10/10 whose HLA-features correspond with those of the recipient: Matched family donor (MFD) or matched unrelated donor (MUD)

9/10 HLA-matched non-sibling donor (related or unrelated):
Related or unrelated SC donors 9/10 whose HLA-features correspond with those of the recipient: 1 antigen mismatched family donor (1MMFD) or 1 antigen mismatched unrelated donor (1MMUD)

MMD: **M**is**m**atched **D**onor:
Related or unrelated SC donors less than 9/10 of whose HLA features correspond with those of the recipient

The correspondence of HLA features between stem cell recipient and donor needs to be given top priority for the selection of the donor (see following overview: donor hierarchy I).
For the selection of the most suitable stem cell donor on the basis of HLA-typing the following guidelines apply:

- the MSD is selected, if a MSD and a 10/10 non-sibling donor or a 9/10 non-sibling donor are available.
- In case no MSD is available, a SCT 10/10 non-sibling donor or a 9/10 non-sibling donor is always preferred to an SCT from an MMD.

If this guideline does not suffice for a decision, because various possible donors within a group are available, also the type of HLA match is taken into consideration:

- a donor with 10/10 HLA identical features is preferred to a donor with 9/10 identical HLA features.
- a donor with an allele mismatch is more suitable than one with an antigen mismatch.
- as for incompatibilities between HLA features the following ranking applies additionally: C mismatch = B mismatch **before** class II mismatch **before** A mismatch

Overview: Donor hierarchy I – according to HLA-typing result

priority	HLA-typing result
1	HLA-identical sibling
2	10/10 identical unrelated or family donor
3	9/10 identical unrelated or family donor
4	less than 9/10 identical unrelated or family donor
in case of mismatch	
1	allele-mismatch
2	antigen-mismatch
in case of further mismatch	
1	C-mismatch
1	B-mismatch
2	class II-mismatch
3	A-mismatch

In addition to the ranking according to the results of HLA-typing the following features need to be considered (see following overview: Donor hierarchy II):

- age of donor
- CMV-Status
- sex
- stem cell source
- availability of donor

Overview: Donor hierarchy II – further decision criteria

priority	criterion	patient status	donor status
1	age		younger donor
2			older donor
1	CMV status	patient CMV IgG positive	donor CMV IgG positive
2			donor CMV IgG negative
1		patient CMV IgG negative	donor CMV IgG negative
2			donor CMV IgG positive
1	sex	female patient	female or male donor
1		male patient	male donor
2			female donor

10.4.3 Eligibility for allogeneic SCT by donor availibility

Patients with early progression of ALCL (Treatment Arm 1; see page 28) are eligible for allogeneic stem cell transplantation. The selection of the donor must follow the given criteria above, but there are no further restrictions of eligibility for allogeneic SCT concerning the HLA-compatibility of donor stem cells.
Patients with CD3 positive ALCL and the occurrence of relapse after the end of frontline therapy (Treatment Arm 2a) are eligible for allogeneic SCT if

- a matched sibling donor or
- a 10/10 matched non-sibling donor is available

Patients of treatment arm 2 are not eligible for allogeneic SCT with a 9/10 compatible non-sibling donor nor with a MMD.

donor group	Treatment arm (see page 28)	
	Arm 1	Arm 2a
MSD	+	+
10/10 non-sibling donor	+	+
9/10 non-sibling donor	+	-
MMD	+	-

10.4.4 Stem cells, donor stimulation and cell manipulation

donor	stem cells
MSD, 10/10 and 9/10 non-sibling donor	Unmanipulated bone marrow should be used as stem cell source in the present study. A minimum NC count of $3x10^8$/kg BW of the patient should be available for the transplantation. Allogeneic peripheral stem cells of G-CSF stimulated donors are a acceptable exception, which needs to be documented. Likewise, the minimum CD34+ cell count should be $5x10^6$/kg BW of the recipient. The analysis of the transplant should include the number of transplanted nucleated cells, the number of CD34+ cells, as well as the number of CD3+ (if applicable CD4+, CD8+) cells.
MMD	In the MMD group the SCT should be carried out with peripheral stem cells. The transplant needs to undergo a CD34+ selection or a CD3+ depletion prior to infusion, and contain a minimum of $10x10^6$/kg BW of the recipient CD34+ cells and a maximum of $3x10^4$/kg BW of the recipient CD3+ cells.

Umbilical cord blood stem cells
The protocol guidelines regarding stem cell manipulation, T-cell depletion and GcHD-prophylaxis do not comply for umbilical cord blood stem cells (ucbsc). The use of ucbsc as stem cell source should be restricted to transplant centres with outstanding experience with this form of stem cell transplantation.

Donor stimulation
If peripheral stem cells are used for SCT, the donor will for 5 days need to be stimulated with rHu-G-CSF 10 µg/kg BW s.c. on each day. In case of insufficient mobilisation on day 4 (<100 CD34+/µL PB) the patient receives an additional 10 µg/kg BW G-CSF on the evening of day 4. On day 5 (and if needed on the following days) leukapheresis and CD34+ selection are carried out.
With family donors it is possible to carry out stem cell collection prior to the start of the conditioning regimen. The cells will, if required, be CD34+ positively selected and cyropreserved until the day of SCT. This guarantees that a sufficient number of stem cells will be available for SCT.

10.4.5 Conditioning regimen for allogeneic SCT

Before the conditioning regimen is started all informal consents need to have been signed and final donor clearance must be available.
Furthermore, the HLA identification of the recipient and donor have been determined and documented, and the degree of compatibility was accepted. The stem cell manipulation was prepared accordingly. The patient's current remission status should be evaluated. The medical pre-examinations of Sc-recipient and donor need to be in line with the prerequisites for performing the planned conditioning regimen and transplantation (see appendix "Medical examination prior to SCT", page 66). A central venous line should be in place.

Conditioning regimen for allogeneic SCT
(see "Sc-donor selection", page 40)

time point	**patients >24 months of age**		**patients ≤ 24 months of age**	
day -8	-		BU	5 mg/kg p.o. in 4 doses
day -7	TBI	2x2 Gy		5 mg/kg p.o.
day -6	TBI	2x2 Gy		5 mg/kg p.o.
day -5	TBI	2x2 Gy		5 mg/kg p.o.
day –4	Thiotepa	2x5 mg/kg iv over 1h 12 hrs. apart	Thiotepa	2x5 mg/kg iv over 1h 12 hrs. apart
day –3	VP 16	40 mg/kg iv	VP 16	40 mg/kg iv over 4 h
day –2	-		-	
day -1	-		-	
day 0	**SCT**		**SCT**	

In case of SCT with a non-sibling donor, ATG 20 mg/kg/d iv is to be added on days -3, -2, -1.

Important note:
In one of the following very rare cases when a patient can not receive the standard conditioning regimen (see bleow), please contact the study centre:

- patients ≤ 24 months of age in whom a MMD SCT is planned
- patients ≤ 24 months of age with disease progression in the CNS
- patients who had previous irradiation of the central neuro-axis and who can not receive the described conditioning regimens (see chapter "irradiation" below)

Irradiation
Total body irradiation (TBI)
Note: Patients who are younger than 24 months at the time of conditioning do not receive total body irradiation (TBI).
Patients who are older than 24 months at the time of conditioning receive TBI. Important note: Patients who received prior to the SCT irradiation of the neuroaxis can receive TBI only under the following conditions:

- **if the previous irradiation-free period is ≥24 months, and the total irradiation dose of TBI together with the previous CNS irradiation does not exceed 30 Gy.**
- **if the previous irradiation-free period is <24 months and the cumulative irradiation dose of TBI together with the previous CNS irradiation does not exceed 24 Gy.**

All patients eligible for TBI receive hyperfractionated total body irradiation of 2 Gy twice daily on three consecutive days. Thus the total dose should be 12 Gy. To minimise late effects the irradiation-free intervals between the individual fractions should be at least 6 hours. Any deviations from this recommendation should be documented in the respective study forms.
To be able to calculate the distribution of dosage to the individual sites, a plan needs to be designed that includes at least 6 CT-layers (cranium, neck, thorax, abdomen, lower extremities). A photon source with an energy >1MeV should be applied for the therapy. According to the ICRU-Report the dose specification is done at a point in the middle of the abdomen (at navel height). The actually applied dose should be determined during at least one fraction via an in vivo dosimetry. 'Spoilers', bolus material and compensators should help to reach a dose homogeneity of ± 5%. The lungs should (according to ICRU 5050) not receive more than 10 Gy. To prevent application of dosages too low at the thorax wall, electrons can be applied additionally. The power on the linear accelerator is to be chosen so that an individual dose (2 Gy) can be applied within less than 30 minutes.

Cranial irradiation
The following rules need to be applied:
- Patients without CNS-involvement do not receive additional cranial irradiation.
- Patients with CNS involvement may receive additional cranial irradiation with a dosage of 6 Gy within the setting of the allogeneic SCT. The irradiation of the cerebral cranium is to be performed immediately before total body irradiation.

Pharmacological conditioning

Thiotepa Thiotepa should be administered as iv infusion over 1 hour. The dosage should be 2x5 mg/kg BW 12 hours apart at day –4.

Etoposide (VP16) Etoposide should be administered in all patients as a single infusion over 4 hours. The dosage should be 40 mg/kg BW (max. 1200 mg/m² BSA).
If etoposide phosphate (Etopophos®, Fa. Bristol) is used, the dosage has to be adapted according to the etoposide amount.

Busulfan (BU) Busulfan should be given to patients who receive no total body irradiation because of age. Children younger than 2 years of age should receive a total dose of 20 mg/kg BW. BU should be given orally at a dose of 1.25 mg/kg BW at 6-hour intervals on 4 consecutive days.
BU is available as 2mg-dose press-coated tablets (labelled 'K2A').
Blood levels of the drug should be measured if possible. If patients vomit during BU-treatment, the following procedure should be followed:
- vomiting within 15 minutes after administration: total dose is given again.
- 15 to 30 minutes after administration: 50% of BU-dose is given again.
- more than 30 minutes after administration: no additional BU is given.

During BU-application a seizure prophylaxis in accordance with local standards is required..

ATG ATG-Fresenius S is an anti-human T-lymphocyte immunoserum which is obtained from rabbits immunised with human T-lymphoblasts of the Jurkat cell-line. ATG-Fresenius S is administered at a dose of 20 mg/kg BW on three consecutive days (day –3 until day –1). The solution is hypotonic and may only be dissolved in physiological NaCl. Furthermore, Heparin may not be administered as mixed infusion or via the same vascular access, as this can lead to a shift in the pH-value. The infusion should be given over 4 hours, and a pre-medication with steroids (max. 2 mg/kg BW) is recommended. The respective emergency medicines need to be ready for immediate intervention and frequent checks of the vital parameters are required.

10.4.6 GvHD-prophylaxis and –therapy

GvHD-prophylaxis

donor	Prophylaxis
MSD	The GvHD-prophylaxis consists of a monomedication with Cyclosporin A (CsA) starting on day –1. It is given at a daily iv dosage of 2 x 1.5mg/kg BW as infusion over 2 hours each. As soon as oral administration is possible, it can be switched to CsA per os. Orally CsA is administered twice daily at a dose of 3mg/kg BW (total dose of 6mg/kg BW). If patients switch from intravenous to oral administration, twice the intravenous dose is given. CsA levels should be measured in the first 4 weeks, CsA levels in the blood should be between 80 and 130ng/ml until day +28 (method of determination: monoclonal antibody, FPIA). This guideline applies only, if no toxicity problems occur and no signs of a GvHD exist. However, as indicator of dosage adaptation the CsA level should be used only from day +5 onwards. In case of toxicity problems the dosage should be decreased. In case of acute GvHD the CsA dose should be increased (see below "GvHD-Therapy Recommendation"). In the absence of GvHD symptoms, the CsA dose is reduced from day +60 onwards (by app. 20% of initial dose each week).
10/10 or 9/10 non-sibling donor	The GvHD-prophylaxis consists of CsA, MTX and ATG. • CsA is administered as outlined for group MSD. However, a dosage adapted to target level (CsA level between 80 and 130ng/ml) should be administered until day +100, only from then on the dosage should be reduced according to the guidelines given above. • MTX is given on days +1, +3 und +6 at a dose of 10mg/m^2 BSA iv. On days +2, +4, +7 Leucovorin iv is given at 15mg/m^2 BSA. • The application and dosage of ATG is described in chapter "Conditioning regimen for allogeneic SCT, page 43/44.
MMD	In this group the GvHD prophylaxis consists in the extraction of lymphocytes from the stem cell transplant via selection methods. The number of transplanted CD3+ cells must not exceed 3x10^4/kg BW of the recipient in order to prevent an acute and chronic GvHD. Additionally the patients receive ATG (see page 43/44). Pharmacological GvHD prophylaxis is not planned for this group.

GvHD-Therapy – Recommendation

For an overview on GvHD staging/grading see appendix "GvHD: clinical staging and grading", page 68.

grade of GvHD	Procedure
grade I (skin-GvHD)	raise CsA levels to 150ng/mL (FPIA method)
grade II	raise CsA levels to 150ng/mL (FPIA method) additional: Prednisolone 2mg/kg BW/d in 3 divided doses, reduction to 1mg/kg BW/d, if 5d <grade II
≥grade III	raise CsA levels to 150ng/mL (FPIA method) prednisolone 5mg/kg BW/d in 3 divided doses, reduction to 2mg/kg BW/d, if 5d <grade III duration of acute GvHD ≥grade III longer than 7d: **optional:** monoclonal antibody, e.g. aCD25/IL2-receptor-AK (Simulect®/Zenapax®), MMF (Mycophenolat-Mofetil), ATG/ALG, FK 506, PUVA (for skin-GvHD), ECP (extracorporeal photophoresis)
if liver >grade II	ECP (extracorporeal photo-immunotherapy) or MMF (Mycophenolat-Mofetil) 30–50mg/kg BW

Since GvHD-prophylaxis is planned for a relatively short period of time, the risk of GvHD is relatively high. Therefore clinical signs of GvHD need to be carefully evaluated once a day. As soon as clinical symptoms occur, a therapy according to the scheme described above should be immediately initiated and documented.

10.5 Autologous SCT

All patients of Treatment Arm 3 and those patients of the Treatment Arm 2 who have no suitable donor available receive (Arm 2b, see chapter Classification of therapeutic groups and treatment plan", page 28) receive autologous SCT.

10.5.1 Stem cells, patient stimulation and cell manipulation

Peripheral blood stem cells should be harvested and cryopreserved after the first and – if necessary – second course CC. Stimulation with G-CSF can be delayed until shortly after the leukocyte nadir. 10µg/kg BW/d of G-CSF should be administered intravenously as continuous infusion over 24 hours. For this purpose, G-CSF can be diluted in 40ml glucose 5% with 1 ml human albumine 20%. Leukocytes should be counted daily and a CD34 cell count should be performed on the fourth day of stimulation. It usually takes 4 – 5 days of stimulation until the CD34 cell count reaches sufficient values (200 – 450 CD34 cells /µl) to collect the necessary cells in a single apheresis procedure. Alternatively, the stimulation may be performed by traditional twice daily subcutaneous injection of 5 µg/kg BW each, which should be doubled when the leukocyte count exceeds 1 000/µl. In special cases collection of autologous bone marrow may be an alternative to peripheral stem cells harvest. A CD34+ cell dose of at least 4-5x10^6/kg BW should be harvested and kryopreserved. If the number of asservated CD34+ cells after the second course of CC is sufficient, this asservate should be used for SCT. Probes for MRD examination should be extracted. The selection of CD34+cells is not routinely recommended.

10.5.2 Conditioning regimen for autologous SCT

Before the conditioning regimen is started all informal consents need to have been signed and quality assurance of the frozen stem cells need to have been done.
The patient's current remission status should be evaluated and documented. The medical pre-examinations of the patient (see appendix "Medical examination prior to SCT", page 66) need to be in line with the prerequisites for performing the planned conditioning regimen and transplantation. A central venous access is used.

Conditioning regimen for autologous SCT

time point				
day -7	BCNU	300 mg/m^2 iv		
day -6	VP 16	200 mg/m^2 iv	ARA-C	2x200 mg/m^2 iv
day -5	VP 16	200 mg/m^2 iv	ARA-C	2x200 mg/m^2 iv
day -4	VP 16	200 mg/m^2 iv	ARA-C	2x200 mg/m^2 iv
day -3	VP 16	200 mg/m^2 iv	ARA-C	2x200 mg/m^2 iv
day -2	Melphalan	140 mg/m^2 iv		
day -1	-			
day 0	**SCT**			

Pharmacological conditioning

BCNU	BCNU should be administered iv at a dosage of 300 mg/m² BSA iv over 1 hour at day –7.
Etoposide (VP16)	Etoposide should be administered in all patients as a single infusion over 1 hour at day –6, -5, -4 and -3. The dosage should be 200 mg/m^2 BSA. If etoposide phosphate (Etopophos®, Fa. Bristol) is used, the dosage has to be adapted according to the etoposide amount.
Cytarabine (ARA-C)	Cytarabin should be administered at day –6, -5, -4 and –3 at a dosage of 2x200 mg/m² BSA as iv infusion over 0,5 hours. The infusions should be administered 12 hours apart.
Melphalan	The alkalyting substance prevents DNA replication and transcription of RNA. Melphalan should be given at a dose of 140 mg/m^2 BSA at day -2. Melphalan is to be applied not later than 3 hours after dissolution as infusion over 15 minutes. It may only be dissolved in physiological NaCl, and may not be mixed with glucose.

11 Drugs

This chapter deals with the most important specific side effects of active substances. The side effects are related to the dosage given in the protocol and represent present knowledge and experience. The following are guidelines only and it is the responsibility of the attending physician to be thoroughly conversant with the full toxicity profile of each of the drugs. Further information may be available from the manufacturers. The attending physician is responsible for all administered substances.

BCNU

Administration: See chapter "Conditioning regimen for autologous SCT", page 46

Toxicity: alopecia, dermatitis, mucositis, neurotoxicity, gastrointestinal irritation (nausea, vomiting, diarrhoea, stomatitis), allergic reactions, livertoxicity, hyperuricaemia, dysfunction of spermatogenesis and ovulation, depression of bone marrow, nephrotoxicity, immunosuppression, pneumonitis

Busulfan (BU)

Administration: See chapter "Conditioning regimen for allogeneic SCT", page 43

Toxicity: Bone marrow depression, allergic reactions, alopecia (may be permanent), amenorrhoea, aspermiogenesis, dysaesthesia, endocardial fibrosis, gastrointestinal irritation (nausea, vomiting, diarrhoea, stomatitis) hemorrhagic cystitis (uncommon), hyperpigmentation of skin, cataract, lung fibrosis, cave: deleterious in connection with lung irradiation!, myasthenia gravis, mucositis, VOD of liver in up to 30% of patients in high-dose settings; usually reversible

Contraindications: previously irradiation of central axial sites

Carboplatin

Administration: See chapter "Course ICM", page 33 and "Course ICI", page 34

Toxicity: gastrointestinal irritation (nausea, vomiting, diarrhoea, stomatitis), anorexia (uncommon), allergic reactions, infections, haemorrhagia, parageusia, mucositis, asthenia, neuritis n. optici incl. aumourosis (uncommon), in combination with additional cytostatic agents: seconday malignancies, HUS (uncommon), cardiovascular adverse events

dose adaptation in case of renal dysfunction[37-39]:

Carboplatin dosing can be based on body surface-area (800 mg/m^2/96hours).

Alternatively, dosing based on renal function (GFR) is possible and gives more precise AUC values. In centers which are experienced with GFR-based dosing, the Carboplatin-target AUC of 10.6 mg/ml*min should be used and GFR has to be measured with a radioisotope. 51Cr-EDTA or Tc99mDTPA clearance should be performed. Serum creatinine levels and creatine clearance are insufficiently accurate GFR-estimates. Dosing of Carboplatin can be calculated by the formula published by Newell and coworkers:

D[mg] = target AUC * GFR [ml/min] + (0.36 * BW [kg]).

In case of reduced renal function, the GFR should be estimated by an abovementioned radioisotope and the carboplatin dose has to be adapted according to the target AUC of 10.6 mg/ml*min in these patients using the formula published by Newell.

Only in case of unavailability of the radioisotope method or when the patient is clinically unstable and has reduced renal function a 24h creatinine clearance or estimation of renal function on the basis of serum creatinine (Schwartz-formula) is acceptable.

CCNU

Administration: See chapter "Course CVA", page 32

Toxicity: alopecia, dermatitis, mucositis, neurotoxicity, gastrointestinal irritation (nausea, vomiting, diarrhoea, stomatitis), allergic reactions, livertoxicity, hyperuricaemia, dysfunction of spermatogenesis and ovulation, depression of bone marrow, nephrotoxicity, immunosuppression, lung fibrosis

Cytarabine

Administration: See chapter "Course CC", page 31, "Course CVA", page 32 and "Conditioning regimen for autologous SCT", page 46

Toxicity: Bone marrow suppression, mucosal membrane inflammation, nausea, vomiting, oral ulceration, fever, arthralgia, diarrhoea, ulceration and bleeding, alopecia and flu-like syndrome.
At higher doses (3 000 mg/m^2) cerebellar toxicity may occur. Gastrointestinal toxicity with diarrhoea, mucositis and vomiting may also be more severe. Pulmonary toxicity is uncommon, but may present with unexplained breathlessness. Conjunctivitis can be distressing, but it may be prevented by the regular use of Prednisolone eye drops.

Dexamethasone

Administration: See chapter "Course CC", page 31

Toxicity: Obesity, hirsutism, fluid and salt retention, hypertension, irritability, glycosuria and hyperglycaemia, pancreatitis, seizures and mental instability. It is reported that the substitution of Dexamethasone for Prednisone during remission Induction may be associated with a higher incidence of septic episodes and deaths and, in post-remission therapy, neurocognitive late effects. In some studies the incidence of osteopathology is reported to be increased in patients receiving Dexamethasone.

Etoposid

Administration: See chapter "Course CC", page 31, "Conditioning regimen for allogeneic SCT", page 43 and "Conditioning regimen for autologous SCT", page 46

Toxicity: bone marrow depression, allergic reactions, hypotensive reaction due to alcohol contents in infusion fluid, alopecia, gastrointestinal irritation (nausea, vomiting, mucositis, ulcerative gastroenteritis, diarrhoea) In allergic and/or hypotensive reactions administer hydrocortisone and antihistamoines and/or catecholamines.

Idarubicine

Administration: See chapter "Course ICI", page 34

Toxicity: acute and chronic cardiotoxicity with cardiomyopathy, severe enterocolitis with perforation, nausea, vomiting, alopecia, depression of bone marrow, phlebitis/thrombophlebitis, liver toxicity (level of bilirubin and transaminases), flush, exanthema, bullous erythema, hypersensitivity after irradiation, red tint of urine.

Ifosfamide

Administration: See chapter "Course ICM", page 33 and "Course ICI", page 34

Toxicity: haemorrhagic cystitis (MESNA uroprotection), nephrotoxicity: tubulopathy with glucosuria, aminoaciduria, loss of phosphate and Ca, full range of tubulopathies from subclinical changes to a full-fledged Fanconi syndrome, bone marrow depression, gastrointestinal irritation (nausea, vomiting, diarrhoea, stomatitis), alopecia, neurotoxicity with transient somnolence and mental disturbance, infertility, immunsuppression. Dose adaptation due to neurotoxicity, dose adaptation due to renal toxicity. Ifosfamide-induced neurotoxocity should be treated with methylene-blue

(e.g. Methylene blue Vitis® 1%, Neopharma, 50mg/5ml): Dose: 1-2 mg/kg BW (max. 50 mg) in glc 5% iv over 30 minutes. This dose should be repeated every 2-4 hours during the first day and continued three times daily until the symptoms resolve. Methylene blue has to be administered solely iv and not i.t.! Care should be taken to continue iv hydration and adequate glucose supplementation. After previous Ifosfamid-induced neurotoxicity, it is suggested to use methylene blue prophylaxes with the following Ifosfamide doses. Starting the day before the first Ifosfamide-infusion, 1-2 mg/kg BW (max. 50 mg) methylene blue should be given in glc 5% iv over 30 minutes and continued 3x daily until 24 hours after the last Ifosfamide dose.

Melphalan

Administration: See chapter "Conditioning regimen for autologous SCT", page 46

Toxicity: bone marrow depression, allergic reactions, alopecia, amenorrhoea, dysaesthesia, gastrointestinal irritation (nausea, vomiting, diarrhoea, stomatitis), mucositis.
Possible late effect: lung fibrosis (uncommon).

Mitoxantrone

Administration: See chapter "Course ICM", page 33

Toxicity: cardiac dysfunction incl. cardiomyopathy, depression of bone marrow, nausea, stomatitis, blue/green tint of urine.

Vinblastine

Administration: See chapter "Course CVA", page 32

Toxicity: peripheral neuropathy (areflexy, paresthesia, muscular weakness, ataxia), cranial nerve palsies, autonomous neuropathy (constipation, paralytic ileus, urinary retention), central neurotoxicity (hallucinations, epileptic seizures, SIADH), arthralgia, myalgia, bone marrow depression, alopecia, arrhythmia

Vindesine

Administration: See chapter "Course CC", page 31

Toxicity: peripheral neuropathy (areflexy, paresthesia, muscular weakness, ataxia), cranial nerve palsies, autonomous neuropathy (constipation, paralytic ileus, urinary retention), central neurotoxicity (hallucinations, epileptic seizures, SIADH), arthralgia, myalgia, bone marrow depression, alopecia, arrhythmia

Intrathecal drugs

Please note details of the suitable solvent for the drug for intrathecal use.

Methotrexate

Administration: Dose is age dependent. See chapter "Course CC", page 31, "Course ICM", page 33 and "Course ICI", page 34

Toxicity: The effects of intrathecal administration include headache, stiff neck, lethargy, nausea and vomiting, confusion and seizures.

Cytarabine

Administration: Dose is age dependent. See chapter "Course CC", page 31, "Course ICM", page 33 and "Course ICI", page 34

Toxicity: The effects of intrathecal administration include headache, stiff neck, lethargy, nausea and vomiting, confusion and seizures.

Prednisolone

Administration: Dose is age dependent. See chapter "Course CC", page 31, "Course ICM", page 33 and "Course ICI", page 34

Toxicity: The effects of intrathecal administration include headache, stiff neck, lethargy, nausea and vomiting, confusion and seizures.

12 Events, adverse events and serious adverse events

12.1 Events

Events are defined as:

- progressive disease (after the start of treatment according to the protocol ALCL-Relapse)
  - o bone marrow progression is diagnosed in case of increase or new occurrence of a significant amount of lymphoma cells in the bone marrow. If disease progression has been diagnosed by biopsy otherwise, then the BM is considered involved, if morphologically identified lymphoma cells are diagnosed in bone marrow slides.
  - o CNS progression is diagnosed, if lymphoma cells are present in the CNS after clearance of CSF was reached and/or in case of (re)appearance of an intra-cerebral tumour
  - o appearance of new manifestations of the ALCL
  - o local manifestations: reappearance or increase in size of residuals more than 25% (in 2-dimensional evaluation)
  - o testes: increase in volume
- secondary malignancy
- late event: malignancy more than 3 years after diagnosis of relapse of the anaplastic large cell lymphoma; no differentiation between progression and second malignancy possible
- death of any cause

Every suspected progression must be assured by biopsy and histological/immunhistochemical examination or cytomorphological, genetical and immuncytological examination of malignant effusions or bone marrow.

In case of progressive disease during Re-Induction or conditioning contact the national study centre or the international data centre in Gießen.

In case of any event the event form (see appendix page 143) has to be filled in and sent to the responsible data centre as soon as possible (at the latest 2 weeks after the occurrence of the event).

12.2 Adverse events

All adverse events that are encountered during the treatment according to the protocol ALCL-Relapse are to be reported on the corresponding toxicity form (see appendix, page 107 ff.). An adverse event is any adverse change from the patient's baseline (pre-treatment) condition, including intercurrent illness, which occurs during the course of a clinical trial after treatment has started, whether considered related to treatment or not. The intensity of the event will be graded according to NCI-Common Toxicity Criteria grading system in the toxicity categories that have recommended gradings. Adverse events not listed in the NCI-CTC grading system will be graded according to a four-point system as follows:

- Grade 1, mild: discomfort noticed, but no disruption of normal daily activity
- Grade 2, moderate: discomfort sufficient to reduce or affect normal daily activity
- Grade 3, severe: incapacitating with inability to work or perform normal daily activity
- Grade 4, life-threatening: (self explanatory)

The maximum grading for each category has to be documented.

12.3 Serious adverse events

12.3.1 Definition of SAE

A serious adverse event (SAE) is any experience that suggests a significant hazard to the patient and/or is a contraindication to the continuation of therapy. In clinical experience, this includes any event that is:

- fatal
- life-threatening
- impair further therapy as per instruction of the protocol
- requires unscheduled in-patient hospitalisation or results in prolongation of hospitalisation

- results in persistent or significant disability or incapacity of the patient
- is medically significant or requires intervention to prevent one or other of the outcomes listed above
- can not be documented on the adverse event form (see appendix page 107 ff.)

Medical and scientific judgement should be exercised in deciding whether expedited reporting to the study centre is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Usually these situations should also be considered serious. Examples of such events are treatment in an emergency unit or at home for allergic bronchospasm; blood coagulation disorders or convulsions that do not result in hospitalisation; or the development of drug dependency or drug abuse.
However, progression of the lymphoma, events related to the lymphoma progression, and planned hospitalisations will not be considered as a reportable SAE.
The term “severe” is a measure of intensity; therefore, a severe adverse event is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.
Any death not related to lymphoma progression whether considered treatment-related or not, must be reported promptly, regardless of when it comes to the attention of the investigator.

12.3.2 Differentiation of expected and unexpected serious adverse events

Unscheduled in-patient hospitalisation or prolongation of hospitalisation or medical interventions due to fever with neutropenia after chemotherapy is an expected serious adverse event. Events fulfilling one of the other the SAE-criteria listed above, are regarded as unexpected SAE.

12.3.3 Reporting of serious adverse events

In case of the occurrence of a unexpected serious adverse events, this is to be reported to the responsible data centre on the serious adverse event form (see appendix, page 144). This form has to be filled in and to be sent by fax to the responsible data centre within 48 hours after the beginning resp. the detection of the SAE.

For the BFM-Group the SAE-form is to be send by fax to:
Prof. Dr. med. A. Reiter
Universitäts-Kinderklinik
Pädiatrische Hämatologie und Onkologie
Feulgenstr. 12
D - 35385 Gießen
Tel.: +49 641 99 43421
Fax: +49 641 99 43629

The responsible data centre will forward the form directly to the international coordination centre, the responsible ethical committe and to local authorities according to local requirements.

13 Organisational aspects and documentation

13.1 Status of study

This is a collaborative study with several equal participating national groups. The core group includes AIEOP (Italy), BFM (Austria, Czechia, Germany, Switzerland), DCOG (Netherlands), BSPHO (Belgium), NOPHO (Denmark, Finland, Iceland, Norway, Sweden), PPLLSG (Poland), SFCE (France), SHOP (Spain) and UKCCSG (United Kingdom). Other national groups may join the study after discussion with the international study committee. Each of these groups has established own infrastructures in their countries regarding data management, quality control of diagnostics and treatment application and consulting support for the participating hospitals. It is agreed that this protocol should exploit these established infrastructures. Moreover, they necessarily form the basis for the quality of this inter-group study as well as for the provision of optimal patient care. Therefore, each participating group remains responsible for its national patients regarding the execution of the protocol and data management. The common constitutional organs of the inter-group study will be the common protocol, a committee consisting of the national reference pathologists, the international study committee and an external data safety and monitoring committee. A biological committee for issues of biological investigations and research is set up (see chapter "Research projects", page 59)

13.2 The Protocol

One common protocol will be used for the international study by all national groups. The finished master protocol in English can be obtained from the NHL-BFM data centre at Gießen, Germany. Translations of the English version of the master protocol into the local language will be prepared, if necessary, by each national group. The data centre of each national group will be responsible for distribution of protocols to hospitals within that national group. Addenda may be added or removed independently by any of the national groups to address local needs, provided they have no bearing on the essential aims of the international protocol. The originals of all documents of the study have to be stored in the responsible data centres for at least 15 years after preparation of the final report.

13.3 Protocol amendments

The completion of the protocol has been done with great care. However, amendments may be necessary. Subsequent to completion, any amendments to the protocol must be agreed by the international study committee and by all the national groups. The international co-ordination centre will be responsible for the issue of amendments and forward the amendments to the national data centres. These will circulate the forms to known participating centres in the trial. However institutions entering patients are advised to check the correctness and up-to-dateness of their protocol.

13.4 International study committee

One or two paediatric haematologists/oncologists of each national group and at least two statisticians will participate in the international study committee of the study. The international study committee shall meet as appropriate to consider patients' treatment, eligibility and outcome to ensure the smooth running of the study.
The information given twice yearly to the international study committee are:

- accrual rate, description of causes of ineligibility
- group allocation
- toxicity data
- description of the events

The members of the international study committee will receive the survival curves of the whole population and the treatment arms. All scientific decisions concerning stopping, continuation or any amendment of the study will be made by the international study committee after discussion with the data safety and monitoring committee.

13.5 Data safety and monitoring committee (DMC)

An independent data safety and monitoring committee composed of 4 international experts will monitor the progress of the study on ethical and scientific backgrounds.
The role of the DMC will be:

- to review accrual rate
- to examine interim analyses
- to monitor toxicity: Every 6 months the statistician for the trial will circulate a report to the members of the DMC about toxicity. The DMC will review these interim toxicity data although this is primarily the responsibility of the international study committee. This biannual procedure prevents against problems of major toxicity.
- Other: The DMC will be asked to review any major modification to the study proposed by the International Study Committee prior to its implementation.

13.6 Master database

The Master Database for the entire study will be held at the NHL-BFM data centre (Children's University Hospital, Feulgenstr. 12, D - 35385 Gießen/Germany).

13.7 Registration

Each national group will carry out registration of patients in their own data centre and each group is responsible for data quality, data plausibility and data completeness of their registered patients. After assurance of diagnosis of a relapsed anaplastic large cell lymphoma, a registration fax has to be sent to the responsible data centre within 14 days after the beginning of treatment (see appendix, page 97). In return the treating hospital will receive both a confirmation of registration and the four-digit registration number, which clearly identifies the patient in the common database. The registration number consists of a first digit which identifies the study group (e.g. "0" for AIEOP) followed by a consecutive three-digit number for each registered patient starting with "000". The registration number may be used for data transfer and for the master database. The use of names or initials as patient identifiers on paper forms and on national databases will be handled according to national practice. Normally the full name will be registered. According to the volition of the patient or guardians, it is possible to use the initials or to make patient data anonymous; even afterwards. All eligible patients will be registered in the study, regardless of whether they are evaluable for trial's result or not. For each study patient there will be an individual file at the responsible data centre, which includes all information concerning this patient. These files will be stored with an open-end. Nevertheless, the participating hospitals are bound to store their patient-files for at least 15 years.

13.8 Forms and data collection

13.8.1 General principles

The international co-ordination centre provides a common set of forms for data collection. Each national group will be responsible for distribution of forms to centres within this national group. Subsequent to completion, amendments to the forms must be agreed by the international study committee. The international co-ordination centre will be responsible for the issue of amended forms. Additional forms may be produced independently by any national group for the collection of data additional to that required for the international study. Each national group shall collect forms for its own patients and is responsible for data quality according to local practice. The master database for the entire study will be held at the BFM data centre (Children's University Hospital, Feulgenstr. 12, D-35385 Gießen/Germany). Each national group forwards the forms directly to the master data centre at Gießen The forms are requested to be sent to the international co-ordination centre at least once every 6 months.

13.8.2 Monitoring and documentation guidelines

The monitoring of the study will be performed centrally by the co-workers of the national data centre. The documentation forms for the participating centres of each group will be examined in the national data centre for plausibility and completeness in a controlled mode. In case of missing or not plausible data these will be requested from the study centre at the investigator in the treating hospital written or by telephone. The investigator will correct the data and forward the data change to the responsible data centre.

Some documentation guidelines:
Please fill in the forms with permanent ink or ball-pen only. Entries with pencil are not acceptable. Corrections are to be made as described in the following:The false entry is crossed out with a simple line. The correct information is inscribed aside and signed by the attending physician; with specification of the date and if necessary the reason for correction. Data fields which cannot be completed because of missing information are to be commented on. The forms are to be filled in promptly. Subsequently, they are to be controlled from the attending physician and to be signed with date. Please send the forms to the responsible data centre promptly (see also the table above). A copy shall remain in the treating hospital. All necessary information inquired is on the documentation forms; supplementary documents are required only in special cases.

13.8.3 Data forms and data flow for each patient

The common set of data collection forms consists of the forms listed below:

- o Documentation overview (about the data flow)
- o Registration
- o Diagnosis of Relapse
- o Sc-donor selection
- o Announcement of SCT
- o Treatment documentation (Courses CC, CVA, ICM, ICI and VBL)
- o Acute toxicity and adverse events during / after reinduction
- o Allograft
- o Autograft
- o Follow up – SCT
- o Follow up – Vinblastine
- o Events
- o Serious Adverse Events (SAE)
- o Histopathological and immunohistochemical review
- o Genetics

13.9 Follow-up

Follow-up-requests should be performed

- once a year for patients during the first five years from registration
- every two years for patients after the fifth year from registration

One, two, three, four and five years after SCT and following every two years the form "Follow up - SCT" form should be filled in (see appendix, page 134). In patients with VBL therapy for 24 months the form “Follow up - VBL” (see appendix, page 142) should be filled in every year after the start of Vinblastine for first five years and after this every two years. For patients with no severe compliction, no diagnose of cGvHD and no late effect the follow up more than 5 years after SCT will be reduced to a request of patient's status once per year.
In case of patient’s death, the corresponding follow up form and the event form (see appendix, page 143) should be completed. The responsible physician in the treating centre should send the completed forms to the national study group, which will then forward them to the international data centre.

14 Statistical considerations

Primary objectives of the study are:

1. to improve the probability of event free survival in children and adolescents with early progression of ALCL or/and a relapse of ALCL with CD3 positive immunophenotype (risk group A)
2. to test whether in patients with relapse of CD3 negative ALCL occurring after the intensive phase of treatment (risk group B) BEAM conditioning regimen (without TBI) for autologous stem cell transplantation is an effective treatment
3. to test whether in patients with late relapse of an CD3 negative ALCL (risk group C) who have not received Vinblastine during first line therapy Vinblastine alone is an effective treatment

Secondary objectives of the study are

1. to test the reproducibility of the newly introduced stratification criteria
2. to control protocol adherence measured by the proportion of patients who are treated according to the protocol among all patients who meet the inclusion criteria of the protocol.
3. to monitor acute and late toxicity of the treatment.

14.1 Criteria of assessment

Primary objectives

The endpoint for the 1st, 2nd and 3rd study question is the Event Free Survival (EFS), defined as minimum time from the date of diagnosis of relapse/progress to a subsequent event (death from any cause, second relapse, progressive disease, secondary malignancy). EFS will be estimated using the Kaplan-Meier method, confidence limitis will be calculated using the bootstrap method[40].

Secondary objectives

The end point for the question of reproducibility of the newly introduced stratification criteria is the proportion of patients who are eligible for allogeneic SCT (early progression, or/and CD3 positive immunophenotype). The endpoint of the question “control for protocol adherence” is the proportion of patients who are treated according to the protocol among all patients who meet the inclusion criteria of the protocol. A patient is judged to be treated according to the protocol if he is transplanted according to his risk classification (autologous/allogeneic) within 4 months.

Secondary end points

- overall survival: defined as time from relapse to death of any cause
- acute and long term toxicity
- rate of acute and chronic GvHD in patients with allogeneic stem cell transplantation
- treatment related mortality

14.2 Analysis

Primary objectives

In an analysis of patients with ALCL relapse after BFM frontline therapy (see “Background and rationale”, page 12) three risk groups could be separated. The estimated probability of a two years pEFS for patients with early progression or/and a relapse of ALCL with CD3 positive immunophenotype (risk group A) was 31% (SE 9%) (8 patients who received allogeneic SCT were excluded from this analysis). The two years pEFS was 53% (SE 12%) and 75% (SE 13%) for risk groups B and C respectively. The aims of the study are to improve the outcome for risk group A and to show that acceptable results can be achieved with less toxic treatment for risk group B and C (non-inferiority to the results of the retrospective analysis).
The estimate for risk group A has been taken as the reference value also for the test of the second and third primary objective. It can not be tolerated that for patients who have a relatively good prognosis (risk groups B + C) the outcome with less intensive treatment drops below the expected outcome of the poor prognosis group. Since almost all events occur within 2 years after diagnosis of relapse and the time to event is not of interest, a one sided confidence interval for the estimated probability of a 2 years EFS can be used to test for difference (allogeneic SCT) or non-inferiority (autologous SCT) and Vinblastine.
In patients who are eligible for allogeneic SCT the test for difference will be considered significant if the lower limit of a one-sided 95% confidence interval of pEFS is above 31%. In patients who are eligible for autologous SCT the test will be considered significant if the lower limit of a one-sided 95% confidence interval of pEFS is above 31%. In patients who are eligible for Vinblastine alone the test will be considered significant if the lower limit of a one-sided 95% confidence interval of pEFS is above 31%.

Analysis of the secondary objectives

The test for the reproducibility of the newly introduced stratification criteria is considered significant, if the two-sided 95% confidence interval for the proportion of patients who are eligible for an allogeneic SCT is included in the interval +/- 15% of the reference rate (50%). The proportion of eligible patients who are

treated according to the protocol is considered acceptable if the lower limit of the one-sided 95% confidence interval for this proportion is above 80%.
Acute toxicity will be analysed for each interim analysis using descriptive methods. Late effects will be analysed every two years after the end of recruitment using descriptive methods.

14.3 Number of subjects required

Since dropouts with follow up times less than 2 years are very unlikely, the power estimates can be based on the binomial distribution. All power calculations were done with DSTPLAN (Version 4.2, Barry W. Brown et al., copyright: The University of Texas M. D. Anderson Cancer Center, Department of Biomathematics, Box 237, 1515 Holcombe Boulevard. Houston, Texas 77030). The probability for a two years pEFS for patients with early progression or/and a relapse of ALCL with CD3 positive immunophenotype (risk group A) treated with chemotherapy only was 31% in the retrospective analysis (8 patients who received allogeneic SCT were excluded from this analysis). The two years pEFS was 53% and 75% for risk groups B and C respectively. This has been taken as the reference value for the test of the first primary objective. It can not be tolerated that for patients who have a relatively good prognosis (risk groups B + C) the outcome with less intensive treatment drops below the expected outcome of the poor prognosis group. Therefore we use the value 31% also as the limit of the equivalence range for the test of the second and third primary objective. With a type I error of 5% the number of patients required to reach a power of 80% is 43 (test for difference in patients who are eligible for allogeneic SCT, null hypothesis pEFS=31%, expected rate 50%) and 33 (test for equivalence in patients who are eligible for autologous SCT, expected pEFS 53%, lower limit acceptable pEFS=31%). With a type I error of 5 % the number of patients required to reach a power above 80% is 9 for patients who are eligible for VBL only with an expected pEFS 75% and a lower limit for the acceptable pEFS of 31%. With a type I error of 5% and a true rate of +/-15% the number of patients required to reach a power of 80% for the test of the proportion of patients who are eligible for allogeneic SCT compared to the hypothetical reference rate of 50% is about 90. With a type I error of 5% and an acceptable limit for the percentage of per-protocol patients of 80% the number of patients required to reach a power of 80% is 78 assuming a true percentage of per-protocol patients of 90%. The expected number of patients diagnosed with relapse of ALCL in Europe is about 16 per year. Of these about 50% are expected to be eligible for allogeneic SCT (early relapse during front line therapy or CD3 positive). About 15% are expected to be eligible for Vinblastine only (very late relapse >1 year after diagnosis and CD3 negative without Vinblastine pre-treatment). The remaining 35% of the patients are eligible for autologous SCT. A total of about 96 patients is necessary to reach the required number of patients for the SCT study questions (N=48/34). With 16 patients per year, the duration of the recruitment will be 6 years. If the distribution of the patients does not follow the expected pattern or drop outs occur during the time of recruitment, the recruitment period has to adopted accordingly.

14.4 Interim analysis

All interim analysis will be monitored by the DMC (see page 54). The rate of protocol compliance and risk group distribution will be monitored at annually intervals on the basis of descriptive analyses. Two interim analysis will be performed after 1/3 and 2/3 of the expected events occured. The O'Brien and Fleming rules will be followed to conclude at each sequential analysis[41].

Stopping rule (toxicity monitoring)
Interim analysis of toxic deaths will take place twice a year under the supervision of the Data Monitoring Committee. The absolute rate of treatment related deaths will be compared to a reference rate in order to detect an absolute excess of toxic deaths with four Wald sequential plans, one for each type of donor (autologous, allogeneic MSD, 10/10 or 9/10 compatible non-sibling donor and MMD). Based on previous experience, we choose the following parameters for these plans: α=5% and β=1% for each and p_0/p_1 according to the analysis group: autologous SCT (p_0=1%, p_1=5%), MSD SCT (p_0=5%, p_1=15%), 10/10 or 9/10 compatible non-sibling donor SCT (p_0=10%, p_1=25%), MMD SCT (p_0=10%, p_1=25%). The lower border of these plans will not be used to draw any consequences for the monitoring. If the number of toxic deaths observed reaches one of the boundaries defined in these sequential plans the steering committee has to decide in co-operation with the DMC, whether the trials have to be stopped.

14.5 Software

Microsoft ACCESS will be used for the management of all trial data, statistical analysis will be done using SAS (SAS Institute Inc., Cary, NC).

15 Ethical aspects and regulatory requirements

15.1 Ethical aspects

The study will be conducted in accordance with the declaration of Helsinki (see chapter "Declaration of Helsinki", page 63).
All centres are expected to obtain approval for the study from their local research ethical committee according to their national policy. An imprint of a current version of a positive votum of the ethical committee of the University Hospital in Giesen is reproduced in the protocol (see "Votum of the ethical committee", page 158). Prior to the registration of the patient and the start of therapy, patients and parents resp. guardians receive a written patient information and consent form, which they might sign after a discussion with the physician in charge (for details see chapter "Patient information and consent forms", page 71 ff.) The patient information (page 72 ff.) and consent form (page 78) for participation in the study ALCL-Relapse is separate from the three versions of patient information for SCT:

- allogeneic SCT with matched donor (page 79 ff. with consent form at page 89)
- allogeneic SCT with mismatched donor (page 84 ff. with consent form at page 89)
- autologous SCT (page 90 ff. with consent form at page 94)

15.2 Regulatory requirements

All national groups and participating centres are expected to control whether the protocol matches with GCP-guidelines and local law/requirements and if required to conduct necessary declarations and formalities.

For the BFM-group the protocol will be deposited at the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) and the Paul Ehrlich Institut, Bundesinstitut für Sera und Impfstoffe (PEI).

15.3 Funding and patient insurance

The initiation of funding for the study ALCL-Relapse is in the responsibility of each study group. No central funding of the trial will be performed.

With regard to patient insurance each study group is asked to check the local requirements and if necessary, to contract insurance for the patients of that study group in accordance with the local requirements.

For the german patients of the BFM-group a patient insurance according to the regulatory requirements of §40 AMG will be concluded.

16 Research projects

A biological committee will be responsible for approval of research projects that should have access to material which was ascertained for tumour cell/DNA/RNA-banking. It is agreed that research projects approved by the biological committee will have access to the material of the patients from all participating groups and to the clinical data of the study in an anonymous way. In turn, data generated in research projects will be made available to the database of the study. The rules for publication of data are described in chapter "Publication rules and presentation of results", page 61.

Participating groups are expected to provide diagnostic material for central review and research projects. In order to provide tumour material for future examination concepts and methods a system of tumour cell banking is established.For the identification of prognostic parameters and for further understanding of the biology of ALCL following examinations are conceived:

- MRD
- T- and B-cell response to ALK (see below)
- Impact of mixed chimersim for the occurrence of relapse
- Cytogenetics
- Matrix comparative genomic hybridisation
- Gene expression profiling
- Proteomic studies

T and B cell immune response to ALK in patients with ALK-positive ALCL.
Drs Kamel Ait-Tahar and Karen Pulford
Cancer patients frequently mount an immune response to their tumour and a link has been reported between the levels of antibodies and the presence of cytotoxic T cell (CTL)[1, 2] and CD4-positive T helper cells[3] to tumour-associated antigens. ALK expression in ALCL is considered to be a marker of a favourable prognosis. While this may be due to the increased sensitivity of the tumour cells to treatment, it may also reflect the existence of an immune response against ALK. Indeed, our report of the presence of antibodies to ALK provided the first evidence to support ALK being an example of a tumour-associated antigen in those patients with ALK-positive ALCL.[4] The subsequent identification of antigenic ALK peptides effective for the production of a CTL response in normal individuals[5] and the confirmation of a CTL response to ALK in patients with ALK-positive ALCL[6] has provided additional evidence to support ALK being the target of an immune response.
The detection of a T and B cell immune response to tumour-associated antigens provides a means of monitoring disease progression and the efficacy of treatment providing important prognostic information for the patient.[7-11] Our preliminary study demonstrated that circulating antibodies to ALK differed in titre at varying times after diagnosis of ALK-positive ALCL with those patients exhibiting higher titres tending to do well.[12] It is also of interest that antibodies and CTL activity to ALK persisted in some patients during periods of remission for intervals of up to 16 years.[6, 12] The identification of tumour-associated antigens has also opened up the possibility of improved therapeutic approaches to treatment of tumours.[1, 13-18]
Previous studies have indicated that bone marrow stem cell transplantation offers a means of effective therapy for patients with haematologic malignancies.[19-21] There is increasing evidence that an important component of this therapy is the graft versus leukaemia/lymphoma activity that occurs through the recognition of tumour-associated antigens on the neoplastic cells by the donor cells.[22-24]. In support of this, Bellucci et al.[21] recently demonstrated a B cell response to myeloma tumour-associated antigens in transplanted patients who were in complete remission. urthermore, the presence of the relevant antibodies was associated with the time of best response following transplantation.
We are already investigating the antibody and CTL response of patients with ALK-positive ALCL from their initial time of diagnosis, during treatment and remission. This study is providing valuable information concerning the relevance of the immune response to prognosis and whether changes might indicate relapse in these patients. The aims of the current project are to

extend this work by investigating the extent of the B and T cell immune responses to ALK proteins in relapsed ALCL patients who have undergone stem cell transplantation. The identification of the presence and magnitude of both a B and T cell response before (in both recipient and donor), during and after treatment should provide valuable data concerning the success of the transplant and prognostic outcome for these patients with relapsing ALK-positive ALCL. The project also opens up the possibility of improved therapeutic methods of treatment for patients with ALK-positive ALCL.

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17 Publication rules and presentation of results

Final analysis of the study ALCL-Relapse will be performed two years after the end of patient enrolment.

After termination of the biometric final analysis a final report will be completed. The final report will contain the clinical report, the statistical report, single analyses, a thorough safety analysis and conclusions. The steering committee of the study will sign it.

Final results of the study will be published irrespective of whether the aims of the study have been reached or not. The results will be presented according to the criteria determined in the CONSORT-Statement[42].

Any data relating to the study must not be reported or published without prior consultation with the international study committee.

18 Appendix

Declaration of Helsinki

Medical examination prior to SCT

GvHD: clinical staging and grading

Reference laboratories: Addresses and notes

Patient information and consent forms

Documentation forms

Contract of participation (clinic)

Participating groups and centres

18.1 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

A. INTRODUCTION

1) The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2) It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty
3) The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4) Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.
5) In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society
6) The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7) In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8) Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9) Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10) It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11) Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12) Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

13) The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious Adverse Events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14) The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15) Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16) Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17) Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18) Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19) Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20) The subjects must be volunteers and informed participants in the research project.
21) The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22) In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23) When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24) For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health

of the population represented and this research cannot instead be performed on legally competent persons.

25) When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26) Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27) Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28) The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29) The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. *(See Footnote*)*

30) At the conclusion of the study, every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

31) The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32) In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

**Footnote*

The WMA herby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reason its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

18.2 Medical examination prior to SCT

recommended recipient examination before SCT

- **Remission documentation:** MRD-Diagnosis (before SCT, 10 ml EDTA BM), others depending on initial diagnosis (within 7 days before start of the conditioning regimen), 10 ml EDTA blood for Pulford. Send samples for MRD and immune response examinations to the national reference centre for genetics in Giessen (address see page 4 and 69).

- **Blood count** with differential blood count and reticulocytes

- **Coagulation:** Quick, PTT, Fibrinogen (if not done already: protein C, protein S, APC, AT III, Prothrombin-mutation, V-Leiden factor, Lp(a) lipoprotein

- **Laboratory:** sodium, potassium, chloride, calcium, phosphate (reabsorption), magnesium, CK, GOT, GPT, LDH, γ-GT, GLDH, CHE, α-amylase, creatinine, urea, uric acid, blood sugar, cholesterol, triglycerides, bilirubin, iron/EBK/transferrin/ferritin, total protein and electrophoresis

- **Urine:** status, sediment, creatinine-clearance, amino acids, phosphate, α1-micro globulin

- **Immunology:** IgG

- **Microbiology:** pharynx smear, sputum, urine and stool for bacteria and fungi, toxoplasmosis-AB, according to diagnostic facilities: aspergillus-galactomannan, Varicella-zoster, herpes-simplex, cytomegaly, measles, mumps, German measles (IgG), HIV I + II, Epstein-Barr (VCA, IgG, IgM, EA), hepatitis A (IgM, IgG), hepatitis B (HB_SAG, HB_SAK, HB_CAK), hepatitis C (IgG)

- **Blood bank:** blood group, isoagglutinin titre, platelet-allo-AB

- **X-ray:** thorax, paranasal sinuses

- **EKG / Echo-KG**

- **Abdomen sonography**

- **Pulmonary function:** spirometry with DLCO (diffusion capacity of lungs for carbon monoxide)

- **Dentist:** dental sanitation; recommended

- **Gynaecologist:** pregnancy test (with girls)

- **Ophthalomolist:** Status of the eyes; e.g. exclusion of cataract

recommended donor examination before SCT

- **Blood count:** with differential blood count and reticulocytes, 10 ml EDTA blood for the immune response examinations of Karen Pulford. Send samples for the immune response examinations of Karen Pulford to the national reference centre for genetics in Giessen (address see page 4 and 69).

- **Coagulation:** Quick, PTT, Fibrinogen

- **Laboratory:** sodium, potassium, chloride, calcium, phosphate, magnesium, CK (CK-MB), GOT, GPT, LDH, γ-GT, GLDH, CHE, α-amylase, creatinine, urea, uric acid, blood sugar, cholesterol, triglycerides, bilirubin, iron/EBK/transferrin/ferritin, total protein and electrophoresis

- **Urine:** status, sediment

- **Microbiology:** toxoplasmosis-AB, varicella-zoster, herpes-simplex, cytomegaly, measles, mumps, German measles (IgG), HIV I + II, Epstein-Barr (VCA, IgG, IgM, EA), hepatitis A (IgM, IgG), hepatitis B (HB_SAG, HB_SAK, HB_CAK), hepatitis C (IgG)

- **Blood bank:** blood group, isoagglutinin-titre

- **X-ray:** thorax if required

- **Pulmonary function test** if required

- **Pregnancy test:** Pregnanediol for potentially pregnant donors

- **at BM/Sc-withdrawal:** if donor and recepient are of same sex: 5 ml EDTA-blood for chimerism (reference for post-SCT)

18.3 GvHD: clinical staging and grading

acute GvHD: clinical stage

stage	Skin	liver	intestinal tract*
0	no rash	Bilirubin <2,0mg/dL	none
1	macular or papular rash <25% of body surface area	Bilirubin 2,0-3,0mg/dL	Diarrhea >5 - ≤ 10mL/kg/day
2	macular papular rash 25-50% of body surface area	Bilirubin 3,1-6,0mg/dL	Diarrhea >10 to ≤ 15mL/kg/day
3	generalized erythroderma	Bilirubin 6,1-15,0mg/dL	Diarrhea >15mL/kg/day
4	generalized erythroderma with bullous formation and desquamation	Bilirubin >15,0mg/dL	

* pediatric criteria

acute GvHD: overall grade

grade	skin-stage	liver-stage		intestinal tract-stage	decrease in clinical performance
I	1 to 2	0	and	0	no
II	1 to 3	1	and/or	1	mild
III	2 to 3	2 to 3	and/or	2 to 3	marked
IV	2 to 4	2 to 4	and/or	2 to 3	extreme

chronic GvHD grading

grade	Organ involvement
limited	Localized skin involvement or hepatic involvement
extensive	Generalized skin involvement or Limited skin involvement and/or hepatic involvement **plus** any of the following: • liver histology showing chronic aggressive hepatitis, bridging necrosis or cirrhosis • involvement of eye: Schirmer's test mit <5mm wetting • involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy • involvement of any other target organ

18.4 Reference laboratories: Addresses and notes

Reference institute for pathology

Koordination der Referenzpathologie	
Prof. Dr. Dr. h.c. R. Parwaresch	Lymphknotenregister Institut für Hämatopathologie der Universität Kiel Niemannsweg 11 24105 Kiel Tel.: 0049 431 597 3425 Fax: 0049 431 597 3426
weitere Referenzpathologen	
Prof. Dr. A. C. Feller	Institut für Pathologie der Universität Lübeck Ratzeburger Allee 160 23538 Lübeck
Prof. Dr. M. L. Hansmann	Senckenbergisches Institut für Pathologie Theodor-Stern-Kai 7 60596 Frankfurt
Prof. Dr. P. Möller	Institut für Pathologie und Rechtsmedizin Albert-Einstein-Allee 11 89081 Ulm
Prof. Dr. H. Müller-Hermelink	Institut für Pathologie Josef-Schneider-Str. 2 97080 Würzburg
Prof. Dr. H. Stein	Konsultations- u. Referenzzentrum für Lymphknoten- und Hämatopathologie Universitäts-Klinikum Benjamin Franklin Hindenburgdamm 30 12200 Berlin

Reference laboratory for genetics (MRD) and processing/banking of tumor cells

Prof. Dr. J. Harbott **Dr. K. Busch**	Onkogenetisches Labor Universitäts-Kinderklinik Pädiatrische Hämatologie und Onkologie Feulgenstr. 12 35385 Gießen Tel.: +49 641 99 43426 Fax: +49 641 99 43485 e-mail: kerstin.busch@paediat.med.uni-giessen.de

Reference laboratory for cytomorphology

Prof. Dr. A. Reiter **Dr. W. Wößmann** **Dr. B. Burkhardt**	Universitäts-Kinderklinik Pädiatrische Hämatologie und Onkologie Feulgenstr. 12 35385 Gießen Tel.: +49 641 99 43627 Fax: +49 641 99 43629

Reference laboratory for chimerism

PD Dr. P. Bader **(SNTR)**	Chimärismuslabor Universitätsklinik für Kinderheilkunde und Jugendmedizin Hoppe-Seyler-Straße 1 72076 Tübingen Tel.: +49 7071 2983781
Prof. Dr. J. Harbott **(xy-FISH)**	Onkogenetisches Labor Universitäts-Kinderklinik Pädiatrische Hämatologie und Onkologie Feulgenstr. 12 35385 Gießen

Laboratory for investigation of T- and B-cell response to ALK

Dr. K. Pulford **Dr. Ait-Tahar**	Nuffield Department of Clinical Laboratory Sciences, Room 4A11, Level 4, Academic block, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, U.K. karen.pulford@ndcls.ox.ac.uk kamel.ait-tahar@ndcls.ox.ac.uk

18.5 Patient information and consent forms

- **Patientenaufklärung für die Teilnahme an der Therapiestudie ALCL-Relapse (S. 72 ff.)**
- **Einwilligungserklärung zur Teilnahme an der Therapiestudie ALCL-Relapse (S. 78)**
- **Patientenaufklärung für die allogene Blutstammzelltransplantation von HLA-passenden Spendern (S. 79 ff.)**
- **Patientenaufklärung für die allogene Blutstammzelltransplantation von Spendern mit unterschiedlichen Gewebsmerkmalen (S. 84 ff)**
- **Einwilligungserklärung zur allogenen Blutstammzelltransplantation (S. 89)**
- **Patientenaufklärung für die autologe Blutstammzelltransplantation (S. 90 ff.)**
- **Einwilligungserklärung zur autologen Blutstammzelltransplantation (S. 94)**

PATIENTENAUFKLÄRUNG

zur Therapiestudie ALCL-Relapse
Therapieprotokoll zur Behandlung rezidivierter großzellig anaplastischer Lymphome im Kindes- und Jugendalter; internationale Multicenter-Studie der Europäischen Studiengruppen-Kooperation zur Behandlung von NHL bei Kindern (EICNHL)

Lieber Patient, liebe Eltern

Bei Ihnen/Ihrem Kind wurde ein Rückfall eines großzellig anaplastischen Non-Hodgkin Lymphoms (ALCL) diagnostiziert. Das Protokoll ALCL-Relapse wurde als Therapieoptimierungs-Studie speziell für Kinder und Jugendliche mit dieser Diagnose erarbeitet.

Information über Therapieoptimierungs-Studien
Therapieoptimierungs-Studien werden durchgeführt, um möglichst viele Patienten mit einer gleichen Erkrankung einer einheitlichen Behandlung zu unterziehen. Die Ergebnisse werden dokumentiert und mit anderen Behandlungsformen verglichen. Dadurch erhält man speziell bei seltenen Erkrankungen Hinweise, welche Veränderungen in der Therapie notwendig sind, um die Behandlung für den Patienten so erfolgreich und schonend wie möglich zu gestalten. Die behandelnden Ärzte verpflichten sich, die Therapie nach einem einheitlichen Protokoll durchzuführen. Im vorliegenden Protokoll sind die entscheidenden Punkte der Therapie festgelegt. Alle wichtigen Behandlungsschritte und -methoden und die vorgeschriebenen Medikamente sind erprobt und auch bei Kindern eingesetzt worden.

Der Therapieplan der Studie ALCL-Relapse wurde in einem internationalen Gremium (European Inter-Group Co-operation on Childhood Non-Hodgkin Lymphoma, abgekürzt EICNHL), bestehend aus Experten bei Lymphomen im Kindes- und Jugendalter, entworfen, diskutiert und abschließend beschlossen. Die Studie wird in mehreren europäischen Ländern durchgeführt. Dadurch können jährlich rund 16 Patienten in die Studie aufgenommen werden, so dass die Studie nach ca. 6 Jahren abgeschlossen werden kann.

Untersuchungsablauf
Nachdem die Diagnose des Rückfalls histologisch oder zytomorphologisch und durch den Nachweis typischer genetischer Veränderungen in den Lymphomzellen bestätigt wurde, werden vor Beginn der Therapie einige Untersuchungen durchgeführt, um die Ausbreitung des Lymphoms festzustellen. Zu diesen Untersuchungen gehören Röntgenuntersuchungen vom Brustkorb, Ultraschalluntersuchungen von Bauch, Brustkorb, Becken, CT oder MRT vom Kopf, Blutabnahmen, Knochenmarkpunktion, Lumbalpunktion und - abhängig vom individuellen Fall - ggf. auch weitere Untersuchungen.

Anpassung der Therapie an das individuelle Risiko der Patienten, einen zweiten Rückfall zu erleiden (Stratifizierung der Therapie)
Die bisherigen Erfahrungen bei Kindern und Jugendlichen mit dieser Erkrankung haben gezeigt, dass die individuelle Heilungschance der Patienten bzw. das individuelle Risiko, dass die Krankheit nach einer Rückfallbehandlung erneut auftritt, sehr unterschiedlich ist. Als wichtige Kriterien haben sich herausgestellt: der Zeitpunkt an dem der Rückfall der Erkrankung eintritt und bestimmte biologische Eigenschaften der Lymphomzellen. Patienten, die schon während der intensiven Phase der Erstbehandlung der Erkrankung einen Rückfall erleiden (oder bei denen das noch vorhandene Lymphom anfängt, wieder zu wachsen), haben das höchste Risiko, nicht mehr von der Krankheit geheilt zu werden. Erste Erfahrungen deuten darauf hin, dass diesen Patienten am ehesten geholfen werden kann, wenn nach einer erneuten Chemotherapie eine sogenannte allogene Blutstammzelltransplantation, d. h. eine Übertragung von Blutstammzellen von einem anderen Menschen, durchgeführt wird. Tritt ein Rückfall erst nach der intensiven Phase der Erstbehandlung der Erkrankung auf, hängt die Heilungschance der Patienten stark ab von den biologischen Eigenschaften der Lymphomzellen, speziell davon, ob sie ein bestimmtes immunologisches Merkmal tragen, das sogenannte CD3 Molekül. Patienten, deren Lymphomzellen, dieses Merkmal nicht tragen, haben mit einer erneuten intensiven Chemotherapie, bei der die Möglichkeit genutzt wird, durch die Transfusion eigener

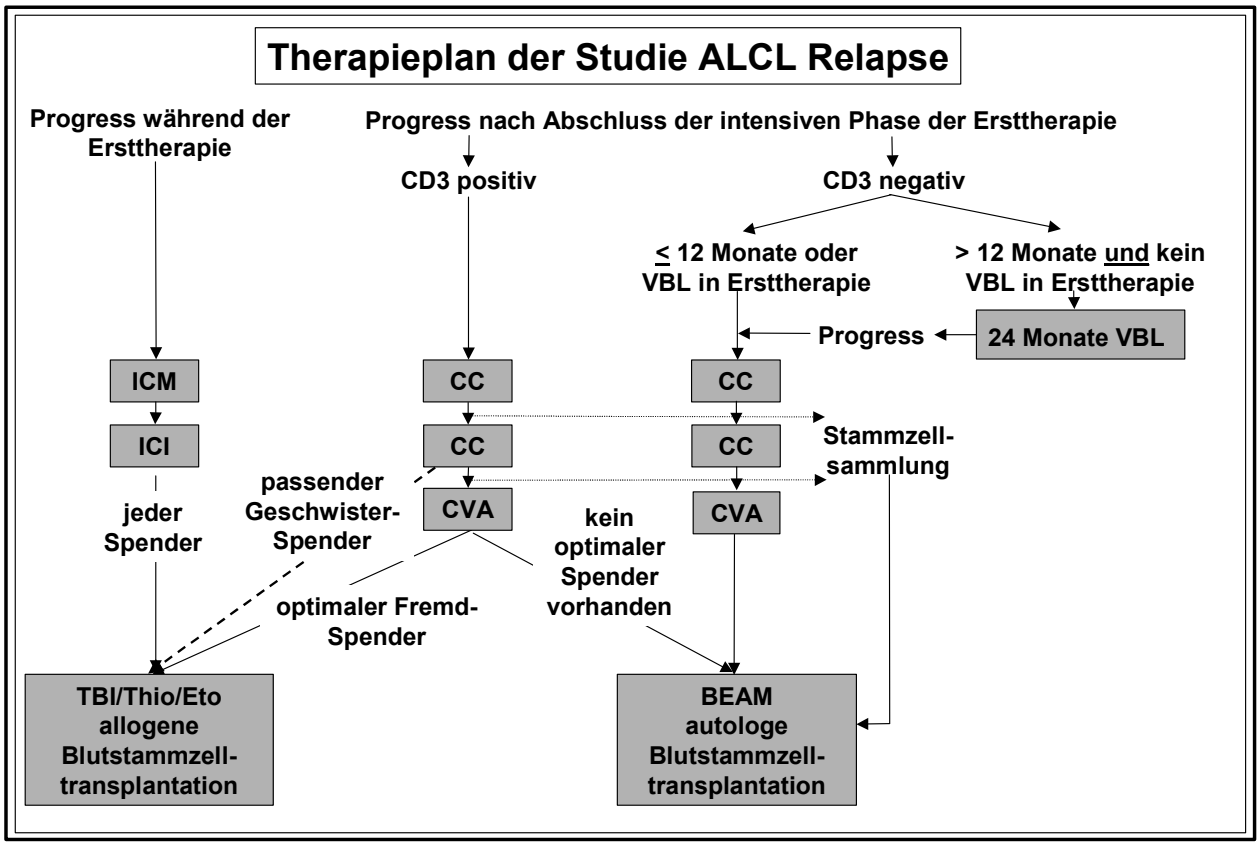
vor der Therapie gewonnener Blutstammzellen, die durch die Therapie geschädigte Funktion des Knochenmarks wiederherzustellen (der sogenannten autologen Blutstammzelltransplantation), gut Heilungschancen. Einzelerfahrungen deuten daraufhin, dass bei einem sehr späten Rückfall bei diesen Patienten möglicherweise sogar mit einer sehr verträglichen wenig intensiven, dafür aber längeren Dauertherapie mit nur einem Chemotherapiemedikament (Vinblastin) eine dauerhafte Heilung erreicht werden kann. Wenn die Lymphomzellen der Patienten jedoch das Merkmal CD3 tragen, waren Behandlungen mit der sogenannten autologen Blutstammzelltransplantation bisher jedoch weniger erfolgreich. Nach einem erneuten Rückfall erreichten jedoch einige dieser Patienten nach Durchführung einer allogenen Blutstammzelltransplantation eine dauerhafte Krankheitsfreiheit.
Die bisherigen Erfahrungen können also so zusammengefasst werden, dass Patienten mit Rückfall eines großzellig anaplastischen Lymphoms eine sehr unterschiedliche Heilungschance haben. Entsprechend weisen die Behandlungsformen, mit denen ein dauerhafter Therapieerfolg erzielt wurde, ein großes Spektrum der mit ihnen verbundenen Belastung für den Patienten auf, das von einer relativ wenig belastenden Vinblastin-Dauertherapie bis zur allogenen Blutstammzelltransplantation mit all ihren Risiken reicht. Eine wichtige weitere Erkenntnis kann aus den bisherigen Erfahrungen abgeleitet werden: Patienten mit Rückfall eines großzellig anaplastischen Lymphoms haben auch nach einem zweiten Rückfall der Erkrankung noch eine gute Chance mit einer weiteren Therapie doch eine dauerhafte Heilung zu erreichen, zumindest, wenn der erste Rückfall nach der intensiven Phase der Erstbehandlung der Erkrankung auftrat.

Das Ziel der vorliegenden Studie ist daher, die Behandlung dem unterschiedlichen Risiko des einzelnen Patienten, einen erneuten Rückfall zu erleiden, anzupassen. Dabei wird auch von der Erkenntnis Gebrauch gemacht, dass diese Patienten auch nach einem zweiten Rückfall der Erkrankung noch eine gute Chance haben, mit einer weiteren Therapie doch eine dauerhafte Heilung zu erreichen. In der vorliegenden Studie wird die Therapie anhand der folgenden Kriterien stratifiziert:

1. Zeitpunkt des Wiederauftretens des Lymphoms
2. Nachweis des immunologischen Merkmals (CD3) auf den Lymphomzellen
3. Verfügbarkeit eines optimalen Spenders für eine Blutstammzelltransplantation
4. Gabe eines bestimmten Medikamentes (Vinblastin) während der Ersttherapie

Patienten, bei denen ein Rückfall während der Ersttherapie auftritt, d.h., bei denen diese Therapie nicht wirksam ist, erhalten zwei Kurse einer anderen Chemotherapie und daran anschließend eine allogene Blutstammzelltransplantation. Da bei diesen Patienten nach bisherigen Erfahrungen die Chance, ohne allogene Blutstammzelltransplantation eine dauerhafte Heilung zu erzielen, sehr gering ist, kommen als Blutstammzellspender nicht nur Familienspender oder fremde Spender in Frage, deren Gewebeverträglichkeitsmerkmale mit denen des Patienten optimal übereinstimmen, sondern auch nicht optimal passende Spender. Auch die Eltern, die in der Regel mit ihrem Kind nur in einer Hälfte der Transplantationsantigene übereinstimmen, können Spender sein. Dazu muss aber das Verfahren der Transplantation entsprechend angepasst werden.
Tritt das Lymphom nach Abschluss der intensiven Phase der Ersttherapie der Erkrankung wieder auf, ist das zweite Stratifizierungskriterium, die Nachweisbarkeit des immunologischen Merkmals CD3 entscheidend. Patienten, bei denen dieses Merkmal nachgewiesen wurde (CD3 positiv) erhalten ebenfalls zwei (ggf. drei) Kurse Chemotherapie. Während dieser Therapie wird die Suche nach einem optimal passenden Familienspender oder Fremdspender durchgeführt. Kann ein solcher Spender gefunden werden, erhalten die Patienten eine allogene Blutstammzelltransplantation. Patienten, bei denen das Merkmal CD3 nachgewiesen wurde, für die kein optimal passender Spender gefunden werden kann, erhalten zunächst einen dritten Kurs Chemotherapie und anschließend eine autologe Blutstammzelltransplantation. Das bedeutet, es werden eigene Blutstammzellen, die vorher in den Pausen zwischen der Chemotherapie gewonnen wurden, zurück übertragen. Diese unterschiedliche Therapie abhängig von der Verfügbarkeit eines optimalen Spenders, ergibt sich durch das Risiko der Transplantation. Dies steigt bei nicht optimal passendem Spender an, so dass man in dieser Situation die risikoärmere autologe Blutstammzelltransplantation empfiehlt. Über das Wesen,

die Durchführung und Risiken der einzelnen Blutstammzell-Transplantationsverfahren werden Sie speziell informiert und Sie müssen dafür auch getrennt Ihr Einverständnis schriftlich erteilen. Bei Patienten, bei denen das Merkmal CD3 nicht auf den Lymphomzellen nachweisbar ist, ist erneut der Zeitpunkt des Wiederauftretens der Erkrankung wichtig. Wenn das Lymphom innerhalb von 12 Monaten nach Diagnosestellung wiederauftritt, erhalten die Patienten eine autologe Blutstammzelltransplantation. Die gleiche Therapie erhalten Patienten, bei denen das Lymphom zwar später als 12 Monate nach Diagnosestellung wiederaufgetreten ist, die jedoch das Medikament Vinblastin bereits in der Ersttherapie erhalten haben. Die übrigen Patienten mit einer spät (> 12 Monate nach Ersterkrankung) wiederaufgetretenen Lymphomerkrankung, die während der Ersttherapie noch kein Vinblastin erhalten haben, werden im Vinblastin-Arm der Studie behandelt. Dieser Arm beinhaltet eine wöchentliche Therapie allein mit dem Medikament Vinblastin für insgesamt 24 Monate.
Die obigen Ausführungen zur Therapiestratifizierung sind in der folgenden Abbildung graphisch zusammengefasst.



Durchführung, Risiken und Nebenwirkungen der Chemotherapie
Auch bei Patienten, die eine Blutstammzelltransplantation erhalten, wird zunächst eine intensive Chemotherapie durchgeführt, um die Lymphomzellen so weit wie möglich zu vernichten. Die Chemotherapie besteht aus zwei bzw. drei aufeinanderfolgenden mehrtägigen Kursen, bei denen mehrere Medikamente kombiniert gegeben werden. Durch die Kombination der Medikamente soll die Chance der Lymphomzellen verringert werden, der Behandlung zu entgehen. Bei Patienten, die einen Rückfall noch während der Erstbehandlung der Erkrankung erleiden, werden die Medikamente Ifosfamid, Carboplatin, Mitoxanthrone und Idarubicin eingesetzt, während bei Patienten mit Rückfall nach der Erstbehandlung Dexamethason, Cytarabin, Vindesin, Etoposid, CCNU, und Vinblastin zum Einsatz kommen. Alle Patienten erhalten zudem zur Ausrottung von Lymphomzellen im Zentralnervensystem die Medikamente Prednisolon, Cytarabin und Methotrexat, die durch eine Lumbalpunktion direkt in das Gehirnwasser eingebracht werden. Die Nebenwirkungen dieser Chemotherapie ähneln den Nebenwirkungen, die Sie bei der Erstbehandlung des ALCL kennengelernt haben. Sie bestehen z.B. aus Übelkeit und Erbrechen, vorübergehendem Haarausfall, Auswirkungen auf die Schleimhäute des Magen-Darm-Traktes, auf das blutbildende Knochenmark und das Blutbild.

Des weiteren führt die Chemotherapie zu einer Schwächung des Immunsystems und als Folge der Therapie können Organschäden auftreten. Zu den Spätfolgen nach Vinblastintherapie zählen die Komplikationen nach zytostatischer Chemotherapie (z.B.: verzögertes Längenwachstum, Hormonminderproduktionen, Gefahr von zweiten Krebserkrankungen, Einschränkungen der Organfunktion) und Komplikationen durch Infektionen (virusbedingte Leberveränderungen, Lungenveränderungen, u.a.). Die speziellen Nebenwirkungen der einzelnen Medikamente werden Ihnen von Ihrem Arzt erklärt.

Parallel zur Chemotherapie werden die Vorbereitungen für die Blutstammzell-Transplantation eingeleitet. Über die Details der Blutstammzelltransplantation werden Sie in einem separaten Gespräch informiert und um die entsprechende Einwilligung gebeten.

Patienten im Vinblastin-Arm erhalten wöchentlich eine Gabe Vinblastin für die Dauer von insgesamt 24 Monaten. Die Nebenwirkungen dieser Chemotherapie können z.B. aus neurologischen Nebenwirkungen wie Missempfindungen, Inappetenz, Verstopfungen, Auswirkungen auf die Schleimhäute des Magen-Darm-Traktes, auf das blutbildende Knochenmark und das Blutbild sowie Infektionen bestehen. Während der Vinblastintherapie werden die auftretenden Nebenwirkungen genau untersucht und dokumentiert. Falls nötig wird die Vinbalstindosis für eine gewisse Zeit reduziert oder vorübergehend ausgesetzt. Durch die Vinblastintherapie ist ein Wiederauftreten des Lymphoms nicht immer zu verhindern. Für diesen Fall würden Ihnen/Ihrem Kind wirksame Therapieoptionen offenstehen.

Supportiv-Therapie und Nachsorgeuntersuchungen
Da die Chemotherapie zu einer vorübergehenden Schwächung des Immunsystems führt, erhalten die Patienten eine prophylaktische Therapie mit einem Antibiotikum, um Infektionen zu verhindern. Aufgrund des geschwächten Abwehrsystems der Patienten sollte der Patient während der Therapie den Kontakt mit Personen, die an Windpocken erkrankt sind, vermeiden.
Um eventuell auftretende Spätfolgen der Therapie möglichst frühzeitig zu erfassen, ist im Protokoll ein detailliertes Nachsorgeprogramm beschrieben, anhand dessen Sie in den ersten Jahren nach der Theraoie in zunehmend größer werdenenden Zeiträumen untersucht werden.

Schwangerschaft
Vor Beginn der Therapie muss eine Schwangerschaft ausgeschlossen werden und während der Therapie eine Schwangerschaftsverhütung sichergestellt sein.

Art der Studie
Es handelt sich um eine Therapieoptimierungs-Studie, die an vielen Behandlungszentren für krebskranke Kinder in Europa durchgeführt wird. In regelmäßigen Abständen wird der Verlauf der Studie analysiert und mit den Ergebnissen anderer Studien verglichen, so dass man Nebenwirkungen oder ungünstige Entwicklungen rechtzeitig erkennen und beeinflussen kann. Sollten neue Erkenntnisse darauf hinweisen, dass andere Methoden wirksamer sind, wird Ihr Arzt Sie darüber informieren. Der Verlauf der Studie wird von einem externen Gremium (Data safety and monitoring committee) überwacht. Dieses Gremium erhält in regelmäßigen Abständen Auswertungen zur laufenden Studie, insbesondere zu den aufgetretenen Nebenwirkungen und überprüft die Daten im Vergleich mit anderen Studien.

Studiendurchführung
Außer den unter „Begleituntersuchungen“ erwähnten zusätzlichen Maßnahmen werden nur die für die Behandlung ohnehin notwendigen Maßnahmen durchgeführt. Zur Studie gehört auch eine Dokumentation der erfolgten Therapie und der Nebenwirkungen.

Freiwilligkeit, Alternative zur Teilnahme an dieser Studie
Die Teilnahme an der Studie ist freiwillig. Sie können die Studienteilnahme jederzeit beenden, ohne dass Ihnen/Ihrem Kind daraus Nachteile entstehen. Als Alternative kommt zum Beispiel die Behandlungsstrategie in Frage, nach der Patienten mit Rückfall eines großzellig anaplastischen Lymphoms in der Studie NHL-BFM 95 behandelt wurden oder eine andere in der wissenschaftlichen Literatur veröffentlichte Behandlungsstrategie.

Vertraulichkeit
Klinische Untersuchungen werden entsprechend den Bedingungen des Bundesdatenschutzgesetzes und nach den geltenden EU-Richtlinien dokumentiert. Patientendaten werden streng vertraulich behandelt.
Zur Kontrolle der Prüfergebnisse kann ein Vergleich der Krankheitsdaten erforderlich werden. Zu diesem Zwecke ist es notwendig, dass zur Verschwiegenheit verpflichtete Mitarbeiter von Behörden oder andere autorisierte Personen Einblick in die Patientenunterlagen nehmen können.
Von Ihnen/Ihrem Kind sollen personenbezogene (Name, Geburtsdatum, Wohnort) und medizinische Daten (Diagnose mit Befunderhebung, Labordaten usw.) gespeichert bzw. an folgende Zentren übermittelt werden:

- **Studienzentrale NHL-BFM**; Studienleiter: Prof. Dr. A. Reiter; Universitätsklinikum Gießen; Universitäts-Kinderklinik; Pädiatrische Hämatologie und Onkologie; Feulgenstr. 12; 35385 Gießen
- **Deutsches Kinderkrebsregister**; Institut für Medizinische Biometrie und Epidemiologie der Universität Mainz; Direktor: Prof. Dr. Schäfer; Projektgruppe Pädiatrische Onkologie; Langenbeckstr. 1; 55101 Mainz
- Referenzpathologie-Institute an den Universitäten Kiel, Lübeck, Berlin, Würzburg, Frankfurt, Ulm (genaue Adresse siehe Studienprotokoll S. 4)
- **Onkogenetisches Labor**; Prof. Dr. J. Harbott; Universitäts-Kinderklinik; Pädiatrische Hämatologie und Onkologie; Feulgenstr. 12; 35385 Gießen
- **Untersuchung der Immunantwort** auf das ALCL, Karen Pulford, Nuffield Department of Clinical Laboratory Sciences, Room 4A11, Level 4, Academic block, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, U.K.

Dies kann nur geschehen, wenn Sie die behandelnden Ärzte zu diesem Zweck von der Schweigepflicht entbinden.

Notfalladresse und Leiter der Therapieoptimierungsstudie
Der verantwortliche Leiter dieser Studie ist Herr Prof. A. Reiter, Zentrum für Kinderheilkunde und Jugendmedizin, Abteilung Hämatologie und Onkologie, Universitätsklinikum Gießen, Feulgenstr. 12, 35385 Gießen.
Verantwortlich für Ihre/die Betreuung Ihres Kindes ist die/der Leiter/in Ihres Behandlungszentrums. Sie sollten Ihr/Ihm alle auftretenden Komplikationen und Probleme sofort mitteilen. Während der Behandlung auftretende Fragen sollten Sie mit Ihrem behandelnden Arzt klären.

Ethikkommission, behördliche Anforderungen und Patientenversicherung
Das Protokoll der Studie wurde der zuständigen Ethikkommission in Gießen vorgelegt und hat ein positives Votum erhalten. Zusätzlich wurde das Protokoll beim Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) und beim Paul-Ehrlich Institut, Bundesamt für Sera und Impfstoffe (PEI) hinterlegt. Für die Patienten der Studie ALCL-Relapse besteht zum Ausgleich eines Vermögensschadens infolge einer studienbedingten Gesundheitsschädigung von Seiten der NHL-BFM Studienzentrale der für klinische Prüfungen gesetzlich vorgeschriebene Versicherungsschutz. Während der Dauer der Studie sollte eine andere medizinische Behandlung mit Ausnahme von Notfallsituationen nur im Einvernehmen mit dem verantwortlichen Arzt erfolgen. Bei Verdacht auf einen studienbedingten Gesundheitsschaden ist der behandelnde Arzt sofort zu benachrichtigen, damit dieser in Ihrem Auftrag die Versicherung informieren kann. Sie können die Information der Versicherung auch selbst übernehmen.

Begleituntersuchungen und begleitende Forschungsprojekte
Um neue Erkenntnisse zur weiteren Verbesserung der Behandlung von Patienten mit Rückfall eines großzellig anaplastischen Lymphoms in der Zukunft zu erlangen, werden mehrere begleitende Untersuchungen und Forschungsprojekte im Zusammenhang mit der Therapieoptimierungsstudie ALCL-Relapse durchgeführt. Zu festgelegten Zeitpunkten bitten wir Sie/Ihr Kind, an den Tagen der vorgeschriebenen Kontroll-Knochenmarkpunktionen (vor Transplantation, Tag +28/+60/+100, 6 Monate und 1 Jahr nach Blutstammzelltransplantation)

Knochenmark und Blut zur Verfügung zu stellen. Damit wird das Verhältnis von Spender- und Empfängerzellen im Blut und Knochenmark („Chimärismus“) untersucht und die Konzentration eventuell noch vorhandener restlicher Lymphomzellen (minimale Resterkrankung oder MRD, dies kann nur durchgeführt werden, wenn Ihre Lymphomzellen/die Lymphomzellen Ihres Kindes einen geeigneten Marker aufweisen) bestimmt. Zusätzlich wird untersucht, ob spezifische Antikörper und Immun-Abwehrzellen gegen Lymphomzellen nachweisbar sind und in welcher Konzentration.
Sie werden/Ihr Kind wird davon keinen direkten persönlichen Nutzen haben, da von keinem dieser Parameter bekannt ist, ob und welche Bedeutung er für Erfolg oder Misserfolg der Behandlung hat. Vielmehr soll in dieser Studie untersucht werden ob und wenn ja, welche Bedeutung ihnen für Erfolg oder Misserfolg der Behandlung der Behandlung zukommt. Bevor diesbezügliche Erkenntnisse gesichert vorliegen, sind Veränderungen der Therapieführung auf der Basis solcher Befunde nicht nur unwissenschaftlich, sondern können für den Patienten sogar eine Gefahr darstellen. Deshalb werden die Ergebnisse der Einzeluntersuchungen nicht mitgeteilt, sondern gesammelt ausgewertet werden. Die Ergebnisse dieser Untersuchung können jedoch für zukünftige Patienten möglicherweise von großer Bedeutung sein. Deshalb sind wir Ihnen sehr dankbar, wenn Sie einwilligen, für diese Untersuchungen Material (zusätzlich jeweils 10 ml Knochenmark und 15 ml Blut) zur Verfügung zu stellen. Die Entnahme dieses Knochenmarkbluts erfolgt bei einer Punktion, die für Sie/Ihr Kind ohnehin notwendig wäre und für die Steuerung der Therapie nach Blutstammzelltransplantation routinemäßig erfolgt.
Eventuell ergeben sich entsprechend dem raschen wissenschaftlichen Fortschritt weitere wichtige Fragestellungen mit Bedeutung zum Wesen und zur besseren Behandlung Ihrer Erkrankung/der Erkrankung Ihres Kindes. Sofern Sie Ihr Einverständnis geben, wird deshalb restliches Material, das für die vorgesehenen Untersuchungen nicht verbraucht wird, in dem zentralen Materialaufarbeitungs-Labor in der Studienzentrale in Gießen gelagert und für zukünftige wichtige Forschungsprojekte zur Verfügung gestellt. Sofern diese Untersuchungen an anderen als den oben angeführten Institutionen durchgeführt werden und zur sinnvollen Auswertung eine Verbindung mit weiteren Daten der Erkrankung, der Therapie und des Verlaufs sowie Daten zu Alter, Geschlecht erforderlich sind, werden diese ausschließlich in vollständig anonymisierter Form unter voller Beachtung der Vorschriften des Datenschutzes weitergegeben.

Abschließend möchten wir Sie bitten, der Teilnahme an dieser Studie zuzustimmen, und hierdurch einen wichtigen Beitrag zum Fortschritt im Kampf gegen Krebs zu leisten.

Ansprechpartner in der behandelnden Klinik: Name	Tel.-Nr.

Einwilligungserklärung zur Teilnahme an der Therapiestudie ALCL-Relapse

Therapieprotokoll zur Behandlung rezidivierter großzellig anaplastischer Lymphome im Kindes- und Jugendalter; internationale Multicenter-Studie der Europäischen Studiengruppen-Kooperation zur Behandlung von NHL bei Kindern (EICNHL)

Name des Patienten: _____

Geburtsdatum: _____

Ich bin/wir sind durch den/die behandelnde/n Arzt/Ärztin_____

am _____

über Diagnose und Verlauf meiner Erkrankung/der Erkrankung unseres Kindes, ferner über Wesen, Bedeutung und Tragweite der Therapieoptimierungsstudie ALCL-Relapse aufgeklärt und eingehend über die bekannten und zu erwartenden Wirkungen (Wirksamkeit), Nebenwirkungen sowie Risiken informiert worden. Mir/Uns wurde genügend Zeit für eine Entscheidung über die Teilnahme an der Therapieoptimierungsstudie ALCL-Relapse eingeräumt und die schriftliche Patinteninformation habe ich zu Kenntnis genommen.

☐ Mit der **Behandlung nach dem Studienprotokoll ALCL-Relapse** erkläre/n ich/wir mich/uns einverstanden, behalte/n mir/uns jedoch vor, jederzeit ohne Angabe von Gründen und ohne dass mir/unserem Kind daraus Nachteile entstehen, aus der Studie auszuscheiden.

☐ Ich/wir bin/sind damit einverstanden, dass **Knochenmarkblut und peripheres Blut für Untersuchungszwecke genutzt bzw. in den autorisierten Stellen tiefgefroren gelagert** wird. Klinische Untersuchungen werden entsprechend den Bedingungen des Bundesdatenschutzgesetzes und der geltenden EU-Richtlinien dokumentiert. Patientendaten werden streng vertraulich behandelt und ohne Angabe eines Namens/des Namens unseres Kindes weitergegeben und ausgewertet. Zur Kontrolle der Prüfergebnisse kann ein Vergleich der Krankheitsdaten erforderlich werden.

☐ Zu diesem Zwecke willige ich ein, dass zur Verschwiegenheit verpflichtete Mitarbeiter von Behörden oder andere **autorisierte Personen Einblick in meine Patientenunterlagen nehmen** können.

Darüber hinaus erkläre/n ich/wir uns damit einverstanden, dass von mir/meinem Kind **personenbezogene** (Name, Geburtsdatum, Wohnort) **und medizinische Daten** (Diagnose mit Befunderhebung, Labordaten usw.) gespeichert bzw. an folgende Zentren

☐ NHL-BFM-Studienzentrale, Gießen
☐ Kinderkrebsregister, Mainz
☐ Refernzpathologie (Kiel, o. Lübeck, o. Frankfurt, o. Ulm, o. Würzburg, o. Berlin)
☐ Onkogenetisches Labor, Gießen
☐ Labor zur Untersuchung der Immunantwort, Oxford

übermittelt werden und entbinde die behandelnden Ärzte zu diesem Zweck von der Schweigepflicht.

Eine Kopie der Patienteninformation und dieser Einverständniserklärung wurde mir/uns übergeben.

_____	_____
Ort, Datum	Patientenunterschrift
_____	_____
Ort, Datum	Unterschrift der sorgeberechtigten Personen

Ich bestätige, dass ich obengenannten Patienten/die Sorgeberechtigten, der/die sein/Ihr Einverständnis für die Teilnahme gegeben hat/haben, bezüglich Zweck, Nutzen, Art und Risiken der Studie aufgeklärt habe.

_____	_____	_____
Ort, Datum	Name des/der behandelnden Arztes/Ärztin Tel.	Unterschrift des/der Arztes/Ärztin

PATIENTENAUFKLÄRUNG

zur Therapiestudie ALCL-Relapse
Therapieprotokoll zur Behandlung rezidivierter großzellig anaplastischer Lymphome im Kindes- und Jugendalter; internationale Multicenter-Studie der Europäischen Studiengruppen-Kooperation zur Behandlung von NHL bei Kindern (EICNHL)

für die allogene Blutstammzelltransplantation von HLA-passenden Spendern bei Kindern und Jugendlichen mit Rückfall eines großzellig anaplastischen Lymphoms

Liebe Patienten, liebe Eltern,
Sie haben beim Beginn der Behandlung des Rückfalls Ihrer Erkrankung/der Erkrankung Ihres Kindes nach entsprechender Aufklärung eingewilligt, dass Sie/Ihr Kind im Rahmen der Therapiestudie ALCL-Relapse behandelt werden/wird. Auf Grund des Zeitpunktes des Auftretens des Rückfalls oder spezieller biologischer Eigenschaften der Lymphomzellen (Ausprägung des Merkmals CD3) gehört zu Ihrem Behandlungsplan/zum Behandlungsplan Ihres Kindes die Durchführung einer sogneannten allogenen Blutstammzelltransplantation. Über diesen speziellen Behandlungsteil werden Sie im Folgenden genauer informiert.

Einführung

Die allogene Stammzelltransplantation (SZT), d.h. die Übertragung von Knochenmark oder Ursprungszellen der Blutbildung (Blut-Stammzellen), die sich auch im fließenden Blut finden, dient der Behandlung Ihrer Erkrankung/der Erkrankung Ihres Kindes. Der Stammzell-übertragung voraus gehen eine intensive Medikamenten- und eventuell Strahlenbehandlung, die das Lymphom beseitigen und die körpereigene Abwehr unterdrücken sollen, damit die neuen Stammzellen nicht abgestoßen werden. An die SZT schließt sich eine Vorbeugung gegen eine Transplant-gegen-Empfängerreaktion („Graft-versus-host-Disease“ - GvHD) an, die ebenfalls mit Medikamenten erfolgt.

In der Therapiestudie ALCL-Relapse sind die Details der Spenderauswahl und der Behandlung während und nach der Transplantation festgelegt. Außer den unter „Begleituntersuchungen“ erwähnten zusätzlichen Maßnahmen, werden nur die für die Transplantation ohnehin notwendigen Maßnahmen durchgeführt.

Wissenschaftlicher Hintergrund

Die bisherigen Erfahrungen bei Kindern und Jugendlichen mit Rückfall eines großzellig anaplastischen Lymphoms haben gezeigt, dass die individuelle Heilungschance der Patienten bzw. das individuelle Risiko, dass die Krankheit nach einer Rückfallbehandlung erneut auftritt, sehr unterschiedlich ist. Erste Beobachtungen deuten darauf hin, dass Patienten, die entweder noch während der intensiven Phase der Erstbehandlung der Erkrankung einen Rückfall erleiden oder deren Lymphomzellen ein spezielles immunologisches Merkmal, das CD3 Antigen, tragen, mit einer sogenannten allogenen Blutstammzelltransplantation, d.h. der Übertragung von gesunden Blut-Stammzellen aus dem Knochenmark von einem gewebsgleichen oder -ähnlichen Familienspender oder einem gut passenden unverwandten Spender, bessere Chancen haben, von der Erkrankung geheilt zu werden. Allerdings waren bisher die Komplikationen nach einer SZT vom unverwandten oder nicht passenden Familienspender höher als nach einer Geschwistertransplantation.

Durchführung, Risiken und Nebenwirkungen der allogenen Stammzelltransplantation

Im folgenden werden die Durchführung der allogenen SZT und die möglicherweise auftretenden Komplikationen sowie eventuelle Spätfolgen beschrieben.

Ablauf der SZT und Komplikationen

Der Termin für die Blutstammzelltransplantation wird unter Berücksichtigung der notwendigen Lymphombehandlung (Re-Induktion), der Maßnahmen zur Gewinnung der Stammzellen und

der notwendigen Therapie vor und während der Transplantation vereinbart. Manchmal kann es zu Verschiebungen der Termine kommen; in diesem Fall wird eventuell eine weitere Chemotherapie notwendig. In der Vorbereitungsphase zur Blutstammzelltransplantation werden verschiedene Blutuntersuchungen und andere diagnostische Maßnahmen durchgeführt. Eventuell wird zu diesem Zeitpunkt - falls nicht bereits erfolgt - auch ein Dauerverweilkatheter für Infusionen und Blutabnahmen implantiert. Die stationäre Aufnahme erfolgt spätestens zum Zeitpunkt der Konditionierung. Die Aufenthaltsdauer im Isolierzimmer richtet sich nach dem Anwachsen der Stammzellen und den Komplikationen, die sich nach der Transplantation eventuell ergeben.

Konditionierung:
Zur Vorbereitung des Patienten zur SZT ist eine „Konditionierung“ unumgänglich, damit die körpereigenen Abwehrmechanismen, die die neuen Stammzellen abstoßen könnten, unterdrückt werden. Die Konditionierung besteht in einer sogenannten Ganzkörperbestrahlung zusammen mit einer sehr intensiven Chemotherapie. Vor Durchführng der Ganzkörperbestrahlung werden Sie von einem Strahlentherpeut speziell über das Vorgehen und die Risiken bei dieser Behandlung informiert. Wenn der Spender nicht ein HLA-identisches Geschwisterkind ist, werden zusätzlich Antikörper gegen Immunzellen verabreicht. Mit dieser Behandlung werden auch eventuell noch vorhandene Lymphomzellen vernichtet oder zumindest reduziert. Die Therapie verursacht aber auch eine erhebliche Abwehrschwäche gegen alle Arten von Infektionen (Bakterien, Viren, Pilze, Parasiten). Diese Infektionen können manchmal unbeherrschbar sein und tödlich verlaufen.
Mit der Konditionierung können folgende Nebenwirkungen verbunden sein:
Übelkeit, Erbrechen, Mundschleimhautentzündung, Speicheldrüsenentzündung, Haarausfall, Einschränkung der Nierenfunktion, Leberveränderungen, Blasenentzündung, in seltenen Fällen auch akute Herz- und Lungenprobleme. Die körpereigene Produktion von roten Blutkörperchen (notwendig für den Sauerstofftransport) und von Blutplättchen (notwendig für die Blutgerinnung) wird unterbrochen; daher müssen diese Blutbestandteile über unterschiedlich lange Zeiträume in Form von Bluttransfusionen zugeführt werden. Trotzdem kann es in seltenen Fällen zu lebensbedrohlichen Organblutungen kommen.

Komplikationen der SZT:
Bei Infektionen oder langsamem Anwachsen der transplantierten Stammzellen kann es notwendig werden, Wachstumsfaktoren für Blutzellen einzusetzen, die diesen Vorgang beschleunigen.
Wenn in Ausnahmefällen die transplantierten Stammzellen nicht anwachsen (Ursachen hierfür können sein: Abstoßung, Infektionen, zu geringe Stammzellmengen), kann eine zweite SZT vom selben oder von einem anderen Spender notwendig werden.
Nach erfolgreicher SZT ist das Abwehrsystem des Patienten noch längere Zeit beeinträchtigt und macht Vorsichts- und Isoliermaßnahmen für den Patienten auch nach der Entlassung aus der Transplantationseinheit notwendig.

Risiken und Nebenwirkungen der GvHD:
Wenn die Spenderzellen im Patienten angewachsen sind („Engraftment“), besteht die Möglichkeit, dass Spender-Abwehrzellen den Patienten als fremd erkennen, und es kann zu akuten und chronischen, manchmal lebensbedrohlichen Unverträglichkeitsreaktionen kommen („Graft versus Host Erkrankung“-GvHD). Sie betreffen vor allem Haut, Schleimhäute, Leber, Darm und eventuell die Lunge und äußern sich als akute und chronische Entzündungsreaktionen. Zur Verhinderung der GvHD werden verschiedene Medikamente gegeben, deren Auswahl von der Art des Spenders abhängt. Nebenwirkungen dieser Medikamente bestehen in akuten Unverträglichkeitsreaktionen (Fieber, Hautveränderungen, Blutdruckabfall), bei langdauernder Verabreichung können sie zu hohem Blutdruck, eingeschränkter Nieren- und Leberfunktion, verstärkter Körperbehaarung und Magenproblemen führen. Die Abwehr gegen Infektionskrankheiten ist herabgesetzt.
Prinzipiell ist jedoch eine leichte Form der GvHD (die manchmal keine Krankheitssymptome verursacht) nicht unbedingt gefährlich, da dieser Effekt zu einer besseren Abwehr von vielleicht

noch vorhandenen Lymphomzellen führen kann („Graft versus Lymphom-Effekt“ – GvL). Ein Graft versus Lymphom-Effekt kann jedoch auch ohne GvHD-Zeichen erfolgen. Zur Diagnose einer eventuell auftretenden GvHD muss unter Umständen eine Hautbiopsie durchgeführt werden.

Mögliche Spätfolgen einer SZT:
Zu den Spätfolgen nach SZT zählen die Komplikationen nach zytostatischer Chemotherapie und Strahlentherapie (z.B.: bleibende Unfruchtbarkeit, verzögertes Längenwachstum, Hormonminderproduktionen, Gefahr von zweiten Krebserkrankungen, Einschränkungen der Organfunktion), die chronische GvHD (Hautveränderungen, Lungenprobleme, Gelenksversteifung, Hornhauttrübung, Infektionen durch Abwehrschwäche), sowie Komplikationen durch Infektionen (virusbedingte Leberveränderungen, Lungenveränderungen, u.a.). Nach langdauernder Behandlung einer GvHD kann es zu verstärkter Knochenbrüchigkeit bzw. zu Hüftproblemen kommen.
Auch durch die allogene SZT ist ein Rückfall der Lymphomkrankheit nicht immer zu verhindern.

Schwangerschaft:
Vor Beginn der Konditionierung muss eine Schwangerschaft ausgeschlossen werden.

Alternative Therapie
Die prinzipielle Alternative zur einer SZT ist die Fortsetzung der Chemotherapie in der Form, wie sie bisher bei Ihnen/Ihrem Kind begonnen wurde. Die Analysen der letzten Jahre deuten allerdings darauf hin, dass die allogene SZT die Chance erhöht, dass kein weiterer Rückfall der Erkrankung auftritt. Diese Studie geht davon aus, dass die Nebenwirkungen der Transplantation geringer als in den letzten Jahren sein werden, da man ein einheitliches Konzept für die Spenderauswahl, Konditionierung und die Vorbeugung und Behandlung von Infektionen und GVHD verfolgt.

Datendokumentation und Vertraulichkeit
Zur Therapiestudie ALCL-Relapse gehört auch eine Dokumentation der erfolgten Therapie und der Nebenwirkungen. Darüber wurden Sie bereits bei Beginn Ihrer Behandlung informiert und Sie wurden um Einwilligung zur Weitergabe der Daten entsprechend den Bedingungen des Bundesdatenschutzgesetzes und nach den geltenden EU-Richtlinien an bestimmte Ihnen genannte Stellen gebeten.

Für die Blutstammzelltransplantation gibt es spezielle Register, national und international, in welche die Transplantationszentren aufgefordert sind, bestimmte Daten zur Durchführung und zum Verlauf von Blutstammzelltransplantationen zu melden. Zum einen stellt dies ein Kontrollinstrument für die Qualität der Arbeit der Transplantationszentren dar. Zum anderen können anhand der großen Patientenzahlen in dem Register übergeordnete wissenschaftliche Fragestellungen untersucht werden, die für die Verbesserung der Wirksamkeit der Transplantation und der Sicherheit der Patienten von großer Bedeutung sind.

Klinische Untersuchungen werden entsprechend den Bedingungen des Bundesdatenschutzgesetzes und nach den geltenden EU-Richtlinien dokumentiert. Patientendaten werden streng vertraulich behandelt und ohne Angabe der Patientennamen anonymisiert an Register innerhalb des Landes, aber auch an übergeordnete Register (European Group for Blood and Marrow Transplantation und International Bone Marrow Transplant Registry) weitergegeben und ausgewertet.

Zur Kontrolle der Prüfergebnisse kann ein Vergleich der Krankheitsdaten erforderlich werden. Zu diesem Zwecke ist es notwendig, dass zur Verschwiegenheit verpflichtete Mitarbeiter von Behörden oder andere autorisierte Personen Einblick in die Patientenunterlagen nehmen können. Von Ihnen/Ihrem Kind sollen personenbezogene (Name, Geburtsdatum, Wohnort) und medizinische Daten (Diagnose mit Befunderhebung, Labordaten usw.) gespeichert bzw. an folgende Zentren übermittelt werden:

- Studienzentrale NHL-BFM; Studienleiter: Prof. Dr. A. Reiter; Universitätsklinikum Gießen; Universitäts-Kinderklinik; Pädiatrische Hämatologie und Onkologie; Feulgenstr. 12; 35385 Gießen
- Pädiatrisches Register für Stammzell-Transplantationen: Prof. Dr. T. Klingebiel, Klinik für Kinderheilkunde III, Goethe Universität Frankfurt a. Main; Theodor Stern Kai 7, 60590 Frankfurt
- Onkogenetisches Labor; Prof. Dr. J. Harbott; Universitäts-Kinderklinik; Pädiatrische Hämatologie und Onkologie; Feulgenstr. 12; 35385 Gießen
- Untersuchung der Immunantwort auf das ALCL, Karen Pulford, Nuffield Department of Clinical Laboratory Sciences, Room 4A11, Level 4, Academic block, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, U.K.

Dies kann nur geschehen, wenn Sie die behandelnden Ärzte zu diesem Zweck von der Schweigepflicht entbinden.

Notfalladresse und Leiter der Therapiestudie
Der verantwortliche Leiter dieser Studie ist Herr Prof. A. Reiter, Zentrum für Kinderheilkunde und Jugendmedizin, Abteilung Hämatologie und Onkologie, Universitätsklinikum Gießen, Feulgenstr. 12, 35385 Gießen.
Verantwortlich für Ihre/die Betreuung Ihres Kindes ist die/der Leiter/in Ihres Transplantationszentrums. Sie sollten Ihr/Ihm alle auftretenden Komplikationen und Probleme sofort mitteilen. Während der Behandlung auftretende Fragen sollten Sie mit Ihrem behandelnden Arzt klären.

Begleituntersuchungen
Bereits bei der Aufklärung bei Beginn Ihrer Behandlung/der Behandlung Ihres Kindes wurden Sie über die begleitenden Forschungsprojekte, die im Rahmen dieser Studie durchgeführt werden, informiert. Da möglicherweise die Klinik, in der die Blutstammzeltransplantation durchgeführt wird, nicht mit Ihrer primär behandelnden Klinik übereinstimmt, werden Sie hier noch einmal über diese Untersuchungen informiert, die auch speziell im Rahmen der Blutstammzelltransplantation durchgeführt werden.
Um neue Erkenntnisse zur weiteren Verbesserung der Behandlung von Patienten mit Rückfall eines großzellig anaplastischen Lymphoms in der Zukunft zu erlangen, werden mehrere begleitende Untersuchungen und Forschungsprojekte im Zusammenhang mit der Therapieoptimierungsstudie ALCL-Relapse durchgeführt. Zu festgelegten Zeitpunkten bitten wir Sie/Ihr Kind, an den Tagen der vorgeschriebenen Kontroll-Knochenmarkpunktionen (vor Transplantation, Tag +28/+60/+100, 6 Monate und 1 Jahr nach Blutstammzelltransplantation) Blut und Knochenmark zur Verfügung zu stellen. Es wird daraus das Verhältnis von Spender- und Empfängerzellen im Blut und Knochenmark („Chimärismus“) untersucht und die Konzentration eventuell noch vorhandener restlicher Lymphomzellen (minimale Resterkrankung oder MRD, kann nur durchgeführt werden, wenn Ihre Lymphomzellen/die Lymphomzellen Ihres Kindes einen geeigneten Marker aufweisen) bestimmt . Zusätzlich wird untersucht, ob spezifische Antikörper und Immun-Abwehrzellen gegen Lymphomzellen nachweisbar sind und welche Konzentration diese aufweisen.

Sie werden/Ihr Kind wird davon keinen direkten persönlichen Nutzen haben, da von keinem dieser Parameter bekannt ist, ob und welche Bedeutung er für Erfolg oder Misserfolg der Behandlung hat. Vielmehr soll in dieser Studie untersucht werden ob und wenn ja, welche Bedeutung ihnen für Erfolg oder Misserfolg der Behandlung der Behandlung zukommt. Bevor diesbezügliche Erkenntnisse gesichert vorliegen, sind Veränderungen der Therapieführung auf der Basis solcher Befunde nicht nur unwissenschaftlich, sondern können für den Patienten sogar eine Gefahr darstellen. Deshalb werden die Ergebnisse der Einzeluntersuchungen nicht mitgeteilt, sondern gesammelt ausgewertet werden. Die Ergebnisse dieser Untersuchung können jedoch für zukünftige Patienten möglicherweise von großer Bedeutung sein. Deshalb sind wir Ihnen sehr dankbar, wenn Sie/Ihr Kind einwilligen, für diese Untersuchungen Material (zusätzlich jeweils 10 ml Knochenmark und 15 ml Blut) zur Verfügung zu stellen. Die Entnahme dieses Knochenmarkbluts erfolgt bei einer Punktion, die für Sie/Ihr Kind ohnehin nötig wäre und

für die Steuerung der Therapie nach Blutstammzelltransplantation routinemäßig durchgeführt wird.

Eventuell ergeben sich entsprechend dem raschen wissenschaftlichen Fortschritt weitere wichtige Fragestellungen mit Bedeutung zum Wesen und zur besseren Behandlung Ihrer Erkrankung/der Erkrankung Ihres Kindes. Sofern Sie Ihr Einverständis geben, wird deshalb restliches Material, das für die vorgesehenen Untersuchungen nicht verbraucht wird, in dem zentralen Materialaufarbeitungs-Labor in der Studienzentrale in Gießen gelagert und für zukünftige wichtige Forschungsprojekte zur Verfügung gestellt. Sofern diese Untersuchungen an anderen als den oben angeführten Institutionen durchgeführt werden und zur sinnvollen Auswertung eine Verbindung mit weiteren Daten der Erkrankung, der Therapie und des Verlaufs sowie Daten zu Alter oder Geschlecht erfoderlich ist, werden diese ausschließlich in vollständig anonymisierter Form unter voller Beachtung der Vorschriften des Datenschutzes weitergegeben.

Abschließend möchten wir Sie bitten, der Teilnahme an dieser Studie zuzustimmen, und hierdurch einen wichtigen Beitrag zum Fortschritt im Kampf gegen Krebs zu leisten.

PATIENTENAUFKLÄRUNG

zur Therapiestudie ALCL-Relapse
Therapieprotokoll zur Behandlung rezidivierter großzellig anaplastischer Lymphome im Kindes- und Jugendalter; internationale Multicenter-Studie der Europäischen Studiengruppen-Kooperation zur Behandlung von NHL bei Kindern (EICNHL)

für die allogene Blutstammzelltransplantation von Spendern mit unterschiedlichen Gewebsmerkmalen bei Kindern und Jugendlichen mit Rückfall eines großzellig anaplastischen Lymphoms

Liebe Patienten, liebe Eltern,
Sie haben beim Beginn der Behandlung des Rückfalls Ihrer Erkrankung/der Erkrankung Ihres Kindes nach entsprechender Aufklärung eingewilligt, dass Sie/Ihr Kind im Rahmen der Therapiestudie ALCL-Relapse behandelt werden/wird. Auf Grund des Zeitpunktes des Auftretens des Rückfalls während der intensiven Phase der Erstbehandlung der Erkrankung gehört zu Ihrem Behandlungsplan/zum Behandlungsplan Ihres Kindes die Durchführung einer sogenannten allogenen Blutstammzelltransplantation. Über diesen speziellen Behandlungsteil werden Sie im Folgenden genauer informiert.

Einführung

Die allogene Stammzelltransplantation (SZT), d.h. die Übertragung von Knochenmark oder Ursprungszellen der Blutbildung (Blut-Stammzellen), die sich auch im fließenden Blut finden, dient der Behandlung Ihrer Erkrankung/der Erkrankung Ihres Kindes. Der Stammzell-übertragung voraus gehen eine intensive Medikamenten- und eventuell Strahlenbehandlung, die das Lymphom beseitigen und die körpereigene Abwehr unterdrücken sollen, damit die neuen Stammzellen nicht abgestoßen werden.

In der Therapiestudie ALCL-Relapse sind die Details der Spenderauswahl und der Behandlung während und nach der Transplantation festgelegt. Außer den unter „Begleituntersuchungen“ erwähnten zusätzlichen Maßnahmen, werden nur die für die Transplantation ohnehin notwendigen Maßnahmen durchgeführt.

Wissenschaftlicher Hintergrund

Die bisherigen Erfahrungen bei Kindern und Jugendlichen mit Rückfall eines großzellig anaplastischen Lymphoms haben gezeigt, dass die individuelle Heilungschance der Patienten bzw. das individuelle Risiko, dass die Krankheit nach einer Rückfallbehandlung erneut auftritt, sehr unterschiedlich ist. Patienten, die noch während der intensiven Phase der Erstbehandlung der Erkrankung einen Rückfall erleiden, haben am ehesten mit einer sogenannten allogenen Blutstammzelltransplantation, d.h. der Übertragung von gesunden Blut-Stammzellen aus dem Knochenmark von einem gewebsgleichen oder -ähnlichen Familienspender oder einem gut passenden unverwandten Spender, Chancen, von der Erkrankung geheilt zu werden. Allerdings waren bisher die Komplikationen nach einer SZT bei einem Spender mit nicht passenden Gewebsverträglichkeitsmerkmalen höher als nach einer Geschwistertransplantation oder der Transplantation von einem optimal passenden Fremdspender. Da bei Ihnen/Ihrem Kind der Rückfall des Lymphoms schon während der Erstbehandlung der Erkrankung eintrat, ist nach heutigem Kenntnisstand auch die Transplantation von einem Spender mit nicht passenden Gewebsverträglichkeitsmerkmalen die beste Chance, eine dauerhafte Heilung zu erreichen, da kein gewebsverträglicher Spender zur Verfügung steht.

Durchführung, Risiken und Nebenwirkungen der allogenen Stammzelltransplantation

Im folgenden werden die Durchführung der allogenen SZT und die möglicherweise auftretenden Komplikationen sowie eventuelle Spätfolgen beschrieben.

Ablauf der SZT und Komplikationen

Der Termin für die Blutstammzelltransplantation wird unter Berücksichtigung der notwendigen Lymphombehandlung (Re-Induktion), der Maßnahmen zur Gewinnung der Stammzellen und der notwendigen Therapie vor und während der Transplantation vereinbart. Manchmal kann es zu Verschiebungen der Termine kommen; in diesem Fall wird eventuell eine weitere Chemotherapie notwendig. In der Vorbereitungsphase zur Blutstammzelltransplantation werden verschiedene Blutuntersuchungen und andere diagnostische Maßnahmen durchgeführt. Eventuell wird zu diesem Zeitpunkt - falls nicht bereits erfolgt - auch ein Dauerverweilkatheter für Infusionen und Blutabnahmen implantiert. Die stationäre Aufnahme erfolgt spätestens zum Zeitpunkt der Konditionierung. Die Aufenthaltsdauer im Isolierzimmer richtet sich nach dem Anwachsen der Stammzellen und den Komplikationen, die sich nach der Transplantation eventuell ergeben.

Stammzellpräparation:

Vor der SZT erfolgt eine Auftrennung der gewonnen Spenderzellen, um eine schwere Transplant-gegen-Empfängerreaktion („Graft-versus-host-Disease"-GvHD) zu verhindern. Da in Ihrem Fall/im Fall Ihres Kindes kein gewebsverträglicher Spender gefunden werden konnte, ist diese Methode derzeit die erfolgversprechendste. Die Blut-Stammzellen des Spenders werden vor der SZT präpariert und in verschiedene Zellarten aufgetrennt („Selektion"). Diese Manipulation beseitigt nicht nur fast alle Abwehrzellen (Lymphozyten) des Spenders sondern auch rote Blutzellen und Plasma.

Konditionierung:

Zur Vorbereitung des Patienten zur SZT ist eine „Konditionierung" unumgänglich, damit die körpereigenen Abwehrmechanismen, die die neuen Stammzellen abstoßen könnten, unterdrückt werden. Die Konditionierung besteht in einer sogenannten Ganzkörperbestrahlung zusammen mit einer sehr intensiven Chemotherapie. Vor Durchführng der Ganzkörperbestrahlung werden Sie von einem Strahlentherpeut speziell über das Vorgehen und die Risiken bei dieser Behandlung informiert. Wenn der Spender nicht ein HLA-identisches Geschwisterkind ist, werden zusätzlich Antikörper gegen Immunzellen verabreicht. Mit dieser Behandlung werden auch eventuell noch vorhandene Lymphomzellen vernichtet oder zumindest reduziert. Die Therapie verursacht aber auch eine erhebliche Abwehrschwäche gegen alle Arten von Infektionen (Bakterien, Viren, Pilze, Parasiten). Diese Infektionen können manchmal unbeherrschbar sein und tödlich verlaufen.

Mit der Konditionierung können folgende Nebenwirkungen verbunden sein:

Übelkeit, Erbrechen, Mundschleimhautentzündung, Speicheldrüsenentzündung, Haarausfall, Einschränkung der Nierenfunktion, Leberveränderungen, Blasenentzündung, in seltenen Fällen auch akute Herz- und Lungenprobleme. Die körpereigene Produktion von roten Blutkörperchen (notwendig für den Sauerstofftransport) und von Blutplättchen (notwendig für die Blutgerinnung) wird unterbrochen; daher müssen diese Blutbestandteile über unterschiedlich lange Zeiträume in Form von Bluttransfusionen zugeführt werden. Trotzdem kann es in seltenen Fällen zu lebensbedrohlichen Organblutungen kommen.

Komplikationen der SZT:

Bei Infektionen oder langsamem Anwachsen der transplantierten Stammzellen kann es notwendig werden, Wachstumsfaktoren für Blutzellen einzusetzen, die diesen Vorgang beschleunigen.

Wenn die transplantierten Stammzellen nicht anwachsen (Ursachen hierfür können sein: Abstoßung, Infektionen, zu geringe Stammzellmengen), kann eine zweite SZT vom selben oder von einem anderen Spender notwendig werden.

Bedingt durch die notwendige Stammzellselektion kommt es zu einer sehr langsamen Erholung der Abwehrfunktion und hiermit besteht ein hohes Risiko für Infektionen mit Baketerien, Pilzen und vor allem Viren. Ebenso besteht die Gefahr, dass es in dieser Zeit zu einem Rückfall des Lymphoms kommt.

Nach erfolgreicher SZT ist das Abwehrsystem des Patienten noch längere Zeit beeinträchtigt und macht Vorsichts- und Isoliermaßnahmen für den Patienten auch nach der Entlassung aus der Transplantationseinheit notwendig.

Risiken und Nebenwirkungen der GvHD:
Wenn die Spenderzellen im Patienten angewachsen sind („Engraftment"), besteht die Möglichkeit, dass Spender-Abwehrzellen den Patienten als fremd erkennen, und es kann zu akuten und chronischen, manchmal lebensbedrohlichen Unverträglichkeitsreaktionen kommen („Graft versus Host Erkrankung"-GvHD). Sie betreffen vor allem Haut, Schleimhäute, Leber, Darm und eventuell die Lunge und äußern sich als akute und chronische Entzündungsreaktionen. Allerdings ist die Reaktion nach der Selektion des Transplantats selten zu erwarten. Zur Behandlung einer eventuell doch auftretenden GvHD werden verschiedene Medikamente gegeben, deren Auswahl von der Art des Spenders abhängt. Nebenwirkungen dieser Medikamente bestehen in akuten Unverträglichkeitsreaktionen (Fieber, Hautveränderungen, Blutdruckabfall), bei langdauernder Verabreichung können sie zu hohem Blutdruck, eingeschränkter Nieren- und Leberfunktion, verstärkter Körperbehaarung und Magenproblemen führen. Die Abwehr gegen Infektionskrankheiten ist herabgesetzt.
Prinzipiell ist jedoch eine leichte Form der GvHD (die manchmal keine Krankheitssymptome verursacht) nicht unbedingt gefährlich, da dieser Effekt zu einer besseren Abwehr von vielleicht noch vorhandenen Lymphomzellen führen kann („Graft versus Lymphom-Effekt" – GvL). Ein Graft versus Lymphom-Effekt kann jedoch auch ohne GvHD-Zeichen erfolgen. Zur Diagnose einer eventuell auftretenden GvHD muss unter Umständen eine Hautbiopsie durchgeführt werden.

Mögliche Spätfolgen einer SZT:
Zu den Spätfolgen nach SZT zählen die Komplikationen nach zytostatischer Chemotherapie und Strahlentherapie (z.B.: bleibende Unfruchtbarkeit, verzögertes Längenwachstum, Hormonminderproduktionen, Gefahr von zweiten Krebserkrankungen, Einschränkungen der Organfunktion), die chronische GvHD (Hautveränderungen, Lungenprobleme, Gelenksversteifung, Hornhauttrübung, Infektionen durch Abwehrschwäche), sowie Komplikationen durch Infektionen (virusbedingte Leberveränderungen, Lungenveränderungen, u.a.). Nach langdauernder Behandlung einer GvHD kann es zu verstärkter Knochenbrüchigkeit bzw. zu Hüftproblemen kommen.
Auch durch die allogene SZT ist ein Rückfall der Lymphomkrankheit nicht immer zu verhindern.

Schwangerschaft:
Vor Beginn der Konditionierung muss eine Schwangerschaft ausgeschlossen werden.

Alternative Therapie
Die prinzipielle Alternative zur einer SZT ist die Fortsetzung der Chemotherapie in der Form, wie sie bisher bei Ihnen/Ihrem Kind begonnen wurde. Die Analysen der letzten Jahre deuten allerdings darauf hin, dass die allogene SZT die Chance erhöht, dass kein weiterer Rückfall der Erkrankung auftritt. Diese Studie geht davon aus, dass die Nebenwirkungen der Transplantation geringer als in den letzten Jahren sein werden, da man ein einheitliches Konzept für die Spenderauswahl, Konditionierung und die Vorbeugung und Behandlung von Infektionen und GvHD verfolgt.

Datendokumentation und Vertraulichkeit
Zur Therapiestudie ALCL-Relapse gehört auch eine Dokumentation der erfolgten Therapie und der Nebenwirkungen. Darüber wurden Sie bereits bei Beginn Ihrer Behandlung informiert und Sie wurden um Einwilligung zur Weitergabe der Daten entsprechend den Bedingungen des Bundesdatenschutzgesetzes und nach den geltenden EU-Richtlinien an bestimmte Ihnen genannte Stellen gebeten.

Für die Blutstammzelltransplantation gibt es spezielle Register, national und international, in welche die Transplantationszentren aufgefordert sind, bestimmte Daten zur Durchführung und

zum Verlauf von Blutstammzelltransplantationen zu melden. Zum einen stellt dies ein Kontrollinstrument für die Qualität der Arbeit der Transplantationszentren dar. Zum anderen können anhand der großen Patientenzahlen in dem Register übergeordnete wissenschaftliche Fragestellungen untersucht werden, die für die Verbesserung der Wirksamkeit der Transplantation und der Sicherheit der Patienten von großer Bedeutung sind.

Klinische Untersuchungen werden entsprechend den Bedingungen des Bundesdatenschutzgesetzes und nach den geltenden EU-Richtlinien dokumentiert. Patientendaten werden streng vertraulich behandelt und ohne Angabe der Patientennamen anonymisiert an Register innerhalb des Landes, aber auch an übergeordnete Register (European Group for Blood and Marrow Transplantation und International Bone Marrow Transplant Registry) weitergegeben und ausgewertet.
Zur Kontrolle der Prüfergebnisse kann ein Vergleich der Krankheitsdaten erforderlich werden. Zu diesem Zwecke ist es notwendig, dass zur Verschwiegenheit verpflichtete Mitarbeiter von Behörden oder andere autorisierte Personen Einblick in die Patientenunterlagen nehmen können. Von Ihnen/Ihrem Kind sollen personenbezogene (Name, Geburtsdatum, Wohnort) und medizinische Daten (Diagnose mit Befunderhebung, Labordaten usw.) gespeichert bzw. an folgende Zentren übermittelt werden:

- Studienzentrale NHL-BFM; Studienleiter: Prof. Dr. A. Reiter; Universitätsklinikum Gießen; Universitäts-Kinderklinik; Pädiatrische Hämatologie und Onkologie; Feulgenstr. 12; 35385 Gießen
- Pädiatrisches Register für Stammzell-Transplantationen: Prof. Dr. T. Klingebiel, Klinik für Kinderheilkunde III, Goethe Universität Frankfurt a. Main; Theodor Stern Kai 7, 60590 Frankfurt
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Notfalladresse und Leiter der Therapiestudie
Der verantwortliche Leiter dieser Studie ist Herr Prof. A. Reiter, Zentrum für Kinderheilkunde und Jugendmedizin, Abteilung Hämatologie und Onkologie, Universitätsklinikum Gießen, Feulgenstr. 12, 35385 Gießen.
Verantwortlich für Ihre/die Betreuung Ihres Kindes ist die/der Leiter/in Ihres Transplantationszentrums. Sie sollten Ihr/Ihm alle auftretenden Komplikationen und Probleme sofort mitteilen. Während der Behandlung auftretende Fragen sollten Sie mit Ihrem behandelnden Arzt klären.

Begleituntersuchungen
Bereits bei der Aufklärung bei Beginn Ihrer Behandlung/der Behandlung Ihres Kindes wurden Sie über die begleitenden Forschungsprojekte, die im Rahmen dieser Studie durchgeführt werden, informiert. Da möglicherweise die Klinik, in der die Blutstammzelltransplantation durchgeführt wird, nicht mit Ihrer primär behandelnden Klinik übereinstimmt, werden Sie hier noch einmal über diese Untersuchungen informiert, die auch speziell im Rahmen der Blutstammzelltransplantation durchgeführt werden.
Um neue Erkenntnisse zur weiteren Verbesserung der Behandlung von Patienten mit Rückfall eines großzellig anaplastischen Lymphoms in der Zukunft zu erlangen, werden mehrere begleitende Untersuchungen und Forschungsprojekte im Zusammenhang mit der Therapieoptimierungsstudie ALCL-Relapse durchgeführt. Zu festgelegten Zeitpunkten bitten wir Sie/Ihr Kind, an den Tagen der vorgeschriebenen Kontroll-Knochenmarkpunktionen (vor Transplantation, Tag +28/+60/+100, 6 Monate und 1 Jahr nach Blutstammzelltransplantation) Blut und Knochenmark zur Verfügung zu stellen. Es wird daraus das Verhältnis von Spender- und Empfängerzellen im Blut und Knochenmark („Chimärismus“) untersucht und die

Konzentration eventuell noch vorhandener restlicher Lymphomzellen (minimale Resterkrankung oder MRD, dies kann nur durchgeführt werden, wenn Ihre Lymphomzellen/die Lymphomzellen Ihres Kindes einen geeigneten Marker aufweisen) bestimmt . Zusätzlich wird untersucht, ob spezifische Antikörper und Immun-Abwehrzellen gegen Lymphomzellen nachweisbar sind und welche Konzentration diese aufweisen.

Sie werden/Ihr Kind wird davon keinen direkten persönlichen Nutzen haben, da von keinem dieser Parameter bekannt ist, ob und welche Bedeutung er für Erfolg oder Misserfolg der Behandlung hat. Vielmehr soll in dieser Studie untersucht werden ob und wenn ja, welche Bedeutung ihnen für Erfolg oder Misserfolg der Behandlung zukommt. Bevor diesbezügliche Erkenntnisse gesichert vorliegen, sind Veränderungen der Therapieführung auf der Basis solcher Befunde nicht nur unwissenschaftlich, sondern können für den Patienten sogar eine Gefahr darstellen. Deshalb werden die Ergebnisse der Einzeluntersuchungen nicht mitgeteilt, sondern gesammelt ausgewertet werden. Die Ergebnisse dieser Untersuchung können jedoch für zukünftige Patienten möglicherweise von großer Bedeutung sein. Deshalb sind wir Ihnen sehr dankbar, wenn Sie/Ihr Kind einwilligen, für diese Untersuchungen Material (zusätzlich jeweils 10 ml Knochenmark und 15 ml Blut) zur Verfügung zu stellen. Die Entnahme dieses Knochenmarkbluts erfolgt bei einer Punktion, die für Sie/Ihr Kind ohnehin nötig wäre und für die Steuerung der Therapie nach Blutstammzelltransplantation routinemäßig durchgeführt wird.

Eventuell ergeben sich entsprechend dem raschen wissenschaftlichen Fortschritt weitere wichtige Fragestellungen mit Bedeutung zum Wesen und zur besseren Behandlung Ihrer Erkrankung/der Erkrankung Ihres Kindes. Sofern Sie Ihr Einverständis geben, wird deshalb restliches Material, das für die vorgesehenen Untersuchungen nicht verbraucht wird, in dem zentralen Materialaufarbeitungs-Labor in der Studienzentrale in Gießen gelagert und für zukünftige wichtige Forschungsprojekte zur Verfügung gestellt. Sofern diese Untersuchungen an anderen als den oben angeführten Institutionen durchgeführt werden und zur sinnvollen Auswertung eine Verbindung mit weiteren Daten der Erkrankung, der Therapie und des Verlaufs sowie Daten zu Alter oder Geschlecht erfoderlich ist, werden diese ausschließlich in vollständig anonymisierter Form unter voller Beachtung der Vorschriften des Datenschutzes weitergegeben.

Abschließend möchten wir Sie bitten, der Teilnahme an dieser Studie zuzustimmen, und hierdurch einen wichtigen Beitrag zum Fortschritt im Kampf gegen Krebs zu leisten.

Einwilligungserklärung zur allogenen Blutstammzelltransplantation im Rahmen der Therapiestudie ALCL-Relapse

Therapieprotokoll zur Behandlung rezidivierter großzellig anaplastischer Lymphome im Kindes- und Jugendalter; internationale Multicenter-Studie der Europäischen Studiengruppen-Kooperation zur Behandlung von NHL bei Kindern (EICNHL)

Name des Patienten: _____

Geburtsdatum: _____

Ich bin/wir sind durch den/die behandelnde/n Arzt/Ärztin_____

am _____ über Diagnose und Verlauf meiner Erkrankung/der Erkrankung unseres Kindes, ferner über Wesen, Bedeutung und Tragweite der Blutstammzelltransplantation aufgeklärt und eingehend über die bekannten und zu erwartenden Wirkungen (Wirksamkeit), Nebenwirkungen sowie Risiken informiert worden. Mir/Uns wurde genügend Zeit für eine Entscheidung über die Teilnahme an der Blutstammzelltransplantation im Rahmen der Therapieoptimierungsstudie eingeräumt.

☐ Mit der Durchführung einer allogenen Blutstamzelltransplantation und der dafür erforderlichen Chemotherapie und ggf. Ganzkörperbestrahlung bei mir/bei unserem Kind erkläre/n ich/wir mich/uns einverstanden. Ich/wir behalte/n mir/uns jedoch vor, jederzeit ohne Angabe von Gründen und ohne dass mir/unserem Kind daraus Nachteile entstehen, aus der Therapiestudie ALCL-Relapse auszuscheiden. Ich bin/wir sind uns jedoch bewusst, dass nach Beginn der Konditionierung zur Blutstammzeltransplantation diese anschließend vollständig zu Ende geführt werden muß.

☐ Ich/wir bin/sind damit einverstanden, dass Knochenmarkblut und peripheres Blut für Untersuchungszwecke in den autorisierten Stellen tiefgefroren gelagert wird.

Klinische Untersuchungen werden entsprechend den Bedingungen des Bundesdatenschutzgesetzes und der geltenden EU-Richtlinien dokumentiert. Patientendaten werden streng vertraulich behandelt und ohne Angabe eines Namens/des Namens unseres Kindes weitergegeben und ausgewertet. Zur Kontrolle der Prüfergebnisse kann ein Vergleich der Krankheitsdaten erforderlich werden.

☐ Zu diesem Zwecke willige ich ein, dass zur Verschwiegenheit verpflichtete Mitarbeiter von Behörden oder andere autorisierte Personen Einblick in meine Patientenunterlagen nehmen können.

Darüber hinaus erkläre/n ich/wir uns damit einverstanden, dass von mir/meinem Kind personenbezogene (Name, Geburtsdatum, Wohnort) und medizinische Daten (Diagnose mit Befunderhebung, Labordaten usw.) gespeichert bzw. an folgende Zentren

☐ NHL-BFM-Studienzentrale, Gießen
☐ Pädiatrisches Stammzelltransplantationsregister, Frankfurt
☐ Onkogenetisches Labor, Gießen
☐ Labor zur Untersuchung der Immunantwort, Oxford

übermittelt werden und entbinde die behandelnden Ärzte zu diesem Zweck von der Schweigepflicht. Eine Kopie der Patienteninformation und dieser Einverständniserklärung wurde mir/uns übergeben.

_____	_____
Ort, Datum	Patientenunterschrift
_____	_____
Ort, Datum	Unterschrift der sorgeberechtigten Personen

Ich bestätige, dass ich obengenannten Patienten/die Sorgeberechtigten, der/die sein/Ihr Einverständnis für die Teilnahme gegeben hat/haben, bezüglich Zweck, Nutzen, Art und Risiken der Studie aufgeklärt habe.

_____	_____	_____
Ort, Datum	Name des/der behandelnden Arztes/Ärztin Tel.	Unterschrift des/der Arztes/Ärztin

PATIENTENAUFKLÄRUNG

zur Therapiestudie ALCL-Relapse
Therapieprotokoll zur Behandlung rezidivierter großzellig anaplastischer Lymphome im Kindes- und Jugendalter; internationale Multicenter-Studie der Europäischen Studiengruppen-Kooperation zur Behandlung von NHL bei Kindern (EICNHL)

für die autologe Blutstammzelltransplantation bei Kindern und Jugendlichen mit Rückfall eines großzellig anaplastischen Lymphoms

Liebe Patienten, liebe Eltern,
Sie haben beim Beginn der Behandlung des Rückfalls Ihrer Erkrankung/der Erkrankung Ihres Kindes nach entsprechender Aufklärung eingewilligt, dass Sie/Ihr Kind im Rahmen der Therapiestudie ALCL-Relapse behandelt werden/wird. Auf Grund des Zeitpunktes des Auftretens des Rückfalls gehört zu Ihrem Behandlungsplan/zum Behandlungsplan Ihres Kindes die Durchführung einer sogenannten autologen Blutstammzelltransplantation. Über diesen speziellen Behandlungsteil werden Sie im Folgenden genauer informiert.

Einführung

Nach heutigem Wissenstand kann mit einer sehr intensiven Chemotherapie bei vielen Patienten das Wiederauftreten der Erkrankung verhindert werden. Dabei kann es aber zu einer irreversiblen Schädigung des Knochenmarkes kommen. Deshalb werden vor dieser Chemotherapie Blutstammzellen aus dem Blut oder Knochenmark des Patienten entnommen, gelagert und nach der Behandlung des Patienten wieder als Infusion zurückgegeben. Dadurch kann sich die Blutbildung im Knochenmark neu aufbauen.
Außer den unter „Begleituntersuchungen“ erwähnten zusätzlichen Maßnahmen, werden nur die für die Transplantation ohnehin notwendigen Maßnahmen durchgeführt.

Wissenschaftlicher Hintergrund

Die bisherigen Erfahrungen bei Kindern und Jugendlichen mit Rückfall eines großzellig anaplastischen Lymphoms haben gezeigt, dass die individuelle Heilungschance der Patienten bzw. das individuelle Risiko, dass die Krankheit nach einer Rückfallbehandlung erneut auftritt, sehr unterschiedlich ist. Erste Beobachtungen deuten darauf hin, dass Patienten, deren Lymphomzellen ein spezielles immunologisches Merkmal, das CD3 Antigen nicht tragen und die innerhalb von 12 Monaten nach Beginn der Erstbehandlung einen Rückfall des Lymphomes erlitten haben, mit einer intensiven Chemotherapie gefolgt von einer sogenannten autologen Blutstammzelltransplantation, d.h. der Rück-Übertragung eigener, vorher gewonnener Blut-Stammzellen bessere Chancen haben, von der Erkrankung geheilt zu werden.
Es gibt Hinweise, dass für Patienten, deren Lymphomzellen das CD3 Antigen tragen, die allogene Blutstammzelltransplantation mit der Übertragung von Blutstammzellen eines Familien- oder Fremdspenders, die optimale Behandlung darstellt. Falls jedoch kein sehr gut passender Familien- oder Fremdspender zur Verfügung stehen sollte, stellt die Blutstammzelltransplantation mit einem nicht optimalen Spender ein höheres Risiko dar. Dieses erhöhte Risiko sollte den Patienten primär nicht zugemutet werden, da in diesem Fall die autologe Blutstammzelltransplantation, d.h. die Rück-Übertragung eigener, vorher gewonnener Blut-Stammzellen nach intensiver Chemotherapie eine aussichtsreiche Therapiemöglichkeit darstellt. Dieses Vorgehen wird von Beobachtungen gestützt, dass die Patienten im Falle eines erneuten Rückfalls nach autologer Blutstammzelltransplantation noch einer allogenen Blutstammzelltransplantation zugeführt werden könnten.

Durchführung, Risiken und Nebenwirkungen der allogenen Stammzelltransplantation

Im folgenden werden die Durchführung der allogenen SZT und die möglicherweise auftretenden Komplikationen sowie eventuelle Spätfolgen beschrieben.

Ablauf der SZT und Komplikationen

Der Termin für die Blutstammzelltransplantation wird unter Berücksichtigung der notwendigen Lymphombehandlung (Re-Induktion), der Maßnahmen zur Gewinnung der Stammzellen und der notwendigen Therapie vor und während der Transplantation vereinbart. Manchmal kann es zu Verschiebungen der Termine kommen; in diesem Fall wird eventuell eine weitere Chemotherapie notwendig. In der Vorbereitungsphase zur Blutstammzelltransplantation werden verschiedene Blutuntersuchungen und andere diagnostische Maßnahmen durchgeführt. Eventuell wird zu diesem Zeitpunkt - falls nicht bereits erfolgt - auch ein Dauerverweilkatheter für Infusionen und Blutabnahmen implantiert. Die stationäre Aufnahme erfolgt spätestens zum Zeitpunkt der Konditionierung. Die Aufenthaltsdauer im Isolierzimmer richtet sich nach dem Anwachsen der Stammzellen und den Komplikationen, die sich nach der Transplantation eventuell ergeben.

Gewinnung und Lagerung der autologen Blutstammzellen

Zur Gewinnung der Blutstammzellen erhalten Sie/Ihr Kind jeweils im Anschluss an die Chemotherapiekurse der Re-Induktion einen Wachstumsfaktor, der das Wachstum von Blutstammzellen im Knochenmark und die Ausschwemmung dieser Zellen ins Blut fördert. Wenn eine gewisse Zahl an Blutstammzellen im Blut nachgewiesen werden kann, werden die Stammzellen entweder aus dem Blut gesammelt oder durch die Punktion von Knochenmark gewonnen.

Chemotherapie

Zunächst erfolgt eine sehr intensive Chemotherapie mit dem Ziel, alle noch vorhandenen Lymphomzellen abzutöten. Im Anschluß daran erfolgt die Rückgabe der autologen Stammzellen. Mit der Chemotherapie können folgende Nebenwirkungen verbunden sein:
Übelkeit, Erbrechen, Mundschleimhautentzündung, Speicheldrüsenentzündung, Haarausfall, Einschränkung der Nierenfunktion, Leberveränderungen, Blasenentzündung, in seltenen Fällen auch akute Herz- und Lungenprobleme. Die körpereigene Produktion von roten Blutkörperchen (notwendig für den Sauerstofftransport) und von Blutplättchen (notwendig für die Blutgerinnung) wird unterbrochen; daher müssen diese Blutbestandteile über unterschiedlich lange Zeiträume in Form von Bluttransfusionen zugeführt werden. Trotzdem kann es in seltenen Fällen zu lebensbedrohlichen Organblutungen kommen. Die Therapie verursacht aber auch eine erhebliche Abwehrschwäche gegen alle Arten von Infektionen (Bakterien, Viren, Pilze, Parasiten). Diese Infektionen können in seltenen Fällen unbeherrschbar sein und tödlich verlaufen.

Komplikationen der SZT:

Bei Infektionen oder langsamem Anwachsen der transplantierten Stammzellen kann es notwendig werden, Wachstumsfaktoren für Blutzellen einzusetzen, die diesen Vorgang beschleunigen.
Nach erfolgreicher SZT ist das Abwehrsystem des Patienten noch längere Zeit beeinträchtigt und macht Vorsichts- und Isoliermaßnahmen für den Patienten auch nach der Entlassung aus der Transplantationseinheit notwendig.

Mögliche Spätfolgen einer SZT:

Zu den Spätfolgen nach SZT zählen die Komplikationen nach zytostatischer Chemotherapie (z.B.: bleibende Unfruchtbarkeit, verzögertes Längenwachstum, Hormonminderproduktionen, Gefahr von zweiten Krebserkrankungen, Einschränkungen der Organfunktion), sowie Komplikationen durch Infektionen (virusbedingte Leberveränderungen, Lungenveränderungen, u.a.).
Auch durch die autologe SZT ist ein Rückfall der Lymphomkrankheit nicht immer zu verhindern.

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Vor Beginn der Konditionierung muss eine Schwangerschaft ausgeschlossen werden.

Alternative Therapie
Die prinzipielle Alternative zur einer SZT ist die Fortsetzung der Chemotherapie in der Form, wie sie bisher bei Ihnen/Ihrem Kind begonnen wurde. Die Analysen der letzten Jahre deuten allerdings darauf hin, dass die autologe SZT die Chance erhöht, dass kein weiterer Rückfall der Erkrankung auftritt.

Datendokumentation und Vertraulichkeit
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Notfalladresse und Leiter der Therapiestudie
Der verantwortliche Leiter dieser Studie ist Herr Prof. A. Reiter, Zentrum für Kinderheilkunde und Jugendmedizin, Abteilung Hämatologie und Onkologie, Universitätsklinikum Gießen, Feulgenstr. 12, 35385 Gießen.
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Begleituntersuchungen

Bereits bei der Aufklärung bei Beginn Ihrer Behandlung/der Behandlung Ihres Kindes wurden Sie über die begleitenden Forschungsprojekte, die im Rahmen dieser Studie durchgeführt werden informiert. Da möglicherweise die Klinik in der die Blutstammzeltransplantation durchgeführt wird, nicht mit Ihrer primär behandelnden Klinik übereinstimmt, werden Sie hier noch einmal über diese Untersuchungen informiert, die auch speziell im Rahmen der Blutstammzelltransplantation durchgeführt werden.

Um neue Erkenntnisse zur weiteren Verbesserung der Behandlung von Patienten mit Rückfall eines großzellig anaplastischen Lymphoms in der Zukunft zu erlangen, werden mehrere begleitende Untersuchungen und Forschungsprojekte im Zusammenhang mit der Therapieoptimierungsstudie ALCL-Relapse durchgeführt. Zu festgelegten Zeitpunkten bitten wir Sie/Ihr Kind, an den Tagen der vorgeschriebenen Kontroll-Knochenmarkpunktionen (vor Transplantation, Tag +28/+60/+100, 6 Monate und 1 Jahr nach Blutstammzelltransplantation) Blut und Knochenmark zur Verfügung zu stellen. Es wird damit die Konzentration eventuell noch vorhandener restlicher Lymphomzellen (minimale Resterkrankung oder MRD, dies kann nur durchgeführt werden, wenn Ihre Lymphomzellen/die Lymphomzellen Ihres Kindes einen geeigneten Marker aufweisen) bestimmt und untersucht, ob spezifische Antikörper und Immun-Abwehrzellen gegen Lymphomzellen nachweisbar sind und in welcher Konzentration.

Sie werden/Ihr Kind wird davon keinen direkten persönlichen Nutzen haben, da von keinem dieser Parameter bekannt ist, ob und welche Bedeutung er für Erfolg oder Misserfolg der Behandlung hat. Vielmehr soll in dieser Studie untersucht werden ob und wenn ja, welche Bedeutung ihnen für Erfolg oder Misserfolg der Behandlung zukommt. Bevor diesbezügliche Erkenntnisse gesichert vorliegen, sind Veränderungen der Therapieführung auf der Basis solcher Befunde nicht nur unwissenschaftlich, sondern können für den Patienten sogar eine Gefahr darstellen. Deshalb werden die Ergebnisse der Einzeluntersuchungen nicht mitgeteilt, sondern gesammelt ausgewertet werden. Die Ergebnisse dieser Untersuchung können jedoch für zukünftige Patienten möglicherweise von großer Bedeutung sein. Deshalb sind wir Ihnen sehr dankbar, wenn Sie/Ihr Kind einwilligen, für diese Untersuchungen Material (zusätzlich jeweils 10 ml Knochenmark und 15 ml Blut) zur Verfügung zu stellen. Die Entnahme dieses Knochenmarkbluts erfolgt bei einer Punktion, die für Sie/Ihr Kind ohnehin erfolgen würde und für die Steuerung der Therapie nach Blutstammzelltransplantation routinemäßig erfolgt.

Eventuell ergeben sich entsprechend dem raschen wissenschaftlichen Fortschritt weitere wichtige Fragestellungen mit Bedeutung zum Wesen und zur besseren Behandlung Ihrer Erkrankung/der Erkrankung Ihres Kindes. Sofern Sie Ihr Einverständis geben, wird deshalb restliches Material, das für die vorgesehenen Untersuchungen nicht verbraucht wird, in dem zentralen Materialaufarbeitungs-Labor in der Studienzentrale in Gießen gelagert und für zukünftige wichtige Forschungsprojekte zur Verfügung gestellt. Sofern diese Untersuchungen an anderen als den oben angeführten Institutionen durchgeführt werden und zur sinnvollen Auswertung eine Verbindung mit weiteren Daten der Erkrankung, der Therapie und des Verlaufs sowie Daten zu Alter, Geschlecht erfoderlich ist, werden diese ausschließlich in vollständig anonymisierter Form unter voller Beachtung der Vorschriften des Datenschutzes weitergegeben.

Abschließend möchten wir Sie bitten, der Teilnahme an dieser Studie zuzustimmen, und hierdurch einen wichtigen Beitrag zum Fortschritt im Kampf gegen Krebs zu leisten.

Einwilligungserklärung zur autologen Blutstammzelltransplantation im Rahmen der Therapiestudie ALCL-Relapse

Therapieprotokoll zur Behandlung rezidivierter großzellig anaplastischer Lymphome im Kindes- und Jugendalter; internationale Multicenter-Studie der Europäischen Studiengruppen-Kooperation zur Behandlung von NHL bei Kindern (EICNHL)

Name des Patienten: _____

Geburtsdatum: _____

Ich bin/wir sind durch den/die behandelnde/n Arzt/Ärztin_____

am _____ über Diagnose und Verlauf meiner Erkrankung/der Erkrankung unseres Kindes, ferner über Wesen, Bedeutung und Tragweite der autologen Blutstammzelltransplantation aufgeklärt und eingehend über die bekannten und zu erwartenden Wirkungen (Wirksamkeit), Nebenwirkungen sowie Risiken informiert worden. Mir/Uns wurde genügend Zeit für eine Entscheidung über die Teilnahme an der Blutstammzelltransplantation im Rahmen der Therapieoptimierungsstudie eingeräumt.

☐ Mit der Durchführung einer autologen Blutstamzelltransplantation und der dafür erforderlichen Chemotherapie bei mir/bei unserem Kind erkläre/n ich/wir mich/uns einverstanden. Ich/wir behalte/n mir/uns jedoch vor, jederzeit ohne Angabe von Gründen und ohne dass mir/unserem Kind daraus Nachteile entstehen, aus der Therapiestudie ALCL-Relapse auszuscheiden. Ich/wir sind uns jedoch bewusst, dass nach Beginn der Konditionierung zur Blutstammzelltransplantation, diese vollständig zu Ende geführt werden muss.

☐ Ich/wir bin/sind damit einverstanden, dass Knochenmarkblut und peripheres Blut für Untersuchungszwecke in den autorisierten Stellen tiefgefroren gelagert wird.

Klinische Untersuchungen werden entsprechend den Bedingungen des Bundesdatenschutzgesetzes und der geltenden EU-Richtlinien dokumentiert. Patientendaten werden streng vertraulich behandelt und ohne Angabe eines Namens/des Namens unseres Kindes weitergegeben und ausgewertet. Zur Kontrolle der Prüfergebnisse kann ein Vergleich der Krankheitsdaten erforderlich werden.

☐ Zu diesem Zwecke willige ich ein, dass zur Verschwiegenheit verpflichtete Mitarbeiter von Behörden oder andere autorisierte Personen Einblick in meine Patientenunterlagen nehmen können.

Darüber hinaus erkläre/n ich/wir uns damit einverstanden, dass von mir/meinem Kind personenbezogene (Name, Geburtsdatum, Wohnort) und medizinische Daten (Diagnose mit Befunderhebung, Labordaten usw.) gespeichert bzw. an folgende Zentren

☐ NHL-BFM-Studienzentrale, Gießen
☐ Pädiatrisches Stammzelltransplantationsregister, Frankfurt
☐ Onkogenetisches Labor, Gießen
☐ Labor zur Untersuchung der Immunantwort, Oxford

übermittelt werden und entbinde die behandelnden Ärzte zu diesem Zweck von der Schweigepflicht. Eine Kopie der Patienteninformation und dieser Einverständniserklärung wurde mir/uns übergeben.

_____	_____
Ort, Datum	Patientenunterschrift
_____	_____
Ort, Datum	Unterschrift der sorgeberechtigten Personen

Ich bestätige, dass ich obengenannten Patienten/die Sorgeberechtigten, der/die sein/Ihr Einverständnis für die Teilnahme gegeben hat/haben, bezüglich Zweck, Nutzen, Art und Risiken der Studie aufgeklärt habe.

_____	_____	_____
Ort, Datum	Name des/der behandelnden Arztes/Ärztin Tel.	Unterschrift des/der Arztes/Ärztin

18.6 Documentation forms

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Documentation overview

(for use in the treating centre)

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__| (if known)

form	**time point**	**sent** (from the hospital to the national data centre)	**date** (dd/mm/yy)
In general			
Registration	after diagnosis of relapse	☐	
Diagnosis of Relapse		☐	
Sc-donor selection *(only for patients with relapse during frontline treatment or CD3 initially positive)*	during Re-induction chemotherapy	☐	
Announcement of SCT *(if SCT is planned)*		☐	
• **Treatment documentation** • **Acute Toxicity and Adverse Event during / after reinduction** *(if reinduction treatment was done)*	after end of reinduction	☐	
Treatment documentation: VBL for 24 months *(if VBL treatment was done)*	every 12 weeks	☐	
Histopathological and Immunohistochemical Review *(to be filled in by the reference pathology centre)*	as soon as possible	☐	
Genetics *(if done)*	as soon as possible	☐	
• **Allograft** • **Autograft**	day +100	☐	
• **Follow up – SCT** • **Follow up – VBL**	• 1, 2, 3, 4 etc years after SCT (or if patient died) • 1, 2, 3, 4 etc years after diagnosis of relapse	☐	
If necessary			
SAE form	within 48 h after occurence	☐	
Event form	within 14 days after occurence	☐	

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Therapy Study ALCL-Relapse

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Registration

All patients who fulfil the registration criteria are registered in the study, regardless whether they are eligible for trial's result evaluation. The registration fax must be sent to the responsible data centre within 14 days.

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) sex: ❑ male ❑ female
(age < 22 years)

Please note: before sending this form to the responsible data centre, the informed consent for data exchange, digital data storage and data processing must be signed by patient / guardian(s)

Eligibility to the study

- Progression or relapse of an anaplastic large cell lymphoma diagnosed by histomorphological and/or cytomorphological characterisation? ❑ no ❑ yes
- Slides of relapsed lymphoma available for national/international pathological and/or cytomorphological review? ❑ no ❑ yes
- Signed informed consent for participation in the study ALCL-Relapse? ❑ no ❑ yes
- For female patients: No evidence for pregnancy or lactation period and assured contraception? ❑ no ❑ yes
- Simultaneous participation in another clinical study? ❑ no ❑ yes
  If "yes": which clinical study _____

Evaluable for trial's results?

- 1st relapse of ALCL? ❑ no ❑ yes
  if no, (subsequent relapse of ALCL) Number of relapse |__|
- significant pre-treatment for first relapse? ❑ no ❑ yes
- adequate hepatic, renal and cardiac function? ❑ no ❑ yes
- HIV infection or AIDS? ❑ no ❑ yes
- severe immunodeficiency? ❑ no ❑ yes
  if "yes": specify: _____
- previous organ transplantation? ❑ no ❑ yes
  if "yes": specify: _____
- Previous malignancy prior to the ALCL? ❑ no ❑ yes
  if "yes": specify: _____
- Other pre-existing disease prohibiting therapy as per instruction of the protocol? ❑ no ❑ yes
  if "yes": specify: _____
- pre-condition prohibiting the conditioning regimen as per instruction of the protocol (see page 43)? ❑ no ❑ yes
  if "yes": specify: _____

Study Group: _____ Treating centre: _____

Responsible physician: _____

Phone:_____ Fax: _____

_____	_____	_____	_____
Hospital-Stamp	Date (dd mm yy)	Name (in block letters) responsible physician	Signature

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Diagnosis of Relapse (page 1/3).

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__|

Please note: before sending this form to the responsible data centre, the informed consent for data exchange, digital data storage and data processing must be signed by patient / guardian(s)

General condition at diagnosis of relapse:

Score	Karnofsky Description (patients older than 16 years)	Lansky Description (Patients younger than 16 years)
100%	normal, no complaints, no evidence of disease.	Fully active, normal.
90%	Able to carry on normal activity; minor signs or symptoms of disease.	Minor restrictions in physically strenuous activity.
80%	normal activity with effort; some signs or symptoms of disease.	Active, but tires more quickly.
70%	Cares for self, unable to carry on normal activity or do active work.	Both greater restriction of and less time spent in play activity.
60%	Requires occasional assistance, but is able to care for most of his/her needs	Up and around, but minimal active play, keeps busy with quieter activities.
50%	Requires considerable assistance and frequent medical care.	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
40%	Disabled, requires special care and assistance.	Mostly in bed; participates in quiet activities.
30%	Severely disabled, hospitalisation indicated. Death not imminent.	In bed; needs assistance even for quiet play.
20%	Very sick, hospitalisation indicated. Death not imminent.	Often sleeping; play entirely limited to very passive activities.
10%	Moribund, fatal processes progressing rapidly.	no play; does not get out of bed.

General signs:

	no	yes
loss in weight (> 10% in last 6 months)	❑	❑
fever (> 38°C for at least 7 days)	❑	❑
night sweat	❑	❑

Diagnosis of relapse: Number of relapse ❑ 1st ❑ 2nd ❑ 3rd ❑ 4th |__| th relapse

- by puncture: ❑ no ❑ yes:

	no	yes
bone marrow	❑	❑
ascites	❑	❑
pleural effusion	❑	❑
pericardial effusion	❑	❑

- by surgery: ❑ no ❑ yes: ❑ fine-needle biopsy ❑ biopsy ❑ (partial-) resection

Date of diagnostic surgery / puncture: |__|__|.|__|__|.|__|__| (dd mm yy)

Diagnostic before start of therapy:

Blood: WBC (x 10^9/l): |__|__|.|__| platelets (x 10^9/l): |__|__|__| Hb (g/l): |__|__|__|
lymphoma-cells (%): |__|__|__|

Lymphoma-cells in bone marrow aspirates (%): |__|__|__| ❑ not done

CSF: nucleated cells /µl CSF: |__|__|__|__|__|
erythrocytes /µl CSF: |__|__|__|__|__|
lymphoma-cells /µl CSF |__|__|__|__|__|

LDH:

Measuring unit of LDH: ❑ U/L
❑ µmol/sl ⇒ translation in U/L with ❑ x 30 ❑ x 60
❑ other measuring unit: _____ ⇒ translation in U/L with: _____

Maximum increase of LDH before start of therapy: |__|__| |__|__|__|,|__|__|
local laboratory: upper normal limit according to age: |__|__| |__|__|__|,|__|__|

Version: April 2004

Therapy Study ALCL-Relapse

Diagnosis of Relapse (page 2/3).

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__|__| (if known)

Monitoring of Minimal Residual Disease (MRD)

Cytogenetic or MRD marker available from frontline therapy: ❑ not done ❑ no
❑ yes, state which and please enclose copy of each diagnostic finding:

marker: |_____| laboratory: |_____|

Local diagnosis / on-site findings:

- local Histology: *(Please send a copy of the report to the responsible data centre!)*
  ❑ relapse of ALCL ❑ CD3 positive ❑ CD3 negative
  ❑ other diagnosis: _____
  ❑ not done
- local Cytomorphology: *(Please send a copy of the report to the responsible data centre!)*
  ❑ relapse of ALCL
  ❑ other diagnosis: _____
  ❑ not done

Reference diagnosis of relapsed ALCL:

- Reference histology initiated: ❑ no ❑ yes, at: _____
  (Please send a copy of the report to the responsible data centre!)
- Reference cytomorphology initiated: ❑ no ❑ yes, at: _____
  result: ❑ relapse of ALCL ❑ other: _____ _____
  (Please send a copy of the report to the responsible data centre!)

Manifestations of relapsed ALCL	clinical examination			ultrasound			x-ray			CT / MRI			PET (optional)			histology / morphology		
	Please tick the appropriate box for each examination and for each localisation, even if examination was not carried out or if there were no pathological findings!																	
	not tested	-	+	not tested	-	+	not tested	-	+	not tested	-	+	not tested	-	+	not tested	-	+
BONE MARROW																❑	❑	❑
CNS																		
CNS: tumour intra-cerebral	❑	❑	❑							❑	❑	❑	❑	❑	❑	❑	❑	❑
intra- medullary	❑	❑	❑							❑	❑	❑	❑	❑	❑	❑	❑	❑
CNS: cerebral nerve palsy	❑	❑	❑															
CNS: lymphoma-cells in CSF																❑	❑	❑
PERIPHERAL LYMPH NODES (LN)																		
LN cervical, submandibular, nuchal	❑	❑	❑	❑	❑	❑				❑	❑	❑	❑	❑	❑	❑	❑	❑
LN supra- / infraclavicular / axillary	❑	❑	❑	❑	❑	❑				❑	❑	❑	❑	❑	❑	❑	❑	❑
LN inguinal	❑	❑	❑	❑	❑	❑				❑	❑	❑	❑	❑	❑	❑	❑	❑
other peripheral LN	❑	❑	❑	❑	❑	❑				❑	❑	❑	❑	❑	❑	❑	❑	❑
HEAD AND NECK																		
area of ear, nose and throat (ENT)	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
other manifestation(s) of head and neck	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
THORAX																		
mediastinum				❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
pleura / pleural effusion	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
pericard / pericardial effusion				❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
lung				❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
other thoracal manifestation(s)	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
ABDOMEN																		
ascites				❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
bowel	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
liver	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
spleen	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
kidney(s) ❑ unilateral ❑ bilateral	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
abdominal LN	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
other abdominal manifestation(s)	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
OTHER LOCALISATIONS																		
testis/ovary/adnexa ❑ unilateral ❑ bilateral	❑	❑	❑	❑	❑	❑				❑	❑	❑	❑	❑	❑	❑	❑	❑
soft tissue ❑ unilocular ❑ multilocular	❑	❑	❑	❑	❑	❑				❑	❑	❑	❑	❑	❑	❑	❑	❑
bone(s) ❑ unilocular ❑ multilocular	❑	❑	❑				❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
↳ bone scan: ❑ not tested ❑ neg. ❑ pos.																		
epidural				❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
other localisation(s): _____	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑

Version: April 2004

Therapy Study ALCL-Relapse

Diagnosis of Relapse (page 3/3).

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__| (if known)

Skin involvement: ❑ no ❑ yes: please give further information:

type of skin lesions: ❑ maculo-papular lesions ❑ ulcerative lesions ❑ other: _____

histology of skin lesions: ❑ not done ❑ negative ❑ positive

only skin lesions overlying an involved node or soft tissue mass ❑ no ❑ yes

history / anamnesis of Ichthyosis: ❑ no ❑ yes
lymphomatoid papulomatosis: ❑ no ❑ yes

Stage (Murphy/St. Jude): ❑ I ❑ II ❑ III ❑ IV

Stage (Ann Arbor): ❑ I ❑ IE ❑ II ❑ IIE ❑ III ❑ IIIE ❑ IIIS ❑ IIIE+S ❑ IV
B-symptoms ❑ no ❑ yes
(fever, night sweats and/or unexplained loss of 10% or more of the body weight in the 6 months preceding diagnosis of relapse)

Frontline treatment (to be filled in only at diagnosis of 1st relapse):

Date of first diagnosis of ALCL: |__|__|.|__|__|.|__|__| (dd mm yy)

CD3 (immunohistochemical / immunological) in first diagnosis of ALCL: ❑ not done ❑ negative ❑ positive

Date of the end of intensive treatment of first ALCL: |__|__|.|__|__|.|__|__| (dd mm yy)
❑ not applicable (relapse during the intensive frontline treatment)

Vinblastine given in frontline treatment? ❑ no ❑ yes, until |__|__|.|__|__|.|__|__| (dd mm yy)

Treatment of relapsed ALCL

Date of the beginning of the protocol treatment ("ALCL-Relapse"): |__|__|.|__|__|.|__|__| (dd mm yy)

Treatment according to protocol ALCL-Relapse

- ❑ Arm 1: progression during frontline therapy
- ❑ Arm 2: relapse after end of frontline therapy; CD3 positive
- ❑ Arm 3: relapse after end of frontline therapy and ≤ 12 months from diagnosis (or > 12 months from diagnosis, but Vinblastine during frontline therapy), CD3 negative
- ❑ Arm 4: relapse: > 12 months from diagnosis, CD3 negative, no Vinblastine during frontline therapy
- ❑ other: _____

Notes:

Hospital-Stamp	Date (dd mm yy)	Name (in block letters)	Signature
		responsible physician	

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Sc-donor selection

(to be filled in only if relapse during frontline treatment or CD3 positive)

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__|

HLA-Typing of the patient and possible family donors initiated:

☐ no
☐ yes, date of the HLA-typing report: |__|__| |__|__| |__|__| (dd/mm/yy)

results of the family analysis:

MSD identified:

☐ no
☐ yes: sex: ☐ m ☐ f CMV IgG: ☐ pos ☐ neg → **donor 1**

best possible other family donor:

HLA-Match: |____| / |10| sex: ☐ m ☐ w CMV IgG: ☐ pos ☐ neg → **donor 2**

degree of relationship:
☐ sibling
☐ parent

search for unrelated donor initiated:

☐ no
☐ yes, date: |__|__| |__|__| |__|__| (dd/mm/yy)

results of the search for an unrelated donor:

best possible unrelated donor:

HLA-Match: |____| / |10| sex: ☐ m ☐ f CMV IgG: ☐ pos ☐ neg → **donor 3**

extended family analysis initiated:

☐ no
☐ yes, date |__|__| |__|__| |__|__| (dd/mm/yy)

results of the extended family analysis:

best possible donor:

HLA-Match: |____| / |10| sex:: ☐ m ☐ f CMV IgG: ☐ pos ☐ neg → **donor 4**

degree of relationship:
☐ aunt/uncle
☐ other: _____

SCT planed:

☐ no, since
- no appropriate donor available ☐ no ☐ yes
- preexisting disease: _____ ☐ no ☐ yes
- progression of ALCL ☐ no ☐ yes
- toxicity of previous treatment: _____ ☐ no ☐ yes
- no consent in SCT ☐ no ☐ yes
- other: _____ ☐ no ☐ yes

☐ yes, ☐ autologous
☐ allogeneic: ☐ donor 1 ☐ donor 2 ☐ donor 3 ☐ donor 4

estimated date of SCT: |__|__| |__|__| |__|__| (dd/mm/yy)

Hospital-Stamp	Date (dd mm yy)	Name (in block letters)	Signature
			responsible physician

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Announcement of SCT

to be filled in by the medical centre which will perform SCT
Please fax this form to the national study centre and (for BFM Austria and Germany) to the PRST.

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__| (if known)

UPN *(for BFM Austria and Germany)*: | _____ |
primary attending hospital | _____ |
number of relapses prior SCT |__|
current status of remission ☐ CR ☐ not in CR
planed SCT ☐ matched sibling donor (MSD)
☐ 10/10 or 9/10 non-sibling donor
☐ mismatched donor (MMD)
☐ autologous SCT
estimated date of SCT |__|__||__|__||__|__|

Was admitted to our hospital at |__|__||__|__||__|__|
responsible physician | _____|
address | _____|
telefon | _____|
fax | _____|
e-mail | _____|

consent for data transfer and storage is available

☐ no
☐ yes, for
☐ national and international data centre of study ALCL-Relapse
BFM Austria and Germany: ☐ PRST ☐ DRST ☐ EBMT ☐ IBMT-R

_____ _____ _____ _____
Hospital-Stamp Date (dd mm yy) Name (in block letters) Signature
responsible physician

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Treatment documentation
Course CC

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__| (if known)

Body weight: |__|__|__|,|__| kg Body height: |__|__|__| cm BSA: |__|,|__|__| m²

day	**1**	**2**	**3**	**4**	**5**
Dexamethasone 20 mg/m²/d	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●
Vindesin 3 mg/m² (max. 5 mg)	●				
Cytarabine (ARA-C) 3 g/m²	● ●	● ●			
Etoposide (VP-16) 100 mg/m²/d			● ●	● ●	●
MTX / ARA-C / PRED i.t. age adjusted dosage					●
date	__ / __ / __	__ / __ / __	__ / __ / __	__ / __ / __	__ / __ / __

Administered dose of cytostatic agents (single dose):

- **Dexamethasone:** in the morning: |__|__|,|__| mg at noon: |__|__|,|__| mg in the evening: |__|__|,|__| mg
- **Vindesin:** |__|,|__|__| mg
- **Cytarabine:** |__|__|__|__| mg
- **Etoposide:** |__|__|__| mg
- **MTX / ARA-C / PRED i.t.:** |__|__| / |__|__| / |__|__| mg

Modification of doses? Additional or omitted cytostatic agents?

❑ no

❑ yes

⇒ please fill in the total dose of the cytostatic agents:

Dexamethasone: |__|__|__|,|__| mg

Vindesin: |__|,|__|__| mg

Cytarabine: |__|__|__|__|__| mg

Etoposide: |__|__|__|__| mg

MTX / ARA-C / PRED i.t.: |__|__| / |__|__| / |__|__| mg

⇒ please specify the mode of modification and give the reasons:

Please fill in a toxicity documentation form (see page 107).

_____ _____ _____ _____

Hospital-Stamp Date (dd mm yy) Name (in block letters) Signature

responsible physician

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Treatment documentation
Course CVA

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__| (if known)

Body weight: |__|__|__|,|__| kg Body height: |__|__|__| cm BSA: |__|,|__|__| m²

day	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**
CCNU 100 mg/m² p.o.	●							
Vinblastine 6 mg/m² (maximum single dose 10 mg)	●					●	●	●
Cytarabine (ARA-C) 100 mg/m²	●	●	●	●	●			
date	__ / __ / __	__ / __ / __	__ / __ / __	__ / __ / __	__ / __ / __	__ / __ / __	__ / __ / __	__ / __ / __

Administered dose of cytostatic agents (single dose):

- **CCNU:** |__|__|__| mg
- **Vinblastine:** |__|__|,|__|__| mg
- **Cytarabine:** |__|__|__| mg

Modification of doses? Additional or omitted cytostatic agents?

❑ no

❑ yes

⇒ please fill in the total dose of the cytostatic agents:

CCNU: |__|__|__| mg

Vinblastine: |__|__|,|__|__| mg

Cytarabine: |__|__|__|__| mg

⇒ please specify the mode of modification and give the reasons:

Please fill in a toxicity documentation form (see page 107).

Hospital-Stamp | Date (dd mm yy) | Name (in block letters) | Signature responsible physician

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Treatment documentation
Course ICM

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__| (if known)

Body weight: |__|__|__|,|__| kg Body height: |__|__|__| cm BSA: |__|,|__|__| m²

day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
MTX/ARA-C/PRED i.t.	●								
Mitoxantrone 8 mg/m²	●	●							
Carboplatin 200mg/m²		▬	▬	▬	▬				
Ifosfamide 2 g/m²/d		▬	▬	▬	▬	▬			
Mesna (1) 500 mg/m²		●							
Mesna (2) 3 000 mg/m²/d		▬	▬	▬	▬	▬	▬	▬	
Hydration 3 000 ml/m²/d	▬	▬	▬	▬	▬	▬	▬	▬	
date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__

Administered dose of cytostatic agents (single dose):

- **Mitoxantrone:** |__|__|,|__| mg
- **Carboplatin:** |__|__|__| mg
- **Ifosfamide:** |__|__|__|__| mg
- **MTX / ARA-C / PRED i.t.:** |__|__| / |__|__| / |__|__| mg

Modification of doses? Additional or omitted cytostatic agents?

❑ no

❑ yes

⇒ please fill in the total dose of the cytostatic agents:

Mitoxantrone: |__|__|,|__| mg

Carboplatin: |__|__|__| mg

Ifosfamide: |__|__|__|__| mg

MTX / ARA-C / PRED i.t.: |__|__| / |__|__| / |__|__| mg

⇒ please specify the mode of modification and give the reasons:

Please fill in a toxicity documentation form (see page 107).

Hospital-Stamp	Date (dd mm yy)	Name (in block letters)	Signature
		responsible physician	

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Treatment documentation
Course ICI

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__| (if known)

Body weight: |__|__|__|,|__| kg Body height: |__|__|__| cm BSA: |__|,|__|__| m²

day	1	2	3	4	5	6	7	8	9
MTX/ARA-C/PRED i.t.	●								
Idarubicine 10 mg/m²/d	●	●							
Carboplatin 200mg/m²/d		▬	▬	▬	▬				
Ifosfamide 2 g/m²/d		▬	▬	▬	▬	▬			
Mesna (1) 500 mg/m²		●							
Mesna (2) 3 000 mg/m²/d		▬	▬	▬	▬	▬	▬	▬	
Hydration 3 000 ml/m²/d	▬	▬	▬	▬	▬	▬	▬	▬	
date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__

Administered dose of cytostatic agents (single dose):

- **Idarubicine:** |__|__|,|__| mg
- **Carboplatin:** |__|__|__| mg
- **Ifosfamide:** |__|__|__|__| mg
- **MTX / ARA-C / PRED i.t.:** |__|__| / |__|__| / |__|__| mg

Modification of doses? Additional or omitted cytostatic agents?

❑ no

❑ yes

⇒ please fill in the total dose of the cytostatic agents:

Idarubicine: |__|__|,|__| mg

Carboplatin: |__|__|__| mg

Ifosfamide: |__|__|__|__| mg

MTX / ARA-C / PRED i.t.: |__|__| / |__|__| / |__|__| mg

⇒ please specify the mode of modification and give the reasons:

Please fill in a toxicity documentation form (see page 107).

Hospital-Stamp | Date (dd mm yy) | Name (in block letters) responsible physician | Signature

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Acute toxicity and adverse events during / after reinduction

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__|__| (if known)

Maximum toxicity during / after: ❑ 1st CC ❑ 2nd CC ❑ CVA ❑ ICM ❑ ICI

Begin of therapy element: |__|__|.|__|__|.|__|__| (dd mm yy) End of therapy element: |__|__|.|__|__|.|__|__| (dd mm yy)

Documented period: |__|__|.|__|__|.|__|__| (dd mm yy) End of documented period: |__|__|.|__|__|.|__|__| (dd mm yy)

Grade	0	1	2	3	4	not tested
Haematology						
Haemoglobin (g/l)	normal for age	100 - < LLN	80 - < 100	65 - < 80	< 65	❑
WBC (x 10^9/l)	≥ 4.0	3.0 - < 4.0	2.0 - < 3.0	1.0 - < 2.0	< 1.0	❑
Granulocytes (x 10^9/l)	≥ 2.0	1.5 - < 2.0	1.0 - < 1.5	0.5 - < 1.0	< 0.5	❑
Platelets (x 10^9/l)	≥ 100	75 - < 100	50 - < 75	10 - < 50	< 10	❑
Infections						
Infection	none	mild	moderate, pathogen not identified; i.v. antibiotics	severe, pathogen identified; i.v. antibiotics	life threatening, with hypotonia	❑
Fever (°C)	< 38	38 - 39	> 39 - 40	> 40 for < 24 h	> 40 for ≥24 h	❑
Mucosal toxicity						
Stomatitis	none	painless ulcer, erythema	painful erythema or ulceration, can still eat	painful erythema or ulceration, cannot eat	TPN required, due to stomatitis	❑
Diarrhea (stool/day)	none	2 - 3	4 – 6 or nightly stool or light cramps	7 - 9 or incontinence or severe cramps	≥10 or bloody diarrhoea or TPN required	❑
Renal toxicity						
Creatinine	normal for age	> UNL - 1.5 x UNL	> 1.5 - 3.0 x UNL	> 3.0 - 6.0 x UNL	> 6 x UNL	❑
Liver toxicity						
Bilirubin	normal for age	> UNL - 1.5 x UNL	> 1.5 - 3.0 x UNL	> 3.0 - 10.0 x UNL	>10.0 x UNL	❑
SGOT / SGPT	normal for age	> UNL - 2.5 x UNL	> 2.5 - 5.0 x UNL	> 5.0 - 20.0 x UNL	> 20 x UNL	❑
Cardiac toxicity						
Cardiac function	normal	asymptomatic decline of resting EF of ≥10% but <20% of baseline value; SF ≥24% but <30%	asymptomatic but resting EF below LLN for laboratory or decline of resting EF ≥20% of baseline value; SF <24%	mild CHF, therapeutically compensated	severe or refractory CHF or requiring intubation	❑
Arrhythmia	none	asymptomatic, not requiring treatment	recurr. / persist., but not requiring treatment	requiring treatment	hypotension, ventr. arrhythmia, defibrillation	❑
Thrombosis						
Thrombosis / embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event (including pulmonary embolism)	❑
Neurological toxicity						
Central neurotoxicity	none	temporary lethargy	somnolence < 50% of the time, moderate disorientation	somnolence ≥ 50% of the time, severe disorientation, hallucination	coma, seizures	❑
Peripheral neurotoxicity	none	paresthesia	severe paresthesia and/or mild weakness	unbearable paresthesia, obvious deficits in motoric function	paralysis	❑
Anaphylaxis						
Anaphylaxis	none	mild	moderate	severe	life threatening	❑

Other toxicity: ❑ no ❑ yes

(specify, and if possible, precise the NCI-grades: 0=normal; 1=mild; 2=moderate; 3=severe; 4=life-threatening)
If case of SAE, please use the SAE-form from page 144

Abbreviations: *EF = ejection fraction* *SF = shortening fraction* *LLN = lower normal limit*
UNL = upper normal limit *TPN = total parenteral nutrition* *CHF = congestive hear failur*

Hospital-Stamp _____ Date (dd mm yy) _____ Name (in block letters) _____ Signature _____
responsible physician

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12,
35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Treatment documentation
VBL for 24 months

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__| (if known) Body weight: |__|__|__|,|__| kg Body height: |__|__|__| cm BSA: |__|,|__|__| m²

full dose VBL iv 6 mg/m²/week |__|__|, |__| mg (maximum single dose 10 mg)

Number of week	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|
Date of VBL injection:												
VBL given [mg]	|__|__|, |__|	|__|__|, |__|	|__|__|, |__|	|__|__|, |__|	|__|__|, |__|	|__|__|, |__|	|__|__|, |__|	|__|__|, |__|	|__|__|, |__|	|__|__|, |__|	|__|__|, |__|
Vinblastine dose: none (0), 1/2 dose (1), 2/3 dose (2), full dose (3)	( )	( )	( )	( )	( )	( )	( )	( )	( )	( )	( )	( )
Reason of modification												
haematological toxicity	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes
neurological toxicity	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes
other toxicity	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes
other reason *(if "yes": specify)*	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes	❑ no ❑ yes
haematological toxicity												
Leukocytes/µl:												
Granulocytes/µl												
Hb g/dl:												
Platelets/µl:												
Ery-Conz. (number):												
Platelet-Conz (number):												
neurotoxicity (grade)*	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
other toxicity • **specify** • **NCI-grade** (see toxicity form)	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|

*) Grade of Neurotoxicity: 0 = none; 1 = parethesias, mild subjective weakness; 2 = severe paresthesias and/or mild weakness; 3 = unbearable paresthesias, deficits in motoric function; 4 = paralysis

_____ _____ _____ _____

Hospital Stamp Date (dd mm yy) responsible physician :Name (in block letters) responsible physician: Signature

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Allograft (page 1/14)

Patient's name	Registration number	date of birth (dd mm yy)	UPN	Sex (m/f)
|_____|	|__|__|__|__|__|__|	|__|__|.|__|__|.|__|__|	|__|__|__|__|__|__|	|__|

This form should be submitted on day 100 and should reflect information until day 100 only.

Day 100 post transplant: |__|__| |__|__| |__|__| (dd/mm/yy)

Patient

HLA Type:

Molecular typing done: Class I ☐ no ☐ yes
Class II ☐ no ☐ yes

|__|__|__|__| A |__|__|__|__| B |__|__|__|__| C |__|__|__|__| DRB1 |__|__|__|__| DQB1
|__|__|__|__| A |__|__|__|__| B |__|__|__|__| C |__|__|__|__| DRB1 |__|__|__|__| DQB1

ABO group: ☐ Rh pos ☐ Rh neg
☐ A ☐ B ☐ AB ☐ 0

Viral status:

	positive	negative	inconclusive	not tested
CMV IgG	☐	☐	☐	☐
EBV IgG	☐	☐	☐	☐
Anti-HBs	☐	☐	☐	☐
Anti-HBc	☐	☐	☐	☐
HbsAg	☐	☐	☐	☐
HCV IgG	☐	☐	☐	☐
HAV IgG	☐	☐	☐	☐
HIV IgG	☐	☐	☐	☐
Toxoplasma IgG	☐	☐	☐	☐
other: |_____|	☐	☐	☐	☐

Molecular status before SCT

cytogenetic or MRD marker:

☐ not done

☐ no

☐ yes: state which and please enclose copy of each diagnostic finding.

marker: |_____| laboratory: |_____|

Disease status before SCT:

status ☐ CR after reinduction
☐ CR never achieved after diagnosis of ALCL relapse
☐ further relapse during / after reinduction

SCT after |__|. relapse. *(Please fill in the number of the relapse.)*

Treatment before SCT

Treatment arm: ☐ Arm 1 (progress during frontline treatment)
☐ Arm 2a (progress after frontline treatment, CD3+, MSD or 10/10 MUD)

Allograft (page 2/14)

Patient's name	Registration number	date of birth (dd mm yy)	UPN
|_____|	|__|__|__|__|__|	|__|__|.|__|__|.|__|__|	|__|__|__|__|

Clinical status before SCT

Please mark the appropriate field for each parameter and complete the data
(for toxicities: maximum value of the week before start of the conditioning regimen).

Performance status

Score	Karnofsky Description (patients older than 16 years)	Lansky Description (Patients younger than 16 years)
100%	normal, no complaints, no evidence of disease.	Fully active, normal.
90%	Able to carry on normal activity; minor signs or symptoms of disease.	Minor restrictions in physically strenuous activity.
80%	normal activity with effort; some signs or symptoms of disease.	Active, but tires more quickly.
70%	Cares for self, unable to carry on normal activity or do active work.	Both greater restriction of and less time spent in play activity.
60%	Requires occasional assistance, but is able to care for most of his/her needs	Up and around, but minimal active play, keeps busy with quieter activities.
50%	Requires considerable assistance and frequent medical care.	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
40%	Disabled, requires special care and assistance.	Mostly in bed; participates in quiet activities.
30%	Severely disabled, hospitalisation indicated. Death not imminent.	In bed; needs assistance even for quiet play.
20%	Very sick, hospitalisation indicated. Death not imminent.	Often sleeping; play entirely limited to very passive activities.
10%	Moribund, fatal processes progressing rapidly.	no play; does not get out of bed.

Gastrointestinal toxicity

Grade	0	1	2	3	4	n.d.
Diarrhea	none	2 – 3 stools/day	4 – 6 stools/day or nocturnal stools or light cramps	7-9 stools/day or incontinence or severe cramps	≥ 10 stools/day or bloody diarrhea or TPN necessary	☐
Vomiting [Number of episodes in 24h]	0	1	2 – 5	6 – 10	> 10 or TPN necessary	☐
Stomatitis	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swollow	painful erythema, edema or ulcers preventing swalloing or requiring IV hydration	TPN because of stomatitis necessary	☐
Nausea	none	able to eat	oral intake significantly decreased	no significant intake requiring IV fluids	TPN necessary	☐

Haematologic toxicity

Grade	0	1	2	3	4	n.d.
Granulocytes [G/L]	≥ 2.0	1.5 – < 2.0	1.0 – < 1.5	0.5 – < 1.0	< 0.5	☐
Hemoglobin [g/dL]	age norm (N)	10.0 – < N	8.0 – < 10.0	6.5 – < 8.0	< 6.5	☐
Leukocytes [G/L]	≥ 4.0	3.0 – < 4.0	2.0 – < 3.0	1.0 – < 2.0	< 1.0	☐
Platelets [G/L]	≥ 100	75 – < 100	50 – < 75	10 – < 50	< 10	☐

Dermatologic/Skin toxicity

Grade	**0**	**1**	**2**	**3**	**4**	n.d.
Changes in the skin	none	erythema	dry desquamination, vasculitis, pruritus	moist desquamination, ulzerations	exfoliative dermatitis, Necrosis	☐

Allograft (page 3/14)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__|

Pulmonary toxicity

Grade	0	1	2	3	4	n.d.
FEV $_1$	≥ 90% of pretreatment or normal value	≥ 75% - <90% of pretreatment or normal value	≥ 50% - <75% of pretreatment or normal value	≥ 25% - <50% of pretreatment or normal value	<25% of pretreatment or normal value	☐
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest requiring suppl. oxygen	decreased O_2 saturation requiring pressure support (CPAP) or assisted ventilation	☐
Pneumonitis, pulmonary infiltrates	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation	☐

Cardiac toxicity

Grade	0	1	2	3	4	n.d.
Arrhythmia	none	asymptomatic, not requiring treatment	recurrent, persistent, not reequiring treatment	therapy required	hypotension, ventr. arrhythmia, defibrillation	☐
Echocardio: LV-SF	≥ 30%	≥ 24% - < 30%	≥ 20% – < 24%	> 15% – < 20%	≤ 15%	☐
Cardiac function	normal	asymptomatic decline of resting ejection fraction of ≥10% but < 20% of baseline value	asymptomatic but resting EF below normal value for laboratory EF or decline of resting EF ≥20% of baseline value	mild CHF, responsive to treatment	severe or refractory CHF or requiring intubation	☐

Infection toxicity

Grade	0	1	2	3	4	n.d.
Fever [°C]	< 38°C	38 – 39°C	> 39 – 40°C	> 40°C für < 24 Std.	> 40°C für ≥ 24 Std.	☐
Infection	none	mild	moderate, pathogen not identified; IV antibiotics	severe, pathogen identified; IV antibiotics	life-threatening, hypotension	☐

If clinically important infections are present or being treated within one month prior to conditioning, specify:

- bacterial: ☐ no ☐ yes, specify: organism: |_____| site: |_____|
- viral: ☐ no ☐ yes, specify: organism: |_____| site: |_____|
- fungal: ☐ no ☐ yes, specify: organism: |_____| site: |_____|
- parasitic: ☐ no ☐ yes, specify: organism: |_____| site: |_____|
- pathogen not identified site: |_____|

Hepatic toxicity

Grade	0	1	2	3	4	n.d.
Bilirubin	within limits of normal	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN	☐
S-GOT/S-GPT	within limits of normal	> ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20 x ULN	☐

Renal toxicity

Grade	0	1	2	3	4	n.d.
Creatinine	within limits of normal	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN	☐
Creatinine-Clearance [ml/Min./1,73m²]	≥ 90	60 – 89	40 – 59	20 – 39	≤ 19	☐
Haematuria	none	microscopic only	intermittent gross bleeding, not clots	persistent gross bleeding or clots; catheterisation or instrumentation	transfusion required	☐
Proteinuria [g/l]	none	< 3	3 – 10.0	> 10.0	nephrotic syndrome	☐

Allograft (page 4/14)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__|

Neurological toxicity

Grade	0	1	2	3	4	n.d.
Peripheral Neurotoxicity	none	paresthesias, mild subjective weakness	severe paresthesias	unbearable paresthesias, deficits in motor funct.	paralysis	☐
Central Neurotoxicity	none	mild somnolence or agitation; drowsiness	somnolence <50% of the time, moderate disorientation	somnolence ≥ 50% of the time, severe disorientation, hallucinations	coma, seizures	☐

Allergy/Immunology

Grade	0	1	2	3	4	n.d.
Allergy	none	transient	asymptomatic bronchospasm	symptomatic bronchospasm, serum sickness	anaphylaxis	☐

Ocular/Visual

Grade	0	1	2	3	4	n.d.
Cataract/ Keratitis	none	asymptomatic cataract, mild keratitis or corneal ulceration	symptomatic cataract or corneal ulceration, glaucoma	massive keratitis, retinopathy, glaucoma	panophthal-mitis, unilateral or bilateral loss of vision	☐

Osteonecrosis

Grade	0	1	2	3	4	n.d.
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic or disabling	☐

other clinically significant coexisting disease or organ impairment:

☐ no ☐ yes

If yes, specify: _____

_____

_____

Do they cause modifications in the conditioning regimen or dose of medication?

☐ no ☐ yes

If yes, please state which: _____

_____

_____

Allograft (page 5/14)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__|

Donor

Relationship to recipient: ☐ unrelated ☐ related:
- ☐ monocygotic twin
- ☐ sibling
- ☐ parent
- ☐ uncle/aunt
- ☐ cousin
- ☐ other: _____

Sex ☐ male ☐ female

Age birth date: |__|__| |__|__| |__|__| (dd/mm/yy) |__|__| years

HLA Type:

Molecular typing done: Class I ☐ no ☐ yes
Class II ☐ no ☐ yes

|__|__|__|__| A |__|__|__|__| B |__|__|__|__| C |__|__|__|__| DRB1 |__|__|__|__| DQB1
|__|__|__|__| A |__|__|__|__| B |__|__|__|__| C |__|__|__|__| DRB1 |__|__|__|__| DQB1

ABO group: ☐ Rh pos ☐ Rh neg
☐ A ☐ B ☐ AB ☐ 0

Viral status:

	positive	negative	inconclusive	not tested
CMV IgG	☐	☐	☐	☐
EBV IgG	☐	☐	☐	☐
Anti-HBs	☐	☐	☐	☐
Anti-HBc	☐	☐	☐	☐
HbsAg	☐	☐	☐	☐
HCV	☐	☐	☐	☐
HIV	☐	☐	☐	☐
HTLVI	☐	☐	☐	☐
other: |_____|	☐	☐	☐	☐

Allograft (page 6/14)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__|

Conditioning Regimen

Body height: |__|__|__| cm Body weight: |__|__|__|,|__| kg BSA: |__|,|__|__| m^2

Therapy

drugs, ATG, mono AB (product name)	daily dose given	mg/kg/d	$mg/m^2/d$	days of administration	total dose given (mg)	dosage according to protocol no	yes
Example: *Endoxan*	*40*	☒	☐	*-3*	*1200*	☐	☒
		☐	☐			☐	☐
		☐	☐			☐	☐
		☐	☐			☐	☐
		☐	☐			☐	☐

if dose modification, specify: |_____|

	no	yes	total dose	number of fractions	days of administration
TBI	☐	☐	|__|__| Gy	|__|__|	|__|__|__|__|__|
CNS boost	☐	☐	|__|__| Gy	|__|__|	|__|__|__|__|__|
other boost	☐	☐	|__|__| Gy	|__|__|	|__|__|__|__|__|

if other, specify: |_____|

Transplantation

Date of transplantation (dd/mm/yy) |__|__| |__|__| |__|__|
Number of this transplantation |__|
Source of stem cells:
☐ BM
☐ PBSC
☐ cord blood

Manipulation of graft:
☐ no ☐ yes
If yes, type of manipulation:
T-Cell-Depletion: ☐ no ☐ yes method: |_____|
CD34+ Selection: ☐ no ☐ yes method: |_____|
other: |_____| ☐ no ☐ yes method: |_____|

Cells infused: Number of nucleated cells: _____*10^8/kg
CD34+ cells: _____*10^6/kg
CD3+ cells: - T-cell depleted graft: _____*10^4/kg
- unmanipulated graft: _____*10^7/kg

Allograft (page 7/14)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__|__|

Cytokines in the immediate post transplant period (till day +28):

☐ no ☐ yes, specify: ☐ G-CSF
☐ other: |_____|
starting day (dd/mm/yy) |__|__| |__|__| |__|__|
starting dose: |____|,|____|µg/kg
length of cytokine treatment: |__|__| days

Engraftment

Evidence of haematopoietic reconstitution: (dd/mm/yy)

Leucocytes	>1,000/µl:	|__|__|	|__|__|	|__|__|	☐ not reached
Neutrophils	>500/µl:	|__|__|	|__|__|	|__|__|	☐ not reached
Platelets	>20,000/µl:	|__|__|	|__|__|	|__|__|	☐ not reached
Platelets	>50,000/µl:	|__|__|	|__|__|	|__|__|	☐ not reached
last platelet transfusion:		|__|__|	|__|__|	|__|__|	☐ transfusions ongoing
last red cell transfusion:		|__|__|	|__|__|	|__|__|	☐ transfusions ongoing

Graft failure:

☐ no ☐ yes, date of diagnosis |__|__| |__|__| |__|__| (dd/mm/yy)

Reason of graft failure:
☐ non-engraftment
☐ rejection (=not reversible with cytokine treatment or reduction of immunosuppression)
☐ other: |_____|

Treatment of graft failure:
☐ no specific treatment
☐ cytokines, specify: |_____|
☐ subsequent transplant
☐ other: |_____|

If subsequent transplant, date: |__|__| |__|__| |__|__| (dd/mm/yy)
type of transplant: ☐ autologous
☐ allogeneic: ☐ related ☐ unrelated

GVHD prophylaxis

Cyclosporine A <u>iv:</u>

☐ no
☐ yes ⇒ starting dose CSA iv |_____| mg/kg/day / target level of CSA: |__|__|__| ng/ml
date of CSA start iv |__|__| |__|__| |__|__| (dd/mm/yy)
date of CSA stop iv |__|__| |__|__| |__|__| (dd/mm/yy) ☐ CSA iv ongoing
total days with CSA iv: |__|__|__|

Cyclosporine A <u>p. o.:</u>

☐ no
☐ yes ⇒ starting dose CSA p.o. |_____| mg/kg/day / target level of CSA: |__|__|__| ng/ml
date of CSA start p.o. |__|__| |__|__| |__|__| (dd/mm/yy)
date of CSA stop p.o. |__|__| |__|__| |__|__| (dd/mm/yy) ☐ CSA p.o. ongoing
total days with CSA p.o.: |__|__|__|

Allograft (page 8/14)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__|

Tapering of CSA:

☐ no
☐ yes ⇒ date of start: |__|__| |__|__| |__|__| (dd/mm/yy)
date of stop: |__|__| |__|__| |__|__| (dd/mm/yy) ☐ tapering ongoing

Methotrexate:

☐ no ☐ yes ⇒ dose MTX: |____| |____| |____| |____| mg/m^2/d
days: +|___| +|___| +|___| +|___|

Leucovorin:

☐ no ☐ yes ⇒ dose Leucovorin |____| |____| |____| |____| mg/m^2/d
days: +|___| +|___| +|___| +|___|

other GVHD prophylaxis:

☐ no

☐ yes ⇒ specify: |_____|
dose: |_____| ☐ mg/kg/day ☐ mg/m^2/d ☐ other: |_____|
starting date: |__|__| |__|__| |__|__| (dd/mm/yy)
date of stop: |__|__| |__|__| |__|__| (dd/mm/yy) ☐ ongoing

Acute GvHD

☐ no ☐ yes, date of onset: |__|__| |__|__| |__|__| (dd/mm/yy)
diagnosis based on: ☐ clinical evidence ☐ histologic evidence

overall grade ☐ 0 ☐ I ☐ II ☐ III ☐ IV

skin: stage: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4
liver: stage: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4
gut: stage: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

aGVHD resolved ☐ no ☐ yes, date |__|__| |__|__| |__|__| (dd/mm/yy)

Acute GvHD treatment

☐ no ☐ yes, specify:

Medication	no yes	product name	maximum dose (units)	total duration of treatment days	ongoing
increase of CSA	☐ ☐		|____| mg/kg/day	|____|	☐
Methylprednisolone	☐ ☐		|____| mg/kg/day	|____|	☐
Mycophenolate-Mofetile	☐ ☐		|____| mg/kg/day	|____|	☐
Tacrolimus	☐ ☐		|____| mg/kg/day	|____|	☐
ALG/ATG	☐ ☐	|_____|	|____| mg/kg/day	|____|	☐
monoclonal AB	☐ ☐	|_____|	|____| ...../...../....	|____|	☐
Photophoresis	☐ ☐			|____|	☐
PUVA	☐ ☐			|____|	☐
other	☐ ☐	|_____|	|____| ...../...../....	|____|	☐

Allograft (page 9/14)

Patient's name	Registration number	date of birth (dd mm yy)	UPN
|________________________________|	|__|__|__|__|__|__|	|__|__|.|__|__|.|__|__|	|__|__|__|__|__|

Chimerism

☐ not done ☐ done, please specify the results

PB/ BM	date of examination	if sorted, type of cells	% of donor cells	Method (FISH, VNTR, other)	Laboratory (city)	Treatment					
						Immunosuppression: none	unchanged	increased	reduced	stopped	DLI
						☐	☐	☐	☐	☐	☐
						☐	☐	☐	☐	☐	☐
						☐	☐	☐	☐	☐	☐
						☐	☐	☐	☐	☐	☐
						☐	☐	☐	☐	☐	☐
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						☐	☐	☐	☐	☐	☐
						☐	☐	☐	☐	☐	☐

Allograft (page 10/14)

Patient's name | Registration number | date of birth (dd mm yy) | UPN

Complications < day 100

Please mark the appropriate field for each parameter
(maximum value till day 100 or date of death respectively) and complete the data.

Gastrointestinal toxicity

Grade	0	1	2	3	4	n.d.
Diarrhea	none	2 – 3 stools/day	4 – 6 stools/day or nocturnal stools or light cramps	7-9 stools/day or incontinence or severe cramps	≥ 10 stools/day or bloody diarrhea or TPN necessary	☐
Vomiting [Number of episodes in 24h]	0	1	2 – 5	6 – 10	> 10 or TPN necessary	☐
Stomatitis	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swollow	painful erythema, edema or ulcers preventing swalloing or requiring IV hydration	TPN because of stomatitis necessary	☐
Nausea	none	able to eat	oral intake significantly decreased	no significant intake requiring IV fluids	TPN necessary	☐

Haematologic toxicity

Grade	0	1	2	3	4	n.d.
Granulocytes [G/L]	≥ 2.0	1.5 – < 2.0	1.0 – < 1.5	0.5 – < 1.0	< 0.5	☐
Hemoglobin [g/dL]	agenorm (N)	10.0 – < N	8.0 – < 10.0	6.5 – < 8.0	< 6.5	☐
Leukocytes [G/L]	≥ 4.0	3.0 – < 4.0	2.0 – < 3.0	1.0 – < 2.0	< 1.0	☐
Platelets [g/l]	≥ 100	75 – < 100	50 – < 75	10 – < 50	< 10	☐

Dermatology/Skin toxicity

Grade	0	1	2	3	4	n.d.
Changes in the skin	none	erythema	dry desquamination, vasculitis, pruritus	moist desquamination, ulzerations	exfoliative dermatitis, necrosis	☐

Pulmonary toxicity

Grade	0	1	2	3	4	n.d.
FEV_1	≥ 90% of pretreatment or normal value	≥ 75% - <90% of pretreatment or normal value	≥ 50% - <75% of pretreatment or normal value	≥ 25% - <50% of pretreatment or normal value	<25% of pretreatment or normal value	☐
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest requiring suppl. oxygen	decreased O_2 saturation requiring pressure support (CPAP) or assisted ventilation	☐
Pneumonitis, pulmonary infiltrates	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation	☐

Cardiac toxicity

Grade	0	1	2	3	4	n.d.
Arrhythmia	none	asymptomatic, not requiring treatment	recurrent, persistent, not reequiring treatment	therapy required	hypotension, ventr. arrhythmia, defibrillation	☐
Echocardio: LV-SF	≥ 30%	≥ 24% - < 30%	≥ 20% – < 24%	> 15% – < 20%	≤ 15%	☐
Cardiac function	normal	asymptomatic decline of resting EF of ≥10% but < 20% of baseline value	asymptomatic but resting EF below normal value for lab. or decline of resting EF ≥20% of baseline value	mild CHF, responsive to treatment	severe or refractory CHF or requiring intubation	☐

Allograft (page 11/14)

Patient's name	Registration number	date of birth (dd mm yy)	UPN
|_____|	|__|__|__|__|__|	|__|__|.|__|__|.|__|__|	|__|__|__|__|

Hepatic toxicity

Grade	0	1	2	3	4	n.d.
Bilirubin	within limits of normal	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN	☐
S-GOT/S-GPT	within limits of normal	> ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20 x ULN	☐

Renal toxicity

Grade	0	1	2	3	4	n.d.
Creatinine	within limits of normal	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN	☐
Creatinine-Clearance [ml/Min./1,73m²]	≥ 90	60 – 89	40 – 59	20 – 39	≤ 19	☐
Hämaturia	none	microscopic only	intermittent gross bleeding, not clots	persistent gross bleeding or clots; req. catheterization or instrumentation	transfusion required	☐
Proteinuria [g/l]	none	< 3	3 – 10.0	> 10.0	nephrotic syndrome	☐

Neurological toxicity

Grade	0	1	2	3	4	n.d.
Peripheral Neurotoxicity	none	paresthesias, mild subjective weakness	severe paresthesias	unbearable pares-thesias, deficits in motor funct.	paralysis	☐
Central Neurotoxicity	none	mild somnolence or agitation; drowsiness	somnolence < 50% of time, moderate disorientation	somnolence ≥ 50% of time, severe disorientation, hallucinations	coma, seizures	☐

Allergy/Immunology

Grade	0	1	2	3	4	n.d.
Allergy	none	transient	asymptomatic bronchospasm	symptomatic bronchospasm, serum sickness	anaphylaxis	☐

Ocular/Visual

Grade	0	1	2	3	4	n.d.
Cataract/ Keratitis	none	asymptomatic cataract, mild keratitis or corneal ulceration	symptomatic cataract or corneal ulceration, glaucoma	massive keratitis, retinopathy, glaucoma	panophthal-mitis, unilateral or bilateral loss of vision	☐

Osteonecrosis

Grade	0	1	2	3	4	n.d.
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic or disabling	☐

Infection toxicity

Grade	0	1	2	3	4	n.d.
Fever [°C]	< 38°C	38 – 39°C	> 39 – 40°C	> 40°C für < 24 Std.	> 40°C für ≥ 24 Std.	☐
Infection	none	mild	moderate, pathogen not identified; IV antibiotics	severe, pathogen identified; IV antibiotics	life-threatening, hypotension	☐

Allograft (page 12/14)

Patient's name |_____| Registration number |__|__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__|

If clinically important infections were present or being treated till day +100, please complete:

pathogen identified :

☐ no, please specify site of infection:

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify: |_____|

☐ yes, please specify:

---

bacterial: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy), specify organism: : |_____|

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify: |_____|

---

viral: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy)

- CMV infection ☐ no ☐ yes
- CMV disease ☐ no ☐ yes
- EBV ☐ no ☐ yes
- Adenovirus ☐ no ☐ yes
- Hepatitis B ☐ no ☐ yes
- Herpes simplex ☐ no ☐ yes
- Hepatitis C ☐ no ☐ yes
- Herpes ☐ no ☐ yes, type: |_____|
- BKV ☐ no ☐ yes
- Varicella-Zoster ☐ no ☐ yes
- other: ☐ no ☐ yes: |_____|

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify: |_____|

---

fungal: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy) ☐ possible ☐ probable ☐ proven

- Aspergillus ssp ☐ no ☐ yes
- Candida ssp ☐ no ☐ yes
- other ☐ no ☐ yes: |_____|

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify:|_____|

---

parasitic: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy)

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify:|_____|

---

other clinically significant coexisting disease or organ impairment:

☐ no ☐ yes, please specify:

- severe bleeding ☐ no ☐ yes
- infarction or thrombosis ☐ no ☐ yes
- VOD ☐ no ☐ yes
- ARDS ☐ no ☐ yes
- acute vascular leak syndrome ☐ no ☐ yes

intensive care measures:

☐ no ☐ yes, please state indication:

- assisted ventilation ☐ no ☐ yes
- haemodialysis ☐ no ☐ yes
- haemofiltration ☐ no ☐ yes
- other ☐ no ☐ yes: |_____|

admittance to ICU? ☐ no ☐ yes

Best response to SCT

☐ continued CR
☐ CR achieved: date CR achieved: |__|__| |__|__| |__|__| (dd/mm/yy)
☐ no CR

Allograft (page 13/14)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__|

Treatment after SCT

☐ no ☐ yes, please specify indication:

- no remission ☐ no ☐ yes
- relapse ☐ no ☐ yes
- mixed chimerism ☐ no ☐ yes
- other ☐ no ☐ yes: |_____|

if yes, kind of treatment:

- reduction or discontinuation of immunosuppression ☐ no ☐ yes
- chemotherapy ☐ no ☐ yes
- donor leukocyte infusion ☐ no ☐ yes

1.DLI: no. of CD3 or CD|__| cells: |_____| /kg |__|__| |__|__||__|__| (dd/mm/yy)

2.DLI: no. of CD3 or CD|__| cells: |_____| /kg |__|__| |__|__||__|__| (dd/mm/yy)

3.DLI: no. of CD3 or CD|__| cells: |_____| /kg |__|__| |__|__||__|__| (dd/mm/yy)

4.DLI: no. of CD3 or CD|__| cells: |_____| /kg |__|__| |__|__||__|__| (dd/mm/yy)

- subsequent SCT ☐ no ☐ yes, date: |__|__| |__|__| |__|__| (dd/mm/yy)
- other treatment ☐ no ☐ yes: |_____|

Cytokines in the post transplant period > day +29 to day +100:

☐ no ☐ yes

if yes, specify: G-CSF: ☐ no ☐ yes
other: ☐ no ☐ yes, |_____|

starting date |__|__| |__|__| |__|__| (dd/mm/yy)

starting dose: |____|,|____|µg/kg

duration of cytokine treatment: |__|__| days

Remission status – day 100 or at date of death

Relapse after SCT: ☐ not applicable (never in CR) ☐ no

☐ yes *(please fill in an event form)*: date of relapse: |__|__| |__|__| |__|__| (dd/mm/yy)

site of relapse: local ☐ no ☐ yes: |_____|
BM ☐ no ☐ yes
CNS ☐ no ☐ yes
other: ☐ no ☐ yes: |_____|

Molecular status – day 100 or at date of death

Cytogenetic or MRD Marker:

☐ not done ☐ no ☐ yes, state which and please enclose copy of each diagnostic finding.

marker: |_____| laboratory: |_____|

Allograft (page 14/14)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__|

Survival status – day 100

☐ alive date of last follow up: |__|__| |__|__| |__|__| (dd/mm/yy)

Performance status criteria (Please mark the appropriate value)

Score	Karnofsky Description (patients elder than 16 years)	Lansky Description (Patients younger than 16 years)
100 %	normal, no complaints, no evidence of disease.	Fully active, normal.
90%	Able to carry on normal activity; minor signs or symptoms of disease.	Minor restrictions in physically strenuous activity.
80%	normal activity with effort; some signs or symptoms of disease.	Active, but tires more quickly
70%	Cares for self, unable to carry on normal activity or do active work.	Both greater restriction of and less time spent in play activity.
60%	Requires occasional assistance, but is able to care for most of his/her needs	Up and around, but minimal active play, keeps busy with quieter activities.
50%	Requires considerable assistance and frequent medical care.	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
40%	Disabled, requires special care and assistance.	Mostly in bed; participates in quiet activities.
30%	Severely disabled, hospitalization indicated. Death not imminent.	In bed; needs assistance even for quiet play.
20%	Very sick, hospitalization indicated. Death not imminent.	Often sleeping; play entirely limited to very passive activities.
10%	Moribund, fatal processes progressing rapidly.	no play; does not get out of bed.

☐ Died ⇒ please fill in an Event form (see page 143)

Date of death: |__|__| |__|__| |__|__| (dd/mm/yy)

Main Cause of death:

- ☐ Relapse or Progression
- ☐ Transplantation Related Cause: (tick all that apply)
  - ☐ GVHD
  - ☐ graft failure
  - ☐ pulmonary toxicity
  - ☐ cardiac toxicity
  - ☐ infection
  - ☐ VOD
  - ☐ post transplant lymphoproliferative disorder
  - ☐ other: |_____|
- ☐ Secondary Malignancy
- ☐ Late Event
- ☐ Other: |_____|
- ☐ Unknown

Notes

_____ _____ _____ _____

Hospital Stamp | Date (dd mm yy) | Name (in block letters) responsible physician | Signature

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Autograft (page 1/11)

Patient's name	Registration number	date of birth (dd mm yy)	UPN	Sex (m/f)
|_____|	|__|__|__|__|__|	|__|__|.|__|__|.|__|__|	|__|__|__|__|	|__|

This form should be submitted on day 100 and should reflect information until day 100 only.

Day 100 post transplant: |__|__| |__|__| |__|__| (dd/mm/yy)

Patient

ABO group: ☐ Rh pos ☐ Rh neg
☐ A ☐ B ☐ AB ☐ 0

Viral status:

	positive	negative	inconclusive	not tested
CMV IgG	☐	☐	☐	☐
EBV IgG	☐	☐	☐	☐
Anti-HBs	☐	☐	☐	☐
Anti-HBc	☐	☐	☐	☐
HbsAg	☐	☐	☐	☐
HCV IgG	☐	☐	☐	☐
HAV IgG	☐	☐	☐	☐
HIV IgG	☐	☐	☐	☐
Toxoplasma IgG	☐	☐	☐	☐
other: |_____|	☐	☐	☐	☐

Molecular status before SCT

cytogenetic or MRD marker:

☐ not done

☐ no

☐ yes: state which and please enclose copy of each diagnostic finding.

marker: |_____| laboratory: |_____|

Disease status before SCT:

status ☐ CR after reinduction
☐ CR never achieved after diagnosis of ALCL relapse
☐ further relapse during / after reinduction

SCT after |__|. relapse. *(Please fill in the number of the relapse.)*

Treatment before SCT

Treatment arm: ☐ Arm 2b (progress after frontline treatment, CD3+, no MSD and no 10/10 non-sibling donor)
☐ Arm 3 (progress after frontline treatment, CD3 negative, relapse ≤ 12 months from diagnosis or > 12 months but VBL in frontline)

Autograft (page 2/11)

Patient's name	Registration number	date of birth (dd mm yy)	UPN	Sex (m/f)
|_____|	|__|__|__|__|__|__|	|__|__|.|__|__|.|__|__|	|__|__|__|__|	|__|

Collection

Source of stem cells: ☐ BM ☐ PBSC

Date of collection / cytapheresis: |__|__|.|__|__|.|__|__| (dd mm yy)

If PBSC:

collection of PBSC after Re-induction course

- ☐ 1st course of re-inductio
- ☐ 2nd course of Re-induction
- ☐ other

cytokines

- ☐ no
- ☐ yes: G-CSF: ☐ no ☐ yes
  GM-CSF: ☐ no ☐ yes
  other: ☐ no ☐ yes

mobilisation courses: number of mobilisation courses: |__|
date of last mobilisation course: |__|__|.|__|__|.|__|__| (dd mm yy)

Stem cell manipulation:

☐ no
☐ yes: please specify : |_____|

Autograft (page 3/11)

Patient's name	Registration number	date of birth (dd mm yy)	UPN	Sex (m/f)
|_____|	|__|__|__|__|__|	|__|__|.|__|__|.|__|__|	|__|__|__|__|__|	|__|

Clinical status before SCT

Please mark the appropriate field for each parameter and complete the data
(for toxicities: maximum value of the week before start of the conditioning regimen).

Performance Status

Score	Karnofsky Description (patients older than 16 years)	Lansky Description (Patients younger than 16 years)
100%	normal, no complaints, no evidence of disease.	Fully active, normal.
90%	Able to carry on normal activity; minor signs or symptoms of disease.	Minor restrictions in physically strenuous activity.
80%	normal activity with effort; some signs or symptoms of disease.	Active, but tires more quickly.
70%	Cares for self, unable to carry on normal activity or do active work.	Both greater restriction of and less time spent in play activity.
60%	Requires occasional assistance, but is able to care for most of his/her needs	Up and around, but minimal active play, keeps busy with quieter activities.
50%	Requires considerable assistance and frequent medical care.	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
40%	Disabled, requires special care and assistance.	Mostly in bed; participates in quiet activities.
30%	Severely disabled, hospitalisation indicated. Death not imminent.	In bed; needs assistance even for quiet play.
20%	Very sick, hospitalisation indicated. Death not imminent.	Often sleeping; play entirely limited to very passive activities.
10%	Moribund, fatal processes progressing rapidly.	no play; does not get out of bed.

Gastrointestinal toxicity

Grade	0	1	2	3	4	n.d.
Diarrhea	none	2 – 3 stools/day	4 – 6 stools/day or nocturnal stools or light cramps	7-9 stools/day or incontinence or severe cramps	≥ 10 stools/day or bloody diarrhea or TPN necessary	☐
Vomiting [Number of episodes in 24h]	0	1	2 – 5	6 – 10	> 10 or TPN necessary	☐
Stomatitis	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swollow	painful erythema, edema or ulcers preventing swalloing or requiring IV hydration	TPN because of stomatitis necessary	☐
Nausea	none	able to eat	oral intake significantly decreased	no significant intake requiring IV fluids	TPN necessary	☐

Haematologic toxicity

Grade	0	1	2	3	4	n.d.
Granulocytes [G/L]	≥ 2.0	1.5 – < 2.0	1.0 – < 1.5	0.5 – < 1.0	< 0.5	☐
Hemoglobin [g/dL]	age norm (N)	10.0 – < N	8.0 – < 10.0	6.5 – < 8.0	< 6.5	☐
Leukocytes [G/L]	≥ 4.0	3.0 – < 4.0	2.0 – < 3.0	1.0 – < 2.0	< 1.0	☐
Platelets [G/L]	≥ 100	75 – < 100	50 – < 75	10 – < 50	< 10	☐

Dermatologic/Skin toxicity

Grade	**0**	**1**	**2**	**3**	**4**	n.d.
Changes in the skin	none	erythema	dry desquamination, vasculitis, pruritus	moist desquamination, ulzerations	exfoliative dermatitis, Necrosis	☐

Autograft (page 4/11)

Patient's name	Registration number	date of birth (dd mm yy)	UPN	Sex (m/f)
|_____|	|__|__|__|__|__|__|	|__|__|.|__|__|.|__|__|	|__|__|__|__|	|__|

Pulmonary toxicity

Grade	0	1	2	3	4	n.d.
FEV $_1$	≥ 90% of pretreatment or normal value	≥ 75% - <90% of pretreatment or normal value	≥ 50% - <75% of pretreatment or normal value	≥ 25% - <50% of pretreatment or normal value	<25% of pretreatment or normal value	☐
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest requiring suppl. oxygen	decreased O_2 saturation requiring pressure support (CPAP) or assisted ventilation	☐
Pneumonitis, pulmonary infiltrates	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation	☐

Cardiac toxicity

Grade	0	1	2	3	4	n.d.
Arrhythmia	none	asymptomatic, not requiring treatment	recurrent, persistent, not reequiring treatment	therapy required	hypotension, ventr. arrhythmia, defibrillation	☐
Echocardio: LV-SF	≥ 30%	≥ 24% - < 30%	≥ 20% – < 24%	> 15% – < 20%	≤ 15%	☐
Cardiac function	normal	asymptomatic decline of resting ejection fraction of ≥10% but < 20% of baseline value	asymptomatic but resting EF below normal value for laboratory EF or decline of resting EF ≥20% of baseline value	mild CHF, responsive to treatment	severe or refractory CHF or requiring intubation	☐

Infection toxicity

Grade	0	1	2	3	4	n.d.
Fever [°C]	< 38°C	38 – 39°C	> 39 – 40°C	> 40°C für < 24 Std.	> 40°C für ≥ 24 Std.	☐
Infection	none	mild	moderate, pathogen not identified; IV antibiotics	severe, pathogen identified; IV antibiotics	life-threatening, hypotension	☐

If clinically important infections are present or being treated within one month prior to conditioning, specify:

- bacterial: ☐ no ☐ yes, specify: organism: |_____| site: |_____|
- viral: ☐ no ☐ yes, specify: organism: |_____| site: |_____|
- fungal: ☐ no ☐ yes, specify: organism: |_____| site: |_____|
- parasitic: ☐ no ☐ yes, specify: organism: |_____| site: |_____|
- pathogen not identified site: |_____|

Hepatic toxicity

Grade	0	1	2	3	4	n.d.
Bilirubin	within limits of normal	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN	☐
S-GOT/S-GPT	within limits of normal	> ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20 x ULN	☐

Renal toxicity

Grade	0	1	2	3	4	n.d.
Creatinine	within limits of normal	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN	☐
Creatinine-Clearance [ml/Min./1,73m²]	≥ 90	60 – 89	40 – 59	20 – 39	≤ 19	☐
Hämaturia	none	microscopic only	intermittent gross bleeding, not clots	persistent gross bleeding or clots; catheterisation or instrumentation	transfusion required	☐
Proteinuria [g/l]	none	< 3	3 – 10.0	> 10.0	nephrotic syndrome	☐

Autograft (page 5/11)

Patient's name | Registration number | date of birth (dd mm yy) | UPN | Sex (m/f)

Neurological toxicity

Grade	0	1	2	3	4	n.d.
Peripheral Neurotoxicity	none	paresthesias, mild subjective weakness	severe paresthesias	unbearable paresthesias, deficits in motor funct.	paralysis	☐
Central Neurotoxicity	none	mild somnolence or agitation; drowsiness	somnolence <50% of the time, moderate disorientation	somnolence ≥ 50% of the time, severe disorientation, hallucinations	coma, seizures	☐

Allergy/Immunology

Grade	0	1	2	3	4	n.d.
Allergy	none	transient	asymptomatic bronchospasm	symptomatic bronchospasm, serum sickness	anaphylaxis	☐

Ocular/Visual

Grade	0	1	2	3	4	n.d.
Cataract/ Keratitis	none	asymptomatic cataract, mild keratitis or corneal ulceration	symptomatic cataract or corneal ulceration, glaucoma	massive keratitis, retinopathy, glaucoma	panophthal-mitis, unilateral or bilateral loss of vision	☐

Osteonecrosis

Grade	0	1	2	3	4	n.d.
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic or disabling	☐

other clinically significant coexisting disease or organ impairment:

☐ no ☐ yes

If yes, specify: _____

_____

_____

Do they cause modifications in the conditioning regimen or dose of medication?

☐ no ☐ yes

If yes, please state which: _____

_____

_____

Autograft (page 6/11)

Patient's name |_____| Registration number |__|__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__| Sex (m/f) |__|

Conditioning regimen

Body height: |__|__|__| cm Body weight: |__|__|__|,|__| kg BSA: |__|,|__|__| m^2

Therapy

drugs, ATG, mono AB (product name)	daily dose given	mg/kg/d	$mg/m^2/d$	days of administration	total dose given (mg)	dosage according to protocol no	yes
Example: *Endoxan*	*40*	☒	☐	*-3*	*1200*	☐	☒
		☐	☐			☐	☐
		☐	☐			☐	☐
		☐	☐			☐	☐
		☐	☐			☐	☐

if dose modification, specify: |_____|

	no	yes	total dose	number of fractions	days of administration
TBI	☐	☐	|__|__| Gy	|__|__|	|__|__|__|__|__|
CNS boost	☐	☐	|__|__| Gy	|__|__|	|__|__|__|__|__|
other boost	☐	☐	|__|__| Gy	|__|__|	|__|__|__|__|__|

if other, specify: |_____|

Transplantation

Date of transplantation (dd/mm/yy) |__|__| |__|__| |__|__|
Number of this transplantation |__|

Manipulation of graft:
☐ no ☐ yes
if yes, type of manipulation:
T-cell-depletion: ☐ no ☐ yes method: |_____|
CD34+ selection: ☐ no ☐ yes method: |_____|
other: |_____| ☐ no ☐ yes method: |_____|

Cells infused: number of nucleated cells: _____*10^8/kg
CD34+ cells: _____*10^6/kg
CD3+ cells: - T-cell depleted graft: _____*10^4/kg
- unmanipulated graft: _____*10^7/kg

Cytokines in the immediate post transplant period (till day +28):
☐ no ☐ yes, specify: ☐ G-CSF
☐ other: |_____|
starting day (dd/mm/yy) |__|__| |__|__| |__|__|
starting dose: |____|,|____|µg/kg
length of cytokine treatment: |__|__| days

Autograft (page 7/11)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__| Sex (m/f) |__|

Engraftment

Evidence of haematopoietic reconstitution: (dd/mm/yy)

Leucocytes	>1,000/µl:	|__|__| |__|__| |__|__|	☐	not reached
Neutrophils	>500/µl:	|__|__| |__|__| |__|__|	☐	not reached
Platelets	>20,000/µl:	|__|__| |__|__| |__|__|	☐	not reached
Platelets	>50,000/µl:	|__|__| |__|__| |__|__|	☐	not reached
last platelet transfusion:		|__|__| |__|__| |__|__|	☐	transfusions ongoing
last red cell transfusion:		|__|__| |__|__| |__|__|	☐	transfusions ongoing

Graft failure:

☐ no ☐ yes, date of diagnosis |__|__| |__|__| |__|__| (dd/mm/yy)

Reason of graft failure:
- ☐ non-engraftment
- ☐ other: |_____|

Treatment of graft failure:
- ☐ no specific treatment
- ☐ cytokines, specify: |_____|
- ☐ subsequent transplant
- ☐ other: |_____|

If subsequent transplant, date: |__|__| |__|__| |__|__| (dd/mm/yy)
type of transplant: ☐ autologous
☐ allogeneic: ☐ related ☐ unrelated

Complications < day 100

Please mark the appropriate field for each parameter
(maximum value till day 100 or date of death respectively) and complete the data.

Gastrointestinal toxicity

Grade	0	1	2	3	4	n.d.
Diarrhea	none	2 – 3 stools/day	4 – 6 stools/day or nocturnal stools or light cramps	7-9 stools/day or incontinence or severe cramps	≥ 10 stools/day or bloody diarrhea or TPN necessary	☐
Vomiting [Number of episodes in 24h]	0	1	2 – 5	6 – 10	> 10 or TPN necessary	☐
Stomatitis	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swollow	painful erythema, edema or ulcers preventing swalloing or requiring IV hydration	TPN because of stomatitis necessary	☐
Nausea	none	able to eat	oral intake significantly decreased	no significant intake requiring IV fluids	TPN necessary	☐

Haematologic toxicity

Grade	0	1	2	3	4	n.d.
Granulocytes [G/L]	≥ 2.0	1.5 – < 2.0	1.0 – < 1.5	0.5 – < 1.0	< 0.5	☐
Hemoglobin [g/dL]	agenorm (N)	10.0 – < N	8.0 – < 10.0	6.5 – < 8.0	< 6.5	☐
Leukocytes [G/L]	≥ 4.0	3.0 – < 4.0	2.0 – < 3.0	1.0 – < 2.0	< 1.0	☐
Platelets [g/l]	≥ 100	75 – < 100	50 – < 75	10 – < 50	< 10	☐

Dermatology/Skin toxicity

Grade	0	1	2	3	4	n.d.
Changes in the skin	none	erythema	dry desquamination, vasculitis, pruritus	moist desquamination, ulzerations	exfoliative dermatitis, necrosis	☐

Autograft (page 8/11)

Patient's name	Registration number	date of birth (dd mm yy)	UPN	Sex (m/f)
|_____|	|__|__|__|__|__|__|	|__|__|.|__|__|.|__|__|	|__|__|__|__|	|__|

Pulmonary toxicity

Grade	0	1	2	3	4	n.d.
FEV $_1$	≥ 90% of pretreatment or normal value	≥ 75% - <90% of pretreatment or normal value	≥ 50% - <75% of pretreatment or normal value	≥ 25% - <50% of pretreatment or normal value	<25% of pretreatment or normal value	☐
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest requiring suppl. oxygen	decreased O_2 saturation requiring pressure support (CPAP) or assisted ventilation	☐
Pneumonitis, pulmonary infiltrates	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation	☐

Cardiac toxicity

Grade	0	1	2	3	4	n.d.
Arrhythmia	none	asymptomatic, not requiring treatment	recurrent, persistent, not reequiring treatment	therapy required	hypotension, ventr. arrhythmia, defibrillation	☐
Echocardio: LV-SF	≥ 30%	≥ 24% - < 30%	≥ 20% – < 24%	> 15% – < 20%	≤ 15%	☐
Cardiac function	normal	asymptomatic decline of resting EF of ≥10% but < 20% of baseline value	asymptomatic but resting EF below normal value for lab. or decline of resting EF ≥20% of baseline value	mild CHF, responsive to treatment	severe or refractory CHF or requiring intubation	☐

Hepatic toxicity

Grade	0	1	2	3	4	n.d.
Bilirubin	within limits of normal	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN	☐
S-GOT/S-GPT	within limits of normal	> ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20 x ULN	☐

Renal toxicity

Grade	0	1	2	3	4	n.d.
Creatinine	within limits of normal	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN	☐
Creatinine-Clearance [ml/Min./1,73m²]	≥ 90	60 – 89	40 – 59	20 – 39	≤ 19	☐
Hämaturia	none	microscopic only	intermittent gross bleeding, not clots	persistent gross bleeding or clots; req. catheterization or instrumentation	transfusion required	☐
Proteinuria [g/l]	none	< 3	3 – 10.0	> 10.0	nephrotic syndrome	☐

Neurological toxicity

Grade	0	1	2	3	4	n.d.
Peripheral Neurotoxicity	none	paresthesias, mild subjective weakness	severe paresthesias	unbearable pares-thesias, deficits in motor funct.	paralysis	☐
Central Neurotoxicity	none	mild somnolence or agitation; drowsiness	somnolence < 50% of time, modrate disorientation	somnolence ≥ 50% of time, severe disorientation, hallucinations	coma, seizures	☐

Allergy/Immunology

Grade	0	1	2	3	4	n.d.
Allergy	none	transient	asymptomatic bronchospasm	symptomatic bronchospasm, serum sickness	anaphylaxis	☐

Autograft (page 9/11)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__|__| Sex (m/f) |__|

Ocular/Visual

Grade	0	1	2	3	4	n.d.
Cataract/ Keratitis	none	asymptomatic cataract, mild keratitis or corneal ulceration	symptomatic cataract or corneal ulceration, glaucoma	massive keratitis, retinopathy, glaucoma	panophthal-mitis, unilateral or bilateral loss of vision	☐

Osteonecrosis

Grade	0	1	2	3	4	n.d.
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic or disabling	☐

Infection toxicity

Grade	0	1	2	3	4	n.d.
Fever [°C]	< 38°C	38 – 39°C	> 39 – 40°C	> 40°C für < 24 Std.	> 40°C für ≥ 24 Std.	☐
Infection	none	mild	moderate, pathogen not identified; IV antibiotics	severe, pathogen identified; IV antibiotics	life-threatening, hypotension	☐

If clinically important infections were present or being treated till day +100, please complete:

pathogen identified :

☐ no, please specify site of infection:

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify: |_____|

☐ yes, please specify:

---

bacterial: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy), specify organism: : |_____|

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify: |_____|

---

viral: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy)

- CMV infection ☐ no ☐ yes
- EBV ☐ no ☐ yes
- Hepatitis B ☐ no ☐ yes
- Hepatitis C ☐ no ☐ yes
- BKV ☐ no ☐ yes
- other: ☐ no ☐ yes: |_____|
- CMV disease ☐ no ☐ yes
- Adenovirus ☐ no ☐ yes
- Herpes simplex ☐ no ☐ yes
- Herpes ☐ no ☐ yes, type: |_____|
- Varicella-Zoster ☐ no ☐ yes

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify: |_____|

---

fungal: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy) ☐ possible ☐ probable ☐ proven

- Aspergillus ssp ☐ no ☐ yes
- Candida ssp ☐ no ☐ yes
- other ☐ no ☐ yes: |_____|

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify:|_____|

---

parasitic: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy)

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify:|_____|

Autograft (page 10/11)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__| Sex (m/f) |__|

other clinically significant coexisting disease or organ impairment:

☐ no ☐ yes, please specify:

- severe bleeding ☐ no ☐ yes
- infarction or thrombosis ☐ no ☐ yes
- VOD ☐ no ☐ yes
- ARDS ☐ no ☐ yes
- acute vascular leak syndrome ☐ no ☐ yes

intensive care measures:

☐ no ☐ yes, please state indication:

- assisted ventilation ☐ no ☐ yes
- haemodialysis ☐ no ☐ yes
- haemofiltration ☐ no ☐ yes
- other ☐ no ☐ yes: |_____|

admittance to ICU?

☐ no ☐ yes

Best response to SCT

☐ continued CR
☐ CR achieved: date CR achieved: |__|__| |__|__| |__|__| (dd/mm/yy)
☐ no remission

Treatment after SCT

☐ no ☐ yes, please specify indication:

- no remission ☐ no ☐ yes
- relapse ☐ no ☐ yes
- other ☐ no ☐ yes: |_____|

if yes, kind of treatment:

- chemotherapy ☐ no ☐ yes
- subsequent SCT ☐ no ☐ yes, date: |__|__| |__|__| |__|__| (dd/mm/yy)
- other treatment ☐ no ☐ yes: |_____|

Cytokines in the post transplant period > day +29 to day +100:

☐ no ☐ yes

if yes, specify: G-CSF: ☐ no ☐ yes
other: ☐ no ☐ yes, |_____|

starting date |__|__| |__|__| |__|__| (dd/mm/yy)

starting dose: |____|,|____|µg/kg

duration of cytokine treatment: |__|__| days

Remission status – day 100 or at date of death

Relapse after SCT: ☐ not applicable (never in CR) ☐ no

☐ yes *(please fill in an event form)*: date of relapse: |__|__| |__|__| |__|__| (dd/mm/yy)

site of relapse:
local ☐ no ☐ yes: |_____|
BM ☐ no ☐ yes
CNS ☐ no ☐ yes
other: ☐ no ☐ yes: |_____|

Autograft (page 11/11)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__| UPN |__|__|__|__|__| Sex (m/f) |__|

Molecular status – day 100 or at date of death

Cytogenetic or MRD Marker:

☐ not done ☐ no ☐ yes, state which and please enclose copy of each diagnostic finding.

marker: |_____| laboratory: |_____|

Survival status – day 100

☐ alive date of last follow up: |__|__| |__|__| |__|__| (dd/mm/yy)

Performance status criteria (Please mark the appropriate value)

Score	Karnofsky Description (patients elder than 16 years)	Lansky Description (Patients younger than 16 years)
100 %	normal, no complaints, no evidence of disease.	Fully active, normal.
90%	Able to carry on normal activity; minor signs or symptoms of disease.	Minor restrictions in physically strenuous activity.
80%	normal activity with effort; some signs or symptoms of disease.	Active, but tires more quickly
70%	Cares for self, unable to carry on normal activity or do active work.	Both greater restriction of and less time spent in play activity.
60%	Requires occasional assistance, but is able to care for most of his/her needs	Up and around, but minimal active play, keeps busy with quieter activities.
50%	Requires considerable assistance and frequent medical care.	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
40%	Disabled, requires special care and assistance.	Mostly in bed; participates in quiet activities.
30%	Severely disabled, hospitalization indicated. Death not imminent.	In bed; needs assistance even for quiet play.
20%	Very sick, hospitalization indicated. Death not imminent.	Often sleeping; play entirely limited to very passive activities.
10%	Moribund, fatal processes progressing rapidly.	no play; does not get out of bed.

☐ Died ⇒ please fill in an Event form (see page 143)

Date of death: |__|__| |__|__| |__|__| (dd/mm/yy)

Main Cause of death:

- ☐ Relapse or Progression
- ☐ Transplantation Related Cause: (tick all that apply)
  - ☐ GVHD
  - ☐ graft failure
  - ☐ pulmonary toxicity
  - ☐ cardiac toxicity
  - ☐ infection
  - ☐ VOD
  - ☐ post transplant lymphoproliferative disorder
  - ☐ other: |_____|
- ☐ Secondary Malignancy
- ☐ Late Event
- ☐ Other: |_____|
- ☐ Unknown

Notes

Hospital Stamp	Date (dd mm yy)	Name (in block letters) responsible physician	Signature

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Follow up – SCT (page 1/8)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__|

☐ **1 year** ☐ **2 years** ☐ **3 years** ☐ **4 years** **|__| years after SCT**

Last Follow up Date reported to the study centre: |__|__| |__|__| |__|__| (dd/mm/yy)
Please report on all events occurring only after the above date.

Disease status – 1 year after SCT or at date of death

☐ continued CR
☐ no remission
☐ relapse:
date of relapse: |__|__| |__|__| |__|__| (dd/mm/yy)
site of relapse: local ☐ no ☐ yes: |_____|
BM ☐ no ☐ yes
CNS ☐ no ☐ yes
other: ☐ no ☐ yes: |_____|

Anti-lymphoma treatment after SCT

☐ no ☐ yes, please specify indication:

- no remission ☐ no ☐ yes
- relapse ☐ no ☐ yes
- mixed chimerism ☐ no ☐ yes *(allogeneic SCT only)*
- other ☐ no ☐ yes: |_____|

if yes, kind of treatment:

- reduction or discontinuation of immunosuppression *(allogeneic SCT only)* ☐ no ☐ yes
- chemotherapy ☐ no ☐ yes
- donor leukocyte infusion *(allogeneic SCT only)* ☐ no ☐ yes

1.DLI: no. of CD3 or CD|__| cells: |_____| /kg |__|__| |__|__| |__|__| (dd/mm/yy)
2.DLI: no. of CD3 or CD|__| cells: |_____| /kg |__|__| |__|__| |__|__| (dd/mm/yy)
3.DLI: no. of CD3 or CD|__| cells: |_____| /kg |__|__| |__|__| |__|__| (dd/mm/yy)
4.DLI: no. of CD3 or CD|__| cells: |_____| /kg |__|__| |__|__| |__|__| (dd/mm/yy)

- subsequent SCT ☐ no ☐ yes, date: |__|__| |__|__| |__|__| (dd/mm/yy)
- other treatment ☐ no ☐ yes: |_____|

Chronic GvHD *(allogeneic SCT only)*

☐ no ☐ yes, date of onset: |__|__| |__|__| |__|__| (dd/mm/yy)
☐ limited
☐ extended
progression from aGvHD: ☐ no
☐ yes

Diagnosis based on: ☐ clinical evidence
☐ histologic evidence

Follow up – SCT (page 2/8)

Patient's name |_____| Registration number |__|__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__|

Indicate organ involvement of chronic GvHD:

Skin / Hair: ☐ no ☐ yes, specify: |_____|
Eyes: ☐ no ☐ yes, specify: |_____|
Mouth: ☐ no ☐ yes, specify: |_____|
Lung: ☐ no ☐ yes, specify: |_____|
GI Tract: ☐ no ☐ yes, specify: |_____|
Liver: ☐ no ☐ yes, specify: |_____|
UG Tract: ☐ no ☐ yes, specify: |_____|
musculoskeletal: ☐ no ☐ yes, specify: |_____|
haematologic: ☐ no ☐ yes, specify: |_____|
other: ☐ no ☐ yes, specify: |_____|

cGvHD resolved: ☐ no ☐ yes, date |__|__| |__|__| |__|__| (dd/mm/yy)

Chronic GvHD Treatment *(allogeneic SCT only)*

☐ no ☐ yes, specify:

Medication	**no**	**yes**	**product name**	**maximum dose (units)**	total duration of treatment **days**	**ongoing**
increase of CSA	☐	☐		|____| mg/kg/day	|____|	☐
Methylprednisolone	☐	☐		|____| mg/kg/day	|____|	☐
Mycophenolate-Mofetile	☐	☐		|____| mg/kg/day	|____|	☐
Tacrolimus	☐	☐		|____| mg/kg/day	|____|	☐
ALG/ATG	☐	☐	|_____|	|____| mg/kg/day	|____|	☐
monoclonal AB	☐	☐	|_____|	|____| ...../...../....	|____|	☐
Photophoresis	☐	☐			|____|	☐
PUVA	☐	☐			|____|	☐
other	☐	☐	|_____|	|____| ...../...../....	|____|	☐

Follow up – SCT (page 3/8)

Patient's name |_____| Registration number |__|__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__|

Complications / Late Effects

Please mark the appropriate field for each parameter (maximum value since last Follow up date; see page 1) and complete the data.

Gastrointestinal toxicity

Grade	0	1	2	3	4	n.d.
Diarrhea	none	2 – 3 stools/day	4 – 6 stools/day or nocturnal stools or light cramps	7-9 stools/day or incontinence or severe cramps	≥ 10 stools/day or bloody diarrhea or TPN necessary	☐
Vomiting [Number of episodes in 24h]	0	1	2 – 5	6 – 10	> 10 or TPN necessary	☐
Stomatitis	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swollow	painful erythema, edema or ulcers preventing swalloing or requiring IV hydration	TPN because of stomatitis necessary	☐
Nausea	none	able to eat	oral intake significantly decreased	no significant intake requiring IV fluids	TPN necessary	☐

Haematologic toxicity

Grade	0	1	2	3	4	n.d.
Granulocytes [G/L]	≥ 2.0	1.5 – < 2.0	1.0 – < 1.5	0.5 – < 1.0	< 0.5	☐
Hemoglobin [g/dL]	age norm (N)	10.0 – < N	8.0 – < 10.0	6.5 – < 8.0	< 6.5	☐
Leukocytes [G/L]	≥ 4.0	3.0 – < 4.0	2.0 – < 3.0	1.0 – < 2.0	< 1.0	☐
Platelets [g/l]	≥ 100	75 – < 100	50 – < 75	10 – < 50	< 10	☐

Dermatology/Skin Toxicity

Grade	0	1	2	3	4	n.d.
Changes in the skin	none	erythema	dry desquamination, vasculitis, pruritus	moist desquamination, ulzerations	exfoliative dermatitis, necrosis	☐

Pulmonary toxicity

Grade	0	1	2	3	4	n.d.
FEV_1	≥ 90% of pretreatment or normal value	≥ 75% - <90% of pretreatment or normal value	≥ 50% - <75% of pretreatment or normal value	≥ 25% - <50% of pretreatment or normal value	<25% of pretreatment or normal value	☐
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest requiring suppl. oxygen	decreased O_2 saturation requiring pressure support (CPAP) or assisted ventilation	☐
Pneumonitis, pulmonary infiltrates	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation	☐

Follow up – SCT (page 4/8)

Patient's name	Registration number	date of birth (dd mm yy)
|_____|	|__|__|__|__|__|	|__|__|.|__|__|.|__|__|

Cardiac toxicity

Grade	0	1	2	3	4	n.d.
Arrhythmia	none	asymptomatic, not requiring treatment	recurrent, persistent, not reequiring treatment	therapy required	hypotension, ventr. arrhythmia, defibrillation	☐
Echocardio: LV-SF	≥ 30%	≥ 24% - < 30%	≥ 20% – < 24%	> 15% – < 20%	≤ 15%	☐
Cardiac function	normal	asymptomatic decline of resting EF of ≥10% but < 20% of baseline value	asymptomatic but resting EF below normal value for lab. or decline of resting EF ≥20% of baseline value	mild CHF, responsive to treatment	severe or refractory CHF or requiring intubation	☐

Hepatic toxicity

Grade	0	1	2	3	4	n.d.
Bilirubin	within limits of normal	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN	☐
S-GOT/S-GPT	within limits of normal	> ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20 x ULN	☐

Renal toxicity

Grade	0	1	2	3	4	n.d.
Creatinine	within limits of normal	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN	☐
Creatinine-Clearance [ml/Min./1,73m²]	≥ 90	60 – 89	40 – 59	20 – 39	≤ 19	☐
Hämaturia	none	microscopic only	intermittent gross bleeding, not clots	persistent gross bleeding or clots; req. catheterization or instrumentation	transfusion required	☐
Proteinuria [g/l]	none	< 3	3 – 10.0	> 10.0	nephrotic syndrome	☐

Neurological toxicity

Grade	0	1	2	3	4	n.d.
Peripheral Neurotoxicity	none	paresthesias, mild subjective weakness	severe paresthesias	unbearable pares-thesias, deficits in motor funct.	paralysis	☐
Central Neurotoxicity	none	mild somnolence or agitation; drowsiness	somnolence < 50% of time, modrate disorientation	somnolence ≥ 50% of time, severe disorientation, hallucinations	coma, seizures	☐

Allergy/Immunology

Grade	0	1	2	3	4	n.d.
Allergy	none	transient	asymptomatic bronchospasm	symptomatic bronchospasm, serum sickness	anaphylaxis	☐

Ocular/Visual

Grade	0	1	2	3	4	n.d.
Cataract/ Keratitis	none	asymptomatic cataract, mild keratitis or corneal ulceration	symptomatic cataract or corneal ulceration, glaucoma	massive keratitis, retinopathy, glaucoma	panophthal-mitis, unilateral or bilateral loss of vision	☐

Osteonecrosis

Grade	0	1	2	3	4	n.d.
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic or disabling	☐

Follow up – SCT (page 5/8)

Patient's name |_____| Registration number |__|__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__|

Infection toxicity

Grade	0	1	2	3	4	n.d.
Fever [°C]	< 38°C	38 – 39°C	> 39 – 40°C	> 40°C für < 24 Std.	> 40°C für ≥ 24 Std.	☐
Infection	none	mild	moderate, pathogen not identified; IV antibiotics	severe, pathogen identified; IV antibiotics	life-threatening, hypotension	☐

Only for the 1-year-Follow up: If clinically important infections were present or being treated after day +100, please complete:

pathogen identified :

☐ no, please specify site of infection:
site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify: |_____|

☐ yes, please specify:

---

bacterial: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy), specify organism: : |_____|
site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify: |_____|

---

viral: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy)

- CMV infection ☐ no ☐ yes
- CMV disease ☐ no ☐ yes
- EBV ☐ no ☐ yes
- Adenovirus ☐ no ☐ yes
- Hepatitis B ☐ no ☐ yes
- Herpes simplex ☐ no ☐ yes
- Hepatitis C ☐ no ☐ yes
- Herpes ☐ no ☐ yes, type: |_____|
- BKV ☐ no ☐ yes
- Varicella-Zoster ☐ no ☐ yes
- other: ☐ no ☐ yes: |_____|

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify: |_____|

---

fungal: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy) ☐ possible ☐ probable ☐ proven

- Aspergillus ssp ☐ no ☐ yes
- Candida ssp ☐ no ☐ yes
- other ☐ no ☐ yes: |_____|

site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify:|_____|

---

parasitic: ☐ no ☐ yes: |__|__| |__|__| |__|__| (dd/mm/yy)
site: ☐ systemic
☐ localized:
☐ lungs ☐ skin ☐ gut ☐ brain ☐ other, specify:|_____|

---

other clinically significant coexisting disease or organ impairment:

☐ no ☐ yes, please specify:

- severe bleeding ☐ no ☐ yes
- infarction or thrombosis ☐ no ☐ yes
- VOD ☐ no ☐ yes
- ARDS ☐ no ☐ yes
- acute vascular leak syndrome ☐ no ☐ yes

Follow up – SCT (page 6/8)

Patient's name |_____| Registration number |__|__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__|

intensive care measures:

☐ no ☐ yes, please state indication:

- assisted ventilation ☐ no ☐ yes
- haemodialysis ☐ no ☐ yes
- haemofiltration ☐ no ☐ yes
- other ☐ no ☐ yes: |_____|

admittance to ICU?

☐ no ☐ yes

Complications / Late Effects: Endocrinological diagnostic investigation

Thyroid Gland:
sonography done: ☐ No ☐ Yes, specify: ☐ normal ☐ pathologic

Laboratory results:

parameter	normal	pathologic	not done
T4	☐	☐	☐
fT4	☐	☐	☐
TSH	☐	☐	☐

hormone substitution: ☐ No ☐ Yes

Gonodal function:

parameter	normal	pathologic	not done
LH	☐	☐	☐
FSH	☐	☐	☐
Prolactin	☐	☐	☐
Oestradiol	☐	☐	☐
Testosterone	☐	☐	☐

hormone substitution: ☐ No ☐ Yes

Other Complications / Late Effects

- growth curve documentation: ☐ No ☐ Yes, specify: ☐ normal ☐ pathologic
  substitution of growth hormone: ☐ No ☐ Yes
- Tanner's stages: Breast |____| Pubic Hair |____| Genitals |____|
- for girls: menarche ☐ No ☐ Yes
- for boys: testes' volume/ml |____| right |____| left
- continuous alopecia ☐ No ☐ Yes
- Skeletal abnormalities ☐ No ☐ Yes
  (e.g. necrosis of the femoral head)
  if yes, specify: |_____|
- additional late effects: ☐ No ☐ Yes
  if yes, specify: |_____|

Follow up – SCT (page 7/8)

Patient's name |_____| Registration number |__|__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__|

Last chimerism result (allogeneic SCT only)

☐ not done ☐ done

if done, please specify results:

PB/ BM	Date of ex-amination	If sorted, type of cells	% of donor cells	Method (FISH, VNTR, other)	Laboratory (city)	Treatment					
						Immunosuppression: none	unchanged	increased	reduced	stopped	DLI
						☐	☐	☐	☐	☐	☐
						☐	☐	☐	☐	☐	☐
						☐	☐	☐	☐	☐	☐
						☐	☐	☐	☐	☐	☐
						☐	☐	☐	☐	☐	☐

Secondary malignancy

☐ no ☐ yes, please fill in an Event form (see page 143)

Survival status

Alive ☐ Date of last follow up: |__|__| |__|__| |__|__| (dd/mm/yy)

Performance status criteria (Please tick the appropriate value)

Score	Karnofsky Description (patients elder than 16 years)	Lansky Description (Patients younger than 16 years)
100	Normal, no complaints, no evidence of disease.	Fully active, normal.
90	Able to carry on normal activity; minor signs or symptoms of disease.	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	Active, but tires more quickly.
70	Cares for self, unable to carry on normal activity or do active work.	Both greater restriction of and less time spent in play activity.
60	Requires occasional assistance, but is able to care for most of his/her needs	Up and around, but minimal active play, keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	No play; does not get out of bed.

Follow up – SCT (page 8/8)

Patient's name	Registration number	date of birth (dd mm yy)
|_____|	|__|__|__|__|__|	|__|__|.|__|__|.|__|__|

☐ Died ⇒ please fill in an Event form (see page 143)

Date of death: |__|__| |__|__| |__|__| (dd/mm/yy)

Main Cause of death:

- ☐ Relapse or Progression
- ☐ Transplantation Related Cause: (tick all that apply)
  - ☐ GVHD
  - ☐ graft failure
  - ☐ pulmonary toxicity
  - ☐ cardiac toxicity
  - ☐ infection
  - ☐ VOD
  - ☐ post transplant lymphoproliferative disorder
  - ☐ other: |_____|
- ☐ Secondary Malignancy
- ☐ Late Event
- ☐ Other: |_____|
- ☐ Unknown

Notes

Hospital Stamp	Date (dd mm yy)	Name (in block letters) responsible physician	Signature

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Follow up – Vinblastine

Patient's name |_____| Registration number |__|__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__|

☐ **1 year** ☐ **2 years** ☐ **3 years** ☐ **4 years** **|__| years after end of VBL**

Last Follow up date reported to the study centre: |__|__| |__|__| |__|__| (dd/mm/yy)
Please report on all events occurring only after the above date.

Disease and Survival Status

Alive? ☐ no ☐ yes ⇒ date of last follow up: |__|__| |__|__| |__|__| (dd/mm/yy)

Event (relapse / progression, secondary malignancy, late event, death) occurred?
☐ no ☐ yes ⇒ *Please fill in an event form!*

Late Effects

Late effect(s):	no	yes		Date of 1st occurrence (dd mm yy)	Specification of late effect(s)	NCI-Grade
• cardiovascular system	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• CNS / peripheral nerves	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• endocrinology	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• lung / respiratory tract	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• psychosocial late effects	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• kidney / urinary tract	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• sensory organs	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• musculoskeletal system	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• liver	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• skin	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• haematology	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• gastrointestinal tract	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|
• other	❑	❑	→	|__|__|.|__|__|.|__|__|	_____	|__|

Notes / Specification of late Effects

_____ Hospital Stamp _____ Date (dd mm yy) _____ Name (in block letters) _____ Signature
responsible physician

Version: April 2004

Therapy Study ALCL-Relapse

Studienleitung: Prof. Dr. A. Reiter, Universitäts-Klinikum Gießen, Kinderklinik, Päd. Hämatologie und Onkologie, Feulgenstr. 12, 35385 Gießen, Tel.: 0641 - 99-43627 (Studienzentrale); -43626 (Studiendokumentation); Fax: 0641 - 9943629

Events

should be sent at lastest two weeks after occurrence of any event

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__| (if known)

Treatment Arm ❑ Arm 1 ❑ Arm 2a ❑ Arm 2b ❑ Arm 3 ❑ Arm 4 (see chapter 7, page 26)

Progression ❑ no ❑ yes, at |__|__|.|__|__|.|__|__| (dd mm yy)

Localisation(s) of progression:

- bone marrow ❑ no ❑ yes
- CNS ❑ no ❑ yes
- testes ❑ no ❑ yes
- reappearance or increase of residuals ❑ no ❑ yes:_____
- appearance of new location(s) ❑ no ❑ yes:_____

Therapy of progression planned/done? ❑ no ❑ yes:_____

Second Malignancy ❑ no ❑ yes, at |__|__|.|__|__|.|__|__| (dd mm yy)

Diagnosis: ❑ AML ❑ MDS other:_____

Therapy after diagnosis of second malignancy

❑ no ❑ yes: _____

Late Event ❑ no ❑ yes, at |__|__|.|__|__|.|__|__| (dd mm yy)

(malignancy more than 3 years after diagnosis of relapsed ALCL; no differentiation between progression and second malignancy possible)

Diagnosis: _____

Therapy after diagnosis of Late Event

❑ no ❑ yes: _____

Patient died ❑ no ❑ yes, at |__|__|.|__|__|.|__|__| (dd mm yy) *Please fill in an Follow up form*

Autopsy: ❑ no ❑ yes

Reason for death:

❑ caused by progression of lymphoma

❑ caused by therapy complications

❑ chemotherapy-related causes

❑ transplantation-related causes

- GvHD ❑ no ❑ yes
- graft failure ❑ no ❑ yes
- pulmonary toxicities ❑ no ❑ yes
- cardiac toxicities ❑ no ❑ yes
- infection ❑ no ❑ yes
- veno occlusive disorder (VOD) ❑ no ❑ yes
- posttransplant lymphoproliferative disorder (LPD) ❑ no ❑ yes
- unknown ❑ no ❑ yes
- other ❑ no ❑ yes, please specify: _____

❑ caused by other reasons:_____

Date of last examination |__|__|.|__|__|.|__|__| (dd mm yy)

Notes:

Hospital Stamp | Date (dd mm yy) | Name (in block letters) responsible physician | Signature

Version: April 2004

Therapy Study ALCL-Relapse

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Serious Adverse Events (SAE)

Please send a Fax to the National Study Centre within 48 hours.

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__|(if known)

Reasons for SAE Report

- death of the patient — please fill in the "Event" form and send it to the responsible data centre ❑ no ❑ yes
- life-threatening event ❑ no ❑ yes
- impairment of further therapy as per instruction of the protocol ❑ no ❑ yes
- unscheduled in-patient hospitalisation or prolongation of hospitalisation ❑ no ❑ yes
- persistent significant disability or incapacity ❑ no ❑ yes
- medically significant event or an event which requires intervention to prevent one or other of the outcomes listed above ❑ no ❑ yes
- unexpected, severe side effects, which can not be documented on the toxicity form ❑ no ❑ yes

NCI-CTC toxicity grading of SAE: ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ unknown / not to arrange

Beginning resp. detection of the SAE: at |__|__|.|__|__|.|__|__| (dd mm yy)

During/after therapy element: ❑ 1st CC ❑ 2nd CC ❑ CVA ❑ ICM ❑ ICI ❑ Conditioning regimen ❑ after SCT ❑ other, please specify:_____

Please describe the event and the taken measures:
(Symptoms, localisation, laboratory reports, diagnostics, duration, therapy and course; if necessary please attach additional sheet)

_____

_____

Medication at the occurrence of the SAE

N°	Medicament	Daily dosage	Application	Dates of therapy (from/to)	Relationship between medication and event					
					not related	unlikely	possible	probable	related	insufficient data to assess
1.					❑	❑	❑	❑	❑	❑
2.					❑	❑	❑	❑	❑	❑
3.					❑	❑	❑	❑	❑	❑
4.					❑	❑	❑	❑	❑	❑
5.					❑	❑	❑	❑	❑	❑
6.					❑	❑	❑	❑	❑	❑
7.					❑	❑	❑	❑	❑	❑
8.					❑	❑	❑	❑	❑	❑
9.					❑	❑	❑	❑	❑	❑
10.					❑	❑	❑	❑	❑	❑

- Is there a relationship possible between the SAE and medication administered before the SAE occurred? ❑ no ❑ yes, _____
- Has (have) one (or several) treatment(s) been stopped? ❑ no ❑ yes, N°: _____
- Did reaction abate after stopping the treatment(s)? ❑ no ❑ yes, N°: _____
- Has (have) one (or several) treatment(s) been reintroduced? ❑ no ❑ yes, N°: _____
- Did reaction reappear after reintroduction? ❑ no ❑ yes, N°: _____
- Was (were) the dosage(s) changed? ❑ no ❑ yes, N°: _____

According to your opinion, SAE is related to:

❑ Disease aggravation, which the patient was in the trial for
❑ Other concomitant disease(s)
❑ Treatment according to Protocol ALCL-Relapse
❑ Other concomitant treatment(s)
❑ Other known or suspected cause(s), please comment: _____

Outcome of the SAE

❑ Ongoing ❑ Recovered without after-effects ❑ Recovered with after-effects
❑ Death due to the SAE ❑ Death unconnected with the SAE

Date of recovering or of death: |__|__|.|__|__|.|__|__| (dd mm yy) or ❑ not applicable (still ongoing)

_____ _____ _____ _____

Hospital Stamp | Date (dd mm yy) | Name (in block letters) responsible physician | Signature

Version: April 2004

Therapy Study ALCL-Relapse

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Histopathological and Immunohistochemical Review page 1/2

(form to be completed by the reference pathology center)

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__|(if known)

Local histology number	|_____|
Type of review ..... National (1) International (2)	|__|
Date of review	|__|__| |__|__| |__|__|__|__|
For the national review, name of the reviewer	|__|__|__|__|__|__|__|__|__|__|
Review histology number	|_____|
Site of biopsy :	
Lymph node ..... no (0) yes (1)	|__|
Skin ..... no (0) yes (1)	|__|
Soft tissue mass ..... no (0) yes (1)	|__|
Other ..... no (0) yes (1)	|__|
Bone marrow biopsy ..... negative (0) positive (1) ND (X)	|__|
If positive ..... no HE (0) after IHC (1)	|__|
Diagnosis :	
ALCL 1	
Hodgkin's disease 2	
B-NHL 3	
T-NHL 4	
NHL NOS (not otherwise specified)..... 5	|__|
Other 6	
Specify :	|__|__|__|__|__|__|__|__|__|__|
Subtype of ALCL according to WHO classification[43]:	
Classical 1	|__|
Giant cell 2	
Small cell 3	
Lymphohistiocytic 4	
Hodgkin's like 5	
Mixed 6	
Component (example : for Classical + small cell + Lymphohistiocytic = 1-3-4).....	
Other 7	|__| |__| |__|
Specify	|__|__|__|__|__|__|__|__|__|__|
Unclassifiable 8	
Other Morphologic parameters :	
Perivascular pattern ..... no (0) yes (1)	|__|
Other ..... no (0) yes (1)	|__|
Specify	|__|__|__|__|__|__|__|__|__|__|

Histopathological and Immunohistochemical Review page 2/2

(to be completed by the reference pathology center)

Patient's name |_____| Registration number |__|__|__|__|__| date of birth (dd mm yy) |__|__|.|__|__|.|__|__|

Immunophenotype on paraffin embedded tissue
(Mandatory antibodies) :

Alk	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
For Alk,	Nuclear and cytoplasmic 1					
	Cytoplasmic restricted 2					
	Cytoplasmic with membrane reinforcement 3					
	Restricted to the membrane 4					|__|
CD30	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CD 2	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CD 3	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CD 5	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CD 20	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CD 43	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CD 56	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
Perforin	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
Granzyme B	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|

Other mandatory antibodies in Alk negative cases :

EMA	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
bcl-2	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CD 15	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CLA (CD45)	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|

Optional antibodies :

Cytotoxic markers :

Tia 1	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|

T cell markers :

CD 4	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CD 7	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CD 8	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|

B cell markers :

CD 79a	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CD 22	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|

Other antibodies :

UCHL1	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
ß-F1	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
LMP 1	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
CD68/KP1 or PGM1	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|
	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|__|__|__|__| |__|
	0 (0)	+ (1)	++ (2)	+++ (3)	ND (4)	|__|__|__|__|__| |__|

Cell lineage :

	null (0)	T/NK (1)	B (2)	Undeterminate (3)	|__|

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Genetics

Surname (or initial): _____ First name (or initial): _____

Date of birth: |__|__|.|__|__|.|__|__| (dd mm yy) Registration number: |__|__|__|__|__|(if known)

Use further forms, if necessary!

Cytogenetic result:

Kind of material: _____ Date of biopsy/puncture: |__|__|.|__|__|.|__|__| (dd mm yy)

culture time ❑ 24 h ❑ 48 h Specimen-/Entrance-number: |__|__|__|__|__|__|__|__|__|__|__|__|

Results:

❑ no evaluable metaphases

❑ number of evaluated metaphases: |__|__|__|

Karyotype (according to ISCN95):

_____

_____

_____

FISH:

Kind of material: _____ Date of biopsy/puncture: |__|__|.|__|__|.|__|__| (dd mm yy)

culture time ❑ 24 h ❑ 48 h Specimen-/Entrance-number: |__|__|__|__|__|__|__|__|__|__|__|__|

- analysed chromosomal region: _____
- used probes: _____
- number of analysed ❑ metaphases: |__|__|__|__| ❑ interphases: |__|__|__|__|
- result: ❑ no result ❑ negative ❑ positive in |__|__|__| % of cells

_____

_____

Results of molecular genetics:

Kind of material: _____ Date of biopsy/puncture: |__|__|.|__|__|.|__|__| (dd mm yy)

Specimen-/Entrance-number: |__|__|__|__|__|__|__|__|__|__|__|__|__|__|

- analysed gene rearrangement: _____
- result: ❑ no result ❑ negative ❑ positive

_____

_____

Stamp _____ Date (dd mm yy) _____ Name (in block letters) _____ Signature responsible scientist _____

18.7 Contract of participation (clinic)

Contract of participation in the study ALCL-Relapse
Hospital (stamp):

Investigator

Name: _____

Phone: _____ Fax: _____ e-mail: _____

Investigator representative

Name: _____

Phone: _____ Fax: _____ e-mail: _____

Investigator representative

Name: _____

Phone: _____ Fax: _____ e-mail: _____

Contact person for study affairs and mail

Name: _____

Phone: _____ Fax: _____ e-mail: _____

Data Management

Name: _____

Phone: _____ Fax: _____ e-mail: _____

I have thoroughly read and reviewed the study protocol ALCL-Relapse. Having read and understood the requirements and conditions of the study protocol, I agree to perform the clinical study according to this protocol, the international good clinical practice principles, the declaration of Helsinki (version 2002) and regulatory authority requirements for source document verification and inspection of the study. Further I will archive the study documents in accordance to valid regulations.
I agree to inform the study chair on problems in diagnostic and therapeutic decision making. I agree to report within 48 hours of any clinical adverse event that is serious, whether considered treatment-related or not.

Investigator: _____
Date and Signature

Investigator representative: _____
Date and Signature

Investigator representative: _____
Date and Signature

I agree to send diagnostic material to the national reference pathology and cytomorphology:

Pathologist: _____ _____
Name Date and Signature

18.8 Participating groups and centres

Principal investigators of the study groups/national reference centres

Study Group	Paediatric Oncologist	Data Management	Statistician	Pathologist
AIEOP				
Name	**Angelo Rosolen**			
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Phone	0043 1 401 70250	00 43 1 401 70 478	00 43 1 401 70 477	00 43 1 400 36 50
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Name	**Alfred Reiter**	**Ulrike Meyer**	**Martin Zimmermann**	**Reza Parwaresch**
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E-mail	alfred.reiter@paediat.med.uni-giessen.de	nhl.studie@paediat.med.uni-giessen.de	zimmermann.martin@mh-hannover.de	rparwaresch@path.uni-kiel.de

Study Group	Paediatric Oncologist	Data Management	Statistician	Pathologist
DCOG				
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Study Group	Paediatric Oncologist	Data Management	Statistician	Pathologist
PPLLSG				
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Fax				
E-mail	denise.williams@addenbrookes.nhs.uk			

Participating centres of paediatric haematology and oncology

A **Augsburg**	Frau Dr. A. Gnekow	I. Kinderklink des KZVA Hämatologie/Onkologie Stenglinstr. 2 86156 Augsburg	Tel.: 0821/400-3405 Fax: 0821/400-3332
AC **AACHEN**	Herr Prof. Dr. R. Mertens	Kinderklinik der med. Fakultät der RWTH Bereich Hämatologie/Onkologie Pauwelsstr. 30 52057 Aachen	Tel.: 0241-8089902 Fax: 0241-8888481
AR **AARAU**	Dr. R. Angst	Kinderklinik Hämatologie/Onkologie Kantonsspital CH - 5000 Aarau	Tel.: 0041/62-838-4906 Fax: 0041/62-838-4709
AU **ST. AUGUSTIN**	Frau Dr. R. Dickerhoff	Johanniter Kinderklinik für den Rhein-Sieg-Kreis Arnold-Janssen-Str. 18-29 53754 Sankt Augustin	Tel.: 02241/249-1 Fax: 02241/249-272
B **BERLIN**	Herr Prof. Dr. G. Henze	Kinderklinik des UKRV Abt. Hämatologie/Onkologie Augustenburger Platz 1 13353 Berlin	Tel.: 030/450-66032 Fax: 030/450-66906
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BI **BIELEFELD**	Herr Dr. N. Jorch	Kinderklinik Gilead Hämatologie - Onkologie Grenzweg 10 33617 Bielefeld-Bethel	Tel.: 0521/144-2712 Fax: 0521/144-6032
BL **BASEL**	Herr Prof. P. Imbach	Baseler Kinderspital Pädiatrische Onkologie/Hämatologie Römergasse 8 CH - 4005 Basel	Tel.: 0041-61/685-6226 Fax: 0041-61/685-6003
BN **BONN**	Herr Prof. Dr. U. Bode	Zentrum für Kinderheilkunde der Universität Bonn Abt. Päd. Hämatologie/Onkologie Adenauerallee 119 53113 Bonn	Tel.: 0228/287-3215 Fax: 0228/287-3220
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BS **BRAUNSCHWEIG**	Herr Prof. Dr. G. Mau	Städtisches Krankenhaus Kinderklinik Holwedestr. 16 38118 Braunschweig	Tel.: 0531/595-1424 Fax: 0531/595-1400

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Gießen, den 6. Mai 2004
Az.: Prof.Fed./Erb

Unser Zeichen: 56/04
Sitzung am: 29.04.2004

Titel: *Treatment protocol for relapsed anaplastic large cell lymphoma of childhood and adolescence. An European Inter-group Co-operation on Childhood Non-Hodgkin Lymphome (EICNHL); International Multicentre Therapy Studie.*

Es handelt sich um eine Erstbegutachtung für den Leiter der Klinischen Prüfung (LKP) ☒
Es handelt sich um eine Anschlussbegutachtung ☐
Eingesandte Unterlagen:
- ☒ Formalisierter Antrag
- ☒ Denkschrift der Deutschen Krebsgesellschaft e.V. und der Deutschen Krebshilfe e.V. betr. Therapieoptimierungsprüfung, Version April 1999
- ☒ Ausführliche Darstellung des Vorhabens (Studienprotokoll, Version I, April 2004)
- ☒ Patienten/Probanden-Information und Einwilligungserklärung der Patienten/Probanden an der Therapiestudie ALCL-Relapse, für allogene Blutstammzelltransplantation von HLA passenden Spendern, für allogene Blutstammzelltransplantation von Spendern mit unterschiedlichen Gewebsmerkmalen, für autologe Blutstammzelltransplantation, jeweils Version April 2004

Der Antrag wurde unter ethischen, medizinisch-wissenschaftlichen und rechtlichen Gesichtspunkten geprüft. Soweit betreffend, wurde **das auf Seite 2 wiedergegebene Protokoll** unter Berücksichtigung des Good Clinical Practice for Trials on Medicinal Products in the European Community (ICH-GCP) erstellt. Es bezieht sich auf die vorgelegte Fassung des Antrags.

Forderungen der Ethik-Kommission, soweit darin aufgeführt, wurden inzwischen erfüllt. ☐
Sie stimmt dem Vorhaben zu. ☒
Sie stimmt dem Vorhaben unter Auflagen zu (siehe S. 2). ☐
Sie stimmt dem Vorhaben nicht zu (siehe S. 2). ☐

Die Ethik-Kommission erwartet, daß Ihr bis 31.12.07 ohne Aufforderung ein kurzer Bericht auf beigefügtem (roten) Formblatt übermittelt wird. Er soll mitteilen, ob das Ziel der Studie erreicht wurde, ob ethische, medizinisch-wissenschaftliche oder rechtliche Probleme aufgetreten sind, und ob das Ergebnis publiziert ist/wird. Unabhängig davon ist die Ethik-Kommission über alle Änderungen des Prüfplans zu unterrichten. Ihr sind alle schweren unerwünschten Wirkungen mitzuteilen, soweit sie im Bereich der Zuständigkeit dieser Ethik-Kommission aufgetreten sind. Bei überregionalen Studien sind sie auch dem LKP mitzuteilen.
Die ärztliche und juristische Verantwortung des Leiters der klinischen Prüfung und der an der Prüfung teilnehmenden Ärzte bleibt entsprechend der Beratungsfunktion der Ethik-Kommission durch unsere Stellungnahme unberührt.

Auszug aus dem Protokoll der Kommissionsitzung vom 29.04.2004:

Herr Prof. Dr. Reiter berichtet. Es handelt sich um eine Therapieoptimierungsstudie bei Kindern mit Rezidiv eines großzelligen anaplastischen Non-Hodgkin-Lymphoms (betr. ca. 20% aller betroffenen Kinder), die mit einer Behandlung nach Maßgabe der neuen Studie (konzipiert in Zusammenarbeit mit mehreren europäischen Studiengruppen) eine wesentlich bessere Heilungschance haben (ca. 50%). Für das multizentrische Vorhaben liegt die Prüfungsleitung bei Prof. Reiter, Erstgutachten: Ethik-Kommission Gießen. Sponsor: Carreras-Stiftung und Klinikum der JLU. Ziel der Studie ist es, die Wirksamkeit der neuen Therapiestrategie zu überprüfen, bei der es sich vorwiegend um Chemotherapie (Re-Induktion) handelt mit folgender entweder allogener oder autologer Stammzelltransplantation. Therapiestratifizierung anhand folgender Parameter: Zeitpunkt des Rezidivs, Immunphänotyp des ALCL, Verfügbarkeit eines Stammzellspenders, Verabreichung von Vinblastin in der first line therapy. Hauptziel: 1. Verbesserung des Event free survival für Kinder und Jugendliche mit frühem Progress des ALCL, 2. Beantwortung der Frage, ob bei Patienten mit Rezidiv das Koordinierungsregime BEAM (ohne Ganzkörperbestrahlung) vor autologer Stammzelltransplantation wirksam ist, Überprüfung der Wirksamkeit einer Vinblastin-Dauertherapie bei Patienten, die Vinblastin noch nicht in der first line-Therapie erhalten hatten, an einem ALCL mit CD3 negativem Immunphänotyp leiden und sehr spät rezidivieren, Therapiedauer 6-24 Monate.
Die Studie wird ausführlich von Herrn Prof. Reiter dargelegt und von der Kommission diskutiert. Ihr liegt eine sehr sorgfältige und ausführliche Planung zugrunde. Die Kommission gibt ein positives Votum ab.

(Ende)

(Prof. Dr. Drs. h.c. K. Federlin)

Die Namen der bei dieser Sitzung anwesenden Mitglieder sind durch Unterstreichung hervorgehoben.
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21 Index of abbreviations

AB	antibody
AIEOP	Associazione Italiana di Ematologia ed Oncologia Pediatrica
ANC	absolute neutrophils count
ARA-C	Cytarabin
ATG	anti human lymphocyte immunglobulines
BFM	Berlin-Frankfurt-Münster
BM	bone marrow
BMP	bone marrow puncture
BSA	body surface area
Ca	calcium
CGH	Comparative Genomic Hybridization
CHF	congestive heart failure
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CR	complete remission
CRT	cranial radiation therapy
CsA	Cyclosporine A
CSF	cerebrospinal fluid
CT	computerized tomography
d	day
DCOG	Dutch Childhood Oncology Group
DFS	disease free survival
DIC	disseminated intravascular coagulation
DMC	Data Safety and Monitoring Committee
EBMT	European Group for blood and marrow transplantation
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Co-operative Oncology Group
ECOP	extracorporal photo-immunotherapy
EDTA	ethylenediaminetetracetic acid
EF	ejection fraction
EFI	event-free interval
EFS	event-free survival
EFS_c	conditional event free survival
EORTC	European Organisation for research and treatment of cancer
FAB	French-American-British (cytomorphological classification)
FACS	fluorescence-activeted cell sorter
FFP	fresh frozen plasma
FK 506	Tacrolimus
FPIA	Flourescence-phosphor-immunoassay
GCP	good clinical practice
G-CSF	granulocytes colony-stimulating factor
GFR	glomerular filtration rate
Glc	glucose
GPOH	Gesellschaft für Pädiatrische Hämatologie und Onkologie
GPT	glutamic-pyruvic-transaminase
GvHD	graft versus host disease
Gy	Gray
h	hour
HD	high-dose
HEPA	high-efficiency particulate air filtration
HIV	human immunodeficiency virus

HLA	human leucocyte antigen
i.m.	intramuscular
i.t.	intrathecal
iv	intravenous
kg	kilogram
LDH	lacate dehydrogenase
LLN	lower limit of normal
LP	lumbar puncture
LRT	local radiotherapy
MD	matched donor
MDD	minimally disseminated disease
MFD	matched family donor
mg	milligram
ml	millilitre
MMD	mismatched donor
MMF	Mycophenolat-Mofetil
MMFD	Mismatched family donor
MMUD	mismatched unrelated donor
MRD	minimal residual disease
MRI	magnetic resonance imaging
MSD	matched sibling donor
MUD	matched unrelated donor
N	number
Na	sodium
NC	nucleated cell
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NOPHO	Nordic Society of Pediatric Haematology and Oncology
OS	overall survival
P	phosphate
p.a.	posterior-anterior
PCR	Polymerase chain reaction
p.o.	per os
pEFS	probability of event-free survival
pOS	probability of overall survival
PPLLSG	Polish Paediatric Leukaemia/Lymphoma Study Group
pts	patients
s.c.	subcutaneous
SAE	serious adverse events
SC	stem cell
SCT	stem cell transplantation
SD	single dose
SE	standard deviation
SELDI	surface enhanced laser desorption/ionization
SF	shortening fraction
SFCE	Société Française des Cancers de l'Enfant
TPM-SMZ	Trimethoprim-Sulfamethoxazole (Cotrim)
TPN	total parenteral nutrition
TRM	treatment related mortality
TBI	total body irradiation
U	units
UKCCSG	United Kingdom Children Cancer Study Group
UNL	upper normal limit
WBC	white blood cell/count
WNL	within normal limits

22 Index