### Study Protocol – Short Version

**Short title** | GMALL 07/2003
---|---
**Full study title** | Multicenter Study To Optimize Treatment of Acute Lymphoblastic Leukemia in Adults (> 15 years) - Treatment Optimization by Evaluation of Minimal Residual Disease -
**Study code / number** | (coming soon)
**Name of the study group** | GMALL
**Study type** | Multicentric
**Disease** | Acute lymphoblastic leukemia (ALL)
**Stage** | de novo
**Age** | 15-65 yrs (*55-65 years if biologically younger according to general condition*)

#### Aims

1. **Improvement of remission duration and survival by**
   - application of a shortened and intensified induction therapy and new consolidation cycles
   - application of a new risk stratification in standard, high and very high risk group
   - application of MRD based risk stratification in standard risk ALL (MRD low, high and intermediate risk)
   - Risk adapted indications for allogeneic, autologous and matched unrelated stem cell transplantation

2. **Prospective evaluation of minimal residual disease (MRD) for**
   - new definition of complete remission
   - analysis of MRD in subgroups of ALL
   - measurement of efficacy of individual treatment elements
   - evaluation of prognostic impact of MRD before and after SCT
   - application of MRD based risk stratification in standard risk ALL for
     - identification of patients with low risk of relapse to allow shortening of treatment from 2 ½ years to 1 year
     - early identification of patients with high relapse risk with the aim of treatment intensification (stem cell transplantation)

3. **Evaluation of feasibility and efficacy of new treatment elements**
   - induction therapy (shortened and intensified)
   - consolidation I (new cycle with HDMTX and HDAC)
   - consolidation II (subgroup specific for B/T lineage ALL in high and very high risk ALL)
   - allogeneic matched unrelated SCT
   - allogeneic non-myeloablative SCT

#### Principal Investigator

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#### Study Center

**Inclusion Criteria**

- Acute lymphoblastic leukemia (pro-B, common, pre-B, early T, thymic T, mature T)
- Age 15-65 yrs (*55-65 years if biologically younger according to general condition*)
- Written informed consent
**Exclusion Criteria**

- Severe comorbidity or leukemia associated complications
- Late relapse of pediatric ALL or ALL as second malignancy
- Cytostatic pre-treatment
- Pregnancy
- Severe psychiatric illness or other circumstances which may compromise cooperation of the patient
- Participation in other clinical trials interfering with the study therapy

**Study Design / Treatment overview**

All patients receive uniform *induction therapy* (pre-phase, induction phase I and II) and *consolidation I* with *stem cell apheresis* (in all standard risk, high and very high risk patients without stem cell donor).

After achievement of CR treatment *stratification I* according to risk factors takes place

**Standard risk patients:** Up to week 49 alternating chemotherapy cycles (HDMTX/ASP, reinduction, HDMTX/ASP, VM26/ARAC, CYCLO/ARAC, HDMTX/ASP) are administered, accompanied by intermittent MRD evaluation (see below).

At the end of the first year *stratification II according to MRD* will take place. In MRD *low risk* patients treatment will be stopped and MRD controls will be continued. In MRD *high risk* patients treatment will be intensified (stem cell transplantation, intensified maintenance or experimental approaches), and in MRD *intermediate risk* intensified maintenance is scheduled.

**High risk patients:** After consolidation I allogeneic SCT (sibling or matched unrelated donor) is recommended. Patients without donor receive consolidation II which adapted to immunologic subtype (T-lineage ALL: CLAEG; B-lineage ALL FLAG-IDA) followed by autologous SCT.

**Very high risk patients:** From the beginning of induction II patients are treated according to a separate protocol with Imatinib parallel to chemotherapy until SCT. Chemotherapy is similar to the high risk group. After SCT Imatinib is given according to MRD level.

**Stratification I according to risk factors**

<table>
<thead>
<tr>
<th>I. Standard Risk (SR):</th>
<th>B-precursor ALL</th>
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<tbody>
<tr>
<td></td>
<td>CR at day 26 (after induction 1) and</td>
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<td></td>
<td>WBC &lt; 30.000/µl for B-precursor ALL</td>
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<td></td>
<td>No proB-ALL</td>
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<td></td>
<td>No t(9;22)/BCR-ABL pos. ALL</td>
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<tr>
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<td>No t(4;11)/ALL1-AF4 pos. ALL</td>
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</table>

Thymic T-ALL

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<th>II. High risk (HR):</th>
<th>B-precursor ALL</th>
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<tbody>
<tr>
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<td>CR first achieved at day 46 (after induction II) or</td>
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<tr>
<td></td>
<td>WBC &gt; 30.000/µl or</td>
</tr>
<tr>
<td></td>
<td>pro B-ALL or</td>
</tr>
<tr>
<td></td>
<td>t(4;11)/ALL1-AF4 pos. ALL or</td>
</tr>
</tbody>
</table>

Early or mature T-ALL

| III. Very high risk (VHR): | t(9;22)/BCR-ABL pos. ALL |

**Overview**

see last page
### Central diagnostics

<table>
<thead>
<tr>
<th><strong>Morphology</strong></th>
<th><strong>Immunophenotyping</strong></th>
</tr>
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</table>
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E-Mail: ethiel@zedat.fu-berlin.de |

<table>
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<tr>
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<th><strong>Molecular genetics</strong></th>
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Fax: ++49 (0)30/8445-4468  
E-Mail: ethiel@zedat.fu-berlin.de |

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<th><strong>MRD</strong></th>
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| Prof. Dr. Michael Kneba  
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EMail: sekretariat@med2.uni-kiel.de or m.kneba@med2.uni-kiel.de | +/- |

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<th><strong>Biometrics</strong></th>
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| Dr. N. Gökbuget (see above)  
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EMail: dorle@messerer.info | Deutsche Krebshilfe e.V. |

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Multicenter Study for Adult ALL – GMALL 07/2003
Overview Total Therapy

Stratification I
according to risk factors

Stratification II
according to MRD

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<tr>
<th>Weeks</th>
<th>Induction</th>
<th>Ki</th>
<th>CNS</th>
<th>T-Lin: CLAEG</th>
<th>B-Lin: FLAG-IDA</th>
<th>Auto SCT*</th>
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<td>SR</td>
<td>KI</td>
<td>I.th. MTX</td>
<td>B-MP</td>
<td>MRD-HR</td>
<td>HD-MTX ASP</td>
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MRD-HR

6MP/MTX

HD-MTX ASP

VM26 ARAC

CYCLO ARAC

ARAC

ASP

MRD

HR

NR

VHR

HR

MRD

Auto SCT*

i.th. MTX

BM/MRD

MRD

IMR

MRD

SCT (allo sibling, MUD or auto)*

End of Therapy

Intensified Maintenance

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<tr>
<th>Weeks</th>
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<th>VM26 ARAC</th>
<th>HD-MTX ASP</th>
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* If donor or autologous stem cells available