SYNOPSIS

Study title
Consolidation therapy with alemtuzumab (MabCampath®) in patients with chronic lymphocytic leukemia who are in complete or partial 2nd remission after cytoreduction with fludarabine or fludarabine plus cyclophosphamide or fludarabine plus cyclophosphamide plus rituximab or bendamustine or bendamustine plus rituximab - a phase I/II study

Rationale
Neither Fludarabine alone (F) or in combination with cyclophosphamide (FC) or in combination with rituximab (FCR) nor bendamustine (B) or bendamustine in combination with rituximab (BR) is not a curative treatment; nearly all patients will eventually relapse. Therefore there is an urgent medical need to look for consolidation therapies which are able to prolong progression free survival or which can shift fludarabine-induced partial remissions to complete remissions or eradicate minimal residual disease in complete - but still PCR-positive - responders. There is no standard post-remission therapy available at the moment. Possible treatment options are high-dose chemotherapy followed by autologous stem cell transplantation or humanized monoclonal antibodies against antigens expressed on CLL cells.

Alemtuzumab is directed against the CD52-antigen which is present in high density on CLL-cells and has shown high response rates and long response duration in patients with fludarabine-refractory CLL. Alemtuzumab was highly effective in clearing peripheral blood and bone marrow from leukemic cells whereas its activity on bulky lymph nodes and splenomegaly was limited. Thus, alemtuzumab seems to be most suitable for the treatment of (minimal) residual disease. A former phase III trial conducted by the GCLLSG (CLL4B protocol) with alemtuzumab in a dosing schedule adapted from refractory CLL (30mg i.v. tiw for 12 weeks) has shown efficacy with a trend to longer progression free survival and a significantly higher rate of molecular remissions, but also significant toxicity including severe infections in the majority of patients being treated with alemtuzumab. The goal of this phase I/II trial is to test at which dose consolidation therapy with alemtuzumab is safe, but still able to induce molecular remissions in patients responding to prior chemotherapy with F or FC or FCR or B or BR.

Objectives
- Safety: Which dose of alemtuzumab as consolidation therapy in patients in 2nd remission after F/FC/FCR/B/BR chemotherapy is safe?
- What is the frequency of CMV reactivations/infections under/after alemtuzumab treatment?
- Which dose of alemtuzumab is efficient to eliminate (minimal) residual disease in peripheral blood and bone marrow? (to turn a clinical PR into a clinical CR? to turn a flow cytometry positive CR into a flow cytometry negative CR? to turn a PCR-positive CR into a PCR-negative CR?)
- How is the pharmacokinetic profile of alemtuzumab?
- How does the pharmacokinetic profile compare between i.v. versus s.c. administration of the drug?
Endpoints

Primary endpoint:
- Dose-limiting toxicity (DLT) and maximal tolerable dose (MTD)
  DLT is defined as a) all grade III/IV non-hematologic toxicity and b) all grade IV hematologic toxicity lasting for more than 2 weeks (excluding lymphopenia) occurring during or within 4 weeks after end of consolidation therapy.

Secondary endpoints:
- Rate of complete MRD response (defined by negativity of 4-colour-cytometry in BOTH peripheral blood AND bone marrow in patients in clinical CR)
  The approved laboratory diagnostics for detection of molecular response is 4-colour flow cytometry. Collaterally, it is possible to take samples for potential PCR-analysis for confirmation if available
  - Rate of immunophenotypic remission using 4-colour flow cytometry
  - Rate of infections (especially CMV infections and reactivations)
  - Rate of severe hematologic and non-hematologic side effects
  - Pharmacokinetics of alemtuzumab (after i.v. and s.c. administration)
  - Progression-free survival, overall survival
  - CR rate (clinical remission rate)

Study design
Open-label, oligocentric two cohort dose escalation phase I/II trial
- cohort A: intravenous administration of alemtuzumab
- cohort B: subcutaneous administration of alemtuzumab
  (will be investigated after i.v. MTD has been determined)

Sample size
- 3 pts per dose level, 3 dose levels (10mg, 20mg, 30mg, once weekly)
- In case of DLT in 1 out of 3 patients, repeat dose level with 3 additional patients
- In case of 2 or more DLTs in one dose level, MTD has been reached at the prior ( = recommended phase II/III dose) dose level. At the recommended phase II/III dose 3 additional pts will eventually be treated (total of 6 pts)
- Dose escalation is only allowed if DLT in 0 out of 3 or in max. 1 out of 6 patients observed
- Dose escalation is stopped and MTD determination eventually omitted in case of unexpected high efficacy, i.e. if elimination of MRD occurs in 3/3 or ≥5/6 patients on a dose level.
- Dose escalation of the s.c. cohort is started with the recommended i.v. dose level, according to the same escalation rules (3 patients per dose level, dose escalation with regard to DLTs or MRD-negativity).

Inclusion criteria
- Established diagnosis of B-CLL according to NCI
- Max. 1 pretreatment (before 2nd line chemotherapy, see below) with chlorambucil or F/FC/FCR/B/BR while pts should not be refractory to F/FC/FCR/B/BR in 1st line
- Complete or partial remission after completion of a 2nd line chemotherapy with F mono or FC or FCR or B or BR (4-6 courses)
- No less than 90 days and no more than 150 days since last dose of F/FC/FCR/B/BR
- Age: ≥ 18
Patients will receive alemtuzumab consolidation after response to second line treatment (F or FC or FCR or B or BR) and receive

Cohort A (alemtuzumab i.v.):

- Beginning of consolidation therapy with alemtuzumab at the earliest 90 days and at the latest 150 days after last dose of chemotherapy.

Dose

- Alemtuzumab will be administered once per week as a 2 h infusion
  - **Dose level I:** 10mg once weekly (start with dose escalation: 3 mg on day 1, 10mg on day 2)
  - **Dose level II:** 20mg once weekly (start with dose escalation: 3mg on day 1, 10mg on day 2, 20mg on day 3)
  - **Dose level III:** 30mg once weekly (start with dose escalation: 3mg on...
Consolidation therapy with Alemtuzumab (MabCampath®) in patients with chronic lymphocytic leukemia who are in complete or partial 2nd remission after cyto-reduction with fludarabine or fludarabine plus cyclophosphamide or fludarabine plus cyclophosphamide plus rituximab or bendamustine or bendamustine plus rituximab - a phase I/II study

**Day 1, 10mg on day 2, 30mg on day 3**

**Cohort B (alemtuzumab s.c.):**

- If in dose level 1 i.v. >= 2 DLTs occurred or after the recommended dose level of i.v. is defined, a dose escalation in the s.c. cohort will be conducted. With the same timing of treatment start, dose escalation (s.c.) is started with the recommended i.v. dose according to the same escalation rules (3 patients per dose level, dose escalation with regard to DLTs or MRD-negativity).

**Duration**

All patients will be treated with alemtuzumab for 8 weeks if no severe toxicity or rapid disease progression is observed.

Therapy with alemtuzumab will be **discontinued** immediately, if

- the disease progresses during treatment with alemtuzumab (worsening of the clinical remission status)
- unacceptable toxicity occurs during treatment with alemtuzumab defined as:
  - grade III or IV non-hematologic toxicities
  - and/or grade IV hematologic toxicities lasting for more than 2 weeks (excluding lymphopenia)
    both defined as DLT.

If hematologic parameters recover in less than 2 weeks, alemtuzumab is re-initiated. If a severe (grade IV) hematologic toxicity occurs a 2nd time, alemtuzumab is permanently stopped. The antibody treatment will also be stopped permanently in case of clinical manifestation of the CMV disease or rising CMV transcripts (weekly PCR) in spite of oral ganciclovir treatment.

**Supportive therapy**

- **Premedication:**
  
  Anti-histamines (2 mg clemastin i.v.) and paracetamol 500 mg p.o. 30 min prior to 1st infusion/injection with alemtuzumab, with the first dose of each escalation and thereafter if clinically indicated.
  
  Prednisone/prednisolone (100mg i.v.) directly before infusions/injections with alemtuzumab, with the first dose of each escalation and thereafter if clinically indicated.

- **G-CSF prophylaxis:**
  
  G-CSF prophylaxis (5µg/kg daily) should be started as soon as leucocytes fall below 1000/µl

- **Infection prophylaxis:**
  
  valacyclovir 500mg p.o. bid (or equivalent) and trimethoprim/cotrimoxazole DS 2x1 p.o. tiw both starting on day 8 and continue during the study and up to a minimum of 4 months following the discontinuation of alemtuzumab or if CD4 cells >= 200/µl
**Evaluations**

Weekly: Vitals signs, physical examination, CBC with differential blood diagnostics and platelet count, CMV monitoring (if antibody diagnostic initially positive), toxicity.

In addition, before initiation of alemtuzumab treatment and after discontinuation of alemtuzumab: performance status, height/weight, chest x-ray, lymph node assessment, spleen and liver measurement, sonography of abdomen, clinical chemistry, bone marrow cytology and histology (at study entry only for CR pts, after week 8 for all patients), immunophenotype of peripheral blood, quantitative immunoglobulins. (Medical history, Binet stage, Coombs test, pregnancy test, immune electrophoresis, before start of study.)

At staging after 4 weeks (additional to weekly assessments): performance status, weight, lymph node assessment, spleen and liver measurement, clinical chemistry

**Central diagnostics**

The following evaluation will be performed centrally at the University of Kiel, Prof. Kneba:

Evaluation of **minimal residual disease (MRD)** in peripheral blood and bone marrow by real time quantitative PCR-analysis (RQ-PCR; TaqMan Technology) of the IgH CDR III region and/or 4-colour flow cytometry to monitor and control responses as follows:

- For 4-colour flow cytometry it is sufficient to send blood immediately before start of consolidation therapy with Alemtuzumab. Only for PCR sequencing, blood has to be sent at study entry (i.e. before start of 2nd line chemotherapy or during 2nd line chemotherapy with F/FC/FCR/B/BR before achievement of a clinical CR
- RQ-PCR and/or 4-colour flow cytometry of peripheral blood for all patients at study entry (after confirmed CR/PR after F or FC or FCR or B or BR; before treatment with alemtuzumab).
- RQ-PCR and/or 4-colour flow cytometry of peripheral blood: every 4 weeks during treatment, at discontinuation of alemtuzumab and thereafter at months 3, 6, 9, 12, 18 and 24 after end of alemtuzumab treatment (follow-up).
- In addition, bone marrow will be analysed for MRD, RQ-PCR and/or 4-colour flow cytometry of bone marrow before treatment with alemtuzumab (in case of CR) and week 8 or at discontinuation of alemtuzumab, thereafter if available at months 3(obligatory in case of clinical CR at this time point), 6, 9, 12, 18, 24 after end of alemtuzumab therapy (follow-up).

The **approved laboratory diagnostics for detection of MRD response is 4-colour flow cytometry. Collaterally, it is possible to take samples for potential PCR-analysis for confirmation if available.**

Monitoring of **T-cell subsets** (CD4, CD8) in peripheral blood before, at discontinuation of alemtuzumab, 3, 6, 9, 12, 18 and 24 months after end of alemtuzumab. To be performed centrally in Kiel.

**CMV monitoring** will be performed centrally at the Max-von-Pettenkofer-Institute, München. Before initiation of alemtuzumab, antibody response status (IgG, IgM) against CMV antigens is tested for all pts; furthermore
CMV-specific T cell subsets are determined before start, 3 and 6 months after end of alemtuzumab treatment. In case of initial negativity in both tests, no further CMV-specific surveillance is required. If at least one test is positive, a CMV-specific monitoring will be performed by a weekly CMV-specific quantitative PCR of peripheral blood. In case of positivity of PCR (>500 copies per ml), confirmation by Clonab-Test (pp65-antigen) is recommended. PCR-positive pts will be treated with Valganciclovir (p.o., 900 mg/d divided in 2 dose; at least for 10 days) while alemtuzumab is continued as long as there are no clinical symptoms of an apparent CMV infection or no rising CMV transcripts detected by weekly PCR. Otherwise, alemtuzumab treatment will be stopped and CMV-treatment shifted to ganciclovir i.v.(10 mg/kg/d, divided into 2 doses, at least for 10 days).

Pharmacokinetics: Pharmacokinetic samples will be taken at week 4, and at week 8, at the following time points: 0, 4, 8, 24, 48, 96, 168h.
First sample has to be taken on a Monday to meet all pharmacokinetic time point requirements.

Study discontinuation

The study will be discontinued prematurely
- if ≥ 2 DLTs occurred in dose level 1 (cohort A and cohort B).
- In addition, the principal investigator will terminate the study if the incidence or severity of adverse events in this or other studies with alemtuzumab indicate a potential health hazard to patients, or if other information from outside the trial precludes continuation of patient recruitment.