

1. PROTOCOL SYNOPSIS

Short Title	T-PLL2 protocol of the German CLL-Study Group (GCLLSG)
Title	Phase II Trial of Combined Immunochemotherapy with Fludarabine, Mitoxantrone, Cyclophosphamide and Alemtuzumab (FMC-Alemtuzumab) in Patients with Previously Treated or Untreated T-Prolymphocytic Leukemia
Sponsor	University of Cologne
Sponsor's representative / Coordinating investigator	Prof. Dr. Michael Hallek, Cologne
Medical advisor	Dr. Georg Hopfinger, Vienna
Rationale	<p>As the median survival time of patients with T-PLL is less than 12 months, the treatment of T-PLL is a special challenge.</p> <p>The overall response rates with conventional chemotherapy or Deoxycoformycin were low (about 30% and 40%), with the monoclonal antibody Alemtuzumab response rates of 50% to 70% were achieved, but the duration of the response was short.</p> <p>In the previous trial (T-PLL 1), the efficacy of the FMC regimen (FMC = Fludarabine, Mitoxantrone and Cyclophosphamide) was tested, a preliminary analysis of 16 patients revealed a response rate of more than 60% after FMC-polychemotherapy and 83% after the subsequent administration of Alemtuzumab.</p> <p>The goal of the T-PLL2-protocol is to assess if the simultaneous administration of FMC-polychemotherapy and -Alemtuzumab with a subsequent Alemtuzumab-maintenance therapy is capable of improving the remission rate and the disease-free survival time in patients with T-PLL.</p>
Study Objective and Endpoints	<p>The objective of the T-PLL2-study is to assess the feasibility, safety and efficacy of simultaneous FMC-Alemtuzumab administration followed by Alemtuzumab-maintenance therapy in patients with T-PLL.</p> <p>Primary endpoints:</p> <ul style="list-style-type: none"> • Remission rate • Number of serious adverse events • Number of life-threatening infections <p>Secondary endpoints:</p> <ul style="list-style-type: none"> • Overall survival time • Progression-free survival time • Duration of remission <p>Response rates in biological subgroups (e.g. gender)</p>
Efficacy Parameters	Response rates (Rate of CR, CRi, nPR, PR, SD and PD).

Safety Assessments	Rate and severity of treatment-induced adverse events.
Inclusion Criteria	<ul style="list-style-type: none"> • Untreated patients with T-prolymphocytic leukemia (T-PLL) according to WHO criteria or pretreated patients (max. one previous treatment) with T-PLL • Age \geq 18 years • WHO performance status of 0-2 • Life expectancy > 6 months • CIRS score \leq 6 • Left ventricular ejection fraction \geq50% confirmed by echocardiogram performed < 6 months before inclusion to the trial and after the end of a possible anthracycline-containing pretreatment • Adequate liver function as indicated by a total bilirubin, AST and ALT \leq 2 the institutional ULN value, unless directly attributable to the T-PLL • Creatinine clearance \geq 70 ml/min calculated according to the formula of Cockcroft and Gault • Seronegativity for HIV, HBV or HCV confirmed by serological testing within 6 weeks prior to registration • Willingness of fertile male and female patients to use a highly effective contraceptive method with a Pearl-Index < 1 during and at least six months after the end of the study treatment (e.g. implants, injectables, oral contraceptives in combination with another contraceptive method, some IUDs, sexual abstinence or vasectomised partner) • Negative serum pregnancy test one week prior to treatment (required for female patients before and <2 years after onset of menopause) • Patient's written informed consent
Exclusion Criteria	<ul style="list-style-type: none"> • Clinically significant auto-immune cytopenia or clinically significant hemolytic anaemia with suspicion of an immune origin, even if the Coombs test is negative • Active secondary malignancy requiring treatment (except basal cell carcinoma or tumour curatively treated by surgery) • Medical condition requiring prolonged use of oral corticosteroids (> 1 month) • Cerebral dysfunction, legal incapacity • Any circumstance at the time of study entry that would preclude completion of the study and required follow-up

<p>Exclusion Criteria (continued)</p>	<ul style="list-style-type: none"> • Active infection or severe infection (WHO 4th degree) within the last three months before inclusion to the study • Participation in any other clinical trial during this study • Known hypersensitivity to any of the study medications (Fludarabine, Cyclophosphamide, Mitoxantrone or Alemtuzumab) • Patients who have already received more than 60% of the recommended maximum cumulative dose of an anthracycline (Epirubicine, Adriamycine or Mitoxantrone). This maximum cumulative dose is defined for the individual substances as follows: <ul style="list-style-type: none"> - Epirubicine: 900mg/m², - Daunorubicin 550 mg/m², (or 400 mg/m² if the patient received mediastinal irradiation) - Adriamycine (Doxorubicine) 550 mg/m² - Mitoxantrone 200 mg/m² • Patients who already received Fludarabine in combination with Cyclophosphamide or Mitoxantrone • Patients who received prior treatment with Alemtuzumab alone or in combination with a purine analogue and who did not achieve a PR that lasted at least 6 months • Patients who are employees of the Sponsor (University of Cologne) or the study sites.
<p>Study Design</p>	<p>This study is an open label, multicentre and prospective phase II trial to determine the efficacy and toxicity of combined immunochemotherapy with FMC (Fludarabine, Cyclophosphamide and Mitoxantrone) and Alemtuzumab followed by a maintenance therapy with Alemtuzumab.</p>
<p>Study Duration</p>	<p>Start of recruitment: June 2010 End of recruitment: June 2012 End of study: December 2015</p>
<p>No. of Patients</p>	<p>16</p>
<p>Participating Countries</p>	<p>Austria and Germany</p>

Study Drug Administration	<p><u>I. First treatment phase: Chemoimmunotherapy A-FMC</u></p> <p>Alemtuzumab:</p> <p><u>Cycle 1+2:</u> 10 mg s.c., days 1-3</p> <p><u>Cycle 3+4:</u> CR: 10 mg s.c., days 1-3 PR/SD: 30 mg s.c., days 1-3</p> <p>Fludarabine: 20 mg/m² i.v., days 1-3</p> <p>Mitoxantrone: 6 mg/m² i.v., day 1</p> <p>Cyclophosphamide: 200 mg/m² i.v., days 1-3</p> <p>Repeat day 29, maximum 4 cycles.</p> <p><u>II. Second treatment phase: Maintenance-treatment with 30mg Alemtuzumab s.c.</u></p> <p>The maintenance therapy will start one month after the Final Staging and will be administered monthly during the first six months plus once in month 10 and 13.</p>
Concomitant therapy	<p><u>I. Premedication</u></p> <p>Patients should be treated with</p> <ul style="list-style-type: none"> - Antihistamine (e.g. Diphenhydramine/Tavegil® 2mg i.v.) - Paracetamol/Acetaminophen (1000mg p.o.) - Prednisolone (e.g. Solu-Decortin® 100mg i.v.) <p>30 minutes before the administration of Alemtuzumab during the first cycle and on the first day of the subsequent cycles of A-FMC and Alemtuzumab-maintenance treatment, plus in cases this premedication is clinically indicated (e.g., when there are adverse effects due to an infusion).</p> <p>If a patient does not show any adverse effects, the premedication may be omitted on day 2 and 3 of each cycle.</p> <p>Any patient considered being at risk of an infusion related reaction and/or tumour lysis syndrome (pts. with a lymphocytosis > 100,000/l) should receive appropriate hydration, urine alkalisation with intravenous bicarbonate and allopurinol before the beginning of treatment and thereafter until the risk is ruled out.</p> <p><u>II. Infection prevention</u></p> <p>Patients should receive</p> <ul style="list-style-type: none"> - Trimethoprim / Sulfamethoxazole (e.g. two tablets Cotrim forte® three times a week) - Valgancyclovir (. 2x 450mg p.o./day)

	<p>or equivalent medications from the beginning until 4 months after the end of the treatment.</p> <p>Prophylactic antifungal medication, e.g., with 100 mg Fluconazole, and use of growth factors like G-CSF and Erythropoietin can be administered according to institutional standards.</p> <p>No live vaccines should be administered during the treatment; responses to inactivated, recombinant and cell wall-vaccines are unreliable and suboptimal in these patients.</p>
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