

## 1. PROTOCOL SYNOPSIS

<p>Short Title</p> <p>Title</p> <p>Head of German CLL Study Group</p> <p>Sponsor's Representative and Coordinating Principal Investigator</p>	<p><b>CLL10 protocol of the German CLL-Study Group (GCLLSG)</b></p> <p><b>Phase III trial of combined immunochemotherapy with Fludarabine, Cyclophosphamide and Rituximab (FCR) versus Bendamustine and Rituximab (BR) alone in patients with previously untreated chronic lymphocytic leukaemia</b></p> <p>Prof. Dr. Michael Hallek</p> <p>Dr. Barbara Eichhorst</p>
<p>Rationale</p>	<p>Although combined chemoimmunotherapy is not a curative treatment for CLL, phase II trials have shown that a high percentage of molecular remissions with very long lasting progression free (PFS) survival can be induced by modern chemoimmunotherapy (FCR) in first line therapy of CLL. The triple combination FCR has been investigated in several phase II and in one phase III study conducted by the GCLLSG in first line therapy of CLL. These studies show the induction of long lasting remissions and a high number of complete remissions with FCR. However, the FCR regimen causes a relatively high percentage of severe cytopenia during and after therapy. Combination therapies based on Bendamustine plus Rituximab ± Mitoxantron (BR or BMR) have shown encouraging activity in patients with relapsed/refractory NHL and in previously treated and untreated CLL. Main side effects of this treatment regimen were cytopenia as well (Table 1). The aim of this phase III trial is to investigate the non-inferiority of the BR combination in comparison to FCR with regard to the efficacy and the incidence of major side effects such as myelosuppression and rate of infections in patients with previously untreated CLL.</p>
<p>Study Objective</p>	<p>The hypothesis is that BR has a non-inferior therapeutic efficacy compared with FCR, but a better safety profile causing less myelosuppression, infections and secondary neoplasias.</p>
<p>Endpoints</p>	<p>The primary endpoint is</p> <ul style="list-style-type: none"> <li>- the progression free survival (PFS) rate after 24 months.</li> </ul> <p>The secondary endpoints of this study are</p> <ul style="list-style-type: none"> <li>- the duration of remission</li> </ul>

	<ul style="list-style-type: none"> <li>- the event free survival (EFS)</li> <li>- the overall survival (OS)</li> <li>- MRD, complete response rates and partial remission rates</li> <li>- response rates and survival times in biological subgroups</li> <li>- rates of toxicities</li> <li>- quality of life</li> </ul>
Inclusion Criteria	<ol style="list-style-type: none"> <li>1. 18 years of age or older.</li> <li>2. Confirmed diagnosis of B-CLL.</li> <li>3. Stage Binet C or stage Binet B and A requiring treatment. Requiring treatment is defined as: <ul style="list-style-type: none"> <li>a) Binet stage B or A plus at least one of the following symptoms: <ul style="list-style-type: none"> <li>- B-Symptoms (night sweats, weight loss <math>\geq 10\%</math> within the previous 6 months, fevers <math>&gt; 38^{\circ}\text{C}</math> or <math>100.4^{\circ}\text{F}</math> for <math>\geq 2</math> weeks without evidence of infection) or constitutional symptoms (fatigue)</li> <li>- progressive lymphocytosis (lymphocytosis is defined as peripheral lymphocyte count <math>&gt; 5 \times 10^9/\text{l}</math>) (increase <math>&gt; 50\%</math> over a 2-month period or doubling of peripheral lymphocyte count <math>&lt; 6</math> months)</li> <li>- evidence of progressive marrow failure as manifested by the development / worsening of anemia and/or thrombocytopenia</li> <li>- massive, progressive or painful splenomegaly or hypersplenism</li> <li>- massive lymph nodes or lymph node clusters (<math>&gt; 10</math> cm in longest diameter) or progressive or symptomatic lymphadenopathy</li> </ul> </li> </ul> </li> <li>4. World Health Organization performance status of 0-2.</li> <li>5. Life expectancy <math>&gt; 6</math> months.</li> <li>6. Adequate liver function as indicated by a total bilirubin, AST, and ALT <math>\leq 2</math> the institutional ULN value, unless directly attributable to the patient's tumor.</li> <li>7. Willingness of fertile male and female patients to use an highlyeffective contraceptive method with a Pearl-Index <math>&lt; 1</math> (such as implants, injectables, oral contraceptives in combination with another contraceptive method, some IUDs, sexual abstinence or vasectomised partner) while on study treatment and for a minimum of six months following study therapy</li> <li>8. Signed, written informed consent.</li> </ol>

	<p>9. Patient is a) male b) female and <math>\geq 2</math> years after the onset of menopause c) female and <math>&lt; 2</math> years after the onset of menopause and has a negative serum pregnancy test one week prior treatment.</p> <p>10. Negative serological Hepatitis B test, negative testing of Hepatitis C RNA, negative HIV test within 6 weeks prior to registration.</p>
Exclusion Criteria	<ol style="list-style-type: none"> <li>1. CIRS-Score <math>&gt; 6</math> or a single score of 4 for one organ category.</li> <li>2. Patients with a 17p deletion detected by FISH (these patients will be treated within the CLL20 or CLL2L protocol of the GCLLSG)</li> <li>3. Creatinine clearance <math>&lt; 70</math> ml/min calculated according to the modified formula of Cockcroft and Gault or directly measured after 24h-urine collection. Creatinine Clearance is to be calculated only in patients with serum creatinine <math>\geq 1.1</math> mg/dl</li> <li>4. Any prior CLL-specific chemotherapy and/or radiotherapy and/or immunotherapy, except for prednisolone treatment administered due to very high lymphocyte counts immediately before first FCR or BR treatment.</li> <li>5. Patients who have progressed with more aggressive B-cell cancers such as Richter's syndrome.</li> <li>6. Active secondary malignancy requiring treatment (except basal cell carcinoma or malignant tumour curatively treated by surgery or successfully treated secondary malignancies in complete remission more than 5 years before enrollment ).</li> <li>7. History of anaphylaxis following exposure to monoclonal antibodies or any of the study drugs.</li> <li>8. Active bacterial, viral or fungal infection.</li> <li>9. Medical condition requiring prolonged use of oral corticosteroids (<math>&gt; 1</math> month).</li> <li>10. Cerebral dysfunction, legal incapacity.</li> <li>11. Pregnant or nursing women, fertile men or women of childbearing potential not using adequate contraception.</li> <li>12. Any circumstance at the time of study entry that would preclude completion of the study or the required follow-up.</li> <li>13. Participation in any other clinical trial</li> </ol>
Study Design	This is a prospective, international, multicentre, open label, 2-arm randomized (1:1) phase III study that compares the efficacy and

	<p>tolerability of the chemotherapy FC (fludarabine and cyclophosphamide) with a possibly better tolerable chemotherapy B (Bendamustine) on the backbone of the future standard in CLL treatment 6x Rituximab 500mg/m<sup>2</sup>. Significance level: <math>\alpha = 0.05</math> (one sided, with one interim analysis and one final analysis using the method of O'Brien and Fleming). Power: 80%. Calculated drop out: 7.5%. Statistical assumptions for sample size calculation: Expected PFS 2 years after FCR therapy = 75%. Test of non-inferiority with less than 7.5% difference in PFS after BR therapy.</p>
Study Duration	<p>Start of recruitment: 10/2008 End of recruitment: 04/2012 End of study: 01/2018</p>
No. of Patients	550 patients (275 in each arm) will be enrolled in the study.
Participating Countries	Austria, Czech Republic, Germany, Switzerland, Denmark
Prephase	Prednisolone 100mg p.o./day for a maximum of 10 days in case of an initial leukocyte count above $100 \times 10^9/l$ may be administered before the first course. Any other prephase is not allowed.
Study Drug Administration	<p>Total of 6 cycles, each with a duration of 28 days:</p> <p><u>FCR-arm:</u> Fludarabine 25 mg/m<sup>2</sup> i.v., days 1-3 Cyclophosphamide 250 mg/m<sup>2</sup>, days 1-3, Rituximab: 375 mg/ m<sup>2</sup> i.v on day 0, cycle 1 Rituximab: 500 mg/m<sup>2</sup> i.v. on day 1, cycle 2-6</p> <p><u>BR-arm:</u> Bendamustine 90mg/m<sup>2</sup> day 1-2 Rituximab 375 mg/m<sup>2</sup> day 0, cycle 1 Rituximab 500 mg/m<sup>2</sup> day 1, cycle 2-6</p>
Concomitant therapy	<p>Premedication: antihistamines, paracetamol/acetaminophen, prednisolon (allopurinol if clinically indicated) prior to first administration of rituximab and thereafter when indicated.</p>

Efficacy Parameters	<p>The primary efficacy endpoint is time from randomization to progression/death.</p> <p>The secondary efficacy parameters overall survival and event-free survival will be measured from randomization to death and from randomization to progressive disease, death or new treatment, respectively.</p> <p>Duration of remission is defined as time from date of first documentation of response to date of the initial documentation of progressive disease or death.</p> <p>Overall response rate includes the number of patients with CRs, incomplete CR or PRs as well as MRD-negative patients.</p>
Safety Assessments	<p>Safety assessments will include safety profile, clinical laboratory tests, and toxicities by using appropriate techniques.</p>