# A Study to Compare the Efficacy and Safety of Obinutuzumab + Venetoclax versus Obinutuzumab + Chlorambucil in Patients With Chronic Lymphocytic Leukemia (CLL14)

**Condition**  
Chronic Lymphocytic Leukemia

**ClinicalTrials.gov Identifier**  
NCT02242942

**EudraCT Number**  
2014-001810-24

**Study Design**  
**Study Type:** Interventional  
**Study Phase:** III  
**Allocation:** Randomized  
**Intervention Model:** Two-Arm Assignment  
**Masking:** Open-Labelled  
**Primary Purpose:** Treatment  
**Estimated Enrollment:** 432 Patients

**Intervention**  
**Drug:** Venetoclax (GDC-0199/ABT-199)  
**Study Arm A:** 6 cycles of obinutuzumab and venetoclax followed by 6 additional cycles of venetoclax.  
**Study Arm B:** 6 cycles of obinutuzumab and chlorambucil followed by 6 additional cycles of chlorambucil.

**Primary Outcome Measure**  
Progression-free survival (PFS), defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause as assessed by the investigator. Disease progression will be assessed by the investigators using the IWCLL criteria (2008).

**Sponsor**  
F. Hoffmann-La Roche Ltd. in collaboration with the German Chronic Lymphocytic Leukaemia Study Group (GCLLSG)

**Co-Sponsor**  
(United States only) AbbVie, Inc.

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**Description**  
This open-label, multicenter, randomized phase III study is designed to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax versus obinutuzumab + chlorambucil in patients with chronic lymphocytic leukemia (CLL) and coexisting medical conditions. The anticipated time on study treatment will be approximately 1 year and the follow-up period will be up to 5 years.
Eligibility Criteria

**Inclusion Criteria**
- Ages eligible for study: 18 years and older
- Genders eligible for study: both
- Documented previously untreated CLL according to the International Workshop on Chronic Lymphocytic Leukemia (IW-CLL) criteria
- CLL requiring treatment according to IWCLL criteria
- Total Cumulative Illness Rating Scale (CIRS) score > 6
- Adequate marrow function independent of growth factor or transfusion support within 2 weeks of screening as per protocol, unless cytopenia is due to marrow involvement of CLL
- Adequate liver function
- Life expectancy > 6 months
- Agreement to use highly effective contraceptive methods per protocol

**Exclusion Criteria**
- Transformation of CLL to aggressive Non-Hodgkin’s lymphoma (Richter’s transformation or pro-lymphocytic leukemia)
- Known central nervous system involvement
- Patients with a history of confirmed progressive multifocal leukoencephalopathy (PML)
- An individual organ/system impairment score of 4 as assessed by the CIRS definition limiting the ability to receive the treatment regimen of this trial with the exception of eyes, ears, nose, throat organ system
- Patients with uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Inadequate renal function
- History of prior malignancy, except for conditions as listed in the protocol if patients have recovered from the acute side effects incurred as a result of previous therapy
- Use of investigational agents or concurrent anti-cancer treatment within the last 4 weeks of registration
- Patients with active bacterial, viral, or fungal infection requiring systemic treatment within the last two months prior to registration
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Hypersensitivity to chlorambucil, obinutuzumab, or GDC-0199 or to any of the excipients
- Pregnant women and nursing mothers
- Positive test results for chronic HBV infection (defined as positive HBsAg serology) or positive test result for hepatitis C (hepatitis C virus (HCV) antibody serology testing)
- Patients with known infection with human immunodeficiency virus (HIV) or human T-cell leukemia virus-1 (HTLV-1)
- Requires the use of warfarin, marcumar, or phenprocoumon
- Received agents known to be strong CYP3A4 inhibitors or inducers within 7 days prior to the first dose of study drug
Commentary

Prof. Dr. med. Michael Hallek
Dr. med. Kirsten Fischer

Why this Trial Is Important to Us

Despite the recent speedy progress made in the treatment of patients with chronic lymphocytic leukemia (CLL), a significant number of patients experience relapsed disease that is associated with progressively shorter durations of response to therapy. The only potentially curative strategy for CLL is allogeneic hematopoietic stem cell transplantation, however, the majority of patients with CLL are not eligible for this therapeutic option because of age or coexisting medical conditions. As a result, a cure for patients with CLL necessitates more effective drugs that also have a safety profile suited for patients who are unfit due to coexisting medical conditions and elderly patients. A chemotherapy-free regimen could meet these expectations.

The BCL-2 inhibitor venetoclax has yielded promising results in patients with relapsed/refractory CLL, both as monotherapy and in combination with rituximab [1–4]. Obinutuzumab is a type 2, glycoengineered anti-CD20-antibody that in combination with chlorambucil resulted in improved overall survival for patients with previously untreated CLL and coexisting medical conditions on the basis of the data of the CLL11 trial [5]. Because obinutuzumab and venetoclax exhibit different mechanisms of action, a combination of both drugs could delay or completely avoid the occurrence of resistance. The safety profiles of both drugs seem to be compatible, especially in light of a chemotherapy-free setting [6].

The CLL14 trial, a collaboration between F. Hoffmann-La Roche, AbbVie and the German CLL Study Group is a multicenter, randomized phase III trial to compare the efficacy and safety of obinutuzumab and venetoclax versus obinutuzumab and chlorambucil in previously untreated patients with CLL and coexisting medical conditions. The target population consists of elderly patients that are not eligible for standard FCR (rituximab, cyclophosphamide, fludarabine) first-line treatment. SEER cancer statistics showed that almost 70% of patients are aged older than 65 years at diagnosis, with a median age of 71 years. Additionally, the vast majority of these patients have one or more clinically relevant comorbidities in addition to their CLL.

In this trial, patients’ medical conditions will be prospectively assessed and scored on the cumulative illness rating scale (CIRS) which has become a standard tool in many clinical trials. Patients with untreated active CLL and with a CIRS score > 6 and/or a creatinine clearance < 70 ml per minute will be randomized to receive either standard treatment with obinutuzumab and chlorambucil or experimental treatment of a chemotherapy-free regimen with obinutuzumab and venetoclax. Standard treatment consists of 6 cycles of obinutuzumab and chlorambucil with 6 additional cycles of chlorambucil, which is considered one of the current standard therapies in this specific patient population. This arm is based on the results of the CLL11 trial demonstrating a survival advantage for the combination therapy of obinutuzumab and chlorambucil over chlorambucil alone [5]. In the experimental arm patients will receive 6 cycles of a chemotherapy-free treatment of obinutuzumab and venetoclax with 6 additional cycles of venetoclax.

The run-in phase of the trial provided initial safety data on the combination of obinutuzumab and venetoclax of 13 patients with previously untreated CLL [7]. We found that initiating treatment with obinutuzumab followed by venetoclax appeared tolerable and effective in this specific fragile elderly patient population. None of the protocol-defined stopping criteria for the run-in phase of the study were met. Based on the independent data monitoring committee review of the safety data, the randomized phase of the study was opened for enrolment in August 2015.

The head-to-head design of the trial, precautionary safety measures, and regular monitoring of safety by an independent data monitoring committee as well as the sponsor and the German CLL Study Group enable early identification of safety signals in the trial and minimize the risk to patients enrolled.

References


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