COLUMBIA UNIVERSITY MEDICAL CENTER

Herbert Irving Comprehensive Cancer Center Protocol

A Single-arm, Multi-center Phase II Trial of Bendamustine/Rituximab Induction Followed by Venetoclax and Rituximab Consolidation for the Frontline Treatment of Chronic Lymphocytic Leukemia (CLL)

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Columbia University Medical Center
Herbert Irving Comprehensive Cancer Center
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TITLE: A single-arm, multicenter phase II trial of bendamustine/rituximab induction followed by venetoclax and rituximab consolidation for the frontline treatment of chronic lymphocytic leukemia

Regulatory Sponsor:	Nicole Lamanna, MD Department of Hematology/Oncology
Funding Source:	AbbVie 5901-B Ammendale Road Beltsville, MD 20705-1266 (847) 938-1091
Study Agent:	Venetoclax
Other Agent:	Rituximab Bendamustine

Affiliate Institutions:

Case Comprehensive Cancer Center
Principal Investigator: Brian Hill, MD, PhD

Columbia University Medical Center
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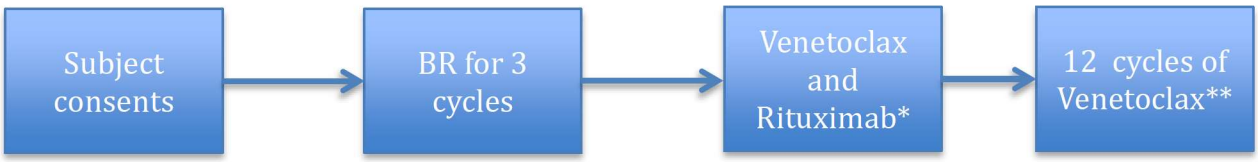
Protocol Synopsis

Title	A single-arm, multicenter phase II trial of bendamustine/rituximab induction followed by venetoclax and rituximab consolidation for the frontline treatment of chronic lymphocytic leukemia
Short Title	BR followed by venetoclax and rituximab for the upfront treatment of CLL
Protocol Number	The standard protocol number used to identify this study.
Phase	Phase 2
Methodology	Single arm
Study Duration	36 months
Study Center(s)	Single-center
Objectives	Primary: 1. To evaluate the efficacy of of bendamustine/rituximab induction followed by venetoclax and rituximab consolidation, as measured by ORR in frontline treatment for CLL. Secondary: 1. Proportion of patients who attain a complete response (CR), proportion of patients who attain a complete remission with incomplete marrow recovery (CRi), the proportion of patients with a partial response (PR), the 2. time to first response (starting from cycle 1 of BR), time to next treatment (TTNT; the number of days from the first cycle of BR to the next treatment program), 3. duration of response (the number of days from first response to recurrence or progression of disease), 4. Progression-free survival (PFS) (the number of days from cycle 1 of BR to progression of disease 5. proportion of patients who attain MRD-negativity, and time to MRD-negativity.
Number of Subjects	Total accrual: 45
Diagnosis and Main Inclusion Criteria	The patient must have a diagnosis of CLL or SLL according to NCI criteria or WHO criteria, respectively. Patients must never have been treated for CLL.

Study Product, Dose, Route, Regimen	1. Bendamustine 50-90 mg/m^2 on days 1-2 for three cycles with each cycle being 28 days. 2. Rituximab 375 mg/m^2 on day 1 or days 1-2 for three cycles with each cycle being 28 days. 3. Venetoclax will then be started in a step-wise fashion per the package insert. Dosing for venetoclax will be as follows: • Cycle 4 days 1-7: 20 mg once daily • Cycle 4 days 8-14: 50 mg once daily • Cycle 4 days 15-21: 100 mg once daily • Cycle 4 days 22-28: 200 mg once daily • Cycle 4 day 29 and thereafter: 400 mg once daily; continue until disease progression, unacceptable toxicity, or 12 cycles duration. 4. Rituximab 375 mg/m^2 cycle 5 day 1 5. Rituximab 500 mg/m^2 cycle 6 day 1 6. Rituximab 500 mg/m^2 cycle 7 day 1 7. Rituximab 500 mg/m^2 cycle 8 day 1 8. Rituximab 500 mg/m^2 cycle 9 day 1 9. Rituximab 500 mg/m^2 cycle 10 day 1
Duration of administration	Bendamustine: 3 cycles. Rituximab: 9 cycles. Venetoclax: 12 cycles.

Statistical Methodology	Initially, the trial used a Simon Two-Stage design and planned to enroll a total of 20 eligible patients: 7 patients in the first stage and 13 patients in the second stage. This study design yielded at least 90% power to detect a 75% response rate (compared to the null hypothesis of 40%) at a significance level of 5% (one-sided). The trial completed the first stage with 7 out of 7 observed responses and proceeded to the second stage. In this new amendment, the sample size for the second stage will be increased by 20 evaluable patients, resulting in a total sample size of 40 evaluable patients. Since the sample size is different from the one originally planned, we calculated the operating characteristics to account for the mid-course changes, keeping the same null and alternative hypotheses, 40% vs 75%, respectively. The results indicate that increasing the total sample size to 40 evaluable patients (33 patients in stage 2) will not affect the initial type I and II errors. Under this scenario, the treatment will be declared positive for meeting the primary endpoint if at least 24 out of 40 patients will achieve a response, yielding a 92% power at a type I error of 0.01. Accounting for dropouts/non-evaluable patients, a total of 45 patients will be enrolled.

Fig 1: Protocol Schema:



*Rituximab given for 6 cycles post venetoclax ramp-up.
**12 full cycles of therapy unless patient experiences progression or toxicity prior to 12 cycles .

1 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Columbia University Medical Center institutional research policies and procedures.

This is a single-arm multicenter phase II study using bendamustine-rituximab (BR) followed by venetoclax and rituximab for the upfront treatment of chronic lymphocytic leuekemia (CLL). The activity, safety, and survival data have been presented previously for BR alone in patients with previously untreated disease and venetoclax alone in relapsed/refractory patients and those with high-risk disease. After pretreatment evaluation, patients will receive three cycles of BR followed by venetoclax via a five-week dose escalation to 400 mg daily. Once patients reach 400 mg of venetoclax daily, patients will receive six cycles (months) of rituximab as consolidation. Total time of venetoclax therapy will be 12 cycles and total time on therapy (BR plus venetoclax plus rituximab) will be 15 cycles . Responses and endpoints will be assessed after 3, 6, 9 (laboratory only), 12, 18, 24, 30, and 36 cycles. Minimal residual disease (MRD) testing will be done after 3, 6, 9, 12, 18, and 24 cycles via an 8-color flow cytometry panel (CD81, CD79b, CD22, CD19, CD43, CD20, CD5, CD3; sensitivity of 1×10^{-5}). Bone marrow testing for MRD can be performed if the peripheral blood is MRD negative (or was MRD negative at the last test). Anti-infective prophylaxis against *H. zoster* and *P. jiroveci* will be mandated. Tumor lysis syndrome (TLS) prophylaxis with allopurinol and/or an alternative will be mandated.

2 STUDY OBJECTIVES

2.1 Primary Endpoint

The primary endpoint will be overall response rate (ORR) after the completion of all therapy, as defined by the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) guidelines update in 2008[1].

3 INVESTIGATIONAL AGENTS AND RATIONALE

Bcl-2 Family Proteins

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma where the t(14;18) chromosomal translocation results in significant over-expression of the protein in B-cells. The Bcl-2 family of genes encodes a family of closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four Bcl-2 Homology (BH) domains[29-32]. Bcl-2 overexpression is a major contributor to the pathogenesis of some types of lymphoid malignancies. Bcl-2 is also overexpressed in acute and chronic leukemias. CLL is a genetic disease where the microRNAs miR15a and miR16-1 that negatively regulate the transcription

of Bcl-2 are deleted or down regulated, resulting in uncontrolled expression of Bcl-2[33,34].

ABT-199 (venetoclax)

ABT-199 is a novel, orally available small molecule Bcl-2 family protein inhibitor that binds with > 500-fold higher affinity (K_i < 0.010 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-XL (K_i – 48 nM) and Bcl-w (K_i – 245 nM)[35]. Overexpression of antiapoptotic Bcl-2 family proteins is associated with increased resistance to chemotherapy, and antagonism of the action of these proteins might enhance response to such therapy and overcome resistance. Antiapoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for antitumor therapy.

Other Agent(s):

Bendamustine

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring[47]. The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride. Its empirical molecular formula is $C_{16}H_{21}Cl_2N_3O_2$ HCl, and its molecular weight is 394.7 daltons.

Rituximab

Rituximab is a chimeric murine/human monoclonal IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences, and human constant region sequences. The antibody is directed specifically against the CD20 antigen found on the surface of normal and malignant B-lymphocytes. CD20 is a hydrophobic transmembrane protein located on pre-B and mature B lymphocytes[53]. The antigen is also found on >90% of B-cell non-Hodgkin lymphomas but is not found on hematopoietic stem cells, early B-lineage precursors, plasma cells, or other normal tissues. CD20 regulates early steps in the activation process of cell cycle initiation and differentiation, and may function as a calcium ion channel.

4 STUDY CALENDAR

5.1 General Design

We will initiate a single-center phase II trial using BR as induction followed by venetoclax and rituximab consolidation for the upfront treatment of chronic lymphocytic leukemia. Subjects will be given this therapy as outlined in the Treatment Map below and in section 12 (Study Calendar). Subjects will receive rituximab and bendamustine for three cycles (each cycle will be 28 days) followed by repeat laboratory and imaging studies to assess response. Subjects will then be classified as having “low”, “medium”, or “high” tumor burden as per the venetoclax package

insert. Appropriate TLS prophylaxis will be given, and all subjects will undergo a five-week dose escalation to 400 mg of venetoclax daily. After the venetoclax ramp-up (cycle 4), six monthly cycles of rituximab will be administered. Responses will be assessed by the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) guidelines update in 2008.[1] Subjects will have response assessments via imaging and laboratory studies at specified time points (see table 12). MRD testing will be done at 4, 11, 16, 24 cycles via an 8-color flow cytometry panel (CD81, CD79b, CD22, CD19, CD43, CD20, CD5, CD3; sensitivity of 1 x 10^{-5}). Bone marrow testing for MRD can be performed if the peripheral blood is MRD negative (or was MRD negative at the last test).

TABLE 2 TREATMENT MAP

Cycle:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Venetoclax				X	X	X	X	X	X	X	X	X	X	X	X
Bendamustine	X	X	X												
Rituximab	X	X	X		X	X	X	X	X	X					

*Each cycle is 28 days for BR. Each cycle of venetoclax is 28 days except for cycle 4 (venetoclax ramp up) which is 35 days.
**Duration of venetoclax will be 12 cycles.
***When starting venetoclax (cycle 4 day 1), at least a 3 week (21 day) interval must occur between then end of cycle 3 of BR and cycle 4 day 1 of venetoclax, but no more than 8 weeks (56 days) in duration.
**** For all procedures at screening and subsequent study assessments/treatments, a +/- 5 day window for non-adverse event related delays will be allowable after discussion and approval by PI. (Please ensure subject has enough study drug if a delay is needed during Cyles 4-15)

*****All screening procedures must take place within 28 days of C1D1

Study Procedures

All study procedures outlined in the Study Calendar in section 12 are discussed in detail in this section, with the exception of adverse event information. All study data will be recorded on case report forms (CRFs).

Procedures performed at Screening will serve as baseline, unless repeated on Week 1 Day 1 prior to dosing; in which case the latter will serve as baseline. Subjects who signed informed consent, and are determined to be a screen failure, will not proceed in study.

Post-Treatment Follow-Up Visit(s)

For subjects who discontinue either BR or venetoclax, the following assessments will be performed every 3 - 6 cycles (post treatment) until discontinuation from the study.

Survival Assessment(s)

Survival information (i.e., the date and cause of death, post treatment cancer therapies, etc.) will be collected via telephone calls and/or clinical visits at 3-6-month intervals after the last study visit for a period of 3 years after the last subject has enrolled on the study.

End of Therapy or Early Discontinuation

For subjects who complete all 15 cycles of therapy or discontinue therapy for any reason, the following assessments will be performed.

- Adverse Event/Concomitant Medication Assessment
- Physical Examination
- Vital Signs
- Hematology and Chemistry (including hepatic function panel)
- ECG

30 Day Safety Follow-Up

Thirty (30) days after a patient completes therapy for any reason (whether end of treatment or early discontinuation), the following assessments will be performed.

- Adverse Event/Concomitant Medication Assessment
- Physical Examination
- Vital Signs
- Hematology and Chemistry (including hepatic function panel)

5 SUBJECT SELECTION AND WITHDRAWAL

Inclusion Criteria

- Subjects must have a diagnosis of CLL according to the IWCLL NCI WG criteria or small lymphocytic lymphoma (SLL) according to the World Health Organization criteria.

- To be considered CLL the subject must have an absolute lymphocytosis in the blood of at least 5,000 lymphocytes per microliter, or bone marrow lymphocytosis greater than or equal to 30% of all nucleated cells

- Subject must have histologic and immunophenotypic analysis that should demonstrate small to moderate size lymphocytes with flow cytometry demonstrating a predominant population of lymphocytes that share both B-cell antigens (CD19, CD20 [typically dim expression] or CD23) as well as CD5 in the absence of other pan-T-cell markers and clonality as evidenced by kappa (κ) or lambda (λ) light chain expression (typically dim immunoglobulin expression) or other genetic method (e.g. immunoglobulin heavy chain variable [*IGHV*] analysis). It is recognized that an occasional subject with CLL may have a slightly aberrant immunophenotype. All such cases need to be reviewed with the principal investigator prior to being registered for the study.
- Subjects must have had no prior therapy for their disease. Topical or inhaled corticosteroids are permitted for other medical conditions, ie asthma or dermatologic reasons.
- Subject must be ≥ 18 years of age.

- Subject must have an Eastern Oncology Cooperative Group (ECOG) performance score of ≤ 2.
- Subjects must have the following (unless due to documented bone marrow failure) :
  - An absolute neutrophil count ≥1.0 10^9/L
  - A hemoglobin ≥ 8 g/dL
  - a platelet count > 50 x 10^9/L

Note: Subjects with inadequate values due to autoimmune hemolytic anemia or autoimmune thrombocytopenia will be eligible for treatment on this protocol regardless of disease stage upon discussion with the principal investigator.

- Subject must have adequate hepatic function per local laboratory reference range as follows:
  - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0X ULN
  - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
- For patients not receiving therapeutic anticoagulation: PT or aPTT ≤1.5 x ULN; for patients on therapeutic anticoagulation or underlying known cause, approval from Principal Investigator may be given for values above 1.5x ULN of PT and/or aPTT
- Subject must have the ability to understand and the willingness to sign a written informed consent document
- Subject agrees to not received treatment with any of the following **within 7 days** prior to the first dose of Venetoclax:

- Steroid therapy for anti-neoplastic intent
- moderate or strong cytochrome P450 3A (CYP3A) inhibitors (see Table 6 for examples)
- moderate or strong CYP3A inducers (see Table 6 for examples)

- Additionally, based on animal data, venetoclax may compromise fertility in males. For this reason, women of child bearing potential and men must agree to use adequate contraception (see below) for at least 90 days prior to study entry and for the duration of study participation. For women of childbearing potential (WCBP): a negative serum β-human chorionic gonadotropin (βhCG) pregnancy test must be performed during screening. WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 24 consecutive months [women ≤ 55 years] or 12 consecutive months [women > 55 years]).

Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men must also refrain from donating sperm for a period of 90 days after the last dose of study drug.

Male and female subjects who are not surgically sterile or postmenopausal must be willing to use medically acceptable methods of birth control from the first dose of study drug to 30 days after the last dose of study drug. Sexually active men, and women using oral contraceptive pills, should also use barrier contraception.

Acceptable forms on contraception include the following:

Total abstinence from sexual intercourse as the preferred life style of the subject; periodic abstinence is not acceptable;

Surgically sterile partner(s); acceptable sterility surgeries are: vasectomy, bilateral tubal ligation, bilateral oophorectomy or hysterectomy;

Intrauterine device (IUD);

Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or cream AND a condom);

Hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to study drug administration.

<u>Exclusion Criteria</u>

- Subject who has been previously treated for CLL or SLL, except with corticosteroids for symptom relief.

- Subject has known allergy to both xanthine oxidase inhibitors and/or rasburicase.
- Subject has a significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, cardiovascular, or hepatic disease that in the opinion of the investigator would adversely affect his/her participating in this study.
- Subject has evidence of other clinically significant uncontrolled condition (s) including, but not limited to:

    a. Uncontrolled and/or active systemic infection (viral, bacterial or fungal)
    b. Chronic hepatitis B virus (HBV) or hepatitis C (HCV) requiring treatment. Note: subjects with serologic evidence of prior vaccination to HBV (i.e. hepatitis B surface (HBs) antigen negative-, anti-HBs antibody positive and anti-hepatitis B core (HBc) antibody negative) or positive anti-HBc antibody from intravenous immunoglobulins (IVIG) may participate.

- Subject is known to be positive for HIV. (HIV testing is not required.)

- NYHA class II-IV heart failure or arrhythmia that is uncontrolled with treatment.

- Pregnant or lactating women. Women and men of childbearing age should use effective contraception (see section 6.1).

- Subject has a history of active malignancies other than CLL within the past 2 years prior to study entry with the exception of: adequately treated in situ carcinoma of the cervix uteri, adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin, or previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.

- Subjects may receive intravenous immunoglobulin (IVIG) for hypogammaglobulinemia while on protocol. Subjects may receive erythropoietin, filgrastim, pegfilgrastim, or sargramostim while on protocol.

- Subject has malabsorption syndrome or other condition that precludes enteral route of administration.

- Subjects with known Richter's syndrome or a history of Richter's syndrome.

- Subjects who are are actively being treated for a non-hematologic autoimmune disease, or are on other immunomodulatory agents (e.g. cyclosporine, tacrolimus, etc.) will be excluded.

- Subjects who have received an allogeneic stem cell transplant.

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to BCL-2 inhibitors, bendamustine, or anti-CD20 monoclonal antibodies.

- Administration or consumption of any of the following **within 3 days** prior to the first dose of study drug:

    - grapefruit or grapefruit products
    - Seville oranges (including marmalade containing Seville oranges)
    - star fruit

6 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints and Analytic Plan

Definition of primary endpoint: The primary endpoint of this trial is the objective response rate defined using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) guidelines update in 2008.

Definition of secondary endpoints: Secondary endpoints include the proportion of patients who attain a complete response (CR), the proportion of patients who attain a complete remission with incomplete marrow recovery (Cri) and the proportion of patients with a partial response (PR). Time to first response (starting from cycle 1 of BR), time to next treatment (TTNT) and the number of days from the first cycle of BR to the next treatment program) will also be quantified as secondary endpoints.

Duration of response is defined as the number of days from first response to recurrence or progression of disease. Progression free survial (PFS) is defined as time from cycle 1 of BR to progression of disease defined by the iWCLL reponse criteria.

The proportions of patients who attain MRD-negativity and time to MRD-negativity will also be evaluated.

Analytic plan: All proportions, including the primary endpoint ORR wil be estimated using 95% confidence interval based on binomial distribution. We will use Kaplan-Meier method to estimate the survival distributions for all time-to-event endpoints and median (95% CI) will be reported, where the case.

All endpoints will be summarized for the overall cohort and also by patient subcategories,such as patients' baseline cytogenetics ie del (13q), trisomy 12, del(11q), del (17p)/TP53 and immunoglobulin heavy chain variable region (*IGHV*) mutational status.

Adverse events and serious adverse events will be recorded as per the National Cancer Institute Common Terminology for Adverse Events (version 4.03).

13.2 Determination of Sample Size

The primary endpoint of this trial is the objective response rate defined using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) guidelines update in 20081. We will use a Simon optimal two-stage design with a target objective response rate of 75% compared to the null response rate of 40% in CLL patients treated with chemoimmunotherapy and the probabilities of type I and type II error set at 0.05 and 0.1 respectively.

Initially, the trial planned to enroll a total of 20 eligible patients: 7 patients in the first stage and 13 patients in the second stage. If at least 4 patients achieved a response in the first stage, an additional 13 patients were to be accrued to the second stage. If at least 12 out of 20 (60%) patients achieved a response, that treatment will be declared positive for attaining the primary endpoint. This study design yielded at least 90% power to detect a 75% response rate (compared to the null hypothesis of 40%) at a significance level of 5% (one-sided). Accounting for dropout patients or not meeting eligibility criteria/screen failures, a total of 25 patients were to be enrolled.

The trial completed the first stage with 7 out of 7 observed responses and proceeded to the second stage. In this new amendment, the sample size for the second stage will be increased by 20 evaluable patients (total of 33 patients in stage 2), resulting in a total sample size of 40 evaluable patients. Since the sample size is different from the one originally planned, we calculated and compared the operating characteristics to account for the mid-course changes, keeping the same null and alternative hypotheses, 40% vs 75%, respectively. Calculations were based on the method proposed by Koyama and Chen: "Proper inference from Simon's two stage designs" (Statistics in Medicine, 2007).

Initial Sample Size
N=20 evaluable patients: Stage 1: N1=7 patients and Stage 2: **N2=13 patients.**
Study will be declared positive if at least 60% objective response rate (12 out of 20 patients).
Type I error (one-sided): 0.045
Power: 0.91
Probability of early termination: 71%
90% CI ORR: (0.41, 0.79)

Modified Sample Size

N=40 evaluable patients: Stage 1: N1=7 patients and Stage 2: **N2=33 patients.**
Study will be declared positive if at least 60% objective response rate (24 out of 40 patients).
Type I error (one-sided): 0.01
Power: 0.92
Probability of early termination: 71%
90% CI ORR: (0.47, 0.78)

The results shown above indicate that increasing the total sample size to 40 evaluable patients (33 patients in stage 2) will not affect the initial type I and II errors. Under this scenario, the treatment will be declared positive for meeting the primary endpoint if at least 24 out of 40 patients will achieve a response, yielding a 92% power at a type I error of 0.01. Accounting for dropout patients or not meeting eligibility criteria/screen failures, a total of 45 patients will be enrolled. Patients will be considered evaluable if they have met at least one time-point for evaluation (i.e. after at least 3 cycles of BR).
Tumor Response Criteria

Complete Remission (CR)

CR requires all of the following criteria:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4×10^9/L (4000/μL)
- Absence of lymphadenopathy (nodes > 15 mm in longest diameter or any extra nodal disease) by physical examination and CT scan
- No hepatomegaly or splenomegaly by physical examination (as determined by measurement below the relevant costal margin)
- Absence of disease or constitutional symptoms (B symptoms: unexplained fevers > 38°C or 100.4°F, drenching night sweats, > 10% body mass weight loss in the preceding 6 months)
- Blood counts above the following laboratory values:
  - Neutrophils > 1.5×10^9/L [1500/μL] (without the need for exogenous growth factors)
  - Platelets > 100×10^9/L [100,000/μL] (without the need for platelet transfusion or exogenous growth factors)
  - Hemoglobin > 110 g/L [11 g/dL] (without the need for blood transfusions or exogenous erythropoietin)
- Bone marrow at least normocellular for age, < 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. A marrow biopsy should be compared to a pre-treatment marrow if available. Subjects who are otherwise in a

complete remission, but bone marrow nodules can be identified histologically should be considered to be nodular PR (nPR). Immunohistochemistry should be performed to define whether these nodules are composed of primarily T cells or lymphocytes other than CLL cells, or CLL cells.

Complete Remission with Incomplete Marrow Recovery (CRi)

Subjects who fulfill the criteria for CR (including bone marrow) but who have persistent cytopenia (anemia or thrombocytopenia or neutropenia) apparently unrelated to CLL but related to drug toxicity will be considered CRi. The marrow evaluation described above should be performed with scrutiny and not show any clonal infiltrate.

Partial Remission (PR)

To be considered a PR at least 2 of the following must be met:

- ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value.
- ≥ 50% reduction in lymphadenopathy.
- ≥ 50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy).

In addition at least **one** of the following criteria must be met:

- Neutrophils > 1,500/µL or ≥ 50% improvement over baseline.
- Platelets > 100,000/µL or ≥ 50% improvement over baseline.
- Hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline without transfusions or exogenous growth factors.

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