UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
FRED HUTCHINSON CANCER RESEARCH CENTER
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MRD-guided abbreviation of bendamustine and rituximab chemotherapy in combination with copanlisib in chronic lymphocytic leukemia/small lymphocytic lymphoma

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Sponsor/Principal Investigator:
Ryan Lynch, MD
Assistant Professor, University of Washington
Assistant Member, Fred Hutchinson Cancer Research Center
Seattle Cancer Care Alliance
825 Eastlake Ave. E, CE3-300
Seattle, WA 98109
Telephone: (206) 606-1739

Statistical Consultant
Ted A. Gooley, Ph.D.
Full Member, Clinical Research Division
Fred Hutchinson Cancer Research Center
1100 Fairview Ave. N., M2-B230
Seattle, WA 98109
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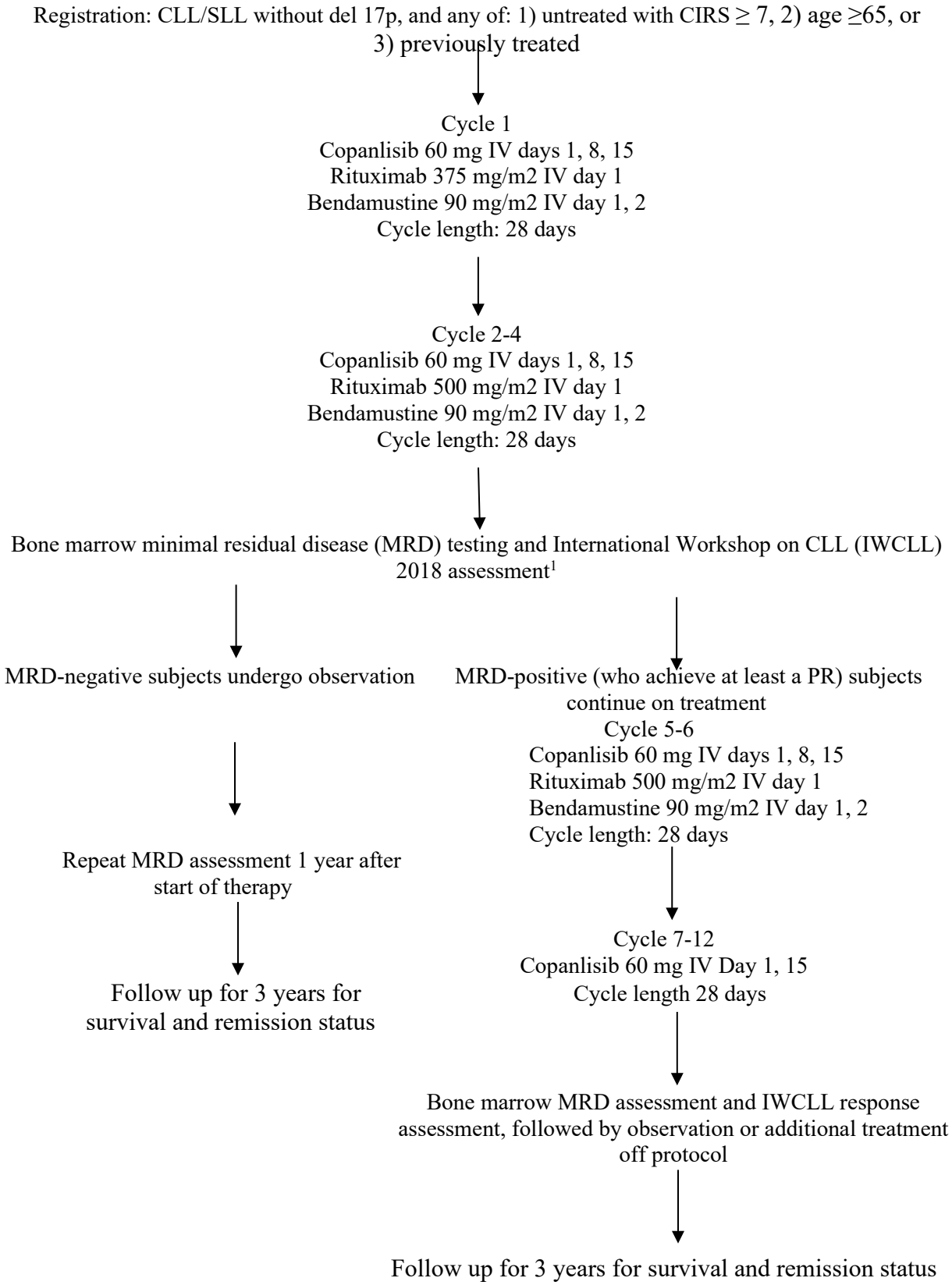
SCHEMA


Registration: CLL/SLL without del 17p, and any of: 1) untreated with CIRS ≥ 7, 2) age ≥65, or 3) previously treated
Cycle 1
Copanlisib 60 mg IV days 1, 8, 15
Rituximab 375 mg/m2 IV day 1
Bendamustine 90 mg/m2 IV day 1, 2
Cycle length: 28 days
Cycle 2-4
Copanlisib 60 mg IV days 1, 8, 15
Rituximab 500 mg/m2 IV day 1
Bendamustine 90 mg/m2 IV day 1, 2
Cycle length: 28 days
Bone marrow minimal residual disease (MRD) testing and International Workshop on CLL (IWCLL) 2018 assessment[1]
MRD-negative subjects undergo observation
Repeat MRD assessment 1 year after start of therapy
Follow up for 3 years for survival and remission status
MRD-positive (who achieve at least a PR) subjects continue on treatment
Cycle 5-6
Copanlisib 60 mg IV days 1, 8, 15
Rituximab 500 mg/m2 IV day 1
Bendamustine 90 mg/m2 IV day 1, 2
Cycle length: 28 days
Cycle 7-12
Copanlisib 60 mg IV Day 1, 15
Cycle length 28 days
Bone marrow MRD assessment and IWCLL response assessment, followed by observation or additional treatment off protocol
Follow up for 3 years for survival and remission status

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1.0 OBJECTIVES

1.1 Primary objective: Estimate the marrow minimal residual disease (MRD)-negative rate by high sensitivity flow cytometry at the end of 4 cycles of therapy

1.2 Secondary objective: Estimate the 1-year marrow MRD-negative rate, 1-year and 3-year PFS, and response rate by IWCLL criteria[1]. We will also assess the MRD conversion rate among those who are MRD-positive after 4 cycles who then complete 12 total cycles of treatment. Estimate safety of this regimen as defined by the proportion of subjects who experience grade 3+ immune-mediated adverse events or any grade 5 adverse event possibly related to copanlisib

2.0 BACKGROUND/RATIONALE

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a B-cell lymphoid neoplasm that is considered to be incurable by standard therapies[2]. Combination chemoimmunotherapy is preferred for the upfront management of symptomatic patients without 17p deletion[3,4]. While treatment with FCR (fludarabine, cyclophosphamide, and rituximab) is associated with superior PFS than RB (bendamustine, rituximab), FCR is associated increased toxicity[3]. Moreover, there was no observed overall survival (OS) difference between the two with a median 37.1 months of follow up. MRD by high sensitivity flow cytometry has been found to be an independent predictor of PFS in CLL patients treated with chemoimmunotherapy[3,5]. Marrow MRD-negative rates for previously untreated patients treated with RB were 63% in the CLL10 trial[3], and were 7-23% with RB in the relapsed refractory setting[6,7]. In a phase II study of untreated patients with CLL who received up to 6 cycles of RB, 58% of patients were MRD-negative at the end of the study, and with a median follow up of 27 months, median event-free survival (EFS) had not been reached[8].

There are several new very effective drugs that have been currently Federal Drug Administration FDA approved for the treatment of relapsed/refractory CLL, including ibrutinib (BTK-inhibitor)[9], venetoclax (BCL2-inhibitor)[10], and idelalisib (PI3Kd-inhibitor)[11]. Unfortunately, long term treatment with idelalisib has been associated with severe cases of immune-mediated grade 3-4 colitis and hepatotoxicity, particularly in the front line setting[12]. In addition, all of these agents are approved for treatment until progression, requiring patients to potentially take these agents for years with associated cost and toxicity.

In relapsed/refractory CLL patients, the addition of idelalisib to RB was associated with improved outcomes.[13] With median follow up of 14 months, the idelalisib arm had a median progression free survival of 20.8 months vs. 11.1 months in the placebo arm. However, serious adverse events like febrile neutropenia, pyrexia, and pneumonia were more common in the idelalisib arm. Newer agents like duvelisib[14] and umbralisib[15] that target the PI3K pathway are being developed to replicate or

improved upon the efficacy of idelalisib with potentially less short and long term toxicity.

Copanlisib is a selective pan-class I PI3K inhibitor that has been tested in relapsed/refractory non-Hodgkin lymphomas[16] and is (FDA) approved for relapsed follicular lymphoma. Alterations in PI3K signaling that lead to increased tumor growth and survival have been found in numerous malignancies, including lymphomas[17]. Copanlisib is active in relapsed/refractory lymphomas including CLL/SLL, and is not associated with colitis and hepatotoxicity like idelalisib[16,18,19]. Efforts are underway to combine copanlisib with standard chemoimmunotherapy in relapsed/refractory indolent non-Hodgkin lymphomas[20].

Rationale for the Combination of C-RB and abbreviated (4-cycle) therapy in MRD-negative patients

The combination of copanlisib + RB (C-RB) in a safety run-in study in relapsed indolent non-Hodgkin lymphoma (NHL) did not result in any dose limiting toxicities (DLTs)[21]. The standard copanlisib 60 mg dose was recommended for the phase III CHRONOS-4 study which is ongoing.

6 cycles of RB has been associated with neutropenia, thrombocytopenia, and infections. In addition, prolonged lymphodepletion, including sustained declines in CD4+ T cells have been observed[22]. A randomized trial combining RB with idelalisib versus placebo in relapsed CLL found that the idelalisib combination was associated with a superior median PFS (20.8 months vs. 11.1 months), but with higher rates of grade 3-4 infections (39% vs. 25%)[13]. Incorporation of MRD analysis may permit patient-specific attenuation of chemotherapy risk while preserving efficacy since higher MRD-negative rates are associated with improved outcomes[8].

Combining copanlisib with a less toxic upfront chemoimmunotherapy regimen like RB may improve outcomes while avoiding toxicity associated with more intensive regimens like FCR.

Summary of Background/Rationale

Most CLL/SLL patients can achieve durable responses to chemoimmunotherapy and/or targeted agents. However, emerging data suggests that patients who attain MRD-negativity have superior outcomes. However, most targeted agents require indefinite treatment which can lead to additional costs and toxicities for patients. We propose a combination of the novel PI3K inhibitor copanlisib with the established regimen of rituximab and bendamustine which may permit high MRD-negative rates and improved patient outcomes.

3.0 DRUG INFORMATION

3.1 Copanlisib

3.1.1 Mechanism of action –
Copanlisib is a novel, selective pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant activity against the p110α and p110δ-isoforms[23]. The PI3K/serine/threonine kinase (AKT)/mammalian target of rapamycin (mTOR) pathway has been shown to be involved in cellular growth and survival. Its constitutive activation leads to increased tumor growth and survival in numerous malignancies, including lymphomas

3.1.2 Summary of toxicities

Please refer to the current FDA-approved package inserts or prescriber information for complete about possible side effects and instructions for preparation, handling, dosing and storage of copanlisib. Common non-hematologic side effects include hyperglycemia (54%), diarrhea (36%), hypertension (35%), and lower respiratory infection (21%).

3.2 Rituximab

3.2.1 Mechanism of action

Rituximab is a monoclonal antibody directed against the CD20 antigen on the surface of B-lymphocytes. CD20 regulates cell cycle initiation; and, possibly, functions as a calcium channel. Rituximab binds to the antigen on the cell surface, activating complement-dependent B-cell cytotoxicity; and to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity

3.2.2 Summary of toxicities

The most common toxicities seen with rituximab are infusion related reactions (58%). 7-9% of patients experience Grade 3 or 4 infusion reactions.

3.3 Bendamustine

3.3.1 Mechanism of action

Bendamustine is an alkylating agent (nitrogen mustard derivative) with a benzimidazole ring (purine analog) which demonstrates only partial cross-resistance (in vitro) with other alkylating agents. It leads to cell death via single and double strand DNA cross-linking. Bendamustine is active against quiescent and dividing cells.

3.3.2 Summary of toxicity

Hematologic toxicity is common, with grade 3-4 adverse events seen in 98% of patients. Other common side effects include nausea (up to 75%), and fatigue (up to 57%).

4.0 STAGING CRITERIA AND RISK STRATIFICATION

4.1 The Rai[24] and Binet[25] Scoring systems will be used to stage patients prior to initiation of therapy. Absence of del 17p must be confirmed by testing performed before study entry, and after the last line of therapy for relapsed/refractory pts (see section 5.2).

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

1. Histologically confirmed, non-17p del CLL/SLL with any of the three following conditions:
   a. No prior CLL/SLL directed therapy and Cumulative Illness Rating Scale (CIRS) score ≥ 7
   b. Age ≥ 65
   c. At least one prior CLL/SLL directed therapy with any CIRS score
2. CLL/SLL requiring treatment as defined by at least one of the following criteria based on IWCLL 2018 guidelines:
   a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
   b. Massive (> 6 cm below left costal margin), progressive or symptomatic splenomegaly
   c. Massive nodes (> 10 cm in longest diameter), or progressive or symptomatic lymphadenopathy
   d. Progressive lymphocytosis with an increase of > 50% over a 2-month period or lymphocyte-doubling time of < 6 months. Lymphocyte-doubling time may be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of < $30x10^9$/L (30,000/μL), lymphocyte-doubling time should not be used as a single parameter to define treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL/SLL (eg, infection, steroid administration) should be excluded.
   e. Constitutional symptoms, defined as any 1 or more of the following disease-related symptoms or signs:
      1. Unintentional weight loss of > 10% within the previous 6 months
      2. Significant fatigue (ie, inability to work or perform usual activities)
      3. Fevers > 100.5° F or 38°C for? 2 weeks without other evidence of infection
      4. Night sweats for > 1 month without evidence of infection
3. ECOG performance status ≤ 2

4. Male or female ≥ 18 years of age
5. Previous exposure to other PI3K inhibitors (except copanlisib) is acceptable provided there is no resistance (resistance defined as no response (response defined as PR or CR)) at any time during therapy, or PD after any response (PR/CR) or after stable disease within 6 months from the end of the therapy with a PI3K inhibitor.
6. Willingness and ability to comply with study and follow-up procedures, and give written informed consent
7. Female subjects of childbearing potential must be surgically sterile, be post-menopausal (per institutional guidelines), or must have a negative serum pregnancy test within 7 days prior to Cycle 1 Day 1 and agree to use medically acceptable contraception throughout the study period and for 4 months after the last dose of either study drug. Men of reproductive potential may not participate unless they agree to use medically acceptable contraception throughout the study period and for 4 months after the last dose of either study drug.
8. Patients must be expected to receive at least 2 cycles of therapy.
9. Patients should have an expected survival if untreated of ≥90 days.
10. Adequate baseline laboratory values collected no more than 7 days before starting study treatment:
    a) Total bilirubin ≤ 1.5 x ULN (< 3 x ULN for patients with Gilbert-Meulengracht syndrome or for patients with cholestasis due to compressive adenopathies of the hepatic hilum).
    b) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver involvement by lymphoma).
    c) Lipase ≤ 1.5 x ULN.
    d) Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula. If not on target, this evaluation may be repeated once after at least 24 hours either according to the MDRD abbreviated formula or by 24 hour sampling. If the later result is within acceptable range, it may be used to fulfill the inclusion criteria instead.
    e) International normalized ratio (INR) ≤ 1.5 and partial thromboplastin time (PTT) ≤ 1.5 x ULN. PT can be used instead of INR if ≤ 1.5 x ULN
    f) Platelet count ≥ 75,000 /mm^3. For patients with confirmed lymphomatous bone marrow infiltration, platelet count ≥ 50,000 /mm^3.
    g) Hemoglobin (Hb) ≥ 8 g/dL. Packed red blood cell transfusion or erythropoietin should not be given less than 7 days before the exam collection.
    h) Absolute neutrophil count (ANC) ≥ 1,000/mm^3. For patients with confirmed lymphomatous bone marrow infiltration, ANC count ≥ 750/mm^3. Myeloid growth factors should not be given less than 7 days before the exam collection

5.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria are not to be enrolled to this study:

1. Presence of chromosome 17p deletion, known p53 deletion, or known p53 mutation that impairs normal function
2. Prior treatment including systemic therapy or radiotherapy within 21 days of study initiation
3. Prior treatment with bendamustine within 2 years
4. Prior treatment with copanlisib
5. Documented evidence of resistance to prior treatment with idelalisib or other PI3K inhibitors defined as: No response (response defined as partial response [PR] or complete response [CR]) at any time during therapy, or Progression (PD) after any response (PR/CR) or after stable disease within 6 months from the end of the therapy with a PI3K inhibitor.
6. Prior treatment including systemic therapy or radiotherapy within 21 days of study initiation
7. Active autoimmune disease or prior autoimmune disease requiring systemic immunosuppression within the past 6 months.
8. Poorly controlled diabetes mellitus defined as hemoglobin A1c > 8.5%
9. Known lymphomatous involvement of the central nervous system.
10. Known history of human immunodeficiency virus (HIV) infection. All patients must be screened for HIV up to 28 days prior to study drug start using a blood test for HIV according to local regulations.
11. Hepatitis B (HBV) or C (HCV) infection. All patients must be screened for HBV and HCV up to 28 days prior to study drug start using the routine hepatitis virus laboratorial panel. Patients positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) will be eligible if they are negative for HBV-DNA, these patients should receive prophylactic antiviral therapy. Patients positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA.
12. Previous or concurrent history of malignancies within 3 years prior to study. Any exceptions beyond those listed below must be approved by the principal investigator:
    a. Cervical carcinoma in situ
    b. Non-melanoma skin cancer
    c. Superficial bladder cancer (Ta [non-invasive tumor], Tis [carcinoma in situ] and T1 [tumor invades lamina propria])
    d. Localized prostate cancer
13. Active, clinically serious infections (> CTCAE Grade 2).
14. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.
15. Proteinuria of ≥ CTCAE Grade 3 as assessed by a 24 h total urine protein quantification or estimated by urine protein : creatinine ratio > 3.5 on a

random urine sample.

16. Unresolved toxicity from prior therapy higher than NCI-CTCAE grade 1 attributed to any prior therapy/procedure excluding alopecia or sensory neuropathy. Concurrent diagnosis of pheochromocytoma.
17. Pregnant or breast-feeding patients. Women of childbearing potential must have a pregnancy test performed a maximum of 7 days before start of treatment, and a negative result must be documented before start of treatment.
18. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study result.
19. Congestive heart failure > New York Heart Association (NYHA) class 2.
20. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months).
21. Myocardial infarction less than 6 months before start of test drug.
22. Uncontrolled arterial hypertension despite optimal medical management (per investigator's assessment)
23. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before the start of study treatment
24. Non-healing wound, ulcer, or bone fracture.
25. Patients with seizure disorder requiring medication.
26. Patients with evidence or history of bleeding diathesis. Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks prior to the start of study treatment.
27. Any illness or medical conditions that are unstable or could jeopardize the safety of the patients and their compliance in the study.
28. History of having received an allogeneic bone marrow or organ transplant.
29. Anti-arrhythmic therapy (beta blockers or digoxin are permitted)
30. Major surgical procedure or significant traumatic injury (as judged by the investigator) less than 28 days before start of treatment, open biopsy less than 7 days before start of treatment.
31. Systemic continuous corticosteroid therapy at a daily dose higher than 15 mg prednisone or equivalent is not allowed. Patients may be using topical or inhaled corticosteroids. Previous corticosteroid therapy must be stopped or reduced to the allowed dose at least 7 days performing the screening CT/MRI. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening. Patients may be using topical or inhaled corticosteroids.
32. Use of CYP3A4 inhibitors and inducers (Appendix 4) . Copanlisib is primarily metabolized by CYP3A4. Therefore, concomitant use of strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir), and strong inducers of

CYP3A4 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) are not permitted from Day -14 of Cycle 1 until the end of treatment visit.

6.0 REGISTRATION

6.1 Subjects must be registered prior to the start of protocol therapy. All of the eligibility requirements must have been met.

7.0 TREATMENT PLAN

7.1 For treatment or dose modification related questions, please contact Dr. Lynch (MedCon may also be used to contact MDs at 206-543-5300).

7.2 Administration of therapeutic agents: Each cycle of therapy is given every 28 days. Copanlisib is given on days 1, 8 and 15 at a fixed dose of 60 mg IV per standard of care. Copanlisib will be administered in a normal saline solution, intravenously, over approximately 1 hour. No intravenous glucose preparations should be administered on the days of infusion. No dose should be given if blood pressure is ≥ 150/90 mmHg. See section 8.1.6 for details on management of blood pressure. Blood pressure should be measured before and after copanlisib infusion. See section 9.0 study calendar for details on treatment windows. Rituximab should be given on day 1 of each cycle that also includes bendamustine. Dosage of rituximab for cycle 1 will be 375 mg/m^2 IV, and will increase to 500 mg/m^2 IV for subsequent cycles per standard of care. Bendamustine will be given on days 1 and 2 of each cycle at 90 mg/m^2. Infusional details should be as per institutional standard of care. The order of administration should be copanlisib, followed by rituximab (pre-medications for rituximab should be given after completion of copanlisib), followed by bendamustine. Further recommendations are listed in section 8. Copanlisib 60 mg IV will be defined as dose level 1, but may be decreased as outlined in table 1, table 2, and section 8.

Subjects should proceed with copanlisib dosing for cycles 7-12 at the same dose level that was administered during cycle 6 according to table 2. Dose level -1 and -2 are identical in the maintenance phase for cycle 7-12. If further decrease in copanlisib dosing is required based on toxicity beyond dose level -1/-2, copanlisib should be permanently discontinued.

Treatment with standard agent bendamustine will be prioritized for cycles 1-6. For example. If a subject on day 1 or 2 of cycles 2-6 requires a hold of copanlisib, but is but does not have bendamustine-related toxicity that would preclude treatment, the bendamustine (and rituximab) should be administered per the schedule and copanlisib dosing skipped without being replaced. Copanlisib can be resumed according the cycle schedule if/when the toxicity resolves to allow further dosing per Section 8. Patients must receive at least 4

cycles of bendamustine in order to proceed to cycle 5. Subjects with at least a partial response and MRD-positive disease after cycle 4 who require discontinuation of bendamustine due to toxicity may continue with the other study agents per protocol from cycle 5 onward

Section 8.3 discusses bendamustine dose modifications which may include discontinuation of this drug while continuing other study agents.

Drug	**Dose**	**Route**	**Days**	**Dose level (Copanlisib only)**
Copanlisib	60 mg	IV	Days 1, 8, 15	1
Copanlisib	45 mg	IV	Days 1, 8, 15	-1
Copanlisib	45 mg	IV	Days 1, 15	-2
Rituximab	375 mg/m^2 (500 mg/m^2 from cycle 2 onward)	IV	Day 1	
Bendamustine	90 mg/m^2	IV	Days 1, 2	

Table 1: Drugs and dosage schedule for proposed study with 28 day cycle length for cycles 1-6. * Copanlisib may be decreased to dose level -1 or dose level -2 as outlined in section 7.2 and section 8.

Drug	**Dose**	**Route**	**Days**	**Dose Level**
Copanlisib	60 mg	IV	Days 1, 15	1
Copanlisib	45 mg	IV	Days 1, 15	-1
Copanlisib	45 mg	IV	Days 1, 15	-2

Table 2: Drugs and dosage schedule for proposed study with 28 day cycle length for cycles 7-12. *Copanlisib may be decreased to dose level -1 or dose level -2 as outlined in section 7.2 and section 8. Subjects should proceed with dosing for cycles 7-12 at the same dose level that was administered during cycle 6. Dose level -1 and -2 are identical in the maintenance phase for cycle 7-12. If further decrease in copanlisib dosing is required based on toxicity beyond dose level -1/-2, copanlisib should be permanently discontinued.

7.2.1 Guidelines for administration of copanlisib, rituximab, and bendamustine

- Method of Administration: Copanlisib, rituximab, and bendamustine will be administered intravenously on the schedule outlined above.
- Potential Drug Interactions: Copanlisib is primarily metabolized by CYP3A4. Therefore, concomitant use of strong inhibitors of CYP3A4 (e.g.,

ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir), and strong inducers of CYP3A4 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) are not permitted from Day -14 of Cycle 1 until the safety follow-up visit. Subjects who require one of these agents during the course of treatment should be removed from the protocol.

- Prophylaxis: Patients are required to start prophylaxis treatment with Pneumocystis jiroveci pneumonia (PCP) and antiviral therapy prior to cycle 1 day 1:
  - Anti-viral Prophylaxis: Valtrex 500 mg daily or Acyclovir 800 mg PO daily.
  - PCP Prophylaxis: Dapsone 100 mg daily or TMP-SMZ 160/800 mg PO daily 3 times per week, or twice daily 2 times per week.
  - NOTE: If PCP or anti-viral therapy is not tolerated, alternate to a different PCP or anti-viral therapy, discontinue, or reduce dose/schedule as per investigator discretion.

7.2.2 Laboratory criteria for treatment: Laboratory criteria for cycle 1 day 1 must meet inclusion criteria outlined in section 5.1. The below criteria must be met on day 1 from cycle 2 onward in order to proceed with treatment

Laboratory test	**Criteria for day 1 dose (cycle 2 and higher)**
Glucose	< 160 mg/dL (fasting) or < 200 mg/dL (non-fasting)
Hemoglobin	≥ 8 g/dL[a]
ANC	≥ 1,000/mm^3 or return to baseline
Platelets	≥ 75,000/mm^3 [e] or return to baseline
ALT	< 2.5 x ULN [b]
AST	< 2.5 x ULN [c]
Total bilirubin	within normal limits [d]
GFR (MDRD)	≥ 40 mL/min/1.73 m^2

Table 3: Laboratory test criteria for day 1 dosing for cycle 2 and higher. Abbreviations: ALT = Alanine aminotransferase; ANC = Absolute neutrophil count; AST = Aspartate aminotransferase; GFR = Glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; ULN = Upper limit of normal.

a: If hemoglobin is < 8 g/dL but ≥ 6 g/dL on the day of planned study drug administration it is permissible to give the study drug dose as scheduled and transfuse within 48 hours after the dose, if the subject is hemodynamically stable and in opinion of investigator benefits outweigh risks. Rationale and treatment should be recorded in source document.
b: < 5 x ULN in subjects with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.
c: < 5 x ULN in subjects with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.
d: < 3 x ULN in subjects with Gilbert-Meulengracht syndrome, subjects with cholestasis due to compressive adenopathies of the hepatic hilum or documented liver involvement by lymphoma.
e: For subjects with lymphomatous bone marrow infiltration at study entry (local assessment), platelet count ≥ 50,000/mm3. This value should be used throughout the study irrespective of bone marrow status changes. Platelet transfusion should not be given less than 7 days before the exam collection.

7.2.3 Additional criteria for administration of copanlisib based on glucose level

Period	Fasting ≥ 8 hours required before first glucose measurements	Pre-dose glucose levels (first glucose measurement)	Fasting required before study drug infusion
Day 1 of cycle 1	Yes	≤ 125 mg/dL (non-diabetic subjects) < 160 mg/dL (diabetic subjects)	Yes [d]
Day 1 of subsequent cycles	Conditional [a, d, e]	< 160 mg/dL (fasting) < 200 mg/dL (non-fasting) [c]	Conditional [a, d, e]
Days 8 and 15 of each cycle [b]	No	< 160 mg/dL (fasting) < 200 mg/dL (non-fasting)	Conditional [a, d, e]

Table 4: Fasting requirements and pre-dose glucose levels

a: The decision regarding meal timing and fasting can be made by the investigator based on the glucose response patterns during prior treatment days. (see text below "Recommendations on meal timing on infusion days" for further details).
b: Day 8 is not applicable during Cycles 7-12
c: In case of non-compliance with the fasting requirement.
d: Diabetic subjects who take insulin treatment at any cycle visit: Timing and content of caloric intake on infusion days will be managed and monitored by the investigator. Consultation with treating physician or diabetes specialist is advised.
e: A low glycemic index meal may be taken at least 4 h before the start of the copanlisib infusion for subjects who have their infusions scheduled at a later hour, or due to their age or medical condition when fasting prior to infusion is not viable.

7.3 Growth factor support: will be at the discretion of the treating team. Growth factors should be avoided whenever possible within 10 days of FDG-PET imaging. Antibiotic and antiemetic prophylaxis will be per institutional standard of care however PJP and anti-viral prophylaxis is required per standard of care during treatment with copanlisib in combination with bendamustine (see Section 7.2.1). Prophylaxis should continue for duration of copanlisib maintenance as well.

7.4 Criteria for removal from protocol treatment

7.4.1 Documented progression of disease by IWCLL 2018 criteria (see appendix 3)[1,26]

7.4.2 If at any time the constraints of this protocol are detrimental to the subject's health and/or the subject no longer wishes to continue protocol therapy, protocol therapy shall be discontinued, the study chair shall be notified, and the reason for discontinuation shall be documented.

7.4.3 Delay of treatment for more than 4 weeks due to related adverse events unless prophylactic measures can be taken for subsequent cycles.

7.4.4 The subject may withdraw from the treatment at any time for any reason.

8.0 DOSAGE MODIFICATIONS

8.1 Dose modification of copanlisib

8.1.1 Hematological toxicity

Neutropenia and febrile neutropenia are listed in the current version of IB as expected adverse events. If the guidelines given in table 5 are not followed, the rationale for other measures is to be documented in detail in the subject's medical record. The use of myeloid growth factors in the therapeutic setting is allowed during study treatment at investigator's discretion

Hematological toxicity (any of the following)	**Study treatment action**

CTCAE Grade ≥ 3 thrombocytopenia	Delay infusion until criteria in table displayed in table 3 are met.[c,d]
Febrile neutropenia or ANC < 500/mm^3 [a]	
INR or PTT CTCAE Grade ≥ 3 with bleeding [b]	
CTCAE Grade ≥ 3 anemia[d]	

Table 5: Dose modifications of copanlisib for hematological toxicity
ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria of Adverse Events, version 4.03; Hb = hemoglobin; INR = international normalized ratio; PTT = partial thromboplastin time; G-CSF = Granulocyte colony-stimulating factor
a: These subjects should recover from neutropenia to ANC ≥ 500/mm^3 without fever. G-CSF should be prescribed when ANC is < 1000/mm^3 as per label.
b: International normalized ratio (INR) and partial thromboplastin time (PTT) should have returned to ≤ 1.5 and ≤ 1.5 x ULN, respectively, with no signs of bleeding.
c: After having fully recovered from toxicity and in the absence of any criteria for further dose reduction or study drug discontinuation, re-escalation is allowed at the investigator's discretion.
d: Treatment with transfusion is allowed at the investigator's discretion

8.1.2 Non- hematological toxicity

Dose modification guidelines for non-hematologic toxicities attributable to copanlisib except for glucose increases, dermatologic toxicity, non-infectious pneumonitis and blood pressure increases are outlined in table 6.

		Study drug action	
Toxicity [a]	Occurrence	For current course of therapy	For next course of therapy
Grade 1-2	Any appearance	No change	No change
Grade 3 [b]	1st appearance	Interruption until grade ≤ 2	No change
	2nd appearance	Interruption until grade ≤ 2	Decrease to dose level -1
	3rd appearance	Interruption until grade ≤ 2	Decrease to dose level -2
	4th appearance	Permanent discontinuation	-
Grade 4	Any appearance	Permanent discontinuation	-
Toxicity requiring delay > 28 days		Permanent discontinuation	-

Table 6: Dose modification of copanlisib for non-hematological toxicity (except glucose increases, dermatologic toxicity, non-infectious pneumonitis and blood pressure increases)
a: Toxicities according to CTCAE version 5.0
b: Despite maximum supportive therapy

8.1.3 Dermatologic toxicity

The guidelines for dose modifications in cases of dermatologic toxicity are outlined in table 7. If these guidelines are not followed, the rationale for other measures will be documented in detail in the subject's medical record.

		Study drug action	
Toxicity [a]	Occurrence	For current course of therapy	For next course of therapy
Grade 1	Any appearance	No change	No change
Grade 2 [b]	1st appearance	Interruption until grade ≤ 2	No change
	2nd appearance	Interruption until grade ≤ 2	Decrease to dose level -1
	3rd appearance	Interruption until grade ≤ 2	Decrease to dose level -2
	4th appearance	Permanent discontinuation	-
Grade 3	1st appearance	Interruption until grade ≤ 2	Decrease to dose level -1
	2nd appearance	Interruption until grade ≤ 2	Decrease to dose level -2
	3rd appearance	Permanent discontinuation	-
Grade 4	Any appearance	Permanent discontinuation	-
Toxicity requiring delay > 28 days		Permanent discontinuation	-

Table 7: Dose modification of copanlisib for dermatologic toxicity
a: Toxicities according to CTCAE version 5
b: Despite maximum supportive therapy

8.1.4 Non-infectious pneumonitis (NIP)

In the event of suspected NIP, copanlisib treatment should be followed as Table 8. Pneumonitis is to be reported as such only in the event of NIP

Suspected or confirmed NIP per CTCAE	Action taken	Re-treatment dose after recovery
Grade 1	No change	NA
Grade 2	Dose interruptions until recovery to grade 0-1	Decrease to dose level -1
Grade 2 second recurrence	Permanent discontinuation	NA
Grade 3	Permanent discontinuation	NA
Grade 4	Permanent discontinuation	NA

Table 8: Dose adjustment in cases of NIP

8.1.5 Glucose increases

Patients who develop transient post-infusion glucose > 250 mg/dL after copanlisib administration may continue treatment. However, the next

infusion must be delayed until the subject's pre-infusion glucose levels return to < 160 mg/dL (fasting) or < 200 mg/dL (non-fasting). Guidelines for the management of glucose increases are given in section 8.1.7

- Continuing occurrence of post-infusion blood glucose > 400 mg/dL based on repeated laboratory analysis despite optimal glucose lowering therapy after 2 infusions of copanlisib will require dose reduction to next lowest dose level
- Further dose reduction is allowed as long as discontinuation criteria was not met.
- Dose re-escalation is allowed when a subject has achieved controlled glucose levels per investigator's judgment.
- Persistent occurrence of post-infusion blood glucose > 400 mg/dL based on laboratory analysis which occurred at the lowest copanlisib dose level despite optimal glucose lowering therapy (after at least one cycle of treatment) with consultation of a diabetes specialist requires permanent discontinuation of the study treatment

8.1.6 Arterial hypertension

No dose should be given if blood pressure is ≥ 150/90 mmHg. Antihypertensive medication may be given to control the increased blood pressure. The phase I study of copanlisib suggested the benefit of dihydropyridine calcium channel blockers (amlodipine or felodipine). Dosing can proceed on the scheduled day if there are at least 2 consecutive measurements < 150/90 mmHg. Otherwise dosing must be delayed. If drug-related arterial hypertension (post-dose blood pressure of CTCAE Grade 3 or ≥ 160/100 mmHg) is not manageable with optimal antihypertensive treatment, the dose for the subsequent copanlisib administrations may be reduced by 1 or 2 dose levels at the investigator's discretion. Treatment of increased blood pressure should be personalized for each subject. For those with pre-existing hypertension, subjects should take their usual doses on the day of copanlisib infusion. Patients with a post-dose blood pressure that may have life-threatening consequences (e.g. malignant arterial hypertension, transient or permanent neurologic deficit, hypertensive crisis) must permanently discontinue the study drug. The guidelines for dose modifications of study treatment in case of arterial hypertension are given in table 9.

Toxicity (CTCAE severity grade)	**Study drug action**	**Recommendation**

Pre-dose measurements BP ≥ 150/90 mmHg	No dose should be given until recovery to < 150/90 mmHg.	Consider administering BP lowering medication. Dosing can proceed on the scheduled day if after at least 2 consecutive measurements BP returns to < 150/90 mmHg. If BP doesn't return to < 150/90 mmHg then delay dosing until next visit.
During infusion: BP ≥ 160/100 mmHg or CTCAE hypertension of grade 3	Infusion can be interrupted or slowed down and administration of BP lowering therapy should be initiated.	Infusion may be resumed immediately when BP has returned to < 150/90 mmHg or otherwise skipped. Subsequent study drug administrations may be reduced by one dose level at the investigator's discretion[b].
Post-dose: Drug related BP of ≥ 160/100 mmHg [a] or CTCAE hypertension of grade 3	-	Administration of BP lowering therapy should be initiated according to local standard of care. Additional measurements to be performed as clinically indicated until recovery to < 150/90 mmHg. Subsequent study drug administrations may be reduced by one dose level at the investigator's discretion[b].
CTCAE hypertension of grade 4	Permanent discontinuation	-

Table 9: Dose modification of study treatment for arterial hypertension
BP = Blood pressure; CTCAE severity grade = Common Terminology Criteria for Adverse Events severity grade
a: Not manageable despite optimal antihypertensive treatment.
b: The lowest dose level is -2; if a subject is already on the lowest dose level and experiences post-dose hypertension of CTCAE Grade 3 or ≥160/100 mmHg, consider more intensive therapy than previously used.

Blood pressure should also be monitored on infusion days as indicated below:

- Blood pressure will be measured until there are two consecutive results < 150/90 mmHg. Provider should be notified for further instructions if two consecutive readings in range cannot be obtained after 4 measurements have been taken. The subject should rest for 5-10 minutes before blood pressure is recorded. If blood pressure is

≥ 150/90 mmHG, the investigator can consider a medical intervention or delaying the infusion of study drug.

- On infusion days: blood pressure will be measured at pre-dose, 30 min (mid infusion), and 60 min (end of infusion). Note: a time window of ±10 min is allowed for all BP measurements, except for the pre-dose measurement. Pre-dose measurement should be taken as close to the start of the drug infusion as possible – if there are delays in initiating copanlisib infusion of more than one hour since last reading, consider repeating blood pressure measurement.
- In addition, blood pressure will be measured 30 minutes after the start of rituximab infusion and at the end of rituximab infusion (deviation of ± 5 minutes is allowed) from Cycle 1 to Cycle 6.

8.1.7 Management of transient post-infusion glucose increases that can occur with copanlisib

Mild to moderate asymptomatic increases of blood glucose may occur with copanlisib infusion, and with larger increases potentially occurring post-prandially. The guidelines for management of transient post-infusion glucose increases on infusion days are given in table 10.

Criteria	Recommendation
Glucose increase of CTCAE Grade 1	Continue study treatment
Glucose increase of CTCAE Grade 2	Hydration as clinically indicated. When planning next infusion prophylaxis with oral glucose lowering medication per standard of care. Consultation with endocrinologist for diabetic patients is recommended
Glucose increases of Grade 3 or 4	Hydration as clinically indicated (orally, IV). Insulin therapy per local standard of care. When planning next infusion consider prophylaxis with oral glucose lowering medication per local standard of care. Consultation with endocrinologist is recommended

Table 10: Management of transient post-infusion glucose increases

8.2 Rituximab dose modification steps: Infusion related reactions and toxicities should be managed per prescriber information institutional standard of care. Pre-medication prior to rituximab should also be administered per institutional standard of care. Recommendations include acetaminophen 650 mg PO and diphenhydramine 25 mg PO. Additional pre-medications may be given for subsequent cycles per institutional standard of care, including corticosteroids. If the investigator does not believe a rituximab infusion can be safely completed due to an infusion reaction, it may be omitted for that cycle and resumed for the subsequent cycle with adequate pre-medications.

8.3 Bendamustine dose modification steps: All subjects who meet inclusion criteria should start with standard dose of 90 mg/m^2 on day 1 and 2. Toxicities should be managed per prescriber information and institutional standard of care. Dose reduction to 60 mg/m2 is proposed as the first dose reduction, when needed. Patients who do not meet criteria listed in table 3 due to hematologic toxicity may have future doses of bendamustine reduced at investigator discretion. This may include discontinuation of bendamustine and continuation of the other study medications from cycle 5 onwards.

8.4 Concomitant therapy

Medications used during the course of the study will be documented.

8.4.1 Prohibited Concomitant Therapy: The administration of concurrent medications intended to treat the primary cancer are not allowed during

protocol therapy. This includes any chemotherapy, investigational agent, biologic agent or other anti-tumor agents. Radiation therapy is also prohibited.

8.4.2 Patients should be strongly discouraged from taking any “alternative” or “naturopathic” medications since these agents may interfere with metabolism of study medications.

9.0 STUDY CALENDAR

	Screening	Treatment during combination therapy (C1-C6)											
		Cycle 1				Cycle 2 to Cycle 4				Cycle 5 to Cycle 6			
Days	D-42 to D-1	D1	D2	D8	D15	D1	D2	D8	D15	D1	D2	D8	D15
Treatment window		+/- 3 days		+/- 2 days		+/- 3 days		+/- 2 days		+/- 3 days		+/- 2 days	
Patient informed consent	X												
Performance Status	X	X		X	X	X				X			
Clinic evaluation/physical exam[a]	X	X		X	X	X				X			
Concomitant Medication Assessment	X	X		X	X	X				X			
Toxicity/AE assessment	X	X		X	X	X				X			
CT/tumor evaluation[b]	X									X			
Bone marrow biopsy and aspirate[b]	X									X			
Tumor chromosomal analysis[c]	X												
12-lead EKG	X												
Lab/monitoring													
Screening labs[d]	X												
Complete blood count with differential	X	X				X				X			
Comprehensive metabolic panel[l]	X	X	X			X				X			
LDH, uric acid, phosphorus	X	X	X										
Glucose[e]	X	X		X	X	X		X	X	X		X	X
Blood pressure[f]	X	X		X	X	X		X	X	X		X	X
Drug administration													
Rituximab		X				X				X			
Bendamustine		X	X			X	X			X	X		
Copanlisib		X[k]		X[k]	X[k]	X[k]		X[k]	X[k]	X[k]		X[k]	X[k]

Days	Treatment		EOT	Survival FU
	Cycle 7-12		Within 14 days of cycle 12 day 15 or within 7 days after decision to stop treatment [g]	Per institutional guidelines[h]
	D1	D15		
Treatment window	+/- 3 days			
Patient informed consent				
Performance Status	X		X	
Clinic evaluation/physical exam[a]	X		X	
Survival status				X
Concomitant Medication Assessment	X		X	
Toxicity/AE assessment	X		X	
CT/tumor evaluation[b]			X[g]	X[i]
Bone marrow biopsy and aspirate			X	
Lab/monitoring				
Complete blood count with differential	X		X	
Comprehensive metabolic panel[l]	X		X	
Glucose[e]	X	X	X	
Blood pressure[f]	X	X	X	
Drug administration				
Copanlisib	X	X		

Abbreviations: AE = Adverse event; C = Cycle; CMV = cytomegalovirus; CT = Computed tomography; D = Day; EKG = Electrocardiogram; EOT = End of treatment; FU = Follow up; HCV = Hepatitis C virus, HIV = Human immunodeficiency virus; MRD = minimal residual disease; PCR = polymerase chain reaction

a: Patient may be seen on additional treatment days at provider discretion for evaluation/management of toxicity.

b: Baseline bone marrow biopsy/aspirate and diagnostic CT of the neck, chest, abdomen, and pelvis should be performed at screening within 42 days of cycle 1 day 1. For interim response assessment, this may be performed any time after cycle 4 day 15 copanlisib infusion, and cycle 5 day 1. As part of this evaluation, a bone marrow biopsy/aspirate with MRD testing by flow cytometry and diagnostic CT neck (if involved), chest, abdomen, and pelvis is also required. Patients will continue on treatment for cycle 5-12 if an MRD

negative CR in the marrow is not achieved BUT has achieved at least a partial response to treatment. For those completing treatment through cycle 12, a repeat bone marrow biopsy/aspirate with marrow MRD testing by flow cytometry and diagnostic CT neck (if involved), chest, abdomen, and pelvis should be performed. Subjects with an MRD-negative complete response in the marrow should discontinue further treatment. In these patients, an optional repeat bone marrow MRD assessment should be performed 1 year (+/- 14 days) after initial assessment.

c: At a minimum this should include analysis for alterations in chromosome 17p. Previous testing is accepted as long as an original report is available. Additional abnormalities if analyzed will be recorded and presented, but are not mandatory

d: Labs within screening window include: HBsAg, HBcAb, anti-HCV antibody, HIV test, serum pregnancy test (if female of child-bearing potential), GFR calculation (MDRD abbreviated formula, may be repeated one time if not within target range or verified with 24 hour urine collection), CMV PCR, hemoglobin A1c, PTT, PT/INR, lipase, quantitative immunoglobulins, complete blood count with differential, comprehensive metabolic panel, and random urine protein/creatinine ratio. If hepatitis B, C, or HIV testing screens positive, this may be confirmed by viral PCR. Patients with positive HBcAb should receive viral prophylaxis per institution standard of care. Repeat CMV PCR testing is not required unless clinically indicated.

e: On day 1 of cycle 1-6, glucose will be measured at pre-dose (can use results from metabolic panel if performed the same day, and post dose of copanlisib administration. Glucose should also be checked after rituximab administration as well as bendamustine administration. On days where copanlisib alone is administered, pre-dose and post dose glucose testing should be performed. On day 2 of cycle 1-6, glucose will only need to be monitored if corticosteroid pre-medications are administered. See sections 8.1.5 and 8.1.7 for more information.

f: See section 8.1.6 for instructions on monitoring of blood pressure.

g: A diagnostic CT should be performed to confirm progression prior to an end of treatment visit. However, it does not need to be within 7 days of an EOT visit. For those completing 12 cycles of treatment, a bone marrow biopsy/aspirate with MRD testing by flow cytometry and diagnostic CT neck (if involved), chest, abdomen, and pelvis should be performed for final response assessment.

h: Patients will receive surveillance and clinical follow up per institutional standard of care. This may include having follow up care at a different oncology clinic. We will periodically assess for survival status (remotely if necessary) until up to 3 years after completion of the study treatment.

i: For those who are MRD negative in the marrow after cycle 4, an optional repeat bone marrow MRD assessment should be performed 1 year (+/- 14 days) after initial assessment.

j: This may be waived in cases of EOT for clear progression of disease either by laboratory testing or CT imaging.

k: There must be at least 7 days between each consecutive infusion of copanlisib.

l: Components of the comprehensive metabolic panel include sodium, potassium, chloride, bicarbonate/CO2, glucose, BUN, creatinine, calcium, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and albumin.

10.0 STUDY PROCEDURES

10.1 Screening

After signing consent, subjects should have laboratory testing (see section 9.0 for details, EKG, bone marrow biopsy/aspirate, and tumor evaluation. Additional detail is listed in section 9.0. Prophylaxis for tumor lysis syndrome with allopurinol or equivalent may be administered at the discretion of the investigator.

10.2 Cycle 1, Day 1, 2

On day 1, clinic evaluation/exam, performance status evaluation, concomitant medication assessment, laboratory testing, blood pressure, and toxicity AE assessment should be performed. Patients should fast prior to cycle 1 day 1, but fasting on subsequent days is at the discretion of the investigator based on any hyperglycemia seen after the first copanlisib infusion. Laboratory values should meet criteria listed in section 5.1 and 7.2.3. See section 7.2 for additional details on administration of therapeutic agents. On day 1 the order of administration should be copanlisib, followed by rituximab (pre-medications for rituximab should be given after completion of copanlisib), followed by bendamustine. Of note, rituximab dosing for cycle 1 is 375 mg/m^2. Blood pressure should be monitored as outlined in section 8.1.6. Glucose will be measured at pre-dose of copanlisib (can use results from metabolic panel if performed the same day), and post dose of copanlisib administration. This can be done with point of care testing. On day 2, no clinic assessment is required per protocol prior to bendamustine administration, though laboratory monitoring for tumor lysis syndrome will be performed in cycle 1 only. Additional laboratory monitoring beyond what is mandated by the protocol may be ordered at the discretion of the investigator.

10.3 Cycles 1 day 8, 15

Subjects will have a clinic evaluation/exam, performance status evaluation, concomitant medication assessment, laboratory testing, blood pressure, and toxicity AE assessment. Fasting is conditional on previous episodes of hyperglycemia. Rituximab dosing increases to 500 mg/m^2 from cycle 2 onwards. Blood pressure should be monitored as outlined in section 8.1.6. Glucose will be measured at pre-dose of copanlisib (can use results from metabolic panel if performed the same day), and post dose of copanlisib administration. Glucose should meet criteria listed in section 7.2.3

10.4 Cycles 2-4

Subjects will have a clinic evaluation/exam, performance status evaluation, concomitant medication assessment, laboratory testing, blood pressure, and toxicity AE assessment on day 1 of each cycle. Additional evaluations on other infusion days are at the discretion of the investigator. Laboratory values must be adequate as outlined in section 7.2.2. Glucose should be monitored as on previous cycles/treatment days of copanlisib administration and treatment altered as outlined in section 7.2.3. After cycle 4 day 15,

but prior to cycle 5 day 1, all subjects will undergo a bone marrow biopsy/aspirate with MRD evaluation, as well as a CT scan of the neck (if previously involved), chest, abdomen, and pelvis. Subjects with a complete response and MRD negativity (using 10^{-4} as the threshold) will not receive further therapy and will undergo observation per institutional guidelines. Those who are MRD positive and with IWCLL response of stable disease or better may continue on study for cycles 5-12. Those with progressive disease should come off study to receive alternate therapy. Subjects with failed MRD testing or an indeterminate result should receive additional therapy on study at the discretion of the investigator after reviewing other response assessments including CT scans and complete blood counts with differential. Options include but are not limited to completing all 12 cycles of therapy, discontinuing therapy with copanlisib after 6 cycles (so that a full course of standard therapy is administered), or coming off protocol to receive additional treatment at the discretion of the treating physician.

10.5 Cycles 5-6

Study procedures for cycles 5-6 should proceed identically to those in cycles 2-4 as outlined in section 9.0 and 10.4. Only patients with MRD-positive disease in the marrow and at least a partial response by IWCLL criteria should proceed with cycle 5 onwards. Subjects with stable disease or progressive disease should discontinue protocol therapy. Since the marrow is more sensitive for MRD, the MRD testing in the marrow will be used to adapt therapy[27]. We will use $< 10^{-4}$ as our threshold for MRD-negativity[28]. No MRD assessment, CT evaluation, or response assessment is required at the completion of cycle 6. Bendamustine may be discontinued from cycle 5 onward due to toxicity at the discretion of the investigator. Subjects who require discontinuation of bendamustine prior to administration of at least 4 doses should be taken off protocol

10.6 Cycle 7-12

Starting with cycle 7, patients will no longer receive rituximab or bendamustine. Subjects will have a clinic evaluation/exam, performance status evaluation, concomitant medication assessment, laboratory testing, blood pressure, and toxicity AE assessment on day 1 of each cycle. Additional evaluations are optional. Copanlisib will be administered on days 1 and 15 with identical lab, glucose, and blood pressure requirements as outlined in sections 7.2.3, 8.1.6, and 9.0.

10.7 EOT assessments/follow up

Follow up after completion of study treatments should be performed per standard of care. Patients completing 12 cycles of treatment should have a repeat bone marrow MRD performed within 14 days of cycle 12 day 15. Survival data should be collected up to 3 years after completion of study. Subjects who are MRD-negative after 4 cycles should have an optional repeat bone marrow MRD assessment at 1 year (+/- 14 days) after completion of the previous assessment. Patients may follow with another oncologist if it is more convenient, with the study team periodically contacting them for updated information on survival and disease status.

11. 0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Definitions of Disease, Criteria for Evaluation and Endpoint Definitions – response will be defined by standard IWCLL 2018 criteria[1,26].

12.0 STATISTICAL CONSIDERATIONS

12.1 This single-arm Phase II clinical trial will use a Simon optimal two-stage design to assess potential efficacy for the primary endpoint or marrow MRD-negativity rate after 4 cycles of RB. Previous data suggest an historical marrow MRD-negativity rate in the study population eligible for the current trial of 20%. We hypothesize that with BR-C the MRD-negative rate will be 40%. Using a Simon two-stage optimal design, up to 12 patients will be enrolled in the first stage. If 2 or fewer responses among 12 (17% or less) patients are observed, consideration will be given the stopping the study due to a lack of efficacy. On the other hand, if at least 3 responses are observed among the first 12 patients, an additional 13 will be enrolled. After the 25th patient, if 8 or more responses are seen (32% or more), we shall conclude that BR-C is potentially efficacious and this would provide sufficient evidence that the true rate of marrow MRD-negativity is in excess of 20% and such a result would warrant a larger trial of MRD-directed BR-C. This design has a one-sided significance level of .099 and a power of 81.5%. The expected number of patients to be enrolled under the null hypothesis that the marrow MRD rate is 20% is 17.7, and the probability of stopping early under the null hypothesis is 0.56.

<u>Safety Stopping Rule</u>

Based on previous data with idelalisib[11,29] and copanlisib[30], we will define a threshold of > 13% of patients experiencing grade 3 or higher immune-related toxicity, or fatal toxicity, at least possibly related to study therapy as excessive.

If this rate of toxicity is observed, the study will be suspended pending review by and ad hoc safety oversight committee. This committee will analyze the data and make a recommendation to continue the study at the current starting dose, deescalate the starting study dose to dose level -1, terminate, or otherwise modify the study. These recommendations will consider the totality of the toxicity data, the patient mix, and efficacy data including frequency of response. Sufficient evidence will be taken to be any observed ratio of toxicities-to-patients treated that has an associated lower one-sided 80% confidence limit that exceeds 13%.

Operationally, the following thresholds for grade 3 or higher immune-related toxicity or deaths related to study therapy will trigger study suspension and review: 2/2-6, 3/7-12, 4/13-18, 5/19, 6/20-24

If the true probability of toxicity is 5%, the probability of an observed toxicity ratio that would trigger a suspension after 10 or 19 patients is approximately .03 and .04, respectively. If the true probability of toxicity is 30%, the probability of an observed toxicity ratio that would trigger a suspension after 10 or 19 patients is approximately .69 and .88, respectively.

We will also suspend the study and refer to ad hoc safety committee if there are 2 deaths at any time that are possibly related to copanlisib.

Given the complexity of the study and heterogeneity of possibilities for reaching the rules for study suspension, we have not pre-specified specific rules for de-escalating the starting dose. The recommendations of the committee will be followed, and the protocol will be modified or terminated accordingly.

During a study suspension, accrual will be halted, but subjects who are already on study may continue treatment per protocol at the discretion of the investigator pending the result of the ad hoc safety oversight committee meeting. However, if the committee recommendation is to terminate the study, all subjects will discontinue study treatment and continue standard of care therapy at the discretion of the treating physician.

12.2 Anticipated accrual: We anticipate accrual of 25 subjects over 3 years.

12.3 Descriptive summary statistics for continuous variables will include sample size, mean, standard deviation (SD), median, minimum and maximum for both baseline and post-baseline measurements (if applicable). Summary statistics for categorical variables will include sample size, frequency and percentages.

13.0 STUDY MONITORING AND REPORTING PROCEDURES

13.1 Adverse Event Reporting

Reporting of AEs and SAEs should commence after first administration of copanlisib and should continue until end of treatment visit. Complete and timely reporting of adverse events (AEs) is required to ensure the safety of subjects. Reporting requirements are determined by the characteristics of the adverse event including the grade (severity), the relationship to the study therapy

(attribution), and the prior experience (expectedness) of the adverse event. The guidelines outlined in this section, as well as the specific direction on each report form must be followed. The NCI Common Terminology Criteria for Adverse Events v5.0 (CTCAE) will be used to classify and grade toxicities. The CTC can be found on the Cancer Therapy Evaluation Program (CTEP) homepage at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

13.2 Definitions and descriptions of terms used in adverse event reporting.

Adverse Event (AE)
An adverse event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure. The investigator should log AEs that are deemed to be clinically significant and assess their attribution to either or both of the study medications.

Serious Adverse Event or Adverse Drug Reaction
A Serious Adverse Event (SAE) or Adverse Drug Reaction (ADR) means any AE/ADR occurring at any dose that results in:

- Death;
- A life-threatening AE/ADR (i.e., the subject was, in the view of the initial reporter/investigator, at immediate risk of death from the AE as it occurred. It does not refer to an AE that hypothetically might have caused death if more severe);
- Inpatient hospitalization or prolongation of existing hospitalization (i.e., hospitalization was required to treat or diagnose the AE/ADR: excludes hospitalization for unrelated reasons);
- A persistent or significant disability or incapacity (disability here means that there is a substantial disruption of a person's ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event (i.e., AEs/ADRs that might not be immediately life-threatening, or result in death or hospitalization might be considered serious when, based upon appropriate medical and scientific judgment, they might jeopardize the subject or might require medical or surgical intervention to prevent one of the other serious outcomes listed above);
- Any suspected transmission via a medicinal product of an infectious agent.

Grade
Grade is defined as the severity of the adverse event. The CTCAE Version 5.0 must be used to determine the grade of the adverse event. If toxicity is not listed in the CTCAE use the following general criteria for grading.

0 – No adverse event or within normal limits
1 – Mild adverse event
2 – Moderate adverse event

3 – Severe adverse event
4 – Life-threatening or disabling adverse event
5 – Fatal adverse event

Attribution
Attribution is defined as the determination of whether an adverse event is related to a medical treatment or procedure. The investigator or authorized sub-investigator will assess attribution according to the following categories

- Unrelated: the adverse event is clearly NOT related to therapy
- Unlikely: the adverse event is doubtfully related to therapy
- Possible: the adverse event may be related to therapy
- Probable: the adverse event is likely related to therapy
- Definite: the adverse event is clearly related to therapy

Unexpected Adverse Event
An unexpected adverse event is any adverse event that is not listed in the current Investigator's Brochure, package insert, protocol, or associated documents; or the specificity or severity of which is not consistent with these documents.

13.3 Routine Reporting

Routine reporting at protocol-mandated clinic visits is required for all grade adverse events. Routine reports include data after each cycle of therapy and 30 days after the last dose of study drugs, or until the subject receives an alternative anti-cancer therapy, whichever date comes first.

13.4 Expedited Reporting

SAE Reporting to Bayer

SAEs require expeditious handling and reporting to Bayer in order to comply with regulatory requirements. All SAEs (regardless of causality assessment) occurring on study or within 30 days of last study treatment should be immediately reported to Bayer at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch within 1 business day of the first knowledge of the event by the treating physician or research personnel on an SAE Form (MedWatch FORM FDA 3500 or equivalent) and followed until resolution (with autopsy report if applicable)

SAE Reporting to Regulatory Agencies

Sponsor-Investigator is responsible for reporting serious, unexpected, suspected adverse reactions (SUSARs) to the FDA in accordance with regulations under 21 CFR 312.32. Sponsor-Investigator is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to the

FDA within 7 calendar days after being notified of the event. Sponsor-Investigator will report other SUSARs to the FDA by a written safety report within 15 calendar days of notification. Other SAEs will be reported to the FDA on an annual basis.

The investigator must report SAEs and follow-up information to the responsible Institutional Review Board (IRB) according to the policies of the IRB.

The following are events of special interest, and will need to be reported to Bayer within 2 business days of awareness by a member of the study team:

Pregnancy

During the course of the study, all female subjects of childbearing potential must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator).

If an investigator suspects that a subject may be pregnant prior to administration of study drug(s), the study drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the subject must not receive any study drug(s), and must be discontinued from the study.

If an investigator suspects that a subject may be pregnant after the subject has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the subject must be discontinued from the study, and the investigator must submit an SAE form to Bayer at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch within 1 business day of the first knowledge of the event by the treating physician or research personnel on an SAE Form (MedWatch FORM FDA 3500 or equivalent) and followed until resolution (with autopsy report if applicable). Abortions (spontaneous, accidental, or therapeutic) must also be reported to Bayer at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch within 1 business day of the first knowledge of the event by the treating physician or research personnel on an SAE Form (MedWatch FORM FDA 3500 or equivalent) and followed until resolution (with autopsy report if applicable).

Study Drug Overdose

Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion is to be reported to Bayer at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch within 1 business day of the first knowledge of the event by the treating physician or research personnel on an SAE Form

(MedWatch FORM FDA 3500 or equivalent) and followed until resolution (with autopsy report if applicable). If a study drug overdose occurs, subjects should stop study drug dosing and be clinically monitored as appropriate, managing symptoms/side effects that may occur.

Secondary / Second Malignancy

Any secondary or second malignancy event must be reported to Bayer at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch within 1 business day of the first knowledge of the event by the treating physician or research personnel on an SAE Form (MedWatch FORM FDA 3500 or equivalent) and followed until resolution (with autopsy report if applicable).

13.5 Data Safety and Monitoring Plan

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutchinson Cancer Research Center (FHCRC) Scientific Review Committee (SRC) and the FHCRC Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

13.6 Required Records and Materials

13.6.1 Original signed informed consent form will be kept with the study coordinating office. A copy will be kept in the subject's clinical chart.

13.6.2 Data will be collected on subject characteristics, disease characteristics, protocol therapy, response to treatment, adverse events and follow-up for relapse and survival. Source documentation may include the subject's medical record from SCCA/UWMC and/or outside providers which would include history and physical exams, documentation of protocol

therapy, labs, scans, x-rays, hospitalizations, operative reports, pathology reports etc.

14.0 ELEMENTS OF INFORMED CONSENT

All Institutional, NCI, State and Federal regulations concerning informed consent will be fulfilled. Written consent will be obtained from all subjects entering the study.

15.0 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

15.1 Pre-Study Documentation

The following documentation will be established in the Sponsor-Investigator's files prior to initiation of the trial: FDA Form 1572 (if study is conducted under an IND); curricula vitae of the PI and all Sub-Investigators; copy of the correspondence from the IRB indicating approval of the protocol and Informed Consent Forms, signed by the IRB/EC chairperson or designee; copy of the Informed Consent Forms that were reviewed and approved by the IRB.

15.2 Study Site Training

Before initiation of the study, the PI, or its designated representatives will review and discuss the following items with the Investigator and clinic staff: the protocol, study procedures, record keeping and administrative requirements, drug accountability, AE reporting, Good Clinical Practice guidelines, and the ability of the site to satisfactorily complete the protocol.

15.3 Ethical Considerations

The investigators agree to conduct this study in accordance with applicable United States FDA clinical trial regulations and guidelines, applicable United States FDA clinical trial regulations and guidelines, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (E6) GCP guidelines, the European Union Directive 2001/20/EC for clinical trials conducted in the European Union, the IRB/EC and local legal requirements and with the Declaration of Helsinki (1989). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

15.4 Informed Consent

The PI/subinvestigator assumes the responsibility of obtaining written Informed Consent for each subject or the subject's legally authorized representative before any study-specific procedures are performed.

Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study. Subjects or parents/legal guardians of all candidate subjects will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available, any known previously experienced adverse reactions, the investigational status of the study drug, and other factors that are part of obtaining a proper Informed Consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate.

Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by FDA regulations and ICH guidelines. A copy of the signed form will be given to the person who signed it, the original signed Consent Form will be filed with the subject's medical records, and copy maintained with the subject's study records. The date and time of time of the Informed Consent must be recorded in the source documents.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the Informed Consent Form must be amended. Any amended Informed Consent must be reviewed by the Sponsor or designee and approved by the IRB/EC prior to use. The revised Informed Consent Form must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment, and must be used to document consent from any new subjects enrolled after the approval date of the amendment.

15.5 Institutional Review Board/Ethics Committee

The PI will assure that an appropriately constituted IRB/EC that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH (E6) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB/EC for its review and approval.

The PI or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB/EC, and that no changes will be made to the protocol without IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

The Investigator or designee will be responsible for submitting periodic progress reports to the IRB/EC at intervals appropriate to the degree of subject risk involved in the study, but not less than once per year and at the completion or termination of the study.

15.6 Subject Privacy

The investigators affirm and uphold the principle of the subject's right to privacy. The investigator shall comply with applicable national and local privacy laws.

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15.0 Appendices

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting.

Appendix 3: Response Criteria: IWCLL 2018

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of −49% to +49%
B	Platelet count	≥100 × 10⁹/L	≥100 × 10⁹/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of −49 to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

For a detailed description of the response parameters, see original reference[1,27].

*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).

†Spleen size is considered normal if ,13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

CR, complete remission (all of the criteria have to be met); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met); PR, partial remission (for a PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD, stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).